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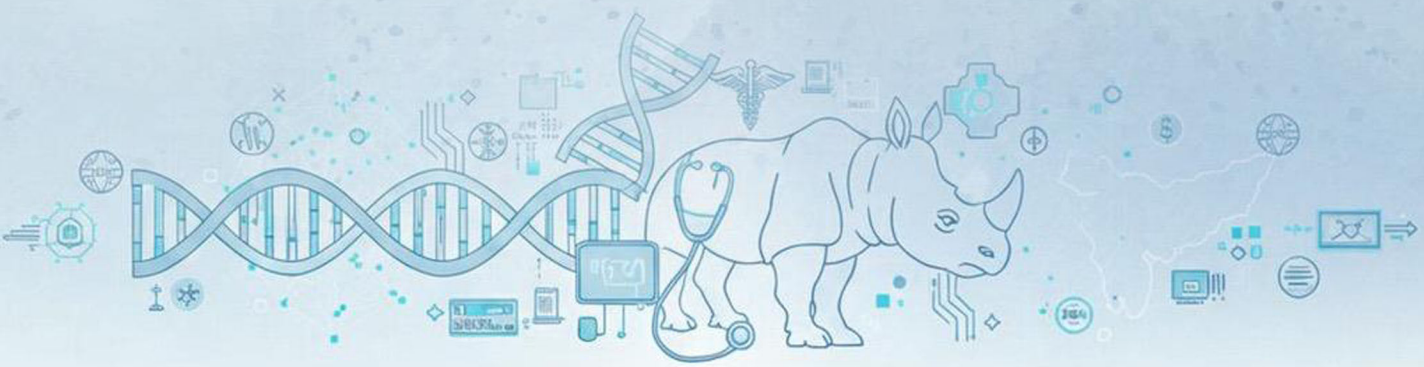

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FROM THE DESK OF CHAIRPERSON (ORGANIZING COMMITTEE) APICON ASSAM 2025

It is with the greatest degree of pride & pleasure & privilege on my behalf that I am going to pen the foreword of the first entirely online version the medicine update being published on the happy occasion of XXXIV APICON ASSAM 2025, in the capacity as chairperson of the organizing committee of the same event. In this voluminous work, care has been taken with humble effort to focus on the latest information and knowledge on various burning issues related to the vast subject of medicine.

In this happy occasion, I also take the privilege to intimate all the esteemed readers that the field of internal medicine has a far-reaching impact on the human lives due to each rapid growth within a short span of past few decades in our north-eastern region of India. It is needless to say that it is an ever-expanding subject & to keep up with the pace with the rest of the world we need to constantly update ourselves in this field both theoretically as well as in the practical field.

I must say that this is the motto of publication of this particular update – to enlighten everyone with greater number of newer topics and offer in-depth knowledge into the subject concerned. No doubt, "Internal Medicine" is a vast subject & can be compared with an ocean and many newer challenges have unfolded in every decade of the recent times. So, meticulous study of these subjects are the need of the hour. Under the stewardship of Prof. Dr. Kalpana Chetia, the entire team entrusted with the responsibility of preparation of the **MEDICINEUPDATE** e-book have tried their level best to include these newer subjects in this online book to unravel the mystery to our newer generation of doctors who would find it interesting and easier to go through and keep themselves at par with their peers. In my humble opinion, senior Physicians will also find this online edition informative and useful.

Lastly, I would like to thank the entire team of the medicine update preparation & compliment the diligent work which have made this volume turn into reality. Though we are unable to encompass the entire gamut of all the relevant topics, I hope it will serve the purpose.

Prof Mihir Kumar Goswami
Chairperson (Organizing Committee)
APICON (ASSAM) 2025

PREFACE

It is with profound joy and a deep sense of purpose that we present Medicine Update 2025, released on the occasion of the 34th Annual Conference of the API Assam Chapter. This year, we gather under the inspiring theme “Intelligent Health Care for Better Outcomes"—a theme that urges us not only to adopt new technologies but to re-envision the very soul of healing.

Medicine has always been a harmonious blend of science and compassion. Today, as we stand at the intersection of rapidly evolving innovations and timeless clinical wisdom, we are offered a remarkable opportunity: to combine our human touch with intelligent tools that elevate our ability to serve. Artificial intelligence, digital health systems, and data-driven insights are no longer distant possibilities—they have become partners that strengthen our clinical judgment, refine our therapeutic decisions, and enable us to understand each patient more holistically.

Medicine Update 2025 is a reflection of that aspiration. Each chapter is shaped by the dedication, insight, and curiosity of physicians, teachers, and researchers committed to transforming knowledge into better patient outcomes. Their contributions remind us that intelligent healthcare is, at its core, profoundly human—empathetic, ethical, and anchored in the desire to improve lives.

As you turn these pages, may you feel encouraged to embrace the future of medicine with courage, clarity, and compassion. May the ideas shared here spark new discussions, inspire innovative practices, and strengthen our collective commitment to excellence in medical care. Together, let us build a future where intelligent systems empower us, where challenges become opportunities, and where our patients remain at the heart of every advancement.

We extend our heartfelt thanks to all contributors, reviewers, and members of the organizing committee whose dedication made this publication possible. Despite our best efforts, inadvertent errors may have crept into the manuscript, and for this we sincerely apologise. May this 34th Conference illuminate new paths of learning and reaffirm our devotion to the noble calling of healing.

Long live API.

Dr. Kalpana Chetia
Editor

ACKNOWLEDGEMENT

It gives us immense pleasure to present Medicine Update 2025. This volume is the result of the collective effort, dedication and academic enthusiasm of many individuals, and we wish to place on record my heartfelt gratitude to all of them.

We are deeply thankful to the Organising Committee for entrusting us with the responsibility of editing this book and for their constant support, encouragement and guidance throughout the process. Their vision and meticulous planning provided the ideal environment for this academic endeavour.

Our sincere thanks to all the contributing authors who, despite their busy clinical schedules, have taken the time to share their knowledge, experience and insights. Their well-researched, lucid and clinically relevant chapters form the backbone of this edition of Medicine Update.

We would like to make a special mention of Prof. Bhupen Barman for his immense contribution as a guide. His help in conceptualising and refining the topics, as well as his continuous academic support, has been invaluable in shaping the content and quality of this book.

We are also grateful to Dr. Nasreen Kausar,Dr. Jacquiline D Shira, Dr. Parag Kumar Das, Dr. Nabaruna Paul and Dr. Kulbinder Singh for their generous assistance at various stages of this work. Their help with coordination, review and critical inputs has made the editorial process smoother and more efficient.

To all those who contributed in ways big and small, our sincere thanks. We hope Medicine Update 2025 will serve as a useful and practical resource for clinicians, postgraduates and students, and will inspire further learning and discussion in the field of medicine.

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Section 1
Cardiology

Chapter

1

Advances in Precision Cardiology with Respect to Genomics and Personalized Therapies

Mriganka Shekhar Chalihaa, Sharad Kumar Maurya

1. Introduction

Cardiology, the study of heart and vascular diseases, has seen a significant transformation in recent years, with advancements in genomics and personalized medicine leading the way. The advent of precision medicine, which tailors medical treatment to individual genetic, environmental, and lifestyle factors, holds immense promise for the treatment and management of cardiovascular diseases (CVDs)[1,2]. Traditionally, cardiovascular medicine has relied on a one-size-fits-all approach, wherein treatments were based on population-wide guidelines and statistical averages. However, this approach does not always account for the unique genetic makeup and molecular profiles of individual patients.

Recent strides in genomics have provided a deeper understanding of the genetic underpinnings of CVDs, enabling clinicians to tailor interventions more effectively and with greater precision. This chapter will explore the role of genomics in precision cardiology, discussing genomic biomarkers, the integration of genomics into clinical practice, the latest advances in genomics for heart disease, and the emerging field of personalized therapies for cardiovascular conditions.

2. Types of Genomic Biomarkers

Genomic biomarkers are measurable molecules in the genome, transcriptome, proteome, or metabolome that serve as indicators of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. In cardiovascular medicine, several types of genomic biomarkers have been identified, each offering insights into the pathophysiology of heart disease and responses to treatment. The key categories of genomic biomarkers in cardiology include:

2.1 Genetic Mutations and Variants

Genetic mutations and polymorphisms are significant in understanding congenital and acquired cardiovascular diseases. For instance:

- Familial Hypercholesterolemia (FH): Mutations in the LDLR, APOB, and PCSK9 genes can predispose individuals to high cholesterol levels and early-onset

coronary artery disease (CAD)[3,4].

- Hypertrophic Cardiomyopathy (HCM): Mutations in cardiac sarcomere proteins such as MYBPC3 and MYH7 are associated with familial forms of HCM, leading to left ventricular hypertrophy and arrhythmias[5].

2.2 Epigenetic Modifications

Epigenetic changes, such as DNA methylation, histone modification, and non-coding RNA regulation, have been shown to play a role in cardiovascular disease. These modifications can be influenced by environmental factors, such as diet and exercise, and may contribute to disease development and progression[6]. For example:

- DNA Methylation: Alterations in DNA methylation patterns have been linked to various forms of cardiovascular disease, including atherosclerosis and heart failure.
- Non-coding RNAs: MicroRNAs (miRNAs) regulate gene expression and can be dysregulated in conditions such as myocardial infarction, arrhythmias, and heart failure.

2.3 Single Nucleotide Polymorphisms (SNPs)

SNPs are the most common form of genetic variation among individuals and can influence susceptibility to cardiovascular diseases. Specific SNPs in genes related to lipid metabolism, inflammation, and vascular function have been associated with an increased risk of CAD and stroke[7]. For instance:

- 9p21 locus: Variants at the 9p21 chromosomal region are strongly associated with an increased risk of coronary artery disease, independent of traditional risk factors like cholesterol and blood pressure.[7]

2.4 Gene Expression Profiles

Gene expression profiling involves measuring the expression levels of thousands of genes simultaneously. These profiles can be used to predict disease risk, prognosis, and treatment response. In cardiovascular diseases, gene expression signatures can provide insight into:

- Myocardial Infarction (MI): Specific gene expression patterns in peripheral blood or cardiac tissue post-MI can predict recovery and risk of heart failure.
- Heart Failure: Gene expression profiles in heart failure patients can help identify patients who will benefit from specific treatments, such as ACE inhibitors or beta-blockers[8,9].

3. Role of Genomics in Precision Cardiology

The integration of genomics into precision cardiology is a revolutionary development, allowing for more individualized diagnosis, risk assessment, and therapeutic strategies. Genomics in cardiology can be classified into several critical roles:

3.1 Early Diagnosis and Risk Stratification

Genomic tools can identify individuals at high genetic risk for cardiovascular diseases before clinical manifestations appear. For example:

- Genetic Screening: Early genetic screening for mutations such as those in the MYH7 gene for hypertrophic cardiomyopathy or in the LDLR gene for familial hypercholesterolemia can enable early intervention and surveillance, potentially preventing life-threatening events such as sudden cardiac death.
- Polygenic Risk Scores (PRS): PRS aggregates the effects of multiple genetic variants to estimate an

individual's genetic predisposition to a particular disease. In cardiovascular risk, PRS can help refine risk assessments beyond traditional factors like cholesterol levels and blood pressure[7].

3.2 Understanding Disease Pathophysiology

Genomic research has uncovered the molecular mechanisms underlying various cardiovascular conditions. For example:

- Atherosclerosis: Gene expression studies have revealed the roles of inflammatory pathways and lipid metabolism genes in the development of atherosclerotic plaques. Identifying the molecular drivers of atherosclerosis can lead to targeted therapies to prevent plaque rupture and reduce cardiovascular events[4].
- Arrhythmias: Understanding the genetic basis of inherited arrhythmias (e.g., Long QT syndrome, Brugada syndrome) through genomic analysis can help predict arrhythmic events and enable the use of targeted therapies, including implantable devices or medications[9].

3.3 Personalized Treatment Strategies

The genomic profile of a patient can inform the selection of optimal therapeutic interventions. For instance:

- Statin Therapy in Hyperlipidemia: Genetic variants in the SLCO1B1 gene affect the metabolism of statins, influencing both their effectiveness and the risk of side effects. Genomic testing can help guide the selection of statin therapy for individuals at risk of statin-induced myopathy[10].
- Anti-coagulation Therapy: Variants in the VKORC1 and CYP2C9 genes can influence the metabolism of warfarin, a common anticoagulant. Pharmacogenomic testing can optimize warfarin dosing to minimize the risk of bleeding or thromboembolism[11,12].

4. Latest Advances in Genomics in Precision Cardiology

Recent technological advancements in genomics, such as next-generation sequencing (NGS) and CRISPR-Cas9 gene editing, have accelerated the pace of discovery in cardiovascular genomics. Some of the most promising advances include:

4.1 Whole Genome Sequencing (WGS) and Whole Exome Sequencing (WES)[13]

Whole genome sequencing (WGS) and whole exome sequencing (WES) have enabled a more comprehensive understanding of cardiovascular diseases at the molecular level. These techniques allow for the identification of novel genetic variants associated with rare and complex heart conditions, as well as the development of precision treatments tailored to an individual's unique genetic makeup.

- WGS in Cardiomyopathies: WGS has led to the discovery of previously unrecognized mutations associated with familial cardiomyopathies, such as dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC).
- WES in Coronary Artery Disease: WES has identified new genes involved in the development of coronary artery disease (CAD), potentially opening avenues for targeted therapies aimed at these genetic pathways.

4.2 CRISPR-Cas9 and Gene Editing in Cardiology[14]

CRISPR-Cas9 gene editing holds the potential for directly correcting genetic mutations associated with cardiovascular diseases. Early preclinical studies have demonstrated the possibility of repairing mutations in genes such as MYBPC3 in animal models of hypertrophic cardiomyopathy, opening the door to potential gene therapies in human patients in the future.

4.3 Epigenetic Modifications in Cardiovascular Disease[7]

The growing field of epigenetics has revealed that environmental factors can alter gene expression in ways that influence cardiovascular health. Epigenetic modifications, including DNA methylation and histone modification, can be used as biomarkers for disease diagnosis, prognosis, and therapeutic monitoring. For instance:

- DNA Methylation in Atherosclerosis: Altered DNA methylation patterns have been identified in individuals with atherosclerosis, and these patterns could serve as early biomarkers for the disease.

5. Latest Personalized Therapies in Precision Cardiology

The field of personalized therapies in cardiology is evolving rapidly, with new treatments emerging that are based on an individual's genetic, molecular, and phenotypic characteristics. Some of the most significant advances include:

5.1 Pharmacogenomics in Cardiovascular Drugs[11]

Pharmacogenomics is the study of how genetic variations affect drug response. In cardiology, pharmacogenomics is being integrated into clinical practice to optimize drug selection and dosing. Some examples include:

- Statins: Genetic testing for variants in SLCO1B1 can help identify patients at higher risk for statin-associated myopathy and guide clinicians in choosing the right statin or adjusting the dose.
- Clopidogrel: Variants in the CYP2C19 gene affect the metabolism of clopidogrel, an antiplatelet medication. Genomic testing can help determine whether a patient will respond to clopidogrel or if an alternative treatment is needed.

5.2 Gene Therapies for Cardiovascular Disease

Gene therapies in cardiovascular diseases are a promising frontier, with several therapeutic approaches being explored to correct or compensate for genetic defects. Some of the potential applications include:

- Gene Therapy for Heart Failure: One of the most exciting areas of research involves the use of gene therapy to regenerate heart tissue and improve cardiac function in heart failure patients. For instance, viral vectors have been used to deliver genes encoding proteins such as SDF-1 (stromal-derived factor-1) or VEGF (vascular endothelial growth factor), which promote angiogenesis and tissue repair in damaged cardiac muscle. Early clinical trials have shown promise in improving heart function and reducing the burden of heart failure symptoms.[15]
- Gene Editing for Familial Hypercholesterolemia (FH): Familial hypercholesterolemia is a genetic

disorder caused by mutations in the LDLR, APOB, or PCSK9 genes, leading to elevated cholesterol levels and increased risk for premature coronary artery disease. Researchers are exploring CRISPR-Cas9-based gene editing approaches to correct these mutations in the liver, where cholesterol regulation primarily occurs. Clinical trials are still in their early stages, but this approach could offer a cure for genetically driven hyperlipidemia.[16]

5.3 Targeted Molecular Therapies

Targeted molecular therapies are designed to specifically inhibit or activate molecular pathways involved in cardiovascular diseases. These therapies are tailored based on the patient's unique genetic and molecular profile, allowing for more effective and safer treatments.

- PCSK9 Inhibitors: Monoclonal antibodies targeting the PCSK9 protein, such as evolocumab and alirocumab, are a groundbreaking treatment for individuals with familial hypercholesterolemia or statin intolerance. These inhibitors lower low-density lipoprotein (LDL) cholesterol levels by preventing PCSK9 from promoting the degradation of LDL receptors on liver cells. Personalized treatment strategies based on genetic screening for PCSK9 mutations can optimize the use of these therapies in specific patient populations.[10]
- Antisense Oligonucleotides: Another example of a targeted molecular therapy involves the use of antisense oligonucleotides (ASOs), which are short, synthetic strands of nucleic acids designed to specifically bind to and modify the expression of target genes. For example, volanesorsen, an ASO targeting apoC-III (a protein involved in triglyceride metabolism), is used in patients with familial chylomicronemia syndrome (FCS), a rare genetic disorder associated with extremely high triglyceride levels. ASOs can be personalized to target specific genetic mutations contributing to dyslipidemia and other cardiovascular diseases.[15]

5.4 Stem Cell Therapy and Regenerative Medicine

Regenerative medicine, particularly stem cell therapy, is emerging as a potential treatment for various forms of heart disease, including myocardial infarction (MI) and heart failure. Stem cells have the ability to differentiate into different cell types, including cardiac muscle cells, and can potentially regenerate damaged heart tissue.

- Cardiac Stem Cell Therapy: Clinical trials have shown that transplanting stem cells into the heart after a myocardial infarction can improve cardiac function, reduce scar tissue formation, and promote tissue repair. Autologous stem cells derived from the patient's own bone marrow or adipose tissue are often used to reduce the risk of immune rejection. Research is ongoing to refine these therapies and enhance their efficacy, with promising results from studies that use stem cells to stimulate angiogenesis and restore myocardial function.[17]
- Induced Pluripotent Stem Cells (iPSCs): iPSCs are a type of stem cell that can be derived from adult cells and reprogrammed to become pluripotent (capable of developing into any cell type). iPSCs are being explored for their potential to create personalized cardiac tissue models for drug testing

and disease modeling, as well as for the development of autologous cell therapies to treat heart disease.[18]

5.5 Advanced Antithrombotic Therapies

The traditional approach to managing cardiovascular events such as stroke and myocardial infarction has involved the use of blood thinners like aspirin and clopidogrel. However, the effectiveness of these therapies can be highly variable based on genetic factors.

- Personalized Antiplatelet Therapy: Variations in the CYP2C19 gene can affect the metabolism of clopidogrel, an antiplatelet medication, leading to suboptimal therapeutic outcomes in some individuals. Pharmacogenomic testing can guide clinicians to choose alternative antiplatelet medications, such as ticagrelor, that are less affected by genetic variation, improving patient outcomes.[11]
- Genetic Testing for Warfarin Dosing: Warfarin, an anticoagulant, is commonly prescribed to prevent thromboembolic events but has a narrow therapeutic window. Variants in the VKORC1 and CYP2C9 genes can significantly influence warfarin's metabolism, necessitating individualized dosing. Pharmacogenetic testing can optimize warfarin dosing and reduce the risks of adverse events, such as bleeding or clotting.[12]

5.6 Immune Checkpoint Inhibitors for Cardiovascular Disease[19]

Though immune checkpoint inhibitors (ICIs) have primarily been developed for cancer immunotherapy, their potential applications in cardiovascular disease are emerging. Some studies suggest that immune modulation could play a role in managing atherosclerosis, myocardial infarction, and even arrhythmias. Genetic and molecular profiling of the immune response to atherosclerotic plaques could lead to the development of immunotherapies aimed at reducing inflammation and promoting plaque stability.

- PD-1/PD-L1 Inhibition: Research into the use of immune checkpoint inhibitors, such as those targeting PD-1 or PD-L1, is ongoing. These inhibitors could potentially be used to modulate the immune response in atherosclerotic disease, reducing inflammation and preventing plaque rupture. However, more research is needed to understand the long-term effects and safety of ICIs in cardiovascular settings.

Conclusion

Advances in genomics and personalized therapies are ushering in a new era for the treatment and management of cardiovascular diseases. Genomic biomarkers are offering insights into the genetic underpinnings of heart disease, allowing for earlier detection, more accurate risk stratification, and the development of personalized treatment plans. Technologies such as whole genome sequencing, CRISPR gene editing, and pharmacogenomics are paving the way for more targeted, effective, and safer interventions in cardiology.

The latest personalized therapies, including gene editing, targeted molecular therapies, stem cell treatments, and pharmacogenomic-guided drug selection, are transforming how cardiovascular

diseases are managed, with the potential to significantly improve patient outcomes. As research progresses, it is likely that these personalized approaches will become more widespread, allowing clinicians to tailor therapies not only to the specific condition but also to the individual's genetic and molecular profile.

The future of precision cardiology promises to be one of more effective, less invasive, and better-targeted treatments, ultimately improving the quality of life and survival rates for individuals with cardiovascular disease. With continued advancements in genomics, personalized therapies, and regenerative medicine, the landscape of cardiovascular care will continue to evolve, offering hope for more effective and individualized solutions to heart disease.

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Chapter

2

Next Generation Heart Failure Management: Devices and Pharmacotherapies

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ABSTRACT

Heart failure (HF) affects over 64 million globally, with management evolving through guideline-directed medical therapy (GDMT) and innovative devicesas perrecent guidelines. For HFrEF, quadruple GDMT (ARNI, beta-blockers, MRAs, SGLT2i) reduces mortality and hospitalizations, with additions like vericiguat and IV iron. In HFmrEF/HFpEF, SGLT2i are pivotal, supplemented by finerenone for cardiorenal protection and semaglutide for obese patients, improving symptoms and quality of life. Novel targets include NO-sGC pathways, calcium handling, and metabolism. Device therapies encompass ICDs/CRTs for prevention, advancing to conduction system pacing (HBP/LBBAP) for superior resynchronization, and emerging options like CCM, BAT, PA monitoring (CardioMEMS), and transcatheter repairs (MitraClip/TriClip) for refractory cases. Multidisciplinary approaches address underutilization, promising enhanced outcomes across HF phenotypes.

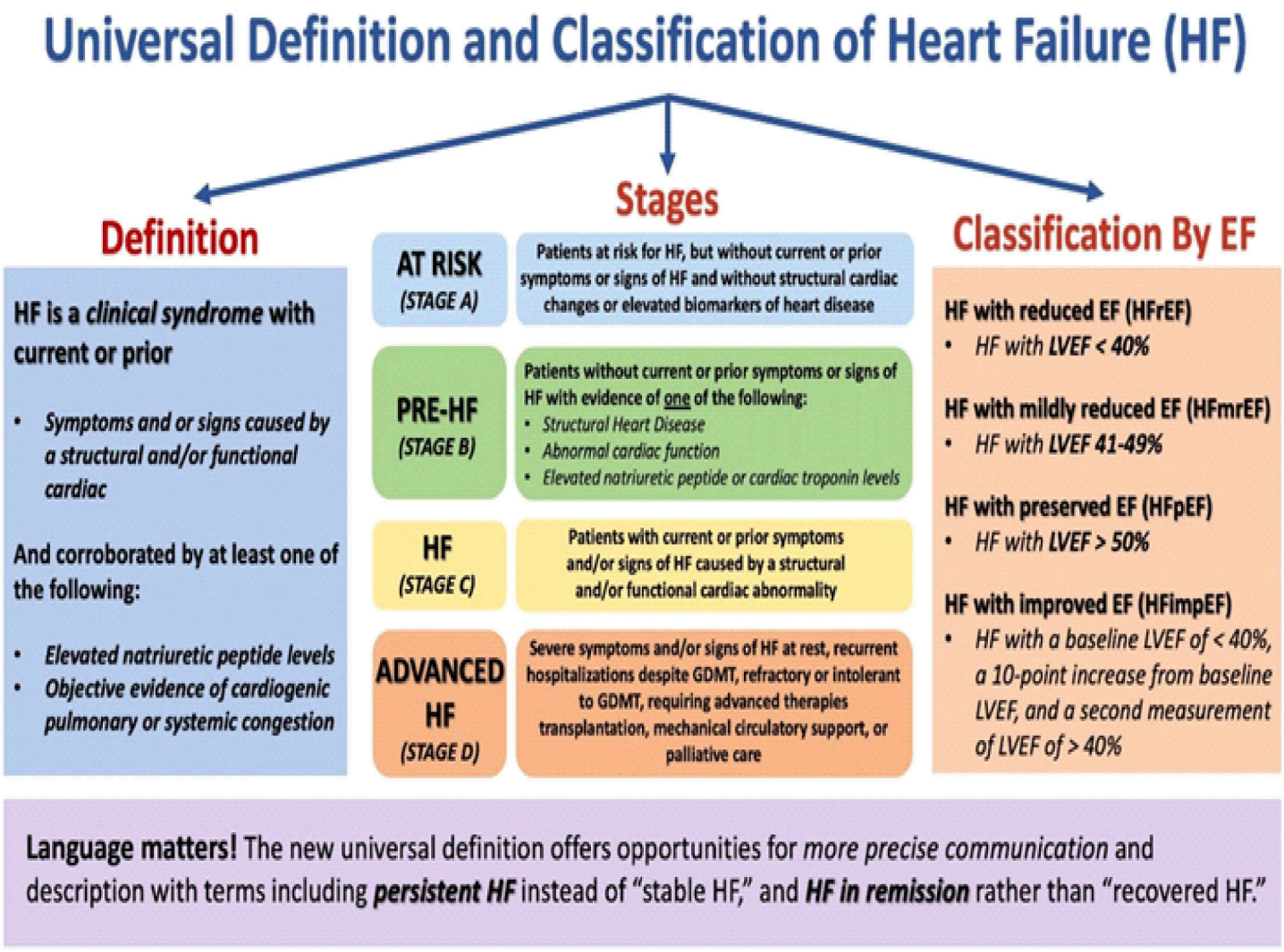
Keywords : Heart Failure, HFrEF, HFmrEF, HFpEF, , Quadruple Therapy, ARNI, Beta-Blockers, MRAs, SGLT2 Inhibitors, Finerenone, Semaglutide, Vericiguat, IV Iron, Conduction System Pacing, His-Bundle Pacing, Left Bundle Branch Area Pacing, Cardiac Resynchronization Therapy, Implantable Cardioverter-Defibrillator, Cardiac Contractility Modulation, Baroreflex Activation Therapy, Pulmonary Artery Pressure Monitoring, CardioMEMS, Transcatheter Edge-to-Edge Repair

Introduction :

Heart failure (HF) remains a global health challenge, affecting over 64 million people worldwide and contributing to substantial morbidity, mortality, and healthcare costs. As of 2025, advancements in management have shifted toward a multifaceted approach, emphasizing guideline-directed medical therapy (GDMT) alongside innovative device interventions. The 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) Guideline for the Management of Heart Failure provides a comprehensive

framework for patient-centric care across HF phenotypes—heart failure with reduced ejection fraction (HFrEF, left ventricular ejection fraction [LVEF] =40%), mildly reduced ejection fraction (HFmrEF, LVEF 41–49%), and preserved ejection fraction (HFpEF, LVEF =50%). Complementing this, the 2021 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, with focused updates in 2023(1), underscore similar principles while incorporating emerging evidence on pharmacotherapies and devices. These guidelines prioritize quadruple therapy for HFrEF, expanded roles for sodium-glucose cotransporter 2 inhibitors (SGLT2i) across phenotypes, and novel devices to address residual risks. This article explores these next-generation strategies, highlighting their evidence base, implementation, and future implications.

Definition and classification of heart failure (2)



Language matters! The new universal definition offers opportunities for *more precise communication* and description with terms including ***persistent HF*** instead of "stable HF," and ***HF in remission*** rather than "recovered HF."

ABCD Staging System and Treatment Plan (2022 ACC/AHA/HFSA)(3)

Stage	Description	Key Criteria	Recommended Interventions
A	At Risk for HF	Risk factors (HTN, DM, CAD, obesity) without structural disease	Lifestyle modification, BP/lipid/glucose control, SGLT2i/ARNI if high risk
B	Pre-HF	Asymptomatic structural/functional abnormality (LVH, reduced EF, valve disease)	Initiate GDMT: ARNI/ACEI/ARB + ß-blocker + SGLT2i; risk factor optimization
C	Symptomatic HF	Structural disease + current/prior symptoms/signs	Full quadruple GDMT + diuretics; consider devices (ICD/CRT/CSP)
D	Advanced HF	Marked symptoms at rest despite maximal GDMT; recurrent hospitalizations	Inotropes, LVAD, transplant, palliation; advanced devices (CCM, BAT)

Pharmacotherapies: Building on Quadruple Therapy Foundations

Pharmacological management has evolved from symptom palliation to disease modification, with GDMT now extending survival by up to 5 years in HFrEF patients through synergistic effects on neurohormonal activation, fluid retention, and myocardial remodeling. Both ACC/AHA and ESC guidelines recommend initiating therapies at low doses and titrating to target levels, guided by multidisciplinary teams to optimize adherence and monitor for side effects like hyperkalemia or hypotension.

Core Therapies for HFrEF

The cornerstone of HFrEF management is quadruple GDMT, comprising an angiotensin receptor-neprilysin inhibitor (ARNI, e.g., sacubitril/valsartan), evidence-based beta blockers (e.g., carvedilol, bisoprolol), mineralocorticoid receptor antagonists (MRAs, e.g., spironolactone), and SGLT2i (e.g., dapagliflozin, empagliflozin). All receive Class 1, Level of Evidence (LOE) A recommendations in both guidelines, reducing cardiovascular (CV) death and HF hospitalizations by 25–31% collectively.

Therapy Class	Key Agents	Class/LOE (ACC/AHA & ESC)	Benefits	Key Trials
ARNI	Sacubitril/valsartan	**Class 1/A**	↓ CV death/HF hospitalization (NNT=14); improves remodeling	PARADIGM-HF

Beta Blockers	Carvedilol, bisoprolol, metoprolol succinate	**Class 1/A**	↓ Mortality/hospitalizations	MERIT-HF, CIBIS-II. COPERNICUS
MRAs	Spironolactone, eplerenone	**Class 1/A**	↓ Mortality (25–30%)	RALES, EMPHASIS-HF
SGLT2i	Dapagliflozin, empagliflozin	**Class 1/A**	↓ CV death/HF events (14–31%); diabetes-independent	DAPA-HF, EMPEROR-Reduced

For patients intolerant to ACE inhibitors/angiotensin receptor blockers (ARBs), hydralazine-isosorbide dinitrate is an alternative (Class 1, LOE B), particularly in self-identified Black patients.

Next-Generation Additions

Recent trials have introduced therapies targeting unmet needs, such as persistent symptoms or comorbidities. Vericiguat, a soluble guanylate cyclase stimulator, earns a Class 2a, LOE B recommendation for high-risk HFrEF patients with recent worsening events, reducing composite CV death/HF hospitalization (HR 0.90; NNT=34) per the VICTORIA trial. Intravenous (IV) iron repletion with ferric carboxymaltose is now Class 1a (ESC) or 2a (ACC/AHA) for iron-deficient patients (ferritin <100 µg/L or 100–300 µg/L with transferrin saturation <20%), improving symptoms, quality of life, and hospitalizations (HR 0.74). Potassium binders like patiromer facilitate MRA/SGLT2i use by mitigating hyperkalemia(1,3).

Extensions to HFmrEF and HFpEF

Evidence is less robust for non-HFrEF phenotypes, but SGLT2i are transformative: Class 2a, LOE B in both guidelines for reducing hospitalizations across all LVEF (EMPEROR-Preserved: HR 0.79; DELIVER: HR 0.85)(3). however,According to the 2023 ESC focused update, SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended with Class 1, Level A evidence in HFpEF to reduce the risk of HF hospitalization and cardiovascular death, irrespective of diabetes status(1).

MRAs and ARNI receive Class 2b recommendations in select HFpEF patients. Diuretics remain essential for congestion (Class 1, LOE C), with ESC emphasizing symptom-guided adjustments to avoid overuse.

In HFpEF, finerenone (non-steroidal MRA) reduces worsening HF events and hospitalizations by 13% (rate ratio 0.87) as shown in the FINEARTS-HF trial (2024)(4), with consistent benefits across LVEF =50%, particularly in patients with recent decompensation or CKD/T2DM; it is now Class 2a/B (ACC/AHA 2025 ECDP) for HFpEF with CKD and Class 2b/B (ESC 2024 update) more broadly, offering cardiorenal protection

with manageable hyperkalemia risk. Semaglutide (GLP-1 RA) significantly improves symptoms (KCCQ +8.1 points), exercise capacity (+34 m in 6MWD), and weight (-13.3%) in obese HFpEF (STEP-HFpEF and STEP-HFpEF DM trials)(5,6), with pooled analyses from SELECT(7) and STEP trials showing a 28% reduction in HF events (HR 0.72); it earns Class 2a/B-NR (ACC/AHA) and Class 2b/B (ESC) recommendations for obese/overweight HFpEF to enhance quality of life and function, independent of diabetes. Both agents are additive to SGLT2i, targeting inflammation, fibrosis, and obesity—key drivers in HFpEF—and represent emerging pillars in phenotype-specific GDMT.

Therapy	**Finerenone**	**Semaglutide**
Key Trials & Outcomes	**FINEARTS-HF (2024)**: ↓ total HF events + CV death by 13% (RR 0.87, P=0.031); consistent in HFpEF (LVEF ≥50%); ↑ KCCQ, ↓ hospitalizations	**STEP-HFpEF (2023) & SELECT pooled (2024)**: ↑ KCCQ +8.1 pts, 6MWD +34 m, ↓ weight 13.3%; ↓ HF events 28% (HR 0.72)
Guideline Recommendation (2025)	**ACC/AHA: Class 2a/B-NR** (HFpEF + CKD/T2DM) **ESC: Class 2b/B** (broad HFpEF)	**ACC/AHA: Class 2a/B-NR** (obese HFpEF) **ESC: Class 2b/B** (obese/overweight HFpEF)

Novel Therapeutic Targets: Beyond Neurohormonal Blockade:

Here is a brief summary of potential novel therapeutic targets which may be explored in the management of heart failure

Target Pathway	**Mechanism**	**Key Agent(s)**	**Status (2025)**	**Class/LOE**	**Landmark Trials**
NO-sGC Pathway	↓ NO bioavailability → impaired vasodilation &remodeling	**Vericiguat** (sGC stimulator)	FDA/EMA approved	**ACC/AHA: 2a/B-RESC: 2a/B**	VICTORIA (8)(HR 0.90 for CV death/HFH; NNT=34)
Intracellular Calcium Dysregulation	Leaky RyR2, ↓ SERCA2a → diastolic dysfunction	**Omecamtivmecarbil** (cardiac myosin activator)	Approved EU/Japan; under FDA review	**ACC/AHA: 2b/B-RESC: 2a/B**	GALACTIC-HF(9) (↓ HFH/CV death; HR 0.92)

Mitochondrial Function	Oxidative stress, ↓ ATP, cardiolipin instability	**Elamipretide (SS-31)**	Investigational	-	Phase 2 (PROGRESS-HF)(10)improves mitochondrial energetics but failed to show benefits
Cardiac Metabolism	Shift to glucose → inefficiency ; ketone utilization	**Empagliflozin, Trimethylamine N-oxide inhibitors**	SGLT2i: Class 1/A	**ACC/AHA:IIA & ESC: 1/A**	EMPA-REG OUTCOME, DAPA-HF (1,3)(ketone hypothesis)
Cardiac Myosin Activation	Enhances contractility without ↑ Ca^{2+}	**Omecamtivmecarbil, Danicamtiv** (Phase 2)	Omecamtiv: Approved in select regions	-	COSMIC-HF, GALACTIC-HF(9,11)

Adjunctive Therapy (1,3)

Here is the summary of adjunctivetherapy recommended in HF beyond the four pillars.

Therapy	Indication	Class/LOE	Key Trials
IV Iron (Ferric carboxymaltose)	Iron deficiency (ferritin <100 or 100–299 + TSAT <20%)	**ACC/AHA: 2a/B-RESC: 1a/A**	AFFIRM-AHF, IRONMAN
Ivabradine	SR, HR ≥70 bpm on max β-blocker	**2a/B-R**	SHIFT
Hydralazine + ISDN	Black patients, intolerant to ACEI/ARB	**1/B-R**	A-HeFT

Device Therapies: From Prevention to Precision Intervention

Devices complement pharmacotherapy by mitigating arrhythmic and hemodynamic risks, with guidelines advocating shared decision-making and advanced HF specialist involvement. Traditional implants like implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) are well-established, but next-generation options target congestion, contractility, and valvular issues.

Established Device Therapies

For HFrEF, primary prevention ICDs (Class 1, LOE A) reduce sudden cardiac death in LVEF =35% (NYHA II–III), while CRT (Class 1, LOE A) improves outcomes in QRS =130 ms with left bundle branch block (LVEF =35%, NYHA II–IV). Both ACC/AHA and ESC align on these, with 2025 ACC/AHA Appropriate Use Criteria refining scenarios for ICD/CRT implantation. In advanced HF, left ventricular assist devices (LVADs) serve as bridges to transplant (Class 1) or destination therapy.

Current Status of CRT and ICD(12,13)

Device	Indication	Class/LOE (ACC/AHA & ESC)	Key Outcomes	Notes
ICD (Primary Prevention)	HFrEF, LVEF ≤35%, NYHA II–III, >40 days post-MI	**1/A**	↓ SCD (HR 0.69)	MADIT-II, SCD-HeFT
CRT-D/P	HFrEF, LVEF ≤35%, QRS ≥130 ms + LBBB, NYHA II–IV	**1/A**	↓ Mortality/HFH (HR 0.64)	COMPANION, MADIT-CRT
CRT Response Rate	~70% with BVP	—	↑ LVEF, ↓ LVESV	30% non-responders

Limitations of Traditional CRT: Pacing-induced dyssynchrony, RV apical pacing ? Pacemaker Induce Cardiomyopathy (PICM) in 15–20% cases

Conduction System Pacing (CSP): The New Standard(13)

Conduction System Pacing (CSP), encompassing His-bundle pacing (HBP) and left bundle branch area pacing (LBBAP), is emerging as the preferred alternative to traditional biventricular pacing in CRT, offering physiological ventricular activation, superior EF improvement, and reduced HF hospitalizations.

Technique	Mechanism	Advantages	Current Status (2025)
His-Bundle Pacing (HBP)	Direct His-Purkinje activation	Physiological QRS, ↓ PICM	**Preferred over BVP in narrow QRS + AV block** (HRS 2025 Consensus)
Left Bundle Branch Area Pacing (LBBAP)	Deep septal lead → LBB capture	Narrow QRS, high success, low threshold	**Class 2a/B-NR (ACC/AHA)Class 2a/B (ESC)** Meta-analyses: ↑ EF +8%, ↓ HFH 40% vs BVP

Limitations of Traditional CRT: Pacing-induced dyssynchrony, RV apical pacing ? Pacemaker Induce Cardiomyopathy (PICM) in 15–20% cases

Next-Generation Innovations

2025 marks expansions in device approvals, particularly for HFpEF and GDMT-intolerant patients. Pulmonary artery (PA) pressure monitoring via CardioMEMS (implantable sensor) is now FDA-approved for all HF phenotypes, including HFpEF, with Class 2b (ACC/AHA) for guiding diuretic therapy and reducing hospitalizations (CHAMPION: 37% reduction; MONITOR-HF: improved quality of life). The Cordella system offers similar remote monitoring.

Novel therapies address specific phenotypes(12,13):

Device	Indication	Class/LOE (Guidelines)	Key Benefits	Trials / Notes
Cardiac Contractility Modulation (CCM, Optimizer III)	NYHA III/IV, LVEF 25–45%, GDMT-refractory, CRT-ineligible	**Class 2b (ESC)** ACC/AHA-M (may be appropriate)	↑ Peak VO_2, 6MWT, QOL; promotes remodeling	FIX-HF-5; FDA-approved 2023
Baroreflex Activation Therapy (BAT, Barostim Neo)	NYHA III (or recent III), LVEF ≤35%, no CRT indication	**Class 2b (ESC)**	↑ LVEF, ↓ NT-proBNP, improves exercise	BeAT-HF

Transcatheter Edge-to-Edge Repair (MitraClip / TriClip)	Severe secondary MR/TR despite GDMT	**Class 2a (ESC for MR)**	↓ Hospitalizations/mortality	COAPT (MR)(14), TRILUMINATE (TR)(15); FDA 2024 for TriClip
Phrenic Nerve Stimulation (remedē)	Central sleep apnea in HF	**N/A (emerging)**	↓ Apnea index, ↑ QOL	FDA-approved for CSA
Transcatheter Left Ventricular Restoration (AccuCinch)	Dilated LV in HFrEF	**Emerging (Phase III)**	↓ LV volume, ↑ QOL	CORCINCH-HF(16)

Patient selection is critical, stratified by GDMT tolerance and heart replacement therapy (HRT) candidacy. For instance, CCM and BAT suit hypotensive or CKD patients, while interatrial shunts (e.g., V-Wave) show promise in HFrEF subgroups despite mixed HFpEF results (RELIEVE-HF). ESC guidelines (Class 2b for BAT/CCM) emphasize these for advanced HF, with ACC/AHA focusing on evidence gaps in HFpEF.

Conclusion

At current era, HF management integrates quadruple pharmacotherapy with precision devices, tailoring interventions to phenotype and comorbidities per ACC/AHA and ESC guidelines. SGLT2i and PA monitoring exemplify paradigm shifts, reducing events across LVEF spectra, while CCM and transcatheter repairs fill gaps in refractory cases. Challenges persist—underutilization, access inequities, and implementation barriers—but multidisciplinary care and ongoing trials (e.g., RESPONDER-HF for shunts) promise further gains. Clinicians must prioritize rapid GDMT optimization and device evaluation to enhance outcomes, reshaping HF as a dynamic, treatable condition.

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Chapter

3

Cardiometabolic Syndrome: Integrating Lipid and Glucose Control

Dr. Pranab jyoti Bhattacharyya, Dr. Maitreyee Bhattacharyya

ABSTRACT

Cardiometabolic Syndrome (CMS) also known as syndrome X, dysmetabolic syndrome, plurimetabolic syndrome, metabolic syndrome and insulin resistance syndrome is characterised by a constellation of metabolic derangements which markedly increase the risk of developing ASCVD in an individual. It also increases the risk of developing type 2 diabetes mellitus by nearly five-fold, which further increases cardiovascular and all-cause mortality. The key metabolic derangements namely insulin resistance and atherogenic dyslipidemia should be timely identified and aggressively managed using a combination of lifestyle modification and pharmacotherapy.

Keywords: Insulin resistance, atherogenic dyslipidemia, Syndrome X

Introduction

Cardiometabolic syndrome, also known as syndrome X, dysmetabolic syndrome, plurimetabolic syndrome, metabolic syndrome and insulin resistance syndrome, is characterised by a constellation of metabolic derangements namely insulin resistance and impaired glucose tolerance, hypertension, intraabdominal adiposity and atherogenic dyslipidemia.1These metabolic derangements, individually and collectively, substantially increase the risk of development of atherosclerotic cardiovascular disease (ASCVD) including premature coronary artery disease.1This systemic metabolic disorder leads to increased morbidity and mortality from both cardiovascular and non-cardiovascular causes. As per the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), it is defined as having at least three of the following five components (Table 1).[1]

Table 1: Components of Cardiometabolic syndrome

Sl No.	Components	Cut off values
1.	Fasting blood glucose	= 100 mg/dL
2.	Abdominal obesity	
	Men	>102 cm WC
	Women	>88 cm WC
3.	Triglycerides	=150 mg/dL
4.	HDL Cholesterol	
	Men	<40 mg/Dl
	Women	<50 mg/dL
5.	Blood pressure	=130/85 mm Hg

Abbreviations: WC: waist circumference, HDL: High-density lipoprotein

A dive into the Metabolic Derangements:

1. Insulin resistance: Insulin resistance is a hallmark feature of cardiometabolic syndrome, which is characterised by reduced cellular sensitivity to insulin. It arises secondary to a combination of genetic susceptibility and environmental factors culminating into adipose tissue dysfunction and chronic inflammation.[2] This leads to elevated blood glucose levels. The pancreatic beta cells respond to insulin resistance and elevated blood glucose levels by insulin hyperproduction which results in hyperinsulinemia.[2] Once the insulin secretion by the pancreatic cells become insufficient to overcome the insulin resistance, hyperglycaemia ensues. This phase of insulin resistance, referred to as "Prediabetes" is an intermediate phase between normal glucose tolerance and type 2 diabetes mellitus.[3] It can either manifest as impaired fasting glucose (due to hepatic insulin resistance) or impaired glucose tolerance (due to muscle insulin resistance).[3] Prediabetesoften leads to the development of type 2 diabetes mellitus if not timely intervened.

   Insulin resistance is a powerful predictor of several cardiometabolic disorders such as endothelial dysfunction, steatotic liver disease, hypertension, left ventricular diastolic dysfunction, chronic kidney disease and ASCVD.[3] The mechanisms underlying these disorders include sympathetic nervous system dysregulation, renin-angiotensin-aldosterone system (RAAS) dysregulation, maladaptive immune responses and mitochondrial dysfunction, all leading to a chronic low-grade inflammatory state with oxidative stress and activation of immune cells.[3] The key features of adipose tissue dysfunction are adipocyte hypertrophy, altered secretion of adipokines and increased release of free fatty acids; all of which impair insulin signalling pathways in target tissues contributing to insulin resistance.[2]

2. Atherogenic dyslipidaemia: It is characterised by (i) Elevated levels of apoB -containing very low-

density lipoproteins (VLDLs) and chylomicrons (also referred to as Triglyceride-rich lipoproteins, TRLs)

(ii) Increased number of small-dense low-density lipoproteins (LDL)

(iii) Low levels of high-density lipoprotein (HDL)-cholesterol.[3]

Insulin resistance along with adipose tissue dysfunction plays a key role in increasing the release of free fatty acids (FFAs)from adipose tissue.[3] The FFAs in combination with hyperglycemia, hyperinsulinemia and low lipoprotein lipase (LPL) activity, trigger hepatic VLDL production which raises the total cholesterol and triglyceride levels.[3] Increased production of TRLs along with impaired clearance of TRL remnants result in postprandial dyslipidemia.[3] With the activation of cholesteryl ester transfer protein, cholesterol from HDL particles get transferred to TRLs, leading to formation of small, dense HDL particles which get rapidly cleared and lower the plasma HDL levels.[3] These changes all contribute to ASCVD risk.

Studies have revealed that the per-particle atherogenicity of TRLs and TRL-remnants are greater than that for LDL.4 This could partially explain the lipid-related excess risk of ASCVD beyond LDL- cholesterol.[4] The atherogenic potential of plasma triglycerides is less clear. Moderate elevation in plasma triglycerides (200-500 mg/dL) reflect the accumulation of TRL remnants and may aid in identifying individuals at a higher risk for ASCVD and all-cause mortality.[5] TRLs have also been related to systemic low-grade inflammation which explains the atherogenic potential.[3]

ApoB is a more accurate marker of cardiovascular risk than LDL or non-HDL cholesterol.[6] It is indicative of total atherogenic lipid burden.[6] Individuals with cardiometabolic syndrome can have atherogenic dyslipidemia even with normal LDL-cholesterol levels.[3,6] This strongly supports the measurement of apoB levels for assessing atherogenic dyslipidemia.

Defining Criteria for Metabolic Derangements:[3]

1. Insulin resistance/Prediabetes:

- Best calculated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula:[7]

[Fasting plasma insulin (mU/L) x plasma fasting glucose (mmol/L)]/22.5

A value of 2.5 or greater is indicative of insulin resistance[8]

- Glycated hemoglobin (HbA1c): 5.7-6.4%
- Fasting plasma glucose: 100-125 mg/dL (Impaired fasting glycemia)
- Plasma glucose 2 hours after oral glucose tolerance test: =140 to 199 mg/dL (Impaired glucose tolerance)

2. Atherogenic dyslipidemia3:

- Fasting triglycerides: = 150 mg/dL; non-fasting triglycerides: = 177 mg/dL
- Non-HDL cholesterol: = 131 mg/dL
- ApoB: = 100 mg/dL

Management Strategies:

1. Lifestyle modifications[3]:

These include increasing physical activity (brisk walking at least 30 min/day), weight loss (at least 7% of body weight), consumption of a healthy diet (rich in fruits, vegetables, nuts,high fibre whole grains, lean proteins, fish, seafood, low fat or fat-free dairy), reducing

stress and cessation of smoking.

2. Pharmacotherapy for glycaemic control[3]:

a) Glucagon-like peptide-1 (GLP-1) receptor agonists & dual and triple peptide agonists: This class of drugs has been demonstrated to have multi-organ protective effects beyond glycemic control and weight loss, across the range of cardiometabolic syndrome including ASCVD, heart failure with preserved ejection fraction (HFpEF), metabolic-associated steatohepatitis (MASH) and chronic kidney disease (CKD). These drugs are enumerated below (Table 2).

Table 2: GLP-1 receptor agonists & dual GLP-1/GIP receptor agonist approved for CMS

Sl No.	GLP-1 receptor agonist	Currently prescribed dosing schedule for Type 2 DM
1.	Dulaglutide	0.75-4.5 mg once weekly sc
2.	Exenatide	5-10 µg twice daily sc
3.	Exenatide (extended-release)	2 mg once weekly sc
4.	Liraglutide	0.6-1.8 mg once daily sc
5.	Lixisenatide	10-20 µg once daily sc
6.	Semaglutide	0.25-1.0 mg once weekly sc
7.	Semaglutide (tablet)	3-14 mg once daily orally
	Dual GLP-1/GIP receptor agonist	
1.	Tirzepatide	2.5-15 mg once weekly sc

Abbreviations: GLP-1: Glucagon-like peptide 1, GIP: Glucose-dependent insulinotropic polypeptide, sc: subcutaneous, DM: Diabetes Mellitus, CMS: cardiometabolic syndrome

b) Sodium-glucose co-transporter 2 inhibitors (Dapagliflozin, Empagliflozin and Sotagliflozin): This class of drugs has been shown to reduce hospitalisation and cardiovascular deaths across the entire spectrum of left ventricular ejection fraction, irrespective of glycemic status.[3,9] They have also been proven to reduce major renal and cardiovascular events, especially heart failure, in individuals with CKD irrespective of diabetes mellitus.[3,9]

c) Other anti-hyperglycemic drugs: Metformin, sulfonylureas, meglitinides, acarbose, Pioglitazone and dipeptidylpeptidase-4 inhibitors can be used for glycemic control, but are without proven renal and cardioprotective effects.[3]

3. Pharmacotherapy for dyslipidemia:

LDL-cholesterol, non-HDL cholesterol and apoB are the targets of treatment; LDL-cholesterol being the primary objective and non-HDL cholesterol and apoB serving as secondary objective of therapy. The various classes of lipid lowering medications which can be used to primarily lower LDL, non-HDL cholesterol and apoBlevels in the cardiometabolic syndrome (in isolation/ combination) are[3]:

A. Statins: First-line therapy for reducing LDL-cholesterol, apoB and non-HDL-cholesterol levels. Dosage could be high intensity (= 50% reduction in LDL levels from baseline) or moderate intensity (= 30% to 49% reduction in LDL levels from baseline).

B. Ezetimibe: Selective inhibitor of intestinal cholesterol absorption. It is administered at a single dose of 10 mg/day, which results in 20% and 11-17% average reduction of LDL-cholesterol and apoBlevels respectively.

C. Bempedoic acid: Oral ATP citrate lyase inhibitor. It is administered at a single dose of 180 mg/day, which results in 17-28% and 15% average reduction of LDL-cholesterol and apoB levels respectively.

D. PCSK9 inhibitors (Alirocumab, Evolocumab): These are humanised monoclonal antibodies which cause a 60% and 44% average reduction of LDL-cholesterol and apoBlevels respectively. Evolocumab is available in India and is administered subcutaneously at a dose of 140 mg every 2 weeks or 420 mg every month.

E. SIRNA (Inclisiran): It inhibits PCSK9 transcription. It is administered as 284 mg sc on day 1 and 90 then twice a year and results in 51% and 43% average reduction of LDL-cholesterol and apoB levels respectively.

Indications for initiating pharmacotherapy for managing hypertriglyceridemia (= 150 mg/dL)[3]:

1. ASCVD
2. Diabetes mellitus with = 1 ASCVD risk factors
3. TG > 500- 1000 mg/dL (Pancreatitis prevention)

The drugs which have been approved for lowering triglyceride levels in Cardiometabolic syndrome are included in table 3.[3]

Table 3: Pharmacotherapy for Lowering Triglycerides in cms[3]

Sl No	Name of drug	Mechanism of action	Dose	Decrease in TG
1.	Statins	Lower the hepatic production & secretion of VLDL particles	Moderate to high intensity OD oral	10-20%
2.	Fenofibrate	PPARα activation	145 mg OD oral	30-45%
3.	Icosapent Ethyl	Suppresses lipogenic gene expression, enhances expression of LPL, β oxidation of FA	2 g BD oral	25%
4.	Saroglitazar	Dual PPARα & γ activation	4 mg OD oral	55%; **also raises HDL level by 10%**
5.	Volanesorsen	ASO inhibiting apoCIII mRNA production	300 mg/week sc	69%
6.	Evinacumab	Monoclonal antibody targeting circulating ANGPTL3 protein	15 mg/kg every 4 weeks iv	62-82%
7.	Olezarsen	GalNAc-conjugated ASO inhibiting apoCIII mRNA production	50 mg or 80 mg every 4 weeks sc	53%

Abbreviations- CMS: Cardiometabolic syndrome, VLDL: Very low-density lipoproteins, PPAR: Peroxisome proliferator-activated receptor, LPL: Lipoprotein lipase, FA: Fatty acids, ASO: Antisense oligonucleotide, ANGPTL3: Angiopoietin-like protein 3, sc: subcutaneous

What do the Guidelines Say?

Although guidelines have been formulated for the prevention and management of micro and macrovascular complications in diabetics, the targets for cardiometabolic syndrome are less clearly defined.

The Lipid association of India 2023 update on cardiovascular risk assessment and lipid management in Indian patients: Consensus statement IV, metabolic syndrome as been identified as a "High-risk feature", which if present identifies an individual to be at high ASCVD risk.[10] This sets LDL target of <70 mg/dL, non-HDL target of <100 mg/dL and apoB target of <80 mg/dL for individuals with metabolic syndrome which is to be achieved through a combination of pharmacotherapy and lifestyle modifications.[10]

Another group of researchers set the target goal for HDL, LDL and triglycerides as >40 mg/dL, <100 mg/dL and <150 mg/dL respectively, to be achieved with a combination of lifestyle modification and pharmacotherapy.1

The 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease has identified metabolic syndrome as a ASCVD risk enhancer, which if present in an individual with intermediate risk for ASCVD, favour the initiation of moderate intensity statin (Class 1) to result in a 30-49% reduction of LDL level.[11]

A HbA1c target of <6.5% is recommended using various pharmacotherapy and lifestyle modifications in individuals with cardiometabolic syndrome.[12]

Conclusion

Cardiometabolic syndrome is a constellation of metabolic derangements which acts as a driver for cardiovascular diseases. It is highly prevalent in South Asians especially Indians. CMS increases the risk of cardiovascular events by two- to three-fold and the risk of type 2 diabetes mellitus by about five-fold, resulting in an overall increase in cardiovascular and all-cause mortality in metabolic syndrome.10,11 This highlights the timely identification of individuals with CMS and aggressively addressing the underlying metabolic derangements (atherogenic dyslipidemia and insulin resistance) through a combination of lifestyle modification and pharmacotherapy to reduce the patient's overall risk profile.

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Chapter

4

Atrial Fibrillation — Novel Anticoagulation and Ablation Techniques Authors

Dr. Farhin Iqbal, Dr. Chitra Priyadarshini

ABSTRACT

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide and a major contributor to stroke, heart failure, and healthcare costs. In recent years, advances in both pharmacologic and interventional strategies have reshaped its management.New anticoagulants, particularly factor X(a) inhibitors, aim to maintain stroke protection with a lower risk of bleeding, while left atrial appendage occlusion (LAAO) devices continue to evolve as alternatives for patients unable to tolerate long-term anticoagulation. Meanwhile, catheter ablation has undergone a transformation with the introduction of pulsed field ablation (PFA), high-power short-duration (HPSD) radiofrequency energy, and improvements in cryoballoon systems, supported by sophisticated imaging and robotic tools.

Introduction

Atrial fibrillation is defined as a supraventricular tachyarrhythmia with uncoordinated atrial activation and ineffective atrial contraction. It is recognized on ECG by irregular R-R intervals, absence of P waves and irregular atrial activity seen as fibrillary wave.

Atrial fibrillation affects millions of people worldwide, and its burden is only expected to rise with aging populations. Management has traditionally revolved around two central goals: reducing stroke risk and controlling arrhythmia-related symptoms. Current ACC/AHA guidelines guideline recognizes lifestyle and risk factor modification as a pillar of AF management to prevent onset, progression, and adverse outcomes.

For decades, vitamin K antagonists such as warfarin were the mainstay of stroke prevention, but these have largely been replaced by direct oral anticoagulants (DOACs), which provide more predictable efficacy and safety. However, bleeding—especially gastrointestinal bleeding—remains a challenge. This has driven interest in novel anticoagulants that offer a better balance between efficacy and safety, along with renewed attention to non-drug strategies such as left atrial appendage occlusion (LAAO).

On the rhythm-control side, catheter ablation has moved from being a last resort to a frontline therapy for many patients with symptomatic AF. Technological innovations are making ablation faster, safer, and more durable, expanding its role in clinical care.[1]

Recommendation for anticoagulation in AF

Current anticoagulation strategies are guided by the estimated annual risk of thromboembolism, most commonly assessed using validated scoring systems such as CHA2DS2-VASc. For individuals with an intermediate risk, where the benefit of therapy is less certain, additional factors may be evaluated to refine decision-making. Online calculators are available for the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation),CHA2DS2-VASc,2 and GARFIELD-AF3 (Global Anticoagulant Registry in the Field-Atrial Fibrillation) risk scores. A patient's absolute risk of stroke is central to recommendations about anticoagulation and can be characterized as low (~<1%/y), intermediate (~1 to ~2%/y), and high (~>2%/y).

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Oral Anticoagulants

Vitamin Kantagonists

Since its introduction in the 1950s, warfarin was the cornerstone of oral anticoagulation therapy until direct oral anticoagulants (DOACs) became available. Its widespread use was limited by important challenges, such as a narrow therapeutic range necessitating regular INR monitoring, susceptibility to multiple drug–drug interactions (particularly through the CYP2C9 pathway), dietary influences, and an overall less favourable safety profile. In contemporary practice, warfarin continues to be the anticoagulant of choice for patients with atrial fibrillation who have mechanical heart valves or moderate-to-severe rheumatic mitral stenosis.

The Role of Established NOACs in Atrial Fibrillation

The biggest shift in stroke prevention for atrial fibrillation over the last decade came with the arrival of the non–vitamin K oral anticoagulants (NOACs). Non–vitamin K antagonist oral anticoagulants (NOACs) have been introduced as effective alternatives to warfarin and other vitamin K antagonists (VKAs) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). These agents are broadly divided into two classes: direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban).

DOAC offer advantages over vitamin K antagonists (VKAs),

1) Lower risk of intracranial bleeding
2) Fixed dosing without routine laboratory monitoring or dietary restriction, and
3) Faster drug onset/offset, facilitating periprocedural planning.

Multiple clinical trials have demonstrated the safety and efficacy of these agents. Moreover, they offer additional benefits, including a rapid onset and offset of action and a predictable anticoagulant response, which eliminates the need for routine laboratory monitoring.

What the Landmark Trials Showed

Each of the NOACs was tested in large, pivotal trials that reshaped practice:

1) Dabigatran (RE-LY trial): Blocks thrombin (factor IIa), stopping fibrin formation.The higher dose (150 mg twice daily) prevented strokes more effectively than warfarin, while the lower dose (110 mg twice daily) matched warfarin with less bleeding2.
2) Rivaroxaban (ROCKET-AF): Selectively inhibits factor Xa, limiting thrombin generation.Noninferior to warfarin, with evidence in a higher-risk population. Recommended dose is 20 mg once daily with food; 15 mg daily for patients with kidney impairment (CrCl 15–49 mL/min)3.
3) Apixaban (ARISTOTLE): Reversible factor Xa inhibitor causes reduced stroke, major bleeding, and even all-cause mortality — making it one of the most widely used NOACs worldwide.Recommended dose is 5 mg twice daily; reduced to 2.5 mg twice daily if the patient meets two or more of the following: age =80, body weight =60 kg, or serum creatinine =1.5 mg/dL4.
4) Edoxaban (ENGAGE AF-TIMI 48): Effective and associated with less bleeding, though used more selectively outside Asia. Recommended dose is60 mg once daily; reduced to 30 mg once daily in patients with kidney impairment (CrCl 15–50 mL/min), low body weight (=60 kg), or those taking certain P-gp inhibitors[5].

Real-world evidence has reinforced these findings, consistently showing that NOACs reduce the risk of devastating intracranial hemorrhage compared with warfarin, though gastrointestinal bleeding remains more frequent with rivaroxaban and high-dose dabigatran.

Despite their success, NOACs are not perfect. Bleeding complications still occur, and some patients — particularly those with mechanical heart valves or significant mitral stenosis — remain ineligible. Cost and accessibility also limit their use in certain regions. These gaps have driven the search for the next generation of anticoagulants.

Emerging Factor XI(a) Inhibitors

Factor XI(a) inhibitors aim to strike a better balance between preventing clot formation and minimizing bleeding. Unlike factor Xa or thrombin, factor XI appears to contribute more to thrombosis than to normal hemostasis. By targeting it, these new agents may reduce strokes without the same bleeding risks.

Drugs such as asundexian, milvexian, and abelacimabhave shown promising early results, with lower bleeding rates and preserved efficacy compared with DOACs. Large phase III trials are underway to confirm these findings, and the cardiology community is watching closely — these agents could reshape AF management in the coming years.

Catheter Ablation

Catheter ablation has become an established therapeutic option for atrial fibrillation (AF). While long-term success rates remain higher in paroxysmal AF compared with persistent AF, its role in rhythm control is well supported by evidence. Current guidelines endorse catheter ablation as a Class I recommendation for patients in whom antiarrhythmic drugs are either ineffective or poorly tolerated, and as a first-line rhythm-control therapy in carefully selected individuals with symptomatic AF. Landmark trials, such as CABANA (2019)7, demonstrated that ablation offers superior rhythm control and improved quality of life compared with drug therapy, while FIRE AND ICE8 (2016) confirmed the non-inferiority of cryoballoon ablation versus radiofrequency ablation. Additionally, the CASTLE-AF trial 9(2018) provided strong evidence that ablation can reduce both hospitalization and mortality in patients with AF and heart failure. Continuoustechnological innovation and optimized ablation protocols have markedly improved the efficacy and safety of pulmonary vein isolation, reinforcing its place as a cornerstone of modern AF management.

The evolution of atrial fibrillation (AF) ablation has been shaped by pivotal discoveries over the past few decades. Initially, the Cox-Maze surgical procedure represented the gold standard for rhythm control, relying on a series of surgical incisions to interrupt re-entrant circuits in the atria. While effective, it was highly invasive and limited in widespread applicability. A turning point came in the late 1990s, when Haïssaguerre et al. demonstrated that the pulmonary veins (PVs) were the predominant source of AF triggers. This insight shifted the strategy from replicating surgical lesion sets to directly isolating the PVs from the left atrium (LA).

Early ablation attempts focused on segmental lesions targeting discrete foci near the PV ostia, but procedural outcomes were inconsistent.

With advances in technology, the approach matured into wide-area circumferential ablation, often

guided by sophisticated electro-anatomic mapping systems, which provided greater accuracy, durability of PV isolation, and improved clinical success.

Today, PV isolation remains the cornerstone of catheter ablation, and ongoing innovations—such as high-power short-duration ablation, pulsed-field ablation, and advanced mapping—are further refining efficacy and safety.

Techiques for Catheter Basd Ablation

1) Radiofrequency Ablation

Radiofrequency ablation is the most established technique for treating AF. It works by delivering controlled heat through a catheter tip, creating small scars in the atrial tissue that block abnormal electrical signals. The main goal is pulmonary vein isolation (PVI), since most AF triggers arise from the veins.

Over time, RFA has advanced from simple point-by-point ablation at the PV openings to wide-area circumferential ablation, which is now the standard approach. Modern tools such as contact force–sensing catheters, saline-irrigated tips, and 3D electroanatomic mapping systems have improved precision and safety. Recently, high-power short-duration (HPSD) ablation has shortened procedures while maintaining durable lesions.

RFA is highly effective, especially for paroxysmal AF, and supported by strong clinical trial evidence. However, it requires skill and experience, takes longer than cryoablation, and carries risks such as tamponade, PV reconnection, and—rarely—esophageal injury.

2) Pulsed Field Ablation (PFA)

PFA represents a major leap forward. Unlike radiofrequency or cryoablation, which destroy tissue with heat or cold, PFA uses electrical pulses to selectively kill heart muscle cells while sparing nearby structures like the esophagus or phrenic nerve.

Clinical studies have shown PFA to be fast, safe, and highly effective in isolating pulmonary veins — the key step in most AF ablations. Procedure times are shorter, complication rates are lower, and enthusiasm for PFA is rapidly growing. Long-term durability is still being studied, but early results are promising.

3) High-Power Short-Duration (HPSD) Radiofrequency

HPSD ablation delivers very high energy over a short time. This creates effective lesions with less collateral damage, shortens procedures, and appears to match or improve outcomes compared with traditional radiofrequency ablation.

4) Cryoballoon and Hybrid Approaches

Cryoballoon ablation remains a reliable single-shot option, particularly for paroxysmal AF. Advances in balloon design and mapping integration have improved safety and efficiency. For patients with persistent AF, hybrid approaches combining surgery and catheter-based therapy are showing value.

Feature	Radiofrequency Ablation (RFA)	Cryoablation	Pulsed-Field Ablation (PFA)
Mechanism	Heat lesions using alternating current (~50–60 °C).	Freezing tissue with liquid nitrous oxide (~-40 °C).	Ultra-short electrical fields cause cell membrane disruption (electroporation).

Main Strategy	Point-by-point or wide-area circumferential pulmonary vein isolation (PVI).	Balloon-based circumferential PVI with a single-shot device.	Balloon or multi-electrode catheter delivers rapid circumferential PVI.
Procedure Time	Longer; requires precise lesion placement.	Shorter; one-shot balloon makes PVI efficient.	Fastest; isolation achieved in seconds.
Durability	High, but gaps may occur if lesions are incomplete.	Good, but sometimes less durable than RFA.	Early data shows excellent durability.
Technology Advances	Contact-force sensing, irrigated tips, high-power short-duration (HPSD), 3D mapping.	Next-gen cryoballoons with better size and compliance.	Still emerging; mapping-integrated systems under study.
Advantages	Flexible, widely available, strong long-term evidence.	Simpler, shorter learning curve, predictable lesion sets.	Tissue-selective, minimal risk to esophagus or phrenic nerve, very rapid.
Limitations	Technically demanding, longer procedures, risk of collateral damage (tamponade, esophageal fistula).	Limited to PV isolation, less adaptable for complex substrates.	Limited long-term data, mostly used in trials/early adoption.
Best Evidence	CABANA, FIRE & ICE, CASTLE-AF.	FIRE & ICE, Cryo4Persistent AF.	ADVENT, inspIRE, ongoing pivotal trials.

Catheter Ablation in Atrial Fibrillation: Class-Based Recommendations

The most recent ACC/AHA/ACCP/HRS guidelines (2023) emphasize a greater role for catheter ablation in the treatment of atrial fibrillation, shifting it from a late-line option to an important therapeutic strategy. The recommendations are best interpreted by class of indication.

Class I (Strong recommendation–procedure should be offered)

Catheter ablation is strongly endorsed for patients who have atrial fibrillation with reduced ejection fraction (HFrEF) and are eligible for rhythm control therapy. Evidence shows that, beyond symptom improvement, ablation in this group can enhance left ventricular function and, in certain studies, lead to better survival and reduced hospitalizations 1. This highlights ablation as a disease-modifying intervention rather than just a symptomatic therapy.

Class IIa (Reasonable to perform – good evidence)

In patients with paroxysmal AF who remain symptomatic, ablation is considered a reasonable first-line option, particularly in younger adults with minimal structural heart changes. Trials have shown that ablation in this setting provides superior rhythm control, fewer recurrences, and better quality of life compared with antiarrhythmic drugs[9].

For patients with persistent AF or those in whom antiarrhythmic drugs are ineffective, poorly tolerated, or undesirable, catheter ablation is also regarded as a sound therapeutic choice to relieve symptoms and improve daily functioning[1].

Class IIb (May be considered – weaker evidence)

In patients with long-standing persistent AF or with marked atrial remodeling and fibrosis, ablation may still be attempted, but success rates are lower and long-term rhythm control less predictable1. Here, patient counseling is critical to balance expectations and procedural risk. Procedural Principles and Anticoagulation.

The foundation of AF ablation continues to be pulmonary vein isolation (PVI). While additional strategies—such as linear lesion sets or non-pulmonary vein trigger ablation—have been studied, they have not consistently provided incremental benefit across all populations and therefore are not universally recommended[9].

All patients undergoing ablation must receive adequate anticoagulation. Procedural anticoagulation with heparin is standard, and oral anticoagulation should be continued for a minimum of two months following ablation. Long-term continuation is determined by the patient's CHA2DS2-VASc score rather than the perceived procedural "success," since stroke risk remains elevated in individuals with persistent underlying risk factors[1].

Conclusion

Over the past decade, the management of atrial fibrillation has undergone a profound transformation. Stroke prevention, once dominated by vitamin K antagonists like warfarin, has been redefined by the introduction of non–vitamin K oral anticoagulants (NOACs). These agents not only simplify therapy with fixed dosing and fewer monitoring requirements but also provide better protection against devastating complications such as intracranial hemorrhage.

On the rhythm-control front, catheter ablation has shifted from being a last resort to a central pillar of treatment for many patients with symptomatic AF. Technological advances such as pulsed-field ablation (PFA) and high-power short-duration (HPSD) radiofrequency energy are revolutionizing the field. These approaches allow faster procedures, minimize collateral damage, and enhance long-term durability of pulmonary vein isolation—the cornerstone of ablation therapy.

Together, these breakthroughs signal the dawn of a new era in atrial fibrillation management—an era that prioritizes precision, safety, and patient-centered care. By combining innovative anticoagulation strategies with evolving ablation technologies, clinicians are better equipped than ever to reduce the burden of stroke, heart failure, and recurrent arrhythmia, while improving both survival and quality of life.

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Chapter

5

Cardiometabolic Syndrome: An Indian Perspective

Dr. Prasanta Dihingia, Dr. Rima Moni Doley, Dr. Abhimanyu Swarup

ABSTRACT

Cardiometabolic syndrome (CMS) represents a growing epidemic in India, driven by rapid urbanization, lifestyle transitions, and a unique "Asian-Indian phenotype." This condition, defined by central obesity, insulin resistance, atherogenic dyslipidemia, dysglycemia, and elevated blood pressure, is strongly linked to early onset cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). National surveys show that more than one in three Indian adults has hypertension and nearly four in ten have abdominal obesity. CMS manifests at lower BMI and younger ages than in Western populations, reflecting higher visceral adiposity and metabolic vulnerability. Waist circumference, BMI, and more recently, waist-to-height ratio have emerged as simple, practical tools for risk assessment. This article reviews the epidemiology, pathophysiology, diagnostic approaches, and prevention strategies relevant to the Indian context, emphasizing population-specific thresholds and integrated models of care. With rising prevalence, CMS demands urgent policy and clinical attention to reduce long-term cardio-metabolic morbidity.

Introduction

India is at the forefront of a non-communicable disease (NCD) transition. Cardiometabolic syndrome (CMS), a cluster of central obesity, dyslipidemia, impaired glucose metabolism, and hypertension, sits at the heart of this shift. Unlike Western nations, India faces a dual burden: infectious diseases continue in parallel with rapidly growing metabolic and vascular disorders.

The 2023 ICMR-INDIAB study covering all states and union territories estimated diabetes prevalence at 11.4%, pre-diabetes at 15.3%, and hypertension at 35.5%.[1] Nearly 40% of adults had abdominal obesity, the physical hallmark of CMS.[1] The consequences are profound, with clustering of these risk factors driving premature myocardial infarction, stroke, chronic kidney disease (CKD), and heart failure.

Section 1: Epidemiology and Burden

Cardiometabolic disorders dominate India's current health profile. The ICMR-INDIAB survey highlighted striking state-wise variation, with urban areas consistently showing higher prevalence.[1] Nevertheless, rural prevalence is also substantial, reflecting diffusion of risk factors beyond cities.

For older adults, the Longitudinal Ageing Study in India (LASI) reported hypertension in ~47% and diabetes in ~12% of those above 45 years. These findings underscore the cumulative effect of metabolic risk across the life course. Rising overweight and obesity rates in both sexes were also confirmed by the National Family Health Survey (NFHS-5).

Compared to Western populations, Indian patients often present with cardiovascular disease at younger ages and lower BMI. This phenomenon reflects ethnic differences in body composition—Indians have a higher percentage of body fat and greater truncal adiposity at the same BMI as Europeans.[2?4] This leads to a disproportionate burden of premature cardiovascular morbidity and mortality.

CMS contributes significantly to India's economic and social burden. The costs of managing diabetes, hypertension, dyslipidemia, and their complications impose long-term pressures on households and the healthcare system. With a relatively young demographic structure, the premature onset of CMS threatens productivity in the most economically active age groups.

Section 2: Pathophysiology and Risk Factors

The Asian-Indian Phenotype

The foundation of CMS in India lies in the "thin-fat" body composition. Even at lower BMI, Indian individuals demonstrate higher visceral fat, smaller subcutaneous fat depots, and greater hepatic lipid accumulation.[2?4] This translates into insulin resistance, dyslipidemia, and higher cardiovascular risk. The thin-fat paradigm, first described in Indian neonates, links early-life undernutrition with later-life metabolic vulnerability.[4]

Dyslipidemia

Indians frequently present with atherogenic dyslipidemia—high triglycerides, low HDL, and small dense LDL particles. This pattern differs from Western profiles dominated by elevated LDL-C.[2]4 Given this, Indian guidelines emphasize non-HDL cholesterol and ApoB-based assessment to guide statin therapy.

Obesity and Sedentarism

Abdominal obesity is disproportionately common in India, with nearly 40% of adults affected.[1] Physical inactivity is widespread, with over half of adults failing to meet recommended activity levels.8 Desk jobs, motorized transport, and limited leisure-time activity drive sedentary lifestyles, particularly in urban settings.

Dietary Transitions

Dietary patterns have shifted from coarse cereals and pulses to refined grains, added sugars, and saturated/trans fats. Average salt intake (8–10 g/day) remains far above the WHO recommendation of <5 g/day. This transition contributes to hypertension, dyslipidemia, and insulin resistance.

Environmental and Psychosocial Exposures

Air pollution, especially long-term PM2.5 exposure, is among the highest globally in India and is linked to

cardiovascular and metabolic diseases.8 Psychosocial stress, long commutes, urban crowding, and inadequate sleep also contribute to obesity and hypertension.

Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD, affecting nearly one-third of adults, is strongly associated with insulin resistance and CMS. It is now integrated into India's NPCDCS program, recognizing its bidirectional links with T2DM and CVD.

Together, these risk factors create a perfect storm for the early and aggressive manifestation of cardiometabolic disorders in India.

Section 3: Diagnosis and Case Definition

Multiple organizations have proposed definitions of metabolic syndrome. The 2009 harmonized statement by IDF/NHLBI/AHA/WHF/IAS/IASO defines metabolic syndrome when at least three of five components are present: central obesity (ethnic cut-offs), triglycerides =150 mg/dL, low HDL, blood pressure =130/85 mmHg, or fasting glucose =100 mg/dL.7

For South Asians, ethnic-specific cut-offs are crucial. Consensus guidelines recommend waist circumference =90 cm for men and =80 cm for women, with overweight defined as BMI =23 kg/m² and obesity as BMI =25 kg/m².5,6

Waist-to-Height Ratio (WHtR)

More recently, Waist-to-Height Ratio (WHtR) has gained attention as a simple, practical alternative to BMI and waist circumference. Using a universal cut-off of 0.5 ("keep your waist less than half your height"), WHtR offers superior prediction of cardiometabolic risk, diabetes, and cardiovascular outcomes across ethnic groups.[1°] Unlike BMI, WHtR incorporates stature, removing the need for population-specific waist cut-offs. Its simplicity and applicability make it a valuable screening tool for India, especially in resource-limited settings.

Thus, diagnosis of CMS in India must rely on lower BMI and waist thresholds, while incorporating emerging measures like WHtR for public health use.

Section 4: Prevention and Management

Primordial and Primary Prevention

Preventive strategies are central to reducing the CMS burden.

Salt reduction: National campaigns and food reformulation can reduce mean intake towards WHO's <5 g/day target.

Trans-fat elimination: India has capped industrial trans-fats at =2%, though enforcement in the informal sector remains challenging.

Dietary improvement: Promotion of whole grains, pulses, fruits, and healthier oils can shift population patterns.

Physical activity: Urban planning to encourage walking, cycling, and safe public spaces is essential.

Air quality: Reducing PM2.5 through cleaner transport and energy has cardiometabolic co-benefits.

Secondary Prevention

Routine screening at primary healthcare centers should include BMI, waist circumference, WHtR, blood pressure, fasting glucose, and lipid profile, especially for adults over 30. Using Indian thresholds ensures earlier detection. Brief lifestyle advice and referral pathways should be integrated into all encounters.

Tertiary Prevention and Management

Management requires a combination of lifestyle modification, pharmacotherapy, and chronic care models.

Hypertension: Protocol-based treatment, as demonstrated by the India Hypertension Control Initiative (IHCI), improves control rates.[16]

Dyslipidemia: Statins are first-line; ezetimibe and fibrates are added in selected cases.?

Diabetes: Metformin remains the base; SGLT2 inhibitors and GLP-1 receptor agonists are recommended in patients with ASCVD, CKD, or heart failure.[31]

NAFLD: Lifestyle change is first-line, with selected roles for pioglitazone and GLP-1 receptor agonists.

Digital health and AI: Registries, reminders, and AI-based algorithms can improve long-term adherence.

Models of Care

Team-based primary care, digital registries, and uninterrupted public drug supply chains form the foundation for sustainable CMS management. Community health workers can support follow-up and adherence in rural and urban areas alike.

Conclusion

Cardiometabolic syndrome represents one of India's most pressing public health challenges. Distinguished from Western populations by earlier onset, higher prevalence at lower BMI, and distinct dyslipidemia patterns, CMS in India demands population-specific diagnostic thresholds and interventions. Waist-to-height ratio provides a practical tool for large-scale screening.

Preventing CMS requires a multi-level approach—primordial and primary prevention through dietary and lifestyle changes, secondary prevention via opportunistic screening, and tertiary prevention with protocol-driven chronic care. Future priorities include integrating cardio-renal-metabolic care, expanding digital health tools, and tailoring interventions to India's diverse states and populations.

Unless addressed urgently, CMS will continue to drive premature cardiovascular and diabetes-related morbidity in India's most productive age groups, straining health systems and economic development.

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Section 2
Neurology

Chapter

6

Breakthroughs in Alzheimer's Disease-Disease Modifying Therapy.

Dr. Munindra Goswami

ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia, characterized by progressive neurodegeneration due to accumulation of amyloid-ß plaques and tau protein tangles in the brain. This leads to gradual cognitive decline and loss of independence. Recent advances have shifted the treatment paradigm towards disease-modifying therapies aimed at altering the underlying pathology. Monoclonal antibodies such as aducanumab and lecanemab target amyloid-ß to reduce plaque burden and slow cognitive deterioration. Emerging tau-directed therapies and agents addressing neuroinflammation, oxidative stress, and metabolic dysfunction are under investigation. Enhanced biomarker technologies now allow for earlier and more precise diagnosis, facilitating personalized treatments. These developments represent a transformative shift from symptomatic management to modifying disease trajectory, offering new hope for improved long-term outcomes in AD.

1. Introduction[1]

Dementia, as conceptualized in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is classified under the term Major Neurocognitive Disorder (Major NCD). This classification reflects a significant shift in how cognitive disorders are understood and diagnosed. Major NCD is characterized by a marked decline in cognitive function from a previously higher level in one or more cognitive domains such as memory, attention, executive function, language, perceptual-motor skills, or social cognition. Importantly, this decline must be severe enough to interfere with independence in everyday activities, including managing finances, medications, or household tasks. The diagnosis requires both subjective concern (from the individual, an informant, or clinician) and objective evidence through standardized assessment

Major NCD must be differentiated from other conditions such as delirium and psychiatric disorders like depression or schizophrenia, as these can also impair

cognition but are not classified as dementia. The DSM-5 framework recognizes a continuum of cognitive impairment, ranging from mild neurocognitive disorder (mild cognitive impairment) to major neurocognitive disorder (dementia), enabling more nuanced diagnosis and management tailored to disease severity.[1]

Alzheimer's disease is the most prevalent cause of major neurocognitive disorder, accounting for approximately 60-80% of cases. It is a neurodegenerative disorder marked by progressive cognitive decline due to characteristic brain changes including amyloid plaques and neurofibrillary tangles. Understanding dementia within this standardized DSM-5 framework facilitates early recognition, precise diagnosis, and effective clinical care planning.

2.1 Epidemiology and risk factors of Alzheimer's[2]

The prevalence of Alzheimer's dementia increases significantly with age, affecting approximately 3% of individuals aged 65 to 74, rising sharply to 32% among those aged 85 and older. Alzheimer's dementia is more prevalent in women than men. The lifetime risk of developing Alzheimer's dementia from age 45 is about 10% for men and 20% for women. Major risk factors include systemic hypertension, dyslipidemia, diabetes, head injury, altered sleep patterns, smoking, and stroke.

2.2 Clinical features and disease progression [3]

The median survival after Alzheimer's disease diagnosis is approximately 4.2 years for men and 5.7 years for women. Mild cognitive impairment due to Alzheimer's disease (MCI AD) is an early stage characterized by noticeable memory or cognitive decline greater than expected for age, which does not yet interfere significantly with daily activities but indicates a higher risk of progressing to Alzheimer's dementia.

Alzheimer's disease typically presents initially with episodic memory impairment due to early involvement of the medial temporal lobe. Semantic memory deficits may appear subsequently. Executive dysfunction, encompassing difficulties in planning, problem-solving, and cognitive flexibility, emerges in mild stages. Language impairment, particularly word-finding difficulty, becomes evident in mild to moderate phases. Visuospatial deficits, commonly manifested as disorientation or getting lost in unfamiliar settings, often present early in the disease course. Neuropsychiatric manifestations in Alzheimer's disease include apathy (72%), agitation (60%), and anxiety (48%). Delusions, commonly involving paranoia or infidelity, are significant as they may precede aggressive behavior.

