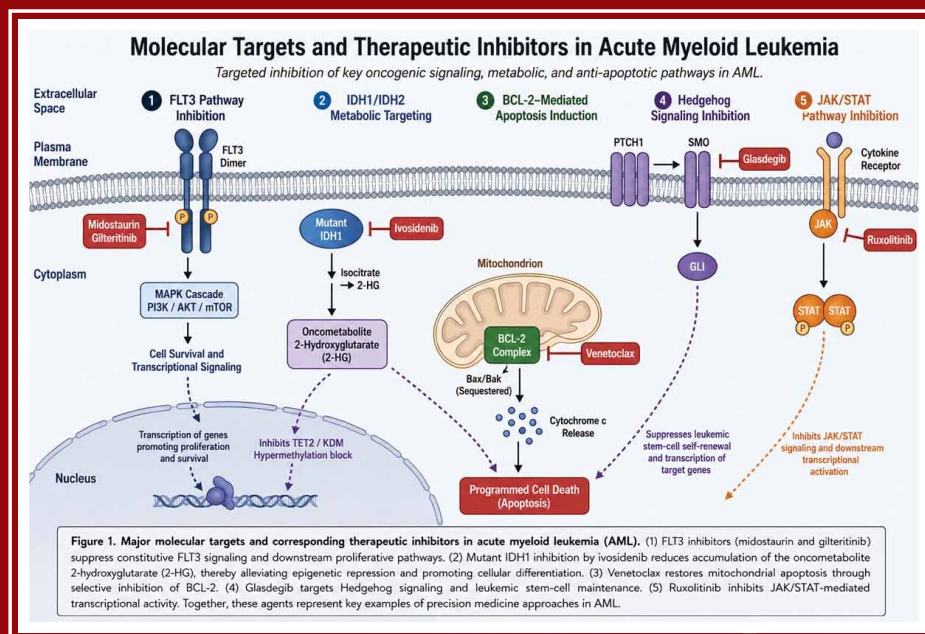




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Major molecular targets and corresponding therapeutic inhibitors in acute myeloid leukemia

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ACHAIKI IATRIKI

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Dear colleagues,

In the current issue, the editorial by Mpakogiannis highlights the spectrum of extraintestinal manifestations of *Clostridioides difficile* infection, raises awareness of their underlying mechanisms and clinical presentations, and emphasizes the importance of early recognition and appropriate management of these uncommon but potentially serious complications.

The current issue features five review articles. The first review by Eleftheriadis et al. summarizes the current understanding of the pathophysiology and diagnosis of heart failure with preserved ejection fraction and provides an overview of contemporary and emerging treatment strategies for this condition. The review by Tsoupra Stamatia critically reviews the current evidence on the clinical presentation, diagnosis, and management of acute and chronic pancreatitis, highlighting advances in risk stratification and multidisciplinary patient care. The review by Perdiki et al. summarizes recent advances in the diagnosis, classification, and management of chronic kidney disease, with particular emphasis on contemporary pharmacological strategies, including RAAS

inhibitors, SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and GLP-1 receptor agonists, and their role in reducing kidney disease progression and cardiovascular risk. The review by Tsamesidis et al. summarizes current clinical and preclinical advances in myeloid neoplasms, focusing on risk stratification, emerging therapies, treatment resistance, and translational strategies. Finally, the review by Efthymiou et al. provides a comprehensive overview of pleural effusion, focusing on its pathophysiology, clinical presentation, diagnostic evaluation, and therapeutic management, with particular emphasis on distinguishing transudative from exudative effusions and on the diagnosis and management of chylothorax and pseudochylothorax.

Yours sincerely,

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Extracolonic manifestations of *Clostridioides difficile* infection: Thinking Beyond the Gut

Konstantinos C. Mpakogiannis¹, Ioanna-Nefeli Mastorogianni¹,
Fotios S. Fousekis², Konstantinos H. Katsanos¹

INTRODUCTION

Clostridioides difficile (*C. difficile*) is a Gram-positive, spore-forming anaerobic bacterium that is widely recognized as the leading cause of antibiotic-associated diarrhea and pseudomembranous colitis [1]. Although *C. difficile* primarily affects the colon, cases of extraintestinal manifestations are increasingly reported in the medical literature [2]. These manifestations include both infectious and non-infectious complications and account for less than 1% of all reported *C. difficile* infections [3].

Risk factors and pathogenesis

Prior exposure to broad-spectrum antibiotics remains the most important predisposing factor, as disruption of the normal intestinal microbiota facilitates colonization and overgrowth of *C. difficile* [4].

Advanced age, prolonged hospitalization, proton pump inhibitor use, immunosuppression, malignancy, diabetes mellitus, chronic liver and kidney disease, cardiovascular disease, and sickle cell disease are other significant risk factors [5].

The development of extraintestinal manifestations is thought to result primarily from disruption of the

intestinal mucosal barrier, as occurs in severe colitis, inflammatory bowel disease, intestinal surgery, bowel perforation, and gastrointestinal malignancies, which facilitates the translocation of *C. difficile* and other microorganisms of the normal intestinal microbiota into the bloodstream, enabling their subsequent dissemination to distant organs [6]. In some cases, however, extraintestinal manifestations occur in the absence of gastrointestinal disease, suggesting that additional mechanisms may be involved [2,7]. These mechanisms may include hematogenous spread from asymptomatic intestinal colonization, toxin-mediated effects, or direct inoculation of the bacterium into tissues during trauma, surgery, or invasive medical procedures [2,6].

Bacteremia and sepsis-like syndrome

Bacteremia is the most frequently reported extraintestinal manifestation of *C. difficile* infection [2]. Underlying malignancy and chronic liver disease are frequently identified in affected patients [8]. Although monomicrobial bacteremia can occur, it is considerably less common than polymicrobial bacteremia and may reflect the presence of an extraintestinal infectious focus [5,6]. The development of sepsis-like syndrome may be attributed to toxin A–induced neutrophil chemotaxis and intestinal barrier dysfunction, which allows toxins and microbes to enter the bloodstream.

Abdominal and pelvic infections and abscesses

Abdominal and pelvic infections represent the most common extraintestinal *C. difficile* infections [2]. These infections occur predominantly in patients with underlying

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ing immunosuppression or conditions that compromise the intestinal barrier [2]. Splenic abscesses may arise through hematogenous dissemination, trauma, or splenic infarction [2]. Clinical manifestations are often nonspecific and include fever, abdominal pain, weight loss, leukocytosis, and elevated inflammatory markers [2]. Liver and pancreatic abscesses are rare [2]. Many intra-abdominal infections are polymicrobial, with *Escherichia coli* and *Enterococcus* species frequently isolated alongside *C. difficile* [2,9]. Hypervirulent ribotype 027 strains have also been implicated in several cases [7].

Central nervous system infections and abscesses

Only a few cases of brain abscesses caused by *C. difficile* have been reported [10,11]. In one case, the infection developed secondary to suppurative otitis media, while another case occurred in a patient with a history of subdural hematoma and asymptomatic intestinal carriage of *C. difficile* [10,11]. Interestingly, some reported CNS infections involve non-toxigenic strains, suggesting that strains with lower intestinal virulence may persist in the gut and cause opportunistic infections [11]. Patients with central nervous system infections and abscesses may present without gastrointestinal symptoms, making diagnosis particularly challenging [2].

Pleuropulmonary infections

Pleuropulmonary infections associated with *C. difficile* include pleural effusions, empyema, and, in severe cases, necrotizing pneumonia [2]. Most reported cases have occurred following thoracic surgery, thoracentesis, chest trauma, or other invasive procedures, suggesting direct inoculation into the respiratory tract as the primary mechanism [12,13]. Patients may present with fever, chest pain, and dyspnea [2].

Bone and joint infections

Bone and joint infections are frequently reported extraintestinal manifestations [2]. Septic arthritis may affect both native and prosthetic joints, although prosthetic joint infections are considerably more common [2]. Native joint infections have been particularly documented in patients with sickle cell disease, where intestinal ischemia and immune dysfunction may facilitate bacterial translocation into the bloodstream [2,14].

Prosthetic joint infections are believed to result mainly from direct contamination during surgery [2]. These infections are usually monomicrobial, supporting

the hypothesis of direct inoculation rather than hematogenous spread [2]. Clinical manifestations include joint pain, swelling, fever, and elevated inflammatory markers [2].

Osteomyelitis caused by *C. difficile* is rare but tends to become chronic [15]. Cases usually involve long bones, often following trauma, surgery, or previous hospitalization [2].

Soft tissue and surgical site infections

Soft tissue infections caused by *C. difficile* include cases of cellulitis, wound infections, abscesses, and necrotizing fasciitis [2]. Trauma and surgical interventions are major predisposing factors, with direct wound contamination from environmental or nosocomial sources of *C. difficile* representing the most likely pathogenic mechanism [2].

Published case reports have identified toxigenic strains in infected wounds, whereas different strains were isolated from the patients' gastrointestinal tracts [16,17]. This observation suggests that infection may originate from environmental contamination [2]. Nevertheless, intestinal colonization may also contribute to infection during abdominal surgical procedures [2].

Clinical presentations range from localized wound infections to rapidly progressive necrotizing soft tissue infections [2].

Cardiovascular infections

Cardiovascular manifestations are rare but potentially life-threatening [2]. Reported cases include mycotic aneurysms, infected vascular grafts and endovascular prostheses, intracardiac vegetations, pericarditis, epicardial patch infections, and pacemaker-associated infections [2].

The most widely accepted pathogenic mechanism involves hematogenous dissemination following bacterial translocation across the gastrointestinal mucosal barrier [2]. Many affected patients have concurrent intestinal disease and positive stool toxin tests [2]. Previous vascular interventions may further increase susceptibility to infection by creating localized anaerobic conditions that favor bacterial proliferation [18].

Reactive arthritis and other non-infectious manifestations

The most common non-infectious extraintestinal manifestation of *C. difficile* infection is reactive arthritis [2].

Reactive arthritis typically develops within days to weeks after the onset of diarrhea and commonly affects the knees, ankles, and wrists [6].

Underlying pathogenesis is believed to result from increased intestinal permeability, which facilitates systemic exposure to bacterial antigens and triggers an aberrant immune response [6]. More than half of affected patients are positive for the HLA-B27 antigen, although its precise role remains uncertain [19].

Other rare non-infectious manifestations include Takotsubo syndrome, leukocytoclastic vasculitis, and syndrome of inappropriate antidiuretic hormone secretion (SIADH), underscoring the potential systemic effects of *C. difficile* toxins and associated immune dysregulation [2,20].

CONCLUSION

Although *C. difficile* is primarily recognized as an intestinal pathogen responsible for pseudomembranous colitis, it may occasionally cause a wide spectrum of extraintestinal manifestations. Increased awareness of these rare manifestations is essential for timely diagnosis and appropriate management, and further research is needed to elucidate their pathogenesis, identify prognostic markers, and optimize therapeutic strategies.

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REFERENCES

- Vedantam G, Clark A, Chu M, McQuade R, Mallozzi M, Viswanathan VK. Clostridium difficile infection: toxins and non-toxin virulence factors, and their contributions to disease establishment and host response. Gut Microb. 2012;3(2):121-34. doi:10.4161/gmic.19399
- Mpakogiannis K, Fousekis FS, Elmes S, Mantellos E, Christaki E, Katsanos KH. Extraintestinal Manifestations of Clostridioides difficile Infections: An Overview. Antibiotics. 2025;14(7):670. doi:10.3390/antibiotics14070670
- Hafeez B, Aitken T, Cockburn E, Tinson AJ. Extraintestinal Clostridium difficile infection presenting as spontaneous bacterial peritonitis. BMJ Case Rep. 2025;18(2):e262106. doi:10.1136/bcr-2024-262106
- Jump RL. Clostridium Difficile Infection in Older Adults. Aging health. 2013;9(4):403-14. doi:10.2217/ahe.13.37
- Libby DB, Bearman G. Bacteremia due to Clostridium difficile—review of the literature. Int J Infect Dis. 2009;13(5):e305-e309. doi:10.1016/j.ijid.2009.01.014
- Jacobs A, Barnard K, Fishel R, Gradon JD. Extracolonic Manifestations of Clostridium difficile Infections. Medicine (Baltimore). 2001;80(2):88-101. doi:10.1097/00005792-200103000-00002
- Urbán E, Terhes G, Gajdács M. Extraintestinal Clostridioides difficile Infections: Epidemiology in a University Hospital in Hungary and Review of the Literature. Antibiotics (Basel). 2020;9(1):16. doi:10.3390/antibiotics9010016
- Kazanjani N, Gjeorgjievski M, Yadav S, Mertens AN, Lauter C. Monomicrobial vs Polymicrobial Clostridium difficile Bacteremia: A Case Report and Review of the Literature. Am J Med. 2015;128(9):e19-e26. doi:10.1016/j.amjmed.2015.05.014
- Chatterjee T, Roy M, Ahmad S. Treatment of Extra-Intestinal Clostridioides difficile Abscess following Acute Appendicitis. Eur J Case Rep Intern Med. 2022;9(9):003489. doi:10.12890/2022_003489
- García-Lechuz JM, Hernangómez S, Juan RS, Peláez T, Alcalá L, Bouza E. Extra-intestinal infections caused by Clostridium difficile. Clin Microbiol Infect. 2001;7(8):453-57. doi:10.1046/j.1469-0691.2001.00313.x
- Gravisse J, Barnaud G, Hanau-Berçot B, Raskine L, Riahi J, Gaillardet J L, et al. Clostridium difficile brain empyema after prolonged intestinal carriage. J Clin Microbiol. 2003;41(1):509-11. doi:10.1128/JCM.41.1.509-511.2003
- Hudson DA, Gibb AP, Gill MJ. Empyema Caused by Clostridium difficile. Can J Infect Dis. 1999;10(2):170-1. doi:10.1155/1999/968940
- Mohamed A, Sostre V, Patel H, Patel P, Ortiz LC, Baddoura WJ. Clostridium difficile Causing Empyema. Case Rep Gastroenterol. 2018;12(3):633-639. doi:10.1159/000493184
- Onwubalili JK. Sickle cell disease and infection. J Infect. 1983;7(1):2-20. doi:10.1016/S0163-4453(83)90863-0
- Pron B, Merckx J, Touzet P, Ferroni A, Poyart C, Berche P, et al. Chronic septic arthritis and osteomyelitis in a prosthetic knee joint due to Clostridium difficile. Eur J Clin Microbiol Infect Dis. 1995;14(7):599-601. doi:10.1007/BF01690732
- Nyc O, Krutova M, Kriz J, Matejkova J, Bebrova E, Hysperska V, et al. Clostridium difficile ribotype 078 cultured from post-surgical non-healing wound in a patient carrying ribotype 014 in the intestinal tract. Folia Microbiol (Praha). 2015;60(6):541-4. doi:10.1007/s12223-015-0392-0
- Onada Y, Endo S, Umemoto T, Kajino T, Amasaki Y, Furu-saki A. Extraintestinal Clostridium difficile infection due to a ribotype different from that isolated from the feces of the patient: A case report. Anaerobe. 2017;47:185-7. doi:10.1016/j.anaerobe.2017.05.018
- Hagiya H, Kimura K, Ueda A, Nishi I, Yamamoto N, Yoshida H, et al. Infective thoracic aortic aneurysm caused by Clostridium difficile after endovascular aortic repair. J Infect Chemother. 2017;23(1):62-4. doi:10.1016/j.jiac.2016.08.002
- Zimmermann O, Köchel H, Bohne W, Pollok-Kopp B, Passenberg P, Groß U. A Case Report and Review of the Literature.

- ture: Reactive Arthritis Caused by *Clostridioides difficile* ribotype 027. *Front Microbiol.* 2022;13:837422. doi:10.3389/fmicb.2022.837422
20. Xia Y, Hu HZ, Liu S, Pothoulakis C, Wood JD. *Clostridium difficile* toxin A excites enteric neurones and suppresses sympathetic neurotransmission in the guinea pig. *Gut.* 2000;46(4):481-6. doi:10.1136/gut.46.4.481

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Treatment of Heart Failure with Preserved Ejection Fraction

Faethontas Eleftheriadis, Antonios Karanasos, Michail Papafaklis,
Anastasios Papoutsoglou, Grigorios Tsigkas, Periklis Davlourous

Abstract

Heart failure with preserved ejection fraction (HFpEF) presents an increasingly significant clinical challenge due to its heterogeneous pathophysiology and high morbidity and mortality, alongside a paucity of established disease-modifying therapies. Complex pathomechanisms are implicated in HFpEF, encompassing arterial stiffness, microvascular inflammation, and structural cardiac changes, including left atrial dysfunction and pulmonary hypertension, while diagnosis of HFpEF might also be challenging and relies on clinical assessment, cardiac imaging, and biomarkers, with dedicated scoring systems developed to assess the probability of this condition. Compounding the diagnostic challenges, effective treatment strategies for HFpEF remain limited. Although goals of treatment remain similar to those of heart failure with reduced ejection fraction, aiming at functional improvement, reduction of heart failure hospitalizations, and mortality reductions, treatment options for HFpEF remain rather limited. The current review aims to present a brief synopsis of the mechanisms of HFpEF and diagnostic approaches and focuses on summarizing the current status of HFpEF treatment, including non-pharmacological interventions, management of comorbidities, and pharmacological treatment. Current drug options comprise diuretics for symptom management and SGLT2 inhibitors as the primary disease-modifying agents, while new therapies, such as finerenone and semaglutide, are emerging. Ongoing clinical trials aim to refine personalized treatment approaches, reflecting the need for a precision medicine approach to improve outcomes in this complex syndrome.

Key words: *Heart failure; cardiac output; heart disease; atrial fibrillation; pulmonary hypertension*

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is increasingly acknowledged and diagnosed in clinical practice, partly as a result of an ageing population and a rise in contributory comorbidities, including obesity and diabetes. HFpEF has been recognized as a complex clinical syndrome, accounting for at least half of patients with heart failure. Due to its heterogeneous pathophysiology and epidemiological patterns, HFpEF is often challenging to diagnose and to develop diagnostic

and therapeutic modalities. Although cardiovascular mortality is lower in HFpEF than in HF with reduced ejection fraction (HFrEF), hospital readmissions are frequent, and quality of life is poor [1,2]. In this review, we focus on the current and investigational treatment strategies for this complex syndrome.

Pathomechanisms of HFpEF

HFpEF was initially thought to be the result of diastolic dysfunction caused by hypertensive left ventricular (LV) remodeling in isolation, exacerbated by abnormal ventricular-arterial coupling and chronotropic incompetence. These mechanisms were noted originally in HFpEF patients with predominantly hypertensive heart

disease, where the primary mechanistic hypotheses centered around hypertension leading to LV hypertrophy with stiff and relatively small left ventricles and, eventually, overt HF [3–5]. Over the past two decades, older adults with isolated hypertensive heart disease have given way to multimorbid patients with obesity, diabetes, and metabolic syndrome as the most common clinical profile in HFpEF. This highlights the fact that the pathomechanisms of HFpEF extend beyond adaptive changes to increased afterload and comprise a variety of factors including systemic inflammation, endothelial dysfunction and altered myocardial energetics.

Arterial stiffness

It is becoming increasingly acknowledged that arterial stiffness plays a significant role in the pathogenesis of HFpEF, impacting prognosis, treatment, and diagnosis. Arterial stiffness, a defining characteristic of vascular aging, increases the afterload on the LV, resulting in diastolic dysfunction, a crucial aspect of HFpEF. The progression of the disease is accelerated by elevated arterial stiffness, which is associated with prevalent cardiovascular risk factors in HFpEF, including obesity, diabetes, and hypertension [3,6].

Microvascular inflammation

Comorbidities in HFpEF lead to a systemic inflammatory state that causes the coronary microvascular endothelium to experience oxidative stress. Cardiomyocytes become stiff and proliferate as a result of decreased PKG activity and decreased cardiac NO bioavailability. This process of myocardial remodeling differs from the one observed in HFrEF, where oxidative stress resulting from ischemia, infection, or toxicity causes cellular death by cardiocyte death and thus promotes cardiac remodeling. The new HFpEF model has significant implications for both diagnosis and treatment [7].

Structural changes in cardiac chambers

The most noticeable abnormalities in HFpEF are impairments in the structure and function of the heart, which affect all four chambers. There are changes in LV relaxation and a decrease in LV compliance, both of which are significant factors in the rise in filling pressures. Atrial fibrillation (AF), which may be regarded as a “biomarker” of underlying LA myopathy and indicative of more advanced HFpEF, is often the result of remodeling and dysfunction of the left atrium (LA) caused by chronic, prolonged, or intermittent elevation of LV

filling pressures in HFpEF [8]. It has been demonstrated that deficits in LA strain are the most reliable imaging indicators that differentiate HFpEF from noncardiac causes of dyspnea, and that LA function abnormalities are more often associated with adverse outcomes than LV function abnormalities [9]. While most patients with HFpEF have LV dysfunction before LA dysfunction, some patients may progress to a primary LA cardiomyopathy, which causes lower LV filling and higher LA pressure, thus resulting in inadequate cardiac output augmentation during exertion.

Initially, HFpEF is characterized by minor changes in cardiac remodeling and mild functional abnormalities, with elevated LV filling pressures observed exclusively during exercise. Over time, LA function and remodeling gradually deteriorate, leading to secondary atrial functional MR and increased incidence of paroxysmal AF. This is the stage where symptoms become more prominent and tend to also present during rest. The natural course of the syndrome is characterized by progressive additional deterioration of LA remodeling and dysfunction with development of permanent AF, worsening pulmonary hemodynamics and subsequent pulmonary vascular remodeling with vasoconstriction, and eventual development of RV and RA dysfunction. These changes may also lead to further impairments in cardiac output and increased pericardial restraint, findings associated with advanced HFpEF. The different stages of HFpEF progression are therefore the reason for the varying clinical presentation, and treatments may differ depending on presentation. Progression through these stages is not inevitable and may follow distinct tempos. Comorbidities, inflammation, and endothelial dysfunction can manifest differently among individuals, further increasing heterogeneity.

Regardless of the cause, sustained elevation in LA pressures leads to worsening pulmonary hypertension (PH), especially in patients with more severe LA cardiomyopathy. Roughly 80% of patients with HFpEF have PH, which starts as a passive result of downstream LA pressure elevation. However, in many patients, these passive changes eventually lead to pulmonary vascular disease and consequent combined post- and pre-capillary pulmonary hypertension, characterized by vascular remodeling and vasoconstriction that affects the totality of the pulmonary vasculature leading to deteriorations in exercise capacity, congestion, pulmonary diffusion, and eventually in increased mortality. The more extreme and difficult to handle spectrum of HFpEF is the

development of overt clinical right HF due to the PH that will eventually lead to additional symptoms due to systemic congestion and worsening cardiac output.

Atrial Fibrillation

More than half of patients with HFpEF experience AF during their lifetime. AF is independently linked to an increased risk of HF hospitalization and death in HFpEF. Since AF is a reliable sign that HFpEF is probably the cause of HF symptoms like dyspnea, the presence of AF has been incorporated into probability scores for the diagnosis of HFpEF [10]. HFpEF contributes to the rise of AF through structural and functional remodeling of the left atrium (LA). HFpEF leads to larger volumes of LA which is a well-established proarrhythmic substrate associated with atrial fibrosis. This contributes to electrical remodeling, increased atrial refractoriness, and development of AF [11,12].

Coronary Artery Disease (CAD)

Patients with HFpEF frequently have coronary artery disease, which is linked to higher mortality and worsening ventricular function. In patients with CAD, revascularization may be linked to improved outcomes and the maintenance of heart function [13].

Diagnosis of HFpEF

Clinical presentation

Identification of symptoms and signs of HF is the initial step in diagnosing HFpEF. The Framingham Diagnostic Criteria describe the major symptoms and signs indicating the presence of HF. A HF diagnosis requires the presence of two major criteria or one major and two minor criteria. Major criteria include orthopnea or paroxysmal nocturnal dyspnea, jugular venous distension, hepatojugular reflux, rales, S3 gallop rhythm, pulmonary edema, and cardiomegaly. The minor criteria include exertional dyspnea, nighttime cough, ankle edema, tachycardia with a heart rate surpassing 120 beats per minute, hepatomegaly, and pleural effusion. Dyspnea or ankle edema are common first presentations of HFpEF [14].

Cardiac imaging

When evaluating patients who may have HFpEF, cardiac imaging is essential. Transthoracic echocardiography (TTE) is the most useful imaging modality for early diagnosis. In addition to assessment of left ventricular ejection fraction (LVEF), the primary criterion used to dis-

tinguish between HFrEF and HFpEF, TTE offers detailed information about the anatomy and physiology of the heart. It detects anomalies in the pericardium, cardiac valves, and myocardium, and the data may be useful in the diagnosis of HFpEF [15]. RV size and function, atrial size, and thorough valve examination are all included in TTE evaluation, which addresses anomalies linked to both anatomy and flow. Importantly, TTE is crucial for the assessment of diastolic function by evaluating LV filling and LA pressures.

Additional non-invasive imaging modalities, besides TTE, may be useful for assessing the structure and function of the heart. For both LV and RV, cardiac MRI provides an accurate and reliably repeatable assessment of heart volumes, mass, and EF. Without using ionizing radiation, cardiac magnetic resonance imaging (MRI) offers remarkable anatomical resolution in all areas of the heart and adjacent structures [16]. It aids in the diagnosis of Fabry disease, cardiac sarcoidosis, cardiac amyloidosis, and hypertrophic cardiomyopathy. Ventricular size, EF, and anomalies of wall motion can also be accurately assessed using ECG-gated cardiac computed tomography (CT). Although radionuclide ventriculography exposes patients to ionizing radiation, it provides extremely repeatable LVEF values. A non-invasive imaging method called positron emission tomography (PET) can reveal details on myocardial fibrosis, inflammation, perfusion, and metabolism [17,18].

In some cases, cardiac catheterization may be necessary to directly measure left ventricular filling pressures and confirm the diagnosis of HFpEF, particularly when non-invasive tests are inconclusive or when there is suspicion of other cardiac conditions. Finally, considering the spectrum of presentations and the fact that several patients may only present with exercise-related symptoms, exercise testing during cardiac catheterization may reveal some additional occult cases of HFpEF.

Biomarkers

Natriuretic peptide assay, including B-type natriuretic peptide (BNP) or N-terminal proB-type natriuretic peptide (NT-proBNP), is commonly used to confirm the presence and severity of HFpEF. Generally, the levels of BNP and NT-proBNP are comparable, rendering either one suitable for clinical use [15,19]. When evaluating dyspnea of potentially cardiac origin, measuring BNP and NT-proBNP levels offers important diagnostic insight, particularly when the cause of dyspnea remains uncertain and physical examination yields inconclusive

results. However, it is important to note that BNP levels can be influenced by factors other than heart failure, such as age, renal function, and obesity.

Diagnostic algorithms – scores

To assist in the diagnosis of HFpEF, two primary scoring systems are commonly used, the H2FPEF score and HFA-PEFF score. In the H2FPEF score, several factors are used, including hypertension, age, gender, atrial fibrillation, elevated BNP, and diastolic dysfunction [20]. HFA-PEFF is a more comprehensive tool that includes several clinical, echocardiographic, and biomarker parameters to assess the probability of HFpEF [21]. Both scoring systems help to stratify patients based on their likelihood of having HFpEF, guiding clinicians in the diagnostic process. These scoring systems can aid in the diagnostic evaluation but should always be used in conjunction with clinical judgment and additional diagnostic tests such as echocardiography, imaging, and biomarker analysis [20,21].

Treatment strategies

The major goals of treatment for patients with HFpEF are alleviation of symptoms, improvement of functional

status, reduction of the risk of hospitalization for HF, and reduction of the associated mortality. Notably, a higher NYHA class is associated with a lower quality of life in HF patients. This often manifests with an increased risk of HF-related hospital admissions, a clinically meaningful endpoint as it has a well-documented association with higher mortality in patients with HF [22]. Considering the high variety of phenotypes and causes of HFpEF, the approach to treatment needs to be inherently personalized, and tailored to the individual patient's specific clinical profile (Figure 1).

Non-pharmacological treatment

Weight reduction

A higher incidence of heart failure and all-cause death are linked to obesity, particularly central obesity. Up to 80% of people with HFpEF are overweight or obese, and obesity is acknowledged as a significant characteristic of HFpEF [23,24]. Obesity and physical inactivity are also associated with a poor prognosis for HFpEF. About half of the HF risk linked to body mass index (BMI) may be explained by low cardiorespiratory fitness, which has been linked to an increased risk of HF across all BMI categories [25]. Changing one's lifestyle to

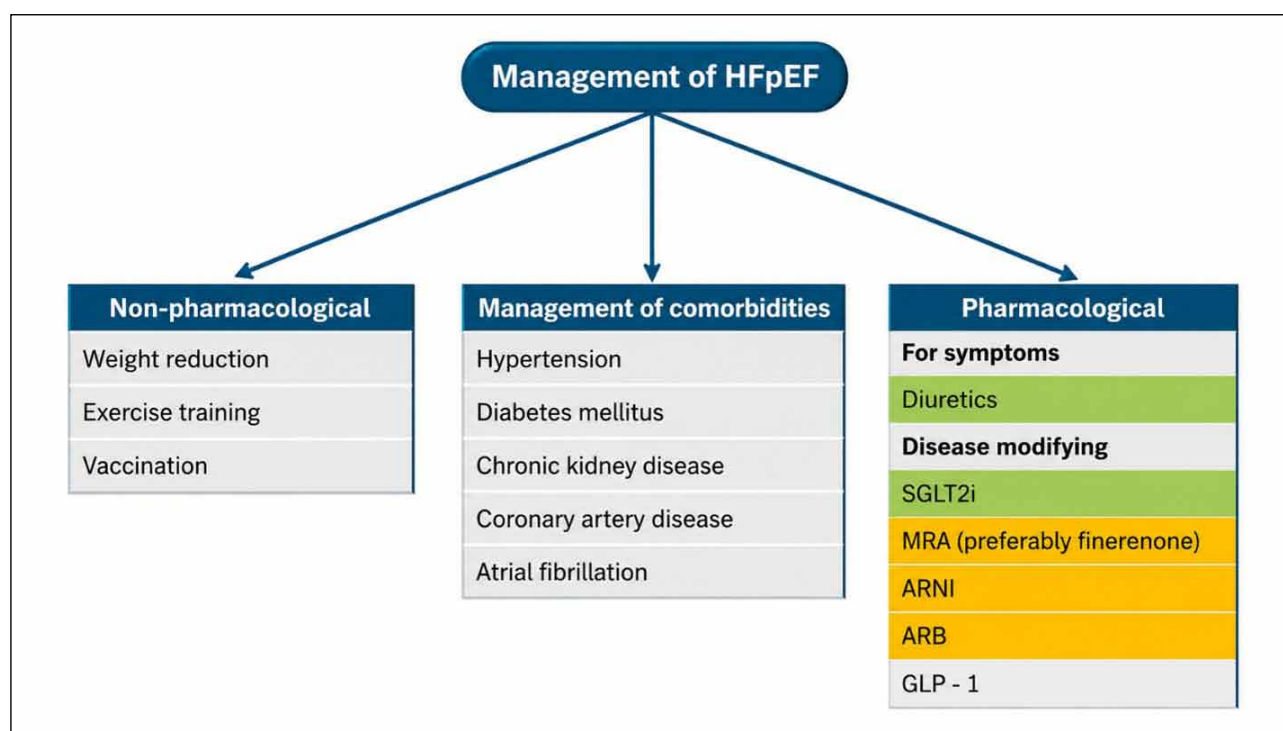


Figure 1. Summary of the treatment of heart failure with preserved ejection fraction. Abbreviations: MRA: mineralocorticoid receptor antagonist; ARNI: angiotensin receptor neprilysin inhibitor; ARB: angiotensin receptor blocker; GLP - 1: glucagon-like peptide 1.

reduce weight and improve physical activity are crucial ways to reduce the risk of heart failure.