Feldman and Woodward described AD progression as: mild (recent memory loss, repetitive questioning, loss of hobbies, anomia, impaired instrumental ADLs), moderate (aphasia, executive dysfunction, impaired basic ADLs), and severe (agitation, complete dependence, sleep disturbance and finally bed bound).

The major atypical presentations of Alzheimer's disease include posterior cortical atrophy, presenting with visuospatial deficits, alexia, and elements of Balint and Gerstmann syndromes with relative preservation of memory; logopenic aphasia, characterized by impaired naming, repetition, and word retrieval with phonological errors but preserved motor speech and grammar; and the frontal variant, which manifests with early behavioral and personality changes

2.3 Genetics in Alzheimer's

The lifetime risk of Alzheimer's disease (AD) dementia in first-degree relatives is approximately 39%, and this risk increases to 54% by the age of 80 if both parents are affected by AD dementia. Mutations in the APP gene on chromosome 21, Presenilin 1 on chromosome 14, and Presenilin 2 on chromosome 1 are responsible for early-onset AD. Apolipoprotein E (APOE) is the most important genetic risk factor for late-onset AD. Approximately 20% of all late-onset AD cases are thought to be related to the APOE e4 allele. Individuals who are e4 homozygotes have a mean age of onset of 68 years with a lifetime AD risk of about 91%, whereas e4 heterozygotes have a mean age of onset of 76 years with a lifetime risk of about 47%.

2.4 Pathophysiology of Alzheimer's disease[4]

Currently various and numerous hypothesis have been postulated in the pathogenesis of Alzheimer's based on which current drug trials have been made

A) Classical Hypothesis are following :

1. Amyloid Hypothesis: APP, a type I membrane protein, is cleaved by a, ß, and ? secretases. ß- and ?-secretases drive the amyloidogenic pathway, producing Aß peptides—Aß42 aggregates into plaques, while Aß40 predominates in vessels. a-secretase initiates the nonamyloidogenic pathway, preventing Aß formation. APOE e4, the strongest genetic risk factor, impairs Aß clearance, promotes aggregation, and alters lipid metabolism, synaptic plasticity, and inflammatory responses, accelerating Alzheimer's disease progression.

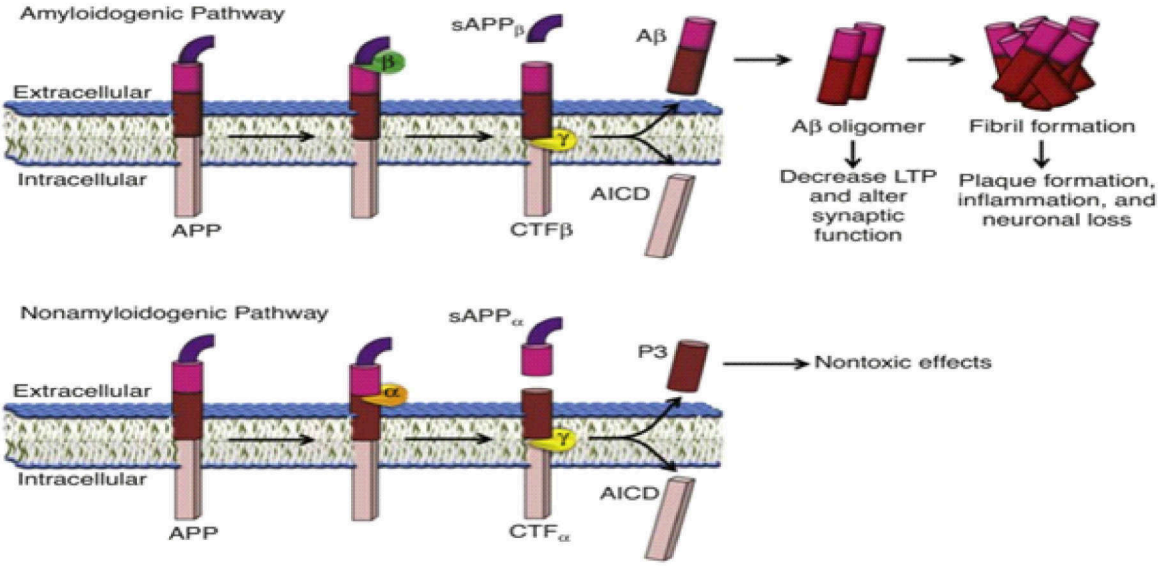

Figure 1. Amyloid Precursor Protein Processing. Aß, Amyloid Beta; AICD, APP intracellular domain; APP, amyloid precursor protein; sAPPa, soluble APP a

2. Tau Hypothesis: Tau, mainly found in neuronal axons, is a microtubule-associated protein that stabilizes the cytoskeleton. When excessively phosphorylated, it detaches, mislocalizes, and aggregates into toxic oligomers, filaments, and tangles. These aggregates damage neurons and spread pathology between cells, driving neurodegeneration.

3. Cholinergic Hypothesis: In Alzheimer's disease, degeneration of basal forebrain cholinergic neurons, especially in the nucleus basalis of Meynert, reduces cortical and hippocampal cholinergic activity, leading to plaque deposition and cognitive decline as proposed by the cholinergic hypothesis.

B) Other non classical emerging mechanistic insightsand these recent advances highlight a far more complex pathophysiology:

1. Neuroinflammation: Chronic microglial activation contributes to synaptic pruning, tau phosphorylation, and Aß aggregation. Genetic studies implicate microglial genes such as TREM2 as critical modulators .

2. Oxidative stress and mitochondrial dysfunction: Excess reactive oxygen species (ROS) from impaired mitochondria amplify tau phosphorylation, Aß production, and neuronal death.

3. Metal ion dyshomeostasis: Abnormal deposition of iron, copper, and zinc accelerates Aß aggregation and oxidative injury, suggesting a role for chelation strategies.

4. Glutamatergic excitotoxicity: Excessive NMDA receptor activation triggers calcium influx, mitochondrial damage, and neuronal apoptosis.

5. Gut–brain axis: Dysbiosis may promote systemic inflammation and Blood Brain Barrier (BBB) dysfunction, linking microbiota to AD onset.

6. Autophagy and lysosomal dysfunction: Defective clearance of misfolded proteins impairs Aß and tau removal, leading to toxic accumulation.

7. Cholesterol and lipid metabolism: APOE4-associated alterations in lipid trafficking exacerbate amyloid deposition and tau pathology.Insulin resistance and neurotrophic signaling deficits: Impaired insulin/IGF signaling and reduced neurotrophic factors (BDNF, NGF) weaken synaptic resilience and promote amyloidogenic pathways

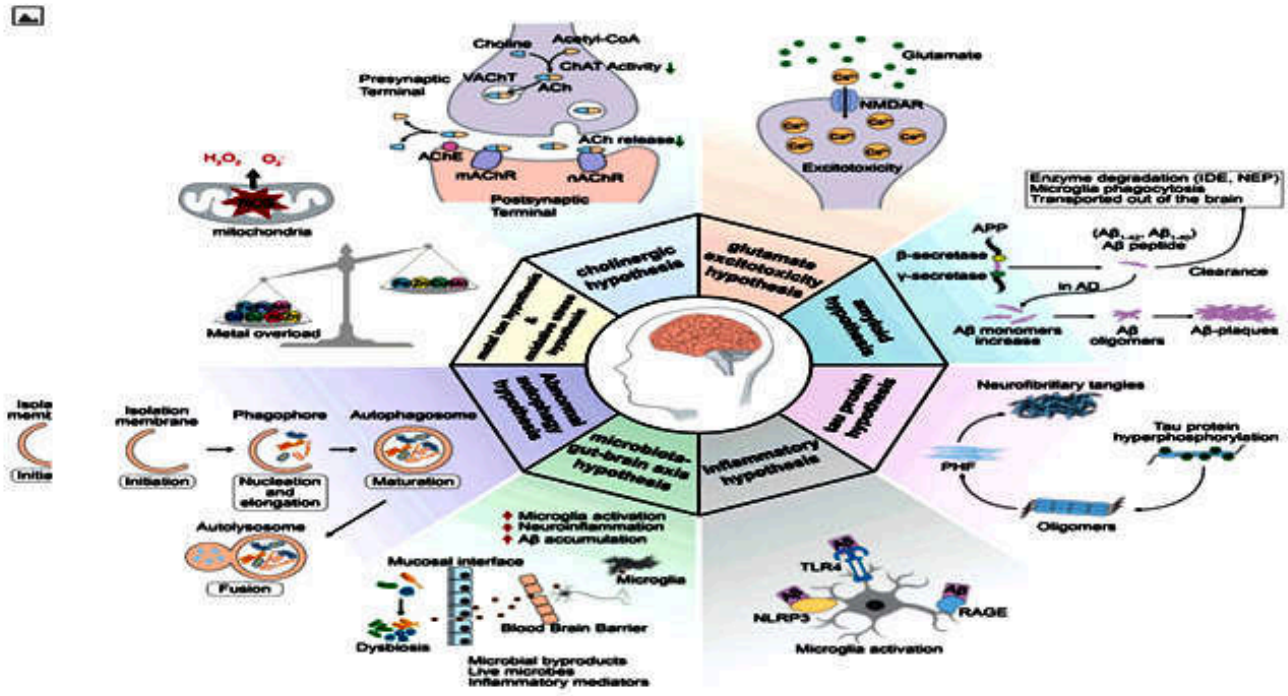

Figure 2. Diagram for the pathogenesis of AD, including the cholinergic hypothesis, the glutamatergic hypothesis,the amyloid hypothesis, the tau protein hypothesis, the inflammatory hypothesis, the microbiota-gut-brain axis hypothesis, the oxidative stress hypothesis, the metal ion hypothesis, and the abnormal autophagy hypothesis

Together, these mechanisms illustrate that AD is not a single-pathway disorder but a network disease with multiple interacting pathological drivers. This has inspired a new generation of therapeutic approaches that go beyond amyloid and tau.

3. Pharmacological therapies in Alzheimer's disease[5]

Pharmacologic management of Alzheimer's disease (AD) predominantly involves acetylcholinesterase inhibitors (AChEIs) and the NMDA receptor antagonist memantine. These drugs act on major neurotransmitter systems implicated in AD, specifically targeting cholinergic and glutamatergic mechanisms to slow symptom progression and improve behavioral outcomes.

AChEIs function by increasing synaptic levels of acetylcholine and prolonging its cholinergic activity, thereby enhancing postsynaptic stimulation and cognition. Tacrine, the first AChEI, was discontinued due to hepatotoxicity, while newer agents such as donepezil, rivastigmine, and galantamine have demonstrated better safety, selectivity, and pharmacokinetics, making them the established first-line choices. However, these drugs are still limited by gastrointestinal adverse effects and challenges with long-term adherence. Innovations in drug delivery—including transdermal donepezil, approved in 2022—offer weekly dosing, bioequivalence to oral formulations, and reduced gastrointestinal side effects, thereby improving convenience compared to oral therapy and the once-daily rivastigmine patch.

Memantine, a noncompetitive NMDA receptor antagonist, is approved for moderate to severe Alzheimer's disease. By regulating excessive glutamatergic activity while preserving physiological transmission, it prevents excitotoxic injury. It also influences dopaminergic pathways, offering cognitive and behavioral benefits. Clinical studies show modest but significant improvements in cognition, daily functioning, and behavioral symptoms, particularly when used with acetylcholinesterase inhibitors in advanced disease.

Therapy	Mechanism of action	Stage of disease to start	Titration and target	Common side effects
Donepezil	AChEI	All	To be started with 5 mg/d once daily; may be increased to 10 mg/d once daily after 4-6 weeks; maximum dose 23 mg/d once daily	Nausea, vomiting, diarrhea, dizziness, vivid dream, bradycardia
Galantamine	AChEI	Mild to moderate	To be started with 8 mg/d given in two divided doses and uptirated to maximum 16-24 mg/d to be given in two divided doses	Nausea, vomiting, diarrhea, dizziness, headache

Rivastigmine	AChEI	Mild to moderate	Oral: 3 mg/d given in two divided doses; maximum 12 mg/d given in two divided doses	Nausea, vomiting, diarrhea, dizziness, drowsiness, headache
Memantine	NMDA receptor antagonist	Moderate to late	To be started with5 mg/d once daily; maximum 20 mg/d (given in two divided doses)	Constipation, dizziness, headache, nonspecific pain, flulike symptoms

4. Disease Modifying Therapies in Alzheimer's disease[6]

Current therapeutic strategies for Alzheimer's disease, including NMDA receptor antagonists and acetylcholinesterase inhibitors, primarily provide symptomatic relief without altering the underlying disease trajectory. The two major pathological hallmarks of Alzheimer's disease—extracellular ß-amyloid plaque deposition and intracellular tau aggregation—are central drivers of neurodegeneration and disease progression. Consequently, the development of effective anti-amyloid therapies holds the potential to transform the therapeutic landscape of Alzheimer's disease.

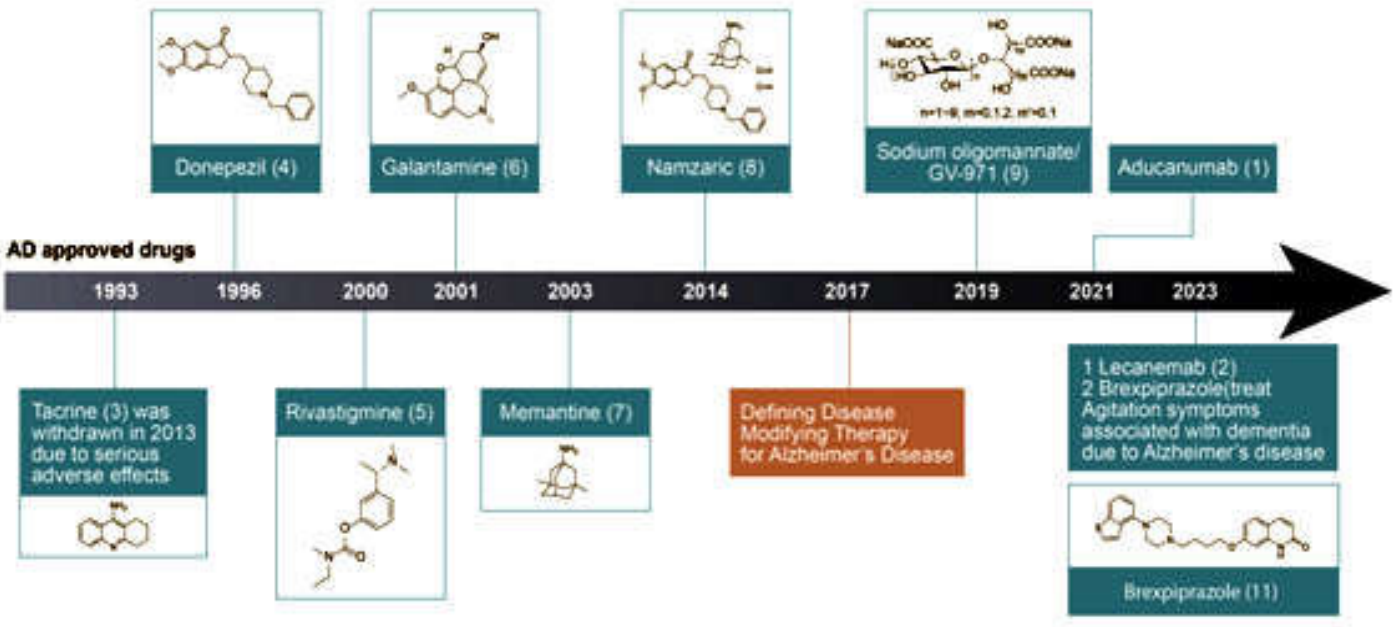

Figure 3.Approved drugs for AD by FDA/China. Notably, the definition of disease-modifying therapies, capable of producing enduring and impactful changes in the clinical progression of AD.

Sodium oligomannate (GV-971), conditionally approved in China (2019), may reduce Alzheimer's pathology by modulating gut dysbiosis-related neuroinflammation and inhibiting amyloid-ß fibrils. Preclinical studies reveal sex-dependent effects on the microbiome and microglial activation. Two phase IV trials on safety and efficacy are expected to complete in 2025.

4.1 Antibodies for amyloid clearance

The FDA has approved two disease-modifying monoclonal antibodies, aducanumab and lecanemab, targeting distinct amyloid-ß conformers . These antibodies engage multiple pathways to facilitate amyloid clearance. Upon CNS penetration, they bind fibrillar aggregates via the fragment antigen-binding domain, forming complexes recognized by microglia through Fc receptors, which triggers phagocytosis .

Beyond microglial involvement, antibodies promote direct aggregate disruption and facilitate efflux of degradation products from the brain . Additionally, the peripheral sink hypothesis posits that antibody binding to circulating amyloid shifts equilibrium, enhancing ß-amyloid efflux from the CNS . Despite these biologically plausible clearance mechanisms, the clinical efficacy of anti-amyloid monoclonal antibodies remains contentious.

Aducanumab, a human IgG1 monoclonal antibody approved in 2021, shows high selectivity for aggregated amyloid-ß and promotes clearance of both insoluble and soluble forms in a dose-dependent manner. Lecanemab, approved in 2023, targets soluble protofibrils and slows Alzheimer's progression. Both require intravenous infusion—aducanumab every four weeks and lecanemab biweekly—with proper dilution. The main adverse effect is amyloid-related imaging abnormalities (ARIAs), including microhemorrhages and vasogenic edema, which may cause headache, dizziness, confusion, seizures, or rarely, death. Corticosteroids may help reduce ARIA severity. Effective therapy requires blood-brain barrier penetration, cognitive benefit, confirmed amyloidosis, and a satisfactory safety profile.

Donanemab targets pyroglutamate-modified Aß, binding specifically to plaques. It has completed phase 3 trials and is in the process of market authorization Brexpiprazole, used for depression and schizophrenia, modulates serotonin, dopamine, and norepinephrine receptors and helps reduce agitation in Alzheimer's disease.

4.2 Emerging Tau-Directed Therapies

- **Semorinemab:** Anti-tau antibody blocking extracellular tau spread; Phase II showed modest functional slowing, limited cognitive effect.
- Gosuranemab and Tilavonemab: Humanized antibodies targeting tau aggregates; currently in clinical trials.
- **BIIB080 (IONIS-MAPTRx):** Antisense oligonucleotide reducing tau mRNA and protein; early trials demonstrated CSF tau reduction.
- **Tideglusib:** GSK-3ß inhibitor reducing tau phosphorylation; early trials showed safety with limited efficacy.
- **LMTX:** Tau aggregation inhibitor disrupting filament formation; Phase III outcomes were mixed.
- **Tau-targeted PROTACs:** Preclinical agents

promoting proteasomal tau degradation, representing a novel approach.

4.3 Other Novel Strategies

- **Anti-inflammatory:**AL002 (TREM2 agonist antibody) – enhances microglial activity and amyloid clearance.
- **Metabolic therapies:** Liraglutide (GLP-1 agonist), Intranasal insulin – improve insulin signaling, cognition, and synaptic function.
- **Neurotrophic agents:** Cerebrolysin, LM11A-31 – mimic or modulate neurotrophic pathways, supporting neuronal survival.
- **Metal chelation/antioxidants:** Deferiprone (iron chelator), Edaravone (free radical scavenger) – reduce oxidative stress and Aß aggregation.
- **Multi-target drugs:** Ladostigil – dual cholinesterase and MAO-B inhibitor, providing symptomatic and neuroprotective effects.

4.4 Next-Generation Drug Development

- **Selective inhibitors and dual-target inhibitors:** Designed to simultaneously block amyloid and tau or other pathological pathways.
- **Allosteric modulators and covalent inhibitors:** Offering higher specificity and fewer side effects.
- Proteolysis-targeting chimeras (PROTACs): Enable selective degradation of pathological proteins such as tau and APP fragments.
- **Protein–protein interaction modulators (PPIs):** Targeting key molecular interfaces to disrupt toxic assemblies

4.5 Broader Research Directions

- Gene editing (CRISPR-Cas9) to correct pathogenic mutations.
- Stem cell therapies to replace lost neurons and restore circuits.
- Advanced imaging and AI analytics for early detection and monitoring treatment response.
- Exploration of viral triggers (HSV, SARS-CoV-2) and their contribution to neuroinflammation.

Conclusion

Alzheimer's disease is a complex neurodegenerative disorder involving amyloid, tau, neuroinflammation, oxidative stress, and metabolic dysfunction. While current therapies mainly offer symptomatic relief, recent advances in disease-modifying treatments—especially amyloid-targeting antibodies and tau-directed approaches—represent significant progress. Concurrent improvements in biomarker technology and precision medicine enable earlier diagnosis and personalized treatment strategies. These developments collectively offer promising avenues to alter disease progression and enhance clinical outcomes, marking a pivotal shift in the management and understanding of Alzheimer's disease.

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Chapter

7

Stroke Management: Innovations in Thrombectomy and Neuroprotection

Dr. Marami Das, Dr. Akankshi Agarwal

ABSTRACT

Acute stroke care is moving from rigid time windows to imaging-guided, physiology-first decisions. This review synthesizes contemporary classification, Indian and Western epidemiology, the ischemic cascade as a therapeutic map, pragmatic CT/CTA-based evaluation, and early management. Evidence now supports mechanical thrombectomy (MT) well beyond 6 hours—up to 24 hours in imaging-selected patients—and increasingly for posterior-circulation basilar occlusions and many large-core infarcts, while trials in low-National Institute of Health Stroke Scale (NIHSS) Large vessel obstruction (LVO) and distal medium-vessel occlusions continue. Technical practice favors first-pass success through integrated strategies (balloon-guided aspiration, stent-retriever, and combined approaches); adjunct intra-arterial alteplase after successful Endovascular Treatment (EVT) shows early functional benefit. Neuroprotection is reframed as a peri-EVT care bundle—optimized oxygenation, glucose and temperature control, anesthesia strategy, tailored blood pressure, and targeted edema mitigation—complemented by evolving pharmacology. Finally, system design (parallel workflows, direct-to-angio models, CT/CTA-first pathways) converts macro-recanalization into durable microvascular reperfusion and improved independence. Together, speed, phenotype-matched selection, and disciplined protection define modern stroke outcomes for patients.

Introduction

Stroke is an acute neurological syndrome caused by a disturbance of cerebral blood flow that results in focal brain injury. Clinically, strokes are first separated into ischemic and hemorrhagic mechanisms. Ischemic stroke results from arterial occlusion—most often due to thromboembolism—and accounts for the majority of cases worldwide. Hemorrhagic stroke encompasses intracerebral hemorrhage and subarachnoid hemorrhage and carries greater early mortality but a lower overall incidence.

Beyond mechanism, etiologic classification

informs secondary prevention and risk stratification. The TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification organizes Acute ischemic stroke (AIS)into five categories based on clinical features and diagnostic testing. This framework is widely used in both clinical practice and research.

Table : 1 Toast Classification of ischemic stroke

TOAST Subtype	Pathophysiology (Definition)	Typical Clinical/Imaging Clues
Large-artery atherosclerosis	In-situ thrombosis or artery-to-artery embolism from an atherosclerotic plaque in a large extracranial or intracranial artery causes the infarct.	Cortical signs may be present; symptoms can fluctuate; vascular imaging often shows ≥50% stenosis or occlusion in a relevant artery.
Cardioembolism	A thrombus or vegetation forms in the heart and embolizes to an intracranial artery, producing an infarct.	Sudden severe deficits; cortical features; multiple vascular territories may be involved; atrial fibrillation or structural heart disease is common.
Small-vessel (lacunar) occlusion	Occlusion of a single deep perforating arteriole from lipohyalinosis or microatheroma causes a small subcortical infarct.	Classic lacunar syndromes (pure motor, pure sensory, ataxic hemiparesis, dysarthria–clumsy hand); MRI shows small (<15–20 mm) deep lesions without cortical signs.
Other determined etiology	A specific non-atherosclerotic, non-cardioembolic mechanism produces ischemia (e.g., dissection, vasculitis, hypercoagulable states, moyamoya, or rare genetic disorders).	Often younger patients or atypical presentations; mechanism identified on targeted testing (arterial wall imaging, serologies, thrombophilia work-up).
Undetermined etiology - cryptogenic/embolic stroke of undetermined significance (ESUS)	No single cause is identified after a standard evaluation, or there are multiple competing causes, or the evaluation is incomplete.	Work-up is negative or inconclusive; an embolic imaging pattern without a clear source suggests ESUS.

Epidemiology

In high-income countries, about 80% of strokes are ischemic and 20% hemorrhagic. While age-adjusted mortality is falling, absolute numbers remain high due to aging populations and widespread vascular risk factors. In India, the annual stroke incidence is 119–145 per 100,000, with consistently higher rates in urban than rural areas. This reflects a rising burden of modifiable risks such as hypertension, diabetes, dyslipidemia, tobacco use, and lifestyle changes. A notable feature in India is the younger age of onset: most patients are under 65, and 20–30% are below 50. Male predominance is common across studies. Urban–rural disparities remain striking, with urban patients benefiting from better healthcare access, timely diagnosis, and earlier treatment, leading to improved outcomes compared to rural populations.[1]

Pathophysiology

When a cerebral artery occludes, cerebral blood flow (CBF) falls below thresholds required for aerobic metabolism. ATP depletion leads to failure of ion pumps, membrane depolarization, and cytotoxic edema. Excess glutamate accumulates and over-activates NMDA and AMPA receptors, which drives calcium influx and downstream activation of proteases, lipases, and endonucleases. Mitochondrial permeability transition, oxidative and nitrosative stress, and DNA damage follow. In parallel, damage-associated molecular patterns activate microglia and endothelium, recruiting leukocytes and upregulating cytokines and matrix metalloproteinases that disrupt the blood–brain barrier.[2]Both apoptotic and necrotic pathways are believed to play a crucial role in ischemia-induced neuronal cell death. A drop in nutrient and oxygen levels in the brain leads to anaerobic glycolysis.[3]A severely hypoperfused ischemic core progresses rapidly to necrosis, while the surrounding penumbra remains structurally viable for a limited period and is the therapeutic target of reperfusion and neuroprotection [4]. Reperfusion is essential but can transiently worsen oxidative stress and microvascular dysfunction; therefore, pairing fast recanalization with targeted protective strategies is biologically rational.

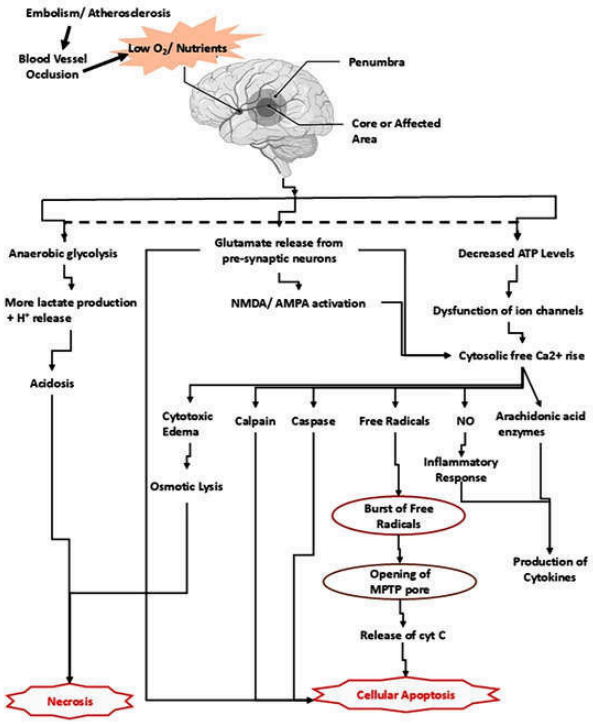

Figure 1: Schematic representation of the biological events in ischemic stroke. The figure explains the events happening during an ischemic stroke finally culminating in cellular death (apoptosis or necrosis)

Evaluation

Prehospital recognition and notification accelerate in-hospital care. On arrival, clinicians confirm the time last known well, review medications and comorbidities, and perform the NIH Stroke Scale. Non-contrast CT excludes hemorrhage and catastrophic mimics, whereas CT angiography identifies large-vessel occlusion and supports activation of the thrombectomy pathway. Perfusion imaging can refine selection in specific circumstances; however, many centers safely treat early-window candidates using CT and CTA alone to avoid delays. Laboratory tests run in parallel, and blood pressure is managed to maintain perfusion pending reperfusion therapies. The evaluation pathway succeeds when imaging, laboratory work, and therapeutic decisions occur in parallel rather than in sequence.

Management

Early measures aim to stabilize physiology, prevent complications, and ready for reperfusion. Care includes maintaining oxygenation, normothermia, controlled glucose, and adequate volume. Blood pressure is individualized: permissive hypertension before reperfusion supports penumbra, while tighter control after thrombolysis/thrombectomy reduces hemorrhage risk. Dysphagia screening, VTE prophylaxis, safe mobilization, and etiology-based antithrombotics (post-imaging) are essential.

Intravenous thrombolysis (IVT) with alteplase or tenecteplase remains central for eligible patients within time windows and without contraindications. In thrombectomy centers, most candidates receive IVT while preparing for EVT, as it may enhance early recanalization without major added risk. Though ongoing trials will clarify subgroup benefits, current practice supports bridging thrombolysis when criteria are met.

Mechanical Thrombectomy

Historical evolution

The modern era of endovascular therapy (EVT) began with 2015 trials showing major benefits of stent-retriever thrombectomy over medical therapy for anterior-circulation large-vessel occlusion (LVO) in early windows. Pooled analyses confirmed benefit across ages and severities, and later trials extended treatment to tissue-selected patients in longer windows.

Patient selection

The primary goal of mechanical thrombectomy in acute ischemic stroke is the rapid restoration of blood flow to salvage the ischemic penumbra and prevent irreversible neuronal injury. In recent years, the indications for thrombectomy have expanded considerably, supported by growing evidence demonstrating its efficacy and superiority over IVT in appropriately selected patients. Landmark studies, including the DAWN, DEFUSE-3, CTP, and CRISP trials, have been pivotal in establishing its clinical utility. The American Heart Association/American Stroke Association (AHA/ASA) guidelines for early management of acute ischemic stroke recommend endovascular mechanical thrombectomy for patients who meet the following criteria[5]

1. Pre-stroke modified Rankin Scale (mRS) score < 2
2. NIH Stroke Scale (NIHSS) = 6 and ASPECTS = 6
3. Procedure initiation within 6 hours of symptom onset
4. Causative occlusion involving the intracranial internal carotid artery (ICA) or the proximal middle cerebral artery (M1 segment)
5. Age = 18 years

Importantly, the DAWN and DEFUSE-3 trials demonstrated that, in carefully selected patients with favourable imaging profiles, mechanical thrombectomy significantly improves functional outcomes even when performed up to 24 hours after symptom onset. Consequently, current guidelines have extended the recommended therapeutic window to 24 hours for such patients, marking a major advancement in the management of large-vessel occlusion strokes.

- 0–6 hour window: EVT is indicated in patients with proximal LVO and preserved brain parenchyma (ASPECTS >6 on non-contrast CT).
- 6–24 hour window: Patient selection is guided by CT perfusion or MRI demonstrating salvageable tissue.

This paradigm ensures exclusion of patients with extensive infarction, where reperfusion may offer limited benefit or increased risk of hemorrhagic transformation. Advances and challenges in EVT[6]

1. Posterior-circulation occlusion (basilar artery)

Posterior circulation LVOs form ~20% of AIS; basilar occlusion has up to 80% risk of death/disability despite best medical treatment (BMT). Early trials (BEST, BASICS) showed no EVT benefit, but ATTENTION (=12 h) and BAOCHE (6–24 h) nearly doubled 90-day independence (46% vs. ~23–24%) using ASPECTS =6 (=8 if >80 y). Both excluded large infarcts and had low IVT use, limiting generalizability. Guidelines weakly favour EVT+BMT over BMT alone, with uncertainty for mild, late, and IVT-treated cases.

2. Large-core infarction

Expansion of EVT beyond conventional windows now includes patients with large infarcts. Three landmark trials showed higher 90-day independence with EVT (˜20–31%) vs. BMT (˜7–13%) without more symptomatic ICH. Meta-analyses suggest EVT may work even in ASPECTS 0–2, fuelling debate on whether LVO patients should be excluded by core size alone.

3. Late time window

DAWN and DEFUSE-3 (2018) extended EVT to 24 h using imaging to identify salvageable tissue. DAWN (6–24 h) included clinical-core mismatch with small infarcts, while DEFUSE-3 (6–16 h) used core/penumbra mismatch, allowing cores =70 mL. Both showed improved outcomes, confirming selected patients benefit well beyond 6 h. Selection depends on

collaterals, infarct growth, ASPECTS, and perfusion.

4. Low NIHSS and LVO

Low NIHSS (=5) strokes are often distal, but ~10% involve LVO with risk of deterioration if untreated. Ongoing RCTs (MOSTE, ENDOLOW) will define EVT's role. A meta-analysis of 11 studies showed no functional benefit (mRS 0–2) with EVT+BMT vs. BMT, making these RCTs critical for guidance.

5. Distal medium-vessel occlusion (DMVO)

Distal medium vessel occlusions (0.75–2 mm) involve M2–M4 MCA, A1–A5 ACA, P1–P5 PCA, and cerebellar arteries, comprising 25–40% of AIS. Traditionally managed with BMT/IVT, which achieves ~50% recanalization, they are now treatable with miniaturized stent-retrievers and aspiration catheters. Evidence remains limited, but ongoing RCTs with devices (Tigertriever 13, Solitaire X, Trevo NXT) are testing EVT, including in IVT-ineligible or IVT-failed patients.

6. Tandem lesions and intracranial atherosclerotic disease (ICAD)

Intracranial occlusions with cervical carotid lesions are usually treated first, with carotid stenting or angioplasty ± stenting in ICAD done as needed for durable reperfusion.

Procedural techniques[7]

Operators pursue complete or near-complete reperfusion with the fewest passes because the first-pass effect correlates with better outcomes and lower complication rates. Three archetypal strategies are used and often combined:

1. Stent-retriever thrombectomy. A self-expanding device is deployed across the thrombus to integrate with clot and is retrieved under active aspiration, often through a balloon-guide catheter that provides proximal flow arrest to reduce distal embolization.
2. Contact aspiration. A large-bore aspiration catheter is advanced to the face of the thrombus and sustained suction is applied to extract it en bloc. Increasingly trackable catheters and larger inner diameters have improved success rates.
3. Combined approaches. Stent-retriever plus aspiration ("Solumbra" variants) and balloon-guide catheters increase clot control, raise first-pass success, and reduce emboli to new territory.

Optimizing the benefits of recanalization and future directions

A major innovation targets the persistent gap between macro-recanalization and microvascular reperfusion. Early randomized evidence CHOICE trial shows that administering intra-arterial alteplase at the end of a technically successful thrombectomy can improve ninety-day outcomes without increasing symptomatic hemorrhage, supporting the concept that lysing distal microthrombi reduces no-reflow and

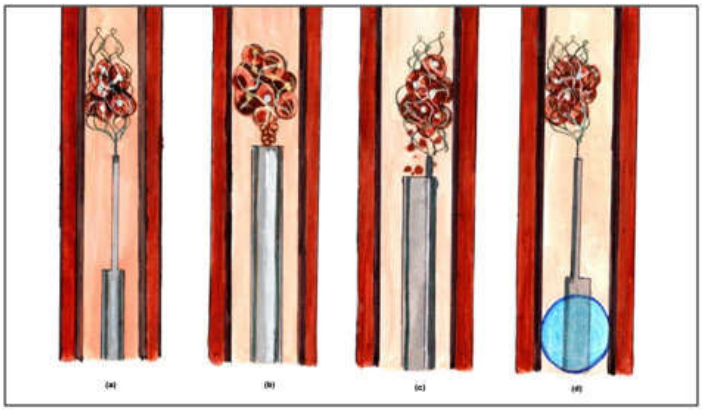

Figure 2:Schematic representation of Procedural Techniques of Thrombectomy- a) Stent Retriever b) Aspiration Catheter c) Solumbra d) Balloon Guide Catheter

Conceptually related engineering directions—such as sequestering aspiration systems that transiently isolate the treatment segment—seek to capture fragments and shield fragile distal vasculature, especially when reaching farther into medium and distal vessels.

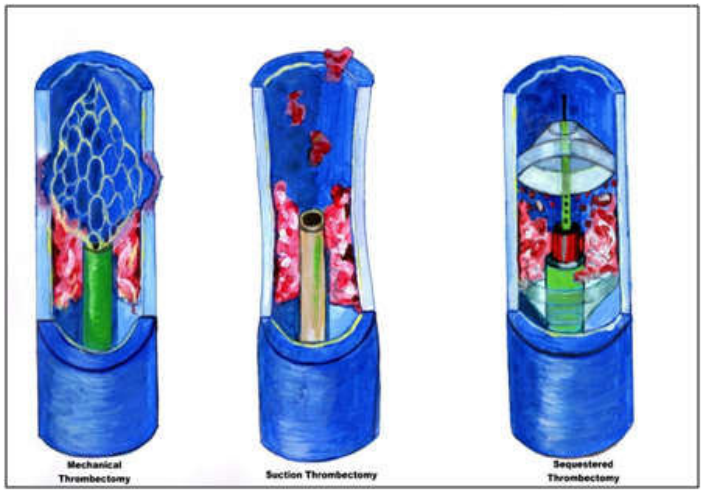

Figure 3: Different types of thrombectomy

Pharmacologic strategies aligned to the ischemic cascade

Table 2: Phase and reperfusion brain injury, Key pathophysiological mechanisms and clinical implications.

Phase	Approximate timing	Key pathophysiological features	Clinical implications
Early phase	0–24 h post-reperfusion	Sudden return of blood flow leads to • oxidative stress (ROS burst) • calcium overload • mitochondrial dysfunction • excitotoxicity • inflammation is initiated	Target for neuroprotection, antioxidants, and free radical scavengers—time window for tPA and thrombectomy
Intermediate phase	24–72 h (3 days)	Inflammatory response intensifies: • microglial activation • leukocyte infiltration • cytokine and chemokine release • apoptosis • continued BBB disruption	Target for anti-inflammatory agents (e.g., minocycline, natalizumab)—monitor for neurological deterioration
Late phase	> 72 h to weeks/months	Transition to repair and remodeling • angiogenesis • neurogenesis • glial scarring • persistent low-grade inflammation • neurodegeneration • progressive cognitive decline	Target for neurorestorative therapies, rehabilitation, and possibly immune modulation

Key Neuroprotective Agents[9]

Table 3: Key Neuroprotective Agents

Drug Class	Key Agents	Main Findings / Outcome
Excitotoxicity / Glutamate Antagonists	NA-1, Memantine, Aptiganel, Selfotel, Gavestinel	NA-1 positive in non-thrombolysed patients; Memantine small RCTs promising; others negative/harmful
GABA Agonists	Clomethiazole	CLASS-I trial negative; no functional benefit
Selective ETB receptor agonist	Sovateltide	Sovateltide was safe and well-tolerated and resulted in improved neurological outcomes in patients with acute cerebral ischemic stroke 90 days post-treatment.
Magnesium	Magnesium sulfate	Small RCTs positive but IMAGES & FAST-MAG negative; limited BBB penetration
Free Radical Scavengers	Edaravone, Edaravone-Dexborneol, Citicoline, NXY-059	Edaravone approved in Japan; edaravone-dexborneol synergistic; citicoline modest benefit; NXY-059 negative
Calcium Channel Blockers	Nimodipine, Verapamil	Nimodipine negative except very early use; Verapamil safe but efficacy unproven
Immune Modulators	Natalizumab, MAPC Stem Cells, Minocycline, Imatinib	Natalizumab worsened outcomes; MAPC and Imatinib possible benefit if early; Minocycline meta-analyses positive
Antioxidants	NAC, Co-ultraPEALut, Butylphthalide, HUK, Melatonin, Uric Acid, Albumin	NAC & butylphthalide promising; Co-ultraPEALut improved cognition; HUK phase IV positive; others inconclusive
Hypoglycemic Agents	Insulin, Glyburide	Intensive insulin control no benefit; Glyburide reduces edema biomarkers, possible survival benefit in ≤70 yrs
Other Agents	Statins, Cerebrolysin, Piracetam, Epo, 3K3A-APC, Dapsone, GTN, Theophylline	Statins protective in cohorts but RCTs negative; Cerebrolysin& Piracetam negative; 3K3A-APC & Dapsone promising; GTN early subgroup benefit; Theophylline limited effect

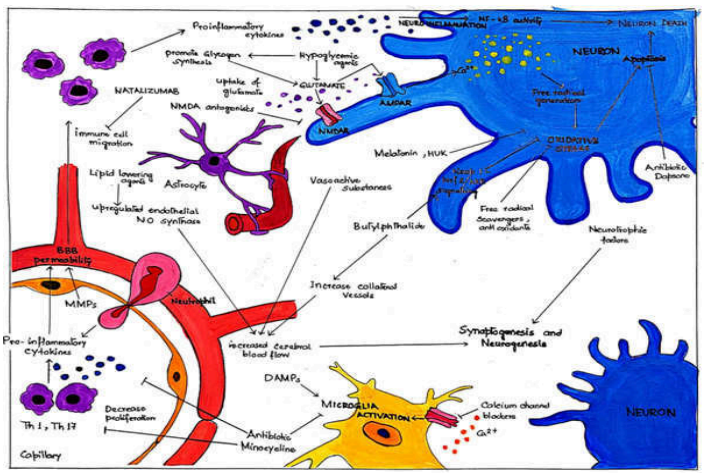

Figure 4: Diagram showing the mechanisms of action of various neuroprotective agents. MMP: matrix metalloproteinase; NMDAR: NMDA receptor; AMPAR: AMPA receptor; HUK: human urinary kallidinogenase; NF-kB: nuclear factor kappa B; Keap1-Nrf2: Kelch-like ECH- associated protein 1-nuclear factor erythroid 2-related factor 2 pathway; ARE: antioxidant response element; Th1: T helper type 1; NO: nitric oxide; Nrf2: nuclear factor erythroid 2-related factor 2[10]

Implementation: a pragmatic neuroprotection bundle around EVT

A pragmatic bundle organizes care along the EVT timeline:

(1) pre-hospital/ED: avoid hypotension and hypoxia, correct glucose extremes, and start temperature control if febrile;

(2) intra-procedural: choose anesthesia to maintain hemodynamic stability, avoid prolonged hypotension, and consider trial-based pharmacologic adjuncts when eligible;

(3) post-reperfusion: maintain controlled blood pressure, treat hyperthermia promptly, manage edema proactively, and reassess anti-thrombotics based on imaging at twenty-four hours.

Conclusion

Modern stroke care is built on fast, reliable reperfusion delivered by systems that minimize delay. Mechanical thrombectomy now benefits carefully selected patients beyond the early window, in posterior circulation occlusions, and even in many large-core infarcts, while research clarifies the role of distal occlusions and low-NIHSS presentations. Technique refinements and pharmacologic adjuncts—especially intra-arterial thrombolysis at the end of thrombectomy—target the microcirculation so that angiographic success produces tissue reperfusion. Neuroprotection has shifted from broad single-agent hopes toward targeted, time-sensitive, and combination strategies that complement IV thrombolysis and EVT. The path forward combines speed, pragmatic imaging, disciplined peri-procedural care, and phenotype-matched protection, with an explicit focus on equitable access so that advanced therapies translate into independence for patients regardless of geography.

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Chapter

8

Neuromodulation for movement disorders: DBS and Beyond

Dr.Tridip Kumar Das

ABSTRACT

Neuromodulation has become an important therapeutic strategy for managing movement disorders by directly influencing neural activity in specific brain circuits. Unlike conventional pharmacological therapies, which often lose effectiveness over time or cause adverse side effects, neuromodulation offers adjustable, reversible, and targeted intervention. Techniques such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), and focused ultrasound have demonstrated significant benefits in conditions like Parkinson's disease, dystonia, essential tremor, and Tourette syndrome. Recent advancements, including adaptive or closed-loop stimulation systems, wireless technology, and integration of artificial intelligence, have further improved the precision, safety, and personalization of these therapies. Additionally, developments in neuroimaging and neurophysiological mapping have enhanced the understanding of neural network dysfunctions underlying movement disorders, leading to more effective targeting and optimization of treatment. Overall, neuromodulation represents a rapidly progressing field with the potential not only to alleviate motor symptoms but also to modify disease progression and improve quality of life in affectedindividuals.

Introduction

Movement disorders, such as Parkinson's disease, essential tremor, dystonia, and Tourette syndrome, are characterized by abnormalities in motor control resulting from dysfunction in neural circuits that regulate movement.[1] Traditional therapeutic approaches, including pharmacological treatments and surgical interventions, often provide only partial or temporary relief and may be associated with adverse effects or loss of efficacy over time. In recent years, neuromodulation has emerged as a promising and rapidly evolving field offering novel, targeted, and reversible therapeutic options.Neuromodulation involves the alteration of nervous system activity through electrical,

magnetic, or chemical stimulation to restore normal neuronal communication and network function.[2] As research continues to uncover the pathophysiological mechanisms underlying movement disorders, neuromodulation offers not only symptomatic relief but also the potential for disease modification through targeted network reorganization.

Stepwise Mechanism of Neuromodulation

1. **Target Identification:**
   A specific part of the nervous system (brain, spinal cord, or peripheral nerve) involved in abnormal signaling is selected for stimulation or modulation.
2. **Signal Delivery:**

- o Electrical neuromodulation: Electrodes deliver mild electrical pulses.
- o Chemical neuromodulation: Neurotransmitters, drugs, or gene vectors are delivered directly to the target site.
- o Magnetic/Ultrasound neuromodulation: External magnetic or acoustic energy alters neuronal activity noninvasively.

3. **NeuronalResponse:**
   The stimulus changes the membrane potential of neurons — either depolarizing (exciting) or hyperpolarizing (inhibiting) them.
4. **Synaptic Modulation:**
   Altered neuronal firing affects neurotransmitter release (e.g., glutamate, GABA, dopamine), modifying synaptic transmission strength.
5. **Network Effect:**
   The changes spread through connected neural circuits, rebalancing excitatory and inhibitory pathways to restore normal function.

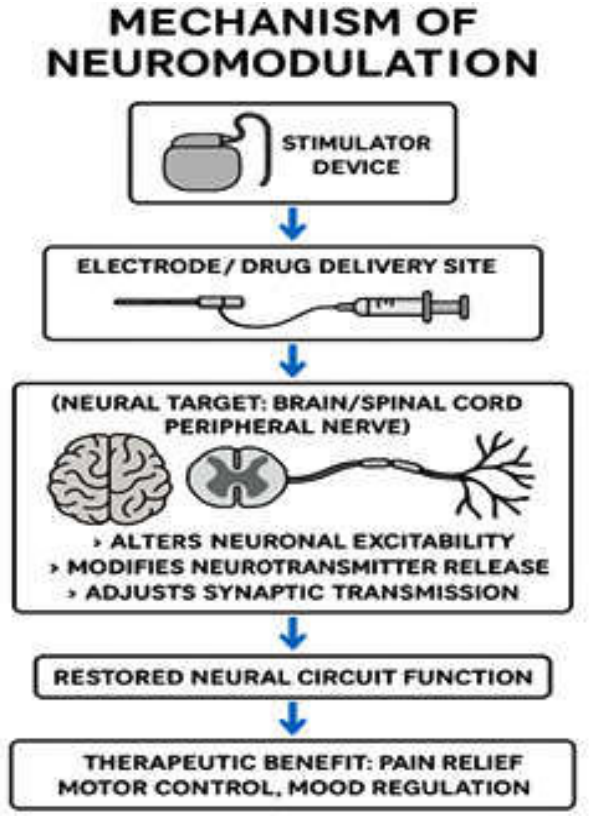

Fig 1. Steps of Neuromodulation

Types of Neuromodulation

Neuromodulation can be classified based on the **method of stimulation** and the **site of application**. Below is a detailed overview:

1. Electrical Neuromodulation

Involves delivery of mild electrical impulses to specific neural structures to alter activity.

- **Spinal Cord Stimulation (SCS):**
  Electrodes placed in the epidural space modulate pain signals by activating inhibitory pathways (used in chronic pain, neuropathic pain).
- **Deep Brain Stimulation (DBS):**
  Electrodes implanted in specific brain nuclei (e.g., subthalamic nucleus) regulate abnormal neuronal firing (used in Parkinson's disease, dystonia, OCD).

- **Vagus Nerve Stimulation (VNS):**
  Stimulates the vagus nerve to modulate brain networks (used in epilepsy, depression).
- **Peripheral Nerve Stimulation (PNS):**
  Targets specific peripheral nerves for pain relief or motor control (used in migraine, neuropathic pain).
- **Sacral Nerve Stimulation (SNS):**
  Stimulates sacral nerves (S2–S4) to restore bladder and bowel control.
- **Cortical Stimulation:**
  Electrodes placed on the motor or sensory cortex to modulate cortical excitability (used in post-stroke pain, motor rehabilitation).

2. Chemical Neuromodulation

Involves delivery of neuroactive substances or drugs directly to nervous tissue.

- **Intrathecal Drug Delivery Systems (IDDS):**
  Pumps deliver analgesics, baclofen, or anesthetics directly into cerebrospinal fluid for pain or spasticity management.
- **Targeted Pharmacological Modulation:**
  Uses neurotransmitter analogs, receptor agonists, or antagonists to adjust synaptic activity locally.

3. Magnetic and Ultrasound Neuromodulation

Noninvasive methods that modulate brain activity without surgery.

- **Transcranial Magnetic Stimulation (TMS):**
  Uses magnetic fields to induce electric currents in cortical neurons (used in depression, stroke recovery).
- **Transcranial Direct Current Stimulation (tDCS):**
  Applies weak direct current through scalp electrodes to modulate cortical excitability.
- **Focused Ultrasound Neuromodulation:**
  Uses acoustic energy to noninvasively stimulate or inhibit deep brain structures.

4. Optogenetic and Emerging Techniques

Advanced research-based methods offering high precision.

- **Optogenetics:**
  Uses light-sensitive ion channels introduced genetically to control neuron firing with light (experimental).
- **Gene-based Neuromodulation:**
  Involves gene therapy vectors altering expression of neurotransmitter systems or ion channels.

Role of Different Types of Neuromodulation in Movement Disorders

Neuromodulation encompasses a range of techniques that modify abnormal neural activity to restore functional motor control in movement disorders such as Parkinson's disease, dystonia, essential tremor, and Tourette syndrome. These interventions can be invasive or non-invasive, targeting specific neural structures to achieve symptomatic relief and, in some cases, induce long-term neural reorganization. The major modalities include Deep Brain Stimulation (DBS), Transcranial Magnetic Stimulation (TMS), Transcranial Direct Current Stimulation (tDCS), Vagus Nerve Stimulation (VNS), and Focused Ultrasound (FUS).[3]

1. Deep Brain Stimulation (DBS)

Mechanism and Target:

DBS is the most established form of invasive

neuromodulation. It involves surgical implantation of electrodes in specific subcortical structures such as the subthalamic nucleus (STN), globus pallidus interna (GPi), or thalamic ventral intermediate nucleus (VIM). These electrodes deliver continuous or adaptive electrical impulses that modify abnormal neuronal firing patterns within the basal ganglia-thalamocortical circuit.

Role in Movement Disorders:

Parkinson's Disease (PD): DBS reduces tremor, rigidity, and bradykinesia, improving motor performance and reducing medication requirements.

Dystonia: GPi-DBS improves sustained muscle contractions and abnormal postures.

Essential Tremor: VIM-DBS effectively suppresses tremor.

Tourette Syndrome: Stimulation of thalamic or limbic regions can reduce tic frequency and severity.

Recent Advances:

Adaptive or closed-loop DBS systems that respond to real-time neural signals have been developed to optimize stimulation and minimize side effects.

2. Transcranial Magnetic Stimulation (TMS)

Mechanism and Target:

TMS is a non-invasive technique that uses magnetic fields to induce electrical currents in cortical neurons, thereby modulating their excitability. Depending on frequency and pattern, TMS can either enhance (high-frequency) or inhibit (low-frequency) cortical activity.

Role in Movement Disorders:

Parkinson's Disease: Repetitive TMS (rTMS) targeting the primary motor cortex and supplementary motor area can improve motor symptoms, gait, and freezing of gait.

Dystonia: Low-frequency rTMS of the premotor or sensory cortex reduces abnormal muscle contractions. Tourette Syndrome: Prefrontal or supplementary motor area stimulation can decrease tics and improve behavioral control.

Recent Advances:

Newer patterned stimulation protocols, such as theta burst stimulation (TBS), offer shorter treatment durations with similar or superior efficacy.

3. Transcranial Direct Current Stimulation (tDCS)

Mechanism and Target:

tDCS delivers low-intensity direct electrical current through scalp electrodes to modulate neuronal membrane potential. Anodal stimulation increases excitability, while cathodal stimulation decreases it.

Role in Movement Disorders:

Parkinson's Disease: Anodal tDCS over the motor cortex enhances motor performance and may complement dopaminergic therapy.

Dystonia: Cathodal stimulation helps normalize hyperexcitability in affected motor regions.

Essential Tremor: Combined with motor training, tDCS may improve tremor control and coordination.

Advantages:

It is portable, inexpensive, and can be used as a home-based adjunct therapy.

4. Vagus Nerve Stimulation (VNS)

Mechanism and Target:

VNS involves delivering electrical impulses to the vagus nerve, influencing widespread brain regions including the locus coeruleus and thalamus. These pathways regulate neurotransmitter release and modulate cortical excitability.

Role in Movement Disorders:

Though primarily approved for epilepsy and depression, VNS has shown potential benefits in Parkinson's disease by improving motor symptoms, mood, and cognitive functions. Experimental studies also suggest neuroprotective and anti-inflammatory effects, which may slow disease progression.

Recent Innovations:

Non-invasive transcutaneous auricular VNS (taVNS) has emerged as a safe alternative that avoids surgical implantation.

5. Focused Ultrasound (FUS)

Mechanism and Target:

FUS uses precisely focused acoustic energy to create either thermal lesions or reversible modulation in deep brain structures without surgical incisions. MR-guided focused ultrasound (MRgFUS) allows real-time imaging and targeting accuracy.

Role in Movement Disorders:

Essential Tremor: Thalamic (VIM) lesioning with FUS offers durable tremor suppression.

Parkinson's Disease: Lesioning of STN or GPi improves tremor and rigidity.

Emerging Use: Low-intensity FUS is being explored for non-destructive neuromodulation and targeted drug delivery across the blood–brain barrier.

Advantages: It is incision-free, precise, and suitable for patients who cannot undergo invasive surgery.

6. Emerging and Hybrid Modalities

Recent innovations include optogenetic stimulation, ultrasound-based neuromodulation, and nanotechnology-assisted systems, which aim to achieve cell-specific, non-invasive, and adaptive modulation. Integration of artificial intelligence and neurofeedback into closed-loop systems promises a new era of personalized therapy for movement disorders. Incorporating feedback control theory into DBS protocols has allowed for adaptive modulation that accounts for the dynamic progression of these disorders, enhancing symptom management in PD. Broccardet. al. has developed and evaluated closed-loop systems, both invasive and non-invasive, that reduce complications and side effects of conventional therapies. A novel non-invasive closed-loop framework based on force neurofeedback is presented by the author, highlighting its potential to provide individualized, optimized rehabilitation. Future developments in closed-loop neuromodulation may further advance personalized therapeutic strategies for movement disorders.[4]

Table 1: Comparative Summary of Neuromodulation Techniques in Movement Disorders

Modality	Mechanism of Action	Common Targets	Primary Indications	Advantages / Key Features
Deep Brain Stimulation (DBS)	Continuous or adaptive electrical stimulation alters abnormal neuronal firing in motor circuits (basal ganglia–thalamocortical loop).	Subthalamic nucleus (STN), Globus pallidus interna (GPi), Ventral intermediate nucleus (VIM).	Parkinson's disease, dystonia, essential tremor, Tourette syndrome.	Highly effective, reversible, adjustable stimulation; long-term benefit; established safety profile.
Transcranial Magnetic Stimulation (TMS)	Magnetic fields induce electric currents that modulate cortical excitability; high-frequency increases and low-frequency decreases activity.	Primary motor cortex, supplementary motor area, premotor cortex, prefrontal cortex.	Parkinson's disease, dystonia, Tourette syndrome.	Non-invasive, outpatient procedure; frequency-specific modulation; minimal adverse effects.
Transcranial Direct Current Stimulation (tDCS)	Low-intensity direct current modifies neuronal membrane potentials—anodal increases and cathodal decreases excitability.	Motor cortex, premotor cortex, cerebellum.	Parkinson's disease, dystonia, essential tremor.	Portable, cost-effective, safe for repeated use; can be combined with rehabilitation therapy.
Vagus Nerve Stimulation (VNS)	Electrical impulses to vagus nerve influence brainstem nuclei and neurotransmitter systems (e.g., locus coeruleus, thalamus).	Vagus nerve (cervical or auricular).	Parkinson's disease (experimental), neurorehabilitation after injury.	Enhances neuroplasticity; potential neuroprotective and anti-inflammatory effects; non-invasive options available (taVNS).
Focused Ultrasound (FUS)	Acoustic energy produces thermal lesions or reversible neuromodulation in deep structures under MRI guidance.	Thalamus (VIM), STN, GPi.	Essential tremor, Parkinson's disease.	Incision-free, precise targeting, real-time MRI monitoring, alternative for non-surgical candidates.
Emerging & Hybrid Modalities	Use of optogenetics, closed-loop systems, AI-integrated feedback, or nanotechnology for targeted modulation. targeted modulation.	Disease-specific neural circuits; network-based targets.	Experimental applications in Parkinson's disease, dystonia, and tremor.	Potential for personalized, adaptive therapy; improved safety and precision.

Conclusion

Neuromodulation has revolutionized the management of movement disorders by providing targeted, adjustable, and often reversible treatment options. Each modality—ranging from invasive DBS to non-invasive TMS and tDCS—plays a distinct role based on disease type, symptom profile, and patient preference. Continued technological innovation, combined with advances in neuroimaging and computational modeling, is expected to enhance the precision, safety, and effectiveness of neuromodulation, moving toward truly individualized care and potentially disease-modifying interventions.

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Section 3
Infectious Disease

Chapter

9

Antimicrobial Resistance: Strategies for 2025 and Beyond

Dr. Chandan Sarmah

ABSTRACT

Antimicrobial resistance (AMR) represents a critical global health crisis driven by the overuse of antimicrobials and the inadequate discovery of new drugs This abstract outlines strategies for 2025 and beyond to combat this threat through a multi-faceted One Health approach, which recognizes the interconnectedness of human, animal, and environmental health. Future efforts will focus on enhancing surveillance to track resistance patterns and consumption across sectors, optimizing antimicrobial stewardship to ensure responsible use, and boosting infection prevention and control programs, including improving access to clean water, sanitation, and hygiene.

Innovation will target the depleted pipeline for new drugs, diagnostics, and vaccines, utilizing incentives for research and development and exploring alternative therapies like phage therapy and immunomodulation. Technological solutions, such as artificial intelligence, will improve diagnostics and optimize treatment plans. Public awareness and education will address the widespread misuse of antimicrobials.

Section 1: The Global Burden and Evolving Landscape of AMR

Antimicrobial resistance (AMR) has emerged as one of the most urgent global health crises of the 21st century. According to the Global Burden of Disease (GBD) 2019 AMR analysis, resistant bacterial infections were directly responsible for nearly 1.27 million deaths and contributed to almost 5 million deaths worldwide. Updated projections for 2025 suggest that without accelerated action, AMR could cause 10 million annual deaths by 2050, surpassing cancer as a leading cause of mortality.

The **drivers of AMR** are multifactorial:

- **Clinical misuse** of antibiotics in human medicine, including over-prescription and incomplete treatment courses.
- **Agricultural use** of antimicrobials in livestock and aquaculture, often for growth promotion rather

than therapy.

- **Environmental contamination,** such as pharmaceutical manufacturing effluents and hospital wastewater, which sustain resistant organisms.
- **Weak surveillance systems** in many low- and middle-income countries (LMICs), preventing timely detection and response.

The microbial landscape itself is evolving. Multidrug-resistant **Gram-negative pathogens** (e.g., carbapenem-resistant *Klebsiella pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa)* are now priority threats due to limited treatment options. Resistant Gram-positive organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE), remain endemic in many regions. Emerging pan-resistant strains, including those resistant to **colistin**, highlight the fragility of last-resort antibiotics.

The COVID-19 pandemic accelerated resistance in several ways. Widespread empiric antibiotic use during viral illness, strained infection prevention practices, and healthcare disruptions created favorable conditions for resistance to spread. Post-pandemic data demonstrate increased **resistant bloodstream infections**, particularly in intensive care units.

By 2025, AMR is recognized not only as a **medical threat** but also as a **developmental, economic, and security issue**. The World Health Organization (WHO), Food and Agriculture Organization (FAO), World Organisation for Animal Health (WOAH), and United Nations Environment Programme (UNEP) have formalized a **Quadripartite Alliance** to address AMR through a **One Health framework**, emphasizing the interconnection between human, animal, and environmental health.

Thus, the global burden of AMR in 2025 reflects both the **biological evolution of pathogens** and the **systemic challenges of health governance, stewardship, and equity.**

Section 2: Advances in Surveillance, Diagnostics, and Stewardship

Surveillance has advanced significantly in the last decade, but gaps remain. The **Global Antimicrobial Resistance and Use Surveillance System (GLASS)**, launched by WHO, has expanded participation from a handful of countries in 2017 to over 120 in 2025. Yet, many LMICs still lack robust laboratory capacity and standardized reporting, limiting the reliability of data. Innovations such as **wastewater surveillance** and **airplane wastewater monitoring** are increasingly used to detect international spread of resistant pathogens, offering early-warning capabilities beyond traditional clinical networks.

Diagnostics have become a cornerstone of resistance management. Rapid molecular assays, next-generation sequencing, and artificial intelligence–driven predictive tools enable earlier detection of resistance genes. Bedside diagnostic stewardship is now recognized as critical: ensuring blood cultures are collected before antibiotics, reducing empiric use, and tailoring therapy more rapidly. Point-of-care platforms in primary care are helping to distinguish bacterial from viral infections, directly reducing unnecessary prescribing.

Antimicrobial stewardship (AMS) remains central to slowing resistance. Evidence shows AMS programs that combine rapid diagnostics, guideline-

based prescribing, and audit-feedback loops reduce inappropriate use and improve patient outcomes. In 2025, stewardship is increasingly linked with digital health: electronic prescribing platforms flag inappropriate prescriptions, and clinical decision support tools suggest narrower-spectrum options.

Infection prevention and control (IPC) complements stewardship. Improved hospital hygiene, isolation of resistant organisms, vaccination programs, and optimized use of personal protective equipment reduce transmission. Importantly, vaccination against pathogens such as Streptococcus pneumoniae and influenza indirectly lowers antibiotic demand by preventing secondary bacterial infections.

Despite progress, challenges persist. Many hospitals in LMICs lack the workforce and infrastructure for stewardship programs. Diagnostics, though increasingly available, remain costly and unevenly distributed. Moreover, behavioral aspects—clinician prescribing habits, patient demand for antibiotics, and cultural perceptions—continue to drive misuse.

By 2025, it is clear that surveillance, diagnostics, and stewardship represent the **first line of defense against AMR**. Scaling them equitably, particularly in resource-constrained settings, remains the most immediate and cost-effective strategy to contain resistance.

Section 3: Therapeutic Innovation and the Antimicrobial Pipeline

A persistent challenge in AMR is the **limited antibiotic development pipeline**. The economics of antibiotic research are unfavorable: short treatment courses, stewardship-driven restricted use, and rapid resistance emergence discourage industry investment. Consequently, most new approvals in the past decade have been **incremental modifications** of existing classes, rather than true novel agents.

The WHO's updated **priority pathogen list** highlights urgent gaps in coverage, particularly for carbapenem-resistant Gram-negatives. As of 2025, fewer than 15 truly novel candidates are in late-stage development. Some promising examples include:

- **Cefiderocol**, a siderophore cephalosporin active against carbapenem-resistant Gram-negatives.
- **Novel ß-lactam/ß-lactamase inhibitor combinations** (e.g., meropenem-vaborbactam, imipenem-relebactam).
- **Zoliflodacin**, a first-in-class oral agent for drug-resistant *Neisseria gonorrhoeae*.

Beyond antibiotics, **non-traditional therapies** are gaining traction:

- **Phage therapy**, with ongoing clinical trials exploring its role in chronic infections.
- **Monoclonal antibodies** targeting specific pathogens or toxins.
- **Host-directed therapies** and immunomodulation to enhance innate resistance.
- **Microbiome modulation** to restore colonization resistance.

Antifungal resistance is also a rising concern, with multidrug-resistant *Candida auris* outbreaks reported globally. New antifungals such as **ibrexafungerp** and **fosmanogepix** are in development, but the pipeline remains limited.

The innovation challenge is not solely scientific but economic. To overcome market failure, several

countries have introduced **pull incentives**—such as the UK's subscription model, where companies are paid an annual fee for providing new antibiotics irrespective of sales volume. Discussions at the **G7 and G20** levels are ongoing to establish global frameworks for financing antibiotic R&D while ensuring equitable access and stewardship.

Ultimately, therapeutic innovation in 2025 is marked by **modest scientific progress** but **increasingly creative policy solutions** to incentivize research. Success will depend on pairing new drug development with robust stewardship and global access frameworks.

Section 4: Strategic Priorities and the Road Ahead

The fight against AMR in 2025 is at a pivotal moment. The WHO-led **Global Action Plan on AMR (GAP)**, first launched in 2015, is undergoing a comprehensive update to set clearer, measurable targets for the next decade. The updated plan emphasizes **One Health integration**, **financing mechanisms**, and **accountability structures** to ensure countries translate commitments into tangible outcomes.

Strategic priorities for the next five years include:

1. Strengthening One Health frameworks

o Expand integrated surveillance to cover human, animal, and environmental reservoirs.

o Regulate antimicrobial use in agriculture, phasing out growth promotion.

o Monitor and mitigate pharmaceutical effluents contributing to environmental resistance.

2. Scaling equitable stewardship and diagnostics

- Mandate AMS programs in all tertiary hospitals.
- Subsidize rapid diagnostics for LMICs.
- Use digital health tools to support prescribers and track usage patterns.

3. Financing sustainable innovation

- Implement global pull incentives to stimulate antibiotic R&D.
- Ensure new antimicrobials are accessible and affordable in LMICs.
- Support research into non-traditional therapies, vaccines, and microbiome science.

4. Investing in workforce and infrastructure

- Train infectious disease specialists, microbiologists, and pharmacists to lead AMS programs.
- Build laboratory networks with interoperable data systems.
- Strengthen supply chains to avoid drug stockouts that drive inappropriate use.

5. Enhancing community engagement and education

- Combat misinformation and patient-driven demand for antibiotics.
- Promote vaccination as a tool to reduce antibiotic consumption.
- Engage civil society to hold governments accountable for AMR commitments.

AMR is not a challenge confined to hospitals—it is a **societal and planetary problem** requiring sustained, coordinated, and well-financed action. If the momentum of 2025—marked by updated global policy, innovative surveillance, and renewed investment—can be translated into durable system changes, the trajectory of AMR can be slowed.

The road ahead will demand **scientific innovation, political will, and community participation**. Without these, AMR threatens to erode

a century of medical progress. With them, it is possible to preserve the power of antimicrobials for future generations.

Conclusion

As of 2025, antimicrobial resistance represents both a profound threat and a critical opportunity. Progress in surveillance, stewardship, and early therapeutic innovation offers hope, but gaps in equity, financing, and policy implementation remain stark. The next decade will determine whether AMR evolves into an uncontrollable crisis or is contained through sustained global collaboration. The tools and knowledge exist—the challenge now is the political, financial, and **societal commitment to act decisively**.

Recent Regulatory Approvals (2025)

- **Emblaveo** (aztreonam-avibactam combination)
  - Approved in the EU in April 2024, UK in June 2024, and by the US FDA in **February 2025**
  - Designed to treat complicated intra-abdominal infections (cIAIs) and other serious infections caused by aerobic Gram-negative bacteria, including those with multi-drug resistance
- **Blujepa**(gepotidacin)
  - FDA approved in **March 2025** for treating uncomplicated urinary tract infections (uUTIs) in females aged 12+
  - It represents the first new class of oral antibiotics for uUTIs in nearly 30 years and shows improved efficacy against common bacteria like E. coli and antibiotic-resistant strains
- **Gepotidacin for Gonorrhoea**
  - In **April 2025**, phase III trial results showed gepotidacin is non-inferior to standard dual therapy (ceftriaxone + azithromycin) for treating gonorrhoea, including resistant strains
  - Further studies are needed across different demographics and infection sites (e.g., throat, rectal)
- **ZEVTERA (ceftobiprole medocaril)** and **XACDURO**
  - **ZEVTERA**, an advanced-generation cephalosporin for MRSA bloodstream infections and pneumonia, gained FDA approval in April 2024; Innoviva received US marketing rights in December 2024
  - **XACDURO**, approved in May 2023, treats hospital-acquired and ventilator-associated pneumonia caused by Acinetobacter
  - Innoviva also has **zoliflodacin**, a potential gonorrhoea treatment, under FDA review with a decision expected by the end of 2025

Emerging Innovations & Ongoing Research

- **Australian Oyster-derived Antimicrobial Proteins**
  - A protein from the blood of the **Sydney rock oyster** shows promising antibacterial activity and enhances antibiotic efficacy in lab tests—especially against biofilms
  - Still in early stages, requiring further

purification and investigation on digestibility and practical use

- **Darobactin D22**(experimental compound)
  - Modified darobactin molecule **D22** shows efficacy in lab and animal models against critical Gram-negative pathogens, including A. baumannii and E. coli
  - Represents a promising candidate for future clinical development.
- **Lariocidin**(new molecule)
  - Discovered by McMaster University researchers, lariocidin demonstrates activity against drug-resistant bacteria without toxicity to human cells
  - Researchers are now optimizing production and molecular modifications to advance toward clinical use.
- **AI & Computational Advances**
  - **OmegAMP**, a diffusion-based AI model, facilitates targeted generation of antimicrobial peptides (AMPs) with desired properties—improving hit rates and specificity
  - **Lipidated SNAPPs** (star-shaped antimicrobial polymers), especially with C12 chains, show enhanced bacterial membrane disruption and bactericidal activity in simulations
  - ML models are predicting AMR in foodborne pathogens like Campylobacter and projecting increased healthcare burdens by 2050

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Chapter

10

Emerging Viral Threats: Preparedness for Pandemics

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ABSTRACT

Emerging viral threats have always presented a major challenge to public health as seen in instances of epidemics and pandemics like SARS-CoV, H1N1 influenza, SARS-CoV-2, Ebola, Zika, and Avian Influenza. Being mostly zoonotic in nature, these viruses have the capacity to spread quickly, are highly transmissible and of diverse fatality rates. Effective management of viral outbreak requires early detection through robust surveillance system, cutting edge genetic sequencing, real time analysis of clinical reports, alongside resilient healthcare infrastructure. Moreover, effective preparedness also depends on several other factors such as community participation, coordination between government and non-government agencies, public- private partnerships as well as coordination at the global level as emphasized by the One Health Approach. Lessons from the previous pandemics highlights the importance of proactive and multidisciplinary strategies, bringing out scientific innovations, training of healthcare professionals as well as combining technological preparedness with community engagement to mitigate the impact of viral pandemics and boost global resilience against the emerging viral threats in future.

Introduction

Viruses have had an intricate role in human history. In some instances, they can emerge with incredible power to alter the very path of history, while in others; they may stay dormant for long periods of time. Devastating epidemics and pandemics in the past have left us with a lasting reminder that the delicate equilibrium between human and the microbial world is susceptible to disturbance. Numerous viruses have posed a threat to global societies and public health since the turn of the twenty-first century. The globe was shaken by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) epidemic in 2002[1], the H1N1 influenza outbreak in 2009, and the most recent SARS-CoV-2 pandemic, which revealed how quickly viruses may affect health throughout the world[2]. These incidents put

light on the idea of "emerging viruses," or those that unexpectedly cross the animal-human barrier, and the difficulties in identifying, containing, and mitigating them. Furthermore, re-emerging viruses like coronavirus and avian influenza demonstrated their evolutionary capabilities with increased vigour.

Thus, being prepared for new viral perils is seen as essential for community resilience, global security, and economic stability in addition to the public health field.

Identifying Emerging Viral Threats

Emerging viral threats possess continuous public health risks because of their high fatality rates, ability to quickly transmit, and potential to spread worldwide. Amongst them, Filoviridae, Ebola and Marburg viruses are zoonotic, single stranded RNA viruses that transmits directly through contact with infected fluids. Ebola, which was first reported in 1976, had an 88% mortality rate and it triggered the largest outbreak in West Africa in between 2014 and 2016 with more than 28,000 cases. Marburg, which was first identified in the year 1967 in Europe from monkeys, had also very high fatality rates going upto 88% 3,4.

In these scenarios; host immunity, genetics, and access to care play crucial role in influencing variations in case fatality rates.

The Flaviviridae family that includes Zika and Dengue viruses are both mosquito borne. Discovered in 1947, the Zika virus gained global attention during the 2015 Brazil outbreak because of its connection to developmental problems, including microcephaly, in children born to infected mothers. Dengue became one of the most prevalent vector borne diseases particularly in Southeast Asia, the Americas, and the Western Pacific with cases rising from 500000 in the year 2000 to 5.2 million in the year 2019[5].

Furthermore, coronaviruses like MERS-CoV, SARS-CoV, and SARS-CoV-2 have shown their worldwide influence. MERS, which was detected at first in Saudi Arabia in the year 2012 was linked to camels and had a high mortality rate but limited person to person transmission. Emerging in China, SARS-CoV in 2002 and SARS-CoV-2 in 2019 (COVID-19) both produced extensive epidemics, whereas COVID-19 became a worldwide pandemic because of its high transmissibility and continuous mutations[6].

Another distinct type of single-stranded RNA influenza virus is the avian influenza virus. The H5N1 and H7N9 strains of avian influenza are thought to be the most prevalent types to infect human and can spread from birds. The high prevalence of viruses in minks has also led scientists to conclude that there is a considerable chance of co-infection with both avian influenza and the more prevalent human influenza. As a result, there may be a higher danger to public health from the potential for novel mutations brought on by co-infection[7].

Finally, multiple outbreaks of mpox, formerly known as monkeypox, which have occurred globally since May 2022 has led The World Health Organisation (WHO) to deem it as a public health emergency due to its increased human transmissibility. A zoonotic double-stranded DNA virus, the monkeypox virus belongs to the Orthopoxvirus genus, which also contains smallpox. Despite having a low death rate, it spreads quickly and causes a large number of hospitalised people[3].

Management and prevention of emerging viral threats depend on a large extent on understanding the origin and identifying the causes. Proper identification of the emergence of virus can help mapping the pathways of zoonotic spillovers before they turn into a global health emergency.

Table 1: A summary of emerging viruses[3]

Virus	Size (Diameter)	Shape	Geo-Regions	Detection Method
Ebola	80 nm, varying length	Rod-shaped	17 countries (mainly Africa)	RT-PCR, LFA, NGS, antigen test
Marburg	<14,000 nm	Rod shaped	11 countries (mainly Africa)	RT-PCR, ELISA
Zika	40-43 nm	sphere	89 countries	RT-PCR, ELISA, RT-LAMP
Dengue	40-50nm	sphere	>100 countries	RT-PCR, ELISA, immunoassay
MERS-CoV	80-120 nm	sphere	27 countries	RT-PCR, CRISPR, biosensor
SARS-CoV	80-120 nm	sphere	China and four other countries	RT-PCR, CRISPR
SARS-CoV-2	80-120 nm	sphere	worldwide	RT-PCR, CRISPR, ELISA, LAMP, LFA, NGS, antigen/ anti-body test
Avian Influenza	100 nm	sphere	worldwide	RT-PCR
Monkeypox	200–250nm(length)	Brick-shaped	110 countries	RT-PCR

Monitoring and Prompt Identification

The potential severity of a pandemic is reliant upon the virus's virulence and transmissibility as well as the population's susceptibility, which might differ based on factors like age and prior viral exposure. The introduction of a new antigenic virus type is likely necessary for a catastrophic pandemic, but this doesn't imply that all newly emerging viruses would cause an exceptionally high burden. Several countries have witnessed improvements in laboratory capacity, monitoring, and disease detection. The new methods of Web-based field reporting and Web-based search pattern analysis can provide useful information that can help the world prepare for the next epidemic.

Superior surveillance techniques covering both human populations and animal reservoirs, agreements on virus and vaccine sharing, better antiviral agents and more effective vaccines, greater production capacity, and faster throughput are amongst the key strategies that needs to be undertaken for pandemic preparedness.

Moreover, advancements in gene sequencing and bioinformatics can play a crucial role in transforming surveillance and help in rapidly identifying viral pathogens and their mutations in near real time. One of the best examples of how prompt sequencing can guide public health strategies, development of vaccines, and diagnostics is the global sharing of SARS-CoV-2 genomes through GISAID. Moreover, analysing diverse data streams, from clinical reports through digital epidemiology tools can prove to be effective in predicting of pandemic outbreak.

However, limitations in laboratory capacity and healthcare infrastructure at the global level stands out to be a major hindrance, especially in the economically weaker countries where the risk of such viral outbreaks is often highest. This highlights the necessity of international collaboration, such as the World Health Organization's Global Outbreak Alert and Response Network (GOARN), which emphasizes on data sharing, resource mobilization and coordinated action. Developing such networks at a global level are critical to achieving rapid containment of viral threats worldwide[8].

Healthcare System Readiness

One of the prime factors influencing how well a population can react to viral outbreaks is a resilient and robust healthcare system. The COVID-19 pandemic was an eye opener for every country in the globe including

the most developed nations. Finding the most important lessons from the COVID-19 response is essential to enhancing health security and health system resilience in order to respond to pandemics and crises with greater effectiveness in the future. Rapid expansion of hospital infrastructure, emergency stockpiling, and training of healthcare workers to fight against such outbreaks are the key strategies for healthcare system readiness. However, access to diagnostics, vaccines, proper healthcare infrastructure are a key challenge and remains a global hurdle, as observed during COVID-19. Preparedness for pandemic responses must extend beyond tertiary healthcare facilities. It is necessary to integrate primary healthcare systems to ensure preparedness rather than solely depending on tertiary care facilities. Several important insights have been highlighted by experts based on the experiences, analysis, and comments. The key lessons learnt about preparedness for pandemic responses can be summarised as follows.

a) Pathogens and genetic sequence data: In order to quickly characterise pathogens, assess risk, implement evidence-based therapies, and implement countermeasures, it is imperative that timely sharing of pathogens, their genetic sequence data, and pertinent metadata be maintained.
b) Resilient health systems focused on primary care: Community health workers and primary health care systems play crucial roles in the pandemic response. Early involvement and sustained participation increase the efficacy.
c) Public-private partnerships: From health care delivery to the manufacturing of pandemic items, logistics and supply management, and risk communication, more efficient private sector involvement holds significant promise for enhancing pandemic response.
d) Public health initiatives and containment operations: It is crucial to have more precise and practical guidelines for quick containment during the early stages of a pandemic.
e) Infodemic risk communication and management: It is essential to promptly and openly disseminate information to the public. It is necessary to improve misinformation management.
f) Information, alerts, and risk assessments: District, and primary health care capacities must improve their public health information and surveillance activities.
g) Digital technology for surveillance and response: More use of digital information technology is needed to enhance monitoring, contact tracing, telemedicine care and treatment, and the planning of public health initiatives, such as immunisation.
h) Psychosocial support and care: From the outset of any medical emergency, mental health and psychosocial services have to be a crucial component of emergency response. In order to reach vulnerable people and treat a variety of psychological difficulties, organisations must be involved.
i) Research and development: To get ready for upcoming pandemics and epidemics, the region's research and development capabilities should be strengthened. Instead of uneven efforts, more extensive and well-coordinated clinical studies should be conducted.

Scientific innovation can also play a key role in our fight against viral outbreaks. Development of universal vaccine platforms, such as mRNA techniques, can offer opportunities for better pandemic responses?

Community Engagement and Global Coordination

The preparation for pandemic extends beyond science and medicine and it encompasses social as well as behavioural aspects of health. Ensuring proper adherence to preventive measures such as quarantine, vaccination, hygiene, community participation and keeping strict vigil on the spread of misinformation is essential while tackling pandemic. Moreover, a well coordination between government, non- government organisations and corporate sectors is quite essential to ensure effective preparedness on a global scale. Worth emphasizing, a set of programs referred to as the One Health Joint Plan of Action, an initiative by the World Health Organisation created through a participatory process with the goal of enhancing coordination, cooperation, communication, and capacity building in all sectors that are in charge of addressing health issues at the interface between humans, animals, plants, and the environment is acknowledged as a crucial paradigm for pandemic prevention[10].

Conclusion

Although emerging viral threats are inevitable, yet the consequences can be controlled to a great extent with proper planning, preparedness and collective decisions. It has been evident from past instances that investing in resilient healthcare infrastructure, robust surveillance system and cooperation within government and non-government agencies has proved to be effective to withstand the shock of pandemics. Moreover, proactive and multidisciplinary strategies like that of One Health model that acknowledges the integrated approach taking humans, animals and ecosystem into consideration can prove to be instrumental in mitigating viral outbreaks since many pandemics arise from zoonotic spillovers.

Developing upon these ideas, the practical implications to tackle pandemic extend not only to healthcare professionals but also to lawmakers at the global level. Moreover, healthcare professionals must get training on a regular basis in terms of identification, prevention and response. Access to vaccination, diagnostics and treatment must be ensured on a global scale irrespective of the socio-economic background of any population.

Preparation for the management of pandemic must also require advanced genomic surveillance in the regions of the globe where there are high risks of such viral outbreaks. Apart from technological preparedness, it is equally important to ensure that communities are well informed and participate in preventive measures. Scientific innovation as well as participation from community can together act as pillars in developing effective preparation strategies to fight against emerging viral threats and strengthen our preparedness for pandemics.

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Chapter

11

HIV Management in a New Era: The Dawn of Long-Acting Therapies and the Pursuit of a Cure

Dr. Atonu Saha, Dr. Ajay Peter Topno

ABSTRACT

The management of Human Immunodeficiency Virus (HIV) is undergoing a transformative shift, moving beyond daily oral antiretroviral therapy (ART) towards a new paradigm defined by long-acting (LA) formulations and ambitious cure research. For over two decades, daily multi-pill regimens have been the cornerstone of care, effectively suppressing viral replication and transforming HIV into a chronic manageable condition. However, treatment fatigue, stigma, and pill burden remain significant challenges. The advent of long-acting injectable cabotegravir and rilpivirine, administered monthly or bi-monthly, represents a monumental leap forward, offering an option that enhances convenience, privacy, and quality of life for virologically suppressed individuals. Concurrently, the scientific pursuit of an HIV cure has intensified. While a sterilizing cure remains elusive, strategies such as "shock and kill" to reactivate and eliminate the latent viral reservoir, gene editing using tools like CRISPR-Cas9 to excise proviral DNA, and immune-based therapies are advancing through preclinical and clinical trials. This article reviews the current evidence for long-acting ART, explores the most promising avenues in HIV cure research, and discusses the future landscape where long-term suppression and curative strategies may converge to end the HIV pandemic.