Exercise training

A significant number of patients with HFpEF have several comorbidities that affect their ability to exercise and contribute to the pathogenesis of HFpEF [26,27]. Exercise-based therapy is becoming a popular non-pharmacological treatment for HFpEF, and it is well known that proper physical activity has many positive impacts on the cardiovascular system. In patients with HFpEF, exercise training enhances peak oxygen consumption and quality of life without significantly altering LV systolic or diastolic function [28].

Vaccination

Pneumonia and respiratory tract infection are important triggers of HF decompensation and cause hospitalization. The risk of pneumonia is high in HF patients especially those with HFpEF [29]. Infections not only increase the in-hospital mortality of HF but also result in poor long-term prognosis [30]. Influenza and pneumococcal vaccines help to prevent respiratory infections that may potentially reduce the risk of exacerbation of HF.

Management of comorbidities

Hypertension and diabetes

Hypertension is the leading cause of HFpEF with a prevalence ranging from 60% to 89% in HFpEF [31]. The systolic blood pressure target for HFpEF should be less than 130 mmHg. The patient's other comorbidities, such as diabetes, chronic kidney disease (CKD), or coronary artery disease (CAD), should guide the personalized choice of antihypertensive agents. The preferred agents for hypertension control in HFpEF include diuretics, angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA) because these agents also have some beneficial effects for HFpEF, in addition to blood pressure reduction. Since chronotropic incompetence is a potential mechanism contributing to exercise functional limitation in HFpEF, the use of beta-blockers in HFpEF may be avoided if there are no other specific indications for beta-blockers. Given the recently demonstrated benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors in improving outcomes in patients with HFpEF, SGLT2 inhibitors should be prescribed as first-line therapy for diabetic patients with HFpEF [32]. However, the use of SGLT2 inhibitors is

not recommended if the estimated glomerular filtration rate (eGFR) is $< 20 \text{ mL/min/1.73 m}^2$.

Chronic Kidney Disease

Evidence-based treatments that slow the progression of CKD should be used to treat patients with HFpEF and CKD. It has been demonstrated that SGLT2 inhibitors enhance renal outcomes in CKD patients. After long-term follow-up, the rate of eGFR decline is slower than in patients not on SGLT2 inhibitors, despite an anticipated initial decline in eGFR of about $4 \text{ mL/min/1.73 m}^2$ upon initiation of SGLT2 inhibitors. Clinical studies also showed that patients receiving angiotensin receptor-neprilysin inhibitors (ARNI) or ARBs experienced a marked slowdown in the fall of eGFR.

Coronary Artery Disease

HFpEF has a high prevalence of CAD. Patients with a low to intermediate pre-test risk of CAD or those with ambiguous non-invasive stress tests should be evaluated for CT coronary angiography in order to assess the severity of CAD and establish the necessity of revascularization. Patients with an intermediate to high pre-test risk of CAD may be candidates for invasive coronary angiography. There are no prospective randomized trials available right now to assess how revascularization affects patients with CAD and HFpEF.

Atrial fibrillation

Anticoagulants continue to be the mainstay of treatment for HFpEF and AF in order to prevent stroke, and the CHA2DS2-VASc score determines when anticoagulation is indicated. There was no evidence in randomized controlled studies that rhythm control with antiarrhythmic drugs was superior to rate control. For rhythm control, ablation of AF might be a more effective method than antiarrhythmic drugs. According to this recommendation, patients who have both HFpEF and AF should have sufficient rate control. First-line medications often consist of beta-blockers and non-dihydropyridine calcium-channel blockers. Digoxin may increase functional capacity and lower NT-proBNP more than bisoprolol in AF patients with heart failure symptoms, according to a recent clinical investigation [33].

Pharmacological treatment

Contrary to HFrEF, where a number of therapies have been demonstrated to improve outcomes including all-cause mortality, HFpEF treatment options have

been fairly limited with respect to reducing clinically significant endpoints. Although several treatments with demonstrated benefits in HFrEF have also been evaluated in HFpEF, most of these agents have not been able to demonstrate a consistent benefit in modifying the course of the disease. Therefore, the mainstay of therapy for HFpEF is the use of diuretics for alleviation of congestion symptoms and the use of SGLT2 inhibitors as the only established disease-modifying treatment. It should be noted however, that ongoing research has indicated a potential role for medications such as finerenone and semaglutide in improving outcomes in HFpEF.

Diuretics

HFpEF patients with volume overload should be treated with diuretics [34]. Loop diuretics should be initiated as the first-line therapy with the type and dose depending on the severity of congestion. Loop diuretics (furosemide, torsemide, bumetanide) are typically used, with the dose adjusted to achieve euvolemia (normal fluid status) without causing excessive dehydration or electrolyte imbalances. For those patients with loop diuretic resistance, sequential nephron blockade can be achieved using thiazide diuretics and/or MRAs. Careful monitoring of electrolytes (especially potassium and magnesium) and renal function is essential.

SGLT2 Inhibitors

SGLT2 Inhibitors are the only medication class that has consistently shown improved outcomes in patients with HFpEF. Both empagliflozin and dapagliflozin have shown clear benefits in the management of HFpEF. EMPEROR-Preserved Trial showed that empagliflozin significantly reduced the composite outcome of cardiovascular death or hospitalization for heart failure in patients with HFpEF [32]. Dapagliflozin in the DELIVER Trial also demonstrated a significant reduction in the composite outcome of cardiovascular death or worsening heart failure in HFpEF patients [35]. As SGLT2 inhibitors have received a strong recommendation (Class 2a, Level of Evidence A) in HFpEF guidelines, they should be considered a cornerstone of therapy for all patients with HFpEF, unless contraindicated [36].

Mineralocorticoid Receptor Antagonists (MRAs)

The benefits of spironolactone were observed at the lower end (up to 55%) of HFpEF, however the TOPCAT trial did not show a mortality benefit or a decrease in HF

hospitalization throughout the entire study in patients with LVEF 45% or higher. The advantages of candesartan, spironolactone, and ARNI were shown to possibly extend to the lower end of the LVEF range of HFpEF in a meta-analysis conducted at the individual patient level. Thus, MRAs may be taken into consideration to reduce HF hospitalizations in a subset of patients with HFpEF [37]. The precise involvement of MRAs, such as finerenone or spironolactone, in HFpEF is currently being determined by a number of ongoing trials (FINEARTS-HF, SPIRRIT, and SPIRIT-HF) [38]. Recently, results from the FINEARTS-HF trial were published, showing that in patients with HFpEF and HFmrEF, treatment with a non-steroidal MRA, finerenone, was associated with a significantly lower incidence of a composite endpoint consisting of total worsening heart failure events and cardiovascular mortality compared to placebo, giving rise to the possibility for another important disease-modifying therapy in HFpEF [39].

Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)

The PARAGON-HF trial, which evaluated sacubitril/valsartan in HFpEF, did not demonstrate a statistically significant reduction in the primary composite endpoint of total hospitalizations for heart failure and cardiovascular death compared to valsartan alone. However, subgroup analyses suggested a potential benefit in women and in patients with lower ejection fractions (within the preserved range, but closer to 50%). ARNIs may be considered in selected HFpEF patients, especially those with LVEF in the lower range of the preserved spectrum and those who tolerate ACE inhibitors or ARBs well.

Angiotensin Receptor Blockers (ARBs)

Candesartan in the CHARM Preserved trial [40] and irbesartan in the I-Preserve trial [41], failed to achieve a significant reduction in the primary outcome compared with placebo for patients with HFpEF. ARBs can be used in HFpEF patients who are intolerant of ACE inhibitors or ARNIs, primarily for blood pressure control and potential RAAS blockade, but their impact on HFpEF-specific outcomes is limited.

Beta-blockers

In the RATE-AF study that compared digoxin with bisoprolol in AF patients with HF symptoms, the primary outcome of quality of life was comparable between patients treated with bisoprolol and digoxin at 6 months [33]. A beta-blocker is not recommended in patients

with HFpEF without compelling indications, such as CAD, prior MI or rate control for AF, especially in those with chronotropic incompetence.

Glucagon-like peptide 1 (GLP-1) agonists–Semaglutide

The STEP-HFpEF-DM and STEP-HFpEF trials showed that semaglutide administration decreased body weight and significantly improved quality of life and the six-minute walk distance in obese patients with HFpEF [42]. There was also a reduction in NT-proBNP levels and notably high reductions in HF-related symptoms and physical limitations in patients with higher NT-proBNP baseline levels. These trials pave the way for a novel disease-modifying therapy in patients with HFpEF, particularly those with a phenotype associated with obesity and cardiometabolic stress.

Future targets

Future therapeutic targets for HFpEF focus on addressing its complex pathophysiology, including inflammation, fibrosis, endothelial dysfunction, and metabolic abnormalities. Key areas of interest include anti-inflammatory and anti-fibrotic agents, enhancement of the NO–cGMP–PKG pathway, and modulation of myocardial energetics and titin stiffness. Other emerging approaches target mitochondrial dysfunction, autonomic imbalance, and coronary microvascular dysfunction. Personalized, phenotype-driven therapies and ongoing clinical trials aim to improve outcomes by defining specific HFpEF phenotypes thus tailoring individualized treatment to the diverse HFpEF population.

A considerable number of clinical trials are currently in progress to explore potential therapeutic options for HFpEF. Given the substantial morbidity and mortality associated with HFpEF, it is imperative that these therapies be more routinely considered and offered to patients as viable adjunctive treatment options. The SUMMIT trial is investigating Tirzepatide in patients with NYHA functional class II–IV, Elevated NT-proBNP, BMI ≥ 30 kg/m², CAMEO-SEMA is evaluating semaglutide, SPIRRIT and SPIRIT-HF are investigating Spironolactone vs placebo, and CADENCE is evaluating Sotatercept in patients with EF $\geq 50\%$ with combined pre- and postcapillary PH PVR ≥ 4 WU, PCWP > 15 but < 30 mm Hg are some of the ongoing trials [43] ENDEAVOR is a phase 2b–3 study of Mitiperstat, therapy that targets comorbidity-induced systemic inflammation which may be a key mechanism underlying HFpEF [44] HERMES is evaluating patients

with HFpEF and HFmrEF, investigating Ziltivekimab, a monoclonal antibody targeting interleukin-6 to reduce systemic inflammation [45].

CONCLUSIONS

More than half of all HF cases are HFpEF, a growing public health concern characterized by increased morbidity and mortality. HFpEF frequently goes undiagnosed, which results in high health resource usage. Considering the variety of the presenting phenotypes and the lack of established disease-modifying therapies, as in HFrEF, there are considerable challenges in the management of HFpEF, and an unmet clinical need. Currently, research is focused on assessing tailored treatment for different subtypes of HFpEF and thoroughly phenotyping HFpEF patients. Future clinical trials using a precision medicine approach in a variety of HFpEF characteristics might be an important step forward in the attempt toward establishing new pathways for diagnosis and management of HFpEF, thus improving outcomes.

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REFERENCES

- 1 Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol.* 2017; 70(20): 2476–86.
- 2 Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail.* 2020; 22(6):1009–18.
- 3 Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med.* 2004;350(19):1953–9.
- 4 Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, et al. Impaired chronotropic and vasodilator

- reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation*. 2006; 114(20):2138–47.
- 5 Kawaguchi M, Hay I, Fetis B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation*. 2003; 107(5):714–20.
 - 6 Lam CSP, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Omnen SR, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation*. 2007; 115(15):1982–90.
 - 7 Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62(4):263–71.
 - 8 Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail*. 2015; 8(2):295–303.
 - 9 Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, et al. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019; 21(4):495–505.
 - 10 von Haehling S, Assmus B, Bekfani T, Dworatzek E, Edelmann F, Hashemi D, et al. Heart failure with preserved ejection fraction: diagnosis, risk assessment, and treatment. *Clin Res Cardiol*. 2024;113(9):1287–305.
 - 11 Knackstedt C, Gramley F, Schimpf T, Mischke K, Zarse M, Plisiene J, et al. Association of echocardiographic atrial size and atrial fibrosis in a sequential model of congestive heart failure and atrial fibrillation. *Cardiovasc Pathol*. 2008; 17(5): 318–24.
 - 12 Karanasos A, Tyrovolas K, Tsiachris D, Efremidis M, Kordalis A, Karpalioti M et al. Left Atrial Function Post Radiofrequency and Cryoballoon Ablation Assessed by Volume-Pressure Loops. *Front Cardiovasc Med*. 2022; 9:830055.
 - 13 Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014; 63(25 Pt A):2817–27.
 - 14 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med*. 1971; 285(26):1441–6.
 - 15 Nauta JF, Hummel YM, van der Meer P, Lam CSP, Voors AA, van Melle JP. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2018; 20(9):1303–11.
 - 16 He J, Yang W, Wu W, Yin G, Zhuang B, Xu J, et al. Heart Failure with Normal Natriuretic Peptide Levels and Preserved Ejection Fraction: A Prospective Clinical and Cardiac MRI Study. *Radiol Cardiothorac Imaging*. 2024; 6(3): e230281.
 - 17 Ashkir Z, Myerson S, Neubauer S, Carlhäll CJ, Ebberts T, Rahman B. Four-dimensional flow cardiac magnetic resonance assessment of left ventricular diastolic function. *Front Cardiovasc Med*. 2022; 9:866131.
 - 18 Quarta G, Gori M, Iorio A, D'Elia E, Moon JC, Iacovoni A, et al. Cardiac magnetic resonance in heart failure with preserved ejection fraction: myocyte, interstitium, microvascular, and metabolic abnormalities. *Eur J Heart Fail*. 2020; 22(7):1065–75.
 - 19 Booth RA, Hill SA, Don-Wauchope A, Santaguida PL, Oremus M, McKelvie R, et al. Performance of BNP and NT-proBNP for diagnosis of heart failure in primary care patients: a systematic review. *Heart Fail Rev*. 2014; 19(4):439–51.
 - 20 Koch DG, Rockey DC, Litwin SS, Tedford RJ. H2FPEF Scores Are Increased in Patients with NASH Cirrhosis and Are Associated with Post-liver Transplant Heart Failure. *Dig Dis Sci*. 2024; 69(8): 3061–8.
 - 21 Li X, Liang Y, Lin X. Diagnostic and prognostic value of the HFA-PEFF score for heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2024; 11:1389813.
 - 22 Iqbal J, Francis L, Reid J, Murray S, Denvir M. Quality of life in patients with chronic heart failure and their carers: a 3-year follow-up study assessing hospitalization and mortality. *Eur J Heart Fail*. 2010;12(9):1002–8.
 - 23 Clerico A, Zaninotto M, Passino C, Plebani M. Obese phenotype and natriuretic peptides in patients with heart failure with preserved ejection fraction. *Clin Chem Lab Med*. 2018; 56(7):1015–25.
 - 24 Kittleson MM, Panjath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023; 81(18):1835–78.
 - 25 Pandey A, Cornwell WK, Willis B, Neeland IJ, Gao A, Leonard D, et al. Body Mass Index and Cardiorespiratory Fitness in Mid-Life and Risk of Heart Failure Hospitalization in Older Age: Findings From the Cooper Center Longitudinal Study. *JACC Heart Fail*. 2017; 5(5):367–74.
 - 26 Shah SJ, Kitzman DW, Borlaug BA, Van Heerebeek L, Zile MR, Kass DA, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. *Circulation*. 2016; 134(1):73–90.
 - 27 Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. *Circ Res*. 2014; 115(1): 79–96.
 - 28 Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail*. 2015; 8(1):33–40.
 - 29 Shen L, Jhund PS, Anand IS, Bhatt AS, Desai AS, Maggioni AP, et al. Incidence and Outcomes of Pneumonia in Patients With Heart Failure. *J Am Coll Cardiol*. 2021; 77(16):1961–73.
 - 30 Chen CY, Lee CH, Lin HW, Lin SH, Li YH. Impact of infection-

- related admission in patients with heart failure: a 10 years national cohort study. *Sci Rep*. 2023; 13(1):6941.
- 31 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006; 355(3): 251–9.
 - 32 Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021; 385(16):1451–61.
 - 33 Kotecha D, Bunting K V., Gill SK, Mehta S, Stanbury M, Jones JC, et al. Effect of Digoxin vs Bisoprolol for Heart Rate Control in Atrial Fibrillation on Patient-Reported Quality of Life: The RATE-AF Randomized Clinical Trial. *JAMA*. 2020;324(24):2497–508.
 - 34 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023; 44(37):3627–39.
 - 35 Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022; 387(12):1089–98.
 - 36 Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022; 79(17):e263–e421.
 - 37 Dewan P, Jackson A, Lam CSP, Pfeffer MA, Zannad F, Pitt B, et al. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail*. 2020; 22(5):898–901.
 - 38 Vaduganathan M, Claggett BL, Lam CSP, Pitt B, Senni M, Shah SJ, et al. Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial. *Eur J Heart Fail*. 2024; 26(6): 1324–33.
 - 39 Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024; 391(16):1475–85.
 - 40 Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003; 362(9386):777–81.
 - 41 Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008; 359(23):2456–67.
 - 42 Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med*. 2023; 389(12):1069–84.
 - 43 Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. *J Am Coll Cardiol*. 2023; 81(18): 1810–34.
 - 44 Lund LH, Lam CSP, Pizzato PE, Gabrielsen A, Michaëlsson E, Nelander K, et al. Rationale and design of ENDEAVOR: A sequential phase 2b–3 randomized clinical trial to evaluate the effect of myeloperoxidase inhibition on symptoms and exercise capacity in heart failure with preserved or mildly reduced ejection fraction. *Eur J Heart Fail*. 2023; 25(9):1696–707.
 - 45 Ministrini S, Liberale L, Puspitasari YM, Han J, Kirmes K, Unkelbach LP, et al. Direct Interleukin-6 Inhibition Blunts Arterial Thrombosis by Reducing Collagen-Mediated Platelet Activation. *Arterioscler Thromb Vasc Biol*. 2025; 45(8):1432–9.

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Acute and Chronic Pancreatitis: Clinical Features, Diagnosis, and Management

Stamatia Tsoupra

Abstract

Acute and chronic pancreatitis are inflammatory disorders of the pancreas, associated with significant morbidity, mortality and healthcare burden. Acute pancreatitis is a common cause of hospital admission, ranging from a mild, self-limited disease to a severe condition complicated by pancreatic necrosis and persistent organ failure. In contrast, chronic pancreatitis is characterized by progressive pancreatic fibrosis, irreversible structural damage, and the eventual development of exocrine and endocrine insufficiency. Despite advances in diagnostic imaging, intensive care management, and minimally invasive therapeutic approaches, pancreatitis remains a substantial diagnostic and therapeutic challenge to clinicians. This review provides a comprehensive overview of the epidemiology, etiology, pathophysiology, clinical presentation, diagnostic strategies, and management of both acute and chronic pancreatitis. Emphasis is placed on disease severity assessment, complication recognition and evidence-based treatment strategies, including updated guidelines and expert-opinion recommendations. A comparative approach is adopted to highlight the main differences and overlaps between acute and chronic pancreatitis, aiming to support early diagnosis, appropriate risk stratification and individualized patient management through a multidisciplinary approach.

Key words: *Acute and chronic pancreatitis; systemic inflammatory response syndrome; pancreatic necrosis; Revised Atlanta Classification and Risk Assessment; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; minimally invasive therapeutic strategies*

INTRODUCTION

Pancreatitis represents a spectrum of inflammatory disorders of the pancreas with variable clinical presentation, treatment response and outcomes. Acute pancreatitis is defined by the sudden onset of pancreatic inflammation, most commonly triggered by gallstones or alcohol consumption, and is characterized by local pancreatic injury and a systemic inflammatory response. While most cases follow a mild and self-limiting course, some cases progress to severe disease, complicated by infected pancreatic necrosis, persistent organ failure, prolonged hospitalization and increased mortality.

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Despite improvements in supportive care and early risk stratification, severe acute pancreatitis remains associated with substantial morbidity and mortality.

In contrast, chronic pancreatitis is a progressive inflammatory condition marked by irreversible destruction of pancreatic parenchyma and fibrosis, along with ductal abnormalities that lead to exocrine pancreatic insufficiency, clinically manifested as pancreatogenic diabetes mellitus and chronic abdominal pain. Alcohol abuse and smoking constitute the primary risk factors, although genetic, autoimmune and idiopathic patterns are increasingly recognized. Recurrent episodes of acute pancreatitis may play a role in disease progression from the acute to the chronic form, indicating that these entities are part of a continuous pathological spectrum. Table 1 summarizes the key clinical and pathophysiological differences between acute and chronic pancreatitis.

Table 1. Key Differences between Acute and Chronic Pancreatitis.

Feature	Acute Pancreatitis	Chronic Pancreatitis
Definition	Acute inflammatory process caused by premature activation of pancreatic enzymes	Progressive inflammatory disorder with irreversible structural damage and fibrosis
Disease course	Sudden onset, usually reversible	Chronic progressive disease
Main etiologies	Gallstones, alcohol, hypertriglyceridemia, drugs, ERCP	Alcohol consumption, smoking, genetic mutations, autoimmune pancreatitis
Pathophysiology	Enzymatic autodigestion and systemic inflammatory response	Chronic inflammation and pancreatic stellate cell activation leading to fibrosis
Structural changes	Edema, necrosis, peripancreatic fluid collections	Pancreatic calcifications, ductal strictures, gland atrophy
Clinical presentation	Acute severe epigastric pain, nausea, vomiting	Chronic abdominal pain, malabsorption, diabetes
Exocrine insufficiency	Rare	Common in advanced disease
Endocrine dysfunction	Rare	Pancreatogenic diabetes mellitus (Type 3c)
Complications	Necrosis, pseudocysts, organ failure	Pseudocysts, biliary obstruction, portal vein thrombosis, pancreatic cancer
Treatment	Supportive care, fluid resuscitation, early nutrition	Lifestyle modification, enzyme replacement, endoscopic or surgical interventions

Clinical suspicion, accurate diagnosis, severity assessment and early intervention are crucial determinants of outcome in both acute and chronic pancreatitis. Advances in cross-sectional imaging, endoscopic techniques, and evidence-based management guidelines have refined clinical practice. However, significant challenges remain regarding optimal risk stratification, complication management and long-term follow-up. The aim of this review is to provide a revised and clinically oriented overview of the underlying pathways of acute and chronic pancreatitis, focusing on clinical features, diagnostic approaches and contemporary management strategies, with particular emphasis on practical decision-making in everyday clinical practice.

Acute Pancreatitis

Etiology and Pathophysiology

Acute pancreatitis is an acute inflammatory disorder of the pancreas resulting from premature activation of pancreatic digestive enzymes within the acinar cells, leading to autodigestion of pancreatic tissue and a variable degree of local and systemic inflammatory response [1,2]. Gallstone disease and excessive alcohol consumption are the most common etiological factors [1,3]. Other recognized causes include hypertriglyceridemia, drug-induced pancreatic injury, post-endoscopic retrograde cholangiopancreatog-

raphy (ERCP) pancreatitis, metabolic disturbances such as hypercalcemia, pancreatic ductal obstruction, genetic mutations, as well as infectious and idiopathic etiologies [1,4].

At the cellular level, acute pancreatitis is initiated by the intrapancreatic activation of trypsinogen, which triggers a cascade of inflammatory signaling pathways and is characterized by the release of cytokines, chemokines, and other vasoactive mediators [2,5]. The ensuing inflammatory response leads to increased vascular permeability, pancreatic interstitial edema, and, in severe cases, parenchymal necrosis and hemorrhage. When the inflammatory process extends beyond the pancreas, systemic inflammatory response syndrome (SIRS) may develop, predisposing patients to multiple organ dysfunction syndrome (MODS) and significantly increasing disease-related mortality [1,6].

Two principal pathogenic mechanisms are recognized: obstruction of the pancreatic duct, most commonly due to gallstones or biliary sludge and, secondly, direct toxic injury to pancreatic acinar cells, especially in alcohol-related disease [1,3]. These mechanisms may coexist, contributing to the heterogeneity observed in clinical presentation and disease severity. Genetic susceptibility, including mutations in PRSS1, SPINK1, CFTR, and CTSC genes, has been increasingly implicated in both idiopathic and recurrent forms of acute

pancreatitis, further highlighting the complex interplay between environmental and host-related factors [4,7].

Classification and Severity Assessment

The clinical and morphological classification of acute pancreatitis has been standardized by the Revised Atlanta Classification (2012) for disease stratification [8]. Based on morphological criteria, acute pancreatitis is categorized into interstitial edematous pancreatitis, characterized by pancreatic enlargement and interstitial edema without necrosis, and necrotizing pancreatitis, which involves pancreatic and/or peripancreatic tissue necrosis [8,9].

Severity is classified into three categories: mild, moderately severe, and severe acute pancreatitis. Most commonly, mild acute pancreatitis is defined by the absence of organ failure and local or systemic complications, typically resolving with conservative management [8]. Moderately severe acute pancreatitis is characterized by transient organ failure lasting less than 48 hours and/or the presence of local or systemic complications. Severe acute pancreatitis is defined by persistent organ failure exceeding 48 hours and is associated with a substantially higher risk of mortality [8,9].

Assessment of disease severity is critical for early risk stratification and appropriate allocation of healthcare resources. Several clinical scoring systems have been developed, including the Ranson criteria and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [10,11]. Although historically important, the Ranson score has demonstrated limited predictive accuracy in meta-analyses and requires 48 hours for full assessment [10]. In contrast, the APACHE II score allows dynamic, daily evaluation of disease severity, particularly in critically ill patients, and has been widely adopted in intensive care settings [11]. Current guideline recommendations emphasize the integration of clinical parameters, laboratory markers and imaging findings, rather than adopting a single prognostic model to identify patients at risk of severe disease [1,6].

Clinical Presentation and Diagnostic Evaluation of Acute Pancreatitis

The clinical presentation of acute pancreatitis is variable and depends on the underlying etiology, the extent of pancreatic injury and the presence of local or systemic complications. The hallmark symptom is severe, persistent epigastric pain with acute onset, frequently radiating to the back and often accompanied by nau-

sea and vomiting [1,3]. In severe cases, patients may present with signs of systemic inflammatory response, including fever, tachycardia, hypotension and altered mental status, reflecting the development of systemic inflammatory response syndrome (SIRS) and early organ dysfunction [6].

Physical examination findings range from mild epigastric tenderness to an acute abdomen in severe forms. Abdominal distension, decreased bowel sounds due to paralytic ileus, and signs of pleural effusion may be observed. Rare findings, such as Cullen's and Grey Turner's signs, indicate retroperitoneal hemorrhage and are associated with severe disease [1].

Laboratory Evaluation

The diagnosis of acute pancreatitis is established when at least two of the following three criteria are present: characteristic abdominal pain, serum amylase and/or lipase levels elevated to at least three times the upper limit of normal and imaging findings consistent with acute pancreatitis [1,8]. Among biochemical markers, serum lipase is considered more specific and remains elevated for a longer duration compared with amylase [1]. Serum amylase typically rises within six–ten hours of symptom onset and normalizes within three–five days. However, its diagnostic accuracy is limited in alcohol-related pancreatitis and hypertriglyceridemia-associated disease, where false-negative results are common [1,4].

Additional laboratory investigations are essential for etiological assessment and severity stratification. These include complete blood count, hematocrit, C-reactive protein, liver function tests, renal function parameters, serum electrolytes, calcium levels and arterial blood gas analysis in selected cases [6]. Elevated blood urea nitrogen and hematocrit at presentation, as well as failure of their early normalization, have been associated with increased disease severity and worse outcomes [6,11].

Imaging Modalities

Abdominal ultrasonography is recommended as the initial imaging modality in patients with suspected acute pancreatitis, primarily to identify gallstones or biliary dilatation [1]. Its sensitivity for pancreatic inflammation is limited by bowel gas and patient body mass. Contrast-enhanced computed tomography (CT) of the abdomen is not routinely required for the initial diagnosis and should be reserved for patients with diagnostic uncertainty, without clinical improvement within 48–72 hours, or suspicion of local complications [1,6]. When

performed after the early inflammatory phase, contrast-enhanced CT provides valuable information regarding the presence and extent of pancreatic necrosis, peripancreatic collections and vascular complications [9].

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) offer superior soft tissue contrast and enhanced detection of early pancreatic inflammation and ductal abnormalities, particularly in patients with contraindications to iodinated contrast agents. Secretin-enhanced MRCP may further delineate pancreatic ductal anatomy and functional abnormalities. Endoscopic ultrasound (EUS) plays an important role in the evaluation of idiopathic or recurrent acute pancreatitis, allowing the detection of microlithiasis, small pancreatic tumors and subtle ductal abnormalities, as well as providing the opportunity for tissue sampling when indicated [1,6].

Differential Diagnosis

The differential diagnosis of acute pancreatitis is broad and includes other causes of intra-abdominal and extra-abdominal pathology, such as perforated peptic ulcer disease, acute cholecystitis, biliary colic, mesenteric ischemia, intestinal obstruction, ruptured abdominal aortic aneurysm, acute myocardial infarction and diabetic ketoacidosis. A systematic diagnostic approach integrating clinical, laboratory and imaging findings is therefore essential to establish the diagnosis and provide appropriate management.

Local and Systemic Complications of Acute Pancreatitis

Complications of acute pancreatitis develop in approximately 20% of patients. According to the Revised Atlanta Classification, they are classified as local or systemic, and they are related to the severity and duration of the inflammatory process and contribute significantly to morbidity and mortality [8].

Local complications include acute peripancreatic fluid collections, pancreatic and peripancreatic necrosis, pseudocysts and walled-off necrosis [8,9]. Acute peripancreatic fluid collections typically occur early in the disease course and often resolve spontaneously. In contrast, pancreatic necrosis may become infected, significantly increasing the risk of sepsis and mortality [6,9].

Pancreatic pseudocysts generally develop several weeks after the onset of acute pancreatitis and are characterized by encapsulated collections of pancreatic fluid without solid necrotic material. Walled-off necrosis represents a mature, encapsulated collection containing

both fluid and necrotic tissue and usually develops after four weeks [8]. Additional local complications include pancreatic ascites due to ductal disruption, hemorrhage secondary to vascular erosion or pseudoaneurysm formation, gastrointestinal bleeding, paralytic ileus, and splenic or portal vein thrombosis.

Systemic complications result from the systemic inflammatory response and may involve multiple organ systems. Respiratory complications, including pleural effusions, atelectasis and acute respiratory distress syndrome (ARDS), are among the most frequent and are associated with poor prognosis. Cardiovascular instability, acute kidney injury, metabolic disturbances such as hypocalcemia and hyperglycemia and hematologic abnormalities may also occur. Persistent organ failure lasting more than 48 hours defines severe acute pancreatitis and is strongly associated with increased mortality, particularly in the presence of infected pancreatic necrosis [6,9].

Management of Acute Pancreatitis

The management of acute pancreatitis is primarily supportive and should be tailored according to disease severity, etiology and the presence of complications. Early recognition of patients at risk for severe disease and prompt initiation of appropriate therapy are essential to improve outcomes.

Initial Supportive Care

Early intravenous fluid resuscitation is a cornerstone of management, with recent randomized trials suggesting that moderate fluid resuscitation strategies may reduce complications compared with aggressive hydration [12]. Balanced crystalloid solutions, especially Ringer's lactate, are generally preferred over normal saline due to their favorable effects on acid-base balance and inflammatory response. Fluid administration, particularly within the first 24 hours, should be guided by frequent clinical and laboratory assessment to avoid both hypovolemia or fluid overload [1,6].