Keywords: HIV, Long-Acting Antiretroviral Therapy, Cabotegravir, Rilpivirine, HIV Cure, Latent Reservoir, Shock and Kill, CRISPR-Cas9, Broadly Neutralizing Antibodies, ART.

Introduction: From Survival to Transformation

The introduction of combination antiretroviral therapy (ART) in the mid-1990s marked a watershed moment in the history of medicine, changing HIV infection from a fatal diagnosis to a manageable chronic condition[1]. For over 25 years, the standard of care has hinged on daily adherence to oral regimens, which potently suppress viral replication, restore immune function, and prevent sexual transmission—a concept known as Undetectable = Untransmittable (U=U).

Despite this phenomenal success, the paradigm of lifelong daily pill-taking is not without its limitations. Pill fatigue, stigma, drug-drug interactions, and the psychological burden of a daily reminder of one's HIV status persist as significant challenges to optimal quality of life and, in some cases, adherence.

We now stand at the precipice of a new era in HIV management, defined by two parallel and revolutionary fronts: the clinical implementation of long-acting (LA) antiretroviral formulations and the relentless scientific pursuit of a cure. This article will provide a comprehensive update on these groundbreaking developments, detailing the evidence for current long-acting therapies, exploring the pipeline of future agents, and demystifying the complex strategies being employed in the quest for an HIV cure.

Long-Acting Antiretroviral Therapies: A Paradigm Shift in Treatment

Long-acting therapies aim to decouple HIV management from daily oral intake, offering sustained drug release over extended periods. This approach holds the promise of improved adherence, reduced stigma, and enhanced patient satisfaction.

2.1 The First-in-Class: Long-Acting Cabotegravir and Rilpivirine

The most significant advancement in LA-ART to date is the approval of the injectable regimen comprising cabotegravir (CAB), a long-acting integrase strand transfer inhibitor (INSTI), and rilpivirine (RPV), a long-acting non-nucleoside reverse transcriptase inhibitor (NNRTI). This two-drug regimen is administered as intramuscular gluteal injections every one or two months.

The approval was based on a series of pivotal phase 3 clinical trials—ATLAS, FLAIR, ATLAS-2M, and SOLAR [2, 3, 4]. These studies demonstrated that in carefully selected, virologically suppressed adults (HIV-1 RNA <50 copies/mL), switching to LA CAB+RPV was non-inferior to continuing daily oral ART in maintaining viral suppression. The ATLAS-2M trial further confirmed that the every-2-month injection schedule was non-inferior to the monthly schedule, offering even greater convenience[4].

Key Considerations for LA CAB+RPV:

- **Patient Selection:** This regimen is not for everyone. It is indicated only for individuals with no history of virological failure and no known or suspected resistance to either drug. Pre-injection oral lead-in is required to assess tolerability.
- **Virologic Failure and Resistance:** While rare, virologic failure on LA CAB+RPV has been observed, often associated with the emergence of resistance mutations to both drug classes[5]. This underscores the importance of adherence to injection appointments to maintain therapeutic drug levels.
- **Injection Site Reactions (ISRs):** ISRs are very common, reported in the majority of participants. However, they are typically mild to moderate (pain, nodules, swelling) and decrease in frequency over time, leading to few discontinuations.
- **Implementation Logistics:** The requirement for healthcare visits every one or two months shifts the burden from the patient to the healthcare system, necessitating new models of care and logistical planning.

2.2 The Future Pipeline of Long-Acting Formulations

The success of CAB+RPV has catalyzed the

development of a broader pipeline of LA agents, aiming to offer more options, improved dosing intervals, and alternative delivery systems.

• **Lenacapavir:** This is a first-in-class capsid inhibitor with an exceptionally long half-life. It has been approved as a subcutaneous injection administered only every six months. Its unique mechanism of action makes it a valuable option for heavily treatment-experienced patients with multidrug-resistant virus, and it is being studied in novel combination regimens for both treatment and pre-exposure prophylaxis (PrEP)[6].

• **Islatravir:** Islatravir is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI) under investigation. It has a long intracellular half-life and was being developed as a monthly oral pill and a subdermal implant for both treatment and PrEP, though development has faced challenges requiring dose reevaluation.

• **Broadly Neutralizing Antibodies (bNAbs):** While primarily explored in cure research, bNAbs like ibalizumab (already approved for multidrug-resistant HIV) and others (e.g., VRC01, 10-1074) are being studied as long-acting agents for treatment and prevention due to their infrequent intravenous or subcutaneous dosing.

The ultimate goal is to create a "toolkit" of long-acting options, including injectables, implants, and infrequent oral pills, allowing for highly individualized HIV management.

The Quest for an HIV Cure: From Concept to Clinical Trials

While long-acting therapies represent a massive leap in quality of life, they are not a cure. Patients still harbour a reservoir of latently infected cells that can rekindle active replication if therapy is stopped. Achieving a cure—defined as either a sterilizing cure (complete eradication of all HIV-infected cells from the body) or a functional cure (long-term viral remission without ART, akin to the "Berlin" and "London" patients)—remains the ultimate goal.

3.1 The Primary Barrier: The Latent Viral Reservoir

The main obstacle to an HIV cure is the establishment of a latent reservoir, primarily in resting memory CD4+ T-cells. These cells contain integrated proviral DNA but do not produce viral particles, making them invisible to the immune system and unaffected by standard ART. This reservoir is long-lived and can spontaneously reactivate if ART is discontinued.

3.2 Promising Cure Strategies

Research is focused on multiple, often complementary, strategies to target and eliminate or control the latent reservoir.

• The "Shock and Kill" Strategy: This two-pronged approach involves using latency-reversing agents (LRAs or "shock" agents) to force the latent virus to express itself, making the infected cells visible. Subsequently, the immune system or adjunctive therapies are harnessed to "kill" these exposed cells. While conceptually sound, challenges have included the inability of LRAs to reactivate all reservoirs uniformly and the failure of the immune system, which is often exhausted in HIV, to effectively clear the reactivated cells. Newer combinations with immune enhancers are being tested to improve efficacy[7].

• **Gene Editing:** Inactivating the Provirus: This

strategy aims to directly target and disrupt the integrated HIV provirus within the host genome. The most prominent tool is CRISPR-Cas9, a gene-editing technology that can be programmed to snip out the HIV DNA or introduce mutations that permanently inactivate the virus. While highly promising in laboratory studies, significant hurdles remain, including delivery to all reservoir cells, potential off-target effects, and the virus's ability to mutate and escape the editing machinery[8].

• **Immune-Based Therapies:** These approaches seek to boost the body's own natural defenses to control or eliminate HIV.

- o Broadly Neutralizing Antibodies (bNAbs): As mentioned, bNAbs can recognize and neutralize a wide range of HIV strains. In cure research, they are being tested to both block new infections and, through Fc-mediated effector functions, help the immune system clear virus-producing cells. Some bNAb combinations have induced short-term viral suppression during analytical treatment interruption (ATI) in clinical trials[9].
- o Therapeutic Vaccines: These vaccines are designed to stimulate a potent, HIV-specific T-cell response in already infected individuals, equipping the immune system to control viral rebound post-ART. While no vaccine has yet led to sustained remission, they are a key component of combination cure strategies.
- o Chimeric Antigen Receptor (CAR) T-Cells: Inspired by their success in oncology, this approach involves engineering a patient's own T-cells to express receptors that specifically target HIV-infected cells. Early-phase trials are underway to assess the safety and feasibility of this powerful but complex technology.

• **Block and Lock:** An alternative to eradication, this strategy aims to reinforce viral latency, effectively putting the reservoir into a deep, permanent state of hibernation ("lock") using small molecules, thereby achieving a functional cure without needing to eliminate every last infected cell.

Case Studies and Proof of Concept

The feasibility of an HIV cure, while rare, has been demonstrated in a handful of remarkable cases that provide invaluable insights.

• **The Berlin Patient (Timothy Ray Brown) and The London Patient (Adam Castillejo):** Both individuals were cured of HIV following allogeneic hematopoietic stem cell transplants from donors with a rare CCR5-delta32 mutation, which confers natural resistance to HIV. The transplant replaced their immune system with one that was resistant to the virus. These cases prove that a cure is possible but also highlight the extreme nature of the intervention, which is too risky and impractical for the millions living with HIV[10].

• **The Mississippi Baby and Visconti Cohort:** These cases represent examples of post-treatment control. The "Mississippi Baby" experienced a period of remission off ART after receiving very early treatment, while the Visconti cohort consists of individuals who started ART during primary infection and subsequently maintained control after treatment cessation. These cases suggest that early intervention may limit the size of the reservoir and facilitate some degree of immune-mediated control.

Challenges and Future Directions

The path forward is fraught with challenges. For long-acting therapies, the key will be to expand access, reduce cost, develop simpler delivery systems (e.g., self-administered injections), and create combinations with higher genetic barriers to resistance.

For cure research, the challenges are even more profound. The reservoir is diverse and anatomically hidden (e.g., in the brain, gut). No single "shock" agent has been fully effective, and immune therapies must overcome HIV-induced immune exhaustion. Safety is paramount, especially for invasive strategies like gene editing. The field is increasingly moving towards combination approaches, such as using an LRA alongside a bNAb and a therapeutic vaccine, to mount a multi-pronged attack on the reservoir.

Conclusion

The landscape of HIV management is more dynamic and hopeful than ever before. The arrival of long-acting injectable ART marks a decisive shift from a daily pill-based model to one centered on patient preference and quality of life, freeing many from the daily reminder of their HIV status. In parallel, the scientific pursuit of a cure, once a distant dream, is now a vibrant and well-funded field of research. While a scalable, safe, and effective cure is not yet on the immediate horizon, the progress made in understanding the reservoir and developing novel immunologic and genetic tools is unprecedented. The convergence of these two fronts—optimized long-term suppression and ambitious curative strategies—heralds a future where we may not only manage HIV with unprecedented ease but ultimately end the pandemic for good.

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Chapter

12

Fungal Infections: New Antifungals and Diagnostic

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ABSTRACT

Fungal infections have become prominent global health threats, escalating the burden on public health systems. The increasing occurrence of invasive fungal infections is due primarily to the extensive application of chemotherapy, immunosuppressive therapies, and broad-spectrum antifungal agents. At present, therapeutic practices utilize multiple categories of antifungal agents, such as azoles, polyenes and echinocandins. Nevertheless, the clinical effectiveness of these treatments is progressively weakened by the emergence of drug resistance, thereby substantially restricting their therapeutic utility. Consequently, there is an imperative need to expedite the discovery of novel antifungal agents. The role of early and accurate diagnosis in the aggressive containment of the fungal infection at the initial stages become crucial thus, preventing the development of a life threatening situation. With the changing demands of clinical mycology, the field of fungal diagnostics has evolved and come a long way from traditional methods of microscopy and culturing to more advanced non-culture based tools.

Introduction

Invasive fungal infections, chiefly attributable to species of *Candida, Aspergillus*, and *Cryptococcus*, exhibit substantially higher mortality rates than superficial fungal infections, which are more frequently encountered.[1] These infections have become increasingly urgent global health issues; the World Health Organization has reported a marked rise in incidence, particularly among immunocompromised individuals, patients in intensive care, and those with respiratory disorders during the ongoing pandemic. Epidemiological analyses indicate that annual fatalities from fungal infections surpass those caused by malaria and breast cancer, with mortality rates rivaling those reported for tuberculosis and Acquired Immune Deficiency Syndrome (AIDS).[2] Furthermore, the prevalence of opportunistic fungal infections is a rising trend associated with the expanded use of chemotherapy,

immunosuppressive therapies, and broad-spectrum antibiotics.

In clinical practice, most antifungal therapies are designed to disrupt key structural components of fungal cells, notably the cell wall and cell membrane. These agents include echinocandins, which inhibit ß-glucan synthesis in the cell wall; azoles and allylamines, which impair ergosterol biosynthesis; and polyenes, which bind ergosterol to compromise membrane integrity. Additionally, antifungal drugs targeting intracellular proteins hinder fungal proliferation by inhibiting nucleic acid synthesis, disrupting the electron transport chain, or impairing microtubule dynamics. Nevertheless, the clinical utility of these therapies is increasingly challenged by the emergence of drug-resistant fungal strains.[2]

New anti-fungal agents are needed to overcome limitation of available antifungals such as poor pharmacokinetic traits, toxicity, drug-drug interactions, limited clinical efficacy, and emerging fungal resistance. Mapping out new drug lies on expanding the number of the ones belonging to well-known families (azoles, polyenes, or beta-d-glucan inhibitors) or designing molecules showing completely new mechanism of action.

Antifungals targeting the cell wall

Unlike human cells, fungi have a cell wall structure, which is an ideal target for antifungal drugs. The fungal cell wall comprises primarily ß-1,3-glucan, ß-1,6-glucan, chitin, and various proteins, all of which are essential for its structural integrity and mechanical resilience. These components interact to form an intricate network that underpins the overall functionality of the fungal cell. The cell wall plays dual role: it acts as a protective barrier against environmental stressors and is critical to fundamental cellular processes such as maintaining cell morphology, facilitating nutrient and ion transport, and modulating signal transduction pathways. Consequently, antifungal therapies that target the synthesis or functionality of these vital cell wall constituents can effectively inhibit fungal growth and reproduction.

Inhibitors of glucan synthase

Glucan synthase, the enzyme that catalyzes ß-(1,3)-D-glucan production, is a membrane -associated protein localized at the plasma membrane that harbors conserved catalytic domains known as FKS. The RHO1 GTPase subunit modulates its activity[77]. Inhibitors of ß-(1,3)-D-glucan synthase constitute a class of compounds that exert antifungal effects by interfering with the biosynthesis of ß-(1,3)-D-glucan. Given that ß-(1,3)-D-glucan is not present in mammalian cells, these inhibitors display remarkable specificity and negligible toxicity. Echinocandin resistance, a significant challenge in antifungal therapy, predominantly originates from genetic mutations affecting ß-(1,3)-D-glucan synthesis, especially those affecting the glucan synthase enzyme[77]. Current efforts in developing glucan synthase inhibitors focus on obstructing the elongation of the glucan polymer by binding to Fks1p, thereby preventing the accumulation of ß-(1,3)-D-glucan within the fungal cell wall and promoting potent antifungal activity.

NEW Beta D glucan inhibitors

Rezafungin -It is a second generation echinocandin whose mechanism of action and spectrum of activity is

similar to the currently available echinocandins, including C. auris. It is a derivative of anidulafungin in which the modification cyclic core conferred the drug a safer profile and long half-life (130 hours) which in turn resulted in high drug exposure, one-week single dose administration, and lower induction of FKS mutations. Rezafungin showed non-inferiority compared to caspofungin for the treatment of patients with candidaemia and FDA approved the drug for the treatment of candidaemia (it is under evaluation by EMA now). Clinical trials assessing the role of rezafungin for the prevention of invasive fungal infections in allogenic SCT, and evaluating pharmacokinetic properties in paediatric patients, are underway.

Ibrexafungerp - It is a semi-synthetic derivative of enfumafungin, a tri-terpenoid noncompetitive inhibitor of 1,3-B-D-glucan synthase enzyme complex. It is not an echinocandin from a chemical point of view, but its mechanism of action is similar to the one of the echinocandins, yet the exact point of drug binding to the enzyme might not be identical. It retains some activity against echinocandin-resistant Candida isolates, can be orally administered, and has shown high penetration into intra-abdominal lesions. Ibrexafungerp has shown encouraging results on treatment of non-neutropenic patients with invasive candidiasis, women with vulvovaginitis (current approved indication), and is under evaluation for the treatment of patients with IFI refractory to other treatments, patients with C. auris infections, or patients with invasive aspergillosis (treatment combined with voriconazole).[3-4]

Inhibitors of chitin synthase

Chitin, a polysaccharide, consists of N-acetylglucosamine (GlcNAc) monomers and constitutes an essential structural element of the fungal cell wall. Chitin biosynthesis is governed by chitin synthase, an enzyme that facilitates the assembly of uridine diphosphateN-acetylglucosamine (UDP-GlcNAc), which functions as a sugar donor.

Nikkomycin Z

Nikkomycin Z (NikZ) is a secondary metabolic compound synthesized by the actinomycete Streptomyces tendae . The chemical structure of NikZ comprises two principal components: a UDP-like aminohexane carboxylic acid (AHA) segment and a distinctive 4-hydroxypyridine-homothreonine (HPHT) peptidyl segment. The AHA portion of NikZ is structurally similar to the UDP moiety of UDP–GlcNAc, whereas the HPHT portion is capable of penetrating deeply into the substrate channel of the enzyme, thereby interfering with the extension of the chitin chain. This dual mechanism of action enables Nikkomycin Z to effectively inhibit chitin synthesis, thereby hindering fungal cell wall formation.

In vitro and *in vivo* experiments confirmed that Nikkomycin Z exhibits robust antifungal activity against a broad spectrum of pathogens. The compound demonstrates efficacy against dimorphic fungi-namely, *Histoplasma capsulatum, Coccidioides* spp., and *Blastomyces dermatitidis-as* well as against additional organisms such as *Sporothrix* spp., *Candida albicans*, and *Aspergillus* spp.

New Azoles

Opelconazole- It is a new synthetic azole designed for topical use and nebulised administration;

the drug shows high exposure and long retention at the site of infection (lungs). Since it is not absorbed, systemic effects such as toxicity and liver drug-drug interactions are avoided. It is an inhibitor of Aspergillus sterol 14-alpha-demethylase (CYP51 enzymes), similarly to posaconazole. Its spectrum of activity has not been well studied yet but it shows in vitro activity against C. auris, C. albicans, C. glabrata, C. krusei, Cryptococcus, A. terreus, and A. fumigatus. In vitro activity against A. flavus, A. niger, and Mucorales is poor. Data from animal models showed efficacy of opelconazole for the treatment and prevention of invasive pulmonary aspergillosis. Clinical data from human is still very limited.

Oteseconazole - It is a synthetic tetra-azole showing a high affinity to the fungal Cyp51 that confers the drug an enhanced specificity for fungal Cyp51 and fewer drug-drug interactions and good tolerability. It has shown in vitro activity against Candida and the potential activity against moulds is unknown. It has been under clinical evaluation for the treatment of superficial Candida infections including vaginitis and onychomycosis; it was approved by the FDA in 2022 for the treatment of vulvovaginal candidiasis.

Isavuconazole - Isavuconazole is a recently approved, second-generation triazole antifungal agent, available in oral and intravenous formulations. The oral preparation has high bioavailibility, and absorption is not significantly affected by food intake. It is approved for use against invasive aspergillosis and mucormycosis. In vitro data suggest that isavuconazole has broad-spectrum antifungal activity, including against candida SPP, Cryptococcus neoformans and trichosporon spp.

Polyenes

Encochleated amphotericin B- Amphotericin B was marketed in the 50's and shows the broadest fungicidal spectrum of in vitro activity. Its use is hampered by toxicity and formulation problems (highly water-insoluble and self-aggregate tendency). Vehicles in the formulation are needed and current formulations allow intravenous administration exclusively. The molecule gets protection into encochleating lipid-based vehicles, which means increasing chemical stability, safety and clinical efficacy, and allowing oral absorption. Encochleated amphotericin B is more stable than liposomes and less prone to oxidation, resists enzyme degradation, and shows slow release of the drug. The spectrum of activity is similar to other formulations of the drug (with limited activity against A. terreus, A. flavus, and A. nidulans) and shows dose-dependent activity. Data from animal models showed efficacy of encochleated amphotericin B for the treatment systemic candidiasis, cryptococcal meningitis, and invasive pulmonary aspergillosis. Clinical data from humans is still very limited.

Acyltransferase Enzyme (Gwt1) Inhibitor

Fosmanogepix. It is a prodrug (manogepix is the active moiety) that inhibits the fungal acyltransferase enzyme (Gwt1), an important component of the glycosylphosphatidylinositol (GPI)-anchored protein maturation pathway, that is essential for trafficking mannoproteins to the fungal cell membrane and wall. Given its new mechanism of action, it shows a broad spectrum of antifungal activity against Candida spp. (except for C. krusei), Cryptococcus and other non-Candida yeasts, Aspergillus spp and Fusarium spp, and

lacks of cross-resistance. The drug is under clinical evaluation for the treatment of candidiasis (including C. auris), aspergillosis, and other mould infections (Scedosporium and Fusarium). Preliminary data (including tolerability and clinical efficacy) are encouraging.[5,6]

Dihydroorotate Dehydrogenase Inhibitors

Olorofim

It is a first-in-class drug belonging to a new family of antifungal agents, the orotomides, whose mechanism of action lies on the inhibition of the pyrimidine bio-synthesis by blocking the action of the enzyme dihydroorotate dehydrogenase (DHODH). Olorofim shows a peculiar spectrum of activity and lacks in vitro activity against Candida spp. and Mucorales. In contrast, it has potent activity against most of clinically relevant Aspergillus spp. (including azole-resistant strains) and Scedosporium. Currently, olorofim is under evaluation for the treatment of invasive mould infections in patients with limited treatment options.[7,8]

Newer diagnostic methods for fungal infections primarily involve.

Molecular and Nucleic Acid-Based Methods

- **Next-Generation Sequencing (NGS):**
  A powerful tool that allows for the detection and identification of fungi by sequencing their genetic material, providing comprehensive and highly sensitive results.[9,10]
- **Real-time PCR:**
  Amplifies fungal DNA or RNA from clinical samples, offering rapid and sensitive detection of specific fungal species.
- **Molecular Biosensors:**
  Emerging technologies that use biosensors to detect fungal components, offering sensitive and potentially point-of-care detection.
- **Microfluidic Chip Technology:**
  Involves miniaturized lab-on-a-chip devices that can process samples and perform tests quickly and efficiently for fungal detection.

Breath-Based and Non-Invasive Methods

- Breath-Based Diagnostics: This method detects volatile organic compounds (VOCs) in a patient's breath, which are altered by the presence of a fungal infection. Various analytical techniques, such as gas chromatography and mass spectrometry, are used to analyze these VOCs.

Antigen-Based Rapid Tests

- Lateral Flow Assays (LFAs): A rapid, low-cost, and portable method for detecting fungal antigens.
- **Cryptococcal Antigen (CrAg) Lateral Flow Assay:**
  A prime example of an LFA, this test is used for early screening of cryptococcal infections, especially in high-risk populations like HIV patients, and is well-suited for resource-limited settings.[9,10]

Maldi-Tof Ms

Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDITOF MS) platforms are widely used in clinical microbiology laboratories to identify bacteria and have increasingly been applied to yeast identification from positive cultures. A sample colony from a culture plates placed onto a MALDI-TOF MS target plate and placed in an ionization chamber, generating a mass spectrum based on the mass-to-charge

ratios of highly conserved ribosomal proteins, generating signature peaks that are then compared to reference samples within a database. This technique requires no prior knowledge of the organism and can be performed on multiple samples simultaneously, giving results in less than 10 mins.

Conclusion

Newer antifungals and advanced diagnostic methods in mycology represent a significant step forward in combating invasive fungal infections, which are associated with high morbidity and mortality. Novel antifungal agents with improved efficacy, broader spectrum, and better safety profile address limitations of conventional drugs, including resistance and toxicity. Simultaneously, emerging diagnostic tools such as molecular assays, antigen detection and imaging techniques enable earlier and more accurate detection, guiding timely therapy. Together, these innovations enhance patient outcomes, reduce delays in treatment, and support precision medicine. Continued research and accessibility are essential to maximize their impact in clinical mycology worldwide.

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Section 4
Gastroenterology

Chapter

13

Microbiome-Targeted Therapies for IBD

Dr. Jacquiline D Shira

Introduction: The Pathogenic Rhythms of Dysbiosis

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and Ulcerative Colitis (UC), stands as a chronic, debilitating condition resulting from a complex interplay of genetic predisposition, environmental factors, and an aberrant immune response directed against the commensal gut microbiota.1 For decades, the therapeutic focus has centered on suppressing the hyperactive immune system through corticosteroids, immunomodulators (like thiopurines), and powerful biologics (such as TNF inhibitors and anti-integrins).[2] While these approaches have revolutionized IBD care, they are not curative, and a significant proportion of patients either fail to respond initially (primary non-response) or lose response over time (secondary non-response).[3] Furthermore, they carry risks of systemic side effects and infection.[4]

The last decade has witnessed a paradigm shift, propelled by advanced sequencing technologies, revealing a consistent and profound dysbiosis—an imbalance in the gut microbial community—in IBD patients.[5] This dysbiosis is characterized by a significant loss of microbial diversity, a reduction in beneficial, short-chain fatty acid (SCFA)-producing bacteria (like Faecalibacteriumprausnitzii and Bifidobacterium species), and an expansion of potentially pro-inflammatory pathobionts (such as Enterobacteriaceae and Proteobacteria).[6] This realization has established the gut microbiota not just as an innocent bystander but as a key pathogenic driver of chronic inflammation, making it an irresistible and rational therapeutic target.[7]

This update explores the evolving landscape of microbiome-targeted therapies, from the established principles of Fecal Microbiota Transplantation (FMT) to the precision engineering of next-generation Live Biotherapeutic Products (LBPs) and beyond, all aimed at restoring the delicate microbial harmony essential for sustained remission.

The Rationale: Why Target the Microbiome?
The gut microbiota exerts its profound influence on IBD pathogenesis through several mechanisms:[8]

1. Barrier Function Disruption: Dysbiosis compromises the integrity of the intestinal epithelial barrier, leading

to increased permeability (leaky gut).[9] This allows bacterial products (e.g., Lipopolysaccharides) to translocate across the mucosa, perpetually triggering the underlying immune system.

2. Metabolite Imbalance: Commensal bacteria are crucial for producing beneficial metabolites, most notably Short-Chain Fatty Acids (SCFAs) like butyrate, propionate, and acetate.[10] Butyrate is the primary energy source for colonocytes and possesses potent anti-inflammatory and immunoregulatory properties, often lacking in IBD.[11]
3. Immune System Education: The microbiota dictates the maturation and function of the host immune system.[12] Dysbiosis shifts the balance towards pro-inflammatory Th1 and Th17 cells and away from protective regulatory T cells (Tregs), fueling the chronic inflammatory cycle.[13]

By targeting the microbiome, the goal is not merely to treat symptoms but to re-establish eubiosis, thereby addressing one of the core etiologies of the disease.[14]

1. Fecal Microbiota Transplantation (FMT): The Proof of Concept

FMT, the infusion of stool from a healthy, rigorously screened donor into the gastrointestinal tract of a recipient, provides the strongest clinical proof-of-concept for microbiome-based therapy.

Efficacy and Current Status in IBD

While FMT has achieved spectacular, guideline-endorsed success rates (often >90%) in treating recurrent Clostridioides difficile infection (rCDI), its role in IBD is more nuanced and disease-specific:

- Ulcerative Colitis (UC): Randomized controlled trials (RCTs) have shown modest but significant efficacy in inducing clinical and endoscopic remission in patients with active mild-to-moderate UC.15 Pooled analyses and meta-analyses, including high-quality recent studies, suggest that FMT can achieve remission rates superior to placebo (ranging from $\sim 20\%-40\%$ clinical remission). Importantly, factors such as the number of FMT treatments, the route of administration (lower GI is often preferred), and the specific composition of the donor stool are key variables that influence success.
- Crohn's Disease (CD): The efficacy of FMT in CD has been generally less pronounced and more inconsistent across studies compared to UC. CD, with its transmural inflammation and common involvement of the small bowel, presents a more complex target for colonic microbial restoration. FMT is currently not a recommended standard therapy for active CD outside of a clinical trial.
- Safety and Standardization: While FMT is generally well-tolerated, safety remains a paramount concern, particularly in immunosuppressed IBD patients. Risks include the theoretical transmission of undetected pathogens and, in rare cases, the induction of new autoimmune phenomena. This necessitates highly stringent donor screening protocols and has spurred the industry towards developing standardized, defined microbial products.

2. Live Biotherapeutic Products (LBPs) and Next-Generation Probiotics

The variability and safety concerns associated with donor stool have accelerated research into defined microbial cocktails, now formally categorized by the

FDA as Live Biotherapeutic Products (LBPs)—live organisms applicable to the prevention, treatment, or cure of human disease.[16]

Defined Microbial Consortia

Instead of the "black box" of whole stool, LBPs use a precisely defined mix of beneficial bacteria aimed at restoring the lost functions of the IBD gut.

- Rationale: These products typically contain multiple commensal species (often 10 to 50 strains) chosen specifically for their ability to produce SCFAs, strengthen the gut barrier, or directly modulate the immune response.
- Clinical Momentum: Several multi-strain LBPs are in various stages of clinical development for IBD. The hypothesis is that a multispecies cocktail is necessary to achieve the ecological complexity and functional redundancy required to displace pathobionts and successfully engraft in a hostile, inflamed gut environment. Early-phase trials have shown promising signals in both UC and CD, focusing on strains like Faecalibacteriumprausnitzii, Bifidobacterium, and Lactobacillus.

Engineered Biotherapeutics

The cutting edge of LBP research involves synthetic biology to engineer bacteria to perform specific therapeutic functions:[17]

- Targeted Delivery: Bacteria can be genetically modified to serve as in vivo bioreactors, producing and delivering therapeutic molecules directly to the inflamed mucosal surface. For example, some strains are engineered to secrete high levels of anti-inflammatory cytokines (e.g., IL-10) or specific enzymes that degrade pro-inflammatory factors, offering highly localized, high-concentration therapy with minimal systemic exposure.
- Host-Response Modulation: These strains can also be engineered to respond to specific signals in the inflamed gut (e.g., high levels of reactive oxygen species), ensuring the therapeutic payload is released only at the site of disease activity.

3. Prebiotics, Synbiotics, and Postbiotics

While less revolutionary than FMT or LBPs, established approaches continue to be refined:

- Prebiotics: These are non-digestible food components (like inulin or fructans) that selectively stimulate the growth and/or activity of beneficial bacteria already residing in the colon.18 They are essentially feed for the good microbes. Clinical data for prebiotics alone in IBD is mixed, often showing limited efficacy in severely inflamed states.
- Synbiotics: The synergistic combination of prebiotics and probiotics (e.g., a Bifidobacterium strain paired with inulin).19Synbiotics are designed to maximize the survival and engraftment of the administered probiotic strain by providing its preferred nutrient source.20 This combined approach has shown more consistent positive signals in reducing clinical symptoms and improving endoscopic scores, particularly in UC.
- Postbiotics: This emerging class refers to the beneficial metabolic products or inanimate microorganisms released by commensal microbes (e.g., purified SCFAs, cell wall fragments). The advantage is stability, dose control, and the elimination of the need for the live bacterium to engraft. Delivering butyrate directly, for instance, is a highly attractive therapeutic strategy currently

under active investigation.

4. Beyond Bacteria: Virobiota and Mycobiota

A deeper understanding of dysbiosis now extends beyond the bacterial component:[21]

- Bacteriophage Therapy (Phages): Phages are viruses that specifically target and lyse bacteria.22 They can be used as precision antibiotics to selectively eliminate pathogenic or pathobiont bacterial species (e.g., specific strains of E. coli or Proteobacteria) without harming beneficial species. Phage-based therapeutics for IBD are in preclinical and early clinical stages, offering a high-precision tool to prune the "bad" components of the dysbiotic flora.
- Mycobiota (Fungi): Fungal species, particularly an increase in Candida albicans, have been observed in IBD patients.23 Emerging therapies are exploring antifungal approaches to rebalance the fungal-bacterial ratio, which may also be critical in restoring mucosal immunity.

Conclusion

Personalizing the Next Generation of Care

The therapeutic landscape for IBD is undergoing a profound transformation driven by microbial science. FMT provided the undeniable proof that manipulation of the gut ecosystem can modify disease course. However, the future lies in precision and personalization.

The current trajectory points toward a patient-centric, stratified approach:

1. Microbial Profiling: Utilizing advanced metagenomics to precisely profile a patient's unique dysbiosis signature.
2. Targeted Intervention: Matching the microbial defect with the most appropriate therapy—whether it is a defined multi-strain LBP, a synthetic E. coli that produces IL-10, or a bacteriophage cocktail to clear a specific pathobiont.
3. Combination Therapy: Integrating microbiome-targeted therapies as adjuvants to conventional immunosuppression to achieve accelerated and deeper remission with lower doses of traditional drugs.[24]

By harnessing the power of the gut's "second genome," the medical community is moving closer to achieving the ultimate goal in IBD management: safe, sustained, and personalized mucosal healing. The promise is not just to treat inflammation, but to restore true biological and microbial resilience.

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Chapter

14

Acute on Chronic Pancreatitis - The Missing Link

Dr. Dibya Jyoti Sharma, Dr. Abhinav Nath, Dr. Ashok Kumar Goala

ABSTRACT

Acute presentation upon chronic pancreatitis (ACP) and an initial acute pancreatitis episode are not the same in terms of pancreatitis severity and progression. The term "acute on chronic pancreatitis" (ACP) describes inflammation of the pancreas combined with the gland's production of free radicals and oxidative stress, which results in abrupt, excruciating abdominal pain that can range in severity. The clinical course, complications and outcome differ significantly between AP and ACP patients. The gap between diagnosis of acute pancreatitis and acute on chronic pancreatitis matters clinically because under-recognition can delay appropriate interventions (imaging, targeted supportive care or endoscopic/surgical drainage) and affect prognostication. It also matters scientifically because without uniform definitions we cannot reliably identify risk factors, compare outcomes, or develop ACP-specific severity scores and treatment trials. Therefore, early recognition can help in improving prognosis of patients with ACP in clinical setting.

Keywords : Acute on chronic pancreatitis,Atlanta,Complications, Pseudocyst, Amylase, Outcome,Organ failure

Introduction

Pancreatitis (acute & chronic) are two manifestations of same disease process and both share similar etiological factors including drugs, alcohol as well as metabolic disorders such as hypercalcemia and hypertriglyceridemia. After surviving the initial episode, people with acute pancreatitis (AP) can experience recurrent pancreatitis episodes (RAP) in the tune of 10-35% cases while some other (10-13%) can evolve into chronic pancreatitis(CP).[1,4] CPresults in progressive, irreversible changes to the pancreatic parenchyma (atrophy, fibrosis) as well as exocrine and endocrine pancreatic insufficiency due to persistent or chronic inflammation of pancreas.[2] Limited number of studies have investigated the condition of acute flare upon chronic pancreatitis and there is no universally accepted

definition of acute on chronic pancreatitis (ACP). Furthermore, the existing literature offers minimal insight into the behaviour, clinical pattern and natural history of ACP patients.Therefore, it is essential to differentiate ACP from AP without underlying CP, because gaining a deeper understanding of the severity and progression of ACP can improve risk assessment and enhance patient care.[3]

A patient is diagnosed with acute pancreatitis if they exhibit two or more of the following three findings: (A) Characteristic abdominal pain (acute onset, persistent and severe epigastric pain that often radiates to the back). (B) elevated serum amylase and/or lipase levels greater than three times the upper normal limit (C) characteristic findings in imaging studies, including abdominal ultrasonography or computed tomography (CT), consistent with acute pancreatitis. Although there no standard definition of ACP, Sharma et al; has defined ACP as patients with AP (diagnosed as per revised Atlanta classification) requiring hospitalisation with evidence of underlying CP (diagnosed by abdominal Ultrasound, CT scan, MRI or EU).[4]

Acute on Chronic Pancreatitis(ACP) may clinically overlap with de-novo acute pancreatitis (AP) but as ACP arises on a fibrotic, structurally altered pancreas, so its pathophysiology, biomarkers and imaging appearances differ.As elevation of pancreatic enzyme are often modest in ACP (frequently <3× ULN) due to underlying fibrosis as well thechronic changesdistort anatomy of pancreas, relying on amylase/lipase or single imaging snapshots can under-recognise true acute activity among ACP patients.[5]

The discrepancy in the severity of attack between AP and ACP was explained by the presence of increased fibrosis surrounding the intra-pancreatic fat which prevents the spread of inflammation in the pancreas. Fibrosis reduced lipolytic flux between acinar cells and adipocytes limiting the acinar adipokines level and also confined the spread of fat necrosis (FN) and peri fat acinar necrosis (PFAN). It also contributed to truncated acinar cell necrosis in comparison to AP (with underlying naive pancreas) where the cushionof fibrosis surrounding the pancreas is not available which lead to widespread necrosis resulting in organ failure and worse outcome.[5,7]

The Atlanta classification divides AP into three categories: mild acute pancreatitis (MAP), moderate severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP). Whereas MSAP is associated with transient organ failure and/or local/systemic issues within 48 hours, and MAP is unrelated to either of these disorders. SAP is associated with persistent organ failure involving one or more organs. Persistent organ failure was defined as having a modified Sequential Organ Failure Assessment (SOFA) score of at least 2 for 48 hours or longer involving at least one organ system (e.g., the respiratory, cardiovascular, or renal systems.Acute peri-pancreatic fluid collection (APFC), pancreatic pseudocyst, acute necrotizing collection (ANC), and walled-off necrosis (WON) are examples of local complications. Organ failure as well as local complications in ACP is also defined in similar pattern as in AP.[4,6]

Etiological Factors

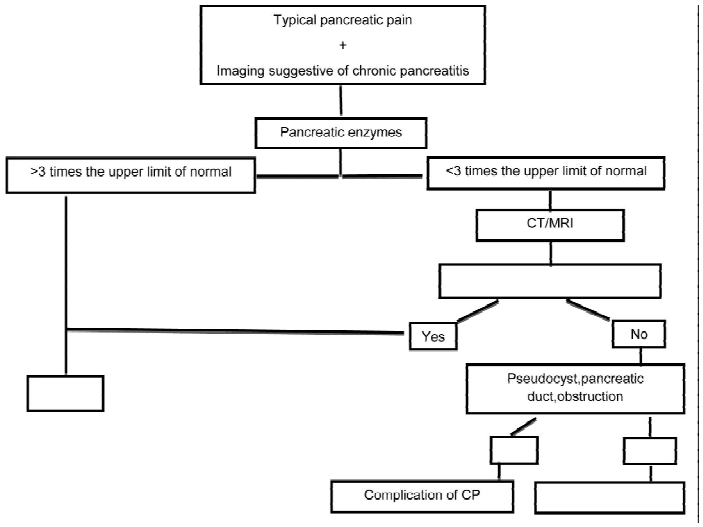
In case of acute pancreatitis, the major etiological factors consist of alcohol consumption and gallstones with alcohol consumption being the predominant among the younger age groups and gallstones being the primary

course among the older generation. Other causes include pharmaceuticals (azathioprine, 6-mercaptopurine, didanosine, valproic acid, angiotensin-converting enzyme inhibitors, and mesalamine); hypertriglyceridemia; gain-of-function mutations in the PRSS1 gene; autoimmune pancreatitis; pancreatic duct injury; and post-endoscopic retrograde cholangiopancreatography (ERCP). Idiopathic causes, biliary blockage, choledochal cysts, toxins, infections (including mumps, coxsackievirus, hepatitis B, and cytomegalovirus), biliary sludge and microlithiasis, and hypercalcemia are other uncommon causes.[7]

The major causes of development of CP include alcohol followed by autoimmune, genetic mutations (SPINK1), tropical, cystic fibrosis, tumour and hypertriglyceridemia while incidence attributing to gall stone is uncommon. The causes of acute attack in ACP are quite similar to etiological factors of AP with increased alcohol intake, gall stone while smoking augment the frequency of attacks in ACP.[8]

Diagnosis:

ACP as such has no defined diagnostic criteria but it is often suspected in patients presenting in a severe pain with prior diagnosis of chronic pancreatitis on imaging. As already stated, the enzymes level(Amylase, lipase) is not raised to 3 times the upper limit in many patients due to underlying fibrosis ofpancreas, therefore amylase, lipase < 3 times normal does not exclude ACP. Hence cross-sectional contrast enhanced imaging is preferred for diagnosis of ACP. Cross sectional imaging of ACP usually detects increased pancreatic and peripancreatic odema, inflammation of surrounding tissue,inflammatory masses and acute splanchnic thrombosis as well as pseudocyst formation.[4,5]



Flowchart 1 : Diagnosis of Acute on Chronic pancreatitis

Feature	Acute Pancreatitis (AP)	Acute-on-Chronic Pancreatitis (ACP)
Underlying gland	Normal pancreas	Fibrotic, duct-distorted CP
Proportion in cohort	~90%	~10%(25% in other series)
Mean age (years)	62.6	56.5
Male:Female	1:1.2	4:1
Enzyme elevation	High(>3 ×ULN)	Low or normal
Organ failure	Common	Less frequent(P=0.019)
ICU need	24%	9%(p=0.005)
Local complications	15%	25%(p=0.049)
Mortality	3-5%(SAP)	ACP Mild-0% Severe-2-3%
In-hospital outcome	Less favourable	More favourable
Pathology driver	Enzymatic autodigestion	Chronic fibrosis+Ductal block

Complications, Prognostic indicators and Outcome

Despite the structural damage present in CP, when patients with CP experience an acute exacerbation or attack (ACP), their systemic inflammatory response, organ-failure rates and in-hospital mortality are lowerthanthosein AP occurring de novo. However, ACP patients typically present with worse baseline imaging (lower CTSI with CTSI<6-51%) and worse nutritional status (lower albumin, lower BMI)suggesting a complex interaction betweenchronic disease burden and acute insult.

The identification of the creatinine/albumin ratio, respiratory failure and BUN as key predictors highlights the interplay of renal dysfunction, nutritional status, and respiratory compromise rather than just pancreatic enzyme or morphological severity.[5]

Local Complications

In terms of local complications, among acute necrotizing pancreatitis(ANP) patients' necrosis of pancreatic tissue (Acute necrotic collection - ANC) due to severe inflammation was the main cause of local morbidity followed by acute peripancreatic fluid collection (APFC) (sterile fluid around the pancreas) seen in acute edematous or interstitial pancreatitis (AEP) which usually resolves spontaneously. Pseudocyst formation (encapsulated fluid collection occurring weeks after an attack) was the third main common complication in cases of acute pancreatitis.Walled Off necrosis (WON) as a complication was seen in very few cases in ANP. However, in case of ACP, the most common complication was pseudocyst formation (26 %) followed bynecrosis of pancreas with collection (ANC) (22.2% cases), the necrosis being delayed due to the underlying fibrosis often associated with ACP. Among the studies it was often seen that majority of cases of pseudocyst required pig tail drainage (11% cases) under imaging guidance constituting one of the reasons of increased hospital stay in ACP.[4,5]

Systemic / Organ Complications

A score of =2 in the modified Marshall scoring system for organ dysfunction was defined as the presence of organ failure, and if organ failure (OF) resolved within 48 hours, it was labelled as transient (4.4%), and when it persisted >48 hours (8.8%), it was labelled as persistent. (3)According to the studies conducted, in case of acute pancreatitis the most common systemic complications were sepsis followed by respiratory complications. Other complications include renal failure and circulatory shock whereas ACP systemic complications are more dependent on the age (37.3+/-13.8 years),sex (Male-75.6%) and weight loss (BMI - <18-31%) with Ards (37.8%) being the most general complication.[4,5]

Period of hospitalization and morbidity

The length of hospitalisation in patients with classic Acute Pancreatitis (without CP) is usually prolonged compared with ACP patients. While mortality rate in SAP(8%) without CP is higher than severe ACP(4%) patients and so is the rate of organ dysfunction as compared to ACP. In comparing imaging scores, ACP patients had higher Balthazar scores and worse CT severity index (CTSI) compared to AP without CP.[4,5,7]

Conclusion

The data compiling from various reports across the world support the concept that ACP is not simply "another AP" but has a distinct prognostic profile — thus reinforcing the need for tailored risk-stratification and management pathways.Closing the gap requires harmonised diagnostic criteria, prospective registries, and studies that compare biomarkers, imaging protocols and outcomes specifically in ACP versus AP and stable CP.In short, ACP is common and important, yet under-characterised — recognising it as a distinct clinical entity is the first step toward better diagnosis, tailored management andimproved patientoutcomes.

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Chapter

15

Antifibrotic Therapies in MAFLD: Where do we Stand?

Dr. Manabendra Nayak

ABSTRACT

Metabolic-associated fatty liver disease (MAFLD) has rapidly become the most common chronic liver disease, causing major adverse liver outcomes, and affects upto 38% of the global adult population. The underlying pathophysiological mechanism are intricate and involve various factors. Lipid peroxidation, pro-inflammatory factors, insulin resistance and dysbiosis of intestinal microbiota are considered as the pathogenic mechanism of MAFLD. It has become apparent that MAFLD increase the risk of chronic kidney disease, developing new onset heart failure and atrial fibrillation. MAFLD is a risk factor for incident type 2 diabetes mellitus, obesity and metabolic syndrome. At present a great impetus for development of Agents targeting MAFLD is going on. Accumulating data on possible treatment options for liver fibrosis are emerging in the literature. Research has demonstrated that Toll like receptors (TLRS) plays a pivotal role in the progression of MAFLD by facilitating the pathophysiological mechanisms. The potential therapeutic approaches for MAFLD that targeting TLRs signalling pathways, including the use of plant extracts, traditional Chinese medicines, probiotics, pharmaceuticals such as peroxisome proliferator activated receptor antagonists and farnesol agonists and lifestyle modification such a dietary changes and physical exercise also considered.

Introduction

The terminology of MAFLD was defined by evidence of hepatic steatosis based on histopathological examination, imaging, or blood biomarkers in association with one of the three criteria, including obesity, type 2 diabetes melitus and evidence of metabolic dysregulation with at least two metabolic risk factors, including high waist circumference, hypertriglyceridemia, hypertension, low high density lipoprotein, insulin resistance and highsensitivity C-reactive protein level. In addition factors have been found to be associated with MAFLD, including sex, race, genetic predisposition, age, diet and gut microbiota.[1] In 2020, the APASL recommendations reclassified non-

alcoholic fatty lever disease (NAFLD) as MAFLD, removing the exclusionary diagnostics criteria.[2] The gold standard for MAFLD diagnosis is liver biopsy, an invasive, method that carries risk. Nowdays, non invasive scoring tools are being developed for MAFLD patient stratification such fibrosis score. In addition, NASH clinical research network Score (NASH CRN) includes the fibrosis stage, and both are very useful to validate the efficacy of treatment.[3] For MAFLD no effective treatment currently available, which can cure the disease, so current treatment consists on the reduction of body weight through, lifestyle intervention. New drug development focuses on the restitution of metabolic derangements and halting inflammatory and fibrogenic pathways.

Which Patients Should be Treated?

For all MAFLD therapies, the effects on systemic health and overall survival are a key consideration, because mortality in patients with MAFLD is significantly driven by cardiovascular events. Recent studies have suggested that MAFLD can be divided into two distinct subgroups, presenting either with an aggressive disease limited to the liver, or a more systemic disease associated with a higher risk for cardio metabolic disease.4 According to EASL-EASD-EASO clinical Practice Guidelines recommend that adults with non-cirrhotic MAFLD and = stage F2 liver fibrosis should be considered for a MAFLD-targeted treatment with resmetirom, the first FDA approved treatment for MAFLD, whereas there are no recommended MAFLD targeted pharmacotherapy's for the cirrhotic stage.[5]

Therapeutic Strategies

There is no unified standard for effective treatment strategies for MAFLD. Clinical treatment options typically rely on altered life style, weight loss and structured exercise. As a key link in MAFLD, treatment strategies targeting TLR4 signalling pathways include various medicine like plant extracts, traditional Chinese medicines, probiotics, as well as commonly used medicines like peroxisome proliferator-activated receptor (PPAR) antagonists and farnesol X receptor (FXR) agonists.[6]

Peroxisome Proliferator Activated Receptors (PPAR)

In MAFLD, PPARs are dysregulated, and the effect of the agonist for PPAR α / γ receptor, pioglitazone, is associated with improvement in steatosis, inflammation and hepatic biomarkers, making it a very compelling choice for MAFLD therapy.[7] Another member of the PPAR family being considered for the treatment of MAFLD is the dual PPAR-α and PPAR- γ agonist saraglitazar for MASH in India, but not yet in other countries.[8] Furthermore, this drug showed confirmed beneficial effects on the liver in a placebo controlled RCT named EVIDENCES-IV, conducted in the US on patients with MAFLD or MASH. Lanifibranor is an experimental triple PPR $\alpha/\beta/\gamma$ agonists. Lanifibrator was well tolerated, and the percentage of patients with meaningful improvements in steatosis, activity and fibrosis scores was significantly higher in the Lanifibrator treated phase 11b study.[9] Seladelpar (MBX-8025) is the only selective PPARS agonist currently in development for the treatment of MAFLD.

Thyromimetics

Clinical evidence for the close relation between thyroid hormones and MAFLD include the fact that hypothyroidism is common in patients with MAFLD.10 In patients who progress to NASH, in parallel with the steatosis increasing, the activity of THR-ß receptor in liver decreases.[10] Resmetirom is the first oral liver directed THR- ß1 selective agonist. In a clinical trial, resmetirom achieved NASH resolution in a subset of patients with control biopsies. Liver steatosis and liver stiffness improved together with fibrosis biomakers, hepatic enzymes and a significant reduction in MAFLD activity was observed.[11] Another orally administered THR-ß agonist targeting the liver, VK 2809, is still under investigation and has not reached the approval phase but shows promising potential.

Incretin Mimetics

Incretins are hormones that are released from the enteroendocrine cells in the ileum and colon. Glucagon-like peptide-1 (GLP-1) and glucose dependent insulin tropic polypeptide (GIP) are secreted by the L-cells and K-cells of intestine. A viable therapeutic option for the treatment of MAFLD is the drug semaglutide. Study reported that semaglutide significantly reduced hepatic steatosis, inflammation, hepato cellular ballooning and Liver stiffness, while the effect on reducing fibrosis stage is still uncertain.12 The dual GLP-1 and glucagon receptor agonist efinopegdutide (MK-6024) is a subcutaneously administered drug that was developed for the treatment of MAFLD and is currently undergoing clinical trials.[13] There are also novel triple GLP 1R/GCGR/GIPR agonists being evaluated such as HM15211.

Sodium-Glucose Co Transporter 2 (SGLT2) Inhibitors:

Reduction of inflammation, steatosis and fibrosis have been suggested as beneficial effects on the liver, for which the clinical efficacy of SGLT2 inhibitors is being investigated in numerous clinical trials.[14] SGLT2 inhibitors reduced body weight, improved dyslipidemia and decreased liver fat content and markers of liver injury, such as ALT and gammaglutamy transferase, while they reduced non-invasive measurements of fibrosis, including liver shiftiness, FIB-4 and the MAFLD fibrosis score in some patients.[14] SGLT2 inhibitors, including empagliflozin, dapagliflozin, canagliflozin and ertugliflozin, have been investigated in patients with MASLD in clinical trials.[14]

Fibroblast Growth Factor 21 (FGF-21) Analogues:

FGF21 analogues, including afruxifermin, pegozafermin, and efimosfermin are being investigated for their therapeutic potential in MAFLD and Liver fibrosis.[15] The action of the hormone fibroblast growth factor 21 (FGF-21) in the liver leads to a reduction in liver fat, as it stimulates fatty acid oxidation and the secretion of triglycerides and very low-density lipoproteins and inhibits de novo Lipogenesis. An FGF-21 analag pegozafermin (B1089-100) was developed as subcutaneous injection for the therapy of MAFLD as well as severe hypertiglyceridemia.[16] Efruxifermin, which exerts an agonistic effect in FGF-21, is another promising drugs for MAFLD treatment.[15]

Long-Chain Omega-3 Fatty Acids:

Leosabutate, a structurally modified omega-3 fatty acid, lead to significant decreases in MAFLD and

fibrosis biomarkers independent of fibossis stage and disease severity in a clinical trial.

Probiotics

Several specific strains of probiotics, such Lactobacillus rhamnossus, Lacto bacillus kefiranafaciens, Bifidobacterium adolescents and Grifola frondosa are considered to treat MAFLD by inhibiting the TLR4/ MY988/JNK/NF-KB/TRAF6/ NLRP3 pathway, reducing the release of inflammatory factors.[17]

Altered Lifestyle

The bioactive components of the diet can have a positive impact on MAFLD by modulating the activity and structure of gut microbiota.[17] This leads to the inhibitions of the TLR4/NEKB signalling pathway, thereby suppressing the expression of inflammatory factors TNF-a and IL-6 as well as preventing de nove adipogenesis.

Plant Extracts

Several studies have demonstrated that certain tea extracts have been provide to reduce the levels of promflammatory factors TNF-a, IL-6, Rnd IL-1ß by improving intestinal microecology and inhibiting TLR4/ NFKB/NLRP3 signalling pathway transduction thereby inhibiting the progression of MAFLD.

Conclusion

The global health problems caused by The MAFLD pandemic cannot be ignored. Given that MAFLD is a multisystemic disease, a multidisciplinary approach is required, and it is likely that monotherapy to treat MAFLD will not provide complete treatment success. Hence, a strategy for combining different types of drugs is necessary. To achieve this, combination therapy targeting different pathological pathways and organ systems needs to be more intensively explored.

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Section 5
Haematology

Chapter

16

Gene Therapies for Hemophilia: A New Era

Dr. Anupam Dutta

ABSTRACT

Gene therapy has emerged as a transformative approach for haemophilia, aiming to achieve sustained endogenous production of clotting factors after a single infusion. Most clinical programs employ adeno-associated viral (AAV) vectors to deliver functional factor VIII (FVIII) or factor IX (FIX) genes to hepatocytes, resulting in long-term secretion of clotting factors into circulation. Landmark trials in haemophilia B using FIX-Padua transgenes (e.g., etranacogene dezaparvovec and fidanacogene elaparvovec) have shown durable expression of FIX at 20–40% of normal with profound reductions in bleeding and factor usage. In haemophilia A, AAV-mediated FVIII delivery has achieved clinically meaningful expression, though durability remains a challenge due to the larger and more complex FVIII gene. Immune responses to viral capsids and pre-existing neutralizing antibodies represent additional barriers. Ongoing innovations in vector design, immune modulation, and alternative platforms promise to broaden access, making gene therapy the closest step yet toward a functional cure for haemophilia.

Keywords: Hemophilia, Gene Therapy, Adeno-Associated Virus (AAV), Factor VIII / Factor IX, Clinical Trials.

Introduction

Haemophilia is a congenital bleeding disorder caused by deficiency of clotting factor VIII (haemophilia A) or factor IX (haemophilia B), leading to recurrent haemarthrosis, soft tissue bleeding, and potentially life-threatening hemorrhage. For decades, replacement therapy with plasma-derived or recombinant factor concentrates has remained the mainstay of management, yet it requires lifelong intravenous infusions and carries the risk of inhibitor development. More recently, non-factor agents such as emicizumab have broadened the therapeutic armamentarium, but they too necessitate repeated administration. Against this backdrop, gene therapy has emerged as a paradigm-shifting strategy,

aiming to provide long-term endogenous production of the missing clotting factor after a single infusion. Most clinical programs have employed adeno-associated viral (AAV) vectors to deliver a functional copy of the FVIII or FIX gene to hepatocytes, which then synthesize and secrete the clotting factor into the circulation.

History of Gene Therapy in Haemophilia

The concept of genetic correction for haemophilia dates back over three decades, with early preclinical experiments in murine and canine models demonstrating durable expression of clotting factors. The first human gene transfer trials in the late 1990s used retroviral and adenoviral vectors, but were hampered by immune responses and short-lived efficacy. The real breakthrough came with the use of liver-directed AAV vectors, which provided a favorable safety profile and sustained transgene expression. A landmark phase 1/2 study published in 2011 showed that a single intravenous infusion of an AAV vector encoding FIX could result in factor IX expression for more than a year, reducing or eliminating the need for prophylactic replacement[1].

Building on this foundation, subsequent trials demonstrated substantial progress. In haemophilia B, the HOPE-B trial evaluated etranacogene dezaparvovec, an AAV5 vector carrying the FIX-Padua variant, showing sustained FIX activity with significant reduction in annualized bleeding rates and factor use[2]. In haemophilia A, the GENEr8-1 trial with valoctocogene roxaparvovec, an AAV5-FVIII vector, reported durable increases in FVIII levels with meaningful reductions in bleeding and factor consumption, though expression declined gradually over time [3]. More recently, long-term follow-up studies have confirmed persistence of clinically relevant clotting factor expression for up to six years in some participants[4].

Thus, gene therapy for haemophilia has evolved from theoretical promise to clinical reality, with regulatory approvals now granted in Europe and the United States. While challenges such as variability in transgene expression, immune-mediated liver inflammation, durability of response, and accessibility remain, gene therapy represents the closest step yet toward a functional cure for this lifelong disorder.

Basic Science and Mechanism of Viral Vector–Based Gene Therapy

Gene therapy using viral vectors is based on the principle of delivering a functional copy of a defective gene into target cells, thereby restoring the production of the missing or dysfunctional protein. Among the various viral platforms, adeno-associated virus (AAV) vectors have become the leading choice in haemophilia because of their favorable safety profile, lack of pathogenicity, and ability to transduce hepatocytes efficiently. In this approach, the viral capsid is engineered to carry a recombinant genome containing the complementary DNA (cDNA) of factor VIII or IX under the control of a liver-specific promoter. Once infused intravenously, the AAV vector enters hepatocytes and delivers the transgene to the nucleus, where it persists as episomal DNA without integrating into the host genome, thus minimizing insertional mutagenesis risk. The transgene is then transcribed and translated by the host's cellular machinery, leading to continuous secretion of clotting factor into the circulation. However, because AAV vectors are non-replicating and episomal, expression may wane over time as hepatocytes divide,

and immune responses against the viral capsid can limit transduction efficiency. Despite these challenges, viral vector–based gene therapy exemplifies a highly targeted and durable molecular strategy to correct monogenic diseases such as haemophilia.

Present Scenario of Gene Therapy in Hemophilia B

The field of gene therapy for haemophilia B has advanced remarkably in the past decade, with several pivotal clinical trials demonstrating durable factor IX (FIX) expression, dramatic reductions in bleeding rates, and decreased dependence on prophylactic infusions. The most clinically advanced approaches have utilized adeno-associated virus (AAV) vectors for liver-directed delivery of a functional FIX transgene, often incorporating the high-activity Padua variant (FIX-R338L), which yields 5–8 fold higher specific activity than wild-type FIX. Among the landmark trials, the HOPE-B phase 3 study evaluated etranacogene dezaparvovec, an AAV5 vector encoding FIX-Padua, in 54 patients with severe or moderately severe haemophilia B. Results demonstrated a mean FIX activity of ~36% of normal at 18 months, accompanied by a 64% reduction in annualized bleeding rates (ABR) and a 97% reduction in annualized FIX use compared with baseline prophylaxis [2]. Importantly, the trial included participants with pre-existing AAV5 antibodies, broadening the potential applicability of this therapy.

Longer-term follow-up has confirmed the durability of these results. A five-year extension of the etranacogene dezaparvovec phase 2b trial showed stable FIX expression at ~20–25% of normal, with sustained hemostatic efficacy and near elimination of spontaneous bleeds, providing strong reassurance about the persistence of benefit [5]. Similarly, the BENEGENE-2 phase 3 trial of fidanacogene elaparvovec (AAV vector encoding FIX-Padua) demonstrated median FIX activity levels of ~27% at two years, with 94% of patients discontinuing routine prophylaxis and marked reductions in both treated bleeds and factor use [6]. These outcomes are clinically significant, as FIX levels above 12–15% are generally sufficient to convert severe haemophilia into a mild phenotype, thereby preventing spontaneous bleeding episodes.

The regulatory impact of these results has been profound. In 2022, etranacogene dezaparvovec (marketed as Hemgenix) received approval from the U.S. Food and Drug Administration and the European Medicines Agency, making haemophilia B the first monogenic disorder with a licensed in vivo gene therapy. While enthusiasm is high, several challenges remain, including variability in individual FIX expression, the need for immunosuppression in some patients to control AAV-related liver inflammation, and uncertainty regarding very long-term durability beyond 10 years. Nevertheless, the present scenario firmly establishes gene therapy as a transformative option for haemophilia B, moving the field closer to the goal of a functional cure.

Gene Therapy in Hemophilia A: Challenges, Limitations, and Strategies

Gene therapy for haemophilia A has generated substantial enthusiasm, yet it has proven to be more technically challenging compared to haemophilia B. The central obstacle lies in the large size and complexity of the factor VIII (FVIII) gene, which at ~9 kb is too long

to be fully accommodated within standard adeno-associated virus (AAV) vectors. To address this, investigators developed B-domain deleted (BDD) FVIII constructs that retain procoagulant activity but fit within the AAV packaging capacity. Despite this innovation, clinical trials have revealed unique hurdles in durability, variability of expression, and immunogenicity.

The GENEr8-1 phase 3 trial of valoctocogene roxaparvovec (AAV5-BDD-FVIII) reported promising early results, with mean FVIII activity of ~42 IU/dL at 1 year and significant reductions in bleeding and factor usage. However, expression declined progressively to ~24 IU/dL by year 2, raising concerns about long-term persistence [7]. This decline appears to be multifactorial, involving episomal loss in dividing hepatocytes, possible transcriptional silencing, and vector-related immunogenicity. Additionally, FVIII transgene expression is more variable between individuals than FIX, complicating dose-response predictability.

Another limitation is immune-mediated hepatotoxicity. Elevations in liver transaminases, likely reflecting T-cell responses against AAV capsid antigens or transduced hepatocytes, have necessitated prolonged corticosteroid use in a significant proportion of participants. While most patients maintain factor expression, this immune modulation adds complexity and potential risk [8]. Furthermore, pre-existing neutralizing antibodies against AAV capsids can exclude many candidates from treatment, highlighting the need for novel vector engineering.

Several strategies are under active investigation to overcome these challenges. Capsid optimization seeks to enhance hepatocyte tropism and reduce immunogenicity, while codon optimization and novel promoter elements are improving FVIII expression efficiency. Alternative delivery platforms, including lentiviral vectors targeting hematopoietic stem cells, are also being explored, offering the possibility of integration and long-term stability. Moreover, advances in non-viral delivery systems such as lipid nanoparticles may eventually bypass vector immunity altogether. Combination approaches, including transient immunosuppression regimens or immune tolerance induction, are being evaluated to mitigate liver inflammation and prolong transgene expression [9].

In summary, while haemophilia A gene therapy faces more pronounced hurdles than haemophilia B, clinical experience demonstrates that meaningful FVIII expression and bleeding protection are achievable. Continued innovation in vector design, immune modulation, and gene transfer strategies will be critical to ensure durable efficacy and broaden patient access, ultimately realizing the curative potential of this therapy.

Status of Gene Therapy in India

India, with an estimated >125,000 persons with haemophilia (PWH), faces a formidable challenge in providing sustainable access to lifelong clotting factor concentrates (CFC) or alternative hemostatic therapies. With only ~20,000 patients identified in the World Federation of Hemophilia (WFH) 2020 global survey, the projected annual cost of replacement therapy exceeds US$ 400 million—an unsustainable figure in the context of national health budgets. This economic reality makes curative, one-time interventions such as gene therapy particularly attractive for the Indian healthcare system.

Two major academic programs are leading the effort. The first, coordinated by Professor Alok Srivastava at the Centre for Stem Cell Research (CSCR), CMC Vellore, is focused on AAV-based gene therapy for haemophilia B. In collaboration with international partners at the University of Florida and Emory University, a codon-optimized FIX Padua construct has been packaged in an AAV3 vector. Preclinical studies in haemophilia mouse and humanized liver mouse models have demonstrated robust FIX expression, laying the groundwork for clinical translation. The major bottleneck has been the establishment of large-scale GMP-grade vector production within India. In parallel, assays for anti-AAV antibodies have revealed a strikingly high seroprevalence (>90% for AAV3), which may limit eligibility for such therapies and underscores the need for alternative capsid strategies.

The second program targets haemophilia A using a lentiviral vector–mediated autologous hematopoietic stem cell (HSC) approach, with a CD68 promoter-driven FVIII transgene. Preclinical studies have shown normalization of FVIII levels in mouse models and demonstrable FVIII expression in human HSC xenografts. Based on these data, regulatory approval has been secured for Phase 1 clinical trials in both India and the USA [10].

In addition, domestic pharmaceutical initiatives in AAV-based gene therapy are underway, though details remain undisclosed. Together, these developments highlight India's commitment to building indigenous gene therapy platforms, addressing both scientific and infrastructural challenges to bring curative therapies closer to patients.

Conclusion

Despite challenges such as durability of expression, immune responses, and manufacturing constraints, gene therapy has already demonstrated transformative clinical benefits in haemophilia. With ongoing innovations, it holds immense promise as a curative option for the future.

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Chapter

17

Anticoagulation in 2025: Practical DOAC Use in Indian Patients

Dr. Usha Rani Pegu, Dr. Kiran Nagargoje

ABSTRACT

The advent of Direct Oral Anticoagulants (DOACs)—dabigatran, rivaroxaban, apixaban, and edoxaban—has revolutionised anticoagulation therapy. In 2025, Indian clinical practice has increasingly adopted DOACs for non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE), owing to predictable pharmacokinetics, minimal monitoring, and superior safety profiles compared to warfarin. However, unique Indian challenges persist—high prevalence of rheumatic valvular disease, renal impairment, variable access to reversal agents, and cost constraints. This chapter summarises the current evidence, practical dosing, monitoring, and special considerations for DOAC use in Indian patients.

Introduction

Anticoagulation has undergone a paradigm shift over the last decade with the increasing use of direct oral anticoagulants (DOACs, also called non-vitamin K oral anticoagulants, NOACs) instead of traditional vitamin-K antagonists (VKAs, e.g., warfarin) in many clinical scenarios. In India, the uptake has been growing but remains constrained by cost, local evidence, rheumatic heart disease prevalence, renal/hepatic variation and clinical logistics. This summary will focus on the practical use of DOACs in Indian patients in 2025 — indication, patient-selection, dosing, monitoring, peri-procedural and bleeding management, special situations, and Indian-specific issues.

Definition

DOACs are oral anticoagulants that act either by direct inhibition of thrombin (Factor IIa) or by inhibition of Factor Xa. Major agents include:

- Dabigatran (direct thrombin inhibitor)
- Rivaroxaban (direct Factor Xa inhibitor)
- Apixaban (direct Factor Xa inhibitor)
- Edoxaban (direct Factor Xa inhibitor) These agents have more predictable pharmacokinetics,

fewer food/drug interactions, no routine coagulation monitoring requirement (in most cases), and have been shown in many trials to be at least as efficacious and safer (especially for intracranial haemorrhage) than warfarin in non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE) treatment/ prevention.

Epidemiology

In the Indian context:

- There is rising detection of atrial fibrillation (AF) and VTE, but precise community data remain limited.
- Use of DOACs in India is increasing, but as noted in a recent review, VKAs (warfarin) continue to dominate in many settings due to cost and system constraints.
- A survey of Indian clinicians found that among DOACs, dabigatran was most preferred (˜72 %) for AF per respondents; rivaroxaban and apixaban were also used.
- Indian consensus guidance (2015) for stroke prevention in AF emphasised that Indian-subpopulation data are sparse and local adaptation is needed. Thus, while DOAC use is well established globally, the Indian scenario retains challenges of access, monitoring infrastructure, cost and special populations (e.g., rheumatic heart disease, renal disease, etc).

Indications

Approved indications in India (2025):

- Stroke prevention in non-valvular atrial fibrillation
- Treatment and secondary prevention of DVT/ PE
- Post-operative VTE prophylaxis (hip/knee replacement)

Contraindications

- Mechanical heart valves, moderate-severe rheumatic mitral stenosis
- Severe renal impairment (CrCl < 15 mL/min)
- Hepatic failure, pregnancy, triple-positive antiphospholipid syndrome

Pathophysiology

DOACs inhibit key steps in the coagulation cascade:

- Dabigatran ? inhibits thrombin directly
- Factor Xa inhibitors ? prevent prothrombin conversion to thrombin This leads to rapid, consistent anticoagulation without affecting vitamin K metabolism. Their short half-life reduces bridging needs and simplifies peri-operative management.

Rationale

The rationale for DOAC use rests on their pharmacologic advantages:

- Faster onset/offset of action, predictable effect, fixed dosing (in many cases)
- No or minimal routine monitoring of anticoagulant activity, unlike warfarin (which requires INR monitoring)
- Fewer dietary restrictions and fewer drug interactions (though still present)

- In trials, compared to VKAs: similar or better efficacy for prevention of stroke/embolicevents, less intracranial bleeding.

Patient Selection & Considerations

Ideal candidates for DOACs

- Patients with NVAF with elevated stroke risk (e.g., CHA2DS2-VASc = 2 for men or =3 for women) and acceptable bleeding risk, who are unwilling/unable to maintain INR monitoring.
- Patients with acute VTE (DVT/PE) without contraindications, especially when warfarin control is likely to be challenging.

Contraindications / Cautions

- Mechanical heart valves, moderate–severe mitral stenosis (rheumatic) — DOACs not indicated.
- Severe renal impairment (CrCl <15 mL/min) or dialysis (depends on agent) — caution or avoid; warfarin may be preferred.
- Significant hepatic impairment, active major bleeding, pregnancy/breastfeeding (data limited) — evaluate case-by-case.
- Extreme body weight (BMI >40–50 kg/m² or weight >120 kg) — limited data; warfarin may be preferred.
- Drug-drug interactions (strong P-glycoprotein, CYP3A4 inducers/inhibitors) — need careful review.

Special Indian Context Considerations

- Chronic kidney disease (CKD): calculate CrCl (Cockcroft-Gault) for dose decisions. Use caution when CrCl <30 mL/min (drug-specific limits). Apixaban has some data for ESRD dosing but follow label and specialist advice. ?
- Elderly: higher bleeding risk — consider dose reduction rules (esp. apixaban) and careful fall-risk mitigation.
- Obesity (BMI >40 or weight >120 kg): DOAC plasma levels may be lower; some guidelines advise considering warfarin or measuring drug levels if available for very high BMI. Use specialist input.
- Pregnancy & breastfeeding: DOACs generally not recommended — use LMWH for anticoagulation in pregnancy unless specialty guidance.
- Cancer: certain DOACs are effective for cancer-associated VTE but consider drug interactions with anti-cancer therapy and bleeding risks.

Investigations

Before initiation: CBC, renal and hepatic function, PT/INR, aPTT, weight, drug-interaction review

During Therapy:

- Annual renal/hepatic reassessment (3–6 monthly if borderline)
- No routine INR or aPTT monitoring required

In emergencies: Use thrombin time (for dabigatran) or anti-Xa assay (for Xa inhibitors) if available.

Management

Selection of agent & dose in Indian setting

While Indian-specific dosing guidelines are not fully standardised, the following practical guidance (derived from global evidence + Indian consensus) may be used:

- Patient's renal function, age, body weight, drug interactions, cost/compliance must drive selection.
- Example doses (in NVAF) from published sources:

o Dabigatran: 150 mg twice daily (if CrCl allows) or lower 110 mg twice daily (depending on age, weight, renal).

o Rivaroxaban: 20 mg once daily with food (CrCl >50 mL/min) — reduce to 15 mg once daily if CrCl 15–50 mL/min (varies by label).

o Apixaban: 5 mg twice daily; reduce to 2.5 mg twice daily if two of the following: age =80 y, weight =60 kg, serum creatinine =1.5 mg/dL.

o Edoxaban: 60 mg once daily (CrCl >50 mL/min, weight >60 kg); reduce to 30 mg once daily if CrCl 15–50 mL/min or weight =60 kg. However, in India, local prescribing must follow the approved label for that agent in India, and consider cost/availability.

Duration of Therapy

- For NVAF: Long-term (lifelong) anticoagulation is typically indicated provided stroke risk persists and bleeding risk acceptable.
- For acute VTE: Standard initial treatment for 3–6 months is common; extended duration determined by risk of recurrence vs bleeding.

Monitoring & Follow-Up

- Monitor renal/hepatic function at baseline, then at least annually (or more frequently if impairment present).
- Monitor adherence, any bleeding events (minor or major), drug interactions, changes in body weight or comorbidity.
- Patient education: emphasise adherence (missed doses may reduce efficacy), what to do if a dose is missed (Indian-literate guidance: for BD regimen take upto 6 h late, for OD upto 12 h — from Indian expert consensus)

Adverse Effects

- Bleeding (major and minor) is the most important adverse effect. While DOACs reduce intracranial haemorrhage compared to warfarin, gastrointestinal bleeding risk may be higher with some DOACs.
- Others: dyspepsia (notably with dabigatran), drug interactions, renal accumulation if impairment present.

Dose Adjustment / Special Situations

- Renal impairment: Many DOACs require dose reduction or avoidance if CrCl <30 mL/min (depends on agent).
- Hepatic impairment: Use caution; avoid in severe liver disease with coagulopathy.
- Extremes of body weight: In patients with BMI >40–50 kg/m² or weight >120 kg, data are limited; warfarin may be preferred.
- Drug interactions: Evaluate concomitant P-gp or CYP3A4 inducers/inhibitors.
- Transitioning from warfarin to DOAC or vice versa: Must ensure warfarin effect is reversed (INR =2) before starting DOAC; or when switching to warfarin start DOAC until INR target reached. Indian consensus covers switching.

Management

Agent	Mechanism	Typical Adult Dose	Dose Adjustments (CrCl)	Notes
Dabigatran	IIa inhibitor	150 mg BD (110 mg BD if eldcrly/rcnal)	↓ dose if CrCl 30–50 mL/min	Avoid <30 mL/min
Rivaroxaban	Xa inhibitor	20 mg OD with food	15 mg OD if CrCl 15–50 mL/min	Once-daily dosing
Apixaban	Xa inhibitor	5 mg BD	2.5 mg BD if ≥80 y, ≤60 kg, SCr ≥1.5 mg/dL	Least renal excretion
Edoxaban	Xa inhibitor	60 mg OD	30 mg OD if CrCl 15–50 mL/min	Needs 5 d LMWH pre-treatment for VTE

Monitoring & Follow-Up

- Monitor renal/hepatic function at baseline, then at least annually (or more frequently if impairment present).
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Management of Bleeding & Reversal

- Major bleeding: Use specific reversal agents where available — e.g., idarucizumab for dabigatran; andexanet alfa for apixaban/rivaroxaban.
- If reversal agent unavailable: consider 4-factor prothrombin complex concentrates (PCC) or activated PCC (FEIBA), tranexamic acid, supportive care.
- After bleeding, resumption of anticoagulation may occur after 1–6 weeks depending on bleed site, risk of thrombosis vs bleeding.

Cost and Access in India

- DOACs are more expensive than warfarin; INR monitoring cost may tilt the overall cost-effectiveness in different settings. Indian reviews emphasise that cost remains a significant barrier for wide adoption.
- In Indian practice, patient's ability to afford drug, follow-up, renal/hepatic monitoring, and access to reversal/bleeding ma4nagement needs to be factored in.

Monitoring & Quality Assurance

- Track renal function (e.g., eGFR/CrCl) at baseline and at least annually (or more frequently if borderline).
- Track haemoglobin/platelet count, signs of occult bleeding.
- Maintain a log of missed doses, side effects, concomitant drugs.
- Institutional or departmental protocols in Indian hospitals should include guidelines on DOAC initiation, procedural management, and bleeding protocols to avoid ad hoc practice variation.
- In academic settings (for your exam): emphasise audit of anticoagulation services (time in therapeutic range for warfarin vs DOAC uptake, major bleeding rates, stroke/embolism outcomes) may help quality improvement.

Complications

- Major bleeding (intracranial haemorrhage, GI bleeding) remains a key risk. DOACs reduce intracranial bleed risk compared to warfarin, but GI bleed risk may be higher in some agents.
- Thromboembolism despite anticoagulation (non-adherence, incorrect dosing, drug interactions, extreme weight/renal dysfunction).
- Drug accumulation in renal impairment leading to increased bleeding risk.
- In Indian context: underuse of anticoagulation in AF (leading to stroke) remains a problem. Also, cost/monitoring barriers may lead to suboptimal use.
- Interaction with antiplatelet therapy: many Indian patients have co-existing coronary disease requiring dual antiplatelets; anticoagulation in this setting raises bleeding risk significantly. E.g., Indian GI society position statement emphasises the high bleeding risk when combining antiplatelets + anticoagulants.

Recent Advances

- A 2025 review provides updated practical guidance on DOAC prescription, lab testing, perioperative and bleeding management.
- Emerging Indian data suggest DOACs may slow progression of chronic kidney disease (CKD) compared to VKAs in AF patients.
- Indian consensus and expert opinion are moving toward more refined recommendations for DOACs in special populations (elderly, renal impairment, obesity) though classic Indian large-scale RCTs are still limited.
- In the Indian context, there is increasing clinician preference for dabigatran and other DOACs in DVT/PE management.

Prognosis

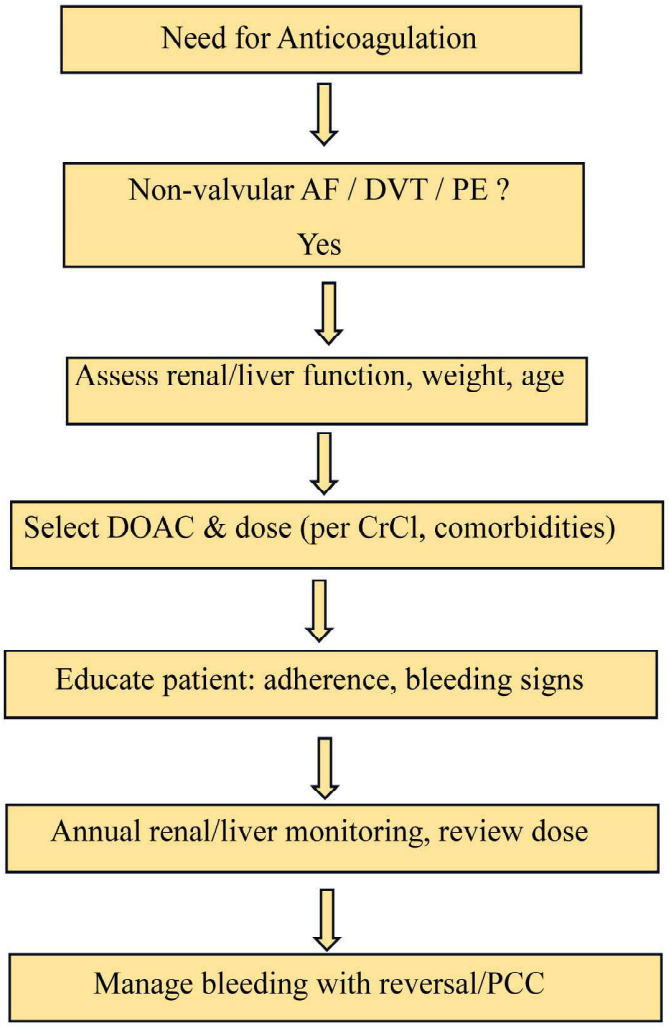
With correct selection, DOACs achieve:

- 60–70 % reduction in stroke/VTE recurrence
- 50 % lower intracranial bleed rate vs warfarin
- Improved quality of life due to no INR monitoring . In Indian practice, outcomes are excellent when renal function is stable and adherence ensured.

Summary Table: Key Practical Points

Aspect	DOAC Advantage	Indian Challenge	Practical Tip
Monitoring	No INR	Limited lab access	Annual renal/liver review
Safety	↓ Intracranial bleed	↑ GI bleed	Prefer apixaban in elderly
Cost	Higher upfront	Cost barrier	Consider generics or warfarin if unaffordable
Valvular AF	Not indicated	Rheumatic common	Continue warfarin
Reversal	Rapid (idarucizumab, andexanet)	Limited availability	Stock PCC + tranexamic acid

Flowchart: Practical Doac Use In India (2025)



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Chapter

18

Sickle Cell Disease: Novel Thrapies and Global Access

Dr. Jina Bhattacharyya, Dr. Prianuz Dewraja

ABSTRACT

Sickle cell disease (SCD) is a major global health burden and the most common monogenic disorder worldwide. It results from a mutation in the ß-globin gene causing hemoglobin polymerization, red cell deformation, hemolysis, and vaso-occlusion. The disease affects multiple organ systems and leads to significant morbidity and reduced life expectancy. Both genetic and environmental modifiers influence its clinical severity. Important genetic factors include fetal hemoglobin levels and co-inheritance of a-thalassemia, while nongenetic influences such as infection, climate, and air quality also play critical roles. Early diagnosis, vaccination, penicillin prophylaxis, hydroxyurea therapy, and hematopoietic stem-cell transplantation have substantially improved survival. Gene therapy is emerging with curative potential; and pharmacologic agents targeting adhesion and HbF induction, show promise. These disease modifying agents play important roles in giving a better quality of life in patients with SCD; however, accessibility of these agentsis not uniform globally especially in developing countries. In India, with the introduction of The National Sickle Cell Anaemia Elimination Program,it is hoped that the accessibility of the novel therapies would be possible to all patients with SCD.

Introduction

Sickle cell disease (SCD) is one of the most prevalent inherited disorders of hemoglobin globally and represents a major public health challenge in low and middle-income countries. It results from a single point mutation in the ß-globin gene, which substitutes valine for glutamic acid at the sixth position, leading to the production of sickle hemoglobin (HbS). Under hypoxic conditions, HbS polymerizes, deforming red blood cells into a sickled shape that causes chronic hemolysis, vaso-occlusion, ischemic injury, and progressive multi-organ complications.[1]

In India, the sickle hemoglobin variant was first identified in 1952 among the tribal population of the Nilgiri Hills in southern India. Over time, SCD has been recognized as a widespread disorder affecting both tribal

and non-tribal communities, particularly in states such as Madhya Pradesh, Maharashtra, Gujarat, Odisha, and Chhattisgarh. Carrier frequencies range widely between 1% and 44%, with India ranking second globally in the number of newborns affected by the sickle gene.

A large proportion of patients, particularly those in rural or underserved regions, remain undiagnosed or are diagnosed late and receive suboptimal treatment. Patients have higher morbidity and mortality and this is mostly because of lack of awareness, poor access to disease modifying therapies, inadequate blood transfusion facilities, and limited neonatal screening. Moreover, social stigma and discrimination further compound the burden, restricting educational and economic opportunities for affected individuals.[2]

The disparity in outcomes between high-income and low-income countries is striking globally. In high-resource settings such as North America and Europe, early diagnosis, prophylactic penicillin, vaccination, hydroxyurea therapy, and hematopoietic stem-cell transplantation have transformed SCD from a fatal childhood disease into a chronic, condition with median survival exceeding 60 years. Conversely, in sub-Saharan Africa and South Asia, where over 75% of affected children are born, mortality remains unacceptably high, with an estimated 50–90% of children dying before their fifth birthday due to preventable causes such as infection and anemia.