Adequate pain control is essential and is typically achieved using opioid analgesics, such as hydromorphone or fentanyl. Oxygen supplementation and respiratory support should be provided as needed, while careful monitoring of vital signs, urine output, hematocrit, and renal function is required to assess response to therapy [1].

Nutritional Support

Early enteral nutrition is recommended once hemodynamic stability is achieved, ideally within 48–72 hours

of admission [13]. Enteral feeding has been shown to preserve gut barrier function, reduce bacterial translocation and decrease the risk of infectious complications compared with parenteral nutrition [14]. Nasogastric feeding is generally safe and effective, with nasojejunal feeding reserved for patients who are unable to tolerate gastric feeding.

Antibiotic Therapy

Routine prophylactic antibiotic administration is not recommended in acute pancreatitis, including cases with sterile pancreatic necrosis. Antibiotics should be reserved for patients with confirmed or strongly suspected infected pancreatic necrosis or for the treatment of extrapancreatic infections [1,6]. When indicated, broad-spectrum antibiotics, such as carbapenems or a combination of a third-generation cephalosporin or fluoroquinolone with metronidazole, are commonly used, guided by microbiological culture results whenever possible.

Endoscopic, Radiologic, and Surgical Interventions

Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy is indicated in patients with gallstone-related acute pancreatitis complicated by acute cholangitis or persistent biliary obstruction [1]. In the absence of these indications, routine early ERCP is not recommended [15].

Management of pancreatic and peripancreatic collections follows a minimally invasive, step-up approach. Percutaneous or endoscopic drainage is preferred as first-line therapy for symptomatic or infected collections, with surgical necrosectomy reserved for patients who fail the less invasive interventions above [6,9]. When feasible, interventions should be delayed for at least four weeks to allow maturation of collections and reduce procedural morbidity [16]. In patients with biliary pancreatitis, cholecystectomy is recommended during the index hospitalization for mild disease or after resolution of inflammation in more severe cases to prevent recurrence.

Chronic Pancreatitis

Definition and Pathophysiology

Chronic pancreatitis is a progressive inflammatory disorder of the pancreas characterized by irreversible structural damage, fibrosis and distortion of the pancreatic ductal system, ultimately leading to loss of exocrine and endocrine function. Chronic pancreatitis, as op-

posed to acute pancreatitis, represents a long-standing process marked by repeated or persistent cellular injury and impaired tissue dys-regeneration [17-20].

At the pathophysiological level, chronic pancreatitis is associated with sustained activation of inflammatory pathways and pancreatic stellate cells, resulting in excessive deposition of extracellular matrix components and progressive fibrosis [18-20]. Over time, cumulative damage leads to acinar cell loss, ductal strictures and eventual islet cell dysfunction, manifesting clinically as malabsorption and pancreatogenic diabetes mellitus [21].

Etiology and Risk Factors

Alcohol abuse remains the predominant etiological factor in chronic pancreatitis, accounting for approximately 70–80% of cases [22,23]. Sustained alcohol consumption has direct toxic effects on pancreatic acinar cells and alters the composition of pancreatic secretions, promoting ductal obstruction. Cigarette smoking has emerged as an independent disease modifier, accelerating progression and increasing the risk of complications [23].

Non-alcoholic causes include genetic disorders, such as mutations in PRSS1, SPINK1, CFTR, and CTRC genes, which are associated with early-onset disease [24]. Auto-immune pancreatitis, a distinct immune-mediated entity often associated with elevated IgG4 levels, represents a potentially reversible cause when recognized earlier [25]. Additional etiologies include anatomic abnormalities, such as pancreas divisum, cystic fibrosis, tropical pancreatitis and idiopathic forms, which account for approximately 10–20% of cases [26-29].

Clinical Manifestations

The clinical presentation of chronic pancreatitis is heterogeneous and non-specific. Chronic or recurrent epigastric pain, often radiating to the back, is the most prominent symptom. Pain severity does not consistently correlate with the extent of structural damage and may diminish in advanced disease due to parenchymal loss and pancreatic burnout [29].

As the disease progresses, destruction of pancreatic parenchyma leads to exocrine pancreatic insufficiency, typically manifesting after loss of more than 90% of exocrine function [30]. Clinical features include steatorrhea, weight loss, fat-soluble vitamin deficiencies and malnutrition [31,32]. Endocrine insufficiency develops later in the disease course and results in pancreatogenic diabetes mellitus, characterized by hard-to-manage

glycemic control and an increased risk of hypoglycemia due to impaired glucagon secretion [33].

Diagnostic Evaluation of Chronic Pancreatitis

The diagnosis of chronic pancreatitis is often challenging, particularly in the early stages of the disease, when structural abnormalities may not be evident and laboratory findings are non-specific [19]. A comprehensive diagnostic strategy incorporates clinical history, laboratory evaluation and imaging modalities, with the selection of investigations determined by disease stage and clinical presentation [34].

Laboratory Assessment

Routine laboratory tests are of limited diagnostic value in chronic pancreatitis. Serum amylase and lipase levels are frequently normal or only mildly elevated, reflecting progressive pancreatic atrophy rather than active inflammation [20]. Evaluation of exocrine pancreatic function is therefore essential in patients with suspected advanced disease. Measurement of fecal elastase-1 is widely used as a non-invasive screening test for exocrine pancreatic insufficiency [35]. Additional tests, such as fecal chymotrypsin measurement or quantitative fecal fat analysis, may provide supportive evidence of malabsorption.

Direct pancreatic functional tests, involving the collection of pancreatic secretions after secretin or cholecystokinin stimulation, represent the reference standard for assessing exocrine function. However, their invasive nature and limited availability restrict their use in daily clinical practice [36]. Indirect tests, such as fecal elastase measurement, are more commonly undertaken due to their simplicity and acceptable diagnostic performance in advanced disease.

Assessment of endocrine function should include fasting plasma glucose, glycated hemoglobin, or oral glucose tolerance testing to detect pancreatogenic diabetes mellitus [33]. Nutritional evaluation, including serum levels of fat-soluble vitamins, albumin, and prealbumin, may be useful in identifying malnutrition and guiding supportive therapy.

Imaging Modalities

Cross-sectional imaging plays a central role in the diagnosis of chronic pancreatitis. Contrast-enhanced computed tomography (CT) is often the initial imaging modality and may demonstrate pancreatic calcifications, glandular atrophy, ductal dilation, and pseudocyst formation, particularly in advanced disease. However,

CT has limited sensitivity for early-stage chronic pancreatitis [37,38].

Magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography (MRCP) provides superior visualization of the pancreatic parenchyma and ductal anatomy. MRCP allows detailed assessment of pancreatic ductal irregularities, strictures, and side-branch abnormalities. Secretin-enhanced MRCP further improves diagnostic accuracy by evaluating ductal compliance and exocrine function [37,38].

Endoscopic ultrasound (EUS) is considered the most sensitive modality for the detection of early chronic pancreatitis. EUS enables high-resolution imaging of the pancreatic parenchyma, the ductal system and early fibrosis [39]. In some controversial cases, EUS-guided fine-needle biopsy may be performed to confirm autoimmune pancreatitis or malignancy.

Local and Systemic Complications of Chronic Pancreatitis

Chronic pancreatitis is associated with a wide spectrum of local and systemic complications that impact patients' quality of life. Their incidence increases with disease duration, and they are consequences of progressive pancreatic fibrosis, ductal obstruction and chronic inflammation [20].

Pancreatic pseudocysts are the most common local complications, and they develop because of ductal disruption or persistent inflammation. Large or complicated collections may cause abdominal pain, gastric outlet obstruction, infection, or hemorrhage [39]. Obstruction of the intrapancreatic portion of the common bile duct due to inflammatory mass formation or fibrosis can result in obstructive jaundice and cholangitis [40].

Vascular complications include thrombosis of the splenic or portal vein, which may lead to segmental portal hypertension and the development of gastric or esophageal varices, predisposing patients to gastrointestinal bleeding [39]. Pancreatic ascites and pleural effusions may occur following ductal leakage, whereas duodenal or colonic obstruction may result from inflammatory strictures or extrinsic compression.

A particularly important consideration is the increased risk of pancreatic ductal adenocarcinoma in patients with long-standing chronic pancreatitis. Differentiating inflammatory pancreatic masses from malignancy remains a diagnostic challenge and necessitates careful surveillance, especially in patients with new-onset symptoms or unexplained clinical deterioration [41].

Systemic complications primarily reflect exocrine pancreatic insufficiency, which leads to maldigestion, weight loss, fat-soluble vitamin deficiencies, malnutrition and sarcopenia. Endocrine insufficiency manifests as pancreatogenic diabetes mellitus, characterized by impaired insulin and glucagon secretion and an increased risk of hypoglycemia (type 3 diabetes) [23,43]. Osteoporosis and osteopenia may develop secondary to malabsorption and vitamin D deficiency, further contributing to long-term morbidity [32].

Management Strategies for Chronic Pancreatitis

The management of chronic pancreatitis requires a multidisciplinary approach aimed at symptom control, prevention of complications and preservation of nutritional and metabolic status [34]. Treatment strategies should be individualized according to disease severity, anatomical findings, and the patient's quality of life.

Lifestyle Modification

Abstinence from alcohol and smoking remains fundamental components of management and are strongly associated with improved symptom control and slower disease progression [22,23]. Nutritional counseling is essential, with emphasis on adequate caloric intake and supplementation of fat-soluble vitamins [42].

Pain Management

Pain control follows a stepwise approach, beginning with non-opioid analgesics and progressing to opioid therapy when necessary. Adjunctive therapies, including antidepressants and neuromodulators, may be beneficial in selected patients. In cases of refractory pain, celiac plexus block or neurolysis may be considered after exclusion of local complications [29].

Management of Pancreatic Insufficiency

Pancreatic enzyme replacement therapy for pancreatic insufficiency should be administered with meals to optimize digestion and nutrient absorption, thereby improving steatorrhea and nutritional status. Endocrine insufficiency is managed with insulin therapy, with careful monitoring due to the increased risk of hypoglycemia in pancreatogenic diabetes [23,43].

Invasive Interventions

Endoscopic therapy plays an important role in selected patients, particularly those with dominant pancreatic duct strictures, intraductal stones or symp-

tomatic pseudocysts. Endoscopic retrograde cholangiopancreatography (ERCP) with ductal stenting or stone extraction may provide symptom relief and delay the need for surgery [43].

Surgical intervention is reserved for patients with refractory pain, complications unresponsive to endoscopic treatment or suspicion of malignancy. Surgical options include decompressive procedures, pancreatic resection, or combined approaches [44,45]. Early referral to specialized centers is recommended to optimize outcomes.

Current Guidelines and Future Perspectives

Over the past decades, the management of both acute and chronic pancreatitis has evolved substantially, guided by evidence-based recommendations issued by international scientific societies. Contemporary guidelines emphasize early risk stratification, judicious use of diagnostic imaging and a shift toward minimally invasive therapeutic strategies, along with balanced crystalloid resuscitation, and avoidance of prophylactic antibiotics in sterile necrosis [1,6].

In acute pancreatitis, current recommendations support early fluid resuscitation with balanced crystalloid solutions, avoidance of prophylactic antibiotics, and early initiation of enteral nutrition. The adoption of a step-up approach for the management of pancreatic necrosis, favoring endoscopic interventions over early surgical necrosectomy, has resulted in reduced morbidity and improved outcomes [43]. Ongoing research focuses on refining prognostic tools, identifying reliable biomarkers for early severity prediction and optimizing individualized treatment pathways.

In chronic pancreatitis, guidelines highlight the importance of etiological classification, lifestyle modification and a multidisciplinary approach to pain management and nutritional support. Advances in endoscopic techniques and surgical strategies have expanded therapeutic options, while emerging insights into the molecular mechanisms of pancreatic fibrosis and inflammation offer potential targets for disease-modifying therapies. Future research is expected to further clarify the role of early intervention in altering disease progression and improving long-term quality of life.

CONCLUSIONS

Acute and chronic pancreatitis represent heterogeneous pancreatic disorders with significant clinical and

healthcare impact. Accurate diagnosis, early assessment of disease severity and timely implementation of evidence-based management are crucial for patient outcomes. Research in diagnostic imaging, supportive care and minimally invasive interventions has improved the prognosis of severe acute pancreatitis. In chronic pancreatitis, prevention of complications, effective symptom control and management of pancreatic insufficiency remain central therapeutic goals. Clinicians' adherence to international guidelines, combined with a personalized approach, is crucial for optimizing patient treatment.

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REFERENCES

- Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, et al. Acute pancreatitis. *Lancet*. 2020;396(10252):726–34.
- Trikudanathan G, Wolbrink DRJ, van Santvoort HC, Mallory S, Freeman M, Besselink MG. Current concepts in severe acute and necrotizing pancreatitis: An Evidence-Based Approach. *Gastroenterology*. 2019;156(7):1994–2007.e3.
- Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9):1400–15.
- Nawaz H, Mounzer R, Yadav D, Yabes JG, Slivka A, Whitcomb DC, et al. Revised Atlanta and determinant-based classification: application in a prospective cohort of acute pancreatitis patients. *Am J Gastroenterol*. 2013;108(12):1911–7.
- Bollen TL, Singh VK, Maurer R, Repas K, van Es HW, Banks PA, et al. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. *Am J Gastroenterol*. 2012;107(4):612–9.
- Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol*. 2013;13(4 Suppl 2):e1–15.
- Whitcomb DC. Genetic risk factors for pancreatic disorders. *Gastroenterology*. 2013;144(6):1292–302.
- Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102–11.
- Van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CHC, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010;362(16):1491–502.
- De Bernardinis M, Violi V, Roncoroni L, Boselli AS, Giunta A, Peracchia A. Discriminant power and information content of Ranson's prognostic signs in acute pancreatitis: a meta-analytic study. *Crit Care Med*. 1999;27(10):2272–83.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818–29.
- de-Madaria E, Buxbaum JL, Maisonneuve P, García de Paredes AG, Zapater P, Guilabert L, et al. Aggressive or moderate fluid resuscitation in acute pancreatitis. *N Engl J Med*. 2022;387(11):989–1000.
- Yao Q, Liu P, Peng S, Xu X, Wu Y. Effects of immediate or early oral feeding on acute pancreatitis: a systematic review and meta-analysis. *Pancreatol*. 2022;22(2):175–84.
- Kumar A, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial. *J Clin Gastroenterol*. 2006;40(5):431–4.
- Schepers NJ, Hallensleben NDL, Besselink MG, Anten MP, Bollen TL, da Costa DW, et al. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *Lancet*. 2020;396(10245):167–76.
- Boxhoorn L, van Dijk SM, van Grinsven J, van Grinsven J, Verdonk RC, Boermeester MA, et al. Immediate versus postponed intervention for infected necrotizing pancreatitis. *N Engl J Med*. 2021;385(15):1372–81.
- Stevens T, Conwell DL, Zuccaro G Jr. Pathogenesis of chronic pancreatitis: an evidence-based review of past theories and recent developments. *Am J Gastroenterol*. 2004;99(11):2256–70.
- Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatol*. 2016;16(2):218–24.
- Majumder S, Chari ST. Chronic pancreatitis. *Lancet*. 2016;387(10031):1957–66.
- Vege SS, Chari ST. Chronic pancreatitis. *N Engl J Med*. 2022;386(9):869–78.
- Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark C, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol*. 2016;1(3):226–37.
- Lugea A, Gerloff A, Su HY, Xu Z, Go A, Hu C, et al. The combination of alcohol and cigarette smoke induces endoplasmic reticulum stress and cell death in pancreatic acinar cells. *Gastroenterology*. 2017;153(6):1674–86.
- Coté GA, Yadav D, Slivka A, Hawes RH, Anderson MA, Burton FR, et al. Alcohol and smoking as risk factors in an epidemiology study of patients with chronic pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9(3):266–73.