Recently there are major advances in the development of novel therapies targeting key mechanisms of SCD pathophysiology. Hydroxyurea remains the cornerstone of pharmacologic therapy, increasing fetal hemoglobin levels and reducing vaso-occlusive crises. Newer therapies such as voxelotor (which inhibits HbS polymerization), crizanlizumab (a P-selectin inhibitor that prevents vaso-occlusion), L-glutamine (which reduces oxidative stress) and many others have shown promising results in improving clinical outcomes. Additionally, gene therapy and gene-editing approaches using lentiviral vectors or CRISPR/Cas9 technology hold curative potential by reactivating fetal hemoglobin production or correcting the sickle mutation itself.

Despite these therapeutic breakthroughs, access continue to be a global challenge. Most novel agents and curative treatments are very expensive and therefore , largely confined to high-income countries. Coordinated international collaboration and national commitment can bring down the gap and make newer pharmacotherapies reach all individuals living with sickle cell disease, regardless of geography or socioeconomic status.(1). Fig 1 shows the approach to management of SCD.

Complications of Sickle Cell Disease

SCD affects nearly every organ system. Acute complications commonly include painful vaso-occlusive crises, acute chest syndrome, stroke, splenic sequestration, and aplastic episodes. Pain crises, the most frequent manifestation, result from microvascular occlusion and tissue hypoxia, and they often require hospitalization. The acute chest syndrome — characterized by new pulmonary infiltrates, fever, and respiratory distress — represents a leading cause of death and is precipitated by infection, fat embolism, or pulmonary infarction. Ischemic and hemorrhagic strokes, particularly in children, arise from large-vessel vasculopathy and are major causes of neurologic morbidity.

Chronic complications stem from cumulative organ damage. Persistent hemolysis and vasculopathy contribute to pulmonary hypertension, renal failure, leg ulcers, avascular necrosis of bone, and retinopathy. Functional hyposplenism develops early in life due to repeated splenic infarction, predisposing children to life-threatening bacterial infections, especially by encapsulated organisms such as Streptococcus pneumoniae.

The disease manifestationsareheterogeneousand there is significant phenotypic variation. Genetic and environmental factors modify disease severity. Coinheritance of a-thalassemia decreases intracellular HbS concentration and reduces hemolysis, while elevated levels of fetal hemoglobin (HbF) inhibit HbS polymerization and ameliorate many complications. Conversely, environmental triggers such as infection, dehydration, cold exposure, and hypoxia often precipitate crises.

Although hydroxyurea therapy, chronic transfusion programs, and stem-cell transplantation have improved outcomes, SCD remains a complex and unpredictable disorder. The only approved curative optionfor SCD is HLA matched allogenic hematopoietic stem cell transplantation; however it is not widely used due to many factors like non-availability of donors, cost and complications associated with it.

Gene therapy is aimed at one time cure of the disease; CRISPR-Cas9-based gene editing platforms target BCL11 A. BCL 11A is a transcription factor and down-regulates production of fetal haemoglobin and promotes HbA production. Casgevy/Exa-cel and Lyfgenia/Lov-cel are two gene therapies approved for SCD in 2023; but they are prohibitively expensive and would not be affordable to majority of SCD patients Pharmacological agents thus remain critical in the treatment of patients with SCD. Newer disease modifying agents are being developed or undergoing different phases of clinical trials.

Pharmacotherapy

Hydroxyurea was the only approved pharmacotherapy for many years until the development of newer disease modifying agents in the last few years. Many of these agents got accelerated approval; some of these agents later on were withdrawn due to safety concerns. These agents can be classified based on different mechanisms of actions. (Table 1).Hb F inducers, anti-adhesion agents, Hb S polymerisation inhibitors, Pyruvate Kinase inhibitors and agents acting on complement pathway have either completed or undergoing different phases of clinical trials.

C.1 Hydroxyurea

HU is an antimetabolite and increases fetal hemoglobin (HbF) expression thereby decreasing the frequency and severity of SCD complications. In the landmark Multicenter Study of Hydroxyurea in Adult Sickle Cell Anemia (MSH) trial,the effectiveness of HU in preventing painful crises was established [22]. A 17.5 year follow up of the MSH participants have suggested better overall survival with no concerns for long term adverse events subsequent trials in the pediatric age groups including infants (PED HUG and BABY HUG) study demonstrated hydroxyurea's safety and effectiveness without affecting growth and development in children and infants. Subsequent clinical trials (BRAINSAFE II, SPIYA) have confirmed effectiveness

of HU in different clinical conditions and age groups. An ongoing open-label extension study called ESCORT-HU (NCT04707235) began in 2020 and is investigating the occurrence of malignancies, leg ulcers, male fertility impairment, and serious unexpected adverse events caused by HU over a 5-year period.

Hydroxyurea in spite of getting approval for so many years is still not widely used ; the reasons of which are lack of awareness, non availability cost concerns, concern for long term toxicities etc. With the introduction of NationalSickle cell Elimination Programme the health system in India is targeting optimum use of hydroxyurea by making it easily available free of cost across India. Hydroxyurea is the drug recommended to be used for all patients with SCD; it is available in both capsule and oral solution and can be safely given to all age groups including infants above…months of age. Even though newer pharmacotherapies are being developed and are undergoing various stages of clinical trials hydroxyurea remains the mainstay of treatment and should be prescribed to all patients with SCD. Starting dose of HU is 10 mg/kg/day, increased by 5 mg/kg every 8 weeks until maximum tolerated dose (MTD) or up to 35 mg/kg/day. The drug needs monitoring with CBC and target absolute neutrophil count (ANC) of > 1500/µL and platelet count of > 80,000/µL. It has to be discontinued in women planning pregnancy and may be continued after the 1st trimester.

C.2 LGlutamine

It is a naturally occurring amino acid used for synthesis of pyrimidine; it was approved by FDA for use in SCD in 2017 as studies had shown lesser VO than placebo; however the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a recommendation against approval of the molecule in view of adverse events.

C.3 Anti-Adhesion Therapies

Crizanlizumab

Crizalinzumab is a P-selectin inhibitor;P-selectin is upregulated in endothelial cells and platelets and is involved in the pathogenesis of VOC and pain crises. SUSTAIN (Phase II) trial and its post hoc analyses had shown significant reduction in VOC and hospitalisations in patients receiving 5mg/kg vs Placebo; SUCCESSOR trial assessed VOC occurrence retrospectively amongst those who had completed SUTAIN study had shown a porolonged effect of crizalinzumab. However STAND (Phase III) trial had shown disappointing result, and based on this EMAhad suspended marketing authorisation of the drug in June 2023. SOLACE kids trial, STEADFAST trial and SPARTAN trial are undergoing to look at specific age and clinical conditions of the SCD. E.g. STEATFAST for SCD nephropathy and SPARTAN for SCD priapism.

Several localized studies on crizanlizumab are also being conducted, primarily focusing on the Middle East and India. SPOTLIGHT was a multicenter, prospective, single-arm NIS study investigating the effectiveness of crizanlizumab in patients from Middle Eastern countries and India. The study primarily measured the annualized rate of healthcare visits and enrolled 44 participants before being terminated in 2023. Another localized study is the ongoing Indian Multi-centric Phase IV Study to Assess the Safety of Crizanlizumab in Sickle Cell Disease Patients .This

study aims to evaluate the safety of crizanlizumab in Indian SCD patients and primarily measures the frequency, severity, and causality of serious adverse events while being treated with crizanlizumab. A total of 140 participants are enrolled, and the study is scheduled to be completed in 2024.

Epeleuton, Famotidine, Inclacumab and IVIG are other antiadhesive molecules undergoing different phases of clinical trials in SCD patients.

C.4 Anti-Polymerization Therapies

Voxelotor:

Voxelotor (oral)inhibits hemoglobin S polymerization and RBC sickling and in turn improves oxygen delivery to vital organs. Voxelotor was approved by the FDA in 2019 for the treatment of SCD in both adults and children 12 years and older based on HOPE trial (Phase III, randomised); however due to safety concerns it has been withdrawn from the market by the manufacturers (Pfizer) in 2024.

Osivelotor (GBT021601):

It is a next-generation voxelotor-type drug that stabilizes Hb in the oxygenated state and inhibits polymerization in SCD subjects. A randomized control study is currently underway to determine the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of GBT021601 in pediatric and adult SCD patients A long-term extension study on GBT021601 in SCD patients is also ongoing and measures the long-term effects of the drug on treatment-emergent adverse events, hemolysis, inflammation, quality of life, and reticulocyte levels.

C.5 Pyruvate Kinase Activators

Mitapivat:

Mitapivat (AG-348) is an oral first-in-class small-molecule allosteric activator of pyruvate kinase and has shown promise in its ability to treat SCD. Previous research has shown that the activation of erythrocyte pyruvate kinase (PKR) results in the increased production of ATP and the lowered production of 2,3-diphosphoglycerate. This increases Hb's affinity for oxygen, reducing HbS polymerization as a result. In 2019, a phase 1 trial of mitapivat in 15 SCD patients showed that mitapivat was well tolerated and reduced sickling, improved anemia, reduced markers of hemolysis, and increased oxygen affinity. A European phase 2, open-label, single-center study of mitapivat in patients with SCD (the ESTIMATE study) was completed in 2023 and found that mitapivat was able to significantly reduce the annual rate of VOC, improve levels of hemoglobin, and decrease markers of hemolysis (NL8517).. The RISE UP study began in 2022 and is evaluating the safety and efficacy of mitapivat in 267 patients with SCD and the study has an estimated completion date of December 2025.

Etavopivat:

Etavopivat (FT-4202), like mitapivat, is an investigational, oral drug shown to increase hemoglobin's affinity to oxygen via the activation of the erythrocyte pyruvate kinase (PKR) [47]. The in vivo and ex vivo treatment of sickled RBCs with etavopivat showed a significant increase in Hb oxygen saturation A randomized, placebo-controlled, double-blind, multicenter phase 2/3 study (HIBISCUS) is currently recruiting pediatric and adult SCD patients (12 to 65

years of age), with the primary endpoint of hemoglobin response and rate of VOC. Another phase 2 study is evaluating etavopivat in patients with beta-thalassemia and SCD. The study measures the proportion of patients with a 20% reduction in blood transfusions and is scheduled to be completed in late 2025.

C.6 Drugs acting on complement pathway

As complement is involved in the pathogenesis of SCD, inhibition of this pathway has been undergoing evaluation and several molecules are undergoing different phases of clinical trials. ALXN1820(humanised bi-specific antibody), Crovalimab,anticomplement C5 monoclonal antibody(CROSSWALK study), Riociguat for SCD patients with PAH and/or Chronic thromboembolic disease).

Gene therapy

Gene therapy has curative potential.There are two ways to do it in SCD:

D.1.gene insertion, where a therapeutic globin gene is introduced. In this approach, patients continue to express native HbS along with antisickling hemoglobin is expression; as a result the phenotype changes to a mild form (sickle cell trait). Lentiviral vectors are mostly used to introduce a new therapeutic globin gene into hematopoietic stem cells (HSCs). However, Lentiviral gene insertion does not directly silence the production of HbS and there is integration of foreign DNA which allows for possibility of insertional mutagenesis.

D.2gene editing,where the disease-causing mutation is corrected.The advent of CRISPR-Cas9 technology, first introduced by Doudna and Charpentier in 2012, has revolutionized gene therapy This breakthrough earned them the Nobel Prize in Chemistry in 2020 and has allowed for precise genetic correction without the need for viral vectors. Due to this targeted genome editing , the integration of foreign DNA into the patient's genome can be avoided, and thus the risk of insertional mutagenesis decreases.

Recently, the FDA has approved therapies within both categories of gene therapy, gene addition and gene editing. LYFGENIA (lovotibeglogene autotemcel) is a gene addition therapy, in which patient CD34 cells are transduced with the lentiviral vector BB305. Treatment results for lyfgenia demonstrated that 94% of patients achieved complete elimination of severe VOEs, with 88% experiencing complete resolution of all VOEs. 86% of patients achieved sustained globin response, defined as transfusion independence with a hemoglobin >3 g/dL greater than baseline or =10 g/dL. Moreover, 100% of patients with a history of stroke achieved transfusion-independence and without stroke recurrence for the duration of the study (44–60 months). The therapy also resulted in sustained hemoglobin levels of 11 g/dL or more, with the therapeutic hemoglobin HbAT87Q accounting for 40% of total hemoglobin. In addition, all patients achieved transfusion independence, with HbAT87Q being expressed in a mean of 85% of red cells8

The second approach, gene editing, is exemplified by Casgevy (exagamglogene autotemcel) in which patient CD34 cells are edited using CTX-001 which uses CRISPR-Cas9 technology to knock down BCL11a. The first patient experienced a rise in baseline hemoglobin from 7.2 to 12 g/dL after 15 months. HbF

levels increased from 9.1 to 43.2% and was expressed in nearly 100% of RBCs 8

D.3 Process of gene therapy and Challenges

Gene therapy approaches require the collection of mobilized autologous CD34+ cells via apheresis, followed by ex vivo gene manipulation. After myeloablative conditioning, the genetically modified stem cells are infused back into the patient.

At this moment the costs associated with gene therapy is in crores which is beyond the reach of majority of patients of SCD. Lyfgenia and Casgevy are priced at $3.1 million and $2.2 million respectively in the United States ; there are additional expenses from treatment-related hospitalizations and supportive care in addition to main cost.

D.4 Gene therapy and India

Indian scientists have developed gene therapy indigenously for SCD by using CRISPR-Cas 9 technology (molecular scissor) to cut the defective gene in the hematopoietic stem cells; the corrected cells are then infused back to the patient.The therapy is developed by CSIR- institute of Genomics and integrative biology and is undergoing clinical trial which is expected to be over by 2026 followed soon by regulatory approval. The gene therapy developed by India, is named as Birsa 101 after the visionary tribal leader Bhagawan Birsa Munda; 101 is for one step beyond erfection. This is being developed as part of the National Sickle Cell Anemia Elimination Programme (2023—2047) and would be be available at a much lower cost than the ones approved by FDA.

Conclusion

Sickle Cell Disease (SCD) remains a major public health challenge worldwide with wide clinical variability and significant social, economic, and healthcare implications. Effective management requires a holistic and standardized approach integrating clinical care, prevention, and community engagement. Acute complications such as vaso-occlusive crises and infections demand urgent, protocol-based management with aggressive pain control, hydration, and transfusion support when necessary. Regular monitoring for chronic organ damage, multidisciplinary care during pregnancy and surgery, and the judicious use of iron chelation and transfusion therapy are critical for improving long-term outcomes. Hydroxyurea is the most commonly used, affordable and easily available disease modifying agents; many new such agents are undergoing clinical trials and once approved by regulatory bodie
s, would make a major change towards the betterment of the QoL of the SCD patients.Hematopoietic stem cell transplantation can lead to cure and indicated for patients with severe disease. Gene therapy is one time curative therapy for patients with SCD; Birsa 101is undergoing clinical trial in India. With both the curative therapy being not available to SCD patientsin general, pharmacotherapy plays amajor role in modifying the disease severity to a great extent.

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Section 6
Pulmonology

Chapter

19

Bilogics in Severe Asthma : Precision Medicine Approaches

Dr. Basanta Hazarika, Dr. Bidisha Devi

Introduction

Asthma, a global health problem, is a chronic lower airway disease which affects around 300 million patients each year all over the world. It is an umbrella diagnosis which includes complex pathophysiological mechanisms and inflammatory pathway with often variable clinical courses. The GINA 2025 defines asthma as a heterogenous disease, usually characterised by chronic airway inflammation with history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and intensity, together with variable expiratory airflow.

It is seen that majority of asthma patients can achieve disease control with standard controller therapy, however, approximately 5% - 10% have severe asthma that remains inadequately controlled despite adherence to standard treatment with a high-dose inhaled corticosteroid (ICS) plus long-acting bronchodilator. Severe asthma is defined by the European Respiratory Society/American Thoracic Society as asthma that requires treatment with high-dose ICS plus a second controller with or without systemic corticosteroids in order to maintain control of the disease or, despite this therapy, have sub optimally controlled disease . Its pathophysiology primarily involves continuous chronic inflammation that results in airway remodelling.

Asthma Endotypes

The earlier classification of asthma into extrinsic (atopic) and intrinsic (idiosyncratic) has been largely replaced by the immunological classification which broadly divides asthma into T2 or T2 high and non T2 endotypes. The endotypes are important to distinguish while we consider biologic therapy. T2-High Asthma occurs in approximately half of patients with asthma and may be slightly more common in patients with severe asthma It is further divided into:

1. Allergic asthma (high IgE)
2. Non-Allergic eosinophilic asthma (normal IgE but high blood/ sputum Eosinophil)

Although an allergen-specific, IgE-dependent process plays a significant role in allergic asthma, T2 cytokines play a dominant role in inflammation in nonallergic eosinophilic asthma. In T2-high asthma,

inhaled allergens, microbes, and pollutants interact with the airway epithelium, leading to subsequently activation of mediators such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 (Figure 1). Initial exposure causes priming of the dendritic cells and Th2 response which further leads to activation of IL-4, IL-5, and IL-13. It causes attraction and activation of basophils, eosinophils, and mast cells; secretion of IgE by B cells; and activation of innate cells such as the airway epithelium and smooth muscle, resulting in bronchoconstriction, airway hyperresponsiveness, mucus production, and airway remodelling if sub optimally controlled.[7,8] Sputum and blood absolute eosinophil counts (AECs), serum IgE, exhaled nitric oxide, and serum periostin are the important biomarkers that help to predict response to biologics.[9]

T2-low asthma, which includes neutrophilic, mixed, or paucigranulocytic asthma, has a comparatively poorly understood pathophysiology. T2-low asthma results in activation of both T1 and T17 cells, and high IL-17A mRNA levels, IL6, IN? and TNF alpha. It shows poor response to ICS with release of inflammatory mediators like lipoxin and LTB4 causing local tissue injury, airway remodelling, airflow obstruction and asthma exacerbations.[9] It may be influenced by the concomitant use of corticosteroids suppressing the underlying eosinophilia.[9]

Asthma Phenotypes

As per endotypes Asthma can be further classified into five phenotypes as below:

1. The early-onset mild atopic asthma
2. Early-onset mild to moderate atopic asthma
3. Early-onset severe atopic group
4. Late-onset non-atopic eosinophilic asthma
5. Late-onset non-atopic non-eosinophilic asthma

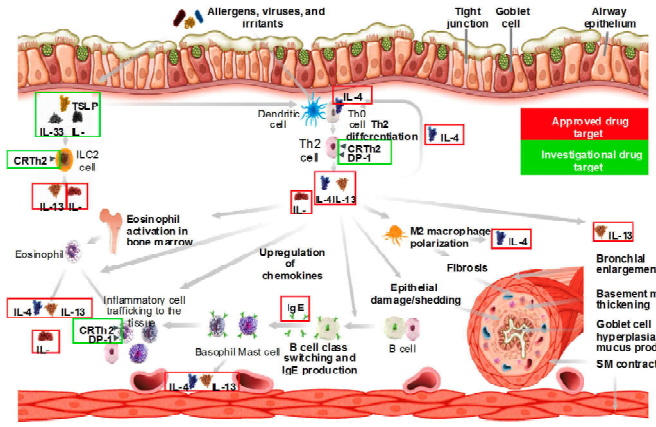

Fig 1: Schematic diagram of the immunopathobiology of asthma with sites of the targeted treatments with approved and investigational monoclonal antibodies marked. In type 2 (T2) asthma, the interaction of environmental exposures with the airway epithelium leads to the release of the mediators IL-33, IL-25, and TSLP (thymic stromal lymphopoietin). In addition, allergens are taken up by dendritic cells and presented to naive T-helper (Th0) cells. A cascade of events as shown ensues that leads to production of the type 2 cytokines IL-4, IL-5, and IL-13; secretion of IgE by B cells; and chemoattraction of mast cells, eosinophils, and basophils. This process lends itself to numerous therapeutic targets that have already been approved by the U.S. Food and Drug Administration (outlined in red) and others that remain in investigation (outlined in green).[11]

(CRTh2 = chemoattractant receptor–homologous molecule expressed on T2 cells; DP-1 = prostaglandin D2 receptor type 1; ILC2 = innate lymphoid cell type 2; M2 macrophage = alternatively activated macrophage; SM = smooth muscle. Modified by permission from Reference 98 from Sanofi.)

Treatment Options Asthma

Inhaled corticosteroids and beta-agonists are the initial treatment of asthma. If symptoms persist and asthma exacerbations remain uncontrolled, long-acting muscarinic antagonists may be employed in addition to the above therapies.[12] Until the development of the first biologic agents, such as omalizumab, in the early 2000s, oral corticosteroids were the last line of defence in the treatment of severe asthma. However, corticosteroid use was associated with many deleterious effects, such as adrenal insufficiency, Cushing syndrome, glaucoma, cataracts, iatrogenic diabetes mellitus, and osteoporosis. Oral corticosteroids additionally do not prevent airway remodelling as they have no effect on IL-33, the cytokine which is responsible for airway remodelling in asthmatic patients.[14]

For most patients, asthma is adequately controlled with these traditional therapies. According to one study, approximately sixty-three percent of patients who were initiated on biologic therapy for asthma had suboptimal medication adherence to traditional therapy.[11] Despite this, approximately 15% of all asthma cases remain uncontrolled, even with the adherent use of these therapies.[11]

Biologics For Asthma

The treatment of asthma is moving toward a personalized treatment strategy that is based on patient-specific characteristics and underlying endotype rather than disease severity alone. Baseline assessment for biologics starts with first confirming the diagnosis of severe asthma by considering patients with uncontrolled symptoms despite being on high dose inhaled corticosteroids and LABA. It is followed by assessment of T 2 inflammatory markers like blood eosinophil, FeNO. Serum periostin is recognised as a biomarker of type 2 inflammation; POSTN gene expression in bronchial epithelial cells gets up regulated by IL13 and IL4.

Omalizumab

Omalizumab is a monoclonal antibodywhich binds to the constant region of free IgE in serum which prevents its interaction with high- and low-affinity IgE receptors, FceRI and FceRII, particularly on mast cells, basophils, and B lymphocytes.[15] It reduces the circulating IgE levels and thus activation of mast cells and release of inflammatory mediators.[1]

The candidates for omalizumab treatment include patients with severe asthma of=6 years of age, body weight 20-150 kg, and sensitive to at least one perennial allergen confirmed by skin tests or specific IgE positivity, and serum total IgE level of 30-1500 IU/mL.[16]

Early-onset asthma with blood eosinophil level of =260 cells/µL, and a fractional exhaled nitric oxide (FeNO) level of =20 ppb are factors associated with a favourable response to omalizumab treatment.[16]

Mepolizumab

Mepolizumab is an IgG1/k class monoclonal that inhibits the binding of IL-5 to its specific receptorwhich is responsible for maturation of eosinophils in the bone marrow and migration to the bronchial mucosa. It also acts by binding free IL-5 which reduces eosinophilic airway inflammationsignificantly by inhibiting free IL-5 in blood and sputum.[17]

Mepolizumab treatment is effective in patients with severe eosinophilic asthma with frequent

exacerbations regardless of BMI or presence of atopy or high serum IgE.Peripheral blood eosinophil counts =150 cells/ µL at the beginning of treatment or =300 cells/µL in the last year, =2 asthma attacks in the last year, presence of nasal polyposis and OCS dependence are found to be associated with better response to mepolizumab.[1]

Reslizumab

Reslizumab is an IgG4? humanized monoclonal antibody against IL-5. It inhibits the activity of eosinophils by binding to high affinity to IL-5, which promotes maturation, activation, survival, migration from the bloodstream, and entry into the airways, reduces the production of eosinophils and shortens their life span.[18]

Patients with uncontrolled severe eosinophilic asthma with Eosinophil >400 cells/µL,=2 asthma exacerbations in previous year, OCS-dependence, nasal polyposis is associated with better response to reslizumab.[1]

Benralizumab

Benralizumab is a humanized monoclonal antibody directed against IL-5 receptor a. It binds to IL-5 receptor a (IL-5Ra) on eosinophils, eosinophilic precursors, and basophils and prevents binding of IL-5 to its receptor thereby causing rapid apoptosis of these cells through antibody-dependent cytotoxicity . It causes near complete depletion of eosinophils rapidly through antibody-dependent cellmediated cytotoxicity.[20]

Patients of uncontrolled severe eosinophilic asthma with higher baseline rates of exacerbations and higher baseline blood eosinophil countsare mostly benefitted by Benralizumab therapy.Blood eosinophil count of =300 cells/µL with =3 exacerbations in the previous one year, use of OCS, presence of nasal polyposis, and age =18 at the time of diagnosis of asthma are factors that are associated with a better response.[1]

Dupilumab

Dupilumab is a human monoclonal antibody that specifically targets the IL-4 receptor-a and inhibits the signalling of both IL-4 and IL-13. It has demonstrated efficacy in asthma, atopic dermatitis, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyposis.[21]

The candidates for dupilumab treatment includes those with severe eosinophilic asthma, patients with OCS-dependent severe asthma (eosinophil count and FeNO need not be high),blood eosinophils =150 cells/ µL and =1500 cells/µL or FeNO =25 ppb, or requirement for maintenance OCS, patients with more than a specified number of severe exacerbations in the last year and severe asthma with moderate to severe atopic dermatitis and chronic rhinosinusitis with nasal polyposis.[1]

Blood eosinophil count =300 cells/µL, experiencing more than one exacerbation in the previous year, FEV1<1.75 L, and elevated fractional exhaled nitric oxide (FeNO) levels have been associated with a favorable response to dupilumab treatment.[1]

Tezepelumab

The bronchial epithelium has gained considerable interest due to its role in the promotion and regulation of bronchial inflammation through the production of cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Among them,

TSLP has been extensively studied as a therapeutic target and is involved in both type 2-high and type 2-low inflammation.[22] Tezepelumab is a human monoclonal antibody which specifically targets TSLP.[22]

It may be considered as a first-line biological agent in patients with poorly controlled, moderate-to severe asthma, regardless of asthma phenotypes.Patients with basal blood eosinophils =150 cells/ μL and higher FeNO are associated with better response to Tezepelumab.[1]

Classification of Biologics: Summary[11]

Therapy	Mechanism of Action	Indication	Dosing and Route	Adverse Effects
Omalizumab	Anti-IgE; prevents IgE from binding to its receptor on mast cells and basophils	>6 yr old with moderate to severe persistent asthma, positive allergy testing, incomplete control with an ICS, and IgE: 30 1,300 IU/ml (United States, age 6–11 yr), 30–700 IU/ml (United States, age > 12 yr), or 30–1,500 IU/ml (European Union)	0.016 mg/kg per IU of IgE (in a 4-wk period) administered every 2–4 wks.c. (150–375 mg in United States; 150–600 mg in European Union)*	Black box warning: z0.1–0.2% risk of anaphylaxis in clinical trials
Mepolizumab	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	>12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC > 150–300 cells/ml	100 mg s.c. every 4 wk	Rarely causes hypersensitivity reactions; can cause activation of zoster
Reslizumab	Anti–IL-5; binds to IL-5 ligand; prevents IL-5 from binding to its receptor	>18 yr old with severe eosinophilic asthma unresponsive to other GINA step 4 5 therapies. Suggested AEC > 400 cells/ml	Weight-based dosing of 3 mg/kg i.v. every 4 wk	Black box warning: z0.3% risk of anaphylaxis in clinical trials
Benralizumab	Anti–IL-5; binds to IL-5 receptor a; causes apoptosis of eosinophils and basophils	>12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC > 300 cells/ml	30 mg s.c. every 4 wk for three doses; followed by every 8 wk subsequently	Rarely causes hypersensitivity reactions
Dupilumab	Anti IL-4R; binds to IL-4 receptor a; blocks signaling of IL-4 and IL-13	>12 yr old with severe eosinophilic asthma unresponsive to other GINA step 4–5 therapies. Suggested AEC > 150 cells/ml and/or FE_{NO} level > 25 ppb	200 or 300 mg s.c. every 2 wk	Rarely causes hypersensitivity reactions; higher incidence of injection site reactions (up to 18%) and hypereosinophilia (4–14%)

Conclusion

Fortunately most patients do not require biologics in asthma. Adherence to their controller medications and addressing the treatable traits are important in masqueraders. The traditional therapies of ICS and SABA/LABA can adequately control asthma in eighty five percent of cases. It is the remaining ten to fifteen percent cases who are the actual candidates for biological therapies. The goal now is towards a personalised approach based on the recognising endotype of asthma.

In summarising, for atopic asthma Omalizumab is preferred agent. In patients of atopic asthma with eosinophilia and non Atopic Asthma, Omalizumab, Anti IL5 or IL-5 receptor a that is Mepolizumab, Resilizumab Benralizumab respectively or Anti IL 4 that is Dupilumab can be used. In patients with Th2 low Asthma – Anti TSLP has some role however bronchial thermoplasty and in some cases Macrolides are commonly indicated.

Further studies and the need to develop new biologics are necessary to improve outcomes in patients particularly with noneosinophilic or T2-low disease. Novel imaging strategies[23] and immunoendotyping to develop new biomarkers[24] will lead to precise methods to identify the specific patients for the appropriate biologic therapies.

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Chapter

20

COPD: Emerging Therapies and Digital Health Integration

Dr. Priyam Goswami, Dr. Subham Kashyap

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a progressive, heterogeneous respiratory condition associated with significant morbidity and mortality. Conventional management—comprising smoking cessation, inhaled bronchodilators, corticosteroids, and pulmonary rehabilitation—provides symptomatic relief but does not halt disease progression. Emerging therapies, including biologics, kinase inhibitors, dual PDE3/4 inhibitors, antifibrotic agents, regenerative medicine, and gene therapy, aim to address underlying inflammation, fibrosis, and structural damage, with early evidence supporting phenotype-specific benefits. The Treatable Traits paradigm enables precision medicine by targeting individualized clinical and biological profiles, improving therapeutic efficacy while minimizing risks. Simultaneously, digital health interventions—such as telemonitoring, mobile health applications, and artificial intelligence—enhance early exacerbation detection, self-management, adherence, and personalized rehabilitation. Integration of novel pharmacotherapies with digital technologies offers synergistic potential to optimize COPD outcomes. However, barriers such as cost, digital literacy, data security remain. Future directions require real-world trials, robust biomarkers, and cost-effectiveness studies to guide widespread implementation.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder characterized by persistent symptoms and airflow limitation due to airway and/or alveolar abnormalities, typically caused by long-term exposure to noxious particles or gases. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD encompasses heterogeneous phenotypes such as emphysema and chronic bronchitis, often accompanied by exacerbations and comorbidities. Standard therapies—smoking cessation, bronchodilators, inhaled corticosteroids and pulmonary rehabilitation—provide symptom control and reduce exacerbation risk, but do

not alter disease progression or address the full spectrum of patient variability. The growing burden of COPD, coupled with its clinical heterogeneity and the limitations of current treatments, highlights the need for novel, personalized approaches. Emerging pharmacotherapies and the "treatable traits" paradigm, combined with digital health technologies—including remote monitoring, telemedicine, and artificial intelligence—offer opportunities to optimize care. This article explores these innovations and their potential to enhance outcomes in COPD management.

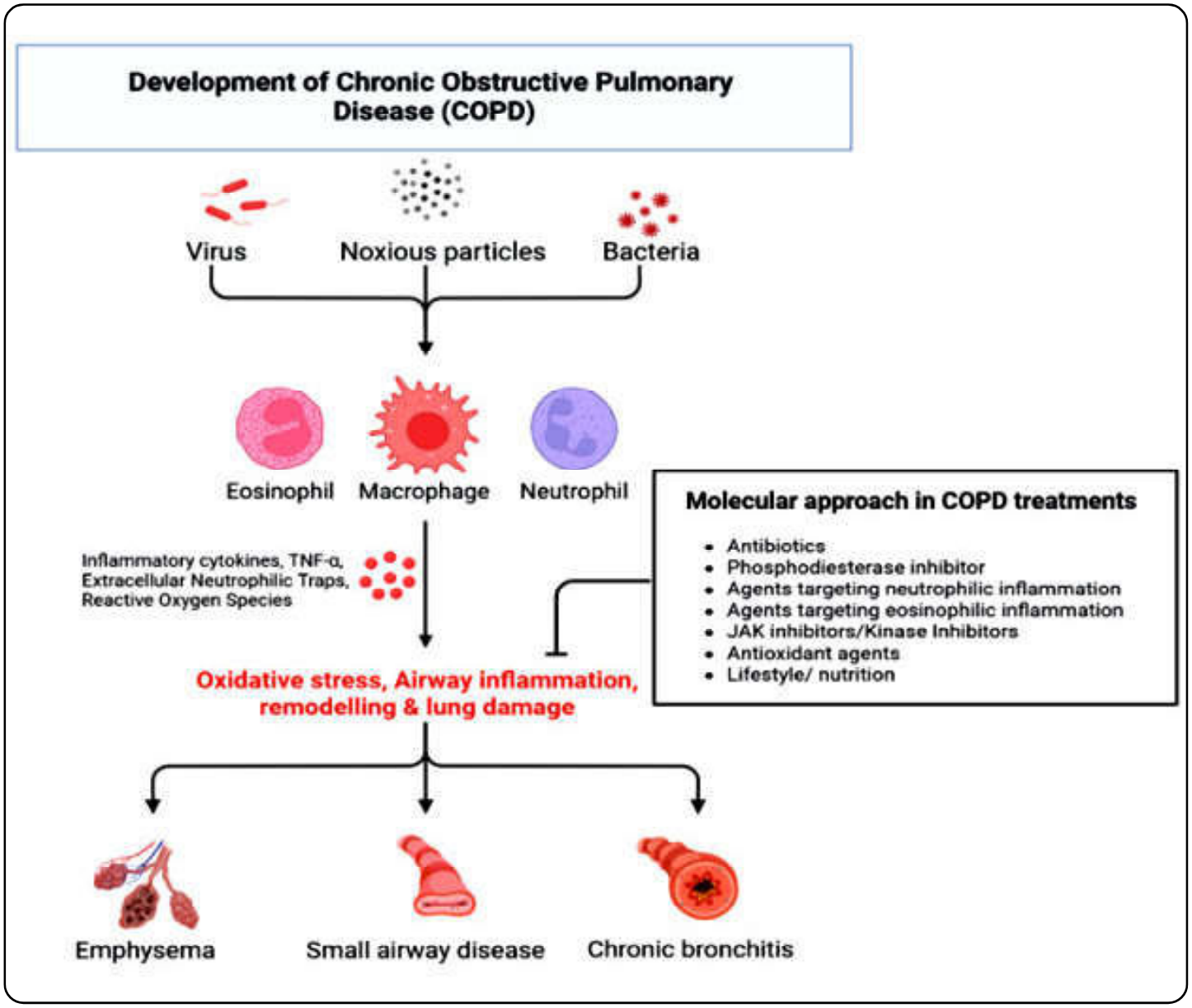

Fig 1: Pathogenesis of COPD

Section 1: Emerging Pharmacological Therapies

Current drug therapy of COPD with inhaled bronchodilators and inhaled corticosteroids provide symptom relief, reduce exacerbations and improve quality of life. However they do not slow disease progression or repair lung damage.

Drug development for COPD has shifted from bronchodilators towards disrupting the recruitment and activation of immune cells and also neutralizing the inflammatory mediators in lung parenchyma. COPD is characterized by chronic neutrophilic inflammation, eosinophilic airway inflammation or both. Moreover chemokines, cytokines, lipid mediators and growth factors sustain chronic inflammation and tissue modeling in COPD. Modulating these pathways can offer therapeutic benefit.

The "treatable trait" paradigm (TT) has emergedas a precision medicine strategy that advocatesfor identifying and targeting specific, modifiable,clinical, physiological, and biological traits ineach patient – traits which may co exist and evolveover time.This approach allows for personalizedtreatment. For example, eosinophilic inflammationmay respond to biologics (eg., ANTI IL5/IL6/IL13)while frequent exacerbations with neutrophilictraits may benefit from PDE inhibitors or macrolides.

TREATABLE TRAITS	
PULMONARY	• Airflow obstruction • Neutrophilic inflammation • Eosinophilic • Chronic bacterial infection
EXTRA PULMONARY	• Low BMI/Obesity • Systemic inflammation • Anxiety and depression • Co-morbidities
OTHERS (BEHAVIORAL)	• Smoking • Inhaler techniques • Adherence issues

Emerging pharmacological interventions align withspecific traits, supporting drug development guidedby patient phenotype or endotype.

Emerging Therapies

1. Biologics and targeted therapies
2. Disease modifying strategies
3. Novel bronchodilators

Biologics and targeted therapies

Biologic therapies represent a significant advancement in TT based interventions.

- One of the most clearly defined TT targeted biologics is Anti Interleukin 5(IL-5) agents like MEPOLIZUMAB and BENRALIZUMAB. They reduce eosinophilic inflammation in airways and as such useful in patients with eosinophilic phenotype(characterized by elevated FENO, eosinophilia with count of> 300/u and ACO)
- Another drug, DUPILUMAB an anti IL-4/IL-13 therapy has been approved by FDA in September 2024as an add on in the eosinophilic phenotype.It targets mucus hyper secretion, airway remodeling and co-morbid asthma.The drug Dupilumab has shown significant clinical

benefit and a decrease in type 2 inflammation in phase3 studies, establishing that IL4 and IL13 are two of the key central drivers of the disease.

- Anti Thymic Stromal Lymphopoietin (TSLP) agents like TEZEPELUMAB and Anti IL-33 agents like ASTEGOLIMAB, ITEPEKIMAB may be useful for allergic co-morbidities and overlapping asthma but has given mixed results.
- PDE4 inhibitors like ROFLUMILAST and TANIMILAST reduce neutrophilic inflammation and hence useful for patients with chronic bronchitis phenotype and high risk of exacerbations. It was approved years ago but side effects limit its use.
- Another FDA approved drug is dual PDE3/4 inhibitor ENSIFENTRINE which tackles neutrophilic inflammation. It offers combined anti-inflammatory and bronchodilatoryeffect.This drug was approved after two Phase 3 trials,which both met their primary endpoint by showing improved lung function. Further a pooled analysis of the two studies showed that it reduced flare ups through 24 weeks by 40% in patients with moderate to severe COPD.
- Other drugs acting on the neutrophilic pathway includes Chemokine receptor 2 (CXCR2) antagonist , Phosphoinositide 3 kinase (P13K delta inhibitor), anti IL17 therapies, neutrophilic elastase inhibitors, DPPI inhibitors etc., all in varying stages of trials and demonstrating varying efficacy.
- Alfa-1- anti Trypsin replacement currently in phase 2 trial is an excellent example of precision medicine approach. AATD is clearly defined and a measurable trait. It aims to counteract unopposed proteolytic activity and helps decrease emphysema progression.

Disease modifying strategies

➢ Therapies to mitigate lung damage.
- EDARAVONE and DEXAMETHASONE has shown synergistic effect in reducing smoke induced lung damage by reactive oxygen species and inflammatory cytokines in rats.
- TRANILAST: anti inflammatory and anti-fibrotic effects demonstrated on animal models in early pulmonary fibrosis and ARDS.
- Inhaled LIGUSTRAZINE has shown reduction in acute lung injury in rat models.

➢ Therapies to regenerate lung tissue
- Stem cell based therapy: Autologous transplantation of P63+ lung progenitor cells has shown improvement in lung function. Stem cell therapy holds promise as a potential treatment for COPD.It involves administration of stem cells,either derived from patients own body or from a donor to promote tissue repair and regeneration within the lungs.Mesenchymal stromal cells,peripheral blood stem cells, Endothelial progenitor cells are other forms of stem cell based therapies under trial.
- Gene therapy for alfa 1 antitrypsin therapy. (BEAM-302)
- Pirfenidone: TGF-beta mediated inhibition of fibrosis is being studied in COPD. It is already in use in Idiopathic pulmonary fibrosis.
- Club cell protein augmentation (CC16): Targets TGF beta and is under trial.

- Others include: DPP4 inhibitors (eg NZ 97); Prostanoid receptor blocker, mesenchymal stromal cell based therapies etc.

While these approaches are promising none are yet established. Large scale trials are needed to confirm safety and efficacy in humans.

Novel bronchodilators

- TAS2R agonist activates TAS2R in airways smooth muscle including bronchodilation via calcium mediated signaling (independent of beta 2 adrenoreceptor). They also have anti inflammatory properties making them ideal for bronchial hyper-responsiveness but clinical translationis limited.
- RHO kinase inhibitors has similar mode of action but also has vasodilator properties.
- PEPDUCINS are another class of newer bronchodilator handling both bronchodilation and persistent airflow obstruction.

All of the above bronchodilators are in early phase of trial.

- Dual PDE3/4 inhibitor ENSIFENTRINE as discussed above is a novel bronchodilator with anti inflammatory effect approved for use.

Thus the development of new treatments for COPD is an ongoing process,and more research is needed to better understand the cellular and molecular mechanisms involved in the disease for development of more effective therapies.

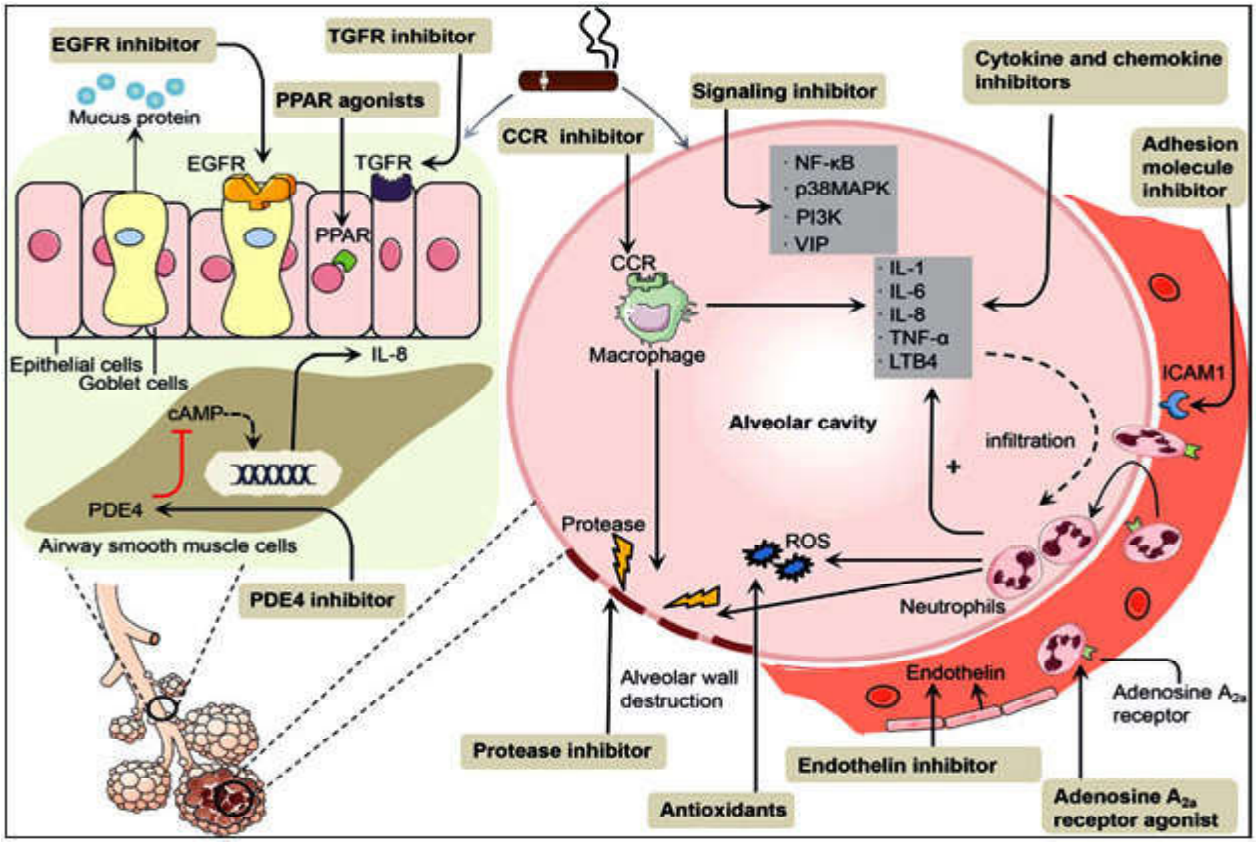

Fig 2: Mechanism of various emerging pharmacological therapies.

Section 2: Digital Health

Digital health encompasses a spectrum of solutions that utilize digital technologies to meet health needs. It includes Health Information technology (HIT), telehealth and telemedicine, mobile health (mHealth), wearable devices, artificial intelligence (AI), machine learning (ML), the Internet of Things (IoT) and digital therapeutics. These technologies have potential to change how COPD is screened, diagnosed, monitored and treated.

➢ Modalities of digital health:

1. mHealth: It refers to the use of cell phone and other wireless technology in healthcare. mHealth tools have been evaluated as user friendly. An example is SMART-COPD Android application operating in conjunction with a wearable activity tracing device designed to support COPD patients in maintaining or increasing physical activity. Apple has developed an ios application which helps users to monitor disease progression and share it with healthcare providers.
2. Wearable devices: Advances in sensor technology have led to the emergence of wearable devices which can constantly collect and track real time physiological and biological information. These devices include wristbands, armbands smart watches, rings etc.
3. Health Information Technology (HIT): HIT has been shown to improve healthcare quality, enhance efficiency, and reduce medical errors and promote patient safety.
4. Electronic Health records (EHR): The replacement of paper records with electronic versions significantly enhances the quality of subjectively reported outcomes. Health providers can input clinical, laboratory and radiological data into EHRs while patients can add information from wearable devices and other sources to be utilized for patient care.
5. Telehealth and Telemedicine: The term Telehealth and Telemedicine is often used interchangeably. However telehealth is more comprehensive with telemedicine being a subcategory of telehealth. Telehealth refers to the utilization of electronic information and telecommunication to aid in the remote delivery of health services. In COPD patients telehealth has shown to increase patient engagement in their own health leading to healthy lifestyle and improved medication adherence.
6. The Internet of Things (IoT): the IoT differs from traditional internet by connecting devices and machines without human intervention. IOT facilitates the continuous collection of clinical information through sensors, applications and remote monitoring. Zhang J. al developed an IOT system for smartphone that facilitates medicine reminders, data collection, health education and communications for COPD self management.
7. Predictive Analysis (AI and ML): Predictive analysis using "Artificial Intelligence" and "Machine Learning" can be used to gauge patient health states and exacerbation likelihood and potentially enhance medical decision making.

➢ Digital health in COPD:

- Facilitation of COPD screening and early diagnosis:

  PFT is the gold standard in COPD diagnosis and management. AI can be implemented for PFT

test result interpretation. It was shown that AI can interpret PFT with great degree of accuracy. Spirometers which are easily transported and can be equipped with data transfer capabilities to mobile devices or computers for study and monitoring by healthcare workers. Integrating digital peak expiratory flow (PEF) and symptom questionnaires increased the sensitivity of COPD screening.

About 70% of COPD patients remain undiagnosed worldwide. CT scan is a useful imaging tool for early COPD diagnosis. AI and ML have been employed for interpreting CT findings and for early diagnosis and staging of COPD.

- Digital health in COPD management :

  COPD patients need continuous monitoring and management. However obtaining in person medical care can be challenging. Telehealth offers a potential solution here. Telehealth may involve virtual interaction between patients and healthcare providers or data may be transmitted by internet for analysis by health care workers. A metanalysis incorporating 6 RCTs found an 80% reduction in exacerbations among patients enrolled in digital health programs.

➢ Electronic Inhaler Monitoring (EIM):

COPD management centersaround inhaler therapies. However a gap exists between results of trial and real world outcome. Accurately measuring inhaler use in clinical setting is challenging. EIM is a digital modality aimed at assessing adherence to inhaled therapy.

➢ Digital COPDself-management plans:

Mobile applications for medication adherence can empower patients to take proactive role in own health management and also reduce workload of healthcare providers. Mobile reminders and digital COPD action plans can be especially beneficial for patients with unintentional non adherence due to forgetfulness.

➢ Pulmonary rehabilitation:

Despite proven efficacy of Pulmonary Rehabilitation programs various obstacles has resulted in low rates utilization globally. The ATS and ERS recommend telerehabilitaton programs to COPD patients where digital technologies are used to provide rehabilitation in their own homes. It is more cost effective and has potential to be more effective.

Section 3: Intregation Of Digital Health Into Existing Health Care Systems

Integrating digital health into healthcare practice has a transformative potential in COPD management. However the process is complex and involves multiple stake holders including patients who transmit data, healthcare providers who receive it and service delivery platform comprising of both private and public entities.

Digital health is associated with risk like telehealth not meeting the standard of care, equipments or system failure, potential for abuse and manipulation,issues of confidentiality and privacy, ,legal implications and so on.

Thus to integratedigital health into clinical workflow will need further research so that health systems can determine the best course of action for selecting or developing a comprehensive digital health solution and plan.

Conclusion

COPD remains a significant global health challenge with high morbidity and mortality. Traditionaltherapies have helped but gaps remain. The treatable trait paradigm with emergingtherapies, target differentmechanisms and show promise in precisely addressing subtypes of COPD. Moreoverintegrating conventional and emerging therapies with digital health tools offers hope and promise for transforming management and prognosis of COPD patients in near future.

Recommendations For Practise And Future Research

- Clinicians can start adopting the treatable traits approach, where feasible by identifying biomarkers and phenotypes to guide therapy choices.
- For newer therapies monitoring outcomes rigorously in real world setting is imperative.
- Healthcare system can plan for digital health integration.
- Future research is needed for development of robust biomarkers and trait assessment tools. More RCTs are needed to study integration of emerging and conventional therapies with digital health integration.

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Chapter

21

Interstitial Lung Disease: Antifibrotic advances

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ABSTRACT

Fibrosing Interstitial Lung Diseases are known to be progressive with rapid decline in lung function ultimately proving fatal for the patients. Moreover, exacerbations can drastically increase mortality. Knowing the multifactorial and diverse mechanisms at play in the pathogenesis, treatment of ILD is challenging for physicians. Antifibrotics already in use, i.e. Pirfenidone and Nintedanib have proven to have some role but issues of tolerability and patient compliance remain. Newer antifibrotics have been studied targeting various pathways that may possibly be involved in the pathogenesis of fibrotic ILDs. Agents like Bexotegrast, Nerandomilast, Admilparant, Anlotinib and Buloxibutid all working via different pathways are being studied and shown to be efficacious in Phase 3 studies.

Introduction

Interstitial lung disease (ILD) refers to a heterogenous collection of lung disorders that are grouped together as they share clinical, radiographic and pathological features [1]. The pathogenesis of ILD is complex and includes many pathways that lead to epithelial cell injury, aberrant scarring and progressive fibrosis. It is said to have been initiated by multiple factors like genetics, toxin exposure, occupational exposures causing oxidative stress and mediated by a cascade of interleukins and cytokines. Though multiple agents have been tried in the management of ILD, most are directed at treating the underlying cause. When fibrosis sets in, only few agents are known to help prevent decline in lung function. Given the progressive nature of the disease, more antifibrotic agents are needed that have proven safety and efficacy. Only two agents, Nintedanib and Pirfenidone are approved worldwide as antifibrotics to be used in Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis, that have shown to have some role in reducing FVC decline. This article will give an insight on newer antifibrotics being developed or under clinical trials that have shown to have promising outcomes.

Antifibrotics

Pirfenidone is an oral antifibrotic agent that acts by targeting TGF- ß mediated fibrosis and tumour necrosis factor inhibition, thereby reducing abnormal collagen deposition in the interstitium. Various landmark trials like CAPACITY-I, CAPACITY-II and ASCEND have proven its efficacy as an antifibrotic in reducing FVC decline and improving progression free survival. It has also shown to cause reduction in exacerbations of ILD and symptomatic improvements in cough and breathlessness[2]. There is no absolute contraindication in using Pirfenidone. It is to be started at 200mg orally thrice daily and should be escalated to the therapeutic dose of 801mg thrice daily (2403mg daily) over a period of time as tolerated by the patients. It has been widely used due to its proven efficacy and it is mostly well tolerated, with few adverse effects, the most common being nausea, photosensitivity and elevated liver enzymes.

Nintedanib is an intracellular inhibitor of tyrosine kinase targeting fibroblast growth factor, vascular endothelial growth factor and platelet-derived growth factor. It displays antifibrotic effects by interfering with fibroblast proliferation, differentiation and migration and extracellular matrix (ECM) secretion along with anti-vascular remodelling. It is approved in treatment of IPF, systemic sclerosis associated ILD and progressive fibrosing ILD. Its efficacy has been proven by slower rates of FVC decline, reduction in acute exacerbations and decrease in 1 year all cause mortality. At a dose of 150mg twice daily, famous trials like IMPULSIS and SENSCIS have demonstrated its efficacy as a therapeutic agent in fibrosing ILDs. Regarding tolerability, mild side effects like diarrhea and elevation in liver enzymes are seen in some patients. It is also to be used cautiously in patients with high cardiovascular risk or high risk of bleeding, and is not preferred in liver failure patients (Child Pugh Class B).

Dual antifibrotics role

Pirfenidone and Nintedanib have both shown to cause reduction in decline in FVC and therefore widely used as antifibrotics in fibrosing ILDs. With this background, the INJOURNEY trial was started to evaluate the role of treatment with Nintedanib and add-on Pirfenidone. Decline in FVC over 12 weeks appeared to be less in patients treated with nintedanib with add-on pirfenidone than with nintedanib alone. The tolerability and safety were manageable.

Newer antifibrotics

Bexotegrast is an oral avß6 and avß1 integrin inhibitor preventing TGF-ß activation[3],[4]. An in vivo mouse model showed dose-dependent reduction of pulmonary collagen deposition and more potent collagen gene inhibition than clinically relevant pirfenidone and nintedanib doses, which validated its efficacy[4]. BEACON-IPF, a phase 2b/3 randomised, double-blind, dose-ranging, placebo-controlled study, is currently recruiting patients to evaluate the efficacy and safety of bexotegrast in IPF.

Phosphodiesterase 4 (PDE4) inhibition, by inhibiting the degradation of cyclic adenosine monophosphate (cAMP), thereby enhances effects of mediators that act through G-protein coupled receptor signalling, such as prostaglandin E2 (PGE2), prostacyclin and adenosine. PGE2 has several antifibrotic actions, including blocking fibroblast

activation, making fibroblasts more prone to apoptosis, and preserving the integrity of alveolar epithelial cells. Phosphodiesterase 4 inhibitors have been studied for their role as antifibrotic in this pathway[5],[6].

Nerandomilast, a specific PDE4B inhibitor has antifibrotic and immunomodulatory properties which have been demonstrated by preclinical data. It has also shown synergy with Nintedanib[7], [8]. Two phase 3 double-blinded RCTs were carried out for determining safety and efficacy of Nerandomilast: FIBRONEER-IPF, which included Idiopathic Pulmonary Fibrosis patients, and FIBRONEER-ILD which included Progressive Pulmonary Fibrosis patients. The results showed that the drug was able to reduce FVC decline from baseline compared to placebo. The adverse event most frequently seen in the study group was diarrhea, although serious adverse events were rare. Thus, the efficacy and tolerability of Nerandomilast is encouraging[9]. Currently, a new drug application has been submitted to the FDA by manufacturers of Nerandomilast based on the encouraging phase 3 clinical data, for treatment of Idiopathic Pulmonary Fibrosis and is awaiting approval.

Another pathway has been researched in relation to pulmonary fibrosis. It involves lysophosphatidic acid (LPA). LPA is a phospholipid produced by hydrolysis of lysophosphatidylcholine and it activates a family of six G protein-coupled receptors, LPA_{1-6} [10]. Among these receptors, lung fibrosis is mediated via LPA1 signalling. By promoting apoptosis of epithelial cells and increasing vascular permeability, there is increased intra-alveolar coagulation, fibroblast recruitment via chemotaxis to the injured sites and increased fibroblast resistance to apoptosis. When studied in animal models with bleomycin-induced fibrosis, high levels of LPA was found in bronchoalveolar lavage, while LPA1 receptor knockout protected them from fibrosis11. LPA levels were similarly increased in bronchoalveolar lung fluid and exhaled breath condensates in patients with IPF[11]. LPA1 antagonism may therefore represent a valuable therapeutic target for IPF and PPF. Admilparant, a LPA1 antagonist, demonstrated efficacy irrespective of background antifibrotic therapy by showing lower FVC changes over 26 weeks compared to placebo in IPF and PPF patients. This was shown in a phase 2 double blind RCT. The safety and tolerability has also been demonstrated[12]. Currently, several phase 3 RCTs are evaluating the role of Admilparant in IPF and PPF. Treprostinil has also shown to have antifibrotic effects through suppression of PPARß activation and fibroblast proliferation.

The hedgehog signalling pathway is functional during embryonic phase for cell proliferation, survival factors and tissue pattern formation but in later life, it aids in normal tissue repair. It is overactive in certain diseases with tissue injuries, like pulmonary fibrosis. It is dysregulated in such diseases leading to overproduction of myofibroblasts and its resistance to apoptosis leading to aberrant collagen deposition[13]. Taladegib, a transmembane protein in this pathway was studied but discontinued due to tolerability issues.

Anlotinib, already approved for the treatment of advanced non-small-cell lung cancer, represents a novel, multitarget small molecule tyrosine kinase inhibitor, with similar targets to nintedanib, such as vascular endothelial growth factor, fibroblast growth factor and platelet-derived growth factor receptors. A phase 3, multicentre, randomised, double-blind, placebo-controlled clinical trial with FVC as a primary endpoint is being conducted

for anlotinib for the treatment of patients with IPF/PPF[14]. This agent is expected to hold promising results in the near future.

Finally, angiotensin type 2 receptor (AT2R) agonism has also been studied as a therapeutic target for lung fibrosis. Apoptotic alveolar cells, macrophages and myofibroblasts enhance production of angiotensinogen leading to angiotensin II binding to angiotensin type 1 receptor (AT1R) and AT2R in experimental models of lung fibrosis[15]. Both AT1R and AT2R are upregulated in fibrosis but AT1R is predominant, and its expression is profibrotic and proinflammatory. Buloxibutid (C21) is an oral, selective AT2 receptor agonist with potential anti-fibrotic properties. A phase 2, multicentre trial called AIR, was done to prove the safety and tolerance of the drug[16]. Buloxibutid was well tolerated with no serious adverse events reported. ASPIRE is a global 52-week phase 2b evaluating the safety and efficacy of buloxibutid as a treatment of IPF. It is recruiting patients and results are much awaited.

Conclusion

ILDs being multifactorial, different pathways need to be targeted for therapy. Newer antifibrotics have encouraging results and may help halt disease progression. Along with immunomodulatory agents, combination therapies may be tried for effectiveness. More research is warranted in this field and a tailor-made approach for every patient may then be tried on the basis of available agents.

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Chapter

22

Host- Directed Therapies in Koch's Infection- Exploring Immunomodulators and Adjunctive Therapies for better outcome

Dr. Mihir Kr. Goswami

TB also known as consumption was and still to some extent a disease with variable prognosis. It was fatal and a disease with high degree of mortality characterized by the wide spread nature before the advent of Antibiotics and was sometimes romanticized during Victorian ages in England as a cause of artistic sensitivity. As there are risks of gross wasting and weight loss, phthisis (from the Greek word for wasting away), the white plague (due to the pale complexion of patients) and scrofula (for TB affection the Neck & lymph glands) are the other names used for this disease. Great individuals who were victims of TB infection include historical figures like Simon Bolivar Ringo Star, Nelson Mandela, Mohammad ALI Jinna (the founder of Pakistan) amongst politicians and also writers like George Orwel, D.H. Lawrence and Anton Chekhov and many other politicians, artists and social activists including Netaji Subhash Bose & Friederic chopic also contracted disease.

In India, approximately2.607 million (26.07 lakh) TB cases were notified in 2024, according to Ministry of Health and Family Welfare (Govt of India). The country's NTEP reported a significant rise in case notifications during the years 2023 and 2024, indicating progress in detection & reporting, although the good news is that the overall incidence in declining. While the figures vary, the estimated incidence of new TB cases for 2023 was around 2.78 million. It is pertinent to mention that India accounts for 28% of the world's new TB cases, but this incidence rate is declining faster than global average. Further another important milestone achieved is the fact that the nation met its 2023 target for initiating treatment in 95% of diagnosed patients.

The treatment of TB evolved from ancient concepts of fresh air and diet to Sanatoriums, and then underwent a revolution with the discovery of streptomycin in 1943 by salmon Waksman, followed by I.N.H and combination therapies in the 1950 s and early 60s, which dramatically improved outcomes by reducing Drug Resistance. One of the key break through was introduction of combination Therapy by the M.R.C (Medical Research Council) to combat Resistance. Today's treatment plans typically involve a combination of antibiotics, with treatment during variability but of

several month's duration to address active or inactive TB. At present, due to continuous R&D activities, newer drugs and diagnostic tools are being developed to combat both Drug-sensitive & DR-TB and improve treatment outcomes.

The history of the TB control program, especially in India, has evolved from the early days of BCG vaccination efforts and the NTCP initiated in 1962 and its evolution into RNTCP starting from1993 and the current NTEP launched in 2020. The key features of the latter programs include- 1) Introduction of DOTS strategy 2) Expansion of network of free diagnosis and treatment 3) Integration of Drug-resistance management & 4) Ongoing thrust towards Universal Drug Susceptibility testing 5) Focus on social determinants of Health to achieve TB elimination. A great influence in the rising TB trend is H.I.V infection. Chances are that only one tenth of immune competent people infected with M Tb will be clinically affected during their life time with active TB, but in contrast, in those with (TB-HIV) infection one tenth of the entire number will develop per year the active TB infection. Moreover half or one third of the Tuberculin positive AIDS patients have the risk of development of active TB infection.

Another contributory factor for resurgence of Koch's infection is the burning issue of DRTB, occurring as a result of mutation of causative organism. The mutations are not dependent upon the presence of drug. Exposed to a single effective anti TB medication, the predominant bacilli, sensitive to that drug are destroyed, the few Drug Resistant mutants likely to be present if bacterial population is large and will multiply freely. While we are waiting for the path- breaking treatment for TB, various pertinent factors should be considered during the ongoing process for search of novel yet effective ATT. If these issues are addressed, we could hope to develop a more effective treatment that could cure MDR-TB/ XDR-TB besides drug sensitive TB. It will Definitely contribute to meet the WHO's as well as that of Ministry of Health and Family Welfare (Govt of India) targets for controlling the global TB pandemic within the prescribed timeline.

Immune Modulatory drugs modify the immune system's activity, either by enhancing (immune stimulators) or lowering (immunosuppressant's) its response. These are used to treat various conditions including autoimmune diseases (like multiple Sclerosis), Malignancies (e.g multiple myeloma) and Asthma. These include Thalidomide, Lenalidomide, Azathioprine and cyclosporine, with some working by stimulating the immune system to combat diseases and others by suppression of prevention of damage.

Immune Modulatory drugs are natural or synthesized compounds that also activate or suppress the immune system by the release of either pro-inflammatory or anti-inflammatory cytokines in order to help the immune system deal with a pathogen more effectively. Proinflammatory responses by cytokines released by T cells such as IFN-y , TNF-a in association with IL- 6, IL-1 and chemokines such as CCL5, CCL9, CXCL10, and CCL2 attracts immune cells at the site of infection and lead to the effective elimination of the pathogen. The pro-inflammatory cytokine response mainly leads to initiating a cascade of events that ultimately leads to the killing of M Tb. The immune Modulatory drugs act on different immune cells such as neutrophils, macrophages, lymphocytes, natural killer(NK) cells to exert their effectors responses aimed

clearing the bacteria from the host. The mechanism of action of immune-modulators has been mentioned herewith.

These immune modulatory drugs have gained tremendous attention in anti-TB therapy as these compounds when administered together with the DOTS regime helps in the early clearance of the infection as well as aids in the prevention of drug –resistance development. Many of the immune Modulatory drugs help mask the side effect of the harsh anti-TB antibiotic therapy. Here, in this article, we discuss these immune modulatory drugs, which display promising effects against TB and hence have been repurposed for use against M Tb. The drugs that we will discuss appear to be the most significantly studied in case of TB. We also highlight their mechanism of action along with any study if present for their use as immune-modulators as an adjunct therapy against TB (Table 1).

Immune Modulatory drugs in TB are compounds which are used alongside ATT (including D.O.T.S) to modulate the host's immune response, enhancing the body's ability to combat M tb and reducing tissue damage caused by inflammation, particularly in DR-TB. Key examples include active vitamin D(1,25- Dihyetroxy Vitamin D3), Histone DeAcetylase (HDAC), inhibitors like sodium phenyl butyrate (PBA), and Arginine, which works by increasing antimicrobial Nitric oxide Production. These Host directed therapies can boost anti microbial immunity, improve, and potentially prevent DrugResistance when used as adjunct therapies. Regardless of the latest resurgence in political will to combat TB, the ailment stays the leading cause of demise from a single infections agent around the globe **(1)** As per the WHO-TB report (2021), during the calendar year of 2020, there were an estimated 1.3 million HIV (-Ve) individuals died of TB and 2.14 lakh among the HIV (-VE). Thereby the **"END TB strategy's"** milestones and aims push public health and interdisciplinary science skills to their limits in combating TB.

Repurposing of drugs reduces the expense of the drug discovery program and enables us to circumvent clinical phase I which is conducted for ensuring safety. Akinpelu et al. defined repurposing with a broader perspective as identifying new indications for existing drugs and failed (demonstrated to have efficacy for a particular indication during phase II or III trials but have no major safety concerns), abandoned, or yet-to-be-pursued as clinical candidates to new disease areas. Drug repurposing is the process of identifying novel medicinal-target interactions of well-established drug therapies with the goal of using them to treat various ailments.

Pharmaceutical corporations and academic researchers are both interested in this tactic again because of its potential to lower costs, de-risk clinical trials, and cut down on the time needed to launch a medicine for a new use. However, identifying new clinical use for molecules that fails during the clinical development stage for its original goal (efficacy for a specific clinical condition) is referred to as drug rescue. Techniques for drug discovery and repurposing primarily rely throughput chemical screens. However, a repurpose screen and a drug discovery screen screen differ significantly from one another. Small libraries of failed or authorized compounds with some understanding of their safety or mechanism of action (MoA) are used for experimental screening to find a repurposing candidate.

Table 1 : Repurposed drugs with their year of introduction and status in TB treatment.

Name of drug	Year of Introduction	Status of the drug	Properties and efficacy against TB
Clofazimine	In 1969 for the treatment of leprosy	Approved	Reduces the treatment length for drug-resistant TB and displays immune-Modulatory properties
Statins	In 1959 for cardiovascular diseases	Phase 2 clinical trials	Anti-inflammatory and immune-Modulatory
NSAIDs	In 1969 for the treatment of rheumatoid arthritis	Phase 3 clinical trials	Anti-inflammatory and immune-Modulatory
Fluoroquinolones	In 1962 for the treatment of bacterial infection	Approved f	By inhibiting the replication and transcription of bacterial DNA
Linezolid	In 1990 for vancomycin-resistant Enterococcus faecium infections	Approved	Acts as a protein synthesis inhibitor
Verapamil	In 1968 for treating blood pressure	Phase 2 clinical trial	Calcium efflux blocker, which reduces the duration of TB therapy
Metfomin	In 1922 to treat diabetes	Phase 2b clinical trial	Immune Modulatory
Amoxicillin/ clavul anic acid	In 1974 for treatment of bacterial infections	Phase 2 clinical trial	Prevents bacterial cell wall synthesis
Carbapenems	In 1976 to inhibit beta lactamase enzyme	Phase 2 clinical trials	Target the cell wall of M.tb bacteria
Sulphonamides and their derivatives	In 1956 against gram positive and gram negative bacteria	Approved	Used as combination therapy against drug resistant TB

Though R&D works for a newer anti TB drug is going on for a long standing period the entire process without any iota of doubt is time consuming. It may even take decades to fulfill this aim . In addition cost & expenditure is another factor which comes into consideration in this aspect. Hence repurposing of DRUGs in such eventuality is definitely a solution. Drug repurposing is also known as drug Repositioning is the strategy of identification of newer therapeutic, investigational or previously failed drugs. As mentioned just now, this approach is an effective substitute for traditional drug discovery which is no doubt a high risk process. By leveraging existing safely data from the earlier developmental stages, Drug repurposing can

enhance the delivery of newer therapeutics which is true in case of KOCH's infection also. It can also maximize the potential value of Drug compounds by delving into the additional medical applications excluding their originally intended uses repurposing is not always a serendipitous incident. By use of the following combined approaches, the process of repurposement may be a systemic & rational process.

Bacterial Ghosts

BGs are immune stimulants which lead to enhanced host immunity against M Tb. Actually these are intact cytoplasm free E. Coli envelopes, initially developed as bacterial vaccine and for adjunct therapy along with immune therapies in Malignancies. BGs are activators of Macrophages which lead to augmented Nitric Oxide Production and patent induction of DCs for effectors immune I lymphocytes proliferation & corresponding cytokines production.[2,3]

In this context, I want to made mention-about a very commonly used drug which is unfortunately frequently sold over the counter. These NSAIDs are a class of drugs which as all of us know-used to treat mainly inflammation[4] which is done by inhibiting prostaglandins, which mediate the inflammatory process. The main mechanism through which NSAIDs work during TB treatment is by reducing the inflammation caused by the influx of monocytes, lymphocytes and neutrophils[5] by virtue of the production of huge amount of (PGE2), the causative factor of inflammatory process. NSAIDs reduce inflammation caused by migration of above mentioned cells during active TB & contribute to improvement in outcome of koch's infection.[6] [7]

It is pertinent to mention that Drug Repurposing also identifies new application of already banned drugs from the market. In Drug designing this very act of repurposing plays an important role, as because it helps to preclinical development. The process may also be designated as Drug Repositioning, drug redirecting or Drug Reprofiling.

In the conclusion it must be mentioned that there is a crying need for a novel and enhanced treatment in the field of Tuberculosis, since the frequency of resistance in the M tb population is alarming. It is imperative for the researchers to study the methodology by which the repurposed drugs affect the balance of the host's immune system and also the management of infection and inflammation. This is because of the fact that host directed therapies mainly focus on the effects of the host's immune system. There is a high degree of possibility for development of a more effective combination therapy which will be designed to contribute to achieve the goal of "End TB strategy" as envisioned by the Honorable Prime Minister Sri Narendra Modi at the End TB summit held in New Delhi in March 2018 , which was further reite rated during the "One World TB summit" of 2023 that was held in Varanasi on World TB day 2023.

Host Directed Therapies in KOCH'S Infection is advantageous because of the fact that it acts by reducing treatment time and prevention of the rising problem of Drug Resistance with maintenance of the point of cost-effectiveness for the benefit of general public. It must be remembered that "SDG- END TB target" aims to reduce mortality to 3.2 per one lakh population by 2030, which is only possible with the adoption of Host Directed Therapies along with the main course of treatment in a protocol zed manner.

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Section 7
Nephrology

Chapter

23

Role of Precision Medicine and Biomarkers in CKD Progression

Dr. Anup Kumar Barman, Dr. Prodip Kr. Doley, Dr. Anannya Goswami

1. Introduction

Chronic kidney disease (CKD) is a global health burden affecting more than 850 million people worldwide[1]. Large meta-analyses report a CKD prevalence of around 10–13% (stages 1–5) and approximately 5–10% for moderate-to-severe CKD (stages 3–5) [2]. It is projected to become the 5th leading cause of years of life lost by 2040 [2]. Biologically, CKD is characterized by sustained alterations in kidney structure and function arising from a wide range of etiologies and associated with a multitude of underlying molecular processes in the kidney. Regardless of theetiology, progressive CKD is characterized by maladaptive activation of the kidney's hemodynamic, inflammatory, and fibrotic pathways [3].This multifaceted burden underscores the urgent need for improved prevention, early detection, personalized treatment and management strategies for CKD[2].Precision medicine is transforming nephrology by shifting from a **"one-size-fits-all"** approach to a **personalized, mechanism-based strategy** for slowing CKD progression.

2. Why Precision Medicine is Needed in CKD

2.1 Precision medicine uses the phenotypes and genotypes of individuals to tailor the best therapeutic approach at the appropriate time, to identify a person's propensity for disease, andprovide timely and targeted prevention. Chronic kidney disease (CKD) exemplifies the need for precision medicine, given its heterogeneous nature. Traditional biomarkers, such as estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (uACR), have long been the cornerstone of CKD diagnosis and management. However, these markers homogenize a diverse group of distinct conditions within CKD. This conflicts with the principles of precision medicine.

2.2 Precision medicine in CKD aims to:

1. Identify individual risk for rapid CKD progression
2. Tailor interventions based on molecular pathways—not just symptoms
3. Improve prediction of therapeutic response
4. Detect kidney injury earlier than conventional markers[4].

3. Precision Medicine Tools in CKD

3.1 1. Multi-Omics Platforms

A. Genomics (DNA-level)

Examples:

APOL1 risk alleles ? rapid CKD progression in African ancestry

UMOD, HNF1B, COL4A3/A4/A5 ? monogenic renal diseases

Used for: diagnosis, risk prediction, family screening.

B. Proteomics

Evaluates protein signatures associated with CKD progression

Key tool: CKD273 proteomic classifier.

C. Metabolomics

Detects changes in small molecules and metabolites

Example:

Kynurenine pathway metabolites

D. Epigenomics

Studies DNA methylation, histone modifications

2. Molecular Imaging Tools

Provides insight into kidney structure and function beyond standard ultrasound.

A. MRI-based tools

Diffusion-weighted MRI → fibrosis

BOLD MRI → oxygenation

B. PET Imaging

Detects inflammation, fibrosis, macrophage activity

3. Digital Health and Artificial Intelligence

AI enhances prediction, classification, and personalized management.

Examples:

Algorithms integrating biomarkers + clinical data Electronic health record based precision prediction tools.

AI-driven risk calculators outperform traditional scores like KDIGO or eGFR trend.

4. Pharmacogenomics

Helps determine how a patient responds to medications.

Examples:

Genetic variants affecting RAAS blockers.

Response to immunosuppressants (e.g., CYP3A5 genotype for tacrolimus dosing).

5. Role of Biomarkers in CKD Progression

It is important to clearly define the intended role of the biomarker, which has been broken down into the following categories:

1. Diagnostic
2. Monitoring
3. Prognostic
4. Predictive
5. Pharmacodynamic/response
6. Safety
7. Susceptibility/risk

3.2 Each individual biomarker should also fulfil the following criteria:

1. **Biological plausibility:** the biomarker should be clearly and understandably connected to the biological mechanisms of the disease .
2. **Measurability:** it should be possible to measure the biomarker accurately and reproducibly using standardized methods .
3. **Validation:** Includes both analytical validation of the biomarker measurement and clinical

validation in terms of ensuring that it reliably predicts the clinical outcome assessments across different populations.

There has been increasing interest in the study of novel blood and urine biomarkers in CKD over the past 20 years. Dedicated longitudinal CKD cohorts, such as the Canadian Study of Prediction of Death, Dialysis and Interim Cardiovascular Events (CanPREDDICT), the Chronic Renal Insufficiency Cohort (CRIC) Study, and the National Unified Renal Translational Research Enterprise (NURTuRE), have been established to facilitate this [5]. Evidence now supports the role of various biomarkers in reflecting the diverse mechanisms driving CKD progression. [6]

3.3 Biomarkers of Inflammation

Inflammation is key in CKD progression, driven by pro-inflammatory cytokines and immune cells. sTNFR1 has been extensively examined as a prognostic biomarker in CKD and can be measured via commercially available ELISA or as part of a Meso Scale Discovery (MSD) multiplex immunoassay platform and has been shown to both predict CKD progression and mortality.[7]. IL-6 can similarly amplify inflammatory and fibrotic processes, playing a direct role in the development of cardiovascular disease. It is reliably measured in serum, and strong evidence supports its use as a prognostic biomarker for cardiovascular events in CKD[7].Importantly, these biomarkers also have actionable targets.

Oxidative Stress

Oxidative stress plays a crucial role in the progression of CKD through the overproduction of ROS. The RENIS study explored the predictive value of oxidative stress biomarkers, specifically urinary 8-oxodG and 8-oxoGuo, as potential early diagnostic indicator of kidney dysfunction. Higher urinary levels of 8-oxoGuo were independently associated with an increased risk of developing low-grade albuminuria, highlighting its potential as a sensitive diagnostic biomarker.[8]Therapeutics aimed at reducing oxidative stress have been explored. While initial studies with xanthine oxidase inhibitors like allopurinol showed some efficacy in slowing kidney function decline, larger RCTs such as PERL and FEATHER, which examined allopurinol and febuxostat, respectively, found no significant differences in the rate of eGFR decline.

Extracellular Matrix Deposition

ECM components such as collagen and fibronectin accumulate excessively when myofibroblasts are activated through pathways like TGF-ß, and Notch.[9]TGF-ß1, measured by ELISA, demonstrated superior predictive accuracy compared to eGFR and uACR for the progression of DKD.An ongoing phase 2 TOP-CKD trial (NCT04258397), aiming to recruit 200 people with an eGFR =20 mL/min/1.73 m2 at risk of progression, will assess the effectiveness of pirfenidone to slow CKD.

Fibrosis

Fibrosis can be considered a final “common pathway” resulting from inflammation and oxidative stress, which significantly limit clinicians’ available therapeutic options. [10]. However, currently, the only validated tool to assess the severity of tissue damage is the kidney biopsy.A number of specific biomarkers of

renal fibrosis have been explored includingTIMP-1. Also, urinary Dickkopf-3 (DKK3), a stress-induced glycoprotein released by tubular epithelial cells, induces tubulointerstitial fibrosis through the Wnt/ß-catenin pathway. It can be measured via commercially available ELISA. Another biomarker of renal fibrosis is klotho, an anti-ageing protein highly expressed in kidney tubular epithelia.

Tubular Injury

The degree of tubular injury on biopsy correlates with CKD progression.Examples are kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), which have been extensively studied in CKD, and both have commercially available assays [11].

Biomarkers to Monitor Response to Treatment

The ESCAPE trial, an RCT looking at the impact of intensified blood pressure control on the progression of CKD in children, measured the novel urinary biomarker DKK3 at regular intervals [13]. The study found that higher levels of urinary DKK3 were linked to a more significant decline in eGFR over 6 months, independent of other clinical variables. Importantly, those with elevated urinary DKK3 levels also experienced greater benefits from RAASi, highlighting its utility as a "response biomarker."PLA2R antibodies monitor membranous nephropathy remission.

Biomarkers in Clinical Trials

While albuminuria remains a generic marker of glomerular damage in IgA nephropathy, measuring pathogenic galactose-deficient IgA1 (Gd-IgA1) as a biomarker [14], as done in the NefIgArd trial, shows promise.

4. Clinical impact of precision medicine in CKD

4.1 For genetic risk, the genotype-phenotype associations for the gene APOL1have been a pivotal moment for precision nephrology.Variants in APOL1 have been found to increase the risk of CKD in Black populations. Those carrying two APOL1 risk alleles have almost a 30-fold increased risk of CKD and cardiovascular-related mortality (odds ratio 1.8).[15].A recent instance of reporting of variants on the PKD1 gene in autosomal dominant polycystic kidney disease (ADPKD) turned out to be the first of its kind performed in a clinical setting using whole-genome sequencing. Clinical trials are highlighting novel interventions as well. In a major multicenter placebo-controlled trial, TEMPO, a vasopressin-2 receptor antagonist was shown to slow the increase in total kidney volume and the decline in kidney function and slow cyst growth. This drug was developed by using genomic information from patients with ADPKD.

4.2 In an Artificial Intelligence in Renal Scarring (AIRS) study, machine learning models for noninvasive quantification of kidney fibrosis from imaging scans have been developed. The Singapore Epidemiology of Eye Diseases used a multiethnic cohort to develop and validate a deep learning algorithm that can detect CKD using retinal images.

5. Challenges and Future Directions in Precision Medicine for CKD

1. High Cost and Limited Accessibility of Biomarker Testing.

2. Insufficient Validation Across Diverse Populations.
3. Difficulty Incorporating Precision Tools Into Daily Clinical Practice.
4. Ethical and Privacy Concerns Around Genetic Information.
5. Limited Long-Term and Real-World Evidence.
6. Need for Clinically Interpretable AI and Prediction Models.

Conclusion

Moving beyond traditional markers such as serum creatinine, eGFR, and albuminuria, emerging biomarker technologies and multi-omics tools offer the ability to detect kidney injury earlier, identify patients at greatest risk for rapid progression, and guide interventions tailored to individual molecular pathways. These advances have the potential to improve prediction of therapeutic response, reduce unnecessary treatment exposure, and ultimately slow CKD progression more effectively. However, the integration of precision-based strategies into routine practice remains challenged. As future research continues to refine biomarker panels, enhance AI-driven predictive model, management of CKD is expected to evolve towards a more personalized, proactive, and mechanism-guided paradigm.

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Chapter

24

Dialysis Innovations: Wearable and Home-Based Systems

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ABSTRACT

Introduction:

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) impose a major global health burden. Conventional in-centrehaemodialysis (HD) is effective but limits patient autonomy and quality of life. Recent innovations focus on patient-centred solutions, including home-based and wearable dialysis systems that offer flexibility, independence, and better physiological outcomes.

Rationale for Innovation:

Traditional HD causes cardiovascular stress, disrupts daily life, and demands high resources. Home-based and wearable systems aim to improve solute control, empower patients, and reduce healthcare burden, especially in resource-limited settings.

Home-Based Dialysis Systems:

Technological advances in compact HD machines, automated peritoneal dialysis (APD), and telehealth monitoring have improved safety and convenience. Frequent home HD shows superior cardiovascular and biochemical outcomes, though barriers like training and cost persist.

Wearable Artificial Kidney Systems:

Miniaturised, sorbent-based devices enable continuous ambulatory dialysis, enhancing mobility and comfort. Despite early clinical success, technical and regulatory challenges remain.

Conclusion:

The evolution toward home-based, wearable, and future implantable artificial kidneys marks a transformative era in renal care, focused on restoring independence, accessibility, and quality of life.

1. Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) continue to impose a substantial global health burden, affecting more than 850 million people worldwide[1]. Dialysis remains the predominant renal replacement therapy for most patients, yet conventional in-centrehaemodialysis (HD) presents major limitations, including inflexibility, reduced quality of life, and incomplete physiological replacement of renal function[2].

Historically, dialysis innovation has focused on improving toxin clearance and haemodynamicstability during treatment. However, recent decades have seen a shift toward patient-centred innovation, emphasising independence, convenience, and improved clinical outcomes. This evolution has led to two major transformative directions: (1) home-based dialysis systems, which allow patients to perform HD or peritoneal dialysis (PD) at home with remote clinical support, and (2) wearable or portable artificial kidney systems, which miniaturise dialysis technology to enable continuous, mobile therapy[3,4].

These developments represent a paradigm shift in renal care—from institutional, intermittent dialysis toward decentralised, personalised, and potentially continuous renal support. This chapter explores the technological, clinical, and societal dimensions of these innovations, focusing on design principles, clinical evidence, challenges, and future directions.

2. Rationale for Innovation in Dialysis

2.1 Limitations of Conventional Haemodialysis

In-centre HD typically involves 3–4-hour sessions, three times per week. Although effective for solute clearance, such intermittent therapy produces significant fluctuations in intravascular volume, blood pressure, and solute concentrations[5]. These oscillations are associated with cardiovascular stress, myocardial stunning, and increased mortality[6].

Furthermore, traditional HD severely limits patient autonomy. The need to attend a dialysis unit multiple times per week disrupts employment, family life, and travel, and has been associated with reduced quality of life and increased depressive symptoms[7].

From a systems perspective, in-centre dialysis is also resource-intensive, requiring large volumes of water (up to 120 L per treatment), staff supervision, and infrastructure. For low- and middle-income countries (LMICs), this represents a major access barrier[8].

2.2 The Case for Home-Based and Wearable Systems

Home-based and wearable systems offer several potential advantages:

- Improved physiological outcomes: More frequent or prolonged dialysis better approximates native kidney function, achieving improved fluid and solute control and reducing cardiovascular stress [9].
- Patient empowerment: Patients can schedule treatments flexibly and participate more actively in their care.
- Reduced healthcare burden: Decentralising dialysis may decrease hospitalisations and infrastructure costs.
- Accessibility: Portable or home-based systems can extend treatment access to rural and resource-poor settings[10].

3. Home-Based Dialysis Systems

3.1 Overview and Modalities

Home-based dialysis encompasses both home haemodialysis (HHD) and home peritoneal dialysis (PD). HHD allows patients to perform treatments using compact, user-friendly machines with simplified water handling and remote monitoring capabilities[11]. PD,

particularly automated peritoneal dialysis (APD), uses cyclers that perform exchanges overnight, often integrated with telemonitoring platforms[12].

3.2 Technological Innovations

Modern HHD machines (e.g., NxStage System One, Tablo, and Physidia S3) are designed for simplicity, safety, and compactness [13].

They employ pre-packaged dialysate, low flow rates, and modular cartridges to enable home operation.

Telehealth integration allows clinicians to remotely monitor treatment parameters such as ultrafiltration volume, conductivity, and pressures [14]. The Baxter AMIA APD system, integrated with the SHARESOURCE platform, exemplifies remote monitoring, enabling clinicians to adjust prescriptions and identify complications early [15].

A notable innovation in PD is on-demand dialysate generation. Baxter's home solution generation system filters tap water to produce sterile PD fluid, reducing the storage burden of fluid bags and transportation logistics [16].

3.3 Clinical and Quality-of-Life Outcomes

Home dialysis, particularly frequent HHD, has demonstrated superior cardiovascular and biochemical outcomes. The FHN Daily and Nocturnal Trials showed improved blood pressure control, regression of left ventricular hypertrophy, and enhanced phosphate clearance with more frequent home treatments [17].

Home dialysis also improves patient-reported outcomes, including satisfaction, sleep quality, and autonomy [18]. However, adherence, training, and psychological readiness remain important determinants of success.

3.4 Barriers to Adoption

Despite its advantages, global uptake of home dialysis remains modest (<15% of dialysis patients). Barriers include [19]:

- Training requirements and caregiver burden
- Home infrastructure limitations (water, space, power)
- Infection risks (especially for PD)
- Regulatory and reimbursement disincentives

3.5 Future Directions in Home Dialysis

Next-generation home systems will integrate AI-driven decision support, automated alarms, and predictive analytics for early complication detection [20]. Efforts to reduce machine footprint, energy use, and cost will enable broader adoption, including in LMICs [21].

4. Wearable and Portable Artificial Kidney Systems

4.1 Concept and Rationale

The wearable artificial kidney (WAK) aims to transform dialysis from an episodic, centre-based procedure into a continuous, ambulatory therapy. By miniaturising components and employing dialysate regeneration technology, WAK systems seek to replicate native renal function more closely [22].

4.2 Technological Components

Key technological pillars include:

- Sorbent-based dialysate regeneration: Recycles a small volume of dialysate by removing urea, creatinine, and electrolytes through sorbent cartridges containing activated charcoal, urease, zirconium phosphate, and hydrous zirconium oxide [23].

- Miniaturised pumps and sensors: Maintain precise control of blood and dialysate flow rates.
- Battery-powered operation: Enables several hours of continuous treatment.
- Wearable form factor: Typically belt-mounted or vest-style, weighing <5 kg in prototypes.

4.3 Clinical Trials and Research

In a pivotal 2016 pilot study by Gura et al. [24], the WAK 2.0 was tested in 10 patients for up to 24 hours. The device achieved urea clearance of 17 ± 10 mL/min and maintained stable electrolyte balance. Patients tolerated the device well and reported improved comfort and mobility. However, technical challenges such as CO2 accumulation, variable flow rates, and cartridge clogging led to early trial termination.

Subsequent development efforts have focused on improving sorbent stability, fluid dynamics, and power efficiency [25]. The REDIAL project at the University of Edinburgh uses data-driven materials innovation to miniaturise membranes and sorbent systems for future wearable devices [26].

4.4 Advantages and Potential Impact

Wearable systems promise transformative benefits:

- Continuous or extended dialysis improving haemodynamic stability and toxin control.
- Greatly enhanced mobility and lifestyle flexibility.
- Reduced infrastructure and staffing demands.
- Potentially lower long-term healthcare costs by reducing complications and hospitalisations [27].

4.5 Technical and Regulatory Challenges

Key barriers to clinical deployment include [28]:

- Device reliability: Preventing leaks, gas bubbles, and clotting.
- Vascular access safety: Reliable connection for mobile patients.
- Battery life and power efficiency: Continuous therapy demands robust energy sources.
- Biocompatibility and miniaturisation: Long-term material safety.
- Regulatory approval: Demonstrating safety and efficacy in large-scale trials.

4.6 Beyond Wearable: Toward Implantable Artificial Kidneys

An emerging direction is the implantable bioartificial kidney (BAK). These devices combine silicon nanopore membranes for filtration with renal tubular cell bioreactors to reabsorb water and solutes[29]. Early prototypes (Kidney Project, UCSF) have demonstrated successful filtration and viability in animal models, with human trials anticipated later this decade[30].

6. Implementation Considerations

6.1 Patient Selection and Training

Home dialysis candidates must demonstrate adequate dexterity, motivation, and support. Structured training programs (typically 3–6 weeks) are crucial [31].

For wearable systems, patient usability, ergonomics, and interface simplicity will be essential for acceptance [32].

6.2 Remote Monitoring and Telehealth

Telehealth platforms (e.g., SHARESOURCE, Nx2me) enable clinicians to monitor treatments, adjust prescriptions, and respond to alarms remotely [33]. Such

systems are central to scaling home dialysis safely.

6.3 Cost and Health-Economic Implications

While setup costs for home dialysis may be higher, overall lifetime costs can be lower due to reduced hospitalisations and staffing needs [34]. Cost models for wearable systems remain theoretical but may follow similar trends as technology scales [35].

6.4 LMIC Considerations

Adoption in LMICs requires low-cost, low-infrastructure designs. Innovations like on-demand PD solution generation and solar-powered HHD units are particularly promising [36]. Simplified telehealth systems using mobile networks can also extend remote supervision.

7. Future Directions

- Miniaturisation and materials innovation: Use of advanced nanomaterials (e.g., MXenes, graphene) for efficient urea adsorption [37].
- Artificial intelligence integration: Algorithms for adaptive control of ultrafiltration and solute removal [38].
- Hybrid home-wearable models: Combining a small wearable device for continuous clearance with a stationary base for regeneration and charging.
- Implantable biohybrid kidneys: Merging biocompatible membranes with living cells to create fully implantable renal devices [39].
- Global equity: Designing cost-effective systems suited to diverse socio-economic contexts [40].

Conclusion

Dialysis technology is entering an era of unprecedented innovation. Home-based systems have already transformed patient autonomy, enabling safer, more frequent treatments that improve survival and quality of life. Wearable and implantable artificial kidneys, though still emerging, hold the potential to liberate patients entirely from dialysis centres and replicate kidney function more naturally.

Realising this vision will require multidisciplinary collaboration across nephrology, bioengineering, materials science, and health policy. Regulatory frameworks, reimbursement strategies, and training infrastructures must evolve to support these advances.

Ultimately, the future of dialysis lies not merely in more efficient toxin removal, but in restoring independence, dignity, and normalcy to patients' lives.

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Chapter

25

Kidney Transplantation: Overcoming Immunological Barriers

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ABSTRACT

Kidney transplantation remains the optimal treatment for end-stage renal disease, yet significant immunological barriers continue to limit transplant access and long-term success. The fundamental immunological barrier stems from human leukocyte antigen (HLA) incompatibility between donor and recipient, leading to allorecognition and rejection responses. Pre-existing sensitization affects approximately 30% of waitlisted candidates, dramatically reducing transplant opportunities and increasing waitlist mortality. Memory T cells constitute another significant barrier, comprising approximately half of the alloreactive T-lymphocyte repertoire and demonstrating resistance to conventional immunosuppressive strategies.

Recent advances in ABO-incompatible and HLA-incompatible transplantation have significantly expanded the donor pool, with survival outcomes approaching those of compatible transplants. Understanding B-cell immunology has revolutionized therapeutic approaches to antibody-mediated rejection (AMR). Novel agents targeting different components of the humoral immune response include anti-CD38 monoclonal antibodies (daratumumab, isatuximab, and felzartamab) that effectively deplete plasma cells responsible for producing donor-specific antibodies (DSAs). Complement inhibition strategies using eculizumab, C1-esterase inhibitor, and newer agents target downstream effector mechanisms of antibody-mediated injury. Innovative approaches, such as imlifidase (an IgG-degrading enzyme), provide rapid IgG cleavage, enabling an "antibody-free window" for transplantation.

Cytokine-targeted therapies represent another promising avenue, with IL-6 pathway inhibition showing particular efficacy. Tocilizumab (anti-IL-6 receptor) and clazakizumab (anti-IL-6) modulate multiple aspects of alloimmunity by reducing T-follicular helper cell responses, plasma cell survival, and inflammatory cascades while promoting regulatory cell populations. Proteasome inhibitors (bortezomib, carfilzomib) target the cellular machinery essential for antibody production, though clinical efficacy has been mixed.

Biomarkers such as donor-derived cell-free DNA and gene expression profiles are revolutionizing rejection monitoring, enabling earlier intervention and personalized immunosuppression. Enhanced HLA epitope matching through algorithms like HLA Matchmaker enables more precise risk stratification and tailored therapeutic interventions.

ABO-incompatible transplantation now achieves patient survival rates of 97-98% and graft survival rates of 93-95% at one year, with the accommodation phenomenon enabling long-term graft survival despite the persistence of ABO antibodies. Modern protocols, which combine antibody removal through plasmapheresis or immunoadsorption, B-cell depletion with rituximab, and intensive immunosuppression, have made ABO-incompatible transplantation a standard practice, accounting for approximately 25% of living donor transplants in some countries.

Despite these advances, challenges remain in managing memory T cell responses, optimizing desensitization protocols, developing cost-effective strategies, and addressing therapy-related toxicities. The integration of kidney paired donation programs, advanced immunological monitoring, and novel therapeutic agents represents a paradigm shift toward precision transplant medicine. Future research should focus on developing durable tolerance induction protocols, improving long-term outcomes in sensitized recipients, and establishing evidence-based guidelines for biomarker-driven immunosuppression management.

Introduction

Background and Historical Context

Chronic Kidney disease has emerged as one of the most prominent causes of death and suffering, affecting more than 10% of the population, amounting to >800 million individuals worldwide.Kidney transplantation offers not only prolonged survival but also significantly improved quality of life for patients with end-stage renal disease (ESRD) [1]. It has evolved dramatically since the first successful transplant between identical twins in 1954, transforming from an experimental procedure to the gold standard treatment. Despite remarkable advances in surgical techniques and immunosuppressive protocols over the past five decades, immunological barriers such as ABO system antibodies and anti-HLA antibodies continue to pose significant challenges to the success and accessibility of transplants. It's postulated that 30% of live donor kidney transplants are not feasible due to these barriers.

The discovery of the major histocompatibility complex and human leukocyte antigen (HLA) system in the 1960s provided the first mechanistic understanding of transplant rejection [2]. The HLA system, encoded by genes located on the short arm of chromosome 6, encompasses the most polymorphic gene complex in the human genome. HLA molecules serve as the molecular fingerprint that distinguishes self from non-self [3]. The extraordinary diversity of HLA alleles, with over 25,000 variants identified, ensures that the likelihood of finding HLA-identical donors among unrelated individuals remains extremely low [3].

The development of immunosuppressive protocols, beginning with azathioprine and corticosteroids, and then advancing to calcineurin

inhibitors such as cyclosporine and tacrolimus, has helped in overcoming the immunological barrier and thereby dramatically improved short-term transplant outcomes [2]. However, the reality of organ shortage has necessitated acceptance of organs beyond the immunological barrier.

Importance and Clinical Significance

Contemporary kidney transplantation faces a complex array of immunological barriers.The subset of highly sensitized patients, defined as those with calculated panel reactive antibody (cPRA) levels exceeding 80%, represents approximately 20% of the waiting list population but accounts for less than 10% of transplants performed annually [5]. These patients have developed broad HLA sensitization through previous transplants, blood transfusions, or pregnancies, making identification of compatible donors extraordinarily difficult.

Recent data demonstrate the transformative potential of strategies that overcome barriers. ABO-incompatible transplantation, once considered impossible, now accounts for approximately 25% of living donor transplants in some countries, with patient and graft survival rates approaching those of compatible transplants [7].

Current Understanding of Immunological Barriers

HLA System and Allorecognition

The HLA system encompasses the most critical transplantation antigens, with class I molecules (HLA-A, -B, -C) expressed on all nucleated cells and class II molecules (HLA-DR, -DQ, -DP) primarily expressed on antigen-presenting cells [3]. The extreme polymorphism of HLA genes ensures genetic diversity, but it also creates significant challenges in matching. T-lymphocyte allorecognition occurs through direct, indirect, and semi-direct pathways. Direct allorecognition involves recipient T cells recognizing intact donor HLA molecules on donor antigen-presenting cells, predominantly driving acute cellular rejection. Indirect allorecognition involves recipient antigen-presenting cells processing donor antigens and presenting derived peptides to recipient T cells, being particularly important in chronic rejection processes [3].

Donor-Specific Antibodies and Sensitization

Pre-formed donor-specific antibodies represent one of the most significant barriers to successful transplantation. These antibodies develop through sensitizing events, including previous transplants, pregnancies, and blood transfusions, creating immunological memory that poses ongoing risks [4][8]. The strength and complement-fixing ability of DSAs correlate directly with rejection risk, with C1q-binding antibodies associated with inferior outcomes.

The introduction of solid-phase immunoassays, particularly the Luminex platform, has revolutionized the detection and quantification of DSA. These assays offer unprecedented sensitivity and specificity, enabling the detection of low-level antibodies that may not be identifiable by traditional crossmatch methods. Mean fluorescence intensity (MFI) values provide semi-quantitative measures of antibody strength, though the clinical significance of different MFI thresholds continues to evolve [8].p

Memory T Cell Responses and Non-HLA Barriers

Memory T cells represent a particularly challenging barrier, possessing several characteristics that make them resistant to conventional immunosuppression [3]. These cells arise from cross-reactivity with pathogen-specific responses (heterologous immunity), previous exposure to alloantigens through pregnancy, transfusion, or transplantation, and homeostatic proliferation following lymphodepletion.

Beyond classical HLA-directed responses, transplant immunology increasingly recognizes the importance of non-HLA antibodies and innate immune activation. Antibodies directed against polymorphic non-HLA targets, including the AT1R, MICA, and various tissue-specific antigens, contribute to the rejection risk independently of HLA sensitization [2]. Studies have shown that anti-AT1R antibodies are present in approximately 27% of transplant recipients and are independently associated with graft loss.

Established Desensitization Strategies

Antibody Removal Techniques

Plasmapheresis remains the cornerstone of antibody removal, with several modalities available depending on clinical requirements and resource availability [7]. Conventional plasma exchange removes antibodies non-specifically but also depletes beneficial proteins, including coagulation factors and immunoglobulins. Double filtration plasmapheresis (DFPP) offers a more selective removal of macromolecules with reduced replacement fluid requirements, whereas immunoadsorption provides the most specific removal of antibodies, preserving other plasma components [7].

B-Cell Targeting and IVIG Therapies

Rituximab, a chimeric anti-CD20 monoclonal antibody, has revolutionized desensitization by providing a pharmacological alternative to splenectomy [7]. The drug depletes circulating and tissue B cells, preventing antibody rebound after removal procedures.

High-dose intravenous immunoglobulin (IVIG) emerged as one of the first successful desensitization approaches. IVIG mechanisms include anti-idiotypic antibody neutralization, Fc receptor saturation, complement consumption, and modulation of T and B cell function [9].

Novel Therapeutic Approaches

Plasma Cell-Directed Therapies

The recognition that long-lived plasma cells residing in bone marrow survival niches are responsible for persistent antibody production has led to the development of targeted plasma cell therapies. Unlike B cells, plasma cells are largely resistant to traditional anti-CD20 therapies like rituximab, necessitating novel approaches [4][9].

Anti-CD38 monoclonal antibodies represent the most promising plasma cell-directed therapy currently in development. Daratumumab, originally developed for multiple myeloma, has shown efficacy in transplant desensitization and AMR treatment [4][9]. Felzartamab represents a newer anti-CD38 agent specifically evaluated for transplant applications. A randomized phase 2 trial demonstrated resolution of morphologic and molecular features of AMR in 82% of felzartamab-treated patients compared to 20% receiving placebo, without significant DSA reductions [10].

Proteasome inhibitors, initially developed for the treatment of multiple myeloma, target the cellular

machinery essential for the production of immunoglobulins. Bortezomib, the first-generation reversible proteasome inhibitor, has shown modest efficacy in treating desensitization and antibody-mediated rejection, although significant toxicity limits its utility [9].

Complement Inhibition and Cytokine-Directed Therapies

Recognition of the role of complement activation in antibody-mediated rejection has led to the development of strategies to inhibit complement [9]. Eculizumab, a monoclonal antibody targeting complement component C5, prevents formation of the membrane attack complex and has shown efficacy in reducing early antibody-mediated rejection rates in sensitized patients.

Interleukin-6 has emerged as a critical mediator of both cellular and humoral immune responses in transplantation. IL-6 promotes T-follicular helper cell development, drives plasma cell differentiation and survival, and maintains inflammatory responses that contribute to chronic allograft injury [4][9]. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, has shown promising results in small clinical studies, reducing DSA strength and numbers while enabling successful transplantation in patients who are difficult to desensitize[9].

Novel Antibody-Directed Strategies

Imlifidase (IdeS), an endopeptidase derived from Streptococcus pyogenes, represents a revolutionary approach to antibody neutralization [9]. The enzyme cleaves explicitly all IgG subclasses into Fab2 and Fc fragments, eliminating complement-dependent and antibody-dependent cellular cytotoxicity while preserving antigen-binding capacity.

Clinical trials have demonstrated that imlifidase can eliminate circulating IgG and HLA antibodies within hours, enabling successful transplantation in highly sensitized patients. In the HighDes trial, imlifidase enabled transplantation in 89.5% of highly sensitized patients with positive crossmatches, with 100% patient survival and 88.9% graft survival at 6 months [9]. The drug's ability to provide an "antibody-free window" for transplantation is particularly valuable for patients with very high antibody levels.

Advanced Biomarkers for Rejection Monitoring

Donor-Derived Cell-Free DNA and Gene Expression Profiling

The development of donor-derived cell-free DNA (dd-cfDNA) assays represents a major advance in non-invasive rejection monitoring [11]. As cells undergo turnover or injury, fragments of cell-free DNA are released into the circulation. In transplant recipients, elevated levels of donor-derived DNA indicate graft injury, whether from rejection, infection, or other causes.Clinical studies demonstrate that dd-cfDNA levels correlate with histologic rejection severity and can predict future graft dysfunction.

Blood-based gene expression profiles provide insights into immune activation states and the risk of rejection. TruGraf (Eurofins-Transplant Genomics), a 57-gene microarray-based assay, was the first CMS-approved gene expression profiling test. The assay demonstrates subclinical rejection in functionally stable

patients, potentially serving as an alternative to surveillance biopsies [11].

Emerging evidence suggests that combining different biomarker modalities may improve diagnostic accuracy. Post-hoc analyses of clinical trials demonstrate that combining dd-cfDNA with gene expression profiling provides superior discrimination of rejection compared to either biomarker alone [11].

ABO-Incompatible and HLA-Incompatible Transplantation

ABO-Incompatible Transplantation Success

ABO-incompatible kidney transplantation has evolved from an experimental procedure to a standard clinical practice in many countries. Modern protocols that combine antibody removal, B-cell depletion, and intensive immunosuppression have achieved outcomes comparable to those of ABO-compatible transplantation. Patient survival rates of 97-98% at one year and graft survival rates of 93-95% demonstrate the success of current approaches [6].

The accommodation phenomenon, whereby grafts function normally despite the presence of persistent ABO antibodies and complement deposition, remains incompletely understood but appears central to long-term success. Proposed mechanisms include graft resistance to humoral injury, upregulation of complement regulatory proteins, and a decrease in antibody production over time [7].

HLA Desensitization and Kidney Paired Donation

Contemporary desensitization protocols achieve transplant rates of 70-85% in highly sensitized patients, with patient and graft survival rates of 95-97% and 90-94% at one year, respectively [5]. However, rejection rates remain elevated at 15-25%, and long-term outcomes continue to lag behind those of non-sensitized recipients.

Kidney paired donation (KPD) programs have emerged as a valuable alternative to desensitization for many HLA-incompatible pairs. National and regional KPD chains enable multiple incompatible pairs to exchange organs, often achieving better HLA matching than would be possible with desensitization [5]. The integration of desensitization with KPD—enabling participation of highly sensitized patients who would otherwise be excluded—represents a significant advance.

Conclusion

The landscape of kidney transplantation has been fundamentally transformed by advances in understanding and targeting immunological barriers. From the early days of transplantation, when HLA incompatibility represented an absolute contraindication, the field has evolved to embrace innovative approaches that successfully challenge traditional immunological constraints. The recognition that antibody-mediated rejection represents the primary cause of long-term graft failure has shifted therapeutic focus from purely T-cell-directed approaches to comprehensive strategies addressing both cellular and humoral immunity.

The success of ABO-incompatible transplantation, with patient survival rates of 97-98% and graft survival rates of 93-95% at one year, demonstrates the potential for barrier-overcoming

strategies to expand transplant access significantly [6]. HLA desensitization has enabled successful transplantation in highly sensitized patients who were previously considered non-transplantable, with transplant rates of 70-85% achieved in patients with a cPRA of>80% [5,13].

Novel therapeutic approaches targeting plasma cells, complement pathways, and cytokine networks offer hope for the most immunologically disadvantaged patients. Anti-CD38 monoclonal antibodies have been shown to deplete antibody-producing plasma cells and modulate the function of effector cells. Imlifidase's ability to eliminate circulating antibodies within hours provides an "antibody-free window" for transplantation [9]. The emergence of sophisticated biomarkers, particularly donor-derived cell-free DNA and gene expression profiling, is revolutionizing post-transplant monitoring [11].

Implications for Practice

The clinical implications of these advances are profound and multifaceted. For highly sensitized patients who previously faced negligible transplant opportunities, novel desensitization strategies offer realistic pathways to successful transplantation with acceptable long-term outcomes.

The integration of biomarker-guided care into routine practice demands careful consideration of test utilization, result interpretation, and cost-effectiveness. Centers must develop protocols for acting on biomarker results, including thresholds for intervention and algorithms for immunosuppression adjustment.

Recommendations for Future Research

Despite remarkable progress in overcoming immunological barriers, numerous research priorities remain critical for advancing the field. The ultimate goal of eliminating chronic immunosuppression through tolerance induction remains elusive but represents the most vital long-term objective. Long-term outcome studies of desensitized patients represent the highest priority research need, as current evidence is limited by relatively short follow-up periods.

While current biomarkers represent significant advances, their clinical utility requires validation through prospective, interventional trials. Studies should evaluate whether biomarker-guided care improves long-term outcomes compared to conventional monitoring. Development of safer and more specific therapeutic agents remains a high priority, with particular promise in targeting specific immune cell populations and pathways.

The integration of artificial intelligence and machine learning in transplant immunology represents an exciting frontier for research. International collaborative research efforts will be essential for advancing knowledge in this specialized field. The landscape of kidney transplantation continues to evolve rapidly, with novel approaches to overcoming immunological barriers offering unprecedented opportunities to expand transplant access and improve outcomes for all patients with end-stage renal disease.

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Section 8
Basic Science

Chapter

26

AI in Drug Discovery: Accelerating Therapeutic Development

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ABSTRACT

Artificial Intelligence (AI) is transforming drug discovery by addressing longstanding challenges of cost, time, and high attrition rates in pharmaceutical R&D. Traditional drug development often exceeds $2.6 billion and spans more than a decade, with failure rates above 90%. AI—particularly machine learning and deep learning—enables rapid, data-driven decision-making by analyzing vast multimodal datasets, including genomics, proteomics, chemical libraries, and electronic health records. Across the drug development pipeline, AI accelerates target identification, de novo molecule design, virtual screening, and ADMET prediction, substantially reducing early-stage failures. Notable achievements, such as Insilico Medicine's accelerated IPF drug program and Exscientia's AI-designed OCD therapy, demonstrate its clinical impact. Breakthroughs like AlphaFold further enhance structure-based design. Despite challenges related to data quality, interpretability, and regulation, AI's integration with automated experimentation, multimodal clinical data, and biological foundation models promises a future of faster, cheaper, and more precise therapeutic development.

Keywords: Artificial Intelligence, Drug Discovery, Machine Learning, Drug Design, Pharmacokinetics.

The Dawn of a Data-Driven Revolution in Medicine

The pharmaceutical industry faces a paradox: the pace of scientific discovery is unprecedented, yet the cost and time required to bring a new drug to market continue to soar, hovering over $2.6 billion and spanning more than a decade for a single compound. The process is a high-risk, high-attrition marathon, with failure rates exceeding 90% in clinical development. This challenging reality has driven a critical search for transformative technologies, culminating in the emergence of **Artificial Intelligence (AI)** as the new epicenter of drug discovery.

AI, specifically its subset **Machine Learning (ML)** and **Deep Learning (DL)**, is not merely optimizing traditional methods; it is fundamentally

rewriting the rulebook. By leveraging the analytical power to process and interpret vast, complex, multi-modal datasets—including genomics, proteomics, transcriptomics, chemical libraries, and electronic health records (EHRs)—AI is enabling scientists to navigate the immense chemical and biological space with unprecedented speed, accuracy, and efficiency. This integration marks a paradigm shift from slow, costly, trial-and-error experimentation to a rapid, predictive, and data-driven approach, promising to deliver safer and more effective therapeutics to patients sooner.

The AI Drug Discovery Pipeline: A Multistage Transformation

The application of AI spans the entire drug development lifecycle, from the earliest conceptual stages of target selection to optimizing the final stages of clinical trials. By replacing sequential, bottleneck-prone steps with parallel, predictive computation, AI models dramatically compress timelines and minimize late-stage attrition.

1. Target Identification and Validation

The initial and most critical hurdle is identifying a therapeutic target—a protein, gene, or pathway—whose modulation can halt or reverse a disease. Traditional methods are slow and often limited by human bias or intuition. AI overcomes this by:

- Mining Multi-Omics Data: Algorithms analyze massive datasets (genomics, transcriptomics, proteomics) to pinpoint causal genes and proteins associated with a disease. For instance, AI can use causal inference methods to distinguish proteins that cause a disease from those that are merely a consequence of it.
- Literature and EHR Analysis:Natural Language Processing (NLP) models can rapidly sift through millions of scientific publications and anonymized patient records to uncover subtle, previously unseen associations between targets, diseases, and patient subgroups, thereby validating a target's relevance.

2. De Novo Drug Design and Virtual Screening

Once a target is validated, the search for a molecule that can interact with it begins. This step has been utterly revolutionized by AI.

- Generative AI for Novel Molecules:Generative Adversarial Networks (GANs) and Reinforcement Learning (RL) models can "dream up" entirely new molecular structures that are optimized from the start for desired properties like potency, non-toxicity, and synthesizability. These molecules may be entirely novel, having never existed in nature or a database, opening up previously inaccessible chemical spaces.
- High-Throughput Virtual Screening (HTVS): AI-powered virtual screening rapidly evaluates billions of chemical compounds (in silico) for their predicted binding affinity to a specific target protein. Deep learning models, such as Graph Convolutional Networks (GCNs), can predict molecular interactions with greater accuracy than previous computational chemistry tools, massively reducing the number of compounds that need to be physically synthesized and tested in a laboratory.

3. Lead Optimization and ADMET Prediction

Moving from a promising compound (a "hit") to a developable drug (a "lead") requires optimizing its

ADMET properties: Absorption, Distribution, Metabolism, Excretion, and Toxicity. This is a primary cause of late-stage drug failure.

- Predictive Toxicology: AI models, like the Deeptox Algorithm, are trained on historical safety data to accurately predict a candidate's potential toxicity and side effects, helping to weed out "dead-end" molecules long before expensive preclinical testing.
- Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling: AI is used to model how the body will handle a drug, predicting optimal dosing and formulation, which is crucial for reducing failure rates in clinical trials.

Success Stories and Accelerated Milestones

The theoretical promise of AI is rapidly translating into tangible clinical milestones.

Insilico Medicine's IPF Drug: In a landmark achievement, Insilico Medicine used its generative AI platform, Pharma.AI, to identify a novel target and design a drug candidate for Idiopathic Pulmonary Fibrosis (IPF). The entire process, from target ID to preclinical candidate selection, took only 18 months, a dramatic acceleration compared to the traditional 4-7 years. This AI-designed molecule has since progressed into human clinical trials.

Exscientia's OCD Drug (DSP-1181): Exscientia achieved a similar feat, moving an AI-designed drug candidate for Obsessive-Compulsive Disorder (OCD) into Phase I clinical trials in just 12 months. Such speed is reshaping expectations for therapeutic development timelines.

The AlphaFold Revolution: DeepMind's AlphaFold is a foundational AI breakthrough, having accurately predicted the structures of nearly all known proteins (over 200 million). Protein structure is fundamental to drug design, and by solving the decades-old "protein-folding problem," AlphaFold provides scientists with the blueprint needed for structure-based drug design, immensely boosting the predictive power of AI models in the field.

Key Advantages: The Business Case for AI

The integration of AI addresses the core inefficiencies of traditional R&D.

Advantage	Description	Impact on R&D
Accelerated Timeline	Screening millions of compounds and identifying targets in days instead of years.	Reduces average time to clinic from ~ 5 years to ~1-2 years.
Reduced Costs	Eliminating the need for extensive, physical high-throughput screening and reducing late-stage clinical failures.	Cuts overall R&D costs by up to 70% in early phases.
Higher Success Rates	Better prediction of efficacy and toxicity properties leads to superior compound selection.	AI-designed drugs have shown higher Phase I success rates (up to 80-90% vs. 40-65% traditionally).
Precision Medicine	Analyzing genomic and clinical data for **patient stratification** to identify subgroups most likely to respond to a specific treatment.	Optimizes clinical trial design and leads to more personalized, effective therapies.
Drug Repurposing	Quickly identifying new uses for existing, approved drugs by mapping drug-target-disease relationships.	Accelerates time-to-market and reduces risk, as the drug's safety profile is already established.

Challenges and the Road Ahead

Despite its successes, AI is not a panacea. Several critical challenges must be addressed for its full potential to be realized.

Data-Centric Challenges

The performance of any AI model is intrinsically linked to the quantity and quality of its training data. The primary obstacles are:

- Data Quality and Standardization: Datasets are often siloed, inconsistent, lack standardization, and may contain gaps or biases. Low-quality "dirty data" leads to flawed predictions.
- The Black Box Phenomenon: Many deep learning models are opaque, making it difficult for human scientists to understand why a particular prediction was made. In a highly regulated industry like medicine, Explainable AI (xAI) is essential for establishing trust and satisfying regulatory bodies like the FDA.

Regulatory and Ethical Hurdles

As AI-designed drugs advance, regulatory frameworks must evolve. The FDA is actively developing guidance on the use of AI to support regulatory decision-making, emphasizing the need for robust validation, transparency, and a clear understanding of the model's limitations. Ethical considerations regarding data privacy, bias in patient stratification, and the moral responsibility of AI-driven outcomes also require careful navigation.

The Future: Integrated, Adaptive, and Personalized

The next decade will see AI move from an augmentation tool to an indispensable core capability. The future trajectory of AI in drug discovery is defined by three interconnected themes:

1. Full Integration of Wet-Lab and Dry-Lab: The most powerful approach involves tight, iterative feedback loops between computational predictions (dry-lab) and automated robotic experimentation (wet-lab). AI guides the experiment, and the resulting experimental data immediately re-trains and refines the AI model, accelerating the learning cycle and maximizing experimental efficiency.
2. Multimodality and Clinical Genomics: Advanced AI models will integrate increasingly complex and diverse data types, including wearable sensor data, clinical imaging, and entire clinical genomic profiles, to create a holistic view of the patient and the disease. This will unlock true personalized medicine.
3. Foundation Models: Similar to the large language models (LLMs) in the consumer tech world, large biological foundation models are emerging. These are pre-trained on massive amounts of biological sequence and structure data (like AlphaFold 2 and 3), providing a powerful base that can be fine-tuned with proprietary company data, democratizing access to powerful AI tools and further lowering computational barriers.

Conclusion

The convergence of biological big data and sophisticated AI algorithms marks the most significant disruption in pharmaceutical research since the advent of molecular biology. AI has decisively proven its ability to accelerate drug discovery, reduce costs, and increase success rates in

the early pipeline, with the first AI-discovered drugs already advancing through clinical trials. While challenges remain concerning data quality and model interpretability, the collective efforts of data scientists, chemists, and biologists are overcoming these hurdles. The successful, scaled adoption of AI is not a distant aspiration; it is the definitive strategy that will unlock new therapeutic avenues, especially for previously "undruggable" targets, and usher in a new era of faster, smarter, and more personalized medicine for all.

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Chapter

27

Cytokine Signaling And Immune Modulation

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ABSTRACT

This article reviews on Cytokine signaling and immune modulation, that includes complex interplay between various cytokine networks in coordinating immune defense mechanism and maintaining tolerance. It explains major cytokine families such as interleukins, interferons, tumor necrosis factors, chemokines and transforming growth factors and their diverse role in immune regulation, disease pathogenesis and inflammation. This article includes cytokine driven mechanisms in autoimmune disorders like Rheumatoid arthritis and systemic lupus erythematosus, also for immunotherapeutic applications in cancer and infectious diseases. JAK STAT Inhibitors, monoclonal antibodies, cytokine targeted immunotherapy represent milestones in precision therapy. The review further discuss on innovations including CRISPR based gene editing and artificial intelligence that are redefining cytokine research. Immunomodulation integrates molecular insights and technological progress to develop personalised therapies in autoimmune and oncological disorders .

Introduction

The ability of immune system to protect the body against pathogens while maintaining self tolerance rely on intricate communication networks, central to which are cytokines, the molecular messengers of immunity. These small secreted proteins plays an important role cellular interactions, inflammation regulation, and determining the outcome of immune responses[1]. Cytokine signaling pathways are sophisticated with advances enabling targeted therapies for autoimmune diseases, cancers and infectious conditions. This review explores various cytokine families, immune cells they influence , their role in various diseases , cutting edge clinical trials and the promising emerging technologies transforming immunology research.

Cytokine Families : An In depth overview

Cytokines are categorized based on structural characteristics, receptors and functional roles . These comprises of interferons, interleukin, chemokines,

tumor necrosis factors and TGF².Interleukins are primarily produced by leukocytes and act predominantly on immune cells . The Interleukin family comprises over 40 members, with distinct roles in immune cell proliferation differentiation and effector functions.

For example, IL 2 Promotes T cell proliferation, whereas IL 4 drives Th2 differentiation. IL 17 produced mainly by Th17 cells , mediates neutrophils recruitment and plays major role in autoimmune pathologies . Recent research emphasizes IL 6as a cytokine with pleotrophic effects , involved in acute inflammation and autoimmune states and a target in monoclonal antibody therapies that inhibit IL 6 signaling to treat conditions like Rheumatoid arthritis.

Type 1 interferon such as interferon alpha and interferon beta are important in responses against viral infections enhancing antigen presentation and activating natural killer cells . Type2 interferon (interferon gamma) primarily activates macrophages, facilitating pathogen clearance and shaping adaptive immunity. Dysregulation of Interferon pathway is implicated in autoimmune diseases like systemic lupus erythematosus.

Tumor necrosis factors , especially TNF alpha are potent mediators of inflammation. They influence various immune cells, induce fever , and promote tissue destruction in chronic inflammatory diseases . TNF Inhibitors , such as infliximab have revolutionized the management of Rheumatoid arthritis and inflammatory bowel diseases.

Chemokines are specialized cytokines directing cell migration. CXCL8 (IL-8) attracts neutrophils, while CCL2 recruits monocytes . Their role extends to cancer metastasis and inflammatory diseases. Targeting chemokine pathways has therapeutic implications in autoimmune disorders.

Transforming growth factor beta is pivotal in immune regulation and tissue homeostasis, that helps in the development of regulatory T cells, Inhibitor T effector cell responses. Its dysregulation contributes to fibrosis and tumor immune evasion.

The immune system comprises diverse cells that produce or respond to cytokines, including T lymphocytes, dendritic cells, B cells , macrophages, NK cells, eosinophils and mast cells. Each type of cell exhibits unique cytokine profiles that shape immune responses.

Th1 cells produce interleukin 2 and interferon gamma that act against pathogens which are intracellular with the help of cell mediated immunity . Th2 cells secrete interleukin 4,5,13 that plays role in allergic responses and humoral immunity. Th17 cells secrete interleukin 17 and 22 Associated with mucosal immunity and autoimmunity. T regulatory cells release Transforming growth factor beta and interleukin 10 that maintains immune tolerance.

Activated Macrophages produce TNF alpha , IL 1beta , IL 6 , orchestrating acute inflammation. Dendritic cells secrete IL 12, pivotal for Th1 polarization, and Express cytokines upon interaction with pathogens.

The dysregulation of cytokine networks underpins many diseases. A balanced cytokine milieu ensures appropriate immunity, but imbalance leads to pathological inflammation, autoimmunity and cancer. In Rheumatoid arthritis, elevated IL 6, TNF alpha and IL 17 contribute to joint destruction. Targeted biologics blocking these cytokines have significantly improved patient outcome.

In SLE , an interferon signature characterized

by high interferon alpha levels correlates with disease activity. Clinical trials with anti Interferon alpha antibodies , such as anifrolumab , show promise .

Cytokines like IL 2 and IL 12 have been used in immunotherapy to boost anti tumor responses. Conversely, tumor produced cytokines create immunosuppressive environments , which can be targeted by checkpoint Inhibitors and cytokine blockade[3]. In severe COVID 19 , dysregulated cytokine release known as cytokine storm involving IL 6, IL 1 beta , TNF alpha exacerbates tissue damage . Therapeutic blockade of IL 6 (Example :- Tocilizumab) is promising in cytokine storm associated with COVID 19.

Recent Clinical trials target cytokine pathways to treat autoimmune and oncologic diseases . The JAK – STAT pathway Inhibitors such as Tofacitinib , Baricitinib are approved for Rheumatoid arthritis and psoriatic arthritis, exemplifying precision targeting of cytokine signaling.

In cancer, cytokine based therapies include chimeric cytokine receptors and checkpoint Inhibitors . Advanced delivery systems such as nanoparticle based cytokine carriers are under investigation to improve specificity and reduce adverse effects4.

Single cell RNA sequencing allows for profiling cytokine expression and receptor diversity across immune cell subsets in health and diseases.

High throughput cytokine profiling using microarrays enables rapid assessment of cytokine signatures in clinical samples, aiding disease diagnosis and monitoring.

Gene editing technology like CRISPR (Clustered regularly interspaced short palindromic repeats) facilitate the manipulation of cytokine genes or signaling components in immune cells advancing experimental and therapeutic applications[5].

Artificial intelligence algorithms expand predictive modeling of cytokine interactions, responses to therapy, and biomarker discovery, driving personalised immunomodulation strategies.

Advances in understanding cytokine signaling pathways open avenues for highly specific immunotherapies. Combining cytokine blockade with cellular therapies, such as CAR-T cells and nanotechnology promises to enhance efficacy and safety.

Conclusion

Cytokines are master regulators of immunity with intricate signaling networks dictating health and disease . The expanding understanding of their roles has led to transformative therapies for autoimmune conditions, cancers, and infectious diseases. Continuous innovation in research technologies , from single cell sequencing to artificial intelligence, promises to unearth novel insights and therapeutic avenues , ultimately tailoring immune responses to individual patient needs.

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Section 9
Recent Advances

Chapter

28

Liquid biopsies: the future of cancer early detection

Dr. Sangitanjan Dutta, Dr. Anjan Jyoti Talukdar, Dr. Shubhadeep Sarkar

Background

Cancer is one of the leading causes of death around the world, with almost 10 million deaths in 2020[1]. Aggressive tumors identification at an earlier stage can enable more effective treatment. The biochemical analysis of cancer related markers using biological fluids has generated great interest in the past decade. Liquid biopsies can identify a wide range of biomolecular features and can give an indication of disease status. Earlier diagnosis of cancer can not only save lives but also significantly reduce treatment costs. As many cancers are asymptomatic in the early stages, current clinical tests lack sensitivity and specificity in early-stage cancers.

Though tissue biopsy remains the gold standard for diagnosis of cancer it cannot be used as a multicancer screening test, it also lacks th7e ability to capture tumor heterogenicity and clonal evolution, which can be obtained by liquid biopsy approaches.

Liquid biopsies

According to the National Cancer Institute a liquid biopsy is: "A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood"[2].

There are several benefits of Liquid biopsy like, lower cost, repeatable and reliable, associated with minimal procedural risk, not affected by sample heterogeneity, not contaminated by the use of preservatives.Furthermore, liquid biopsies can be carried out rapidly, provide genomic, proteomic and metabolomic information, and are less invasive than tissue biopsies[3].

However liquid biopsies are not considered a standard method for the diagnosis and conformation of diseases such as cancer. Instead, they are predominantly used as aancillary test to tissue biopsy.

Current liquid biopsy techniques for detection of cancer

1. Circulating tumor cells (CTCs)

Circulating tumor cells (CTCs) are cancer cells released into the bloodstream or lymphatic system,

potentially causing metastases. They are rare (<10 CTCs/mL) and mainly detected using the epithelial marker EpCAM. Due to low abundance, sensitive technologies are needed. The CellSearch system is a FDA approved liquid biopsy technique that identifies and quantifies CTCs to assess prognosis in metastatic breast, colorectal, and prostate cancers[4].

2. Cell-free DNA (cfDNA)

Cell-free DNA (cfDNA) are DNA fragments released into body fluids via different mechanisms like apoptosis, necrosis, or secretion . Circulating tumor DNA (ctDNA) is the tumor-derived fraction (~1–2%) of the cfDNA [5], identifiable by tumor-specific mutations or methylation. ctDNA aids in prognosis, treatment monitoring, and relapse detection, though its low levels and short half-life limit early cancer detection.

3. Cell free RNA (cfRNA)

Like Cell free DNA, cell-free RNA (cfRNA) are RNA fragments released into the bloodstream by apoptosis or necrosis, with circulating tumor RNA (ctRNA) derived from cancer cells. RNA is less stable than DNA, limiting its clinical use. Messenger RNA (mRNA) and non-coding RNAs, especially microRNAs (miRNAs), are promising biomarkers due to tissue-specific expression and higher stability. miRNAs can be detected in blood and urine, showing 81% sensitivity and 85% specificity for hematological cancer diagnosis[6].

4. Methylation Markers

DNA methylation involves adding a methyl group to cytosine, forming 5-methylcytosine. Abnormal methylation patterns are linked to cancer and serve as diagnostic and risk markers. In liquid biopsy, tumor-specific methylation markers detected in cf DNA enable noninvasive cancer detection, identification of tissue of origin, and monitoring of disease progression or recurrence, offering high specificity for early diagnosis and prognosis[7].

5. Extracellular vesicles (EVs)

These are small membranous particles found in bodily fluids that mediate intercellular communication and carry biomolecules like proteins, RNAs, and DNA fragments. Tumor-derived EVs reflect the molecular fingerprint of their cell of origin, making them promising cancer biomarkers. EVs are more stable than ctDNA and CTCs but face challenges in isolation and standardization. EV-based liquid biopsies, such as ExoDx Prostate, enable noninvasive cancer detection and monitoring[8].

6. Proteins

Protein biomarkers in liquid biopsies can aid cancer detection and monitoring, as they reflect cellular functions and may reveal novel biomarkers. Accuracy is limited, so panels or combined protein-DNA assays are explored. Examples include PSA for prostate cancer, which has specificity issues and high false positives, and CA-125 for ovarian cancer, which is more reliable in advanced stages but limited for early detection and can be elevated in non-cancer conditions.

7. Tumor-Educated Platelets (TEPs)

Tumor-Educated Platelets (TEPs) are platelets altered by tumor cells, changing their RNA to support

tumor growth and spread[9]. Education occurs via direct tumor binding, uptake of tumor molecules or vesicles, and changes in platelet precursors. TEPs can act as liquid biopsy biomarkers for cancers like NSCLC, glioblastoma, and sarcoma, with mRNA sequencing detecting cancer with 96% accuracy and identifying tumor type with 71% accuracy. They are abundant, easy to isolate, and RNA-responsive, but no commercial tests exist yet.

8. Autoantibodies

Autoantibodies targeting cancer cell antigen serve as biomarkers for early detection and inflammation[10]. Autoantibody-based liquid biopsies, such as Oncimmune'sEarlyCDT-Lung, show promise in early lung cancer detection with up to 98% sensitivity at 49% specificity , however there is ongoing research on this domain.

9. Spectroscopic Liquid Biopsy

Spectroscopic Liquid Biopsy uses ATR-FTIR spectroscopy with machine learning to analyze biofluids for cancer. FTIR detects molecular patterns from both tumor and body response, including proteins, lipids, metabolites, exosomes, of DNA, and methylation markers. It has been used on blood, serum, urine, and EVs for cancers like bladder, brain, ovarian, colorectal, and lung. Limitations include low molecular resolution and the need for AI to interpret results. Studies show it can detect brain tumors early, even very small ones, overcoming limits of other liquid biopsies affected by the blood–brain barrier.

Comparison of Liquid Biopsy Tests for Early Detection of Single Cancers

Company (Country)	Test	Target Detection	Molecular Origin	Specifi -city (%)	Sensit -ivity (%)	Turn-around Time
Dxcover (UK)	Dxcover Brain Cancer Liquid Biopsy	Brain cancer	Pan-omic spectroscopic assay from blood serum	45	96	1 day
Guardant Health (USA)	Shield™	Colorectal cancer	Qualitative blood test	92	91	~2 weeks
Novigenix (Switzerland)	Colox	Colorectal cancer	Peripheral blood mononuclear cells	92.2	78.1	1–2 weeks
Biodesix (USA)	Nodify CDT	Lung cancer	Autoantibodies via ELISA from blood	98	28	1 day

Biodesix (USA)	OncimmuncEarlyCDT-Lung (Stage I/II)	Lung cancer	Autoantibodies via ELISA from blood	90.3	52.2	10 working days
Abcodia (UK)	ROCA	Ovarian cancer	CA-125 measurements from blood	87.6	87.1	7 days
ExoDx (USA)	ExoDx (EPI) Prostate Intelliscore	Prostate cancer	RNA from urine exosomes	30.1	92.3	1 week
MDx Health (Belgium)	SelectMdx	Prostate cancer	mRNA biomarkers from urine	53	89	5 days
OPKO (USA)	4Kscore Test	Prostate cancer	Blood test measuring four kallikreins and clinical data	27.4	96.9	2–3 days

Table adapted from: Connal S, Cameron JM, Sala A, Brennan PM, Palmer DS, Palmer JD, Perlow H, Baker MJ. Liquid biopsies: the future of cancer early detection. J Transl Med. 2023 Feb 11;21(1):118.

Multi-Cancer Detection

Screening for individual cancers is often impractical due to low prevalence, but multi-cancer tests could identify several cancers at once, helping catch early, non-specific symptoms and prioritize patients for further diagnostics.

Several liquid biopsy approaches are being developed for multi-cancer detection:

- **Galleri (Grail, USA):** Uses cfDNA and machine learning to detect multiple cancers. Overall sensitivity 51.5%, specificity 99.5%; early-stage detection remains challenging (16.8% for stage I). NHS-Galleri and PATHFINDER trials are validating its clinical use.
- **PanSeer (Singlera Oncology, USA):** Detects ctDNA methylation in plasma up to 4 years before conventional diagnosis. Specificity 96.1%, sensitivity 87.6–94.9% for post- and pre-diagnosis samples. Detects five cancer types.
- CancerSEEK (Exact Sciences, USA): Combines genetic and protein biomarkers. Specificity >99%; sensitivity 43–78% depending on cancer stage. Stage I detection is limited.
- Dxcover® Cancer Liquid Biopsy (UK): Uses serum spectroscopy to detect tumor- and immune-derived signals across multiple cancers. Sensitivity-tuned model: 98% sensitivity, 58% specificity; specificity-tuned: 56% sensitivity, 99% specificity. Effective at detecting early-stage (I–II) cancers.

These tests show promise for rapid, non-invasive, early detection of multiple cancers, though further validation is needed.

Conclusion

Liquid biopsy is a promising, minimally invasive approach for cancer detection, prognosis, and monitoring. Unlike tissue biopsy, it captures tumor heterogeneity and can be repeated easily. While current liquid biopsy approaches mainly focus on tumor-derived biomarkers such as cfDNA, their sensitivity, specificity and standardization remains a challenge. To improve early detection, the definition of a liquid biopsy should be broadened to include both tumor and non-tumor derived information, as non-tumor signals often dominate in the earliest stages of disease.

Combining highly sensitive screening tests with highly specific orthogonal testsbased on fundamentally different biological principlescould provide a powerful two-step strategy for accurate early cancer detection. Such an integrated system would enhance both sensitivity and specificity, offering a more effective and efficient pathway toward early diagnosis and improved patient outcomes.

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Chapter

29

mRNA Technology: Beyond Vaccines

Dr. Bhupen Barman, Dr. Ashwini C

ABSTRACT

The use of messenger Ribose nucleic acid (mRNA) as therapeutic intervention has revolutionised the filed of vaccine production and cancer immunotherapy. This gained more popularity after COVID 19, when vaccines were prepared in a short span of time to counter the spread of disease. The application of mRNA-based technology revolves around the principle of Central Dogma of life proposed by Watson and Crick. The mRNA modified in order to reduce the toxicity and increase the efficiency is translated to produce almost any protein in the target cells. However, this mRNA is at risk of reduced uptake and degradation by host cells. In order to ameliorate these obstacles, mRNA is embedded within delivery particles such as lipid nanoparticles, polymers. The therapeutic applications include vaccines against infectious diseases, cancer immunotherapy, protein replacement therapy and therapeutic genome editing. This recent advance in biotechnology has enabled treatment of inborn errors of metabolism simple which was once considered an intractable disease.

Introduction

The utilisation of messenger Ribose nucleic acid (mRNA)in various therapeutic fields is governed by the principle of Watson and Crick model of central dogma of life- where Deoxy ribose nucleic acid (DNA) is transcribed into Ribose nucleic acid (RNA) which in turn is translated into proteins. Thus, introducing Messenger RNA into any cell, results in production of a desired protein[1] which plays different roles such as enzyme replacement therapy in inborn errors of metabolism due to enzyme deficiency, vaccine triggering immunogenicity or even cancer immunotherapy.

The mRNA sequence design

mRNA is a bio-active compound comprising of ribose nucleic acids in a single strand containing codons, that code for a specific protein.

The important functional regions of mRNA include[2]

- 5' cap:
  - Consists of modified guanine nucleotides.

- It is necessary for initiation of translation by recruiting translation initiation factors and protection of mRNA molecule from degradation by exonucleases.

➢ 3' polyA tail:
- Consists of multiple of adenine nucleotides.
- It is necessary for stabilisation of mRNA molecule and transportation of mRNA from nucleus to cytoplasm.

➢ Open reading frame (ORF)
- Contains the coding sequences that are translated into desired proteins or antigens.

➢ 5' untranslated regions (UTR)
- Contains codons that are not translated.
- It contains codons that help in binding of ribosomes, and identification of start codons that aiding in initiation of translation process.

➢ 3' untranslated regions (UTR)
- Contains codons that are not translated.
- It contains nucleotides that affects the stability and half life of mRNA thus influencing the duration of translation process.

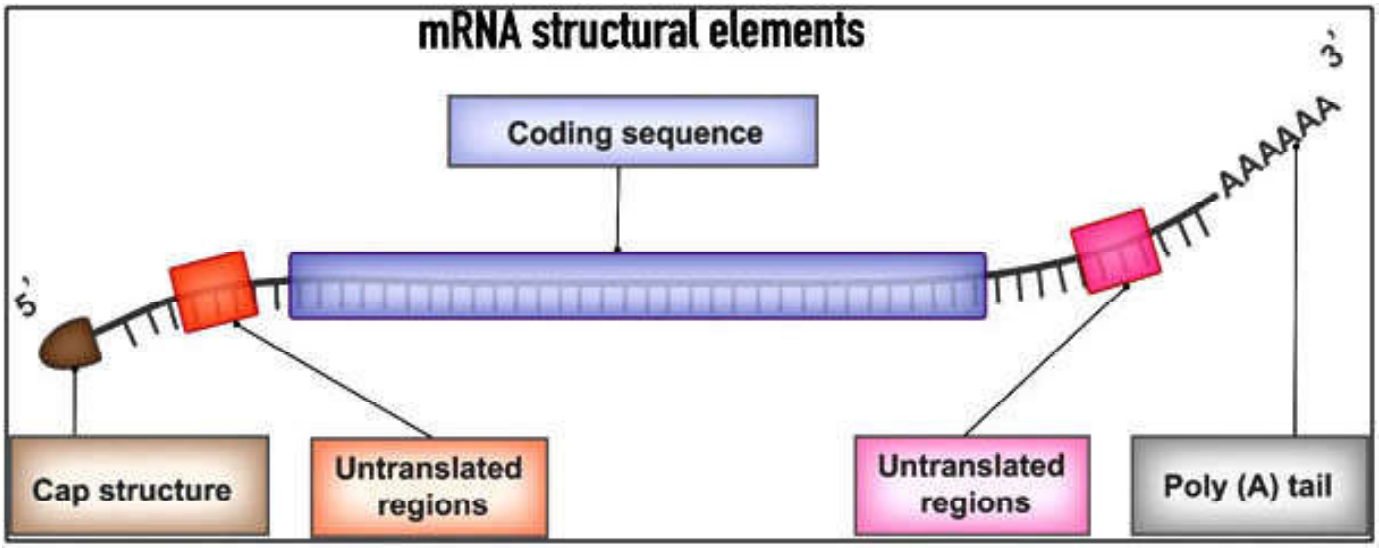


Figure 1: Structure of mRNA

Types of synthetic mRNA[4]

1. Non replicating mRNA (nrRNA)- conventional synthetic linear RNA
2. Self-amplifying mRNA(saRNA)- these are self-replicating RNAs, hence in comparison to nrRNA lower doses yield desired protein quantity.
3. Circular RNA (circRNA)- the RNA is held in circular form with the help of covalent bonds, that prevent degradation by exonucleases and significantly prolonging the half-life of circRNA.

mRNA delivery vehicles

The naked mRNAs have low efficiency owing to high risk of degradation by enzymes, and reduced cellular uptake. Nanoparticle based delivery systems overcome this problem by embedding the mRNA within their core, thus protecting mRNA from degradation by enzymes and enhancing cellular uptake via passive

process such as endocytosis.

The various nanoparticles used are,

- Lipid nanoparticles
  - Consists of ionisable lipids, cholesterol, phospholipids and polyethylene glycol (PEG)-lipids.
  - mRNA is embedded within the lipid core, protecting it from the degrading enzymes and enhancing its cellular uptake.
  - Inside the acidic environment of the cytoplasm of cell, mRNA is slowly released and translated into desired proteins.
- Polymer nanoparticles
  - Made of polyethyleneimine, dendrimers and poly(lactic-co-glycolic acid)
  - They are the most potent non-viral vectors
  - The limitations include toxicity and non-biodegradability.
- Peptide nanoparticles
  - They consist of self-assembled peptides, that surround the mRNA
  - By traversing the cell membrane, they directly deliver the mRNA into the cytoplasm
- Virus like particles
  - They resemble viral particles except for the infectious genome.

Routes of administration of mRNA vaccines

Intramuscular, intravenous, subcutaneous, intra dermal, intra nasal, intra nodal and intra splenic routes.

Therapeutic application of mRNA

- Direct effect: mRNA based therapeutics where cell is utilised like a factory to produce proteins that directly act on infections or cancers or produce enzymes in inborn errors of metabolism
- Indirect effect: mRNA based therapeutics where proteins produced act like antigens to boost host immunity.

The various therapeutic uses of mRNA include,

1. Vaccination against infectious diseases
   a. COVID 19: COVID 19 pandemic caused by the virus severe acute respiratory syndrome-Coronavirus 2 (SARS Cov-2) emerged in Wuhan, China spread worldwide in the late 2019. It is transmitted via aerosols and direct contact. It causes symptoms varying from mild upper respiratory tract infection to severe pneumonia. In the absence of specific treatment for this infection, preventive measures such as social distancing, wearing masks including vaccination became the cornerstone of infection control.mRNA vaccines were developed by Pfizer/BioNTech and Moderna within a period of 11 months, played a great role prevention of infection.
   b. Influenza: There are mainly 4 types of influenza virus namely- A, B C and D. The annual antigenic drift produces novel strains to which the antibodies produced because of previous infection or immunisation becomes ineffective. The development of new vaccines effective against emerging viral strains is a complex and time-consuming process. However, mRNA-based vaccines have the potential to be true game changers due to their ability to be designed and produced rapidly within a short period.

c. Various mRNA based vaccines against Human Immunodeficiency Virus (HIV), respiratory Syncytial Virus (RSV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Human Cytomegalovirus (HCMV), Rabies virus and dengue virus are under trial[5].

2. Cancer immunotherapy

The various cancer modes of cancer immunotherapy include[6],

- ✓ Immune Checkpoint Blockade (ICB)
- ✓ Chimeric Antigen Receptor T cells (CAR-T cells)
- ✓ Vaccines

ICB releases immunosuppression and CAR-T cell therapy directly kills the tumour cells where as vaccines boost immune system against tumour cells.

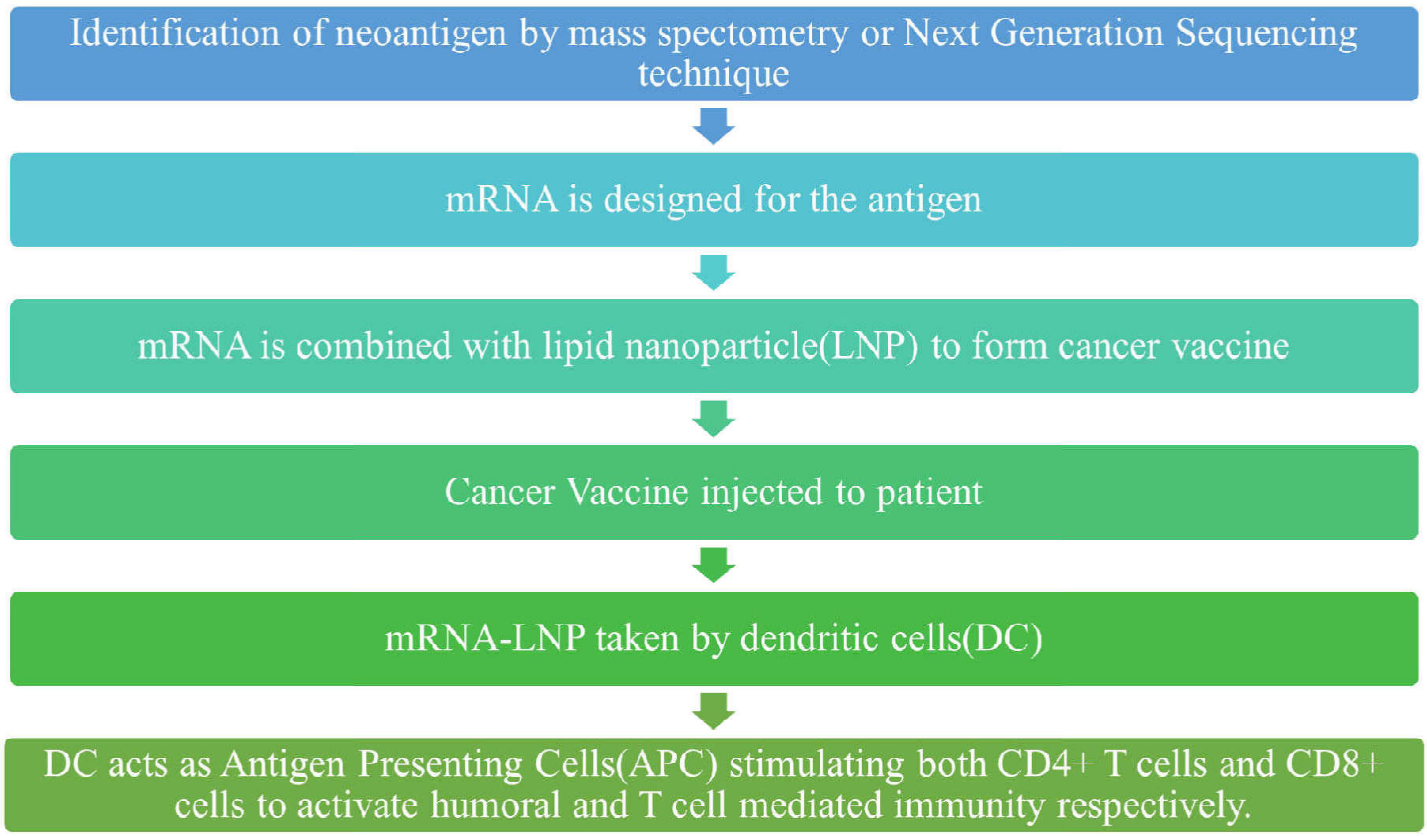
Mechanism of cancer vaccine:

There are 2 types of antigens associated with cancer

i. Tumour Associated Antigen (TAA):
   - It is non-specific, present both in tumour and normal tissue but highly concentrated in tumour tissue.

ii. Tumour Specific Antigen (TSA) or Neoantigen:
   - It is specific for tumour tissue

The flowchart given below summarises the development of cancer vaccine



Flowchart 1: Development of cancer vaccine.

The various applications in cancer which are under trial are as below[5]:

a. Melanoma
b. Renal cell carcinoma
c. Acute myeloid leukaemia
d. Glioblastoma

A major limitation of cancer vaccines is the development of immune tolerance. The tumor cells evade immunosurveillance by augmentation of immunosuppressive molecules leading to both central and peripheral tolerance. This immune escape mechanism significantly reduces the efficacy of cancer vaccines.

3. Protein replacement therapy

mRNA can be used to produce any desired protein in vivo, which can be utilised as a replacement to missing or malfunctioning protein. These are currently in preclinical or clinical trials. Few examples are given below[5].

a. Cystic fibrosis: It is an inherited autosomal recessive disorder, caused by malfunctioning CFTR protein leading to defective chloride channel. Inhaled mRNA drugs are under trial for this disorder
b. Haemophilia: These are inherited disorders characterised by deficiency of clotting factors (Eg: Haemophilia A- Factor VIII deficiency, Haemophilia B- Factor IX deficiency), which result in bleeding manifestations. mRNA drugs can be used to replace these clotting factors.
c. Metabolic diseases: Below is the table describing some of the metabolic disorders and associated enzyme deficiency. mRNA drugs can be utilised to produce these deficient enzymes in vivo.

Table 1: Metabolic diseases caused by enzyme deficiencies.

Disorder	Deficient/ Malfunctioning enzyme
Hepatorenal tyrosinemia	Fumarylacetoacetate-hydrolase
Acute intermittent porphyria	Porphobilinogen deaminase
Fabry disease	α-galactosidase A
Methylmalonic acidemia	Methylmalonyl-CoA mutase
Crigler-Najjar syndrome type 1	Uridine diphosphate glucuronosyltransferase (UGT1A1)
Ornithine transcarboxylase deficiency	

4. Therapeutic gene editing

   Gene editing is a technique where precise changes can be made in human genome. Targeted endonucleases enable this manipulation of genome by inserting or deleting certain genes[8].

Mechanism:

They introduce a break at the target site on double stranded DNA followed by DNA repair either by Non Homology End Joining(NHEJ) or Homology Directed Repair(HDR).

The various nucleases are,

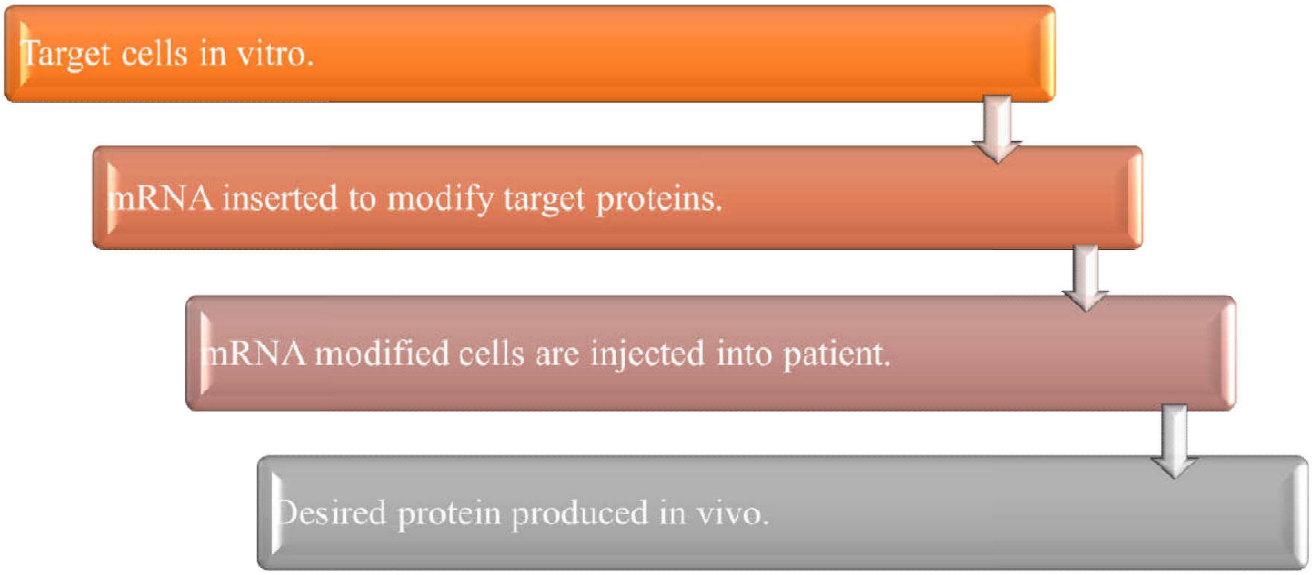
a. Zinc finger nucleases (ZFNs)
b. Transcription activator-like effector nucleases (TALENs)
c. Clustered regularly interspaced short palindromic repeat (CRISPR)-associated protein (CRISPR/Cas) nucleases mRNA can encode these endonucleases in vivo.

Applications

- ✓ Transthyretin (TTR) editing to reduce amyloidosis
- ✓ Proprotein convertase subtilisin/kexin type 9 (PCSK9) editing to reduce low density lipoprotein
- ✓ Angiopoietin like 3 (ANGPTL3) editing to reduce Low density lipoprotein cholesterol (LDL-C) and Triglycerides
- ✓ Polo-like kinase 1(PLK1) editing to reduce tumour growth
- ✓ Antithrombin (AT) editing to treat hemophilia
- ✓ Phenylalanine hydroxylase (PAH) editing to treat phenylketonuria
- ✓ Exon 45 skipping to restore dystrophin function

5. mRNA based cell therapies

   Mechanism: Illustrated in flowchart 2



Flowchart 2: Utilisation of mRNA in cell based therapies

Currently the following are in clinical trials for mRNA-based cell therapies[4].

i. TriMix-based immunotherapy (ECI-006)
ii. Autologous cell therapy CAR-T MCY-M11 (MaxCyte)
iii. Carte sian therapy

6. Antibody therapy

Antibodies-encoding mRNA can be used to produce antibodies in large extent which can be used against various infections and cancers.

Examples:

1. Treatment of HER2 positive breast cancer
2. Anti-human CD20 monoclonal antibody (rituximab) for the treatment of non-Hodgkin's lymphoma
3. Anti-PD-1 monoclonal antibody for the treatment of intestinal cancer

Merits of mRNA based therapy[4]:

a. Reduced risk of infection as mRNA is produced through enzymes in vitro
b. Safer than DNA based therapeutics since integration into human genome is not required.
c. Any desired protein can be synthesized by manipulating mRNA sequence
d. Widespread application beyond vaccines which include cancer immunotherapy, protein replacement therapy, genome editing.

Limitations of mRNA based therapy[9]:

a. Risk of immunogenicity
b. Sub therapeutic protein production
c. Difficulty in large scale production
d. Risk of degradation by nucleases

Conclusion

The use of mRNA technology across various fields represents a remarkable scientific achievement of the modern era. Using this technique almost any desired protein can be produced either in vivo or in vitro. The use of mRNA technology is no longer confined to vaccine development; it now encompasses a wide range of therapeutic applications, including cancer immunotherapy, protein replacement therapy, antibody therapy, mRNA-based cell therapy, and genome-editing therapy. This breakthrough has offered new hope in the fight against challenging human diseases such as cancer, inborn errors of metabolism, and cardiovascular and cerebrovascular disorders like Alzheimer's disease, which were once considered refractory to treatment. Moreover, mRNA technology has proven to play an indispensable role in genome editing, stem cell therapy, and CAR-T cell therapy.However, the key challenges to tackle include designing robust delivery devices to enhance targeted cellular uptake, improving the stability of mRNA to prolong the efficacy, aiming at large scale production in order to meet global demand without compromising the quality and reducing the unintended immunogenicity. With continued research, mRNA technology holds the potential to improve health and enhance quality of life by addressing disorders that remain unmanageable with conventional therapies.

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Chapter

30

Wearable Technology in Managing Chronic Health

Dr. Ruth Khawbung, Dr. Parag Kumar Das, Dr. Nithi Mahanta, Dr. Arup Choudhury

Introduction

The rapid evolution of digital health has ushered in a new era where technology and medicine merge seamlessly. One of the most transformative innovations in this landscape is wearable technology — compact, intelligent devices designed to continuously monitor physiological and biochemical signals from the human body. The intersection of biotechnology, electronics, and data science has produced one of the most revolutionary tools in healthcare: wearable biosensors. These miniaturized, body-adherent devices capture vital physiological and biochemical signals continuously, transforming how both clinicians and individuals monitor health. Moving beyond episodic hospital-based diagnostics, wearable biosensors enable continuous monitoring in real-world environments, giving clinicians real-time data to guide intervention.

Since their inception, biosensors have evolved from simple step counters to multifunctional platforms capable of measuring a wide range of biological variables—such as interstitial glucose, cortisol, lactate, and electrolyte levels. The evolution of sensor materials, flexible electronics, and wireless communication (Bluetooth, NFC, Wi-Fi) has made it feasible to produce comfortable, portable, and accurate systems. Combined with AI-driven analytics, wearable biosensors provide predictive insights into chronic conditions such as cardiovascular disease (CVD), diabetes, and respiratory disorders, Inflammatory Bowel Disease (IBD) and Non-Alcoholic Fatty Liver Disease (NAFLD), demand lifelong care, frequent follow-ups, and constant vigilance. These conditions fluctuate over time, often without obvious symptoms until significant progression occurs. Traditional clinical monitoring — periodic blood tests, imaging, or biopsies — offers only snapshots in time. Wearables, in contrast, provide a living timeline of health data, empowering both patients and clinicians with continuous, real-time insights.

By transforming passive observation into proactive intervention, wearable technologies are redefining chronic disease management from reactive treatment to predictive, preventive, and personalized care.

Components and Operating Principles

A typical wearable biosensor comprises four key elements:

Bioreceptor: Detects the analyte of interest through biological interactions (e.g., enzyme, antibody, nucleic acid).

Transducer: Converts the biochemical signal into a measurable physical one, often electrical or optical. Signal Processing Unit: Amplifies and filters the raw signal for digital conversion.

Communication Interface: Transmits processed data to connected devices or cloud systems for storage and analysis.

Substrates composed of flexible polymers like PDMS or polyurethane enable skin conformity, while advanced nanomaterials enhance sensitivity and selectivity. Examples include gold nanostructures, graphene oxide, and metal–organic frameworks (MOFs) that allow multi-analyte detection in small sample volumes.

Types of Wearable Biosensors

Wearable biosensors are commonly categorized by their detection mechanisms:

Type	Detection ode	Applications
Electrochemical	easures ionic changes or electron flow	Glucose, lactate, uric acid
Optical	Detects light absorption/scattering	Oxygen saturation, pulse rate
Thermal	onitors body temperature fluctuations	Fever, metabolic rate
Piezoelectric	Tracks mechanical deformation	Respiration, movement
Acoustic	Uses ultrasound for vascular metrics	Blood pressure

Recent research emphasizes multimodal sensing, integrating several of these mechanisms for enhanced reliability even under motion or sweat interference.

Overview of Wearable Technology in Health

Wearable devices are smart electronic systems worn directly on the body — in the form of watches, patches, clothing, or accessories — that collect data on heart rate, movement, sleep, body temperature, and even biochemical markers in sweat or interstitial fluid.

The past decade has witnessed an explosion in wearable innovations. Fitness trackers and smartwatches now measure heart rate variability (HRV), oxygen saturation, and sleep architecture. Meanwhile, biosensor patches and sweat analyzers can detect inflammatory molecules like interleukins (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-a).

Recent research has demonstrated their medical value:

In IBD, fluctuations in heart rate and cytokine levels detected by wearables can signal inflammation days before a clinical flare (Pathak et al., 2025). In NAFLD, sweat sensors provide biochemical profiles that reflect metabolic and hepatic health, offering a non-invasive substitute for traditional liver function tests (Yang et al., 2023). Wearables thus represent the convergence of engineering, data science, and clinical medicine, making healthcare continuous, patient-centered, and accessible beyond the clinic walls.

Clinical Applications

Chronic Disease Management

Chronic diseases such as diabetes, CVD, and hypertension remain the leading causes of mortality worldwide. Wearable biosensors offer proactive management by continuously tracking biomarkers. Continuous glucose monitors (CGMs) like Dexcom G7

utilize electrochemical sensing of interstitial glucose levels while transmitting readings wirelessly to mobile interfaces, facilitating immediate insulin adjustment.

Cardiovascular and Metabolic Health

ECG-based patches and wristbands help in long-term cardiac rhythm monitoring, delivering early alerts for arrhythmias and ischemic episodes. Similarly, lactate and sweat-sensing biosensors provide non-invasive markers of metabolic state and dehydration, improving endurance training and rehabilitation outcomes.

Stress and Mental Health Tracking

New biosensors can evaluate psycho-physiological conditions by tracking cortisol levels in sweat or skin conductance. Integrated platforms like Empatica Embrace Plus combine electrodermal activity, temperature, and blood volume pulse to quantify stress responses in real-time.

Neonatal and Elderly Monitoring

Ultra-soft biosensor patches designed for neonates capture oxygen levels, heart rate, and respiratory motion without wires, reducing infection risk and improving clinical response time. For the elderly, biosensors embedded in smart textiles enable fall detection and cardiovascular surveillance within home settings.[7][3]

Technological Advancements and Innovations in Wearable Biosensing

The last two years have seen transformative progress in wearable biosensors, pushing the boundaries of sensitivity, stability, and clinical applicability. This evolution is driven by breakthroughs in nanomaterials, microfluidics, flexible electronics, and AI-driven signal processing, enabling continuous, real-time health monitoring with unprecedented accuracy.

1. Graphene-Based Electrochemical Biosensors

Graphene has emerged as the gold standard for next-generation biosensing due to its:

Single-atom thickness; Exceptional electrical conductivity (up to 106 S/m) ;Large specific surface area (~2630 m^2/g)

These properties significantly enhance electron transfer kinetics, enabling ultra-sensitive detection of biomarkers such as glucose, lactate, cortisol, uric acid, and electrolytes in sweat.

Recent prototypes (2024) demonstrated:

Sensitivity in the nanomolar range; Response times < 2 seconds; Flexibility permitting direct integration onto skin patches and wound dressings;ñ

Clinically, sweat-based glucose sensing (correlation coefficient r ˜ 0.82–0.91 with blood glucose) shows promise in supporting diabetes self-management without invasive finger-pricks.

2. Microneedle-Based Interstitial Fluid Biosensors

Microneedle (MN) platforms have rapidly advanced into mainstream clinical research because they can painlessly access interstitial fluid (ISF)—a biomarker-rich medium with analyte concentrations closely approximating plasma.

Modern MN biosensors incorporate:

a) Silicon, stainless steel, or dissolvable polymeric needles

b) Enzyme-functionalized electrodes (e.g., glucose oxidase)

3. Hybrid Smart Textiles

Hybrid smart textiles combine conductive fibers, nanocomposite threads, and embedded wireless nodes, creating fabric-based biosensing systems capable of whole-body physiological tracking.

Key advancements include: Textile-based ECG systems with signal-to-noise ratio comparable to clinical leads. Continuous respiratory monitoring using microstrain sensors. Sweat pH, chloride, and electrolyte sensing integrated into athletic and medical garment

4. AI-Powered Multimodal Diagnostic Rings

The evolution of smart rings into clinical-grade diagnostic devices marks a turning point in personalized health. PPG-based SpO2 sensing (accuracy 95–98%), Miniaturized single-lead ECG, Ballistocardiography for micro-pulse detection, Skin temperature and galvanic skin response sensors are some recently advances in wearable biosensors.

5. Smart Contact Lenses

Smart ocular biosensors leverage the continuous production of tear fluid to detect biomarkers non-invasively. Recent advancements include:
Graphene or gold nanowire circuits embedded within soft hydrogel lenses Microcoil antennas for wireless energy harvesting,

Sensors for: Intraocular pressure (IOP) (precision ±1–2 mmHg)

Tear glucose (useful for adjunctive diabetes monitoring) Lactate, indicative of ocular surface ischemia

Few Major Wearable Technologies of recent times and Their Research Insights

1. Fitness Trackers and Smartwatches

Fitness trackers and smartwatches are the most common and user-friendly wearables. Devices like Fitbit, Apple Watch, Oura Ring, and Garmin combine accelerometers, optical heart-rate sensors, and gyroscopes to record parameters such as step count, sleep efficiency, energy expenditure, and HRV.

Research Highlights:

A comprehensive review by Pathak et al. (2025) included 37 studies evaluating wearable devices in IBD. Of these, 15 studies assessed physical activity, revealing that patients in active disease states had 20–25% lower daily step counts compared to those in remission.

One pediatric trial found that children with IBD who underwent physical activity training tracked via Fitbit demonstrated improved bone mineral density and fatigue recovery.

HRV analysis from Apple Watch and Oura Ring data revealed that during flare-ups, resting heart rate increased while HRV decreased, reflecting sympathetic dominance and systemic inflammation.

Several longitudinal studies have confirmed that physical inactivity correlates with higher relapse rates, emphasizing how wearable-derived data can support preventive intervention.

Clinical Implication:

These devices provide a non-invasive, inexpensive way to assess disease activity, treatment response, and general well-being — especially useful for monitoring patients remotely between hospital visits.

2. Wearable Biosensor Patches

Description:

These thin, flexible patches adhere to the skin like a sticker and contain microelectronic sensors capable of analyzing sweat or interstitial fluid for biochemical markers. They transform physiological monitoring into biochemical surveillance.

Key Research Findings:

The IBD-AWARE Patch (Hirten et al., 2023–24) measures inflammatory proteins such as IL-6, TNF-a, CRP, and calprotectin. Its readings strongly correlate with laboratory blood results (correlation coefficient $R^2 = 0.72$).

The SWEATSENSOR Patch demonstrated high sensitivity (detecting 0.1–10 mg/mL of calprotectin) and was able to differentiate between remission and active inflammation with over 85% accuracy.

Another biosensor system, the VitalPatch, combines physiological parameters like ECG, respiration rate, and skin temperature to track stress and inflammatory activity.

Significance:

Such devices enable clinicians to visualize inflammatory trends continuously and intervene early. For patients, they replace invasive tests with a painless, wearable solution — making long-term monitoring more convenient and humane.

3. Smart T-Shirts and Intelligent Textiles

Description:

Smart textiles represent a fusion of fashion and function. These garments embed conductive fibers, digital microphones, or stretchable electrodes that detect physiological signals during normal wear.

Research Evidence:

Baronetto et al. (2025) developed a Smart T-shirt equipped with a digital acoustic sensor linked to an AI algorithm (Efficient U-Net) that can interpret bowel sounds.

The T-shirt accurately distinguished intestinal motility patterns and sound frequency variations associated with bowel inflammation or obstruction.
Its washable, flexible design ensures comfort and long-term usability — an essential advantage for chronic-disease patients who require daily monitoring.

Applications:

Beyond IBD, such smart clothing has potential in irritable bowel syndrome, post-surgical gut recovery, and even cardiorespiratory monitoring, creating continuous medical feedback loops without discomfort.

4. Virtual Reality (VR) Therapeutic Devices

Description:

VR headsets, though not biochemical sensors, are wearable tools that target the psychological dimensions of chronic illness. They immerse patients in interactive, calming environments to reduce stress, pain, and treatment-related anxiety.

Supporting Research:

Wren et al. (2021) tested a 6-minute VR mindfulness session on young IBD patients during infusions. Participants reported an average 60% reduction in anxiety and pain scores immediately after the session.

Lewandowski et al. (2021) found similar benefits in adult patients, reporting significant increases in

relaxation and well-being during treatment sessions (p = 0.046).

Several small-scale trials suggest that VR-based distraction therapy enhances patient compliance and reduces perceived treatment burden.

Clinical Role:

These findings emphasize the holistic utility of wearable technologies — not only monitoring the physical body but also supporting emotional resilience and mental recovery in chronic care.

5. Wearable Sweat Sensors

Description:

Sweat sensors are considered the next frontier of wearable diagnostics. They collect and analyze perspiration using microfluidic systems and electrochemical biosensors, offering real-time biochemical insights into metabolic and inflammatory health.

Research Findings:

Yang et al. (2023) found that specific metabolites in sweat — particularly amino acids, fatty acids, and glucose — closely matched serum markers of liver function in NAFLD patients.

Sun et al. (2018) reported unique sweat metabolite signatures in individuals with fatty liver disease, showing elevated lactate and fatty acid levels compared to healthy participants.

Nelson et al. (2020) demonstrated that sweat-based monitoring could detect early liver dysfunction, potentially reducing the need for frequent blood draws.

In IBD research, Jagannath et al. (2023) successfully measured calprotectin and CRP in sweat, confirming their feasibility as non-invasive markers of gut inflammation.