24. Mounzer R, Whitcomb DC. Genetics of acute and chronic pancreatitis. *Curr Opin Gastroenterol*. 2013;29(5):544–51.
25. Okazaki K, Uchida K. Current Concept of Autoimmune Pancreatitis and IgG4-related Disease. *Am J Gastroenterol*. 2018;113(10):1412–6.
26. Romagnuolo J, Talluri J, Kennard E, Sandhu BS, Sherman S, Cote GA, et al. Clinical profile, etiology, and treatment of chronic pancreatitis in North American women: analysis of a large multicenter cohort. *Pancreas*. 2016;45(7):934–40.
27. Wilcox CM, Sandhu BS, Singh V, Gelrud A, Abberbock J, Sherman S, et al. Racial Differences in the Clinical Profile, Causes, and Outcome of Chronic Pancreatitis. *Am J Gastroenterol*. 2016;111(10):1488–96.
28. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1252–61.
29. Drewes AM, Bouwense SAW, Campbell CM, Ceyhan GO, Delhaye M, Ekin Demir I, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. *Pancreatology*. 2017;17(5):720–31.
30. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. *Gastroenterology*. 2015;149(6):1490–500e1.
31. Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. *Gastroenterology*. 2023;165(5):1292–301.
32. Duggan SN, Smyth ND, Murphy A, Macnaughton D, O’Keefe SJD, Conlon KC. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2014;12(2):219–28.
33. Mohapatra S, Majumder S, Smyrk TC, Zhang L, Matveyenko A, Kudva YC, et al. Diabetes Mellitus Is Associated With an Exocrine Pancreatopathy: Conclusions From a Review of Literature. *Pancreas*. 2016;45(8):1104–10.
34. Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG Clinical Guideline: Chronic pancreatitis. *Am J Gastroenterol*. 2020;115(3):322–39.
35. Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic Performance of Measurement of Fecal Elastase-1 in Detection of Exocrine Pancreatic Insufficiency: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16(8):1220–8e4.
36. Kothari D, Ketwaroo G, Sawhney MS, Freedman SD, Sheth SG. Comparison of Combined Endoscopic Ultrasonography and Endoscopic Secretin Testing With the Traditional Secretin Pancreatic Function Test in Patients With Suspected Chronic Pancreatitis: A Prospective Crossover Study. *Pancreas*. 2017;46(6):770–5.
37. Frøkjær JB, Akisik F, Farooq A, Akpinar B, Dasyam A, Drewes AM, et al. Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis. *Pancreatology*. 2018;18(7):764–73.
38. Issa Y, Kempeneers MA, van Santvoort HC, Bollen TL, Bipat S, Boermeester MA. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. *Eur Radiol*. 2017;27(9):3820–44.
39. Mutignani M, Dokas S, Tringali A, Forti E, Pugliese F, Cintolo M, et al. Pancreatic leaks and fistulae: An Endoscopy-Oriented Classification. *Dig Dis Sci*. 2017;62(10):2648–57.
40. Hammel P, Couvelard A, O’Toole D, Ratouis A, Sauvanet A, Fléjou JF, et al. Regression of liver fibrosis after biliary drainage in patients with chronic pancreatitis and stenosis of the common bile duct. *N Engl J Med*. 2001;344(6):418–23.
41. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. *Lancet Gastroenterol Hepatol*. 2016;1(1):45–55.
42. Martínez-Moneo E, Stigliano S, Hedström A, Kaczka A, Malvik M, Waldthaler A, et al. Deficiency of fat-soluble vitamins in chronic pancreatitis: a systematic review and meta-analysis. *Pancreatology*. 2016;16(6):988–94.
43. Cahen DL, Gouma DJ, Nio Y, Rauws EAJ, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med*. 2007;356(7):676–84.
44. Issa Y, Kempeneers MA, Bruno MJ, Fockens P, Poley JW, Ahmed Ali U, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. *JAMA*. 2020;323(3):237–47.
45. Zhao X, Cui N, Wang X, Cui Y. Surgical strategies in the treatment of chronic pancreatitis: An updated systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2017;96(9):e6220.

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Advances in the Management of Chronic Kidney Disease

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Abstract

Chronic Kidney Disease (CKD) is a major public health problem, affecting a large proportion of the global population and is associated with increased cardiovascular morbidity and mortality. Recent advances in diagnosis, including updated clinical guidelines, and numerous clinical trials that support new therapeutic options, have expanded the understanding of CKD. This review provides an overview of current evidence on the diagnosis, classification, and management of CKD, with a particular focus on pharmacologic interventions. In addition to the established use of renin-angiotensin system inhibitors (RAASi) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), nonsteroidal mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide-1 (GLP-1) receptor agonists have shown kidney and cardiovascular benefits in patients with CKD with or without concomitant diabetes mellitus.

Key words: *Chronic kidney disease; renin–angiotensin system inhibitors; SGLT2 inhibitors; mineralocorticoid receptor antagonists; GLP-1 receptor agonists*

INTRODUCTION

CKD is a progressive disease with high global prevalence (approximately 9%) [1]. It remains a major health problem linked to increased cardiovascular morbidity and mortality. CKD is defined as abnormalities of kidney structure or function that persist for at least three months and have implications for health [2]. The latest guidelines classify CKD based on cause, glomerular filtration rate (GFR) category (G1–G5), and albuminuria category (A1–A3). These three components help determine the severity and risk of CKD (Table 1).

The KDIGO CKD risk grid uses estimated glomerular filtration rate (eGFR) and albuminuria to stratify prognosis in CKD. It was developed from large cohort studies showing that lower eGFR and higher urinary albumin excretion in combination predict outcomes

such as CKD progression, kidney failure, cardiovascular events and mortality. The color coding represents risk gradients across these two dimensions, providing an outcome-oriented assessment that is more informative than eGFR staging alone.

Despite the increasing burden of CKD, there is no universal agreement on the effectiveness of population-wide screening programs [3]. Screening is typically considered for individuals at high risk, such as those with diabetes or hypertension. The rationale for targeted screening in these groups is that early identification may improve outcomes by enabling timely intervention. Screening should be performed using both urinary albumin measurement and eGFR. Following incidental detection of an elevated uACR, hematuria or a reduced eGFR, testing should be repeated to confirm the presence of CKD [2]. While eGFR testing rates are consistently high, UACR testing rates remain low. This results in underdiagnosis and undertreatment, putting many individuals at risk of CKD progression and CVD [4].

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Table 1. CKD stages and cardiovascular risk based on eGFR and albuminuria categories [2].

		Persistent albuminuria categories		
		A1 <30 mg/g	A2 30–300 mg/g	A3 >300 mg/g
GFR categories (ml/min/1.73 m ²)	G1 ≥90	Low risk	moderately increased risk	high risk
	G2 60–89	Low risk	moderately increased risk	high risk
	G3a 45–59	moderately increased risk	high risk	very high risk
	G3b 30–44	high risk	very high risk	very high risk
	G4 15–29	very high risk	very high risk	very high risk
	G5 <15	very high risk	very high risk	very high risk

The initial assessment of albuminuria should be based on measuring the urine albumin-to-creatinine ratio (ACR) or, alternatively, on urine dipstick testing for albumin with automated reading and ACR quantification. If total urine protein is measured, a measurement of the urine protein-to-creatinine ratio (PCR) is preferred. If not available, urine dipstick testing for total protein with automated or manual reading may be performed. In all cases, a first-morning midstream urine sample is recommended for both adults and children. If an ACR value exceeding 30 mg/g is detected in a random urine sample, the result should be confirmed by repeat testing using a subsequent first morning void in the midstream urine sample [2].

Establishing Chronicity

CKD is defined by kidney abnormalities persisting for at least 3 months (or more than 90 days), a threshold used to distinguish CKD from acute kidney disease (AKD) and acute kidney injury (AKI), which differ in etiology, management and outcomes. Evidence of chronicity can be established through prior documentation of reduced eGFR, prior albuminuria or urine sediment abnormalities, imaging suggestive of chronic damage (e.g. reduced kidney size or cortical thinning), histopathological features (fibrosis or atrophy), relevant medical history (conditions that cause or accelerate CKD), or repeat measurements that confirm persistence beyond three months.

Chronicity should not be determined by a single abnormal eGFR or ACR, as these values may only reflect recent AKI/AKD. When CKD is clinically likely based on supporting evidence, initiating CKD-directed management at first presentation may be appropriate to avoid delaying management. Repeat testing remains important for accurate diagnosis and staging.

Etiology of CKD

Beyond establishing chronicity and stage, the cause of CKD remains important, as it guides more appropriate therapy to slow progression to kidney failure (e.g. in glomerular diseases), provides further information about the risk of progression (e.g. in IgA prediction tools), and helps to understand contributing factors [5].

To determine the etiology of CKD, we must use a comprehensive assessment that includes clinical context, personal and family medical history, social and environmental factors, medication review, physical examination, laboratory investigations, imaging modalities, as well as genetic and pathological analyses for diagnosis. Healthcare providers must consider referrals to expert centers.

CKD Management

Management of CKD should follow a comprehensive treatment strategy to slow disease progression and

reduce associated complications. Risk factors for CKD progression, cardiovascular disease (CVD), and other complications are closely interconnected; therefore, their management must be integrated [6]. CKD treatment and risk modification target both CKD manifestations (such as hypertension, anemia, dyslipidemia, CKD–mineral and bone disease, potassium imbalance, metabolic acidosis, and reproductive or pregnancy-related complications) and CKD outcomes (progression to kidney failure, cardiovascular events, hospitalization, infections, gout, and mortality).

Lifestyle Modifications

People with CKD should be supported in adopting lifestyle behaviors that reduce cardiovascular risk, including regular physical activity tailored to tolerance and frailty, weight management to achieve an optimal BMI, and complete avoidance of tobacco products. Where appropriate and available, referral to other specialties (renal dietitians and nutrition providers, smoking cessation programs, physical and occupational therapy, psychological support) should be offered to facilitate sustained behavior change.

Management of dyslipidemia is based upon the use of statins. Adults with CKD G3–G5 are advised to maintain a protein intake of 0.8 g/kg body weight/day. Sodium intake should remain below 2 g/day (or 5 g of sodium chloride/day) across all patients with CKD [2].

Pharmacologic pillars for slowing CKD progression

Contemporary pharmacological therapy is built on four complementary pillars that reduce kidney disease progression and cardiovascular risk. Renin–angiotensin–aldosterone system (RAAS) inhibitors continue to serve as the cornerstone, effectively reducing intraglomerular pressure and albuminuria. Sodium–glucose cotransporter-2 (SGLT2) inhibitors offer additional kidney and cardiovascular protection through mechanisms involving hemodynamic, metabolic, and anti-inflammatory pathways. Nonsteroidal mineralocorticoid receptor antagonists (MRAs) further decrease inflammation and fibrosis, particularly in patients with persistent albuminuria. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) offer cardiometabolic and kidney advantages, particularly for individuals with type 2 diabetes (T2D). The integration of these therapies represents a multi-dimensional mechanism-based approach designed to sustainably decelerate CKD progression and reduce cardiovascular morbidity and mortality.

Renin-Angiotensin-Aldosterone System Inhibitors (RAASi)

Mechanism of Action and Pathophysiologic Rationale

The RAAS is a key regulatory axis that maintains organ perfusion and regulates blood pressure through sodium and water retention, vasoconstriction, and volume expansion. Its principal components include renin (kidney-derived), angiotensin II (generated via ACE-mediated activation of angiotensin I), and aldosterone (secreted from the adrenal cortex). Angiotensin II plays the most important role, as it causes vasoconstriction in the postglomerular arterioles, thereby increasing hydraulic pressure and promoting ultrafiltration of plasma proteins [7]. Chronic RAAS activation may also accelerate inflammation, fibrosis, and structural damage in the kidney, heart, and vasculature, thus playing a major role in the elevated cardiovascular risk observed in hypertension, diabetes, and cardiovascular disease [8]. Pharmacologic RAAS inhibition with ACE inhibitors and angiotensin receptor blockers has been shown to delay CKD progression and reduce cardiovascular events, establishing these agents as foundational therapies in CKD.

Evidence from Landmark Trials

The 1993 study by Lewis et al. evaluated the effect of captopril in patients with insulin-dependent diabetes and established diabetic nephropathy. In this randomized, placebo-controlled trial involving 409 patients, captopril was compared to placebo in addition to conventional therapy [9]. The addition of captopril significantly reduced the risk of doubling of serum creatinine compared with placebo. Importantly, these benefits were independent of blood pressure reduction, demonstrating a specific renoprotective effect of ACE inhibition. This landmark trial established ACE inhibitors as standard therapy for diabetic nephropathy and fundamentally changed the management of CKD in diabetes.

The RENAAL and IDNT trials that followed evaluated the renal protective effects of angiotensin II receptor blockers (ARBs) in patients with T2D and diabetic nephropathy [10,11]. In the RENAAL trial, losartan was compared with placebo in patients with T2D and proteinuric CKD. Losartan significantly reduced the risk of the primary outcome (doubling of serum creatinine, end-stage kidney disease (ESKD), or death) by 16%, demonstrating a renoprotective effect beyond blood pressure control. Similarly, in the IDNT trial, irbesartan was compared with amlodipine and placebo in a high-risk population. Irbesartan reduced the risk of the same

renal outcome by 20% compared with the placebo group and by 23% compared with the amlodipine group.

Both trials established ARBs as standard therapy for diabetic kidney disease, although a substantial residual renal risk remained despite RAAS blockade. While these trials were conducted in patients with diabetic nephropathy, they strongly influenced the adoption of RAAS inhibition across proteinuric CKD.

Guideline Recommendations and Clinical Implementation

RAASi (ACEi or ARB) are recommended for people with CKD stages G1–G4 and severely increased albuminuria (A3) without diabetes, and are suggested for those with CKD G1–G4 and moderately increased albuminuria (A2) without diabetes. In people with diabetes, RAASi initiation is recommended for CKD G1–G4 with moderately to severely increased albuminuria (A2–A3). In all CKD populations, combination therapy with an ACE inhibitor plus an ARB and/or a direct renin inhibitor should be avoided, regardless of diabetes status, due to an unfavorable risk–benefit profile.

Changes in blood pressure, serum creatinine, and serum potassium should be monitored within 2–4 weeks after initiation or dose escalation of a RAASi, depending on baseline GFR and serum potassium levels. Hyperkalemia associated with RAASi therapy can often be managed with potassium-lowering measures rather than reducing the dose or discontinuing the RAASi. Treatment with an ACE inhibitor or ARB should be continued unless serum creatinine increases by more than 30% within four weeks of treatment initiation or dose escalation.

Of utmost importance, ACE inhibitors or ARBs should be administered at the highest approved dose tolerated to achieve the described benefits, as the efficacy observed in clinical trials was demonstrated at these dose levels. Furthermore, RAAS inhibitors should generally be continued in people with CKD even when eGFR declines below 30 mL/min/1.73 m². Evidence from the STOP-ACEi trial (n=411; mean eGFR ~13 mL/min/1.73 m²) showed that routine discontinuation of RAAS inhibitors in advanced CKD (G4–G5) did not result in renal or cardiovascular benefit [12].

Sodium–Glucose Cotransporter 2 Inhibitors (SGLT2i)

Mechanism of Action and Pathophysiologic Rationale

Sodium–glucose cotransporter 2 (SGLT2) inhibitors

act in the proximal convoluted tubule of the kidney to reduce reabsorption of filtered glucose and sodium. Normally, nearly all filtered glucose (~180 g/day) is reabsorbed from the tubular lumen into proximal tubular cells via SGLT2 on the luminal membrane, with energy provided by the Na⁺/K⁺ATPase on the basolateral membrane. SGLT2 inhibition increases urinary glucose excretion (glycosuria) and induces natriuresis, leading to osmotic diuresis and modest reductions in plasma glucose and blood pressure. Enhanced sodium delivery to the macula densa restores tubuloglomerular feedback, resulting in afferent arteriolar vasoconstriction, lower intraglomerular pressure, and attenuation of hyperfiltration, a key mechanism underlying the renal protective effects of SGLT2 inhibitors [13]. Beyond hemodynamic changes, SGLT2 inhibitors also exert beneficial metabolic and anti-inflammatory effects that contribute to reduced progression of CKD and lower cardiovascular risk.