Broader Potential:

Sweat sensors could soon serve as portable laboratories, continuously monitoring disease status and treatment response. Their integration with smartphone apps allows instant data visualization and remote physician access, enabling personalized, data-driven decision-making.

Utility and Benefits

Wearable devices deliver several transformative benefits:

Continuous, real-time data: They detect subtle physiological and biochemical changes earlier than traditional tests.

Non-invasive and painless: Sweat and skin sensors eliminate the need for repeated blood samples.

Personalized healthcare: Data-driven insights allow clinicians to tailor interventions to individual needs.

Early disease prediction: HRV and cytokine trends can forecast flare-ups days before symptoms arise.

Telemedicine integration: Seamless data transmission supports remote monitoring and virtual consultations.

Improved patient engagement: Empowering patients with their own data enhances adherence and motivation.

Economic benefits: By reducing hospital visits and emergency interventions, wearables lower healthcare costs.

Drawbacks and Limitations

Despite their promise, several challenges remain:

Data reliability: Sweat composition can vary with hydration, diet, or ambient conditions, affecting accuracy.

Standardization gaps: Calibration methods and biomarker thresholds differ between studies.

Data privacy concerns: Continuous monitoring and cloud storage raise questions of cybersecurity.

User adherence: Long-term wearability, skin irritation, or device maintenance can limit compliance.

Clinical validation: Most devices are still in early trial stages; large, multi-center studies are needed for regulatory approval.

Future Perspectives

The coming decade will see wearables evolve into multifunctional, AI-integrated health platforms.

Artificial intelligence and machine learning will analyze complex patterns to predict disease flares or metabolic changes with remarkable accuracy.

Smart fabrics and nanotechnology-based biosensors will provide comfort, flexibility, and biochemical sensitivity at once.

Closed-loop systems could automatically adjust medication dosages or trigger clinical alerts.

Integration with electronic health records (EHRs) will enable seamless clinician access and population-level analytics.

These advancements will shift chronic disease management from hospital-based to home-based ecosystems, where early prediction and precision care define the new standard.

Conclusion

Economic benefits: By reducing hospital visits and emergency interventions, wearables lower healthcare costs.

Drawbacks and Limitations

Despite their promise, several challenges remain:

Wearable technology has evolved from simple step counters into sophisticated, intelligent health companions.

In IBD, they allow early detection of inflammatory flares, activity assessment, and even emotional therapy through virtual reality.

In NAFLD, they promise a painless way to monitor liver health through molecular traces in sweat.

As innovation continues, these devices will become essential components of everyday care — democratizing medicine, enhancing quality of life, and empowering patients with control over their health. In the future, healthcare won't just be delivered in hospitals — it will live on our wrists, in our clothes, and even in every drop of sweat that tells our story.

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Section 10
Emergency Medicine

Chapter

31

Sepsis Management: Biomarkers and Rapid Interventions

Dr. Kishore K Talukdar

ABSTRACT

Sepsis is a leading cause of global morbidity and mortality, responsible for nearly 11 million deaths annually. Despite advances in critical care, diagnostic delays and therapeutic uncertainties persist, particularly in resource-limited settings. Biomarkers such as C-reactive protein, procalcitonin, presepsin, mid-regional pro-adrenomedullin, neutrophil CD64, and fungal markers including ß-D-glucan and galactomannan have emerged as valuable adjuncts in identifying infection, guiding antimicrobial stewardship, and predicting prognosis. At the same time, rapid interventions, timely antibiotics, early resuscitation, and prompt source control remain cornerstones of evidence-based management. This review synthesizes current evidence on biomarkers and rapid interventions, highlighting their practical applicability, limitations, and integration into sepsis bundles. Special attention is given to fungal biomarkers, which are increasingly important in critically ill and immunocompromised patients. Future directions include multi-biomarker panels, precision medicine, and artificial intelligence–enabled diagnostic tools, with a focus on cost-effective and accessible solutions for global equity.

Introduction

Sepsis continues to pose a significant global healthcare burden. The Global Burden of Disease study estimates 48.9 million incident cases of sepsis in 2017, with 11 million related deaths-accounting for almost 20% of global mortality [1,2]. Despite improvements in supportive care and antimicrobial therapy, outcomes remain poor, with mortality ranging between 25-40% in septic shock.

Early diagnosis and timely therapy are critical for survival, but sepsis recognition remains challenging. Its clinical presentation overlaps with other systemic inflammatory states, while blood cultures-the diagnostic gold standard-require 48-72 hours and are frequently negative. In this context, biomarkers and rapid interventions provide complementary strategies: biomarkers help identify sepsis earlier, refine

antimicrobial use, and stratify prognosis, while rapid interventions such as antibiotics, resuscitation, and source control directly influence survival.

This review examines the evidence and real-world applicability of biomarkers and rapid interventions in sepsis management, including bacterial and fungal sepsis, and explores future directions for integrating precision medicine and digital health into care pathways.

1. Biomarkers in Sepsis: Real-World Utility

1.1 Traditional Biomarkers

C-ReactiveProtein (CRP):

An acute-phase reactant produced by hepatocytes in response to IL-6, CRP rises within 6–8 hours of infection and correlates with inflammatory burden. CRP is widely available and inexpensive, making it one of the most used biomarkers worldwide. Elevated CRP (>100 mg/L) is common in bacterial infections but also rises in trauma, burns, and autoimmune flares. Its main utility lies in serial monitoring rather than single values. In European ICU cohorts, persistently elevated CRP was associated with treatment failure, whereas declining levels correlated with favorable outcomes [3].

Procalcitonin (PCT):

PCT is more specific to bacterial infection and rises within 2-4 hours [4]. Large randomized controlled trials have demonstrated real-world applicability. In the PRORATA trial (France, 621 patients), PCT-guided therapy reduced antibiotic exposure by 23% without increasing mortality [5]. Similarly, the multicenter SAPS trial (Netherlands, 1,546 patients) showed PCT-guided strategies safely reduced antibiotic duration and associated adverse events [6].

1.2 Novel Biomarkers

Presepsin(sCD14-ST):

Presepsin rises earlier than PCT and CRP, and meta-analyses suggest a pooled sensitivity of 0.86 and specificity of 0.78 for sepsis diagnosis [7]. Real-world studies in Emergency Department patients show presepsin may be particularly helpful in differentiating sepsis from non-infectious systemic inflammatory response.

Mid-regional pro-adrenomedullin (MR-proADM): MR-proADM reflects endothelial dysfunction and has demonstrated strong prognostic value. In the large multinational TRIAGE study (6,086 patients), MR-proADM outperformed lactate in predicting 28-day mortality and ICU admission [8]. Its incorporation into risk scores may support triage decisions.

sTREM-1:

Elevated sTREM-1 levels in plasma or BAL fluid correlate with bacterial and fungal infections [9]. A meta-analysis demonstrated a pooled sensitivity of 0.82 for sepsis diagnosis, making it useful in selected populations, particularly those with pneumonia.

1.3 Neutrophil CD64 (nCD64)

Neutrophil CD64 is a high-affinity IgG receptor expressed at low levels on resting neutrophils. In infection and sepsis, proinflammatory cytokines (e.g., IFN-?, G-CSF) upregulate nCD64 within 4–6 hours, reflecting early innate immune activation [10].

Meta-analytic data (>3,000 patients) demonstrate high diagnostic performance for bacterial infection with pooled sensitivity 0.87 and specificity 0.89 [11]. nCD64 levels correlate with severity (higher SOFA) and adverse

outcomes in ICU cohorts [12] and the marker rises earlier than CRP or PCT in many cases.

Practicality in sepsis management:

i. **Diagnostic aid:** Particularly helpful for distinguishing sepsis from postoperative SIRS or autoimmune flares when clinical features overlap.

ii. **Combination strategies:** When combined with PCT or CRP, nCD64 increases diagnostic accuracy (e.g., sensitivity >90% in multicenter data) and reduces false negatives [13,14].

iii. **Turnaround and feasibility:** Flow cytometry–based assays can yield results in 1–2 hours; newer automated analyzers have improved feasibility in tertiary ICUs.

iv. **Limitations:** Requires cytometry infrastructure and expertise; elevations may occur in severe viral infections or systemic inflammation.

Clinical impact: nCD64 adds an immune-activation dimension to biochemical biomarkers, improving early diagnostic confidence and supporting stewardship in equivocal or culture-negative presentations.

1.4 Fungal Biomarkers in Sepsis

Fungal infections complicate sepsis in 15-20% of ICU patients, particularly those with broad-spectrum antibiotic exposure, central venous catheters, parenteral nutrition, or immunosuppression. Mortality from invasive candidiasis and aspergillosis remains high (40-60%). Conventional cultures are slow and insensitive, underscoring the need for fungal biomarkers.

i. ß-D-glucan (BDG): Meta-analysis data (16 studies, 2,979 patients) show BDG has pooled sensitivity of 77% and specificity of 85% for invasive fungal infections [15]. Repeated negative BDG assays have a high negative predictive value, supporting antifungal stewardship.

ii. Mannan and anti-mannan antibodies: When combined, sensitivity rises to 83%, allowing earlier detection of candidemia than blood culture [16].

iii. Galactomannan (GM): Widely validated for invasive aspergillosis, especially in hematology and transplant cohorts. Serum GM positivity may precede radiological findings, while BAL GM offers superior sensitivity in ICU populations [17].

iv. T2Candida panel: Provides culture-independent identification of Candida species within 3-5 hours. In the DIRECT trial, sensitivity was 91% with specificity of 99% [18]. This enables early targeted antifungal therapy, though cost and limited availability remain barriers.

Clinical impact: Integration of BDG, GM and T2Candida into stewardship programs has reduced unnecessary antifungal use while enabling earlier therapy in true invasive fungal disease.

A summary of key biomarkers, their clinical utility, and limitations is presented in **Table 1**.

Table 1: Biomarkers in Sepsis: Clinical Utility and Limitations

Biomarker	Source/Target	Diagnostic Utility	Prognostic Value	Limitations/Challenges	Clinical Application
C-reactive protein (CRP)	Acute-phase reactant (liver)	Elevated in bacterial infections; rises in 6–8 h	Serial decline ↔ response	Nonspecific (trauma, burns, autoimmune)	Monitoring resolution in ICU/ward
Procalcitonin (PCT)	Prohormone of calcitonin	Rises in bacterial sepsis (2–4 h); less affected by viral/sterile inflammation	Guides de-escalation; tracks severity	Elevated in renal failure; higher cost than CRP	Stewardship protocols; reduces duration (PRORATA, SAPS)
Presepsin (sCD14-ST)	Soluble CD14 subtype	Early rise; differentiates sepsis vs SIRS	Moderate severity correlation	Limited availability; cost	ED/early recognition adjunct
MR-proADM	Endothelial dysfunction	Not diagnostic; indicates severe disease	Strong predictor of ICU admission/mortality	Mostly high-resource availability	Triage/risk stratification

Biomarker	Source/Target	Diagnostic Utility	Prognostic Value	Limitations/Challenges	Clinical Application
sTREM-1	Myeloid activation	Elevated in bacterial/fungal pneumonia	Moderate	Moderate specificity; availability	Adjunct in pneumonia (BAL, plasma)
Neutrophil CD64 (nCD64)	(FcγRI) Fc gamma receptor I upregulation on neutrophils	Early immune-activation signal; high sensitivity/specificity for bacterial infection	Correlates with SOFA and mortality	Requires flow cytometry; can rise in severe viral inflammation	Combine with PCT/CRP for early, accurate diagnosis
β-D-glucan (BDG)	Fungal cell wall	Pan-fungal; sens. ~77%, spec. ~85%	Serial negatives help rule out IFI	False positives (dialysis, IVIG, severe sepsis)	Antifungal stewardship; rule-out in ICU
Mannan/Anti-mannan	Candida antigen/antibody	Early candidemia detection; better combined	May precede culture	Limited alone	Adjunct in suspected invasive candidiasis
Galactomannan (GM)	Aspergillus polysaccharide	Sensitive for IA; BAL superior to serum in ICU	Early pulmonary marker	False pos. with some antibiotics	Hematology/transplant cornerstone
T2Candida panel	Candida DNA (culture-independent)	Rapid (<5 h), sens. >90%	Enables early targeted therapy	Cost/availability	Early, species-specific candidemia dx
Lactate	Anaerobic metabolism	Not diagnostic; hypoperfusion marker	Strong mortality correlation; clearance predicts response	Nonspecific elevations possible	Bedside severity & resuscitation

2. Rapid Interventions in Sepsis Care

2.1 Early Resuscitation

The original EGDT trial demonstrated a 16% absolute mortality reduction with structured early resuscitation [19]. However, subsequent large RCTs-ProCESS (US, 1,341 patients) and ARISE (Australia/ New Zealand, 1,600 patients)showed no mortality benefit over usual care, emphasizing timeliness of fluids and vasopressors rather than rigid targets [20,21].

Real-world application:Guidelines recommend 30 mL/kg crystalloid within the first 3 hours, with dynamic reassessment.

2.2 Timely Antimicrobial Therapy

Multiple studies confirm that delayed antibiotic initiation increases mortality. Kumar et al. (2006, 2,154 patients) reported an 8% increase in mortality per hour of delay in septic shock [22].

Practical strategies:

i. Draw blood cultures (=2 sets, ~10 mL each) promptly but initiate empiric antibiotics without waiting.

ii. Choose empiric regimens based on local antibiograms and patient history.

iii. Stewardship protocols, supported by biomarkers (e.g., PCT, BDG with their prior citations [6,15]), facilitate early de-escalation, reducing resistance and adverse events.

2.3 Source Control

A review of >5,000 patients confirmed delays beyond 12 hours in achieving definitive source control were associated with significantly higher mortality [23]. Common interventions include drainage of abscesses, removal of infected devices, or surgical debridement.

2.4 Rapid Diagnostics

i. Lactate: Elevated lactate indicates tissue hypoxia or global hypoperfusion, even before hypotension develops. Bedside lactate >2 mmol/L correlates with increased mortality and guides resuscitation intensity; early lactate clearance is associated with improved outcomes [24].

ii. Multiplex PCR panels: Reduce time to pathogen identification by 24-36 hours compared with culture, enabling earlier targeted therapy.

iii. Artificial intelligence: Machine-learning algorithms using EHR data predict sepsis onset 4-6 hours earlier than clinician recognition, with improved outcomes in implementation studies [25].

3. Clinical Integration and Applicability

3.1 Sepsis Bundles

The 2021 Surviving Sepsis Campaign recommends the "1-hour bundle": lactate measurement, cultures, antibiotics, fluids, and vasopressors [25]. Biomarkers supplement these bundles by refining therapy decisions rather than delaying initial management.

3.2 Stewardship Programs

Randomized trials confirm that biomarker-guided therapy reduces unnecessary antimicrobial exposure. In real-world hospital networks, PCT-guided protocols have been associated with lower antibiotic use, reduced Clostridioides difficile infections, and shorter length of stay [5,6]. Similarly, BDG and GM testing are being incorporated into antifungal stewardship to prevent indiscriminate antifungal use.

3.3 Prognostication and Triage

Combining MR-proADM with lactate improves prediction of ICU admission and mortality [26]. Real-world cohort studies show such combinations support triage decisions in ED and ward settings.

3.4 Barriers to Implementation

i. Delays in biomarker availability in resource-limited hospitals.
ii. High costs of advanced assays (MR-proADM, T2Candida).
iii. Lack of clinician familiarity with interpretation.

An integrated approach to sepsis care is shown in Figure1. It emphasizes how early biomarker-based recognition guides timely risk assessment and rapid interventionsleading to improved survival and rational antimicrobial use.

Initial Biomarkers	→	Risk Stratification	→	Rapid Interventions	→	Improved Outcomes
CRP, PCT, Presepsin, MR-proADM, BDG, GM, T2Candida		Differentiate bacterial vs fungal sepsis; Prognosis (SOFA, lactate, *MR*-proADM)		Antibiotics, Antifungals, Fluids, Vasopressors, Source Control		Reduced mortality, optimized stewardship, precision-based sepsis care

Figure 1. Sepsis Management Pathway

4. Future Perspectives

4.1 Multi-Biomarker Panels

Combining bacterial and fungal markers (e.g., PCT + nCD64 + MR-proADM + BDG) may improve accuracy and guide early targeted therapy.

4.2 Precision Medicine

Sepsis endotyping via transcriptomic analysis may identify patients who would benefit from immunomodulatory therapies [27].

4.3 AI and Digital Health

EHR-integrated predictive models are already improving sepsis detection in real-world hospital systems [25].

4.4 Global Health Equity

Most sepsis deaths occur in low and middle-income countries [28]. Development of low-cost, point-of-care biomarker tests is essential for global impact.

Conclusion

Sepsis remains a leading cause of preventable mortality worldwide. Biomarkers enhance diagnosis, stewardship, and prognostication, while rapid interventions remain the foundation of therapy. Real-world evidence supports the integration of PCT, CRP, MR-proADM, nCD64, and fungal biomarkers (BDG,

GM, T2Candida) into clinical workflows. However, challenges of cost, accessibility, and interpretation remain.

Keypractice implications:

i. Antibiotics and resuscitation must begin within 1 hour; biomarkers should guide but never delay therapy.
ii. Biomarkersparticularly PCT, nCD64, and BDG-play a central role in stewardship by supporting de-escalation.
iii. Source control remains non-negotiable for survival.
iv. Emerging tools like AI, multiplex PCR, and transcriptomics hold promise but require validation in diverse populations.

Future priorities: Validation of multi-biomarker panels, expansion of precision medicine approaches, and development of affordable assays to ensure global equity in sepsis care.

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Chapter

32

Thromboelastography (TEG) in Emergency and Critical Care: Principles, Applications, and Clinical Implications

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ABSTRACT

Sepsis is a leading cause of global morbidity and mortality, responsible for nearly 11 million deaths annually. Despite advances in critical care, diagnostic delays and therapeutic uncertainties persist, particularly in resource-limited settings. Biomarkers such as C-reactive protein, procalcitonin, presepsin, mid-regional pro-adrenomedullin, neutrophil CD64, and fungal markers including ß-D-glucan and galactomannan have emerged as valuable adjuncts in identifying infection, guiding antimicrobial stewardship, and predicting prognosis. At the same time, rapid interventions, timely antibiotics, early resuscitation, and prompt source control remain cornerstones of evidence-based management. This review synthesizes current evidence on biomarkers and rapid interventions, highlighting their practical applicability, limitations, and integration into sepsis bundles. Special attention is given to fungal biomarkers, which are increasingly important in critically ill and immunocompromised patients. Future directions include multi-biomarker panels, precision medicine, and artificial intelligence–enabled diagnostic tools, with a focus on cost-effective and accessible solutions for global equity.

Introduction

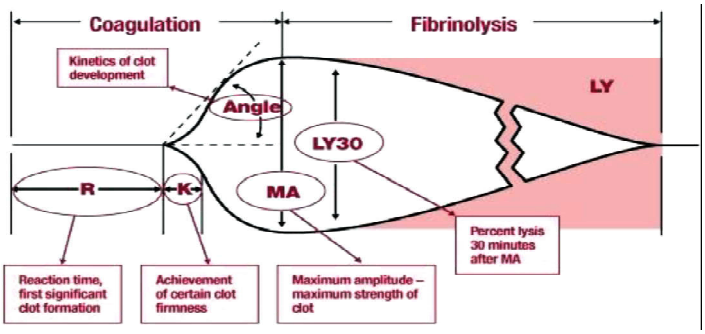
Coagulation represents a delicate balance between pro- and anticoagulant mechanisms that maintain blood in a fluid state while allowing effective clot formation following injury. Conventional coagulation tests—such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen concentration, and platelet count—measure isolated elements of this system under artificial laboratory conditions. These assays provide limited insight into the dynamic process of clot initiation, propagation, and dissolution. Thromboelastography (TEG), first described by Hartert in 1948, was developed to evaluate the viscoelastic characteristics of whole blood as it transitions from a liquid to a solid and back again[1]. Unlike routine tests that focus on plasma, TEG assesses

the interactions of platelets, fibrinogen, and clotting factors in real time, offering a comprehensive picture of hemostasis. In contemporary practice, TEG is increasingly integrated into perioperative medicine, trauma resuscitation, obstetric hemorrhage management, liver transplantation, and critical care [2]. By identifying the specific component of coagulation dysfunction, TEG allows clinicians to individualize transfusion therapy and minimize unnecessary use of blood products. This approach aligns closely with modern patient blood management principles and precision medicine initiatives.

Section 1: Principle and Methodology

1.1 Fundamental Concept

TEG evaluates the physical properties of a developing clot in whole blood. A small volume of citrated blood is placed into a heated cup that oscillates gently through a defined angle (4°45'). Suspended in the sample is a pin connected to a torsion wire. As fibrin strands form and strengthen, they transmit rotational forces between the cup and the pin. These forces are converted into electrical signals and plotted as a curve known as the thromboelastogram [3]. This curve visually represents the sequential stages of coagulation—from initial fibrin formation, through clot strengthening and stability, to eventual breakdown.



1.2 Evolution of TEG Technology

Traditional mechanical systems have gradually been replaced by automated resonance-based devices such as the TEG 6s, which uses microfluidic cartridges rather than open cuvettes. These modern analyzers require minimal operator handling, use smaller blood volumes, and provide faster, standardized results.

1.3 Key Parameters and Interpretation

A thromboelastogram generates multiple parameters, each reflecting a distinct aspect of hemostasis:

TEG Value	Normal*	Description	Measures
TEG-ACT (rapid)	80 - 140 sec	"Activated clotting time" to initial fibrin formation	clotting factors (extrinsic/intrinsic pathways)
R time (conventional)	5.0 - 10.0 min	"Reaction time" to initial fibrin formation	clotting factors (intrinsic pathway)
K time	1.0 - 3.0 min	"Kinetic time" for fibrin cross linkage to reach 20 mm clot strength	fibrinogen, platelet number
α angle	53.0 - 72.0 degrees	Angle from baseline to slop of tracing that represents clot formation	fibrinogen, platelet number
MA	50.0 - 70.0 mm	Maximum amplitude of tracing	platelet number and function
G value	5.3 - 12.4 dynes/cm^2	Calculated value of clot strength	entire coagulation cascade
LY 30	0 - 3%	Clot lysis at 30 minutes following MA	fibrinolysis

Together, these parameters provide a comprehensive view of the coagulation cascade, platelet contribution, and fibrinolytic activity. TEG allows classification of coagulation patterns into normal and abnormal. Abnormal patterns include hypo coagulable, hypercoagulable, and hyper fibrinolytic states. Hypo coagulable patterns exhibit prolonged R and K, low a-angle, and reduced MA, commonly seen in trauma, liver failure, or dilutional coagulopathy. Hypercoagulable tracings show shortened R, steep a-angle, and elevated MA, often associated with thrombophilia or early sepsis. Hyperfibrinolysis is characterized by rapid clot strength reduction post-MA and elevated LY30.

Section 2: Clinical Applications

2.1 Trauma and Massive Hemorrhage

Traumatic bleeding often leads to a multifactorial coagulopathy resulting from dilution, hypothermia, acidosis, and tissue injury. TEG enables rapid differentiation of these abnormalities, identifying whether coagulopathy arises from clotting factor deficiency, fibrinogen depletion, platelet dysfunction, or excessive fibrinolysis [4]. Evidence supports the use of TEG-guided transfusion in massive transfusion protocols, leading to fewer blood product transfusions and improved survival[5].

TEG Value	Transfuse
TEG-ACT > 140	FFP
R time > 10	FFP
K time > 3	cryoprecipitate
α angle < 53	cryoprecipitate +/- platelets
MA < 50	platelets
LY30 > 3%	tranexamic acid

2.2 Cardiac Surgery

During cardiopulmonary bypass, hemodilution and mechanical activation of coagulation pathways frequently produce complex hemostatic disturbances. Standard coagulation tests are too slow to guide intraoperative transfusion effectively. TEG, by providing near-real-time feedback, allows tailored replacement of plasma, platelets, or cryoprecipitate, reducing postoperative bleeding and transfusion requirements [6].

2.3 Liver Disease and Transplantation

Cirrhotic and transplant patients exhibit both hypo coagulable and hypercoagulable states due to altered synthesis and clearance of coagulation proteins. TEG captures this delicate balance better than PT or aPTT. During liver transplantation, TEG-based transfusion protocols have consistently lowered blood product usage and improved early graft outcomes [7].

2.4 Obstetric Hemorrhage

Pregnancy induces a physiologic hypercoagulable state, but certain obstetric emergencies—such as postpartum hemorrhage (PPH) or HELLP syndrome—may cause abrupt coagulopathy. TEG rapidly identifies low fibrinogen levels, guiding targeted cryoprecipitate or fibrinogen concentrate therapy [8]. Early correction of fibrinogen deficits based on TEG results correlates with improved maternal outcomes.

2.5 Sepsis and Critical Illness

Sepsis triggers a dynamic shift between hypercoagulability and hypocoagulability. Early TEG profiles often show increased clot strength and shortened clot times, while later stages demonstrate impaired coagulation and fibrinolysis consistent with disseminated intravascular coagulation. Serial TEG monitoring assists in prognosis and guides anticoagulation or replacement therapy decisions [9].

Section 3: Advantages and Limitations

3.1 Strengths of TEG

1. Global View of Hemostasis: TEG reflects the combined effect of all hemostatic components rather than isolated factor levels.
2. Rapid and Bedside Use: Results are available within minutes, essential during active bleeding or surgery.
3. Transfusion Stewardship: TEG supports precision

transfusion, minimizing overuse of plasma, platelets, and cryoprecipitate.

4. Dynamic Monitoring: Serial tracings reveal changes in coagulation during surgery, trauma resuscitation, or sepsis progression.
5. Predictive Utility: Certain parameters (e.g., low MA or elevated LY30) can predict postoperative bleeding or thrombotic risk.

3.2 Recognized Limitations

1. Operator Sensitivity: Manual techniques require meticulous handling; errors in sample preparation can distort results.
2. Incomplete Detection Spectrum: Mild platelet disorders and von Willebrand disease may remain undetected.
3. Inter-Device Variability: Differences among TEG and ROTEM instruments hinder universal reference ranges.
4. Resource Requirements: Equipment cost and consumable expenses restrict use in smaller centers.
5. Pre-Analytical Factors: Time from venipuncture to testing, temperature, and anticoagulant type can all influence results.

Section 4: Future Perspectives and Innovations

4.1 ROTEM and Next-Generation Devices

Rotational thromboelastometry (ROTEM) is conceptually similar to TEG but reverses the mechanics: the pin rotates while the cup remains still. Using multiple reagents, ROTEM differentiates between intrinsic, extrinsic, and fibrinolytic pathways[10]. Newer cartridge-based systems such as TEG 6s have enhanced reproducibility and simplified operation, promoting wider clinical use.

4.2 Artificial Intelligence and Predictive Analytics

Machine learning models are being developed to interpret complex TEG data sets automatically. Such algorithms could predict bleeding or thrombosis risk earlier than human analysis, providing decision support for intensivists and surgeons.

4.3 Integration with Platelet Mapping

TEG with platelet mapping (TEG-PM) measures the degree of platelet inhibition caused by antiplatelet drugs like aspirin or clopidogrel. This adaptation is particularly useful for cardiac and neurovascular procedures, where individualized antiplatelet management is crucial.

4.4 Application in COVID-19 and Thromboinflammation

During the COVID-19 pandemic, TEG revealed that critically ill patients often exhibited profound hypercoagulability. TEG findings guided anticoagulant dosing and provided insight into the thromboinflammatory nature of severe infection.

4.5 Path Toward Standardization

Despite widespread use, TEG interpretation varies among institutions. Establishing uniform reference intervals, standardized reagents, and training programs will be essential to enhance reproducibility and global adoption.

Conclusion

Thromboelastography has transformed our approach to hemostatic assessment by providing a dynamic, holistic evaluation of clot formation, stability, and lysis. Unlike conventional plasma-based tests, it captures the interplay between cellular and plasma components of coagulation in real time. Its utility in trauma, cardiac surgery, liver transplantation, obstetric hemorrhage, and sepsis underscores its value as both a diagnostic and management tool. TEG-guided transfusion protocols consistently demonstrate reductions in blood product use and related complications, translating to improved patient outcomes. However, broader implementation will require solutions to current limitations—standardization, cost reduction, and expanded clinician training. With continuing innovation, including integration with artificial intelligence and advanced microfluidic technology, TEG is poised to remain an indispensable instrument in modern hemostatic management and precision medicine.

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Section 11
Diabetes

Chapter

33

Closed-Loop Insulin Delivery Systems: The Artificial Pancreas

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ABSTRACT

The management of diabetes has undergone a remarkable transformation over the past century. Newer insulins and modern technology now enable exogenous insulin administration in insulin-requiring diabetics to such great precision that it is able to replicate normal human ß-cell physiology. The closed-loop insulin delivery system is popularly referred to as the "artificial pancreas." The system combines real-time continuous glucose monitoring, subcutaneous insulin infusion via a pump, and computer-driven algorithms that automatically adjust insulin delivery in response to glucose fluctuations. Type 1 diabetics, as observed in clinical trials and real-world data, show significant improvements in glycaemic control, reduced risk of hypoglycaemia, and improved quality of life [1–3]. Newer insulin formulations, algorithms, and integration with digital health are progressively overcoming the challenges related to cost, sensor accuracy, and accessibility. The fundamental shift in how diabetes is managed through better glycaemic metrics is likely to be through this automated physiologic replacement.

Introduction

India, crowned the "diabetes capital of the world," contributes significantly, with an estimated 101 million individuals living with diabetes and nearly 136 million with prediabetes, to the steep upward trajectory of a major global health challenge. Conventional insulin regimens, whether multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) pumps, require constant patient involvement and carry the risk of hypoglycaemia, glycaemic variability, and treatment fatigue. Healthy pancreatic ß-cell function is both dynamic and adaptive in nature. Replicating the same by exogenous insulin regimens and devices has shown many fundamental limitations. The concept of a closed-loop insulin delivery system, or artificial pancreas, addresses this gap. By integrating continuous glucose monitoring with insulin pumps controlled by mathematical algorithms, these systems aim to automate

insulin delivery, reducing patient burden while improving metabolic outcomes[1,4].

Physiological

Basis Pancreatic ß-cells sense blood glucose fluctuations and secrete insulin in a pulsatile manner to maintain glucose homeostasis. This secretion is rapid, biphasic, and finely tuned to meals, exercise, stress, and circadian rhythms. Additionally, a-cells secrete glucagon to prevent hypoglycaemia, ensuring a tightly regulated system of counterbalance. In type 1 diabetes, complete ß-cell destruction eliminates this feedback loop, while in advanced type 2 diabetes, insulin resistance and relative ß-cell failure impair the body's adaptive capacity. The artificial pancreas seeks to recreate this loop: glucose sensing ? algorithmic processing ? automated insulin delivery. The challenge lies in sensor lag, delayed absorption of subcutaneous insulin compared to endogenous secretion, and unpredictable external influences such as diet and physical activity[5].

Evolution of Automated Insulin Delivery:

1. **Multiple Daily Injections (MDI):** Traditional basal–bolus regimen improved flexibility but required patient vigilance.
2. **Insulin Pens and Early Pumps:** Provided programmable basal rates and on-demand boluses but relied on manual adjustment.
3. **Sensor-Augmented Pump Therapy:** Integration of CGMs with pumps allowed patient-driven adjustments.
4. **Threshold Suspend and Predictive Low-Glucose Suspend (PLGS):** Suspended insulin delivery when hypoglycaemia was imminent, improving safety[7].
5. **Closed-Loop Systems:** Algorithm-driven automation—initially hybrid closed-loop (requiring meal announcements) and gradually moving toward fully automated models[1,2,4].

Components of a Closed-Loop System

Three major components are integrated:

1. Continuous Glucose Monitor (CGM) – modern devices with MARD <10%, real-time smartphone connectivity[2].
2. Insulin Pump (CSII) – delivers rapid-acting insulin analogues, options include tubed and patch pumps.
3. Control Algorithms – PID, MPC, fuzzy logic, and AI-driven adaptive learning[6].

Together, these components create a dynamic loop that can autonomously adjust insulin delivery in real time.

Types of Closed-Loop Systems

1. Hybrid Closed Loop (HCL): Adjusts basal insulin delivery, requires meal boluses. Examples: Medtronic 670G/780G, Tandem Control-IQ, Omnipod 5[1,3].
2. Fully Automated (FCL): No manual input required; still under development[5].
3. Dual-Hormone Systems: Experimental combinations of insulin and glucagon[5].
4. Do-It-Yourself (DIY) Looping: Open-source systems (OpenAPS, Loop, AndroidAPS), facing regulatory concerns[6].

Clinical Evidence & Outcomes

Numerous randomized controlled trials and meta-analyses confirm the efficacy of closed-loop systems:

- HbA1c Reduction: Trials consistently demonstrate reductions of 0.3–0.5% compared with standard therapy [1,2].
- Time-in-Range (TIR): Increases of 10–15%, equivalent to 2–3 extra hours/day in range [1,2,3].
- Hypoglycaemia: Significant reduction in both frequency and severity, especially nocturnal episodes[3].
- Pediatric and Adolescent Populations: Improved glycemic control and parental reassurance[4].
- Pregnancy & Hospital Use: Early studies suggest benefits, though evidence is emerging [5].

Notable trials include: NEJM 2019 (CamAPS FX, [2]); Tandem Control-IQ pivotal trial (2020, [1]); and real-world registry data (Europe, US) [3,6].

Challenges & Limitations Closed-loop systems face hurdles:

- Cost & Accessibility: Barriers in low- and middle-income countries, including India.
- Device Burden: Wearing CGM + pump, infusion set changes.
- Insulin Kinetics: Subcutaneous absorption slower than physiologic secretion.
- Sensor Limitations: Interstitial lag, accuracy issues, frequent replacements [7].
- Training & Adherence: Need for patient education and technical literacy.
- Regulatory Barriers: Differing approval processes globally.

Future Directions:

- Next-generation insulins (ultra-rapid, smart insulins).
- Multi-hormone systems (insulin + glucagon, pramlintide, GLP-1).
- Fully implantable closed-loop systems [5].
- AI- and machine-learning-driven adaptive algorithms [6].
- Expansion beyond T1DM: advanced T2DM, gestational diabetes, inpatient care.

Conclusion

Closed-loop insulin delivery systems mark a paradigm shift in diabetes care. By approximating physiologic insulin secretion, they have already improved glycaemic outcomes, safety, and quality of life for thousands of patients [1–4]. For physicians, these systems demand new skills in device management, patient training, and digital health data interpretation. While challenges of cost and accessibility remain significant in India, ongoing innovations suggest that closed-loop therapy will become increasingly mainstream. The "artificial pancreas" is no longer futuristic—it is present-day reality. Newer, fully automated solutions may ultimately normalize life expectancy and daily living for people with diabetes [5–7].

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Chapter

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Type 2 Diabetes: Novel Oral and Injectable Therapies

Dr. Sarat Keot

ABSTRACT

The limitations of traditional drugs in managing and preventing complications of type 2 diabetes mellitus(T2DM) have driven the development of newer, more effective pharmacological options. The multiple metabolic defects of T2DM are being targeted by novel oral and injectable agents. The advanced oral therapies such as DPP-4 inhibitors, SGLT2 inhibitors, oral GLP-1 receptor agonists, glucokinase activators, and imeglimin target to correct different metabolic defects associated with type 2 diabetes like lowering hepatic glucose output, improving ß-cell function, enhancing insulin secretion, decreasing reabsorption of glucose. The non-insulin injectable therapies including GLP-1 receptor agonists, dual and triple incretin agonists, amylin analogs, and innovative weekly insulins are developed and undergoing different clinical trials for better metabolic outcomes and patient compliance. All these major advancements have led towards personalized diabetes care, with additional benefits in weight management, cardiorenal protection, and reduced hypoglycemia risk.

Keywords: Type 2 diabetes mellitus; Novel oral agents; Injectable therapies; DPP-4 inhibitors; SGLT2 inhibitors; GLP-1 receptor agonists; Dual and triple incretin agonists; Amylin analogs; Imeglimin; Glucokinase activators; Personalized diabetes care; Cardiorenal protection; Weight management; Hypoglycemia risk.

Introduction

Insulin resistance, impaired insulin secretion, and dysregulated glucose homeostasis are considered as the main metabolic defects associated with type 2 diabetes, although some new pathophysiologic processes attributed as a cause are under study. Despite advances in understanding its pathophysiology, the worldwide burden of T2DM is alarmingly increasing, posing a constant challenge to the healthcare system, significantly affecting morbidity, mortality and healthcare costs. Conventional therapeutic approaches—such as metformin, sulfonylureas, thiazolidinediones, and

insulin—have provided substantial benefits in glycemic control; however, many patients eventually experience therapeutic failure, weight gain, hypoglycemia, or other adverse effects, thereby necessitating new treatment approaches.

In recent years, the development of novel oral and injectable agents has transformed the management landscape of T2DM. These newer therapies, including sodium–glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dual and triple incretin receptor agonists, and innovative insulin formulations, not only improve glycemic outcomes but also offer additional benefits such as weight reduction, cardiovascular and renal protection, and reduced risk of hypoglycemia. The introduction of these newer therapeutic strategies have led to a paradigm shift toward comprehensive, patient-centric diabetes care.

Novel Oral Hypoglycemic Agents

Over the past few years, the management of T2DM has evolved significantly with the introduction of novel oral hypoglycemic agents (OHAs). These drugs target cardiovascular, renal, and metabolic risks along with glycemic control. Traditional agents such as metformin, sulfonylureas, and thiazolidinediones have been supplemented by newer classes including Dipeptidyl Peptidase-4 (DPP-4) inhibitors, Sodium–Glucose Cotransporter-2 (SGLT2) inhibitors, oral GLP-1 agonists targeting multiple metabolic pathways.

1. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Mechanism of Action:

DPP-4 inhibitors, also known as "gliptins," inhibit the enzyme DPP-4, which rapidly degrades incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), causing prolonged incretin activity. These agents increase insulin secretion and suppress glucagon release in a glucose-dependent manner, thereby decreasing the risk of hypoglycemia.

- Linagliptin-25 mg once daily, can be used in advanced CKD.
- Saxagliptin-5 mg once daily, reduced to 2.5mg if eGFR<45.
- Sitagliptin-50 mg, 100 mg once daily.
- Vildagliptin-50 mg twice daily, 50 mg once daily if eGFR<45, not recommended in hepatic dysfunction, perform LFT before initiating.
- Alogliptin- 25 mg once daily.[1]

Emerging DPP-4 inhibitors:

Trelagliptin- a new compound approved in Japan, given once weekly, has shown efficacy and tolerance as antidiabetic agent. Its convenient dosing is expected to improve medication adherence.[2]
Prusogliptin (DBPR108)- a novel DPP-4 inhibitor undergoing clinical trials in China.

Efficacy and Safety:

DPP-4 inhibitors typically lower HbA1c by 0.5–0.8%. They are weight neutral and have a low risk of hypoglycemia when used as monotherapy or in combination with metformin. Cardiovascular safety of DPP-4 inhibitors are confirmed by different Cardiovascular Outcome Trials(CVOT) like TECOS(Sitagliptin), SAVOR-TIMI 53(Saxagliptin)and EXAMINE(Alogliptin), though saxagliptin is associated with an increased risk of hospitalization for heart failure.

Clinical Use:

They are often used as second-line agents after metformin, particularly in patients who cannot tolerate SGLT2 inhibitors or GLP-1 receptor agonists.

2. Sodium–Glucose Cotransporter-2 (SGLT2) Inhibitors

Mechanism of Action:

SGLT2 inhibitors, or "gliflozins," block glucose reabsorption in the proximal renal tubules, promoting urinary glucose excretion and thereby lowering plasma glucose levels.

Examples: Empagliflozin, Dapagliflozin, Canagliflozin, Ertugliflozin.

Bexagliflozin- approved by FDA in January 2023, for type 2 diabetes.

Sotaglifozin- approved by FDA in 2023 for specific types of heart failure.

Efficacy and Safety:

Different studies have shown reduction of HbA1c by about 0.7–1.0% along with modest weight loss (2–3 kg)over 6 months and mildly reduced blood pressure (by about 5 mmHg of systolic and 2 mmHg of diastolic blood pressure).The risk of hypoglycemia is also low unless associated with insulin or secretogogues.[3]

Adverse effects include genital mycotic infections, urinary tract infections, and dehydration. Rare but serious risks include euglycemic diabetic ketoacidosis (DKA) and Fournier's gangrene.

Cardiovascular and Renal Benefits:

Several landmark trials have established their cardiorenal protective effects:

EMPA-REG OUTCOME (empagliflozin) showed significant reductions in MACE, cardiovascular death and hospitalization for heart failure.

The CANVAS (canagliflozin) program demonstrated significant reduction in CV events and the progression of albuminuria in type 2 diabetes mellitus. The DECLARE-TIMI 58 (dapagliflozin) showed reduced hospitalization for heart failure and renal failure progression was found to be reduced for patients without cardiovascular diseases.

DAPA-CKD (Dapagliflozin) and CREDENCE (Canagliflozin) trials demonstrated renal protection even in patients with chronic kidney disease (CKD), including those without diabetes.

Clinical Use:

SGLT2 inhibitors are now recommended not only for glycemic control but also for heart failure and CKD management, irrespective of diabetic status.

3. GLP-1 agonist

Mechanism of Action:

GLP-1 receptor agonists stimulate insulin secretion and inhibit glucagon release in a glucose dependent manner. It also delays gastric emptying and promotes weight loss.

- Oral semaglutide(by Novo Nordisk) is the first oral GLP-1 receptor agonist approved by FDA for managing diabetes. It has proven cardiovascular benefit. The recommended starting dose is 3 mg daily for the first month, then increase to 7 mg daily after 1 month. Can be further increased to 14 mg daily. Oral semaglutide has proven efficacy in type 2 diabetes through several randomized controlled trials(PIONEER 1-8). In prospective

studies, HbA1C reduction varied from -0.9% to -1.6%, weight loss varied from -4.7 kg to -8.2 kg. The most common side effects are gastrointestional issues like nausea, diarrhoea, stomach pain, decreased appetite, constipation, bloating etc. (4)

- Orforglipron is an investigational non peptide oral GLP-1 receptor agonist given once daily developed by Eli Lilly. Clinical trials have shown its potential for managing obesity and diabetes. The most common side effects are mild to moderate gastrointestinal issues like nausea, diarrhoea, constipation etc.

4. Glucokinase Activators (GKAs)

Mechanism of Action:

Glucokinase acts as a glucose sensor in pancreatic ß-cells and regulates hepatic glucose metabolism. GKAs increase the enzyme's affinity for glucose, thereby enhancing insulin secretion and reducing hepatic glucose output.

Examples: Dorzagliatin and TTP399

Clinical Status and Efficacy:

Dorzagliatin, developed in China, has shown HbA1c reductions of 0.6–1.0% and improved ß-cell function. It represents a promising step toward addressing the underlying pathophysiology of T2DM rather than merely symptom control.

5. Imeglimin:

A first-in-class agent that acts on mitochondrial bioenergetics to improve insulin sensitivity and enhance ß-cell function. Approved in Japan (2021) and in India(2022), imeglimin offers a novel mechanism distinct from existing OHAs. Early studies show HbA1c reductions of about 0.72–0.92%, with good safety and tolerability. (TIMES 1 and TIMES 2). Imeglimin is given 500 mg BID and can be increased to 1000 mg BID. It can be used as monotherapy or as add-on therapy with other OHA.[5]\

Newer insulins:

Long acting insulin analogues like glargine U-100, glargine U-300 and degludec are already in use for last several years. Similarly short acting insulin analogues like Insulin aspart, lispro, faster acting aspart(Fiasp) are also in use. Combination of long acting insulin analogue degludec with short acting insulin analogue aspart in the same co-formulation(IDegAsp) has shown remarkable beneficial effect in comparison to other long-acting insulins.

Once weekly basal insulin:

Insulin Icodec(by Novo Nordisk) is an ultra long-acting novel basal insulin analogue designed for once weekly administration in individuals with diabetes. This analogue insulin contains 3 amino acid substitution and a C20 eicosane fatty diacid chain, which allows it to bind reversibly to albumin. This modification extends icodec's half life to around 196 hrs(7 days). 1 unit of Icodec provides the same glucose lowering effect as 1 unit of daily basal insulin, making the equivalent once weekly dose seven times that of a daily basal insulin. Usually initiated with a weekly dose of 70 units with 20 units dose titration as needed. It is approved and launched for treatment of both type 1 and type 2 diabetes in the European Union, Canada, Australia, Japan and

Switzerland. It has not received approval from FDA till date.[7]

Clinical trial data, primarily from the ONWARDS program(phase 3 trials), showed similar or in some cases superior reduction in HbA1C compared to once daily basal insulin like insulin glargine and insulin degludec in patients with type 2 diabetes. Its once weekly dosing significantly reduces the frequency of injections which can improve patient adherence and quality of life. The risk of clinically significant hypoglycemia with icodec is comparable to daily basal insulin.[8]

Insulin efsitora alfa(developed by Eli Lilly) is an ultra long-acting basal insulin given once weekly which has completed phase 3 program(QWINT-1). Phase 3 trials showed efsitora alfa was non-inferior to once daily insulin glargine in lowering HbA1C in insulin-naive patients.[9]

Combination injectables:

IDegLira, developed by Novo Nordisk, is a fixed-ratio combination therapy consisting of insulin degludec and liraglutide, a GLP-1 receptor agonist, administered once daily via subcutaneous injection. This formulation is designed to overcome common challenges of conventional insulin therapy, particularly the risks of hypoglycemia and weight gain. Each dose step of IDegLira delivers 1 unit of insulin degludec along with 0.036 mg of liraglutide, offering both basal insulin coverage and incretin-based benefits in a single preparation.

Similarly, IGlarLixi, produced by Sanofi, combines insulin glargine with lixisenatide, another GLP-1 receptor agonist, in a fixed-ratio formulation. In this combination, insulin glargine provides prolonged basal insulin action, while lixisenatide acts as a prandial GLP-1 RA that enhances glucose-dependent insulin secretion and suppresses glucagon release, thereby reducing postprandial glucose excursions and minimizing hypoglycemia risk. Each dose step of IGlarLixi contains 1 unit of insulin glargine and 0.33 mg of lixisenatide.

CagriSema, developed by Novo Nordisk, is a once-weekly injectable combination of cagrilintide and semaglutide designed for the management of type 2 diabetes mellitus. In a phase 2 clinical study, CagriSema showed highly encouraging results, producing substantial improvements in HbA1c levels, body weight reduction, and time-in-range compared to either agent used alone. Over a 32-week treatment period, the therapy achieved a 2.2% decrease in HbA1c—surpassing the effect of cagrilintide monotherapy and demonstrating efficacy comparable to semaglutide. Additionally, CagriSema led to a notable 15.6% reduction in body weight, highlighting its strong potential for both glycemic and weight management.[10]

Conclusion

The emergence of novel oral and injectable therapies has significantly transformed the management approach to type 2 diabetes mellitus. Beyond achieving glycemic control, newer drug classes such as SGLT2 inhibitors, oral and injectable GLP-1 receptor agonists, dual and triple incretin agonists, glucokinase activators, and innovative insulin formulations provide substantial metabolic, cardiovascular, and renal benefits. Their diverse mechanisms address core pathophysiological defects

including insulin resistance, ß-cell dysfunction, and dysregulated glucagon secretion, while also promoting weight loss and minimizing hypoglycemia. The development of once-weekly basal insulins and combination injectable regimens enhances therapeutic convenience and patient adherence. As clinical trials continue to demonstrate superior efficacy and safety outcomes, these modern agents are increasingly integrated into personalized treatment algorithms. Overall, the evolution of diabetes pharmacotherapy reflects a paradigm shift toward comprehensive, patient-centered care focused not only on glucose lowering but also on reducing long-term complications and improving quality of life.

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Chapter

35

Diabetic Nephropathy- Pathophysiology, Prevention and Treatment

Dr. Devesh Kr. Singh

Introduction

Diabetic nephropathy is defined as chronic loss of kidney function occurring in those with Diabetes mellitus. It is also known as Diabetic Kidney disease(DKD) . It is the leading cause of end-stage renal disease (ESRD) in world wide. As a microvascular complication, diabetic nephropathy affects individuals with both type 1 diabetes (T1D) and type 2 diabetes (T2D). The condition presents with persistent albuminuria and a progressive decline in the glomerular filtration rate (GFR). Substantial evidence indicates that early, aggressive treatment can delay or prevent the progression of the disorder. While diabetic nephropathy can develop in both T1D and T2D, the majority of diabetes cases (>90%) are T2D, which is primarily insulin-resistant. Nearly 101 million population in indiahave Diabetes ,while 537 million of adult population have Diabetes world wide. 40% of patients with Diabetes end up with Diabetic Nephropathy.

Recent studies have led to updates in treatment guidelines, making it essential to review this extensive topic for providing optimal care to patients with diabetes and kidney disease. Recent guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) and several renal organizations recommend using the terms "diabetes and chronic kidney disease (CKD)" or "diabetic kidney disease (DKD)" instead of "diabetic nephropathy." However, all these terms are currently used in the literature. Additionally, the Kidney Disease Outcomes Quality Initiative (KDOQI) work group emphasizes the need for long-term multidisciplinary teams to address the widespread impact of diabetes and highlights the importance of holistic care and lifestyle modifications for effective management.

Etiology

Hyperglycemia triggers the production of reactive oxygen species and activates several molecular pathways. These include the formation of advanced glycemic end products, increased oxidation, activation of nuclear factor kappa B (NF-?B) and protein kinase C, upregulation of transforming growth factor-beta (TGF-ß) and heightened lipotoxicity.

At the cellular level, hyperglycemia stimulates

abnormal cell signaling, enhances matrix formation, and thickens the glomerular basement membrane (GBM). A significant feature is marked inflammation, driven by elevated levels of cytokines and chemokines, leading to fibrosis and increased vascular permeability. These interconnected pathways drive the onset and progression of diabetic nephropathy by promoting inflammation, fibrosis, endothelial dysfunction, and podocyte damage. Gaining insight into these mechanisms can lead to the development of novel therapeutic strategies.

Macrophage Activation

Hyperglycemia leads to the production of glucose degradation products and glycation end products, intensifying inflammation and promoting macrophage infiltration in the kidneys, a key factor in diabetic nephropathy. Immune complexes and cytokines, such as TGF-ß1 (secreted by macrophages) and intracellular cell adhesion molecule-1 (ICAM-1, produced by renal tubular cells), are critical in this process. An autopsy series identified a correlation between the presence of CD163+ macrophages in renal tissue and the severity of diabetic nephropathy, interstitial fibrosis, tubular atrophy, and glomerulosclerosis. Macrophages contribute to renal fibrosis by attracting fibroblasts and can themselves transform into myofibroblasts, further driving fibrotic progression.

Macrophages also activate the renin-angiotensin-aldosterone system (RAAS), leading to alterations in renal hemodynamics. RAAS activation further recruits macrophages through the actions of monocyte chemoattractant protein-1 (MCP-1), osteopontin, and various adhesion molecules, including selective, ICAM-1, PECAM-1, and VCAM(Vascular Cell Adhesion Molecule).

Endothelial Cell Damage

Endothelial cell damage is one of the earliest pathological changes in diabetic nephropathy. This damage generates reactive oxygen species, which are major contributors to the progression of diabetic nephropathy. Hyperglycemia and hemodynamic changes trigger the release of cell adhesion molecules (as noted earlier), glycosaminoglycans, and chemokines, which further amplify the immune response. This response involves direct endothelial damage and is further exacerbated by the transition of endothelial cells into mesenchymal cells.

Podocyte Damage

Podocytes are essential components of the glomerular filtration barrier, and their injury leads to proteinuria. Podocyte injury may involve hypertrophy, reduced density, and apoptosis. Contributing factors to podocyte damage include lipotoxicity (ie, increased lipid synthesis and decreased degradation), oxidative stress, mitochondrial dysfunction, vascular dysfunction (eg, shear stress from hyperfiltration), and impaired autophagy.Additionally, podocyte damage is associated with reduced nephrin expression and inhibition of insulin-like growth factor-1 (IGF-1)/insulin receptor signaling pathways.

Polyol Pathway and Uric Acid

The polyol pathway contributes to diabetic nephropathy through the accumulation of fructose and sorbitol, glucose byproducts that increase osmotic pressure, leading to edema and cell membrane rupture. Structurally similar to glucose, fructose is metabolized by the liver, and under normal physiological conditions,

only small amounts of dietary fructose appear in the plasma. However, fructose metabolism produces urate as a byproduct, which can contribute to insulin resistance, endothelial dysfunction, and renal tubular injury.

Hyperuricemia also activates the RAAS and may be a risk factor for cardiovascular disease.In addition, fructose also contributes to oxidative stress, which is a key contributor to diabetic nephropathy. Aldolase reductase, which catalyzes the rate-limiting step of the polyol pathway, has been targeted in studies, which show that aldolase reductase inhibitors can reverse diabetic nephropathy lesions in animal models.

Genetics

Genetics is crucial for the development of diabetic nephropathy, with both genetic and environmental factors contributing to its onset. Individuals with a family history of diabetes or kidney disease are at higher risk of developing diabetic nephropathy. Certain genes have been associated with the development of diabetic nephropathy, which include variations in the following genes:

- APOL1: Variants in this gene are strongly associated with hypertension and various renal diseases, such as focal and segmental glomerulosclerosis. ACE: Polymorphismsin the angiotensin-converting enzyme (ACE) gene have been linked to diabetic nephropathy and may have a role in the renoprotective effects of ACE inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapies.
- COL4A3, COL4A4, and COL4A5: These genes encode for collagen type IV, which is a critical structural component of the GBM. Mutations in these genes have been associated with increased susceptibility to diabetic nephropathy.

Pathophysiology

Patients with T2D may present with albuminuria at the time of diabetes diagnosis, whereas diabetic nephropathy typically develops 15 to 20 years after the onset of T1D. Approximately 30% of patients with T1D and 40% of those with T2D develop diabetic nephropathy, primarily because the exact onset of T2D is often unclear. Structural and functional changes occur in the kidney on account of diabetes and result in proteinuria, hypertension, and progressive reduction of kidney function, which are hallmarks of diabetic nephropathy.

The 3 main pathological lesions of diabetic nephropathy include diffuse mesangial cell expansion, GBM thickening, and arteriolar hyalinization. However, almost all kidney compartments, including the glomerular capillary wall, podocytes, mesangium, tubulointerstitium, and renal vasculature, are affected. Diabetic nephropathy typically aligns with the progression of albuminuria, advancing from normal albumin levels to microalbuminuria (moderately increased albuminuria) and eventually to macroalbuminuria (severely increased albuminuria). Aggressive treatment can partially reverse this progression.

The glomerular filtration barrier is a highly regulated structure consisting of capillary endothelial cells, GBM, and podocytes. The GBM is 3 to 6 times thicker than capillaries in other parts of the body and is highly fenestrated, with fenestrations covering up to 50% of the endothelial surface. Primarily composed of type

IV collagen and negatively charged proteoglycans, the GBM functions as a selective filter, permitting the passage of water and small solutes while excluding large proteins, such as albumin, when intact.

Nephrin is a key component of the GBM that helps maintain the integrity of the slit diaphragms, the primary barrier preventing protein loss in urine. Reduced nephrin expression is an early event in the development of diabetic nephropathy. Synaptopodin, another protein localized to podocyte foot processes, is also downregulated in diabetic nephropathy. MCP-1 further reduces the expression of both nephrin and synaptopodin and is associated with albuminuria.

Hyperfiltration is one of the earliest pathological changes observed in diabetic nephropathy, involving both the glomeruli and renal tubules. This phenomenon is partially mediated by hyperglycemia-induced upregulation of apical sodium-glucose cotransporter-1 (SGLT1) and -2 (SGLT2) and basolateral glucose transporters, along with decreased vascular resistance. Under normoglycemic conditions, approximately 160 g/d of glucose is filtered by the kidneys, with nearly all reabsorbed in the proximal tubule via SGLT2.

Hyperfiltration is also mediated by vascular regulation. Prostaglandins and atrial natriuretic peptides are 2 potential mediators that reduce arteriolar resistance, further contributing to hyperfiltration. Both are elevated in patients with diabetic nephropathy, particularly those with severe albuminuria (>3.0 g/d). Endothelial dysfunction is another factor linked to glomerular hyperfiltration, with increased endothelin-1 levels observed in patients with T2D and proteinuria. Although endothelin receptor blockers have not shown efficacy to date, ongoing research continues in this area.

Histopathology

Abnormal renal pathology is evident even before the onset of microalbuminuria. Characteristic lesions observed on light microscopy include thickened glomerular and tubular basement membranes, diffuse mesangial expansion, and arteriolar hyalinosis.

The pathological classification includes:

- Class I: GBM thickening
- Class IIa: Mild mesangial expansion
- Class IIb: Severe mesangial expansion
- Class III: Nodular glomerulosclerosis (Kimmelstiel-Wilson nodules)
- Class IV: Advanced diabetic nephropathy with over 50% glomerulosclerosis and associated lesions

History and Physical Examination

A longer duration of diabetes mellitus, poor glycemic control, and uncontrolled hypertension are significant risk factors for developing diabetic nephropathy. Additional risk factors include obesity, smoking, hyperlipidemia, and a family history of diabetes or kidney disease. Patients may also present with associated conditions such as peripheral vascular disease, hypertension, coronary artery disease, and diabetic retinopathy. Notably, diabetic retinopathy has a particularly strong correlation with diabetic nephropathy, as previously highlighted.

Patients with diabetic nephropathy often exhibit similar physical characteristics to other individuals with diabetes. In the early stages, patients are typically asymptomatic, with the condition often identified through screening that reveals proteinuria levels between 30 and 300 mg/g creatinine. As the disease progresses,

patients may present with symptoms such as fatigue, foamy urine (indicative of urine protein (>3.5 g/d), and pedal edema due to hypoalbuminemia and nephrotic syndrome.

Other generalized findings associated with diabetes mellitus include the following:

- Fatigue
- Dizziness
- Polydipsia and polyuria
- Polyphagia
- Blurred vision or vision loss
- Tingling or numbness
- Peripheral neuropathy
- Foot ulcers
- Delayed wound healing
- Frequent infections
- Nausea, vomiting, and abdominal pain
- Acanthosis Nigricans (commonly seen in T2D)
- Unexplained weight loss (commonly seen in T1D)

Evaluation

Proteinuria

Proteinuria is the hallmark of diabetic nephropathy. Diagnosing DKD is more challenging in T2D than in T1D, as the exact onset of T2D is often unclear. History and physical exam are crucial in diagnosing diabetic nephropathy in T2D. Patients diagnosed with T1D should have proteinuria checked within 5 years of diagnosis, while those diagnosed with T2D should be screened at the time of diagnosis and annually thereafter. Increased proteinuria is an indicator of declining kidney function and should be treated aggressively.

Diabetic nephropathy is diagnosed by persistent albuminuria on 2 or more occasions, separated by at least 3 months, using early morning urine samples. Persistent albuminuria is defined as 300 mg/d or greater. Moderately increased albuminuria, a marker of early diabetic nephropathy, is between 30 and 300 mg over 24 hours. Severe albuminuria is classified as greater than 300 mg of albuminuria per day. Moderately increased albuminuria can also be defined as a spot urine-to-creatinine ratio of 20 to 200 mg/g or 20 to 200 µg/min.

Urinary Biomarkers

Given the relative nonspecificity and delayed utility of creatinine change and albuminuria as markers of diabetic nephropathy, other molecules are being explored as potential markers. In recent years, there has been growing interest in studying markers of tubulointerstitial injury rather than focusing solely on the glomerulus. Additionally, non-albuminuric proteinuria, which indicates tubulointerstitial injury, is strongly associated with DKD. Some evidence even suggests that proximal tubular damage may occur earlier than glomerular damage.

Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) are elevated in early diabetic nephropathy, even before the onset of albuminuria, and correlate with a decline in decreased GFR.Urinary KIM-1 is associated with proximal tubule damage, while NGAL is associated with damage to the loop of Henle and distal tubule. NGAL is also an early marker of acute kidney injury (AKI), with serum elevations detectable within hours of the causative insult and up to 24 to 72 hours before creatinine levels.Urinary NGAL also appears before albuminuria.

Treatment / Management

The management of diabetic nephropathy focuses on 4 key areas, including cardiovascular risk reduction, glycemic control, blood pressure (BP) control, and inhibition of the renin-angiotensin system (RAS). Modifying risk factors, such as tobacco cessation and implementing optimal lipid control strategies, is essential for reducing cardiovascular risk.

Glycemic Control

Intensive glycemic control is most effective when initiated before the onset of diabetic complications, with reduced efficacy when started later. Therefore, early intensive glycemic control is highly recommended. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that T2D patients who achieved early glycemic control with a hemoglobin A1c (HbA1c) of 7.0% maintained improved microvascular outcomes and lower mortality even after the study ended, despite HbA1c values converging between the 2 groups.

The Diabetes Control and Complications Trial (DCCT) showed comparable results in T1D patients.The long-term benefits of early glucose-lowering therapy, particularly when HbA1c is kept below 6.5% during the first year of diagnosis, have been referred to as the "legacy effect" or "metabolic memory." However, long-term intensive glucose control is not always beneficial, as some studies have shown worse all-cause and cardiovascular outcomes in T2D patients due to hypoglycemic events associated with aggressive glycemic control. The KDOQI and KDIGO guidelines recommend an HbA1c goal of approximately 7.0% to help mitigate the development of microvascular complications.

Other less commonly used methods for evaluating glycemic control include glycated albumin and fructosamine; however, these measurements are not well-validated. While HbA1c is the most accurate measure of long-term glycemic control, it may not accurately reflect episodes of hypoglycemia or severe hyperglycemia, both of which are more prevalent in CKD. Although the National Kidney Foundation (NKF)-KDOQI guidelines suggest an HbA1c goal of around 7.0%, individualized targets based on the patient's overall clinical condition are recommended.

Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

The KDIGO guidelines recommend a BP target of less than 120/80 mm Hg for individuals with diabetes, allowing for individualization based on patient-specific factors. ACEIs or ARBs are advised for all diabetic patients with hypertension unless contraindicated. In addition, these medications should be titrated to the highest tolerated dose. The use of ACEIs or ARBs in cases of albuminuria without hypertension remains insufficiently studied and should be considered on an individual basis. Kidney transplant recipients with diabetes and hypertension should also receive RAAS inhibition as part of their management. Evidence supports the use of these medications in hypertensive dialysis patients, as discontinuing ACEIs or ARBs has been associated with higher rates of cardiovascular death, myocardial infarction, and ischemic stroke. KDIGO guidelines recommend strict dietary compliance and the use of potassium binders, if necessary, to manage ACEI/ARB-associated hyperkalemia.

Studies demonstrate the benefits of ARBs in

delaying the progression of kidney disease, as evidenced by the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study) and IDNT (Irbesartan Diabetic Nephropathy Trial) trials. The UKPDS highlighted the positive impact of BP control on diabetes-related complications, including mortality, cardiovascular events, and microvascular outcomes. However, aggressive systolic BP control (<120 mm Hg) compared to standard therapy (<140 mm Hg) showed no significant differences in cardiovascular outcomes or progression to ESRD.

The HOPE, LIFE, and ALLHAT trials confirmed the benefit of ACEIs in slowing CKD for individuals with an estimated GFR (eGFR) of more than 60 mL/min/1.73m2. In addition, studies such as IRMA2 (Irbesartan in Microalbuminuria, Type 2 Diabetic Nephropathy Trial) have shown the benefit of ARBs in preventing proteinuria in patients with microalbuminuria. Studies in patients with T1D and overt proteinuria have shown that ACEIs can slow the progression of diabetic nephropathy. The IDNT and RENAAL studies demonstrated similar benefits in T2D patients. These studies provide strong evidence that RAAS-blocking medications help slow the progression of diabetic nephropathy, independent of their effect on BP. However, the use of multiple RAS-blocking agents can lead to adverse outcomes, including acute renal failure, and is no longer recommended. Additionally, the treatment of diabetic patients with RAAS inhibition who do not have hypertension or albuminuria is discouraged.

Metformin and Glucagon-Like Peptide-1 Receptor Agonists

The KDIGO guidelines and the American Diabetes Association (ADA) suggest using metformin alongside dietary modifications as first-line treatment for T2D patients with CKD and an eGFR greater than 30 mL/min/1.73m2. Metformin has demonstrated significant benefits in CKD progression, cardiovascular outcomes, and all-cause mortality. However, metformin should not be initiated in individuals with an eGFR of less than 45 mL/min/1.73m2, as they are at risk of progressing to an eGFR of less than 30 mL/min/1.73m2 and developing lactic acidosis. The metformin dosage should be halved for eGFR between 45 and 60 mL/min/1.73m2. Metformin should also be withheld during inpatient admissions to prevent complications from potential renal insults. Additionally, metformin may reduce vitamin B12 and folate levels, necessitating regular monitoring and supplementation as needed.

The European Society of Cardiology recommends glucagon-like peptide-1 receptor agonists (GLP1RAs) or SGLT2 inhibitors (SGLT2Is) as first-line agents for patients with high cardiovascular risk. The KDIGO guidelines advise using GLP1RAs when glycemic control is not achieved with metformin or SGLT2Is. GLP1RAs should be titrated gradually and avoided in combination with dipeptidyl peptidase-4 inhibitors. Robust evidence supports the use of GLP1RAs and SGLT2Is to improve outcomes across diverse patient populations.

Mineralocorticoid Antagonists

Mineralocorticoid receptor activation has been strongly associated with inflammation, fibrosis, and adverse hemodynamic remodeling in cardiac and renal diseases. Spironolactone and eplerenone, steroidal mineralocorticoid antagonists, have demonstrated

efficacy, particularly in patients with heart failure and reduced ejection fraction. Additionally, these agents have been shown to effectively reduce proteinuria in CKD, with comparable benefits in proteinuria caused by diabetes mellitus and other conditions.

Finerenone is a selective, nonsteroidal mineralocorticoid antagonist approved for managing CKD associated with T2D. Finerenone functions as a bulky, passive antagonist of the mineralocorticoid receptor. The medication has been shown to reduce albuminuria and improve renal and cardiovascular outcomes in patients with CKD and T2D, as demonstrated in multiple studies, including FIDELITY-DKD, FIGARO-DKD, and FINEARTS-HF. Finerenone has demonstrated effectiveness in patients with and without reduced ejection fraction. Additionally, evidence suggests it may help prevent or delay the onset of heart failure in individuals with T2D and CKD.

Esaxerenone, which has a mechanism of action similar to finerenone, is not approved by the Food and Drug Administration (FDA); however, it is used in Japan and other countries, where it has been shown to reduce albuminuria in patients with T2D.

Sodium-Glucose Cotransporter-2 Inhibitors

SGLT2Is reduce glucose reabsorption in the proximal tubule, leading to increased glucosuria, decreased capillary hypertension, and reduced albuminuria, GFR loss, and metabolic demand on nephrons. They also mitigate macula densa sodium hypersensitivity, decreasing glomerular hypertension and energy expenditure. Another key mechanism is the stimulation of hypoxia-inducible factors (HIFs), which enhance erythropoietin production.This class of medications has demonstrated effectiveness in both patients with and without T2D through glucose-dependent and glucose-independent mechanisms. Unlike many diabetic agents, SGLT2Is generally do not cause hypoglycemia, as their glucose-lowering effect halts when filtered glucose levels approach 80 g/d. Additionally, SGLT2Is increase glucagon secretion, stimulating hepatic gluconeogenesis.

The beneficial effects of SGLT2Is extend beyond glucose control. These medications promote a metabolic shift from carbohydrate to lipid utilization, resulting in visceral and subcutaneous fat reduction, as well as overall weight loss. The free fatty acids released during this process are converted into ketone bodies, which serve as an energy source for renal and cardiac cells. Another renoprotective mechanism of SGLT2Is is the blockade of glucose reabsorption, which also reduces the accompanying absorption of sodium, chloride, and free water. This reduction helps mitigate the glomerular hyperfiltration commonly observed in diabetes, thereby preserving GFR. These mechanisms collectively contribute to renoprotection in both diabetic and nondiabetic patients.

Several cardiovascular outcome trials have demonstrated the positive effects of SGLT2Is on kidney outcomes, including reductions in albuminuria and other adverse renal events. These findings have generated interest in using primary renal outcomes as a dedicated endpoint. Notable randomized controlled trials include EMPA-REG, CANVAS, and DECLARE-TIMI. Additionally, the DAPA-CKD trial highlighted the benefits of SGLT2Is on renal and cardiovascular outcomes in patients without T2D. The CREDENCE trial, which compared SGLT2Is to placebo in patients

with T2D and albuminuric CKD, was terminated early due to a 30% relative risk reduction in renal and cardiovascular events observed in the treatment group.

Additional Treatments

Shenkangis a traditional Chinese medicine. Animal studies have demonstrated that Shenkang injections can reduce fibrosis and increase nephrin expression. Isoquercitrin, a natural compound found in various plants, has demonstrated potential as an antidiabetic agent due to its physiological properties. Studies have shown that it inhibits the SGLT2 pathway and reduces blood sugar levels in animal models, suggesting its promise as a therapeutic agent.

Renal Replacement

Once ESRD develops with an eGFR of 10 to 15 mL/min/1.73m2, renal replacement therapy may be required. Dialysis options include peritoneal dialysis, hemodialysis, and renal transplantation. Renal transplant is generally preferred for patients with good functional status, and patients should be referred to a transplant center when their GFR declines to approximately 20 mL/min/1.73m2. A study found that 47% of patients on the renal transplant list also have diabetes—a percentage that is expected to increase. Simultaneous pancreas and kidney transplants are becoming more common and have shown excellent outcomes. Studies indicate better outcomes for diabetic patients who receive both organs compared to those who receive only a kidney transplant.However, DKD can recur in the transplanted kidney in about 7% of cases, with the use of tacrolimus being particularly associated with this recurrence.

Differential Diagnosis

Several conditions can mimic diabetic nephropathy, but they are usually differentiated from diabetic nephropathy based on patient history and laboratory parameters. Some of these include:

- Multiple myeloma
- Amyloidosis
- Membranous nephropathy
- Renal artery stenosis
- Tubulointerstitial nephritis
- Hypertensive nephropathy
- Focal segmental glomerulosclerosis
- Infection-related glomerulonephritis

Prognosis

Diabetic nephropathy is associated with high morbidity and mortality. Microalbuminuria is an independent risk factor for cardiovascular mortality, and the majority of patients ultimately die from ESRD. Additionally, diabetic retinopathy is commonly associated with diabetic nephropathy.

Preventativemeasures and Patient Education

- Protein intake should be around 0.8 g/kg of body weight in patients with diabetes and CKD.
- A higher recommendation of 1.0 to 1.2 g/kg may apply to diabetic patients on dialysis.
- Significant evidence suggests that consuming plant protein is associated with a lower risk of CKD and proteinuria progression compared to animal protein.
- HbA1c should be maintained at less than 7.0%, but treatment plans should be individualized.
- BP should be kept at less than 120/80 mm Hg.

- Sodium intake should be limited to less than 2.3 g/d in patients with diabetes and an eGFR of less than 30 mL/min/1.73m2.
- Nephrotoxic agents and drugs should be avoided.
- Urine albumin levels should be regularly monitored.
- Patients who consistently monitor blood glucose levels at home tend to experience a delay in the progression of renal dysfunction.
- Regular Exercise.
- Smoking Cessation.
- Strict moderation of alcohol intake.
- Minimum 7 hours of sound sleep daily.

Conclusion

Diabetic nephropathy is a severe condition with lifelong consequences, marked by high morbidity and mortality rates. While there is no cure, and treatment options have limitations, prevention and early intervention remain crucial. The care of patients with diabetic nephropathy involves a multidisciplinary healthcare team, including internal medicine specialists, hospitalists, endocrinologists, nephrologists, cardiologists, and pathologists. Patient-centered care requires a collaborative approach, with contributions from physicians, advanced practice providers, nurses, pharmacists, and other healthcare professionals. Dietitians play a vital role in helping patients plan diets that ensure adequate protein intake and help maintain optimal blood sugar levels.

First and foremost, healthcare providers must have the clinical skills and expertise required to diagnose, evaluate, and treat this condition effectively. This includes proficiency in interpreting laboratory results, recognizing potential complications, and understanding the variationsof managing medications appropriately. Ethical considerations are crucial when determining treatment options and respecting patient autonomy in decision-making.

Lastly, care coordination is essential for ensuring seamless and efficient patient care. Physicians, advanced practitioners, nurses, pharmacists, and other healthcare professionals must collaborate to streamline the patient's journey from diagnosis to treatment and follow-up.

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Chapter

36

Emerging Role of Anti-Inflammatory Agents in Type 2 Diabetes: A Review of Clinical Evidence and Therapeutic Promise

Dr.Bhaskar Brahma, Dr. Aditya Saha

ABSTRACT

Type 2 diabetes mellitus (T2DM), affecting over 500 million people globally, is increasingly recognized as a chronic inflammatory disease rather than solely a disorder of insulin resistance and ß-cell dysfunction. Low-grade inflammation mediated by cytokines such as IL-1ß, TNF-a, and IL-6 contributes to impaired insulin signaling, ß-cell apoptosis, and macrovascular complications. This evolving understanding has opened new therapeutic possibilities through repurposing anti-inflammatory agents. IL-1 blockers (canakinumab, anakinra) improve glycemic parameters and reduce cardiovascular events but are limited by infection risk and cost. Colchicine, by inhibiting the NLRP3 inflammasome, shows promise as an affordable, oral agent with cardiovascular benefit. Other drugs such as salsalate demonstrate modest efficacy, while TNF-a inhibitors and methotrexate remain inconclusive. Anti-inflammatory therapy represents a novel adjunctive strategy in T2DM management, with ongoing trials needed to clarify long-term safety, patient selection, and clinical integration.

Keywords : Type 2 diabetes mellitus , inflammation, anti-inflammatory therapy

Introduction

Type 2 diabetes mellitus (T2DM) has entered into lives of more than 500 million individuals worldwide , this has led to its notorious status as one of top ranking global health concerns. Traditionally viewed as a disease of insulin resistance and relative insulin deficiency, T2DM is increasingly being understood as a chronic inflammatory disorder with deep immuno-metabolic underpinnings. Despite the availability of numerous glucose-lowering therapies, cardiovascular complications still claim lion's share of mortality and morbidity in individuals with T2DM.

While conventional treatment paradigms focus primarily on glucose regulation, recent breakthroughs in clinical research have revealed a critical role for low-grade chronic inflammation in both the pathophysiology

and progression of T2DM and its complications. This evolving understanding has opened new therapeutic avenues—particularly the repurposing of anti-inflammatory agents not only to improve glycemic control but also to reduce cardiovascular risk.[1]

In this review, we will try to understand the pathophysiological basis of inflammation in T2DM which will help us to understand the rationale behind the possible use of anti-inflammatory drugs . We will also look into the major clinical trials investigating IL-1 blockers, colchicine, and other agents. Finally , we will conclude with a take home message regarding its the potential clinical relevance, limitations, and future directions of incorporating these therapies into the management of T2DM.

Pathophysiology

The Inflammatory Basis of Type 2 Diabetes

Characteristics of T2DM includes its constellation of pathophysiological mechanisms include issue of resistance to insulin's actions in periphery, blunted insulin secretion from ßeta cells of pancreas , and dysregulated hepatic glucose production. Increasing evidence points to a central role of chronic inflammation in these processes.(1)

Adipose tissue in insulin-resistant states becomes infiltrated by pro-inflammatory macrophages and T cells, leading to increased local and systemic release of cytokines with pro inflammatory role such as 'tumor necrosis factor-alpha' (TNF-a), 'interleukin-6' (IL-6), and 'interleukin-1 beta' (IL-1ß). Such cytokines interfere with signaling pathways of insulin through mechanisms like phosphorylation of serine residues of 'insulin receptor substrate (IRS) proteins', 'nuclear factor kappa-light-chain-enhancer of activated B cells' (NF-?B) activation, and increased 'reactive oxygen species' (ROS).

In the pancreatic islets, IL-1ß contributes to programmed death of ß-cell, lessens secretion of insulin and amplifies the inflammatory cascade. Simultaneously, the 'NLRP3 inflammasome' gets activated , it is a cytosolic protein complex that senses metabolic danger signals such as free fatty acids and hyperglycemia. This in turn leads to further production of IL-1ß and IL-18, creating a self-perpetuating loop of inflammation and metabolic dysfunction.[2]

This inflammatory state is not confined to glucose metabolism alone. It promotes endothelial dysfunction, accelerates atherosclerosis, and contributes to plaque instability—thus playing a central role in the macrovascular complications of T2DM. These insights have led to a new therapeutic approach: targeting inflammation to manage both metabolic dysregulation and cardiovascular risk.

Possible Mechanisms of Action of Anti-Inflammatory Drugs in T2DM(3)

IL-1 Blockers (Canakinumab, Anakinra):

IL-1ß is produced in response to metabolic stress and drives ß-cell death, reduces insulin secretion, and worsens systemic insulin resistance. IL-1 blockade can be achieved either through monoclonal antibodies like canakinumab (targeting IL-1ß directly) or through receptor antagonists like anakinra (blocking IL-1 receptor).

- Canakinumab neutralizes IL-1ß, thereby dampening the inflammasome-driven inflammatory response. It reduces markers of systemic

inflammation such as 'high-sensitivity C-reactive protein' (hsCRP) and IL-6, with potential secondary benefits on insulin resistance and endothelial function.

- Anakinra causes competitive inhibition of IL-1a and IL-1ß binding to the IL-1 receptor, preventing downstream inflammatory signaling. It has shown promise in improving ß-cell function and glycemic control in small clinical studies.

Colchicine:

Colchicine is an alkaloid obtained from Colchicum autumnale, has been for a long time used in therapy of gout and pericarditis. Its mechanism of action includes inhibition of microtubule polymerization, suppression of neutrophil adhesion and chemotaxis, and most notably, inhibition of the NLRP3 inflammasome, leading to reduced IL-1ß production.

Colchicine's broad anti-inflammatory effects may have dual benefits in T2DM by mitigating insulin resistance and reducing the inflammatory burden that contributes to atherosclerosis. Unlike biologics, colchicine is inexpensive, orally available, and has an established safety profile in long-term cardiovascular use.

Other Agents (Salsalate, TNF-a Inhibitors, Methotrexate):

- Salsalate, a prodrug of salicylate, inhibits I?B kinase-ß and NF-?B signaling. It has shown modest glycemic and inflammatory benefits in pilot trials.
- TNF-a inhibitors like etanercept and infliximab theoretically counteract insulin resistance by inhibiting a key cytokine; however, clinical trials have yielded inconsistent and largely negative results in T2DM populations.
- Methotrexate, a widely used anti-inflammatory agent in rheumatology, was tested for cardiovascular prevention in the CIRT trial but failed to show benefit in reducing inflammatory markers or cardiovascular outcomes in high-risk patients with or without diabetes.

Discussion of Clinical Trials

Canakinumab (CANTOS Trial)(4)

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), published in NEJM in 2017, enrolled over ten thousand patients with prior history of myocardial infarction and levels of hsCRP levels greater than 2mg/dl .Patients were randomized to receive subcutaneous canakinumab (50, 150, or 300 mg) or placebo every 3 months.

The trial showed a promising result ($p < 0.05$) of reduction in major adverse cardiovascular events (MACE) in the 150 mg group, independent of 'LDL-C levels', suggesting that of inflammation plays an important role in atherothrombosis. Notably, post hoc analyses suggested modest improvements in glycemic parameters among participants with T2DM. However, increased risk of infection and high cost are limitations to widespread adoption.

Anakinra (Larsen et al., 2007)(5)

In a double-blind, placebo-controlled trial conducted in seventy patients with T2DM, anakinra administered for 13 weeks resulted in significant reductions in IL-6 and CRP and improved glycemic control (HbA1c reduction of ~0.5%). Improvements in

C-peptide levels suggested enhanced ß-cell secretory function. However, the short duration and small sample size limit the generalizability of results.

Colchicine (COLCOT and LoDoCo2 Trials)

The COLCOT trial (published in NEJM, 2019) randomized 4,745 patients within 30 days of MI to receive colchicine 0.5 mg daily or placebo. Colchicine markedly decreased the primary composite outcome of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent revascularization.[6]

The LoDoCo2 trial (2020) enrolled 5,522 patients with stable coronary artery disease and showed that low-dose colchicine significantly reduced cardiovascular events over a median follow-up of 28.6 months. Subgroup analyses in both trials confirmed similar benefit in patients with T2DM, reinforcing the role of inflammation as a modifiable risk factor.[7]

Colchicine in Insulin Resistance (Demidowich et al., 2020)(8)

In a smaller randomized trial involving obese, insulin-resistant adults, colchicine (0.6 mg twice daily for 3 months) significantly reduced CRP, IL-6, and white blood cell counts. While the improvement in insulin sensitivity did not reach statistical significance, trends were favorable. The study highlights the need for larger, longer-term metabolic outcome trials.

Salsalate (TINSAL-T2D Trial)(9)

In this NIH-funded multicenter trial, salsalate (3 g/day) lowered HbA1c by approximately 0.3–0.4% over 48 weeks in patients with T2DM. It also reduced CRP levels. However, mild adverse effects, including increased urinary albumin excretion and modest weight gain, tempered enthusiasm for its clinical use.

Methotrexate and TNF-a Inhibitors(10)

The CIRT trial found that methotrexate did not reduce cardiovascular events or levels of IL-1ß, IL-6, or CRP. Trials of TNF-a inhibitors in insulin-resistant and diabetic patients have shown limited and inconsistent benefit on glycemic endpoints and remain investigational.

Clinical Implications and Future Directions

The integration of anti-inflammatory agents into diabetes management represents a novel, mechanistically driven strategy aimed at addressing residual cardiovascular risk and improving metabolic outcomes. However, key questions remain.

Clinical Considerations:

- Patient Selection: Ideal candidates may include patients with T2DM and known cardiovascular disease or elevated inflammatory markers (e.g., hsCRP>2 mg/L).
- Treatment Duration and Safety: Long-term safety and infection risk must be considered, especially with biologic agents.
- Cost-Effectiveness: High costs of IL-1 blockers remain a significant barrier. Colchicine, by contrast, is widely available and inexpensive.
- Drug Interactions: Colchicine requires caution in patients with renal or hepatic dysfunction due to its narrow therapeutic index.

Conclusion

Anti-inflammatory therapy represents an exciting frontier in the evolving treatment paradigm for T2DM. Agents such as IL-1 blockers and colchicine have shown promise in reducing cardiovascular risk and improving metabolic parameters by targeting the underlying inflammatory milieu. While these therapies are not yet part of standard diabetes management, they offer a glimpse into a future where inflammation-modulating agents are integrated alongside traditional glucose-lowering therapies to provide more comprehensive, outcome-driven care.

Ongoing research will help delineate their role, refine patient selection, and assess long-term efficacy and safety. As our understanding of the immune-metabolic axis in T2DM deepens, anti-inflammatory therapies may become indispensable tools in the effort to reduce the dual burden of diabetes and cardiovascular disease.