Evidence from Landmark Trials

The hallmark CREDENCE trial (published in 2019) evaluated the effects of canagliflozin 100 mg daily in patients with T2D and CKD who were already receiving stable background RAAS blockade [12]. A total of 4,401 participants were randomized, with a mean follow-up of 2.62 years. Eligible patients had an eGFR between 30 and 90 mL/min/1.73 m² and significant albuminuria, defined as a urine albumin-to-creatinine ratio of 300 to 5,000 mg/g, reflecting a population at high kidney and cardiovascular risk. The primary endpoint was end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes. Canagliflozin significantly reduced the risk of the primary outcome compared with placebo, corresponding to a 30% relative risk reduction. The renal-specific outcome (ESKD or doubling of serum creatinine) was also significantly reduced by 34% in patients treated with canagliflozin. These findings demonstrated that, in patients with T2D and albuminuric CKD already treated with RAASi, canagliflozin provided substantial additional renal and cardiovascular protection.

The DAPA-CKD trial evaluated dapagliflozin 10 mg daily in patients with CKD of various etiologies, including those with and without T2D. All participants were receiving background therapy with an ACE inhibitor or ARB [14]. Eligible patients had an eGFR between 25 and 75 mL/min/1.73 m² and significant albuminuria (UACR 200–5000 mg/g). A total of 4,304 patients were randomized and followed for a median of 2.4 years.

The primary outcome was a sustained $\geq 50\%$ decline in eGFR, end-stage kidney disease, or death from renal or cardiovascular causes. During follow-up, a primary event occurred in 9.2% of patients receiving dapagliflozin, compared with 14.5% in the placebo group, corresponding to a 39% relative risk reduction. The number needed to treat (NNT) to prevent one primary outcome event was 19. Patients treated with dapagliflozin showed a slower long-term decline in kidney function. Although an initial greater fall in eGFR was observed during the first two weeks of therapy, this was followed by a slower decline slope in renal function compared with placebo.

The EMPA-KIDNEY trial evaluated empagliflozin 10 mg daily in patients with CKD of various etiologies, including individuals with and without T2D [15]. All participants were receiving background therapy with an ACE inhibitor or ARB when indicated. Eligible patients had an eGFR of 20–45 mL/min/1.73 m², or an eGFR of 45–90 mL/min/1.73 m² with a urine albumin-to-creatinine ratio (UACR) >200 mg/g. A total of 6,609 patients were randomized and followed for a median of two years. The primary outcome was a sustained $\geq 40\%$ decline in eGFR, end-stage kidney disease, or death from renal or cardiovascular causes. Disease progression or cardiovascular death occurred in 13.1% of patients in the empagliflozin group compared with 16.9% in the placebo group, corresponding to a 28% relative risk reduction. The benefits of empagliflozin were consistent in patients with or without diabetes and were independent of baseline eGFR. There was some evidence suggesting that the proportional risk reduction may have been greater among patients with higher baseline albuminuria. Overall, empagliflozin significantly slowed kidney disease progression and reduced cardiovascular risk across a broad CKD population.

A large meta-analysis of major SGLT2 inhibitor trials, comparing SGLT2 inhibitors with placebo in people with and without diabetes, showed that SGLT2 inhibitors significantly reduced the risk of kidney disease progression, indicating a $\sim 37\%$ relative risk reduction, with broadly consistent effects across diabetes status, and decreased the risk of acute kidney injury corresponding to a $\sim 23\%$ reduction [16].

Guideline Recommendations and Clinical Implementation

Treatment with an SGLT2 inhibitor is recommended for patients with T2D and CKD who have an eGFR ≥ 20

mL/min/1.73 m² (Grade 1A). Once therapy has been initiated, continuation of the SGLT2 inhibitor is appropriate even if eGFR falls below 20 mL/min/1.73 m², unless the medication is not tolerated or kidney replacement therapy (KRT) is started. Temporary discontinuation should be considered during periods of prolonged fasting, surgical procedures, or critical medical illness, when the risk of ketosis may be increased.

In addition, treatment with an SGLT2 inhibitor is recommended for adults with CKD (Grade 1A) who have either an eGFR ≥ 20 mL/min/1.73 m² with a urine albumin-to-creatinine ratio (ACR) ≥ 200 mg/g (≥ 20 mg/mmol), or heart failure, regardless of the level of albuminuria.

It should be noted that SGLT2i initiation does not require alteration of frequency of CKD monitoring as the reversible decrease in eGFR on initiation is generally not an indication to discontinue therapy.

The latest guidelines also suggest treating patients with eGFR 20 to 45 mL/min/1.73 m² and ACR <200 mg/g (<20 mg/mmol) with an SGLT2i.

Mineralocorticoid Receptor Antagonists

Mechanism of Action and Pathophysiologic Rationale

Aldosterone is the principal mineralocorticoid hormone. It is produced in the zona glomerulosa of the adrenal cortex, primarily in response to hyperkalemia or sodium depletion, and represents a downstream effector of renin–angiotensin system activation. Studies have also demonstrated aldosterone synthesis in peripheral tissues [17]. Aldosterone is central to the regulation of blood pressure and extracellular fluid volume, by promoting renal sodium reabsorption and enhancing potassium excretion, by interacting with the MRs that are expressed in the renal epithelial cells in the distal nephron [18].

It is now well known that MR is also expressed in non-epithelial tissues, such as the heart, adipocytes, podocytes, inflammatory cells, endothelial cells, and vascular smooth muscle cells. Multiple studies have shown that aldosterone and MR activation play a role in various aspects of renal and cardiovascular damage. Aldosterone binding to MR stimulates NADPH oxidase activity, leading to increased reactive oxygen species (ROS) generation, reduced nitric oxide (NO) bioavailability, and activation of intracellular signaling pathways such as p38 MAPK, SGK-1, NF- κ B, and AP-1. These molecular cascades promote the production of pro-inflammatory cytokines and profibrotic mediators

(e.g., TGF- β , CTGF, osteopontin), resulting in inflammation and fibrosis (Figure 1) [19].

In the heart, this process contributes to myocardial hypertrophy, ventricular remodeling, ischemia, arrhythmias, and myocardial injury. In the kidneys, it promotes glomerular hypertrophy, glomerulosclerosis, proteinuria, reduced renal blood flow, and progressive renal injury. Mineralocorticoid receptor antagonists (MRAs) interrupt these pathways, thereby reducing oxidative stress, inflammation, and fibrosis, and protecting both cardiac and renal function.

Spironolactone and eplerenone are steroidal, flat-structured compounds, whereas finerenone is a bulkier, nonsteroidal molecule. While spironolactone demonstrates high potency at the MR, it has lower selectivity and is associated with central nervous system penetration and more frequent sex hormone related adverse effects due to off-target receptor interactions. Eplerenone offers greater selectivity than spironolactone but has lower MR potency and a shorter half-life.

Finerenone, in contrast, combines high potency with greater selectivity for the MR and minimal off-target hormonal effects. It has limited CNS penetration, no active metabolites, and a shorter half-life. Compared with steroidal MRAs, finerenone exerts a more balanced

cardiorenal protective effect with a comparatively modest impact on blood pressure [20].

Evidence from Landmark Trials

One of the first clinical evaluations of the albuminuria-lowering effect of selective mineralocorticoid receptor blockade with eplerenone in T2D was conducted in a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial involving 268 patients with T2D and albuminuria, which was published in 2006. Participants received background therapy with the ACE inhibitor enalapril and were randomized to add eplerenone 50 mg, eplerenone 100 mg, or placebo. The addition of eplerenone at either dose produced a clinically meaningful and statistically significant reduction in albumin excretion compared with enalapril plus placebo, demonstrating that selective aldosterone blockade can provide incremental antiproteinuric benefit on top of renin–angiotensin system inhibition in albuminuric T2D [21]. A recent prospective clinical study demonstrated that, among patients with glomerular diseases, add-on eplerenone therapy resulted in a significant reduction in proteinuria, was well tolerated, and did not cause meaningful short-term deterioration in kidney function. These findings support the conclusion that eplerenone

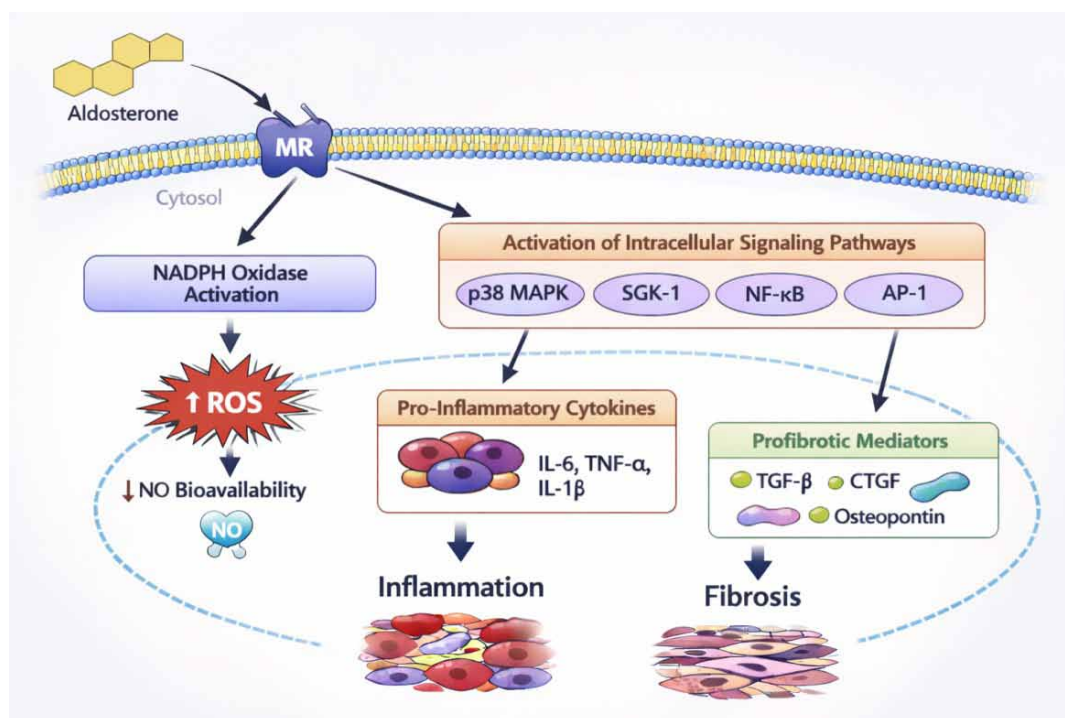


Figure 1. Intracellular cascade after MR activation.

may offer antiproteinuric benefits beyond standard therapy across various etiologies of proteinuric CKD [22].

Later trials explored the benefits of non-steroidal MRAs. The FIDELIO-DKD trial evaluated the efficacy and safety of finerenone, on top of standard of care, in patients with T2D and advanced CKD. Eligible patients had an eGFR of 25–60 mL/min/1.73 m² with moderately increased albuminuria (ACR 30–300 mg/g) plus diabetic retinopathy, or an eGFR of 25–75 mL/min/1.73 m² with severely increased albuminuria (ACR 300–5000 mg/g). The primary outcome included kidney failure (end-stage kidney disease defined as initiation of dialysis for ≥90 days or kidney transplantation), sustained eGFR <15 mL/min/1.73 m², a sustained ≥40% decline in eGFR from baseline, or death from renal causes. Finerenone significantly reduced the risk of kidney disease progression compared with placebo. In addition, treatment was associated with a lower risk of cardiovascular events.

The FIGARO-DKD trial followed, evaluating the efficacy and safety of finerenone, on top of standard of care in patients with T2D and CKD stages 1–4 with moderately to severely increased albuminuria [23]. Eligible patients had either a urine albumin-to-creatinine ratio (UACR) of 30–300 mg/g with an eGFR of 25–90 mL/min/1.73 m² or a UACR of 300–5000 mg/g with an eGFR ≥60 mL/min/1.73 m². The primary cardiovascular outcome included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Finerenone significantly reduced the risk of the primary cardiovascular outcome compared with placebo, with the benefit largely driven by a reduction in hospitalization for heart failure. Overall, in patients with T2D and earlier-stage CKD with albuminuria, finerenone improved cardiovascular outcomes when added to optimized background therapy, complementing the kidney-focused benefits demonstrated in FIDELIO-DKD in a more advanced CKD population.

The CONFIDENCE trial was a randomized, double-blind, three-arm Phase 2 study in adults with CKD (eGFR 30–90 mL/min/1.73 m²), significant albuminuria (UACR 100–5000 mg/g), and T2D already treated with RAAS blockade. Participants were assigned to receive finerenone, empagliflozin, or both. At 180 days, initial combination therapy led to a significantly greater reduction in UACR than either agent alone, with a 29% greater reduction than with finerenone alone and a 32% greater reduction than with empagliflozin alone. The combination generally did not result in serious adverse events. These findings support the albuminuria-lowering

effect of finerenone and empagliflozin in patients with CKD and T2D. They also indicate that treatment can be initiated with both agents simultaneously [24].

There is currently no definitive evidence supporting the use of nonsteroidal MRAs in patients with CKD without diabetes. However, this question is being addressed in the ongoing FIND-CKD trial [25].

Guideline Recommendations and Clinical Implementation

A nonsteroidal MRA with proven kidney or cardiovascular benefit is suggested for adults with T2D, an eGFR >25 mL/min/1.73 m², normal serum potassium, and persistent albuminuria (>30 mg/g) despite treatment with a maximally tolerated dose of a renin–angiotensin system inhibitor (RAASi). Where indicated, a nonsteroidal MRA may be added to therapy with a RAASi and an SGLT2 inhibitor for adults with T2D and CKD.

To reduce the risk of hyperkalemia, candidates should have consistently normal serum potassium at baseline, and serum potassium should be monitored regularly after initiation. Selection should prioritize agents with documented renal and/or cardiovascular outcome benefits. In contrast, steroidal MRAs may be used for indications such as heart failure, hyperaldosteronism, or resistant hypertension, but carry a higher risk of hyperkalemia and a reversible decline in GFR, particularly in patients with low baseline kidney function.

Serum potassium should be carefully monitored during treatment with a nonsteroidal MRA such as finerenone, following protocols derived from the FIDELIO-DKD and FIGARO-DKD trials. Finerenone may be initiated in patients with normal baseline potassium (generally ≤4.8 mmol/L), with dose selection based on eGFR. Potassium should be reassessed approximately one month after initiation and periodically thereafter (e.g. every 4 months). If potassium rises to 4.9–5.5 mmol/L, treatment may be continued with close monitoring. If potassium exceeds 5.5 mmol/L, finerenone should be temporarily withheld, contributing factors addressed, and therapy reconsidered once potassium returns to ≤5.0 mmol/L. These thresholds are based on trial design and regulatory guidance (including FDA labeling, which recommends initiation at K⁺ <5.0 mmol/L) and may vary across regions. Serum creatinine and eGFR should be assessed concurrently with potassium throughout treatment (Table 2).

An oral potassium binder can help control potassium levels while allowing continuation of therapy.

Table 2. Guidance for the initiation of finerenone and monitoring of serum potassium levels (adopted based on the KDIGO guidelines).