Ongoing studies such as CANOPY (testing canakinumab for cancer and cardiovascular endpoints) and COLCARDIO-T2D (targeting colchicine in T2DM) may provide definitive evidence for broader clinical application. Future directions include biomarker-guided therapy, development of safer oral IL-1 inhibitors, and integration with metabolic and lipid-lowering agents.

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Section 12
Endocrinology

Chapter

37

Thyroid Cancer- Targeted Therapies and Active Surveillance

Dr. Subhalakshmi Das, Dr. Biswajit Das

ABSTRACT

Thyroid cancer represents the most prevalent endocrine malignancy, with an increasing incidence worldwide. Recent advances in molecular biology and diagnostic imaging have enabled risk-adapted strategies such as active surveillance for low-risk papillary microcarcinoma and precision-targeted therapy for advanced or radioiodine (RAI)-refractory disease. Active surveillance offers a safe alternative to immediate surgery in carefully selected patients, reducing overtreatment while maintaining excellent oncologic outcomes. Conversely, molecular profiling has identified actionable genetic alterations—such as BRAF, RET, and NTRK fusions—guiding the use of tyrosine kinase inhibitors and selective targeted agents, which have significantly improved progression-free survival in advanced disease. A personalized approach integrating these strategies ensures optimal patient outcomes with minimal morbidity. Continued research is needed to refine patient selection criteria, expand therapeutic targets, and integrate molecular diagnostics into clinical practice for comprehensive management of thyroid cancer.

Keywords: Thyroid cancer, Active surveillance, Targeted therapy, Tyrosine kinase inhibitors, Molecular profiling

Introduction

Thyroid cancer is actually the most common endocrine gland cancer and makes up about 3% of all cancers in the world.[1] The number of cases has definitely gone up in the last twenty years primarily due to the widespread use of neck ultrasonography and fine-needle aspiration cytology leading to detection of small, subclinical lesions.[2] Moreover, some patients develop aggressive disease that does not respond to radioiodine treatment. Moreover, anaplastic and medullary thyroid cancers show more aggressive behavior and do not respond well to standard treatments.[3,4]

In the past the three main ways to treat thyroid cancer were surgery, radioactive iodine treatment, and hormone suppression therapy. These methods were definitely the standard approach for managing this

disease.[5] As per recent studies in cancer research, key gene changes like BRAF, RET, RAS, and NTRK mutations cause tumor growth.[6] This has helped make targeted treatments that give new hope for advanced and spreading cancers, while doctors now watch low-risk cases carefully instead of treating them right away to reduce overtreatment.[7]

This review actually looks at how thyroid cancer treatment is changing, with focus on targeted therapies and active surveillance. It definitely covers current evidence, clinical effects, and future research areas.

Section 1: Molecular Pathogenesis and Rationale for Targeted Therapy

The characterization of thyroid malignancies by genetic means has revolutionized the knowledge and treatment of disease biology. The Cancer Genome Atlas (TCGA) project unique molecular sequence in papillary thyroid carcinoma (PTC).[8] In about 60% of the PTC cases are having the mutation in the BRAF V600Egenes, leading to sequential activation of the MAPK pathway and enhancing the proliferation rate. Rearrangements of RET/PTC genes and RAS mutations are also amongst the significant carcinogenic drivers.[8]

Parafollicular C-cells are the sources of Medullary thyroid carcinoma (MTC) and germline or somatic RET proto-oncogene mutations is the main feature of MTC.? A rare variety of thyroid malignancy isAnaplastic Thyroid Carcinoma (ATC) which exhibits complex molecular alterationsmainly in the genesTP53, TERT, and PIK3CA mutations and is also associated with coexisting mutations in BRAF V600E genes.[10]

Thyroid carcinoma arises from thyroid follicular or parafollicular cells. The main risk factors are radiation exposure, genetic factors, low iodine intake, female predominance, pre-existing thyroid disease, and environmental and lifestyle factors.

Section 2: Current Targeted Therapies in Thyroid Cancer

2.1 Multikinase Inhibitors in RAI-Refractory Differentiated Thyroid Cancer

Two oral multikinase inhibitors are sorafenib and lenvatinib which have proven efficacy in Radioactive Iodine Therapy mainly in refractory DTC. Genetic target for Sorafenib is VEGFR, PDGFR, and RAF kinases, while lenvatinibblocks the genes VEGFR, FGFR, RET, and KIT.[12] In the DECISION trial, sorafenib enhances median progression-free survival (PFS) from 5.8 to 10.8 months in comparison to placebo group.[12] Similarly, the SELECT trial showed that lenvatinibhighly enhanced PFS (18.3 vs 3.6 months) and attained an response rate of 65%.[13] Adverse effects are mainly fatigue, hypertension, diarrhea, and proteinuria.These are generally of lower grade and dose modifications shows improvement of side effects.[13]

2.2 Targeted Therapy in Medullary Thyroid Carcinoma

Management of MTC has improved with the development of drugs like vandetanib and cabozantinib, both of them approved for progressive metastatic disease. Targets for Vandetanibare genes RET, VEGFR2, and EGFR, attaining median PFS of 30.5 months in comparison to 19.3 months as seen in placebo group.[14] Cabozantinibtargets MET, VEGFR2, and RET with same kind of outcome.[14] However, both of them carry notable side effects like diarrhea, QT prolongation, and hand-foot syndrome which require careful monitoring and dose modification.[14]

Selective RET inhibitors like selpercatinib and pralsetinib are a major breakthrough in the targeted therapy of thyroid malignancies. They are highly specific for RET alterations and have less side effects. Selpercatinib in the phase III trial obtained objective response rates over 70% for both MTC & RET fusion positive DTC. These offer long lasting response as well as improved tolerability.[15]

2.3 BRAF and MEK Inhibitors in Anaplastic Thyroid Carcinoma

Anaplastic thyroid carcinoma (ATC) is amongst the most fatal malignancies. For cases with mutations in BRAF V600Egenes, dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) therapy together has shown better outcomes. This lead to their FDA approval for combined use.[16] Multimodal approaches with targeted therapy, surgery and RAI gives better outcomes and improves survival.[17]

2.4 NTRK Fusion and Redifferentiation Therapies

A minority of DTCs harbor NTRK gene fusions amenable to larotrectinib or entrectinib therapy. These selective inhibitors yield response rates exceeding 70% with manageable toxicity profiles.[18] Another emerging concept is redifferentiation therapy—restoring RAI avidity in refractory tumors using MEK or BRAF inhibitors. Studies have shown improves RAI uptake up to 60%. This permits further treatment with RAI.[19]

Section 3: Active Surveillance in Low-Risk Thyroid Cancer:

3.1 Concept and Rationale

Active surveillance is the close observation and record of low-risk thyroid malignancies that does not require immediate surgery. This strategy was obtained from long-term studies carried out in in Japan that revealed that many sub-centimetric papillary microcarcinomas remain inactive for a long duration with very less progression.[20]

The main aim of active surveillance is to abort overtreatment and surgical morbidity simultaneously, maintaining oncologic safety.[20] As the prognosis of papillary thyroid microcarcinoma (PTMC) is excellent, so immediate surgery may not provide benefit in case of survival but rather exposes patients to surgical complications such as hypocalcemia or recurrent laryngeal nerve injury.[21]

3.2 Selection Criteria

Candidates suitable for AS typically fulfill the following:[22]

1. Tumor =1 cm confined to the thyroid.
2. Absence of nodal or distant metastases.
3. No evidence of extrathyroidal extension or aggressive cytology.
4. Tumor away from vital structures such as trachea or recurrent laryngeal nerve.
5. Cases with less probability loss to follow up.

Criteria of execution include aggressive histological variants (tall cell, hobnail, diffuse sclerosing), past history of familial syndromes, and history of radiation exposure.[23]

3.3 Outcomes of Active Surveillance

In a 7000 cases meta-analysis who were under active surveillance showed that tumor growth is (>3 mm) and nodal metastasis rate of 1% during follow-up of 5–

10 years.[24] Only 12–15% eventually required surgery. This is due to progression of the disease mostly.Although the postoperative outcomes were equivalent to those treated initially.[24] Disease-specific mortality has not been reported in amongst the patients who were selected appropriately.[25]

Psychological aspects are critical. While manysome experience anxiety related to the "watchful waiting" approach. On the other hand some tolerate it well²6 So it is necessary to take a shared decision-making with the patient party after proper patient education and counselling.[26]

3.4 Global Acceptance and Barriers

Organizations likeAmerican Thyroid Association (ATA) and European Thyroid Association (ETA) therefore endorse guidelines for active surveillance of very low-risk DTC.[27] Due to lack of infrastructure for standardized follow-up and patient concerns regarding progression ,particularly in resource-constrained settings,adoption of these guidelines outside specialized centers remains limited.[27] In developing nations, limitations are due to limited high quality ultrasonography and multi-disciplinary care.[28]

Section 4: Integrating Active Surveillance and Targeted Therapy in Personalized Thyroid Cancer Care

The future of thyroid cancer treatment depends on precision oncology. This are like individualized treatment with matching therapy intensity to disease risk.²? For very low-risk DTC, surveillance improves safety, offers cost-effectiveness, minimize unnecessary interventions. For advanced or refractory disease, targeted therapy improves precision-based systemic treatment according to genetic profile.

Clinical decision-making requires careful risk stratification integrating clinical, imaging, and molecular parameters.[3°] Biomarker-guided therapy (BRAF, RET, NTRK mutations) should be routinely incorporated into diagnostic pathways for advanced disease.[31]

Combining targeted therapy with conventional modalities is another frontier. For instance, integrating lenvatinib with immunotherapy (e.g., pembrolizumab) has shown synergistic antitumor activity in preliminary studies of ATC and poorly differentiated carcinoma.[32] Equally, active surveillance protocols should evolve with refined imaging techniques and predictive biomarkers to identify patients who may safely defer intervention.[33] In the future, circulating tumor DNA (ctDNA) or microRNA profiling could guide both escalation and de-escalation of therapy.[33]

From a systems perspective, multidisciplinary teams—including endocrinologists, oncologists, surgeons, and radiologists—must coordinate care to optimize patient outcomes.[3]4 In countries like India, establishing AS registries and expanding molecular diagnostics at tertiary centers such as Assam Medical College and Hospital would enhance local applicability of global guidelines.[3]4

Conclusion

Thyroid cancer exemplifies the spectrum of oncology—from indolent microcarcinomas requiring minimal intervention to aggressive, lethal anaplastic disease demanding advanced molecular therapy. Active surveillance and targeted therapy represent two ends of this continuum, united by the principle of

individualized care.

- Active surveillance is safe for low-risk papillary microcarcinoma, preventing overtreatment without compromising outcomes.
- Targeted therapies—including multikinase, selective RET, and BRAF/MEK inhibitors—have transformed management of advanced and refractory thyroid cancers.
- Molecular profiling is essential to guide therapy selection and identify candidates for precision treatment.
- Future research should focus on predictive biomarkers for progression under AS, strategies to overcome resistance to targeted therapy, and cost-effective implementation of precision oncology in low- and middle-income countries.

By aligning therapy intensity with biological risk, clinicians can optimize outcomes, minimize morbidity, and advance a truly personalized approach to thyroid cancer management.

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Chapter

38

Adrenal Disorders – Advances in Diagnosis and Management

Dr. Uma Kaimal Saikia

Introduction

The adrenal gland also known as the suprarenal gland due to its location above the kidney is an essential endocrine organ secreting multiple hormones. Though first described by Bartholomeus Eustachias in 1563, its function was a subject of conjecture till 1855 when Thomas Addison reported on its role in human disease and described cases of adrenal insufficiency. Adrenal function as we know now is critical for life and adrenal disorders are associated with significant mortality and morbidity.

Both the adrenal glands though functioning similarly display asymmetry with the right being smaller than the left. Each gland is composed of two distinct regions- an outer cortex and an inner medulla. The adrenal cortex secretes mineralocorticoids primarily aldosterone from the zona glomerulosa, glucocorticoids mainly cortisol from the zona fasciculata and adrenal androgens from the zona reticularis. Aldosterone secretion is primarily regulated by the renin angiotensin system whereas cortisol and androgen secretion is regulated by the hypothalamo pituitary adrenal (HPA) axis. The adrenal medulla which is derived from the cells of the neural crest produces catecholamines i.e. dopamine, adrenaline and noradrenaline which are released into the circulation in response to neural stimuli in the "fight or flight response".

Disorders of the adrenal gland may be due to hypofunction (adrenal insufficiency), hyperfunction (Cushing's syndrome, primary aldosteronism) or adrenal tumours (incidentalomas, pheochromocytomas and adrenal carcinomas). In the recent years primary aldosteronism has emerged as an underdiagnosed, treatable cause of secondary or resistant hypertension. Medical treatment of Cushing's syndrome is now an option for patients with failed pituitary surgery or patients unable to undergo surgery. Newer formulations of hydrocortisone replacement therapy for adrenal insufficiency are being tried. Better imaging modalities as well as nuclear imaging has resulted in improved diagnosis and localisation of adrenal and pituitary lesions. The commonly encountered clinical conditions with advances in diagnosis and management are hereby discussed.

Primary Adrenal Insufficiency (PAI)

Since the classic description of Addison's disease by Thomas Addison in 1855, adrenal insufficiency is recognized as a disorder with significant morbidity and mortality. The prevalence ranges from 4 -11 cases per 100,000 population[1]. Autoimmune adrenalitis is probably the most common cause followed by infections, infiltrations and metastasis. Inherited causes are also important including congenital adrenal hypoplasia and congenital adrenal hyperplasia (CAH) as listed below.

- Autoimmune-Sporadic, Autoimmune polyendocrinopathy Type I and Type II
- Infections- Tuberculosis, Cytomegalovirus, HIV, Fungal.
- Adrenal metastasis
- Infiltrations- amyloidosis, hemochromatosis
- Congenital Adrenal Hypoplasia- DAX 1 and SF1 mutations.
- Congenital Adrenal Hyperplasia- 21hyroxylase deficiency (commonest) due to CYP21A2 mutations, 3betaHSD deficiency, 17 alpha hydroxylase deficiency.
- Drugs – ketoconazole, mitotane, etomidate, abiraterone (used in Ca prostate)

Diagnosis- Symptoms may be non specific including fatigue, weight loss, anorexia, nausea, diarrhoea and hence a high index of suspicion is necessary. Mineralocorticoid deficiency can lead to salt craving and postural hypotension. Hyperpigmentation due to increased ACTH levels is characteristic of primary adrenal insufficiency. Signs and symptoms of androgen excess will be present in females with CAH due to 21 hydroxylase deficiency due to increased shunting of cortisol precursors into the androgen pathway leading to hirsutism, oligomenorrhoea or amenorrhoea, acne, clitoromegaly and male pattern balding.

Routine biochemistry reveals hyponatremia (90%), hyperkalemia (65%) along with hypercalcemia and hypoglycemia. Confirmatory diagnosis rests on obtaining a morning serum cortisol at 8AM along with a paired ACTH sample. A morning cortisol < 5µg/dl along with a plasma ACTH > 2 fold the upper limit of the reference range confirms PAI. A morning basal cortisol >14.5µg/dl indicates an intact hypothalamo pituitary adrenal (HPA) axis. Intermediate values of cortisol require an i.v corticotropin (ACTH)stimulation test. Here 250µg of cosynotropin (synthetic ACTH) is given i.v with the plasma cortisol measured after 30 min or 60 min. A peak cortisol > 18µg/dl rules out adrenal insufficiency [2]. A simultaneous measurement of plasma renin and aldosterone is also recommended to rule out mineralocorticoid deficiency. Diagnosis of CAH due to 21 hydroxylase deficiency rests on elevated serum levels of 17ahydroxy progesterone (17OHP) levels either basal or after ACTH stimulation, high testosterone and androstenedione levels and high plasma renin activity (PRA).

Once PAI is confirmed, evaluation is needed to establish the cause. Antibodies to 21 hydroxylase are present in autoimmune adrenal insufficiency. Its use is however restricted due to problems in availability of the test. Adrenal imaging is needed to rule out infections or infiltrations which is best performed by a CT scan. If CAH is diagnosed genetic testing is recommended for mutations in the CYP21A2 gene and genetic councelling.

Treatment of PAI

Glucocorticoid replacement- Hydrocortisone 15-25mg/day in adults in 2 or 3 divided doses and in children 6-8mg/m2/day orally with higher doses in the morning is recommended (1). An extended release formulation of hydrocortisone Plenadren is a once daily tablet with an immediate release and extended release part. Overall this has been shown in some studies to reduce weight, BMI and waist circumference [3].

Mineralocorticoid replacement- Fludrocortisone 0.025-0.2mg/day (children) and 0.05-0.4mg/day in adults is given along with liberal salt intake.

Monitoring for improvement in clinical symptoms, edema, blood pressure along with serum sodium and potassium levels is needed. Patients with CAH also need monitoring of PRA, 17OHP levels and serum testosterone or androstenedione levels.

Primary Aldosteronism (PA)

Primary aldosteronism is characterized by excessive aldosterone secretion from one or both adrenal glands and is increasingly being recognized as a cause of hypertension. Cardiovascular complications in PA are more than in primary hypertension and hence diagnosing and treating PA is of importance. Latest guidelines[4] recommend that all individuals with hypertension should be screened for PA as individuals with PA lateralized to one side can be cured by adrenalectomy. Initial biochemical evaluation includes measurement of serum potassium which should be corrected as hypokalemia may lead to falsely low aldosterone levels.

Screening for PA is done by measurement of plasma aldosterone concentration (PAC) and renin levels (concentration or activity) in a morning sample with the patient seated and no sodium restriction for a few days prior to the test. It is advisable to not start on mineralocorticoid receptor antagonists(MRA) before this test or if already on this should be withdrawn for 6 weeks. Other medications like diuretics may interfere with the test in high doses. A plasma renin activity (PRA) = 1ng/ml/hr or a direct renin concentration (DRC) = 8.2mu/L with plasma aldosterone = 10ng/dl and increased aldosterone to renin ratio (ARR) i.e. aldosterone(ng/dl) / PRA (ng/ml/hr) >20 or aldosterone (pmol/L) / DRC (mu/L) >70 meets criteria for PA (3). A confirmatory testing for aldosterone suppression by a saline loading test to verify autonomous aldosterone secretion is not needed in the following situations :

1. Subjects with hypertension and hypokalemia with PAC> 15ng/dl and PRA < 0.2ng/ml/hr or DRC <2mu/L.
2. Subjects unwilling for adrenal venous sampling and adrenalectomy. These patients can be started on MRA like spironolactone or eplerenone.
3. Subjects with family members having germline mutations associated with familial hyperaldosteronism.

Treatment of PA includes both medical and surgical therapies. The primary modality for localisation of unilateral disease is a CT scan of the adrenals. If a single >1cm lipid rich adenoma is found on one side in a patient with unequivocal PA, one can proceed directly to a unilateral adrenalectomy. However if there are doubtful findings on CT scan or if = 1cm, an adrenal venous sampling (AVS) is recommended to localise aldosterone excess. This involves catheterization of both the adrenal veins with sampling for cortisol and

aldosterone from each side. In patients with unilateral hyperaldosteronism the cortisol corrected aldosterone ratio (ratio of PAC/cortisol from dominant side to that from non dominant side) is > 4:1. Surgery results in normalization of blood pressure in 30-60% of patients with correction of hypokalemia in all . Medical therapy is needed in patients with bilateral disease or candidates unfit for surgery. Spironolactone is the drug of choice which is inexpensive and readily available. The goal of therapy is normalization of serum potassium levels and blood pressure and a PRA>1ng/ml/hr.

Cushing's Syndrome

The most common cause of endogenous Cushing's syndrome is Cushing's disease due to an ACTH secreting pituitary adenoma followed by adrenal lesions (ACTH independent) in 10-15 % of cases and ectopic ACTH secretion in upto 15%. Of the adrenal causes of Cushing's syndrome, adrenal adenomas are the commonest with some cases of adrenal carcinoma, primary pigmented nodular hyperplasia and macronodular hyperplasia. Certain questions need to be answered in the evaluation of a patient suspected to have Cushing's syndrome[1].

1. Is this exogenous Cushing's syndrome?

As iatrogenic or exogenous disease is common due to steroid abuse or use of indigenous medications, a morning 8 am sample for basal cortisol is taken. A suppressed plasma cortisol is indicative of exogenous Cushing's syndrome.

2. Does the patient have endogenous Cushing's syndrome ?

Most guidelines require at least two of the following tests to be positive to make a diagnosis of Cushing's syndrome.

- ***Diurnal/circadian rhythm of plasma cortisol***- Plasma cortisol levels in normal subjects reach a nadir around midnight and are <2µg/dl with levels highest in the morning. This rhythm is lost in Cushing's syndrome and a midnight plasma cortisol >7.5µg/dl indicates Cushing's syndrome. However any stress and intercurrent illness can lead to false positive results.
- ***Salivary cortisol***- A midnight salivary cortisol level >2ng/ml is a very sensitive and specific test to diagnose Cushing's syndrome. False positive results may occur with increasing age and presence of hypertension and diabetes mellitus.
- ***Urinary free cortisol excretion***- This is a less sensitive test than salivary cortisol and is cumbersome as it requires a 24 hour collection. False negative results may be obtained in 8-15% of patients with Cushing's syndrome.

Overnight Dexamethasone(ONDST)/ Low dose Dexamethasone suppression test(LDDST)- The overnight test is a convenient test to screen patients in the outpatient department . This involves administration of 1 mg of oral dexamethasone at 11PM followed by estimation of plasma cortisol at 8 AM the next day. A level <1.8µg/dl rules out Cushing's syndrome. Though the sensitivity of the test is around 95% the specificity is lower. The LDDST uses dexamethasone given in a dose of 0.5mg every 6 hrs for 48 hrs (8 doses) followed by measurement of plasma cortisol at 8 AM the next day. Levels less than 1.8µg/dl exclude Cushing's syndrome with a sensitivity and specificity > 98%.

3. What is the aetiology of Cushing's syndrome?

It is necessary to identify ACTH dependant

causes (pituitary or ectopic) versus ACTH independent causes (adrenal adenomas and carcinoma).

- ***Morning Plasma ACTH***– Samples have to be taken in the morning in ice cold tubes, serum separated immediately and stored at -40 degrees C. An ACTH value >90pg/ml suggests ectopic ACTH secretion while <10pg/ml suggests ACTH independent causes. Pituitary ACTH dependant Cushing's disease have intermediate values.
- ***High Dose Dexamethasone Suppression Test (HDDST)***- Here 2 mg of dexamethasone is given 6hrly for 2 days. A suppression of =50% of plasma cortisol from the baseline is suggestive of pituitary Cushing's disease.
- ***Inferior Petrosal Sinus Sampling(IPSS)***- Catheterization of IPS on both sides and measurement of the ratio of ACTH in the IPS to peripheral vein is used to distinguish ectopic ACTH secretion from pituitary ACTH excess. In the ectopic ACTH syndrome the ratio is less than 1.4:1 whereas in Cushing's disease it is >2[1].

4. Imaging modalities
   - ***MRI brain***- Cushing's disease is usually due to microadenomas of the pituitary for which MRI is the imaging of choice with a sensitivity of 60% and specificity of 87% [1].
   - ***CT adrenals*** – Adrenal CT is essential if an ACTH independent cause is suspected on biochemical testing.
   - ***CT abdomen/thorax/pelvis***- If an ectopic source of ACTH secretion is suspected imaging of these sites is needed to localise the tumor and plan for surgical resection.
   - ***Nuclear Imaging***- This becomes necessary in patients suspected to have the ectopic ACTH syndrome which express somatostatin receptors. Hence gallium or indium labelled scans are employed i.e. 111In- labelled octreotide or 68Ga-DOTATE- PET- CT.
5. Medical management of Cushing's syndrome- In patients who are unfit for surgery or refuse surgery or in cases of non remission or relapse after surgery, medical management is one of the options available [5]
   - ***Metyrapone***- An inhibitor of 11beta hydroxylase, the drug reduces plasma cortisol levels with an overall effectivity in about 50% of patients.
   - ***Osilodrostat***- This is a more potent inhibitor of 11 beta hydroxylase which has been shown to normalize cortisol levels and improve the clinical features.
   - ***Ketoconazole***- This is a time tested drug which inhibits several enzymes in the steroidogenic pathway. The main side effect is elevation of liver enzymes which need to be monitored frequently.
   - ***Mitotane***- This is an adrenolytic drug used in adrenal carcinoma.
   - ***Somatostatin analogues***- Pasireotide is a multireceptor 1,2, 3, 5 blocker which is being used in Cushing's syndrome. The main side effect is hyperglycemia.

Adrenal incidentalomas

With the increasing use of abdominal imaging for various reasons adrenal incidentalomas (AI) are being detected which are defined as adrenal masses detected on imaging not performed for suspected adrenal disease. The work up of a patient found to have an AI focusses on two primary issues- functionality and presence of

malignancy. A detailed discussion on the approach to AI is beyond the scope of this chapter. However these masses need evaluation and follow up if surgery is not advised.

Conclusion

Adrenal disorders are not rare and may present to the physician in various ways. A thorough knowledge of the pathways of adrenal steroidogenesis and the regulation of the hypothalamo pituitary adrenal axis is essential for proper evaluation and management. The advent of newer diagnostic techniques especially nuclear imaging along with newer medications offer hope to patients with adrenal disorders thus improving mortality and morbidity.

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Chapter

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Bone Health: Novel Therapies for Osteoporosis

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Introduction

Osteoporosis is a chronic skeletal disorder characterized by reduced bone mass and microarchitectural deterioration, resulting in increased bone fragility and susceptibility to fractures. Globally, it affects nearly one in five adults, with a pooled prevalence of 19.7% for osteoporosis and 40.4% for osteopenia, as demonstrated in a recent meta-analysis encompassing over 340,000 participants worldwide[1]. The prevalence shows wide geographic variation, ranging from 4.1% in the Netherlands to 52.0% in Turkey. In India, osteoporosis poses a major public health challenge, with a higher prevalence in women (26.3%) compared to men (10.9%). Among postmenopausal women, the reported prevalence ranges between 8% and 62%, depending on age, region, and assessment criteria [2]. India also bears one of the highest global burdens of osteoporotic fractures, with hip fractures occurring nearly a decade earlier than in Western populations and associated with 20–30% one-year mortality [3].

Despite effective antiresorptive and anabolic therapies, many patients remain undertreated or experience fractures during treatment. Long-term bisphosphonate use is limited by atypical femoral fractures and osteonecrosis of the jaw; denosumab discontinuation can trigger rebound bone loss, and PTH analogs have duration restrictions. Moreover, bone mineral density (BMD) alone inadequately reflects fracture risk, as bone quality and microarchitecture also determine strength. Advances in osteocyte signaling, the Wnt/ß-catenin pathway, and osteoclast enzymology have opened new therapeutic avenues capable of restoring bone health more physiologically.

Mechanistic Advances in Bone Biology

Bone remodelling depends on the coordinated activity of osteoclasts, osteoblasts, and osteocytes. Osteocytes, the most abundant bone cells, act as mechano-sensors and regulate bone turnover through secretion of signalling molecules such as sclerostin, RANKL, and osteoprotegerin (OPG). The RANK–RANKL–OPG axis governs osteoclast differentiation and activity. Denosumab, a monoclonal antibody to RANKL, was the first successful clinical translation of this pathway.

The Wnt/ß-catenin pathway plays a pivotal role in osteoblast differentiation. Osteocyte-derived inhibitors like sclerostin and Dickkopf-1 (DKK1) suppress bone formation. Neutralizing these inhibitors reactivates osteogenesis, forming the basis for therapies such as romosozumab.

Meanwhile, cathepsin K, an osteoclastic enzyme responsible for collagen degradation, represents another key target. Inhibition of cathepsin K suppresses resorption while preserving osteoclast-osteoblast coupling signals, offering a selective antiresorptive mechanism.

The recognition that bone quality—architecture, turnover, and microdamage repair—is as important as BMD has shifted therapeutic goals toward restoring balanced remodelling rather than merely halting loss.

Current Treatment Landscape

Modern osteoporosis management combines antiresorptive agents, which inhibit bone breakdown, with anabolic agents that promote bone formation. The choice of therapy is guided by baseline fracture risk, prior treatment exposure, comorbidities, and cost.

Bisphosphonates—alendronate, risedronate, ibandronate, and zoledronic acid—remain the mainstay of therapy. They inhibit farnesyl pyrophosphate synthase in the mevalonate pathway, suppressing osteoclast function and reducing vertebral and hip fractures by 40–60% [4]. Annual IV zoledronic acid improves adherence compared to oral formulations. Long-term therapy (>5 years) carries small risks of atypical femoral fractures and osteonecrosis of the jaw; hence, reassessment and "drug holidays" are advised in low-risk patients.

Denosumab (60 mg subcutaneously every 6 months) provides potent, reversible antiresorptive action by blocking RANKL. The FREEDOM trial demonstrated significant reduction in vertebral (68%), hip (40%), and non-vertebral (20%) fractures [5]. Its ease of use improves adherence, but discontinuation leads to rebound bone loss and multiple vertebral fractures if not followed by a bisphosphonate [6]. Hypocalcemia risk mandates vitamin D and calcium repletion before each dose.

Teriparatide (recombinant PTH 1–34, 20 µg SC daily) is the first true anabolic therapy, increasing trabecular bone formation and improving microarchitecture. It reduces vertebral and non-vertebral fractures by up to 65% [7]. Duration is limited to 2 years, after which transition to an antiresorptive is required. Abaloparatide, a PTHrPanalog, offers similar anabolic effects with fewer hypercalcemic events [8].

Romosozumab, a monoclonal antibody against sclerostin, represents a breakthrough dual-action agent. It increases bone formation and simultaneously decreases resorption. In the FRAME trial, romosozumab reduced vertebral fractures by 73% over 12 months compared with placebo, while the ARCH trial showed a 48% reduction versus alendronate [9,10]. Treatment is limited to one year, followed by maintenance antiresorptive therapy. Caution is warranted in patients with recent cardiovascular events due to a small but observed risk signal.

Sequential therapy—starting with an anabolic agent followed by an antiresorptive—yields superior BMD gains and sustained fracture protection compared to the reverse sequence [11]. This approach, endorsed by the Endocrine Society and IOF, optimizes the "anabolic window."

Non-pharmacologic strategies remain

foundational: adequate calcium (1,000–1,200 mg/day), vitamin D (800–1,000 IU/day), regular weight-bearing exercise, fall prevention, smoking cessation, and minimizing glucocorticoid exposure all enhance therapeutic efficacy.

Novel and Emerging Therapeutic Strategies

Over the past decade, our understanding of bone cell signaling and remodeling has accelerated the discovery of new pharmacologic classes that go beyond traditional antiresorptive and anabolic mechanisms. These emerging therapies aim not only to prevent further bone loss but to restore skeletal structure, improve microarchitecture, and sustain long-term remodeling balance. The major categories include Wnt pathway modulators, cathepsin K inhibitors, activin and TGF-ß pathway inhibitors, and novel delivery and regenerative strategies.

1. Sclerostin Inhibition: Romosozumab and Beyond

The Wnt/ß-catenin signaling pathway plays a central role in osteoblast differentiation and bone formation. Sclerostin, a glycoprotein secreted by osteocytes, inhibits this pathway by binding to LRP5/6 receptors, thereby reducing osteoblast activity. Romosozumab is a humanized monoclonal antibody that neutralizes sclerostin, leading to simultaneous stimulation of bone formation and suppression of resorption — a "dual effect" unique among currently approved agents.

In the FRAME trial (7,180 postmenopausal women with osteoporosis), monthly romosozumab (210 mg SC for 12 months) followed by denosumab resulted in a 73% reduction in new vertebral fractures and a 36% reduction in clinical fractures compared with placebo, with mean BMD gains of 13% at the lumbar spine and 6% at the total hip [9]. The ARCH trial (4,093 women at very high fracture risk) compared romosozumab for 12 months followed by alendronate versus alendronate alone and demonstrated a 48% lower risk of new vertebral fractures, 27% reduction in clinical fractures, and 38% fewer hip fractures[10].

Romosozumab also produced faster and larger BMD gains compared with teriparatide in the STRUCTURE trial (lumbar spine +9.8% vs +5.4% at 12 months)[17].

Cardiovascular safety concerns emerged from the ARCH study (serious CV events: 2.5% vs 1.9% with alendronate), leading to recommendations to avoid use in patients with recent myocardial infarction or stroke. Nevertheless, for patients at very high fracture risk or multiple vertebral fractures, romosozumab serves as an ideal bridge therapy before long-term antiresorptive maintenance.

Beyond romosozumab, next-generation sclerostin inhibitors with modified Fc fragments and dual antibodies targeting both sclerostin and DKK1 (e.g., BHQ880, DKN-01) are in early-phase studies and show additive anabolic potential[12]. Such agents could provide stronger and longer-lasting bone formation with reduced dosing frequency.

2. Dickkopf-1 (DKK1) and Wnt Co-modulators

DKK1 is another osteocyte-derived antagonist of Wntsignaling. Elevated DKK1 levels are associated with low bone turnover states, including glucocorticoid-induced osteoporosis. Monoclonal antibodies against DKK1 (e.g., BHQ880, DKN-01) have demonstrated increased osteoblast activity and trabecular bone volume

in preclinical and early human studies[12]. Phase II data in multiple myeloma–related bone disease showed improved BMD and reduced skeletal lesions without major toxicity[18].

Although not yet approved for osteoporosis, DKK1 blockade represents a potential synergistic target when combined with sclerostin inhibition — amplifying the anabolic response while maintaining physiologic resorption.

3. Cathepsin K Inhibition: Selective Antiresorptive Innovation

Cathepsin K, a cysteine protease abundantly expressed in osteoclasts, degrades type I collagen during bone resorption. Traditional antiresorptives suppress osteoclast numbers, impairing bone formation coupling; by contrast, cathepsin K inhibitors reduce resorption without eliminating osteoclasts, thereby preserving remodeling communication.

The LOFT trial evaluated odanacatib (50 mg weekly) in 16,000 postmenopausal women and showed reductions in vertebral (54%), hip (47%), and non-vertebral (23%) fractures after 5 years compared with placebo [13]. BMD gains were 11% at the spine and 9% at the hip, comparable to potent bisphosphonates. However, the trial was halted due to increased stroke risk (hazard ratio 1.37). Subsequent analyses suggested off-target inhibition of cathepsins in vascular tissue. Next-generation inhibitors such as ONO-5334 and MIV-711 aim to improve selectivity and cardiovascular safety, with ongoing early clinical evaluation[19].

4. Activin and TGF-ß Pathway Modulation

The TGF-ß/activin signalling pathway regulates osteoblast and osteoclast differentiation. Excessive activin A activity promotes bone resorption and inhibits formation. Ligand traps such as sotatercept (ACE-011) and ACE-536 (luspatercept) act as activin receptor type IIA decoys, binding activin A and related ligands to enhance bone formation.

In a phase II study, sotatercept increased lumbar spine BMD by 5.3% over 6 months in postmenopausal women [14]. These agents are being investigated for osteoporosis and glucocorticoid-induced bone loss, with the added potential of improving muscle mass and hematopoiesis — a dual benefit in elderly patients.

5. Small-Molecule and Peptide Anabolics

Beyond PTH analogs, research focuses on sustained-release teriparatide implants, oral calcilytics, and PTH1 receptor agonists that mimic intermittent PTH exposure without injections. EB613, an oral PTH (1-34) analog, recently completed phase II studies showing dose-dependent BMD gains of +3.5% at lumbar spine over 6 months, suggesting feasibility for non-injectable anabolic therapy[20].

Calcilytics (e.g., encaleret), which transiently block calcium-sensing receptors, induce endogenous PTH pulses and may serve as oral anabolics, though current data are preliminary.

6. Drug Delivery and Bone-Targeted Nanocarriers

Innovations in targeted drug delivery seek to enhance skeletal specificity, prolong release, and reduce systemic toxicity.

Bisphosphonate-conjugated nanoparticles deliver antiresorptives or anabolic peptides directly to hydroxyapatite-rich bone surfaces, increasing efficacy

while minimizing GI and renal exposure [15].

Liposomal teriparatide formulations extend peptide half-life and allow weekly dosing.

Calcium phosphate–based nanocarriers can co-deliver drugs and imaging tracers, enabling "theranostic" use.

Animal models show enhanced fracture healing, improved trabecular density, and reduced side effects, but translation to human therapy remains in progress.

7. Regenerative and Tissue Engineering Approaches

Regenerative strategies aim to rebuild bone microarchitecture rather than simply preserve it.

Mesenchymal stem cells (MSCs) enhance bone formation via paracrine signalling; autologous MSC infusions have improved BMD and bone turnover markers in early human studies [16].

Gene-edited osteoprogenitors expressing anabolic cytokines like BMP-2 or VEGF show promise in restoring trabecular microstructure.

Biomimetic scaffolds, composed of calcium phosphate or collagen matrices impregnated with teriparatide, FGF-2, or platelet-rich plasma, have been successfully used in pilot studies to treat non-healing osteoporotic fractures [16].

Though currently experimental, these approaches represent the future frontier — integrating endocrinology, bioengineering, and regenerative medicine to restore bone at both molecular and structural levels.

8. Clinical Perspective

The cumulative evidence indicates that anabolic-first sequential therapy remains the most effective clinical strategy for severe osteoporosis, while dual-target biologics and bone-targeted delivery systems will likely dominate future treatment paradigms.

Among investigational options, romosozumab has demonstrated the strongest clinical benefit and real-world feasibility. Cathepsin K inhibitors and activin ligand traps represent the next mechanistic wave once safety concerns are addressed. Future innovations will focus on precision therapy — selecting patients based on turnover markers, genetic predisposition, and microarchitectural imaging rather than BMD alone.

Clinical Application in the Indian Context

India faces a dual burden of high disease prevalence and limited access to advanced therapy. Studies from tertiary centers report osteoporosis in 40–50% of postmenopausal women [2]. Vitamin D deficiency exceeds 70%, and calcium intake averages only 400–600 mg/day [3].

Bisphosphonates remain first-line due to low cost and robust evidence. Denosumab is preferred in renal impairment or intolerance to oral agents but requires planned transition. Teriparatide is used for severe or multiple-fracture osteoporosis; romosozumab, though potent, is limited by cost and availability.

Sequential anabolic ? antiresorptive therapy provides maximal and durable benefit. Nutritional optimization, fall prevention, and patient adherence remain critical to long-term success.

From a public-health perspective, including osteoporosis medications under Ayushman Bharat and expanding fracture liaison services (FLS) can improve secondary prevention. Development of Indian registries for real-world efficacy and safety data is urgently needed.

Future Directions and Conclusions

Osteoporosis management is evolving from preventing bone loss to restoring skeletal integrity. The next decade will see dual Wnt modulation, selective cathepsin K inhibition, and activin pathway manipulation entering practice, supported by nanotechnology and regenerative medicine.

In India, improving screening, awareness, and affordability must accompany scientific advances. Integration of AI-based fracture risk models and personalized therapy algorithms will make care more precise.

Osteoporosis is no longer an inevitable part of aging—it is a treatable and potentially reversible skeletal disorder when approached with mechanism-based, patient-centered, and contextually appropriate therapy.

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Section 13
Rheumatology

Chapter

40

JAK Inhibitors in Autoimmune Diseases

Dr Suramita Chanda, Dr. Sanjeeb Kakati

ABSTRACT

Janus kinase (JAK) inhibitors have revolutionized the management of autoimmune disorders by providing a targeted approach to immunomodulation. These orally administered agents disrupt the JAK-STAT signaling pathway, which is integral to the mediation of cytokine-driven inflammatory responses that results in conditions like rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, and inflammatory bowel disease. Their ability to bring about rapid improvements has benefited many patients with inadequate responses to conventional disease-modifying antirheumatic drugs (DMARDs) or biologic therapies. JAK inhibitors offer distinct advantages, including swift onset of action and convenience of oral dosing. However, clinicians must remain vigilant for potential risks such as increased infections, thrombosis, and laboratory abnormalities. As our understanding of their mechanisms advances, the introduction of more selective next-generation JAK inhibitors holds the promise of enhanced safety and efficacy. Despite their demonstrable successes, optimizing patient selection and long-term monitoring is critical. Real-world experiences and ongoing clinical trials continue to refine the positioning of JAK inhibitors within the therapeutic landscape. This article explores the mechanisms of action, scope of clinical efficacy, safety profiles and evolving therapeutic landscape in the use of JAK inhibitors.

Introduction

Autoimmune diseases are chronic diseases that affect millions of people worldwide, resulting from an inappropriate immune response that targets the body's own tissues. This abnormal immunity is characterized by persistent inflammation, tissue damage, and loss of normal function in organs such as joints, skin, and organs such as the lungs and the gastrointestinal tract. The last two decades have witnessed remarkable innovations in the treatment of autoimmune disorders, with the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway emerging as a pivotal target for intervention. JAK inhibitors, a class of small-molecule drugs, have been at the forefront of this

therapeutic revolution. Their approval for various autoimmune diseases signifies a significant paradigm shift—transforming management strategies, broadening options for patients with refractory disease, and introducing convenient oral regimens previously unavailable with traditional biologic drugs (1,2). This article delves into the scientific rationale for JAK inhibition, evaluates the current clinical evidence across different autoimmune conditions, explores their safety and monitoring requirements, and discusses evolving perspectives shaping the future of this therapy.

Over several decades, treatment has evolved from broad immunosuppression (e.g., corticosteroids) to more precisely targeted biologic therapies (e.g., anti-TNF, anti-IL-6, anti-B cell). Yet unmet needs remain as many patients fail to respond, suffer from side effects. Also biologics (typically injectables) have limitations, in terms of cost, convenience, and route of administration.

A significant paradigm shift in autoimmune therapy has been the targeting of intracellular signaling, especially the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway. The JAK-STAT axis is central to the signaling of many cytokines and growth factors: once a cytokine binds its receptor on the cell surface, associated JAK kinases are activated which in turn phosphorylate STAT transcription factors; STATs dimerise, translocate to the nucleus, and modulate expression of genes controlling proliferation, differentiation, survival, and effector functions. Disruption or dysregulation of JAK-STAT signalling is implicated in the pathogenesis of many autoimmune and inflammatory disorders.

Small molecule inhibitors of JAKs have been developed to modulate this pathway. By intervening inside the cell, they can block several cytokine signals simultaneously. This potentially offers broader control of inflammation than targeting a single cytokine with a monoclonal antibody.

Early work focused on relatively non-selective ("pan-JAK") inhibitors, which inhibit more than one JAK isoform. These showed good efficacy in diseases such as rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis, including in patients who had failed traditional disease-modifying antirheumatic drugs (csDMARDs) or biologics. More recently, more selective JAK inhibitors (targeting predominantly JAK1 or TYK2 for example) are in development or already approved, with the hope of preserving efficacy while reducing off-target effects.

A key advantage of JAK inhibitors is their mode of delivery and pharmacology. Being small molecules (oral agents in many cases), they avoid the need for injections or infusions, improve patient convenience, and often show good bioavailability and rapid onset of action. Also, their intracellular action allows modulation of multiple cytokine pathways simultaneously.

However, as many immunoregulatory and homeostatic cytokines also use JAK-STAT signaling, the inhibition is not completely selective, especially with pan-JAK inhibitors. This raises concerns about infections (including opportunistic), risk of malignancy, hematologic toxicity (cytopenias), lipid alterations, and potentially cardiovascular or thrombotic complications. The safety profile differs depending on the selectivity, dose, disease indication, and patient risk factors. Clinically, several agents have been approved: **tofacitinib, baricitinib, upadacitinib, filgotinib,**

among others, mainly for moderate to severe RA (especially in patients who do not respond or tolerate csDMARDs or biologics). Application has expanded to psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and skin autoimmune diseases. There is also encouraging data in autoinflammatory disorders and interferonopathies.

Because of safety concerns, regulatory guidance recommends careful baseline screening (e.g. for latent infections like Tuberculosis, hepatic/renal function, complete blood count, cardiovascular risk), monitoring during therapy, using the lowest effective dose, and choosing more selective agents in patients with higher risk profiles.

Section 1: Mechanism of JAK-STAT Pathway

Cytokines play a central role in initiating and propagating inflammatory processes characteristic of autoimmune diseases. Most cytokine receptors rely on the JAK-STAT pathway for transduction of their effects. It consists of four non-redundant tyrosine kinases: JAK1, JAK2, JAK3, and TYK2. Upon cytokine-receptor engagement, JAKs phosphorylate STAT proteins, which in turn dimerize and get translocated to the nucleus to promote transcription of pro-inflammatory genes[2,3].

JAK inhibitors interrupt this signaling cascade by competitively binding to the adenosine triphosphate (ATP) binding site within the JAK enzymes. As a result, harmful signaling from multiple cytokines—such as interleukin-6, interferons, and others—is diminished, reducing inflammation and autoimmunity. Clinical agents differ in their selectivity; for example, tofacitinib inhibits JAK1 and JAK3, while baricitinib is more selective for JAK1 and JAK2, and upadacitinib preferentially inhibits JAK1 (3,4). Selectivity has implications not only for efficacy against specific diseases, but also for the side-effect profiles, as off-target JAK inhibition may influence hematopoiesis, immune surveillance, and lipid metabolism (3,5)

JAK Inhibitors :

JAK Inhibitors JAK INHIBITOR	PRIMARY TARGET	SELECTIVITY PROFILE
TOFACITINIB	JAK1, JAK3>JAK2	Pan-JAK (moderate selectivity)
BARICITINIB	JAK1,JAK2	JAK1/JAK2 selective
UPADACITINIB	JAK1	Selective for JAK1
FIGOTINIB	JAK1	Selective for JAK1
PERCITINIB	JAK3>JAK1/JAK2	Moderate selectivity
DECERNOTINIB	JAK3	JAK3 selective

Section 2: Clinical Efficacy in Autoimmune Diseases

Rheumatoid Arthritis

JAK inhibitors have most strongly demonstrated their efficacy in rheumatoid arthritis (RA). Large randomized clinical trials show that tofacitinib, baricitinib, and upadacitinib produce meaningful improvements in disease activity, inhibit radiographic progression, and enhance quality of life, even for patients who have failed multiple DMARDs or biologic agents[1,6]. Onset of action is typically rapid, with patients noting benefits within weeks.

Psoriatic Arthritis and Ankylosing Spondylitis

The utility of JAK inhibitors has expanded to psoriatic arthritis and ankylosing spondylitis, as shown by recent approval and guideline recommendations. These agents address both joint and skin manifestations, offering benefit where TNF inhibitors or other biologics may not suffice (4,9). Symptom reduction, improved function,

and lessened active enthesitis have been documented even in challenging, treatment-resistant cases.

Inflammatory Bowel Disease

Tofacitinib is currently the most established JAK inhibitor for ulcerative colitis, where it has provided rapid induction and sustained remission. Upadacitinib and filgotinib are under active investigation for Crohn's disease and ulcerative colitis, with data supporting their use in moderate-to-severe disease unresponsive to anti-TNF or conventional therapy [5,8].

Dermatologic and Other Immune Diseases

JAK inhibitors are increasingly studied and used for disorders like atopic dermatitis, alopecia areata, vitiligo, and lupus. Efficacy in these areas is variable but promising, with improvements in skin lesions and quality of life [7,9]. Ongoing trials aim to define their role in less common autoimmune diseases and as part of combination regimens.

Section 3: Safety Profile and Monitoring

While the pharmacologic targeting of JAKs has clear therapeutic value, patient safety remains a chief concern.

Infection Risk

The most widely recognized adverse effect is increased susceptibility to infections, particularly herpes zoster and opportunistic infections such as tuberculosis, cytomegalovirus, and fungal diseases. This risk is higher in elderly patients and those with comorbidities [6,10]. Vaccination and screening before initiation are mandatory.

Thromboembolic and Cardiovascular Events

Some JAK inhibitors, especially at higher doses, have been linked with a higher risk of venous thromboembolism (VTE) and possibly major cardiovascular events. These findings have prompted regulatory warnings and demand careful attention to risk factors before and during treatment [4,6].

Malignancy and Laboratory Changes

Malignancy risk appears modestly elevated, particularly for lymphoma and lung cancer, although causality is not definitively established. Laboratory abnormalities such as cytopenias, elevated liver enzymes, and raised cholesterol are fairly common and necessitate regular monitoring [3,5].

Comparative Safety and Selectivity

Newer, more selective JAK inhibitors (such as upadacitinib and filgotinib) may confer a lower risk of certain side effects, but longitudinal studies are needed. The balancing act between efficacy and safety is evolving, requiring individualized patient counseling and shared decision-making.

Section 4: Evolving Therapeutic Landscape and Unmet Needs

Remarkable advances continue as new JAK inhibitors and novel targeted kinase inhibitors are developed. Agents such as deucravacitinib, a selective TYK2 inhibitor, show promising efficacy with fewer infections and lower laboratory toxicity in psoriasis trials. Research is focused on defining biomarkers for patient selection, head-to-head trials to guide first-line and alternative therapy sequencing, evaluating long-term

disease modification and safety, investigating combination regimens to exploit synergistic benefits. Personalized approaches, considering co-morbidities, genetic susceptibility, and patient preference, are crucial to maximizing benefits. Guidelines recommend careful screening, risk stratification, dose individualization, and vigilant follow-up to optimize outcomes for each individual.

Conclusion

Janus kinase (JAK) inhibitors have revolutionized the therapeutic landscape of autoimmune and inflammatory diseases. By targeting intracellular signaling pathways central to cytokine-mediated immune activation, these small-molecule agents offer a mechanism of action distinct from conventional biologics. Their ability to modulate multiple cytokine signals simultaneously provides broad immunoregulatory effects that translate into meaningful clinical improvements across a variety of conditions, including rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, atopic dermatitis, and beyond.

One of the defining advantages of JAK inhibitors is their oral administration, which offers a convenient alternative to injectable biologics, improving treatment adherence and patient satisfaction. Moreover, their rapid onset of action and versatility across immune-mediated diseases make them particularly valuable for individuals who are either refractory to or intolerant of older biologic therapies. This flexibility has positioned JAK inhibitors as an essential option in personalized treatment strategies.

However, as with any potent immunomodulatory therapy, safety remains a paramount concern. Clinical trials and real-world data have underscored the need for vigilance regarding risks of serious infection, venous thromboembolism, and malignancy. Appropriate patient selection, pre-treatment screening, and ongoing monitoring are crucial to mitigating these risks. The balance between efficacy and safety continues to drive regulatory and clinical discussions about their optimal use.

Next-generation JAK inhibitors aim to improve selectivity and safety, refining the targeting of specific JAK isoforms (JAK1, JAK2, JAK3, TYK2) to minimize off-target effects while preserving therapeutic benefit. Parallel efforts are exploring combination regimens, biomarker-guided therapy, and long-term real-world outcomes to better define their role within the expanding immunotherapy armamentarium. JAK inhibitors symbolize a shift toward precision and patient-centered care in autoimmune disease management—where therapy is not only effective but also tailored to individual risk profiles, disease characteristics, and treatment goals. As ongoing research continues to expand our understanding, these agents are poised to remain a cornerstone of modern immunomodulatory therapy.

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Chapter

41

Systemic Lupus Erythematosus-Biologics and Precision Medicine

Dr. Swikrita Talukdar, Dr. Simi Sehnaz

ABSTRACT

Systemic lupus erythematosus (SLE) is a clinically heterogenous, multisystem autoimmune disease that remains therapeutically challenging. Over the last decade, biologic therapies and targeted small molecules have expanded treatment options for patients with refractory disease and lupus nephritis, but response rates remain variable. Rapid advances in molecular profiling (genomics, transcriptomics, proteomics, single cell sequencing) and computational tools are ushering in precision medicine approaches that aim to match patients to the therapy most likely to succeed and to predict flares and organ-specific outcomes.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder that primarily affects women of reproductive age, with a striking femaleto-male ratio of nearly 9:1. Its clinical presentation ranges from mild mucocutaneous manifestations to severe renal, neurological, or hematologic involvement. Because of its wide spectrum and tendency to mimic other diseases, SLE is often referred to as one of medicine's "great imitators." The high degree of heterogeneity in disease presentation and course makes diagnosis and management particularly challenging.

The etiology of SLE is multifactorial, involving a delicate interplay between genetic predisposition and environmental triggers. Although monozygotic twin concordance rates of 20–30% highlight a genetic contribution, they also emphasize a pivotal role for environmental factors, including ultraviolet (UV) radiation, cigarette smoking, viral infections, certain medications, and gut microbiota influences. UV exposure is especially relevant because it induces keratinocyte apoptosis, increases autoantigen exposure, and triggers inflammation in genetically susceptible individuals.

The 2019 EULAR/ACR and 2012 SLICC classification criteria are widely used in both clinical and research settings, although they were originally designed for clinical trials rather than for diagnostic

purposes. Given the varied presentation of SLE, relying solely on classification criteria can be insufficient; clinical judgement remains essential.

A contemporary framework divides SLE into two broad categories: Type 1 lupus, which includes classic findings such as arthritis, nephritis and vasculitis; and Type 2 lupus, which includes symptoms such as fatigue, diffuse body pain, depression, cognitive dysfunction, sleep disturbances, anxiety and/ or brain fog. Type 1 manifestations often respond to standard immunosuppression while Type 2 manifestations usually do not. This dichotomy provides an opportunity for more tailored therapeutic strategies and highlights the need for biomarkers capable of distinguishing between inflammatory versus non-inflammatory disease activity.

Pathogenesis of SLE

SLE pathogenesis reflects dysregulation across both innate and adaptive immune pathways. Autoantibodies—including anti-nuclear antibody (ANA), antidouble-stranded DNA (anti-dsDNA) antibody, anti-Smith (anti-Sm) antibody, and antiphospholipid antibodies—often appear years before clinical disease onset. These autoantibodies form immune complexes that deposit in tissues, activate complement, and trigger inflammation.

Understanding these molecular pathways has driven the development of biologic agents designed to specifically inhibit disease-mediating targets. Let us briefly review the major mechanisms involved in the pathogenesis.

1. Overproduction of Immuno-Activating Materials

Genetic, epigenetic, and environmental factors enhance activation of Toll-like receptor (TLR) pathways, particularly TLR7 and TLR9, leading to increased production of type I interferons (IFNs). Type I IFN and related cytokines play a central role in SLE by activating dendritic cells, promoting B cell differentiation, enhancing antigen presentation, and amplifying T cell activation. Plasmacytoid\ dendritic cells (pDCs) are especially important because they are major producers of type I IFNs. The resulting IFN-rich microenvironment sustains autoimmunity.

Innate lymphoid cells (ILCs) further promote disease by presenting antigens to T cells and generating cytokines. The interaction between CD40 on B cells and CD40L on activated T cells enhances B cell maturation and autoantibody production, reinforcing the autoimmune loop.

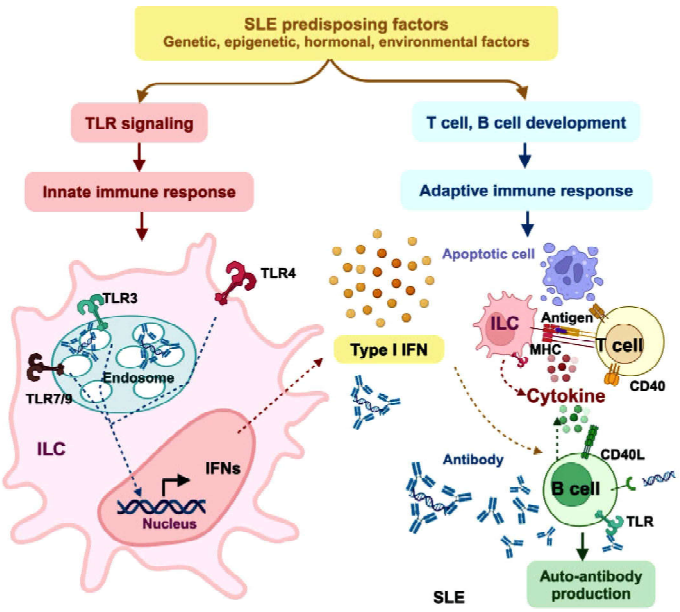


Fig 1: SLE pathogenesis via over-activating immune response

2. Skewed Cytokine Microenvironment

On exposure to autoantigens, naïve CD4+ T cells differentiate into specialized subsets depending on the cytokine milieu. In SLE, Th2 and Th17 pathways are

often upregulated. Th2 cytokines promote humoral immunity and encourage autoantibody production, while Th17 cytokines such as IL-17 correlate strongly with disease severity and tissue inflammation. Meanwhile, regulatory T cells (Tregs), responsible for immune tolerance, are reduced in number or dysfunctional in many SLE patients. The imbalance between Th17 and Treg activity is a major contributor to chronic inflammation.

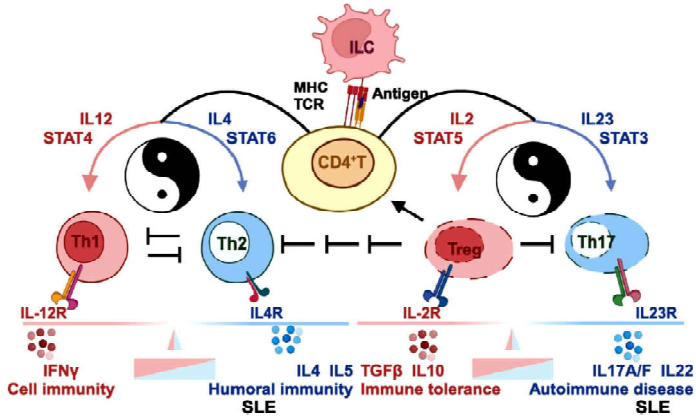


Fig 2: SLE pathogenesis via skewing cytokine microenvironment

3. Inpaired Clearance of Apoptotic Debris

Deficiencies in the complement system, particularly C1q, impair the efficient clearance of immune complexes and apoptotic material. Accumulated nuclear debris becomes a continuous source of autoantigens, perpetuating autoantibody production. Complement dysfunction is strongly linked to lupus nephritis and earlyonset SLE.

Targeted Therapies for SLE

Over the past decade, treatment for SLE has shifted from broad immunosuppressive strategies toward targeted therapies that modulate specific pathways. These therapies aim to reduce disease activity, prevent organ damage, and minimize glucocorticoid exposure. Current approved targeted therapies for SLE include belimumab, anifrolumab, rituximab (used off-label), and voclosporin for lupus nephritis. Each has a distinct mechanism of action tailored to specific aspects of SLE pathogenesis. The availability of multiple therapeutic options with different mechanisms requires careful treatment selection. Patient-specific factors, including disease manifestations, biomarker profiles, and genetic factors, guide treatment decisions.

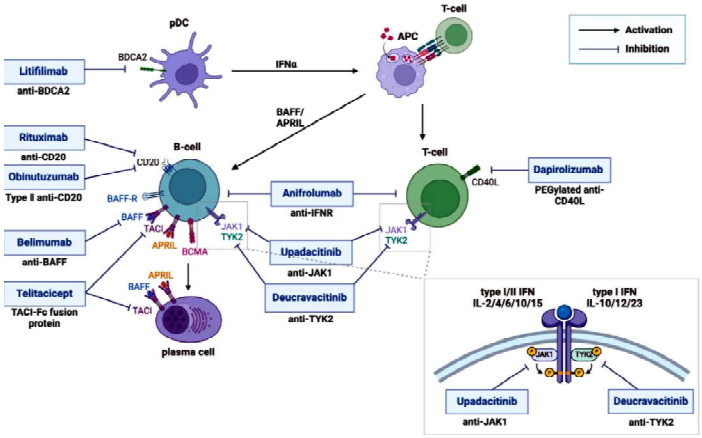


Fig 3: Therapeutic targets in systemic lupus erythematosus.

Current Therapies

1. Belimumab

Belimumab is a monoclonal antibody targeting BAFF (B cell activating factor), a cytokine central to B cell survival and differentiation. Excess BAFF promotes the survival of autoreactive B cells. By neutralizing BAFF, belimumab reduces autoantibody-producing B cell populations.

Clinical trials such as BLISS-52 (B-Lymphocyte Immunotherapy for Systemic SLE-52), BLISS-76, and BLISS-LN have demonstrated improvements in global disease activity, reduced flare frequency, and steroid-sparing effects. Long-term studies also support its safety and sustained efficacy.

The EULAR recommendations support adding belimumab in patients who do not respond to hydroxychloroquine or cannot reduce glucocorticoids to acceptable maintenance doses. For active proliferative lupus nephritis (LN), belimumab can be combined with glucocorticoids and either mycophenolate or low-dose intravenous cyclophosphamide. The (Kidney Disease: Improving Global Outcomes) KDIGO guideline also includes belimumab with mycophenolate or low-dose intravenous cyclophosphamide among four first-line options, particularly for patients with high flare risk or progressive kidney disease.

2. Anifrolumab

Anifrolumab targets the type I interferon receptor (IFNAR1), effectively blocking downstream signaling of all type I IFNs. Given the central role of type I IFN in SLE, this therapy represents a significant advancement. The TULIP-1 (Treatment of Uncontrolled Lupus via the Interferon Pathway-1) and TULIP-2 trials demonstrated significant improvements in skin disease, arthritis and reduced oral glucocorticoid use with an overall acceptable safety profile but an increased risk of Herpes Zoster (HZ) during the initial treatment phase that decreases over time. Patients with a high interferon gene signature (IGS) responded particularly well. Anifrolumab is now considered a first-line biologic for non-renal SLE, especially those with predominant cutaneous disease.

3. Rituximab

Rituximab targets CD20 on mature B cells, leading to B cell depletion. Although major clinical trials failed to show statistical benefit, real-world experience strongly supports its use in refractory SLE, particularly lupus nephritis, neuropsychiatric lupus, and severe immune cytopenias. Combination approaches (rituximab followed by belimumab) are showing promise, with biomarkers such as IgA2 anti-dsDNA predicting response.

4. Voclosporin

Voclosporin is a novel calcineurin inhibitor (CNI) used for lupus nephritis. It is more potent and predictable than traditional CNIs and does not require drug-level monitoring. The AURORA-1 (Aurinia Renal Response in Active Lupus with Voclosporin-1) and AURORA-2 trials demonstrated significant and sustained improvements in renal response and proteinuria reduction. It is particularly beneficial for patients with high-grade proteinuria.

Emerging Therapies

1. Novel Biological Agents In Development

Ongoing research has yielded new therapeutic approaches for SLE beyond current standard treatments. The table gives an outline of selected agents showing particular promise in phase II and III studies.

Table 1: Novel biologics in development

Agent	Mechanism of Action	Trial Phase	Patient Population	Primary Endpoint (Treatment vs. Placebo)	Key Secondary Outcome
Obinutuzumab	Type II anti-CD20 mAb	II	Active/chronic LN	CRR at week 52: 35% vs. 23%	CRR at week 104: 41% vs. 23%
Dapirolizumab pegol	PEGylated anti-CD40L	III	Moderate to severely active SLE, stable LN	Dose–response relationship of BICLA response rates at week 24: none	BICLA response rate: 48.8–54.5% vs. 37.2%
Telitacicept	TACI-Fc fusion protein (BlyS/APRIL inhibitor)	IIb	Active SLE	SRI-4 response rate at week 48: 71.0–75.8% vs. 33.9%	GC dose reduction with 240 mg dose
Litifilimab	Anti-BDCA2	II	SLE (SLEDAI-2K ≥ 4)	Total number of active joints at week 24: 19.0 ± 8.4 vs. 21.6 ± 8.5	Most secondary endpoints not met
Upadacitinib	JAK1 inhibitor	II	Moderate to severely active SLE	SRI-4 response rate and GC dose ≤ 10 mg QD at week 24: 54.8% vs. 37.3%	SRI-4, BICLA, LLDAS response rate at week 48: 45.2% vs. 32.0%, 53.2% vs. 25.3%, 50.0% vs. 24.0%. Overall flares at week 24: 1.9 vs. 2.8.
Deucravatinib	TYK2 inhibitor	II	Active SLE	SRI-4 response rate at week 32: 58% vs. 34%	BICLA, CLASI 50, LLDAS response rates, active joint count at week 48: 57.1% vs. 34.4%, 47.3% vs. 25.6%, 36.6% vs. 13.3%, −8.9 vs. −7.6.

Abbreviations: APRIL, A proliferation-inducing ligand; BDCA2, blood dendritic cell antigen 2; BICLA, British Isles Lupus Assessment Group-based Composite Lupus Assessment; BlyS, B cell activating factor; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CRR, complete renal response; GC, glucocorticoids; JAK1, Janus kinase 1; LLDAS, Lupus Low Disease Activity State; LN, lupus nephritis; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI-4, SLE Responder Index 4; TYK2, tyrosine kinase 2.

2. Car T Cell Therapy

CAR T cell therapy targeting CD19-positive B cells is an emerging treatment for refractory SLE. Early reports show dramatic and sustained remission, although risks such as cytokine release syndrome and neurotoxicity require specialized management. This therapy has the potential to "reset" the autoimmune system.

3. T Cell Engager Therapy

T cell engagers (TCEs) use bispecific antibodies to redirect T cells to autoreactive B cells. These agents do not require cell processing like CAR T therapy and offer flexible dosing. Early data suggest they may offer a safer, more scalable approach to deep immune modulation.

Precision Medicine In SLE

SLE remains challenging to manage despite the recent advances in its treatment, due to its heterogeneous clinical presentation and unpredictable disease course. Current SLE classification relies primarily on clinical manifestations and serological findings, often failing to capture the underlying molecular heterogeneity driving disease activity and organ damage. The concept of precision medicine offers the potential to overcome this limitation in SLE treatment by tailoring therapies to individual patient characteristics and disease mechanisms.

1. Genetic Factors In Sle Pathogenesis And Patient Stratification

Genomic studies have identified variants in Platelet-Derived Growth Factor Receptor Alpha (PDGFRA), Hyaluronan Synthase 2 (HAS2), and Integrin subunit alpha M (ITGAM) that predispose to specific organ involvement. Epigenetic markers and microRNA profiles further refine predictions of disease activity and treatment response.

2. Biomarker-Based Patient Stratification

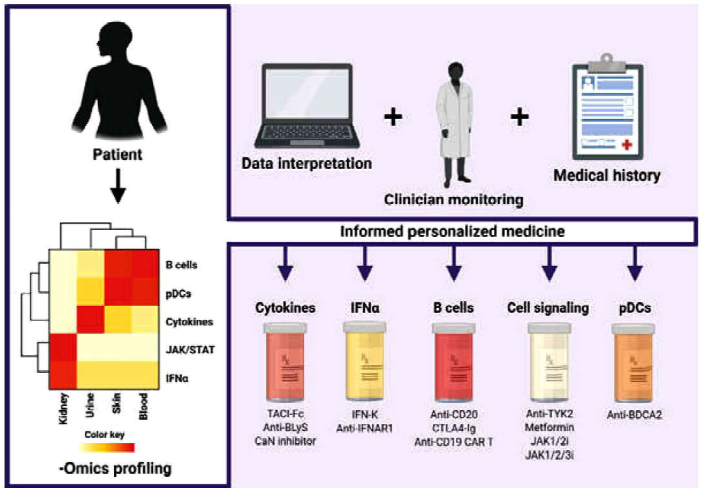
Biomarkers such as interferon gene signature (IGS), C-X-C motif chemokine ligand 10 (CXCL10), galectin-9, Siglec-1, BAFF, A Proliferation-Inducing Ligand (APRIL), Monocyte Chemoattractant Protein- 1 (MCP-1) and Neutrophil Gelatinase- Associated Lipocalin (NGAL) help stratify patients, predict flares, and identify those likely to respond to specific therapies.

3. Predicting Treatment Response

Predicting which patients are most likely to benefit from a given therapy is a key goal of precision medicine, which is particularly crucial in SLE, where treatment responses can vary widely. For example, patients with high IGS may be more likely to respond to anifrolumab. Further refinement of treatment response prediction may come from understanding the dynamic interplay between genetic variants, gene expression, and environmental factors.

Patient profiling for personalised SLE treatment can be done by constructing profiles from multiple-omics approaches (i.e., transcriptomics, metabolomics, proteomics, epigenomics, and genomics) that can

highlight the key players in each individual patient's clinical and molecular manifestations. Interpretation of these profiles within the context of patient's medical history and clinician's monitoring can form personalized medicine regimens. Thus, specific drug targets and mechanisms can be matched to patient characteristics to optimize the likelihood of treatment success.



Abbreviations used: BDCA2, blood DC antigen 2; BLyS, B lymphocyte stimulator; CaN, calcineurin, CAR, chimeric antigen receptor; IFN, interferon; IFNAR, interferon alpha and beta receptor; IFN-K, IFN-a kinoid; JAK/STAT, Janus kinase/signal transducer and activator of transcription; pDC, plasmacytoid dendritic cell; TACI, transmembrane activator and calcium modulator and cyclophylin ligand interactor; TYK2, tyrosine kinase 2

Fig 4: Framework for informed personalised medicine in SLE.

4. Artificial Intelligence And Data-Driven Modelling

Machine learning approaches integrating clinical, serologic, and molecular data are being used to predict flares, optimize drug selection, and personalize monitoring schedules.

Challenges And Future Directions

Despite significant progress, challenges include limited access to biologics in low-resource settings, high treatment costs, and the need for validated biomarkers across diverse populations. Treatment sequencing and combination strategies also require further research. CAR T therapy and TCEs show promise but require longterm data.

Conclusion

Biologics and precision medicine have transformed the landscape of SLE management. Targeted therapies such as belimumab and anifrolumab have improved outcomes, reduced flare rates, and minimized glucocorticoid use. Emerging therapies—including CAR T cells, TCEs, and biomarker-driven treatment algorithms—represent the next frontier. The ultimate goal is sustained remission with minimal toxicity, shifting SLE toward a manageable chronic condition.

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Chapter

42

IgG4-Related Disease: Advances in Understanding Pathogenesis

Dr. Madhumita Priyadarshini Das

ABSTRACT

IgG4-related disease (IgG4-RD) is a recently recognized immune-mediated condition that unites a wide spectrum of disorders once thought unrelated. Characterized by fibroinflammatory lesions, storiform fibrosis, and IgG4-positive plasma cells infiltration, it can affect virtually any organ—most often the pancreas, salivary glands, kidneys, and vascular structures. Its presentation is highly variable and often mimics cancer, infections, or other autoimmune diseases, making timely diagnosis difficult but essential, as untreated disease may lead to irreversible fibrosis and organ failure. Since its unification in the early 2000s, our understanding has expanded dramatically, from its historical origins in Mikulicz's disease to modern recognition as a systemic disorder with unique pathophysiology involving dysregulated B- and T-cell responses. Diagnosis requires careful integration of clinical, serological, radiological, and histological findings. Treatment has advanced from steroids to B-cell–targeted biologics, offering hope for sustained remission. This chapter explores IgG4-RD's origins, manifestations, pathology, diagnosis, and evolving management strategies.

Introduction

IgG4-related disease is a newly recognized immune-mediated disorder marked by systemic fibrosis and protean manifestations. Often mimicking cancer, infections, or autoimmunity, it poses significant diagnostic challenges. A high index of suspicion and early recognition through integrated clinical and pathological assessment is vital, as timely treatment prevents progression to irreversible fibrosis and organ damage.

IgG4-RD: The Origin

The history of IgG4-RD spans more than a century. In 1892, Johann von Mikulicz described chronic salivary gland swelling (Mikulicz's syndrome). Soon after, Küttner reported submandibular tumefaction, and Riedel documented fibrosing thyroiditis.[1] For decades these were considered separate entities. In 1963, Bartholomew highlighted their overlap with retroperitoneal fibrosis and sclerosing cholangitis.[1]

A breakthrough came in the early 2000s when Japanese investigators linked elevated serum IgG4 to lymphoplasmacytic sclerosing pancreatitis (now Type 1 autoimmune pancreatitis).[2] Pathological features—storiform fibrosis and IgG4-positive plasma cell infiltration—were soon recognized in multiple fibrosing disorders. By 2011, an international consensus in Boston unified these conditions under the term IgG4-related disease.[3]

Epidemiology: IgG4-RD

IgG4-RD most often presents in the fifth to seventh decades, though all ages can be affected. Men predominate in pancreatobiliary and retroperitoneal forms, whereas women more often show head and neck involvement. Estimated incidence in the USA is 0.78–1.39 per 100,000 person-years. In Japan, pancreatic disease alone has an incidence of 3.1 per 100,000.[4]

The disease develops insidiously, usually without fever or marked inflammatory markers, and is often discovered incidentally on imaging.[2]

IgG4-RD: Organ Systems

IgG4-RD can involve almost any organ. Pancreas, biliary tract, salivary glands, kidneys, lungs, orbit, lymph nodes, thyroid, aorta, pericardium, skin, and retroperitoneum are common sites. Clinical and histologic overlap with malignancy, sarcoidosis, and autoimmune disease makes diagnosis challenging.

Previously-Recognized Conditions reclassified under the IgG4-Related Disease Spectrum.

Mikulicz's disease
Küttner'stumor
Riedel's thyroiditis
Eosinophilic angiocentric fibrosis
Multifocal fibrosclerosis
Lymphoplasmacytic sclerosing pancreatitis / autoimmune pancreatitis
Inflammatory pseudotumor
Fibrosing mediastinitis
Sclerosing mesenteritis
Retroperitoneal fibrosis (Ormond's disease)
Periaortitis /periarteritis
Inflammatory aortic aneurysm
Cutaneous pseudolymphoma
Idiopathic hypertrophic pachymeningitis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits

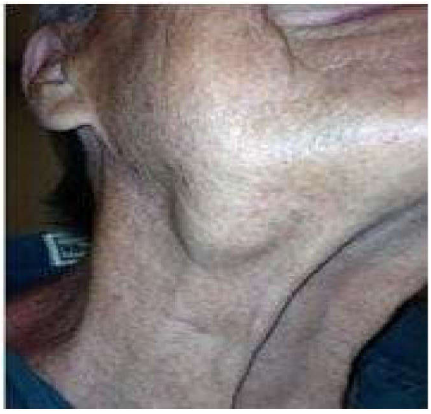

Figure 1: Tumefactive Enlargement of Submandibular Gland In Igg4-Rd(5)

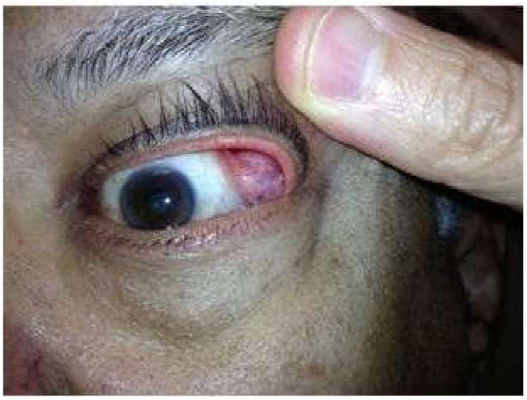

Figure 2: Dacryoadenitis. Lacrimal Gland Swelling In Igg4-Rd (5)

Organ System/Tissue (2)	Preferred Name/New Nomenclature
Pancreas	IgG4-related pancreatitis (Type 1 autoimmune pancreatitis)
Lacrimal glands	IgG4-related dacryoadenitis
Orbital soft tissue	IgG4-related orbital inflammation / inflammatory pseudotumor
Extra-ocular muscle	IgG4-related orbital myositis
Salivary glands	IgG4-related sialadenitis (e.g., parotitis or submandibular gland disease)
Pachymeninges	IgG4-related pachymeningitis
Hypophysis (Pituitary)	IgG4-related hypophysitis
Thyroid	IgG4-related thyroiditis (e.g., Riedel's thyroiditis)
Aorta	IgG4-related aortitis / periaortitis
Mediastinum	IgG4-related mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis
Mesentery	IgG4-related mesenteritis
Skin	IgG4-related skin disease
Lymph node	IgG4-related lymphadenopathy
Bile ducts	IgG4-related sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis
Liver	IgG4-related hepatopathy
Lung	IgG4-related lung disease
Pleura / Pericardium	IgG4-related pleuritis / pericarditis
Kidney	IgG4-related kidney disease (TIN, membranous GN, renal pyelitis)
Breast	IgG4-related mastitis
Prostate	IgG4-related prostatitis

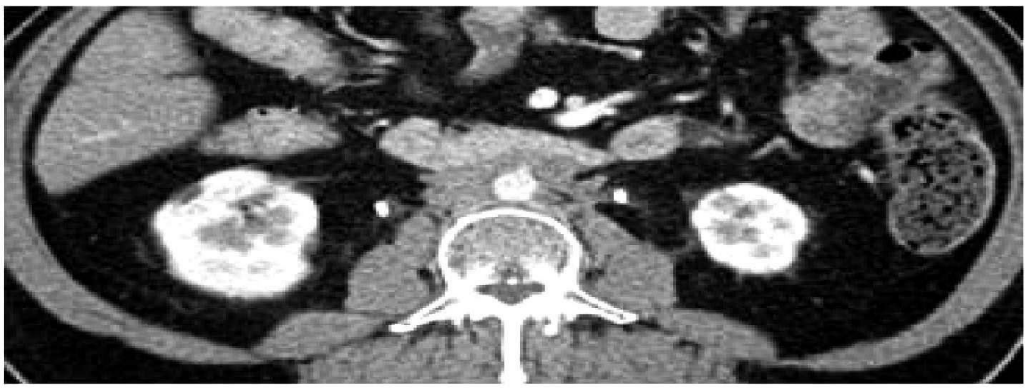

Figure 3: Retroperitoneal fibrosis. ct shows an inflammatory mass around the abdominal aorta.[5]

Organ Manifestations(2,5)

Organ/System	Manifestations
Orbits/Periorbital	Painless swelling, dacryoadenitis, orbital pseudotumor, myositis, scleritis
Meninges	Headache, cranial nerve palsies, compressive lesions
Ear, Nose, Sinuses	Allergic rhinitis, nasal polyps, asthma, bone-destructive masses
Salivary Glands	Bilateral parotid/submandibular swelling (Mikulicz pattern)
Pituitary/Hypothalamus	Mass lesions, hormone deficiencies, diabetes insipidus
Thyroid	Riedel's thyroiditis (hard, fibrotic thyroid)
Retroperitoneum	Fibrosis causing ureteral obstruction, hydronephrosis, renal failure
Aorta	Aortitis, aneurysm, or dissection
Kidneys	Tubulointerstitial nephritis, membranous GN, hypocomplementemia
Pancreas	Type 1 autoimmune pancreatitis, "sausage-shaped" pancreas
Lungs	Pseudotumors, airway disease, interstitial pneumonia, paravertebral masses, pulmonary nodules, bronchovascular bundle thickening
Biliary Tree/Liver	Obstructive jaundice, mimics Primary sclerosing cholangitis or cholangiocarcinoma
Other Sites	Pericarditis, fibrosing mediastinitis, sclerosing mesenteritis, breast pseudotumor

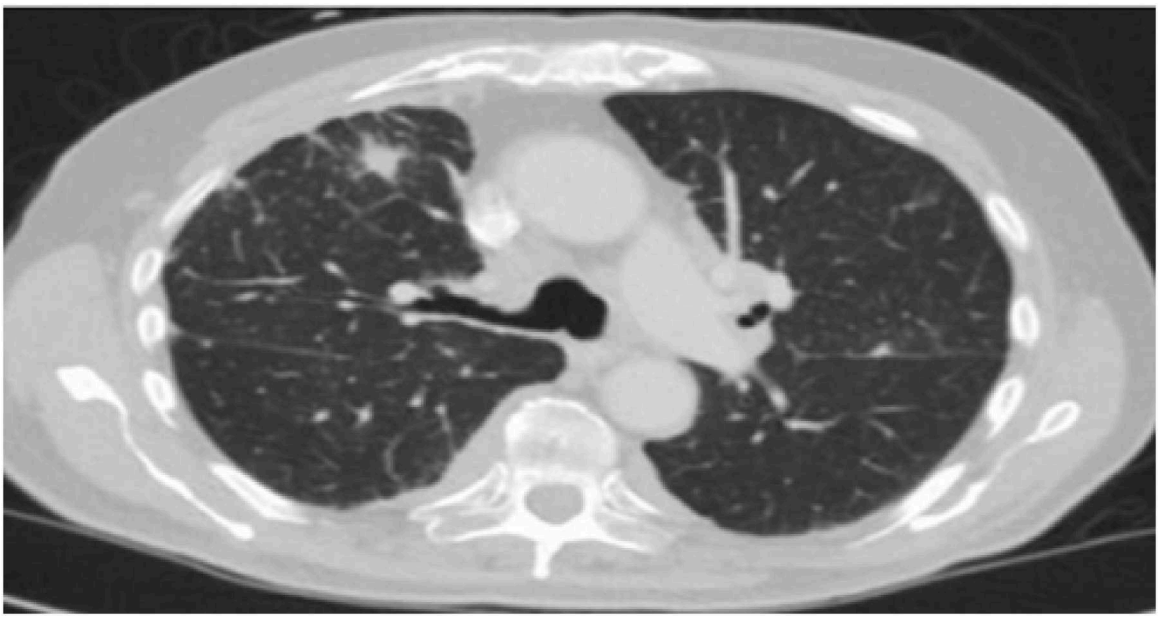

Figure 4: CT Chest shows bronchial wall thickening and a pulmonary nodule in anterior right upper lobe.[5]

Histopathology: IgG4-RD(2)

Feature	Details
Histopathological Hallmarks	Dense lymphoplasmacytic infiltrates, storiform fibrosis, obliterative phlebitis, mild to moderate eosinophilia, germinal centres, lymphoid follicles
Lesion Characteristics	Tumefactive masses that infiltrate and damage tissue
Vascular Involvement	Obliterative venulitis is the hallmark; arteritis rare but possible, especially in lungs
Uncommon Features	Intense neutrophilic infiltration, granulomas, giant cells, fibrinoid necrosis (suggest alternative diagnoses)
Cellular Composition	Predominantly CD4+ T cells; B cells in germinal centres; plasma cells (CD19+, CD138+, IgG4+) confirmed by immunohistochemistry
Diagnosis requirements	1) IgG4+ plasma cell count; 2) IgG4:total IgG ratio; 3) Fibrosis pattern, especially in late/acellular stages

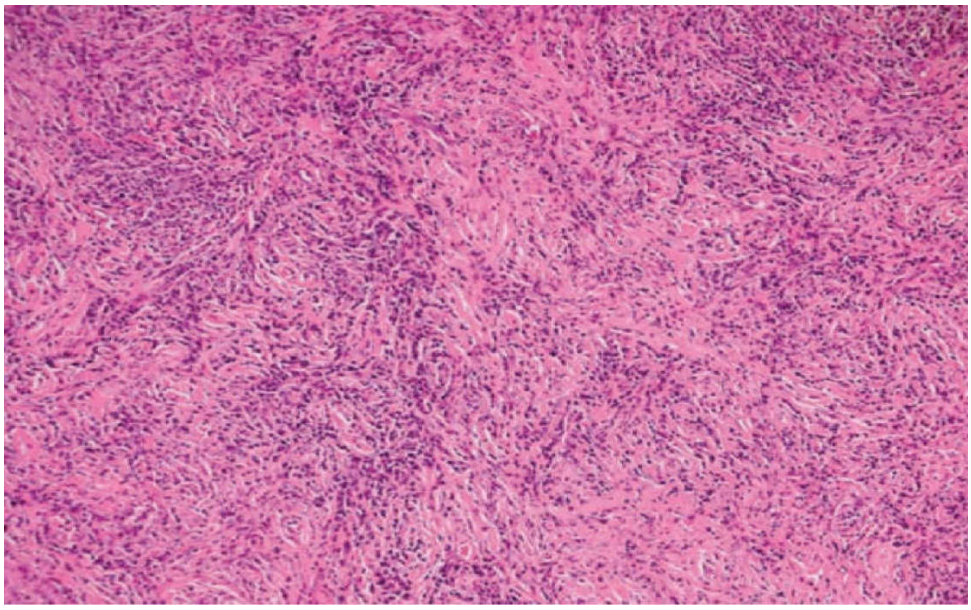

Figure 5: Histopathology shows Dense lymphoplasmacytic and Eosinophilic infiltrates with storiform ("basket-weave") fibrosis, abundant fibroblasts, and fibrotic strands.(2)

Pathophysiology: IgG4-RD

IgG4 itself is considered anti-inflammatory, with poor complement activation due to its weak interaction with Fc? receptors and C1q and unique Fab-arm exchange preventing immune complex formation. It inhibits IgG1 responses, decreases IL-8 production by neutrophils, and suppresses adaptive immune function.[6]

Genetic associations include HLA-DRB1 and FCGR2B(4). Immune mechanisms involve:

Immune Component(6)	Role/Effect in IgG4-Related Disease
Innate Immune Cells (macrophages, neutrophils, dendritic cells)	Produce profibrotic cytokines IL-4, IL-13, TGF-β that promote fibrosis
M2 Macrophages	Enhance Th2 immune response
CD4+ T Cells (especially SLAMF7+ effector memory cells)	Drive disease progression by releasing profibrotic cytokines and cytotoxic mediators
Pattern Recognition Receptors (e.g., TLR2, NOD2)	Bias immune response toward Th2; stimulate BAFF and APRIL production, promoting IgG4 class switching
Complement Activation (C5a receptor)	Further promotes Th2 polarization, increasing IL-4, IL-5, IL-10, IL-13, and TGF-β
T-B Cell Interactions	Mediated by BAFF, APRIL, and IL-21; lead to expansion of IgG4-producing B cells

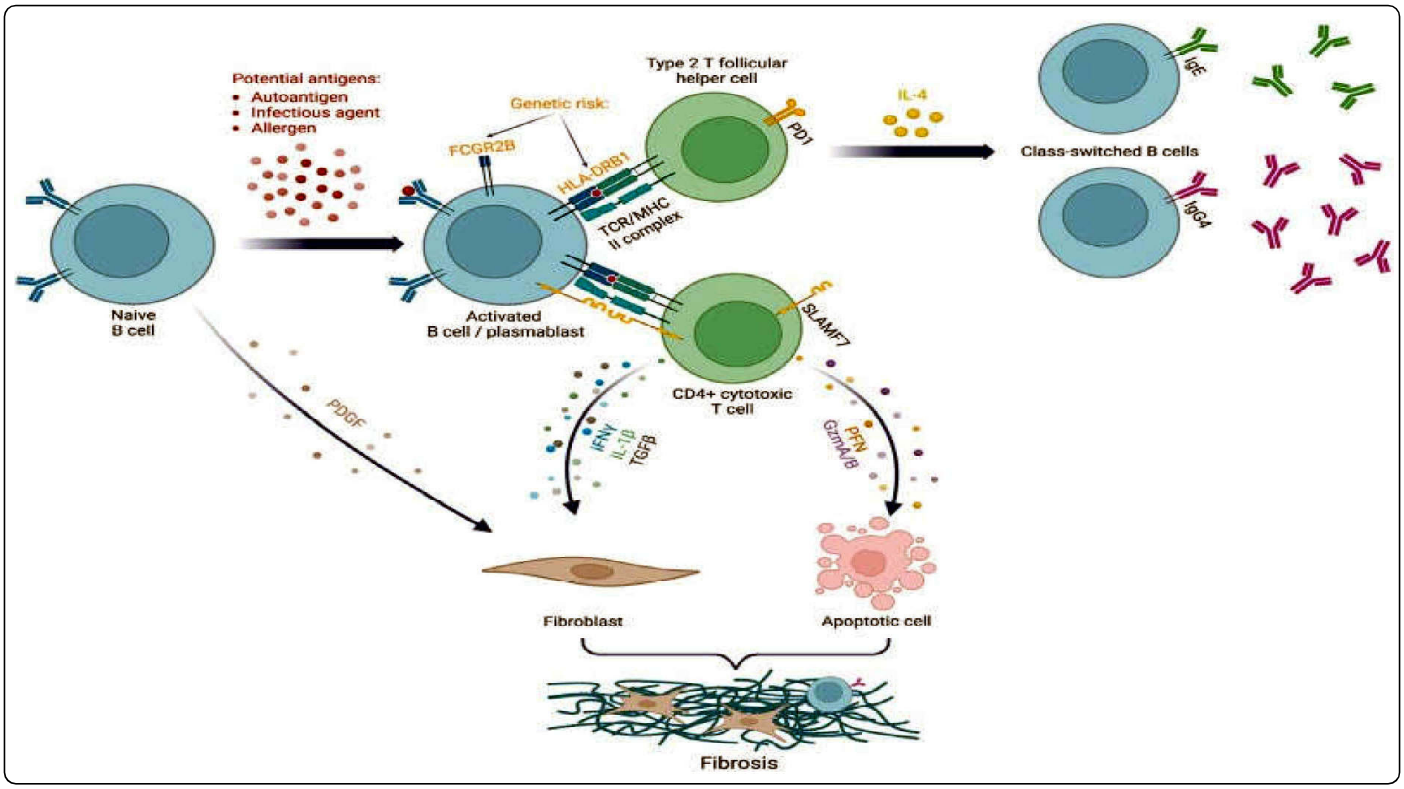

Figure 6: Pathophysiology of IgG4 related disease(4)

Diagnostic Criteria: IgG4-RD(7,8)

The Japanese Comprehensive Clinical Diagnostic (CCD) Criteria for IgG4-RD

Criteria	Details
1. Clinical Examination	Characteristic diffuse/localized swelling or masses in single or multiple organs
2. Haematological Examination	Elevated serum IgG4 concentrations (>135 mg/dL)
3. Histopathological Examination	- Marked lymphocyte and plasmacytic infiltration and fibrosis
	- Infiltration of IgG4+ plasma cells: IgG4+/IgG+ ratio >40% and >10 IgG4+ plasma cells/HPF
Diagnosis Categories	Definite: Criteria 1 + 2 + 3
	Probable: Criteria 1 + 3
	Possible: Criteria 1 + 2
Additional Notes	Individual organ-specific diagnostic criteria should be used to differentiate from malignancy

The Mayo Clinic HISORt Criteria for the Diagnosis of AIP(Autoimmune Pancreatitis)

Criteria	Details
1. Histopathology (one or both criteria required)	- Characteristic appearances within biopsy or resection material*
	- At least ten IgG4-positive plasma cells per high power field within areas of lymphoplasmacytic infiltrate
2. Imaging and Serology (3 criteria required)	- Diffusely enlarged pancreas with delayed and "rim" enhancement
	- Irregular pancreatic duct
	- Increased serum IgG4 concentration
3. Response to Steroid Therapy (3 criteria required)	- Unexplained pancreatic disease after full clinical workup, including exclusion of cancer
	- Raised serum IgG4 concentration and/or extrapancreatic organ involvement with increased tissue IgG4-positive plasma cells
	- Resolution or marked improvement with steroid therapy
***Note**	Includes lymphoplasmacytic infiltrate, "storiform" fibrosis, and obliterative phlebitis; inflammatory cell infiltrate alone is insufficient to meet this criterion

Serology: IgG4-RD(2)5

Serum IgG4 is often elevated, especially in multi-organ disease, but up to 30% of patients have normal levels despite typical disease manifestations. Diagnosis must therefore integrate serology with clinical and pathological evidence.

Biomarkers of Disease Activity and Relapse Predictors: IgG4-RD(4)

Disease activity can however be monitored with certain laboratory tests and organ specific markers.

Test	Change may herald an IgG4-related disease flare
General laboratory tests	
Immunoglobulin G4	↑
Immunoglobulin E	↑
Eosinophil count	↑
Complement components 3 and 4	↓
ESR	↑
Plasmablast count	↑
Memory B cell count	↑
Organ-specific laboratory tests	
Lipase	↑
Alanine transaminase, aspartate transaminase	↑
Alkaline phosphatase, gamma-glutamyl transferase, bilirubin	↑
Creatinine	↑
Total urine protein to creatinine ratio	↑

The catch points for IgG4-RD disease activity are summarised below(4)

Category	Details
Common Monitoring Tests	- Serum IgG4 and IgE - Complement (C3, C4) - Eosinophil count
Serum IgG4	- Most frequently used marker - Decreases with treatment - May remain elevated in remission - Rising levels may precede flare
Relapse Indicators	- Recurrence of: • Hypocomplementemia • Elevated IgE • Eosinophilia
High-Risk Features for Relapse	- High IgG4 at baseline - Multi-organ involvement - Atopy - Eosinophilia - Elevated IgE
Organ-Specific Markers	- Kidney: Urinary protein - Biliary tract: Bilirubin, ALP

Monitoring and Management of IgG4-RD(4)

Relapse is frequent, often silent. Clinical evaluation, labs, and imaging (when organ disease is present) are used for follow-up every 3–6 months.

Rising IgG4 without symptoms ("serological relapse") requires personalised approach with closer monitoring, consider treatment only if high-risk organs were previously affected.

Active Disease vs Damage(4)

Fibrosis complicates assessment: lab abnormalities may persist after inflammation resolves, while imaging lesions such as retroperitoneal fibrosis may represent scarring rather than activity.

Key distinctions:

- Active disease worsens over time; damage remains stable.
- Steroids relieve active inflammation but not fibrosis.
- Unexpected deterioration despite treatment should prompt evaluation for malignancy.

IgG4-RD: Is it a Vasculitis?(9)

IgG4-RD frequently involves vessels of all sizes. Histology shows phlebitis and occasionally arteritis. The aorta, coronary, and medium-sized arteries can be affected, leading to aneurysm, stenosis, and infarction. At Massachusetts General Hospital cohort study, 4% of IgG4-RD patients had coronary involvement, exclusively men with long disease duration and high IgG4. Findings included wall thickening, stenosis, calcification, and aneurysms, sometimes causing myocardial infarction or cardiomyopathy.

Some propose classifying IgG4-RD as a primary variable-vessel vasculitis, though consensus is lacking as of now.

Treatment: IgG4-RD

Treatment	Details
1. Glucocorticoids (First-line)(2,7)	Most patients respond well to steroid therapy. Early initiation is important to prevent permanent fibrosis.
Japanese protocol (mainly for autoimmune pancreatitis): (7)	Prednisolone 0.6 mg/kg/day for 2–4 weeks, then tapered to 5 mg/day over 3–6 months, followed by maintenance of 2.5–3 mg/day for up to 3 years.
Mayo Clinic protocol: (7)	Prednisone 40 mg/day for 4 weeks, tapered by 5 mg/week over 7 weeks (total 11 weeks), then discontinued.
	Maintenance therapy may lower relapse rates compared to stopping steroids entirely, though further research is needed.
2. Rituximab (Second-line)(2)	Used for patients who do not respond to steroids or who relapse. - Administered as 1 g intravenous infusion twice, 15 days apart. - Quickly reduces IgG4 levels and circulating plasmablasts. Induces remission by preventing replenishment of short-lived IgG4-producing plasma cells. (7) - Can be considered as first-line treatment in steroid-intolerant or severe cases.
3. Other Immunosuppressants (Off-label)	- Includes Azathioprine (2 mg/kg/day), Mycophenolate Mofetil (up to 2.5 g/day), and Methotrexate. Effectiveness is not well established.(7)
4. Emerging Targeted Therapies	- Bortezomib (a proteasome inhibitor) shows potential in treating IgG4-related lung and orbital involvement. (7) - Other targets under investigation include BTK inhibitors and SLAMF7 pathway blockers.(2)
5. New FDA-Approved Targeted Therapy	- *Inebilizumab-cdon (Uplizna, Amgen*), a CD19+ B-cell targeting agent.(10) Approved based on the MITIGATE Phase 3 trial(10)demonstrating an 87% reduction in disease flares compared to placebo.

Conclusion

IgG4-RD has evolved from an enigmatic condition, with its diverse presentations that often mimic malignancy or autoimmunity, into a recognizable, treatable multisystem disease. Advances from glucocorticoids to B cell–targeted biologics have significantly transformed outcomes. Timely recognition and sustained vigilance thus remain the cornerstones of improving patient outcomes as our understanding continues to evolve with time.

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Chapter

43

Gout Management: New Urate Lowering Therapies

Dr. Pradip Kumar Sarma

ABSTRACT

Gout is the commonest inflammatory arthritis in human. It occurs due to the deposition of monosodium urate crystal in the joints and other tissues secondary to chronic hyperuricemia. Many conventional urate-lowering therapies (ULTs) e.g. allopurinol, febuxostat, probenecid and pegloticase remain main stay of treatment; but their limitations include hypersensitivity, intolerance, contraindications due to comorbidities, cardiovascular safety and inadequate response in some patients. In recent years, novel agents and strategies have emerged, including selective uricosurics, immunomodulation-enhanced uricase therapy, and biologics targeting inflammatory pathways. This review summarizes the advances in pharmacotherapy in urate-lowering therapyand discusses implications for practice.

Introduction

Gout is also called "the king of the diseases and the diseases of the kings." Gout represents a global health burden, with prevalence increasing in both developed and developing countries. The increased prevalence is multifactorial: increased longevity (prevalence of gout increases with age), more people suffering from diabetes, hypertension, obesity, metabolic syndrome, more use of low dose aspirin, diuretic, better survival for patients with end stage renal disease, congestive cardiac failure etc.- all of which are risk factors for hyperuricemia and gout. Till now there is a limited number of drugs available to treat hyperuricemia and gout.

Sustained serum uric acid (SUA) levels above the solubility threshold (>6.8 mg/dL) drive crystal deposition and recurrent arthritis[1]. Achieving and maintaining target SUA <6 mg/dL, or <5 mg/dL in severe disease like tophaceous gout, is central to management.

Current treatment can be divided into two parts:

1. Treatment of acute attack: Non-steroidal anti-inflammatory drugs or cox 2 inhibitor; local, parenteral or intra-articular steroid and Colchicine alone or in combination depending upon disease severity.

2. Uric acid lowering drug:
   a. Diet and exercise are one of the cornerstones of therapy and should be advised for all patients with hyperuricemia.
   b. Hypouricemic drugs: not all patients with the 1st attack of gout needs hypouricemic drugs; the indications for ULTs are:
      i. Recurrent attacks of gout = 2 per year
      ii. Presence of tophi
      iii. Gout arthropathy
      iv. Radiographic changes of gout
      v. Multiple joint involvement
      vi. Nephrolithiasis

Patients experiencing their 1stflare or infrequent flares don't need ULT except in presence of chronic kidney disease stage >3, cardiovascular disease, SUA >9 mg/dl and Urolithiasis.

Traditional urate lowering drugs

- Uricosurics – Benzbromarone, Probenecid and Sulfinpyrazone
- Xanthine oxidase inhibitors (XOI): allopurinol and febuxostat
- Polyethylene glycan conjugated porcine-baboon uricase: pegloticase

These therapies provide benefit for most patients. However, there are some issues with them and along with poor adherence necessitate newer therapies [2].

Limitations of Conventional ULTs

- Allopurinol: First-line xanthine oxidase inhibitor XOI, but hypersensitivity risk (e.g. in HLA-B*58:01 carriers) limits its use in some ethnic groups[3]. Dose titration is often suboptimal in clinical practice. Though up to 800 to 900 mg daily of allopurinol can be used if required, most of the physicians or patients don't use beyond 300 mg daily even if target SUA is not reached. Needs caution in patients with advanced kidney disease.
- Febuxostat: potent urate-lowering agent but CARES trial raised cardiovascular concerns[4].
- Probenecid/Benzbromarone: Limited use in renal impairment and risk of nephrolithiasis.
- Pegloticase: Effective in refractory gout but highly immunogenic and costly[5].

Though gout is an ancient disease, the development in the newer therapies has been slow. However, we have witnessed remarkable advances in the treatment of gout in the 21st century. It started with the development of new XOIs e.g. febuxostat and topiroxostat followed by pegylated uricase and later on newer uricosuric agents (Figure 1).

Gout is a transportopathy

In recent years, the focus of pathogenesis of hyperuricemia and gout has been on uric acid handling by the kidney. Hyperuricemia can be caused by both over production (like in high cell turn over states e.g. myeloproliferative disorders, psoriasis, Paget's disease, tumor lysis syndrome, in genetic disorders etc.) or under excretion of uric acid; however, it occurs due to underexcretion in approximately 90% of the patients. Underexcretion is mostly due to abnormalities in the uric acid transportation mechanism in the renal tubules and gut. Gout is now considered to be more of a transportopathy.

Role of various urate transporters are now known in the renal and intestinal excretion as well as renal reabsorption:

- Urate transporter-1 (URAT-1): renal reabsorption at the proximal convo-luted tubule.
- Organic anion transporter 1 (OAT1) and OAT3: urate secretion.
- Adenosine triphosphate-binding cassette transporter G 2 (ABCG2):renal urate secretion and in gastrointestinal urate excretion.

Newer Urate-Lowering Therapies (summarized in table 1)

1. Selective Uricosurics or Selective urate reabsorption inhibitor (SURI)

Lesinurad: originally developed for HIV treatment. A metabolite of a non-nucleoside reverse-transcriptase inhibitor. Selectively inhibits URAT-1 and OAT4, thereby reduces renal reabsorption of uric acid, promoting its excretion and lowering serum urate levels. It has minimal drug interactions, as it does not affect OAT-1 or OAT-3. It is typically administered at a dose of 200 mg daily in combination with a XOI, which leads to sustained lowering of serum urate. Combining lesinurad with febuxostat has demonstrated superior efficacy compared to febuxostat alone.

Common adverse effects: renal dysfunction & nephrolithiasis.

Contraindication: tumor lysis syndrome, Lesch–Nyhan syndrome, renal transplant recipients, low creatinine clearance (<30 ml/min), unstable angina, uncontrolled hypertension, decompensated heart failure, and recent myocardial infarction.

Dotinurad: Selective URAT1 inhibitor, approved in Japan with strong urate-lowering efficacy and renal tolerability [6].

Verinurad: High-affinity URAT1 inhibitor studied in combination with XOIs, showing robust urate reduction without increased nephrolithiasis risk [7].

Tranilast: originally developed for allergy. Found to have urate-lowering effect due to the inhibition of URAT-1 and glucose transporter. Reduces urate crystal associated inflammation.

Levotofisopam: benzodiazepine derivative. Increases the fractional excretion of urate. Mechanism of action is uncertain.

Canaglifozin: sodium glucose cotransporter 2 inhibitor; increases urinary glucose excretion. Lower serum uric acid levels by 13% at doses of 100–300 mg.

UR-1102: potent inhibitor of URAT-1, OAT1, and OAT3.

2. Next-Generation XOIs:XOIs can be used both in overproducers and under-excretors.

Topiroxostat: Non-purine selective XOI available in Japan and South Korea [8]. It is mainly inactivated in the liver and eliminated via urine and faeces. Can be used in patients with chronic kidney disease.

LC350189: Novel selective XOI. Found to be comparable to febuxostat.

3. Optimized Uricase Therapy

Pegloticase combined with methotrexate improves durability of urate lowering by reducing immunogenicity [9].

4. Dual-Action Agents

Arhalofenate : It has a long half life of about 50 hours. It reduces serum uric acid levels byincreasing urinary uric acid and the fractional excretion of uric acid by selective inhibition of URAT-1 and OAT 4 leading to tubular reabsorption of uric acid. It also reduces gout

flares by inhibiting the urate crystal-induced production of IL-1ß through action on peroxisome proliferator-activated receptor (PPAR)-?. Combination of arhalofenate with febuxostat is synergistic, while combination with allopurinol does not have any additional advantage over allopurinol monotherapy. It can reduce urate even in the presence of renal insufficiency. As it acts on OAT 4, it is effective in patients on diuretic therapy. It also has lipid and glucose lowering action.

Merbarone: Type-II DNA Topoisomerase inhibitor. It causes profound hypouricemia by inhibitionof XO and URAT-1. Can be used in severe tophaceous gout.

AC 201: an IL-1ß modulator, it reduces gout flares by IL-1ß inhibition; has a uricosuric action by increasing the fractional excretion of uric acid.

KUX-1151: used in Japan. Inhibits both XO and URAT1.

5. Anti Inflammatory therapies:

The pathogenesis of gout: monosodium urate crystals are phagocytosed by macrophages and forms NOD-like receptor protein 3 (NLRP3) inflammasome; this in turn activate the caspases which leads to inflammatory cascade resulting in release of cytokines, like interleukin (IL)-1ß and IL-18. The binding of active IL-1 to its endothelial receptor causes signal transduction, release of inflammatory mediators, and neutrophil recruitment, which are responsible for acute attack of gout. Following drugs inhibiting any of the steps in this pathway are beneficial the treatment of gout: Anakinra: IL-1 receptor antagonist.

Canakinumab: human anti-IL-1ß monoclonal antibody.

Gevokizumab: humanized anti-IL-1ß monoclonal antibody.

Rilonacept: fusion protein acting as a soluble receptor binding IL-1a and IL-1.

Pralnacasan: reversible caspase-1 inhibitor.

Emricasan: irreversible orally active pancaspase inhibitor.

Dapansutrile: NLRP3 inflammasome inhibitor.

6. Emerging therapies:

Purine nucleoside phosphorylase(PNP) inhibitors: PNP is the enzyme which converts purines intohypoxanthine. Ulodesine is a PNP inhibitor whichhas synergisticaction when combined with allopurinol. It causes reduction in xanthine and hypoxanthine.

Marine active 10: commercial tuna extract from a hot water skipjack and yellowfin tuna.It increases hypoxanthine phosphoribosyl transferase levels in the liver. Hypoxanthine phosphoribosyl transferase utilizes hypoxanthine and guanine for purine synthesis, thereby inhibiting uric acid synthesis.

Transporter modulators (GLUT9, ABCG2) identified by genetic studies mayprovide future urate-lowering pathways.

SGLT2 inhibitors, used in diabetes, provide modest urate reduction and cardiometabolic benefit.

7. Old drugs in new bottle

Adrenocorticotropic hormone (ACTH): Though mechanism of action of ACTH in gout is not exactly known, it triggers the release of endogenous steroids and downregulates inflammatory responses by activating melanocortin 3 receptors (MC3R) on innate immune cells such as macrophages which significantly reduces inflammatory response to MSU crystals by reducing

activities of nuclear factor-?B and heme oxygenase. ACTH is also thought to inhibit IL-1. ACTH can be an option for treatment of gout in patients with multiple comorbidities like postoperative patients and those on steroids for other conditions such as post renal transplant. A single injection of 60 IU IM of ACTH is more effective than corticosteroids.

Fenofibrate: It exerts hypouricemic action by inhibition of URAT1.It is a PPAR activator, downregulating COX2 expression resulting in anti-inflammatory action which may be helpful in preventing gout fares.

Losartan: an Angiotensin II receptor blocker, it increases the fractional clearance of uric acid by targeting URAT 1, independent of angiotensin blockade. It counters thiazide induced hyperuricemia. Among the uricosurics it has a unique property of reducing the formation of renal stone by increasing the urinary pH.

Amlodipine: It reduces the long-term risk of gout compared with other antihypertensives. It significantly increases the glomerular filtration rate and urate clearance and isfound to be an effective option in renal transplant recipients with Cyclosporin induced hyperuricemia and hypertension.

Atorvastatin: though the exact mechanism is unclear, atorvastatin is thought to exert hypouricemic action by augmenting the fractional excretion of uric acid by reducing the proximal tubular reabsorption. Other statins do not have this effect. Hypouricemic effect is independent of the lipid lowering effect.

Integration into Guidelines

The ACR 2020 and EULAR 2023 guidelines recommend allopurinol as first-line therapy, febuxostat as an alternative, and pegloticase for refractory gout. Recent updates highlight URAT1 inhibitors such as dotinurad and strategies like pegloticase plus methotrexate where available.

Summary of safety considerations for newer drugs :

- URAT1 inhibitors: Require renal monitoring, though lower stone risk than older uricosurics.
- Topiroxostat: Favorable renal profile, long-term CV safety under evaluation.
- Pegloticase + immunomodulators: Immunos-uppression risks must be weighed against benefits.
- Arhalofenate: Further safety data awaited.

Future Perspectives :

Precision medicine (HLA-B*58:01, transporter genetics) may tailor ULT choice. Combination therapy (XOI + URAT1 inhibitor) expected to dominate. Agents with metabolic benefits (SGLT2 inhibitors, GLP-1 agonists) may integrate gout and comorbidity management.

Conclusion

The landscape of gout management is shifting beyond traditional ULTs. New agents such as dotinurad, verinurad, topiroxostat, and optimized pegloticase regimens provide effective alternatives. Dual-action drugs and novel pathways promise further refinements. Cost, safety, and access remain challenges, but future management will emphasize precision medicine and rational combination therapy for durable remission.

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Section 14
Geriatrics

Chapter

44

Frailty in Geriatrics: Assessment and Intervention

Dr. Anuradha Deuri, Dr. Dinnur Ahmed

ABSTRACT

Frailty, a prevalent clinical syndrome in older adults, is characterized by increased vulnerability to stressors due to diminished physiological reserves. Unlike normal aging, frailty reflects reduced resilience, in which minor stressors can lead to adverse outcomes. It is defined as a multidimensional state of decreased strength, endurance, and physiological function, with sarcopenia playing a central role. Several validated tools exist for assessing frailty. Frailty has profound consequences on health outcomes, but it is not irreversible. Early detection and timely intervention can improve outcomes using a multidomain approach. Frailty requires a holistic, patient-centered, and multidisciplinary approach, making it a cornerstone of modern geriatric practice.

Introduction

Frailty is a common and important clinical syndrome in older adults, Frailty is defined as a state of increased vulnerability characterized by a decline in physiological reserve and function across multiple systems[1]. Sarcopenia, which is defined as a progressive and generalized loss of skeletal muscle mass and strength, plays a central role[1].Unlike normal aging, frailty reflects a state of decreased resilience where even minor stressors, such as infections or medication changes, can lead to significant adverse outcomes. It is associated with falls, hospitalization, disability, institutionalization, and mortality, making its recognition and management central to geriatric care.

Pathophysiology

Chronic low-grade inflammation, hormonal imbalance, nutritional deficiencies, and accumulation of comorbidities contribute to the frailty process. Unlike single disease entities, frailty arises from cumulative deficits across systems, reflecting the biological age rather than chronological age of the patient.

Frailty is a three-dimensional process involving changes at the cellular, physiological, and phenotypical levels.[1]

1. **Cellular Changes**
   - Altered mitochondrial function
   - Increased oxidative stress and DNA damage
   - Telomere shortening
   - Stem cell exhaustion
2. **Physiologic Alterations**
   - Chronic inflammation
   - Cell mediator dysfunction (e.g., reduced nitric oxide production by endothelium)
   - Sarcopenia
   - Energy imbalance

Fried and colleagues described frailty as a vicious cycle of reduced energetics and physiologic reserve, where the mechanisms of decline overlap with the diagnostic features of the syndrome.

3. **Phenotypical Manifestations**
   - Overall decline in physical function
   - Cognitive impairment

Assessment of Frailty

Frailty assessment is central in geriatric medicine because early identification allows targeted interventions to prevent adverse outcomes. Several validated models and tools are available:

Identifying Frailty

Key Frailty Syndromes

- Instability / Falls
- Immobility / Reduced Mobility
- Incontinence
- Delirium
- Increased susceptibility to medication side effects.

Frailty Assessment Tools

- Fried frailty index
- RockwoodFrailty index
- Clinical frail scale
- Edmonton Frail scale
- PRISMA-7 Questionnaire
- Timed Up and Go (TUG) Test

1. Fried's Frailty Phenotype (Physical Model)[2]

Frailty is defined as a clinical syndrome characterized by the presence of at least three of the following:

1. Unintentional weight loss (>4.5 kg or >5% body weight/year)
2. Self-reported exhaustion
3. Weakness (low grip strength, adjusted for sex and BMI)
4. Slowness (slow gait speed, adjusted for sex and height)
5. Low physical activity

Strengths: Simple, well-validated, and widely used in research.

Limitations: Focuses only on physical aspects and may miss cognitive/social dimensions.

2. Rockwood's Frailty Index (Cumulative Deficit Model)[3]

- Developed by Rockwood and Mitnitski (2007).
- Frailty results from accumulated health deficits (symptoms, comorbidities, and functional impairments).
- FI = (number of deficits present) ÷ (total number assessed, usually 30–70).
- Example: If 15 out of 50 deficits are present ? FI

= 0.30 ? frail.

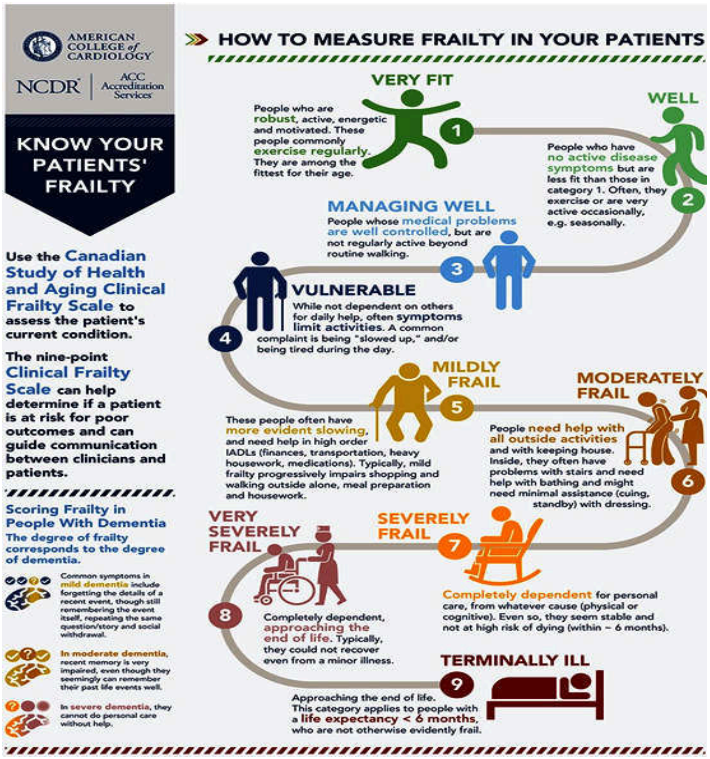
- Cut-off: FI =0.25 = frailty.

Strengths: Holistic and accounts for multidimensional health decline.

Limitations: Time-consuming and requires comprehensive data collection.

3. Clinical Frailty Scale (CFS)[4]

Clinical Frailty Scale (CFS) is one of the most widely used and well-validated instruments. Developed from the Canadian Study of Health and Aging, The major advantages of the CFS are its validity, ease of use, and applicability in routine clinical settings. . It has been employed to predict outcomes in older adults hospitalized with acute illnesses , as well asin icu settings. Application of the CFS requires clinical judgment, making it susceptible to inter-observer variability.



4. Edmonton Frail Scale (EFS)[5]

The Edmonton Frail Scale (EFS) was developed by Rolfson et al. in 2006 and comprises 11 items covering 9 key dimensions of frailty, consistent with the domains assessed in the Comprehensive Geriatric Assessment (CGA). These dimensions include cognitive function, general health, functional independence, social support, nutrition, mood, continence, functional performance, and medication use. Cognitive status is evaluated using the Clock Drawing Test (CDT), while physical performance is measured by the Timed Up and Go (TUG) test. The scoring range for the EFS is 0 to 17, with higher scores reflecting greater frailty severity.

5. Simple Screening Tools

- Gait Speed Test: <0.8 m/s over 4 meters suggests frailty risk.
- PRISMA-7 Questionnaire: Seven yes/no questions; =3 suggests frailty.
- Timed Up and Go (TUG) test: >12 seconds indicates frailty/functional decline.

Clinical Consequences

Frailty has profound consequences on health outcomes. Frail individuals are at higher risk of falls, fractures, poor surgical recovery, medication side effects, and accelerated cognitive decline. Hospital stays tend to be longer, with increased rates of readmissions and institutionalization. Mortality rates are consistently higher compared to robust older adults.

Intervention Strategies

Frailty is not an irreversible state; rather, early detection and timely intervention can improve the

outcomes.The multidomain approach is the most effective.

1. **Exercise (Cornerstone Intervention)**
   - Exercise is the most consistently effective intervention, producing physiological benefits across multiple systems, including musculoskeletal, immune, and endocrine.
   - Resistance training: Increases muscle mass and strength (counteracts sarcopenia).
   - Balance and gait training: Reduces the risk of falls.
   - Aerobic activity: Improves cardiovascular endurance.

Structured exercise programs improve mobility, muscle strength, and reduce frailty scores.

2. **Nutrition**
   - Malnutrition and weight loss contribute to frailty, but evidence for nutritional interventions is limited
   - Protein intake: 1.2–1.5 g/kg/day is recommended for older adults with frailty.
   - Vitamin D supplementation (=800 IU/day) reduces the risk of falls and fractures.
   - Balanced nutrition with adequate protein, healthy fats such as omega 3 fatty acid,conjugated linoleic acid, fish oil, and supplementation of micronutrients with antioxidant properties such as Vitamin E, vitamin C, zinc, and selenium strengthens immunity in the elderly and helps slow down immunosenescence.[6]

3. **Medication Review (Deprescribing)**
   - Frail older adults are highly vulnerable to polypharmacy and drug side effects.
   - Careful medication review using the Beers and STOPP/START criteria helps minimize inappropriate prescribing, prevent omissions, and improve the safety and quality of geriatric care.
   - Drugs with symptom relief or clear mortality benefits should be prioritized.
   - Anticholinergics, sedatives, and unnecessary cardiovascular drugs should be avoided.[7]

4. **Comorbidity Management**

Healthy aging depends on early frailty detection and effective comorbidity management in elderly patients, along with proactive prevention and intervention strategies.

Hypertension: Blood pressure (BP) control is essential, but targets must balance benefits and risks (hypotension and falls).The HYVET and SPRINT trials showed that BP control reduces cardiovascular events in patients >80 years of age.In healthy older adults with a low fall risk, lower targets (<130 mmHg) may be beneficial.In frail elderly individuals with multiple comorbidities, a less strict target (<150 mmHg) is safer.

Diabetes: The American Diabetes Association 2025 guideline provide a 4Ms framework: Mentation, Medications, Mobility, and what Matters Most for age-friendly health.Older adults who are otherwise healthy with few coexisting chronic conditions can have adult glycemic goals of HbA1c < 7-7.5% and time in range 70%,avoid hypoglycemia, and individualize glycemic goals using the 4 Ms.

Cardiovascular disease: Reconsider invasive procedures; weigh benefits versus, risk, prefer medical management if their life expectancy is limited.

Osteoporosis: Nonsteroidal anti-inflammatory drugs should be used with caution after 65 years of age. Paracetamol can be used as an alternative for pain.In high-fracture-risk patients, vitamin D and calcium supplementation, fall prevention, and possibly bisphosphonates if life expectancy is > 1–2 years are prioritized.[8]

COPD/asthma: Simplify the inhaler regimen and avoid the use of excessive corticosteroids.

Chronic kidney disease: Avoid nephrotoxic drugs, dose adjustment, and dialysis decisions based on function and quality of life.

Cancer: Often prefer supportive or palliative over aggressive therapy.

5. Psychosocial Interventions

- Social engagement reduces isolation and depression.
- Cognitive stimulation therapy (CST) helps in frailty with cognitive decline.
- Therefore, screening for depression and anxiety is crucial.

6. Fall Prevention

- Home environment modifications (removal of loose rugs and installation of grab bars).
- Vision and hearing correction were also performed.
- Appropriate use of walking aids.
- Multifactorial fall-prevention programs reduce the risk of injuries.[9]

7. Vaccination

Although vaccines tend to be less effective in the elderly than in younger adults, their importance remains well established, particularly against pneumococcal pneumonia, tetanus, influenza,covid 19, varicella zoster.

8. Comprehensive Geriatric Assessment (CGA)(10)

- The gold standard in frailty management.
- CGA is a multidimensional, interdisciplinary diagnostic and treatment process designed to evaluate the medical, psychological, functional, and social capabilities of elderly individuals. Its goal is to create a coordinated and integrated plan for long-term management and follow-up.

Components of CGA

- **Medical:**
  - Detailed medical history, polypharmacy.
  - Nutritional status and medication reviews.
- **Functional:**
  - Activities of Daily Living (ADLs) and Instrumental ADLs (IADLs).
  - Mobility, fall risk, and rehabilitation needs.
- **Psychological:**
  - Cognition, memory, mood, and depression screening were performed.
- **Social:**
  - Living arrangements, family and caregiver support, finances, and social resources are also important factors.
  - Spiritual needs.

Who Should Receive CGA?

Elderly patients with =3 “red flags”

- Age >75 years.
- Dependence in ADLs/IADLs.

- Living alone.
- Falls, delirium, or confusion.
- Incontinence.
- =2 hospital admissions/year.
- "Failure to thrive" or poor overall health.

Components of CGA

1. **Medical:**
   - o Detailed medical history, Comorbid conditions and disease severity, Problem list
   - o Nutritional status and medication reviews.
2. **Functional:**
   - o Activities of Daily Living (ADLs) and Instrumental ADLs (IADLs).
   - o Mobility, fall risk, and rehabilitation needs.
3. **Psychological:**
   - o Cognition, memory, mood, and depression screening were performed.
4. **Social:**
   - o Living arrangements, family and caregiver support, finances, and social resources are also important factors.
   - o Spiritual needs.

Conclusion

Frailty represents a critical syndrome in geriatrics, affecting up to 50% of those over 85 years of age. It is a dynamic, partly reversible process. Early identification using simple screening tools combined with multidomain interventions, such as exercise, nutrition, medication optimization, and psychosocial support, can mitigate its progression and improve outcomes. Effective management requires a holistic, patient-centered, and multidisciplinary approach, making frailty a cornerstone of modern geriatric practice.

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Chapter

45

Cognitive Health In Aging: Pharmacological and Non-Pharmacological Approaches

Dr. B. C. Kalita, Dr. Varsha Sahani

Definition of aging

Aging is the progressive, time-dependent decline in physiological integrity that leads to impaired function and increased vulnerability to death.

At the organismal level ageing is characterized by gradual loss of homeostatic reserve across multiple organ systems and accumulation of molecular and cellular damage, producing the clinical phenomena of frailty, multimorbidity and increased susceptibility to neurodegenerative disease.[1,5]

Common pillar of healthy aging

1. Physical Activity
2. Nutrition
3. Social Engagement
4. Cognitive Stimulation
5. Mental Well Being.

Epidemiology

The world population is ageing fast. In 2020 there were 1 billion people over 60 years of age. In 2030, 1.4 billion people will be more than 60 years of age (1/6th people in the world). In India, as per 2011 census, there were nearly 104 million people above 60 years of age and this number will grow to 230 million by 2036.

Loneliness & social isolation are key risk factors for mental health. 1/6th of the older experience abuse, 14% of adult = 70 years living with mental disorder (GHE 2021) & 6.8% of mental disorder patient = 70 years have disability.

Cognition

Cognitive health is defined as the ability to clearly think, learn, and remember, and to perform everyday activities, and it exists on a continuum from optimal function to severe impairment.

Cognitive aging refers to changes in cognitive functioning associated with advancing age. These range from normal age- related mild changes in processing speed, working memory and episodic memory to clinically significant syndromes such as mild cognitive impairment (MCI).

Maintaining cognitive health in older adults involves a healthy lifestyle (physical activity & good

sleep hygiene, balanced diet, social engagement, managing chronic conditions e.g., high BP, Type 2 DM, avoiding smoking, limiting alcohol intake). Mental health in aging is crucial with common condition including depression, anxiety, dementia.

Triggers

There are many triggers for cognitive dysfunction in elderly. Major life events & age related changes can contribute to psychological distress.

- Bereavement & loss (major triggers) specially spouses and friends
- Social isolation & loneliness
- Retirement – loss of purpose & routine
- Caregiver stress specially if elderly person is alone
- Ageism influence negative attitude
- Chronic illness/co-morbidities

Major causes of Cognitive decline in elderly

- Medications – poly pharmacy, tranquilizers, sedative, anticholinergics
- Blood chemistry – Na+, sugar
- Problem with hormones – estrogen, thyroid hormones
- Multivitamin deficiency – low level of B12, B6, folate
- Delirium, depression
- Substance abuse – smoking, alcoholism and other substances
- Injury – Head injury, fracture bone, CVA(stroke), etc.
- Neurodegenerative condition e.g. IPD, LBD, Alzheimer disease
- Toxins

Physiological changes with aging that affect Cognition

Aging produces widespread structural, cellular and biochemical changes that influence brain function both directly and indirectly via systemic pathways.[5]

1. Brain structure and connectivity: normal aging is associated with global brain volume loss(cortical thinning and ventricular enlargement) and regionally greater reductions in prefrontal cortex and hippocampus—areas critical for executive function and episodic memory. Ageing also alters white-matter integrity (microstructural decline, small vessel disease), reducing network efficiency. [1,5]
2. Neuronal and synaptic changes : there is loss of dendritic spines and synaptic density, alterations in neurotransmitter systems (reduced cholinergic and dopaminergic function), and impaired synaptic plasticity (long-term potentiation), which together impair learning and memory. [1,5]
3. Vascular and metabolic changes: age-related endothelial dysfunction, arterial stiffness and small vessel disease increase risk of cerebral hypoperfusion and white matter lesions. Systemic metabolic disorders (insulin resistance, diabetes) accentuate neurodegenerative processes and vascular cognitive impairment. [5,6]
4. Metabolic and body composition changes
   - Body composition: ↓ lean muscle mass, ↑ fat mass, especially visceral.
   - Basal metabolic rate: ↓ 1–2%perdecade.
   - Water content: ↓ totalbodywater↑riskof dehydration.

Common Age-Related Mental Or Cognitive Dysfunction

Normal age-associated cognitive change: mild

slowing of processing speed, reduced multitasking, minor declines in episodic memory retrieval; everyday independence preserved. [1,2]

Subjective Cognitive Decline (Scd): self-reported worsening cognition without objective impairment on testing; can precede mci.[2]

Mild Cognitive Impairment (MCI): objective cognitive decline greater than expected for age that does not substantially impair activities of daily living; amnestic mci often progresses to Alzheimer disease(ad)at higher rates.[1]

Major Neurocognitive Disorder / Dementia: significant cognitive decline in one or more domains (memory, executive function, language, visuospatial) sufficient to interfere with independence; common causes are alzheimer disease, vascular dementia, mixed alzheimer- vascular pathology, lewy body disease and fronto temporal degeneration. [1,5]

Neuropsychiatric symptoms(depression, apathy, anxiety, psychosis) commonly co-occur and complicate diagnosis and management. Vascular cognitive impairment— ranging from multi-infarct dementia to subcortical ischemic disease— is particularly relevant in india where vascular risk factors are common.[3,6]

Principles Of Treatment Of Cognitive Aging:

A) Prevention & promotion of cognitive dysfunction

Supporting healthy aging few of them are :

- Measures to reduce financial insecurities
- Safe & accessible housing and transport
- Social support for them & care givers
- Support for healthy behaviours
- Health & social programme to be targeted

Protection from ageism & abuse is critical, needs anti discriminatory policies & laws, educational intervention, intergeneration activities.

Management aims differ by stage (primary prevention, secondary prevention in high-risk or mci, symptomatic treatment for dementia, and tertiary care to maintain function and reduce caregiver burden). Few aymptoms to watch for cognitive aging by near one or caregivers e.g., Mood & energy changes, behavioural changes, cognitive & physical symptoms, hallucinations, memory, thinking process than normal aging.

Core principles of management include

1. Risk-factor modification and prevention
2. Early detection and diagnosis
3. Multi domain interventions
4. Symptomatic pharmacotherapy
5. Supportive and palliative care

Non-pharmacological approaches

Non-pharmacological interventions are foundational across prevention and disease-specific care. Evidence from randomized trials and systematic reviews supports a multimodal, individualized approach:

1. Physical exercise — aerobic and resistance training improve cardio respiratory fitness and are associated with better cognitive outcomes (executive function, attention, processing speed). Regular moderate exercise reduces dementia risk and can slow cognitive decline in MCI.[7,8]
2. Cognitive training and stimulation — structured cognitive training improves trained domains (memory, speed, reasoning) and may generalize to functional gains when combined with real-world activities. Group cognitive stimulation therapy can

improve cognition and quality of life in mild–moderate dementia. [7,9]

3. Social engagement and complex mental activities — maintaining social networks, education, volunteer work and mentally stimulating occupations is associated with reduced cognitive decline; social participation can potentiate cognitive training benefits. [8,9]
4. Nutrition and metabolic optimization — mediterranean-style diets, adequate protein, vitamin d and b-vitamin status (where deficiency is present) are associated with better cognitive outcomes; management of diabetes and dyslipidemia is crucial. Evidence for specific supplements is limited and inconsistent; nutritional interventions are most effective as part of a broader lifestyle package. [7]
5. Hearing Correction And Sleep Management — addressing sensory deficits (hearing aids), treatment of obstructive sleep apnea and improving sleep quality reduce cognitive load and may slow decline.[5,9]

Pharmacological Approaches

Pharmacologic management is disease- and symptom- specific. Approaches fall into:

(a) Symptomatic agents for established dementia, and

(b) disease-modifying therapies under investigation or approved for specific pathologies.

Symptomatic pharmacotherapy (approved, commonly used)

1. Cholinesterase inhibitors (donepezil, rivastigmine, galantamine): indicated for mild-to-moderate alzheimer disease; improve cognition and global function modestly and may stabilize behavioral symptoms for months to years. Adverse effects include gastrointestinal symptoms, bradycardia and syncope.[1,9]
2. Memantine: an NMDA receptor antagonist used in moderate-to-severe alzheimer disease; can be combined with a cholinesterase inhibitor and may improve function and behavior.[1]
3. Medications for vascular cognitive impairment: no specific licensed agents reverse vascular cognitive impairment; management emphasizes secondary prevention of vascular events (antihypertensives, antiplatelet therapy as indicated), statins where appropriate, glucose control and lifestyle measures.[1,5]
4. Treatment of neuropsychiatric symptoms: behavioral strategies are first-line; anti psychotics may be used cautiously for severe psychosis or agitation due to increased mortality risk and cerebrovascular adverse events. Antidepressants treat co morbid depression; sedative-hypnotics should generally be avoided.[1]

Conclusion

Cognitive ageing reflects the interplay between intrinsic brain ageing processes and modifiable systemic risk factors. Evidence supports a dual approach:

1. population and individual risk-factor modification and sustained multimodal non-pharmacological programs to prevent or slow decline.

2. targeted pharmacologic therapy for symptomatic relief and, for carefully selected patients, use of disease-modifying agents under specialist supervision. For India, the rising absolute burden of cognitive disorders requires urgent health-system planning that couples prevention (vascular risk control, education, lifestyle)with improved diagnostic and care pathways adapted to local resources. Continued research— especially implementation trials of scalable multimodal interventions and careful assessment of new disease-modifying therapies—remains essential.[1,9]

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Section 15
Miscellaneous

Chapter

46

Rare Diseases : Orphan Drugs & Genetic Therapies

Dr. Manoj Kumar Gogoi

ABSTRACT

Rare diseases, affecting a small percentage of the population, present significant challenges due to limited research, delayed diagnosis, and lack of effective treatments. This article explores the development and impact of orphan drugs & emerging genetic therapies as pivotal solutions in addressing these conditions. Orphan drugs incentivized through regulatory frameworks like the Orphan Drug's Act, have accelerated treatment availability for numerous rare diseases. However, high development costs and pricing remains barriers. The article highlights breakthroughs in genetic therapies, including gene editing and replacement techniques, which offer curative potential for previously untreatable disorders such as spinal muscular atrophy and certain inherited retinal diseases. Case studies demonstrate the transformative impact of these therapies on patient outcomes. Key findings emphasize the somemay presentin childisease communities. The article concludes by advocating for sustained investments in research and streamlined regulatory pathways to foster future advancements.

Introduction

Rare diseasesrepresent aheterogeneous groupof conditionsthat collectivelyaffect millionsof people worldwide, despite theirindividual rarity. By definition, a raredisease isone thataffects asmall percentageof the population. The thresholdvaries by region: In theUnited States, itrefers toconditions affectingfewer than200,000 people, while inthe EuropeanUnion itapplies tothose witha prevalenceof lessthan 1in 2,000 individuals. Despite theirrelative infrequency, more than7,000 rarediseases havebeen identified, and togetherthey affectover 400million people globally.

The majorityof rarediseases are chronic, progressive, degenerative, and frequently life-threatening. Importantly, up to 80% ofrare diseasesare thoughtto havea geneticorigin, oftenmanifesting earlyin life,thoughsomemay presentin adulthood.The lackof knowledge, diagnostic challenges, and therapeuticlimitations createimmense medical, social, and economicburdens for patients, families, and

healthcare systems.

Over thepast three decades, regulatory, scientific, and therapeuticinnovations havetransformed thelandscape forrare disease management. The adventof orphandrug legislationand advancesin geneticand molecularmedicine haveoffered new hope. This manuscriptexplores thelandscape oforphan drugs, genetic therapies, challenges, and futureperspectives inrare disease care.

Epidemiology and Burden of Rare Diseases

Although individually rare, collectively raredisease posea significantglobal health issue:

Prevalence: 3.5 – 5.9% of the global population.
Onset: Around 50 – 70% manifestin childhood.
Mortality and Morbidity: Approximately 30% of children withrare diseasesdie beforethe ageof 5.

SOCIOECONOMIC IMPACT: Patients oftenundergo a "diagnosticodyssey" lasting years, with repeated consultations, misdiagnoses, and financial burden.

The rarityof theseconditions posesmajor challenges: small patientpopulations limitclinical trial feasibility, commercial incentivesfor drugdevelopment are low, and manydiseases lacksufficient scientific understanding.

ORPHAN DRUGS: Concept and Legislation.
Definition: " Orphan drugs"are medicinalproducts developedspecially to diagnose, prevent, or treatrare diseases. The termreflects theidea thatsuch drugswere once "orphans" of thepharmaceutical industry, as companieshad littlefinancial incentiveto investin them.

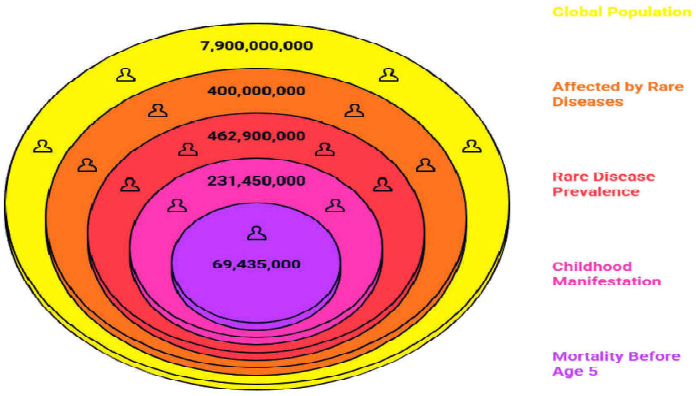
Regulatory Milestones

United StatesOrphan Drug Act (1983) provided financialincentives includingtax credits, research grants, andseven yearsof market exclusivity. It alsocatalyzed growthin raredisease drug development. European UnionOrphan Regulation (2000), offered 10years ofmarket exclusivity, fee reductions, and protocol assistance.

Japan (1993), Austria (1997), Canada (2019) enacted similarframeworks tostimulate orphandrug development.

IMPACT: Before theOrphan Drug Act (1993), fewer than10 therapiesexisted forrare diseases. By 2023, more than600 orphandrugs hadbeen approvedin the U.S. and over200 inthe EU.

Many ofthese treatmentsaddress lysosom-alstorage disorders, rare cancers, neuromuscular diseases, and hematologic conditions.



Challenges Inorphan Drug Development:

- Scientific challenges.
- Limited naturalhistory data.
- Small patientcohorts hinderrandomised controlled trials.
- Heterogenity indisease phenotypeand progression.
- Economic challenges: High costof developmentand limitedmarket sizelead tovery highdrug prices. Average annualcost perpatient forsome therapiesexceeds USD 300,000.
- Ethical challenges: Equitable accesssin lowand middleincome countries. Secondly, balancing innovationincentives with affordability.

Genetic Therapiesin Rare Diseases

Genetic therapiesrepresent aparadigm shiftin medicine, movingfrom symptomsmanagement todisease modificationor even cure. Given thatmost rarediseases havegenetic origins, theseapproaches holdimmense promise.

Types Of genetic Therapies:

A. **Gene Replacement Therapy:** Introduction offunctional copiesof defective genes. Example: Onasemnogeneabeparvovec (Zolgensma) forspinal muscular atrophy (SMA).

B. **Gene Silencing/ RNA- based Therapies:** Use of ofoligonucleotides (ASO) or small interfering RNA (siRNA) toreduce harmfulgene expression. Example: Nusinersen(Spinraza) for SMA, Patisiranfor hereditarytransthyretin amyloidosis.

C. **Gene Editing:** CRISPR- Cas9 andrelated technologiesenable precisegenome modifications. Ongoing clinicaltrials forsickle celldisease and beta-thalassemia.

D. **Cell- based Gene Therapy:** Ex- vivo modificationof patient'scells followedby reinfusion. Example: CAR-T therapiesfor rarehematological malignancies.

E. **mRNA-n based Approaches:** Inspired by COVID-19 vaccines, mRNAtherapy holdspotential forrare metabolicand proteindeficiency disorders.

Success Stories

Spinal Muscular Atrophy(SMA), once fatalin earlychildhood, SMAoutcomes havedramatically improvedwith therapieslike nusinersen, onasemnogeneabeparvovec, andrisdiplam.

Inherited Retinal Diseases: Voretigene-neparvovec (Luxturna): the first FDA-approved invivo genetherapy for RPE65 mutationassociated retinal dystrophy.

Hemophilia : Gene therapytrials forfactor VIIIand IXdeficiency haveshown sustainedclotting factor production, reducing bleeding episodes.

Beta-Thalassemia andSickle Cell Disease: CRISPR – based exvivo editingof hematopoi-eticstem cells(e.g., exa-cel)shows curative potential.

Limitations And Risks: Safety concernslike riskof immunereactions, insertional mutagenesis, of- target effects.

Durability: Longevity oftherapeutic effectremains uncertainfor somegene therapies.

Accessibility and Cost

Treatment withZolgensma pricedat over USD 2 millionper dose. So, affordability remainsa global barrier.

Ethical Considerations: Germline editingremains controversialand equityconcerns intrial participationand drug availability.

Global Perspectives:

High – income countrieshave benefittedmost, with active regulatorysupport, rarедisease registries, andreimbursement mechanisms. Low andmiddle incomecountries facediagnostic gaps, lack of registries, and limitedaccess toexpensive orphan drugs. Global collaborationssuch as IRDIRC (InternationalRare DiseaseResearch Consortium) aimto accelerated-iagnosis andtherapy development.

Future Directions:

- Next generationgene editing: Base editingand primeediting for greater precision.
- Personalized orphan drugs: " N- of- 1 therapiestailored for ultra- rare conditions.
- Artificial intelligenceand big data.
- Improved raredisease diagnosis , patient stratification , and drug repurposing.
- Expanded newborn screening.
- Early detectionenabling timely intervention.
- Policy reforms.
- Balancing innovationincentives withaffordability andequitable access.

Conclusion

Rare diseases, once consideredneglected and untreatable, are increasingly at the forefront ofmedical innovation. Orphan drugpolicies havecatalyzed progress, leading tohundreds ofnew therapies. Genetic therapies, from gene replacement to CRISPR- based editing, offer thepossibility ofcuring previously intractable conditions. Despite remarkableadvances, challenges remain: high costs, limited accessibility, safety concerns, and theneed for long-term follow-up. Global cooperation, innovative financing, ethical frameworks, and technologicaladvances willbe crucial in ensuringthat thepromise oforphan drugsand genetictherapies translates into equitable carefor allpatients withrare diseases. The trajectoryof rare disease medicine illustratesa profound transformation – where once patientsfaced neglect and despair, they nowstand onthe cuspof therapeutic revolution

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Chapter

47

Telemedicine: Innovations in Remote Care Delivery

Dr. Md Jamil, Dr. Pradnya Patil

ABSTRACT

Telemedicine has revolutionized healthcare by enabling medical services to be delivered remotely through digital communication technologies. It bridges the gap between patients and healthcare providers, particularly in resource-limited regions. India's eSanjeevani platform, the world's largest telemedicine network, operates on provider-to-provider and patient-to-provider models, enhancing accessibility and efficiency within primary care. Integration of point-of-care testing has expanded telemedicine's diagnostic capacity, while the Hospital at Home model allows multidisciplinary teams to manage patients remotely, reducing hospital load and costs. Telemedicine has led reduction in non-urgent hospital visits, improving convenience and chronic disease management. However, limitations include the inability to perform physical examinations, challenges in patient rapport, and data security concerns. Despite these, telemedicine continues to evolve with artificial intelligence anddigital integration, establishing itself as a cornerstone of patient-centered healthcare.

Keywords: Telemedicine, eSanjeevani, Point-of-care testing, Hospital at Home, Digital health

Introduction

The word Telemedicine originates from the Greek word "tele" meaning "distant" or "far away", and the Latin word "mederi" meaning "to heal".[1] Hence, Telemedicine literally translates to healing from a distance. It is an evolving field in healthcare that utilizes communication technologies to deliver medical services remotely.

Telemedicine has emerged as a vital bridge between healthcare providers and patients, particularly in areas with limited medical infrastructure. In resource-poor countries, the scarcity of specialists and diagnostic facilities often limits access to adequate care. Conversely, in the high-resource nations, time constraints and busy lifestyles reduce opportunities for in-person consultations. Telemedicine effectively addresses both these challenges by providing convenient, accessible, and efficient healthcare solutions.

eSanjeevani - National Telemedicine Service

It is the world's largest documented telemedicine service in the primary healthcare under the Ministry of Health and Family Welfare (MoHFW), Government of India.[2]

eSanjeevani is a cloud-based platform that is implemented in two variants:

1. Healthcare Provider-to-Healthcare Provider telemedicine platform: this variant provides assisted teleconsultations for patients who walk into Ayushman Arogya Mandirs (earlier called Health & Wellness Centers). Community Health officers in Ayushman Arogya Mandirs facilitate the teleconsultation for patients who are connected to the doctors and specialists in hubs established in secondary/tertiary level health facilities and medical colleges. This variant is based on a Hub-and-Spoke model.
2. Patient to Healthcare Provider telemedicine platform: it empowers citizens to access health services in the confines of their homes through smartphones or laptops, etc.

Telemedicine Practice Guidelines

These guidelines, released in March 2020, give practical advice to doctors for the effective and safe use of Telemedicine for patient care.[3]

Integration of PoCT with Telemedicine

A range of point-of-care testing (PoCT) and rapid diagnostic tests (RDTs) has been increasingly used with Telemedicine. It not only expands the scope of Telemedicine to include diagnostic aspects of patient care butalso helps in continuous evaluation of the patient from a distant location. Results from these devices are captured wirelessly and transmitted directly to the patient's caregiver. These results are analyzed, and the treating doctor can modify the treatment accordingly. Standard devices integrated in Telemedicine are a multipara monitor, a glucose monitoring device, etc.[4,5]

Hospital at Home (HaH)

Telemedicine-controlled Hospital at Home (HaH) services are an alternative option for hospital care in resource-limited situations, where there is a scarcity of experienced physicians and a limited number of hospital beds.Patient can be treated at home by a multidisciplinary team through Telemedicine. HaH helps to reduce the hospital burden, unnecessary traveling costs and time, and also protects the patient from hospital-associated infections.Several publications reviewed the potential of assimilating AI into different telehealth domains: tele-diagnosis, tele-interactions, and tele-monitoring that can be utilized in Hospital at Home care.[6,7]

Advantages of Telemedicine

Telemedicine significantly reduces the cost of medical care incurred by transportation and loss of daily earnings. It decreases patient travel and minimizes long waiting periods at hospitals.

Telemedicine has resulted in a reduction in non-urgent hospital visits and a decrease in outpatient follow-up consultations. This not only enhances patient convenience but also enables the healthcare system to allocate more resources to emergency and critical care services.

Telemedicine is particularly beneficial in chronic disease management. Conditions such as diabetes

mellitus and hypertension require regular monitoring and follow-up, but patients often become noncompliant due to frequent hospital visits. Through Telemedicine, clinicians can review reports, adjust medications, and encourage treatment adherence, thereby preventing complications such as end-organ damage.

Limitations

Despite its growing significance, Telemedicine cannot replace direct physical examination, which remains crucial for accurate diagnosis and comprehensive patient care. Building doctor-patient rapport and trust can be challenging in Telemedicine consultations. Other limitations include technical constraints, data privacy concerns, and a lack of standardized clinical protocols for remote assessment. Addressing this issue is essential for the safe and effective expansion of telemedicine services.

Conclusion

Telemedicine, meaning "healing from a distance", represents a significant advancement in healthcare delivery by merging technology with medicine. Its proven role in reducing hospital visits, improving chronic disease follow-up, and enhancing access to expert consultation underscores its transformative potential. As the world continues to adopt artificial intelligence and digital innovations, overcoming the current limitations of Telemedicine will be vital for realizing the full potential as a cornerstone of modern, patient-centered healthcare.

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Chapter

48

Medical Ethics: Navigating AI and Big Data in Healthcare

Dr. A. Swami

ABSTRACT

The advent of artificial intelligence has opened an exciting field in health care. AI is increasingly being incorporated into diagnosis of different diseases, development of treatment protocols and drug development. AI development requires analysis of a huge amount of data from all aspects of patient care and the development of computer models which are subsequently put into practice.However, like all new technologies, the use of AI has presented an ethical dilemma thereby putting AI-based health care in the grey zone of medical ethics. There is a real possibility of infringement on the rights of patients when AI is used, as machine learning uses patient data to develop algorithms.There is also a possibility of physicians becoming increasingly dependent on AI in health care, thereby depriving the patient of the human touch in treatment. Also, questions have been raised on the culpability of the doctor or the companies developing AI in the unfortunate case of adverse events.

Introduction

Medical ethics is an applied branch of ethics which guides the clinical practice and research in medical science. It is based on four pillars – beneficence, non-maleficence, autonomy and justice. Though medical ethics is not a substitute for law, in real life medical ethics and law are considered in the same breath.

All doctors are sworn to follow medical ethics in the practice of medicine. But the advent of AI has presented a clinical conundrum – follow medical ethics and compromise on a part of patient confidentiality or give the patient a chance for better diagnosis, patient risk identification and treatment.

How does AI work?

In the simplest form, artificial intelligence refers to the development of computer systems and algorithms for tasks that typically require human intelligence. AI encompasses machine learning, deep learning and natural process learning.

Each of the processes requires processing of a huge amount of data to develop presentation-level essentials for adaptable accomplishments. The data is generated from millions of patient records – which comprise history, examination findings, tests done on the patient to diagnose the disease, treatment provided and prognosis. These data are sourced from electronic health records, medical imaging, genomic and wearable data and clinical trial registries.

The first prediction of AI was in science fiction movies a few decades back, of which there are multitudes. While AI may still not take over the way science fiction had predicted, there are a vast array of concerns [1,3] while incorporating AI in health care, especially ethical issues, and this has to be addressed while we incorporate artificial intelligence in our lives.

Case example: Dr Grok

In 2024, SpaceX founder Elon Musk called for users of his social media platform X (formerly Twitter) to upload medical scans like CT scans, X-rays and MRI scans[2, 5] to the AI chatbot Grok for analysis. He claimed that the images would be used to train Grok, which apparently already had a good predictive accuracy. The internet obliged and flooded Grok with sensitive medical images, which raised alarms about data privacy, misdiagnosis and potential misuse[3].

Benefits of AI in Healthcare

The integration of AI with healthcare is inevitable, and it has excited as well as terrified stakeholders. For patients, AI promises better accessibility, increased accuracy, easier follow-up and reduced waiting periods [5]. For healthcare workers, it provides comprehensive diagnostic tools, reduces administrative workload and can even predict patient outcomes [1]. Medical research also gets a share in the pie: collaboration with AI will lead to better understanding of disease and aid in drug development.

The application of healthcare AI systems can be seen in various forms. In diagnostics, AI-based image recognition algorithms are proving to be extremely valuable in assessing tissue specimens and radiological scans [6]. These systems use specific algorithms and can detect malignancies like prostate cancer through radiology-pathology integration [6,7]. Results are reproducible and not subject to interobserver variation, and the accuracy rates are likely to increase as research continues. Such systems decrease lag time, augment clinical decision-making and provide a better roadmap for management.AI-integrated robotic surgeries are being tested, combining the precision of robots with intraoperative insights [7] and incorporating augmented reality 3D model (AR3D) to excise tissue specimens in the surgical field [7]. The latest models of AI can even predict with a fair degree of accuracy the nature of neoplasms discovered during endoscopic procedures.

Ethical challenges

However, all these benefits are not without their fair share of issues. While some rejoice at the advent and incorporation of AI into healthcare, others raise ethical questions as the rapid development of AI has overtaken the framing of regulations about its use. AI developers like Google and Microsoft are proudly predicting the replacement of human healthcare workers, but the bigger concern at hand is the compromise of the

four fundamentals of medical ethics, viz., autonomy, beneficence, non-maleficence, and justice [3,8].

Application of AI in health care requires processing of humongous data. For proper application the data need to be wide-based, encompassing as many parameters as possible. However, as humans have multiple genotypic and phenotypic variabilities, the data developed in a given region may not be applicable to other population groups. The application of AI can therefore give erroneous results and thereby faulty clinical decision-making.

Autonomy and informed consent

In the process of medical care of patients, multiple steps are involved, including interaction with the physician/doctor, explanation of the nature of the ailments to the patient/attendants and subsequent informed consent by the patient about the choice of therapy. In the present world, the patient has full autonomy to accept or refuse a treatment after being given a comprehensive review of the process, its potential complications and its expected outcome.

If AI is incorporated in health care, the decisions could be guided by artificial intelligence models like clinical decision support systems. CDSS can provide personal treatment recommendations, a choice of medicines and therapeutic procedures, risk prediction and outcome forecasting. The application of CDSS to life-and-death scenarios, as in healthcare, is mired with ethical concerns due to the 'black box problem' when it is unclear as to how exactly the system derives its results [3]. With AI systems, human elements such as faith, trust and confidence are left out of the equation, which are major proponents of the patient's decision, and hence obtaining informed consent becomes a challenge. The approach of different communities to life-and-death situations is variable owing to social and religious beliefs, financial issues, etc. AI application in decision-making may not consider the issues and thereby leave behind a lacuna.

Misdiagnosis and reliability

Experts also opine that AI health bots will lead to a rise in misdiagnosis and self-diagnosis that will impact the overburdened healthcare system negatively[9]. Like, in the case of Grok: Musk's mighty claims were proven untrue when the bot failed to diagnose fractures and issued misdiagnoses of brain tumours [2]. In the Indian scenario, such an experimental tool is little better than quacks that run amok with traditional diagnoses and remedies and further delay access to actual treatment[3]. There is no doubt that AI has great potential in diagnostics, but experts like Dr Suchi Saria, director of the machine learning and healthcare lab at John Hopkins, advise caution as the technology is still in the nascent stage[10].

Data privacy and ownership

Musk's experiment with Grok also resulted in the resurfacing of an old concern: data privacy and ownership [3]. AI is also being integrated into electronic health record systems for the purpose of making those more efficient [1, 2]. In the absence of strict regulations concerning AI, it is unclear who actually owns the sensitive information which is stored in these systems [11-13]. Enthusiastic users are happy to participate in

training AI, but such altruism is not safeguarded by privacy laws like HIPAA in the USA [11] and GDPR in the EU [12], which explicitly forbid other digital health services from sharing or profiting from patient information. In India, the Digital Personal Data Protection Act was passed in 2023 to regulate the handling and processing of digital information [13], but implementation is still in the works [3].

Black boxes

As AI is developed at an exponential pace, the deep learning models are often considered black boxes, i.e., their logic is opaque and difficult for humans to understand. The patient and the healthcare professionals need to understand the logic behind the decision made by AI, which may not be available in every AI algorithm.

For the rich, by the rich?

Accessibility was once considered as one of the great benefits AI would bring into the healthcare forte[14]. The idea was that AI would enable low-resource countries to access advanced medical care, but of late, experts have become sceptical [14]. AI models are extremely expensive in the initial phase due to high research and development. This creates the possibility of AI-based systems being accessible only to the rich and mighty – something of an ethical concern.

Accountability and Liability

While most of the ethical concerns explored in this piece can be settled by training and framing of legislation, the questions of accountability and liability pose the biggest challenges to AI incorporation [15]. It is inevitable now that AI shall be used by medical professionals across all disciplines, and therefore, addressing this concern is of paramount importance [15]. A number of questions arise in this regard, like:

- Who takes the blame when a guidance system predicts a wrong outcome – the developer or the doctor/hospital?
- In a malpractice suit, is the clinician or the AI developer the primary defendant?
- Can a medical practitioner be held liable for an error made by an artificial intelligence system?

Under common law, acts done in good faith with informed consent protect doctors from liability [15]. When AI enters this delicate equation and guides medical decisions, the burden of liability will shift. There is always a real possibility of AI bias in the diagnosis and treatment of disease, and the human touch, which is so vital in the healing process, may go missing[15].

Drug Development and Bioterrorism

AI is used extensively in the development of new drugs, which is normally a time-consuming process and is prohibitively expensive. AI models used for drug development use pre-generated information on different population groups, genomics, previous drug development and clinical trials. However, if the data is not exhaustive, there is always a possibility that the algorithmic bias may be exacerbated, leading to unforeseen effects on certain population groups, which can be an ethical concern. The same AI-generated tools to develop drugs in the hands of unscrupulous people may help in the development of drugs/compounds inimical to human health and can be a potential narcoterrorism and bioterrorism risk.

Conclusion

As artificial intelligence advances at lightning pace, promising revolutionary changes in healthcare and medicine, the ethical challenges raised deserve a long hard look [3]. Framing stringent rules and protocols concerning the application of these systems is the need of the hour [15]. Transparency, autonomy and accountability have to be guaranteed before AI is integrated as a partner in evidence-based medicine[3,8]. With the collaboration of developers, medical professionals, legal experts and legislators, AI can be a valuable asset without compromising medical ethics and patient rights [3].

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Chapter

49

Listening, Understanding, Healing: The Unassessed Core of the Post-Graduate Practical Examination

Dr. Ayondyuti Bora, Dr. Sanjeeb Kakati, Dr. Eric Livingston

Introduction

Man, a social being, has always lived in perpetual struggle with disease — his oldest and most enduring adversary. Whilst medical science has advanced by leaps and bounds and artificial intelligence continues to revolutionise healthcare; the doctor-patient relationship has paradoxically become more strained.[1] The growing rift between doctors and patients in today's world can be attributed to several factors, with a significant one being the gap in communication. Doctors often overrate their own communication abilities, perceiving themselves as more effective communicators than their patients actually experience.[2]

Why are Communication Skills Necessary?

Any physician who has had to deliver bad news, confront deeply held beliefs, or de-escalate heightened emotions will recognise the critical role communication plays in such moments — often determining whether the outcome is constructive or detrimental.[2] As with many people-centred professions, communication skills are fundamental to the practice of medicine. They form the backbone of numerous critical aspects of patient care—including initial consultations, exploration of symptoms, counselling, discussion of treatment options and their complications, follow-up advice, management of sensitive situations such as bereavement or medical errors, and the effective obtaining of informed consent with clear explanation of complex procedures and associated risks.[2]

Poor communication, both among healthcare professionals and between practitioners and patientscan lead to serious misunderstandings that contribute to diagnostic errors, inappropriate or delayed treatments, compromised patient safety, and even legal repercussions such as malpractice claims.[1] For example, a report by National Academies of Sciences, Engineering, and Medicine highlighted issues in diagnosis owing to communication deficits.[3] Both the Francis Report[4] and the Ockenden Report[5] cited a lack of effective communication as a contributory factor in avoidable patient harm.

Communication in high-stakes examinations

There was a growing realisation in Western

nations of the need to formally assess communication skills in medical training to address and reduce shortcomings arising from ineffective doctor–patient communication. A good example is the MRCP PACES (Practical Assessment of Clinical Examination Skills), where communication has long been recognised as a central pillar of professional competency, evaluated alongside clinical knowledge and examination technique. In 2001, the UK Royal Colleges formally introduced Communication Station, specifically dedicated to evaluating communication and professional behaviour.[6] By 2023, this station evolved to include two separate 10-minute scenarios, each involving a surrogate who responds authentically to the candidate's communication and professional behaviour. During the 10-minute encounter, examiners observe without interruption and subsequently assess the candidate's performance.[7]

The scenarios are not designed to assess detailed medical knowledge of the condition under discussion, but rather the doctor's ability to interact and communicate effectively with the patient. While an understanding of the relevant ethical and legal principles remains important, the true essence of the encounter lies in conducting the conversation in a way that is attuned to the patient's concerns—demonstrating empathy, sensitivity, and compassion where appropriate.[8] During the assessment, examiners closely observe how the doctor communicates, looking for evidence of the core principles of effective clinical interaction—clarity, empathy, respect, and professionalism. These qualities distinguish a competent clinician, particularly when engaging in counselling, managing emotionally charged situations, or delivering difficult news with understanding and composure.

The communication scenarios used in the PACES examination undergo a rigorous and carefully structured development process to ensure fairness, realism, and educational value. They are initially created by a Scenario Writing Group, composed of physicians from different specialties who draw on their clinical experience to design realistic situations reflecting common communication challenges faced in practice. These draft scenarios are then discussed within the group to refine content, objectives, and tone. Once approved, the scenarios are passed on to the Scenario Editorial Committee, where each one is independently reviewed and edited by two committee members before being discussed collectively in meetings held three times a year. This iterative process ensures that every scenario is clear, balanced, and feasible to complete within the time constraints of the exam. Importantly, once a scenario is used in a live examination, examiners provide feedback on its clarity, timing, and overall effectiveness. Based on this feedback, scenarios are revised and refined for future use.[9]

In PACES, communication is not merely confined to a single station (or stations, since PACES23); it is also assessed as a skill during the long clinical scenarios, evaluated individually. This integration of communication assessment throughout the examination makes PACES particularly challenging and underscores the importance of mastering both clinical and interpersonal competencies. Examiners evaluate seven key skills: physical examination, identifying physical signs, clinical communication, formulating differential diagnoses, clinical judgement, managing patients' concerns, and maintaining patient welfare.[7]

"Clinical judgement" is assessed through interactions with the patient as well as responses to the examiner, reflecting the candidate's ability to reason, make appropriate decisions under observation, and communicate those decisions clearly to the patient in an understandable manner, rather than being limited to a question-and-answer session with the examiner. "Managing patients' concerns" particularly showcases the doctor's ability to understand the patient's perspective, explain the management plan clearly, and avoid medical jargon, thereby promoting comprehension, trust, and shared decision-making. "Maintaining patient welfare" is closely linked to communication; rude or insensitive interaction can be detrimental, negatively affecting the candidate's score. Consequently, even within the long clinical scenario, the candidate must efficiently combine all these skills—demonstrating technical proficiency, effective communication, emotional responsiveness, and patient-centred care under time pressure.

Communication Skills in India: Current Status and the Gap in Post-Graduate Assessment

In India, the AETCOM (Attitude, Ethics and Communication) programme (introduced by the National Medical Commission) began in 2018 as part of the undergraduate (MBBS) curriculum to inculcate communication, ethics and attitude competencies.10 Studies evaluating the AETCOM modules have shown significant improvement in under-graduate students' communication competencies. For example, in Maharashtra, an interventional study showed that third-year MBBS students improved their scores substantially after the AETCOM communication skills training module.[11] Likewise, pilot studies in Gujarat showed marked improvement in communication skills.12In line with the revised Competency-Based Medical Education (CBME) guidelines, the NMC's 2024 curriculum emphasises the longitudinal AETCOM programme and identifies effective and empathetic communication as a critical competency[13] ; however, despite these advances at the undergraduate level, postgraduate practical examinations in India still lack a formal, structured, station-based assessment of communication skills similar to the MRCP-PACES model.

As medical graduates transition into the role of consultants or senior registrars, the responsibility for communication, team-leadership, breaking bad news, obtaining consent, and managing complex patient-family-dynamics increases significantly — yet the examination system has not kept pace in assessing these competencies formally. This gap suggests a disconnect: while training may embed communication modules, the postgraduate credentialing process remains essentially knowledge and skill-centred, without the structured assessment of communication behaviour, counselling or professional interaction.

Hindrances in Starting Communication Scenarios in Post Graduate Final Examinations in India

Creating realistic and standardized communication scenarios for examinations is also challenging due to the diverse structure of healthcare in India. The expectations, doctor–patient dynamics, and available resources differ greatly between government hospitals and private sectors. As a result, designing

communication cases that reflect the full range of clinical realities while maintaining fairness and consistency across centers becomes a significant difficulty.

In the context of postgraduate final examinations in India, initiating Communication scenario can pose unique challenges. A doctor may need to function almost like a polyglot, switching between several languages or dialects to ensure mutual understanding.

India's vast linguistic and cultural diversity often makes the opening phase of doctor–patient interaction complex.[14] Cultural variations influence patients' beliefs about illness, attitudes toward doctors, and patterns of expressing distress. What is perceived as polite or empathetic communication in one region may appear abrupt or overly formal in another, making it difficult for candidates to strike the right tone under examination pressure. A simple yet telling example lies in the process of introduction and greeting: in many Western contexts, it is customary and respectful for doctors to seek permission and then addressa patient by their first name, whereas in India, such practice may be considered inappropriate or disrespectful. In real life, some patients may find being addressed as "Sir/Madam," "Uncle/Aunty," by surnames, "Mr./Mrs.," or terms such as "Mahoday/Mahodaya" surprising, inappropriate, or even offensive, while others may accept it; however, addressing a patient by their first name is generally not considered appropriate in India, and there is no fixed way to approach this issue.

A few challenges also arise from legal considerations, which vary across different states, and their medico-legal application is often not straightforward. For example, although the guidelines[15,16] regarding DNACPR (Do Not Attempt Cardiopulmonary Resuscitation) have been laid, their implementation is inconsistent and not well followed across India. There is a need for uniform laws and standardized protocols nationwide to guide clinical practice in such scenarios, ensuring legal clarity and protecting both patients and clinicians.

Bridging the Gap: Proposed Approach for Post-Graduate Exams

Given the evidence, there is a compelling,yet challenging need for formally integrating communication-skills assessment into postgraduate practical examinations. A proposed model could include:

- Introducing at least one dedicated station in the practical exam, analogous to communication station in MRCP-PACES, where candidates engage with a simulated patient for a set time (e.g., 10 minutes) to assess communication and professionalism.
- These scenarios should intentionally exclude in-depth assessment of detailed medical knowledge related to the condition under discussion; instead they should assess the candidate's ability to build rapport, extract the patient's concerns, explain management options in understandable language, deal with emotions (e.g., anxiety, anger), and check for understanding.
- Communication skills should also be assessed during long clinical cases, allowing candidates to demonstrate effective interaction while performing history-taking, physical examination, differential diagnosis, and patient management (including managing concerns of the patient), thereby reflecting real-life clinicalpractice more accurately.

- Examiners should observe candidates and use structured checklists or validated scales—such as the Kalamazoo Consensus[17] (in Communication scenarios) (Fig. 1) or the Calgary-Cambridge Framework[18] (in Long Clinical Scenarios) (Fig. 2), while adapting them to reflect relevant Indian perspectives.
- Formative and summative assessment of communication skills should be integrated throughout postgraduate training, not limited to the final examination, promoting progressive development and reflection.
- Incorporate feedback mechanisms post-station so that trainees receive actionable insights into their communication performance, thereby fulfilling a developmental role rather than purely an examination hurdle.
- Institutions should embed communication-skills training into the postgraduate curriculum through workshops, simulated patient interactions, role-plays, and reflective exercises, aligned with assessment criteria to reinforce both learning and competency demonstration.

Faculty and Examiner training

Since the AETCOM framework is already established across undergraduate medical education in India10, extending these principles to postgraduate practical examinations should not pose a major challenge. The existing structure provides a strong foundation upon which communication skills training, evaluation tools, and standardized assessment stations can be readily developed and implemented.

Appendix

Kalamazoo Consensus Framework for Good Communication

Building a Relationship
Opening the Discussion
Gathering Information
Understanding the Patient's Perspective
Sharing Information
Reaching an Agreement
Providing Closure

Figure – 1. Adapted from Essential Elements of Communication in Medical Encounters: The Kalamazoo Consensus Statement[18]

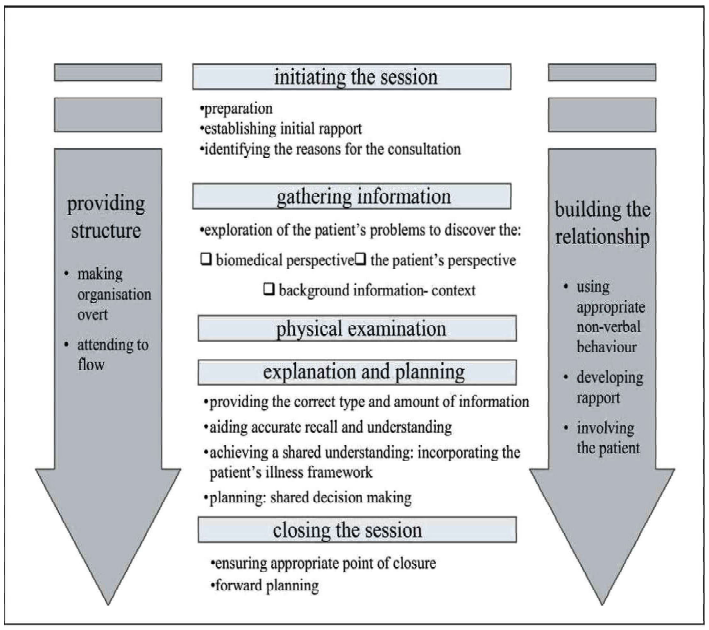

Figure 2 : Calgary-Cambridge Framework19

Conclusion

Being an effective communicator in medicine is not optional — it is central to healing. In postgraduate training and assessment, the absence of deliberate evaluation of communication skills represents a missed opportunity. While the undergraduate AETCOM curriculum in India has advanced significantly, postgraduate practical

examinations must now evolve to reflect the reality that clinical competence encompasses not only what a doctor knows or does, but also how the doctor engages, listens, explains, and supports.Embedding structured communication assessment into postgraduate examinations—involving dedicated stations, integration into clinical scenarios, and culturally as well as legally appropriate guidelinesis an arduous task, no doubt. But if implemented, it will, in turn, better prepare future consultants not only to treat disease but also to heal human beings.

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