K ⁺ (mmol/L)	Action	Monitoring
≤4.8	Initiate finerenone 10 mg daily if eGFR 25–59 or 20 mg daily if eGFR ≥60 Increase dose to 20 mg daily if started at 10 mg and K ⁺ remains ≤4.8 mmol/L; Restart at 10 mg daily if previously held for hyperkalemia and K ⁺ is now ≤5.0 mmol/L	Monitor K ⁺ at 1 month, then every 4 months
4.9–5.5	Continue finerenone 10 mg or 20 mg	Check K ⁺ every 4 months
>5.5	Hold finerenone Consider adjustment of diet or concomitant medications to mitigate hyperkalemia Restart finerenone when K ⁺ is ≤5.0 mmol/L	Recheck K ⁺ ; restart if ≤5.0

Sodium zirconium cyclosilicate is a selective potassium binder that acts throughout the gastrointestinal tract by capturing free potassium in the intestinal lumen. This mechanism lowers serum potassium levels and increases fecal potassium excretion. Its onset of action is rapid, with reductions in serum potassium observed as early as one hour after administration. The recommended initial dose is 10 g three times daily, administered orally, and normokalemia is typically achieved within 24–48 hours. For maintenance therapy, the usual dose is 5 g once daily, with the option to titrate to 10 g once daily based on the patient's potassium levels and clinical response [26].

GLP-1 Receptor Agonists

Mechanism of Action and Pathophysiologic Rationale

Glucagon-Like Peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells at low basal levels during fasting and is rapidly elevated after food intake. It enhances glucose-dependent insulin secretion via GLP-1 receptors on pancreatic β -cells and supports insulin synthesis, while also suppressing glucagon release in a glucose-dependent manner, contributing importantly to postprandial glucose control. Beyond the pancreas, GLP-1 slows gastric emptying and intestinal motility, reducing the rate of nutrient absorption. It also acts through central and vagal pathways to increase satiety and decrease appetite and may improve postprandial nutrient handling in peripheral tissues [27].

In peripheral tissues, it improves glucose uptake in skeletal muscle, reduces hepatic glucose production and steatosis, and enhances adipose tissue perfusion and metabolic activity. Cardiovascular effects include improved glucose utilization, vasodilation, cardiopro-

tection, and increased cardiac output. In the kidney, GLP-1 promotes natriuresis and diuresis, contributing to blood pressure reduction. Additionally, GLP-1 appears to exert anti-inflammatory effects. Overall, GLP-1 integrates pancreatic, metabolic, renal, and cardiovascular pathways to optimize postprandial glucose handling and energy homeostasis [28].

Evidence from Landmark Trials

In the SUSTAIN-6 trial, 3,297 patients with T2D were randomized to receive once-weekly semaglutide (0.5 or 1.0 mg) or placebo and followed for a median of 2.1 years [24]. Most participants (83%) had established cardiovascular disease, chronic kidney disease, or both, representing a high-risk population. The primary endpoint was cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Semaglutide significantly reduced the risk of major adverse cardiovascular events compared with placebo, demonstrating cardiovascular benefit in patients with T2D at high risk. New or worsening nephropathy occurred in 3.8% of the patients in the semaglutide group versus 6.1% in the placebo group. A reduced incidence of macroalbuminuria was also reported in the semaglutide group.

In the LEADER trial renal analysis, 9,340 patients with T2D at high cardiovascular risk were randomized to liraglutide or placebo and followed for a median of 3.84 years [29]. The prespecified renal endpoint—new-onset persistent macroalbuminuria, persistent doubling of serum creatinine, end-stage kidney disease, or death from renal causes—occurred less frequently with liraglutide than with placebo. This benefit was driven mainly by a reduction in new-onset persistent macroalbuminuria, while rates of creatinine doubling and kidney replace-

ment therapy did not differ significantly between groups.

In contrast to the SUSTAIN-6 and LEADER trials, where renal benefits were largely driven by reductions in albuminuria in broader high-cardiovascular-risk populations, the more recent FLOW trial specifically enrolled patients with T2D and established CKD. A total of 3,533 patients with reduced eGFR and significant albuminuria were randomized and followed for a median of 3.4 years [30]. The primary outcome (kidney failure, over 50% decline in eGFR, or death from renal or cardiovascular causes) occurred 24% less frequently in the semaglutide group compared with placebo. Similar benefits were observed for the kidney-specific outcomes and for cardiovascular death. Unlike the earlier cardiovascular outcome trials, this study demonstrated a clear protective effect of semaglutide on hard kidney endpoints in a population with established CKD, extending the evidence beyond albuminuria reduction to meaningful slowing of kidney disease progression.

Guideline Recommendations and Clinical Implementation

In adults with T2D and CKD who do not achieve individualized glycemic targets despite treatment with metformin and an SGLT2 inhibitor or for those who cannot use one or both of these agents, a long-acting GLP-1 receptor agonist is recommended. When selecting a GLP-1 receptor agonist, priority should be given to agents with demonstrated cardiovascular benefit.

CONCLUSION

The approach to managing CKD has shifted from mostly supportive care to treatments targeting the main pathways of disease progression and cardiovascular risk. The best markers for predicting outcomes in CKD remain albuminuria and a declining eGFR. Early detection and correct staging of CKD can help the immediate commencement of appropriate treatment. Within this framework, pharmacologic treatment is now anchored by four complementary pillars that act on distinct mechanisms of injury.

Renin-angiotensin-aldosterone system inhibitors remain central to treatment, as they reduce albuminuria and slow CKD progression. However, individual use of RAAS inhibitors does not eliminate all renal and cardiovascular risks. Sodium-glucose co-transporter 2 inhibitors have been added to treatment options by providing both kidney and cardiac protection for people with CKD, even those without diabetes. Current

guidelines recommend SGLT2 inhibitors as part of the main therapy for CKD, even at lower eGFR levels and for patients with heart failure, regardless of albuminuria.

Nonsteroidal MRAs add extra antifibrotic and anti-inflammatory benefits, especially for people with T2D and concomitant albuminuria. It is important to monitor potassium levels closely and have a clear management plan for complications. There is still not much evidence for nonsteroidal MRAs in people with CKD who do not have diabetes, but ongoing studies like the FIND-CKD study should help clarify their role.

GLP-1 receptor agonists offer cardiac and metabolic benefits, along with proven renal protection. These results support the guideline recommendation for the use of long-acting GLP-1 receptor agonists for patients who cannot achieve blood sugar goals with metformin and SGLT2 inhibitors.

Using RAAS inhibitors, SGLT2 inhibitors, nonsteroidal MRAs, and GLP-1 receptor agonists together provides a more complete approach to CKD care in patients with T2D. This strategy helps slow the progression to kidney failure and lowers the risk of cardiovascular events. Future studies should focus on the best ways to combine these treatments, improve screening, and clarify the role of these emerging therapies across non-diabetic CKD populations as well.

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REFERENCES

1. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020; 395(10225):709–33.
2. Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4S):S117–314.
3. Levin A, Okpechi IG, Caskey FJ, Yang C-W, Tonelli M, Jha V. Perspectives on early detection of chronic kidney disease: the facts, the questions, and a proposed framework for 2023 and beyond. *Kidney Int*. 2023;103(6):1004–8.

4. Zannad F, Mcguire DK, Ortiz A. Treatment strategies to reduce cardiovascular risk in persons with chronic kidney disease and Type 2 diabetes. *J Intern Med.* 2025;297(5):460-78.
5. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021;100(4):S1-276.
6. Webster A, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. *Lancet.* 2017; 389(10075): 1238–52.
7. Remuzzi G, Perico N, Macia M, Ruggenenti P. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int.* 2005;68(Suppl 99):S57-65.
8. Ksiazek SH, Hu L, Andò S, Pirklbauer M, Säemann MD, Ruotolo C, et al. Renin–Angiotensin–Aldosterone System: From History to Practice of a Secular Topic. *Int J Mol Sci.* 2024;25(7):4035.
9. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. *N Engl J Med.* 1993;329(20):1456-62.
10. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. *N Engl J Med.* 2001;345(12):851-60.
11. Brenner BM, Cooper ME, De Zeeuw D, Keane WF, Mitch WE, Parving H-H, et al. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2001;345(12):861-9.
12. Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, et al. Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease. *N Engl J Med.* 2022;387(22):2021-32.
13. Salvatore T, Galiero R, Caturano A, Rinaldi L, Di Martino A, Albanese G, et al. An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors. *Int J Mol Sci.* 2022;23(7):3651.
14. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383(15):1436-46.
15. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2023;388(2):117-27.
16. Apperloo EM, Neuen BL, Fletcher RA, Jongs N, Anker SD, Bhatt DL, et al. Efficacy and safety of SGLT2 inhibitors with and without glucagon-like peptide 1 receptor agonists: a SMART-C collaborative meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol.* 2024;12(8):545-57.
17. Taves MD, Gomez-Sanchez CE, Soma KK. Extra-adrenal glucocorticoids and mineralocorticoids: evidence for local synthesis, regulation, and function. *Am J Physiol Endocrinol Metab.* 2011;301(1):E11–24.
18. Laragh JH, Angers M, Kelly WG, Lieberman S. Hypotensive agents and pressor substances. The effect of epinephrine, norepinephrine, angiotensin II, and others on the secretory rate of aldosterone in man. *JAMA.* 1960;174:234-40.
19. Bauersachs J, Jaisser F, Toto R. Mineralocorticoid Receptor Activation and Mineralocorticoid Receptor Antagonist Treatment in Cardiac and Renal Diseases. *Hypertension.* 2015;65(2):257-63.
20. Epstein M, Kovesdy CP, Clase CM, Sood MM, Pecoits-Filho R. Aldosterone, Mineralocorticoid Receptor Activation, and CKD: A Review of Evolving Treatment Paradigms. *Am J Kidney Dis.* 2022;80(5):658-66.
21. Epstein M, Williams GH, Weinberger M, Lewin A, Krause S, Mukherjee R, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol.* 2006;1(5):940-51.
22. Papasotiriou M, Georgopoulou GA, Mpratsiakou A, Ntrinas T, Lyras G, Goumenos DS, et al. A Prospective Study of Eplerenone in the Treatment of Patients with Glomerulonephritis. *Biomedicines.* 2023;11(12):3340.
23. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *N Engl J Med.* 2021;385(24):2252-63.
24. Agarwal R, Green JB, Heerspink HJL, Mann JFE, McGill JB, Mottl AK, et al. Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes. *N Engl J Med.* 2025;393(6):533-43.
25. Heerspink HJL, Agarwal R, Bakris GL, Cherney DZI, Lam CSP, Neuen BL, et al. Design and baseline characteristics of the Finerenone, in addition to standard of care, on the progression of kidney disease in patients with Non-Diabetic Chronic Kidney Disease (FIND-CKD) randomized trial. *Nephrol Dial Transplant.* 2025;40(2):308-19.
26. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, et al. Sodium Zirconium Cyclosilicate in Hyperkalemia. *N Engl J Med.* 2015;372(3):222-31.
27. Muskiet MHA, Tonneijck L, Smits MM, van Baar MJB, Kramer MHH, Hoorn EJ, et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. *Nat Rev Nephrol.* 2017;13(10):605-28.
28. Tandy N, Platt PR, Irwin N. Metabolic responses and benefits of glucagon-like peptide-1 (GLP-1) receptor ligands. *Br J Pharmacol.* 2022;179(4):526-41.
29. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. *N Engl J Med.* 2017;377(9):839-48.
30. Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *N Engl J Med.* 2024;391(2):109-21.

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Current Directions in Clinical and Preclinical Research on Myeloid Neoplasms

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Abstract

Myeloid neoplasms, including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), have entered a precision era defined by genomic disease classification, biologically informed risk stratification, and rapidly expanding targeted therapeutics. Contemporary classification systems incorporate recurrent genetic abnormalities and unify clinical entities across bone marrow blast cell thresholds, enabling alignment of therapeutic development with molecular biology. In lower-risk MDS, erythroid maturation and telomerase inhibition have moved treatment endpoints beyond symptomatic transfusion reduction, toward durable transfusion independence and potential disease modification. In higher-risk MDS and AML, BCL-2 inhibition, next-generation hypomethylating strategies, and targeted agents against FLT3, IDH1/2, and menin-dependent transcriptional programs have redefined standards of care for specific genotypes. Parallel preclinical pipelines emphasize immunotherapies (CD47 blockade, bispecific antibodies, cellular therapies), epigenetic reprogramming, and metabolic targeting, with measurable residual disease (MRD) guiding response-adaptive sequencing. This narrative review synthesizes pivotal clinical trials, mechanistic rationale, resistance biology, and emerging translational directions expected to shape management of myeloid neoplasms through the next decade.

Key words: Myelodysplastic syndromes; acute myeloid leukemia; targeted therapy; translational research; MRD

Abbreviations

2-HG: 2-hydroxyglutarate, Allo-HSCT: Allogeneic hematopoietic stem cell transplantation, AML: Acute myeloid leukemia, AML-EB / MDS-EB: Myelodysplastic syndromes / Acute myeloid leukemia with excess blasts, AZA: Azacitidine, CAR-NK: Chimeric antigen receptor-Natural Killer, CAR-T: Chimeric antigen receptor-T cell, CCUS: Clonal cytopenia of undetermined significance, CCR: Conventional care regimens, CHIP: Clonal hematopoiesis of indeterminate potential, CMML: Chronic myelomonocytic leukemia, CR/CRh: Complete remission / Complete remission with partial hematologic recovery, EFS: Event-free survival, ESA: Erythropoiesis-stimulating

agent, Hb: Hemoglobin, HIF: Hypoxia-inducible factor, HMA: Hypomethylating agent, ICC: International Consensus Classification, IPSS-M: Molecular International Prognostic Scoring System, IPSS-R: Revised International Prognostic Scoring System, LDAC: Low-dose cytarabine, LPS: Lipopolysaccharides, LSC: Leukemic stem cell, LSD1: Lysine-specific demethylase 1, MDS: Myelodysplastic syndromes, MPN: Myeloproliferative neoplasm, MRD: Measurable (or Minimal) residual disease, NGS: Next-generation sequencing, OS: Overall survival, PCR: Polymerase chain reaction, PRO: Patient-reported outcome, PV/ET: Polycythemia vera / Essential thrombocythemia, R/R: Relapsed / Refractory, RBC: Red blood cell, RS+: Ring sideroblast-positive, TD: Transfusion-dependent, TI: Transfusion independence, t-MN: Therapy-related myeloid neoplasms, VEN: Venetoclax, WHO: World Health Organization

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INTRODUCTION

Myeloid neoplasms comprise a heterogeneous group of clonal disorders arising from hematopoietic stem and progenitor cells, characterized by dysregulated differentiation, ineffective hematopoiesis, and variable risk of leukemic transformation. For decades, diagnosis and risk assessment relied on morphology and cytogenetics. The widespread adoption of next-generation sequencing (NGS) has revealed recurrent driver mutations, clonal architectures, and targetable dependencies, shifting the field toward biologically defined entities and precision therapeutics [1,2]. The 2022 WHO and the International Consensus Classification (ICC) integrate genetic abnormalities into disease definitions and acknowledge biologic continuity across traditional blast-count boundaries (e.g., MDS/AML) [3,4].

These conceptual changes have immediate practical consequences: trial enrollment is increasingly enriched with molecularly based eligibility and response criteria, response metrics incorporate measurable residual disease (MRD), and therapeutic sequencing is shaped by genotype, fitness, and clonal dynamics.

This narrative review summarizes current directions in clinical and preclinical research on myeloid neoplasms with emphasis on (i) early clonal states and genomics-integrated risk models, (ii) practice-shaping

trials and evolving standards in lower-risk MDS, higher-risk MDS, and AML, (iii) resistance biology and rational combinations, and (iv) emerging translational platforms including immunotherapy, epigenetic and inflammatory pathway-targeting, metabolic interventions, and data-driven decision support. Key contemporary trials, representative investigational directions and related pathways discussed in this review are summarized in Figure 1 and Tables 1 and 2.

Molecular background and risk stratification

Early clonal states: CHIP and CCUS

Age-associated clonal hematopoiesis of indeterminate potential (CHIP) is defined by somatic mutations—most commonly in DNMT3A, TET2, and ASXL1—detectable in peripheral blood in individuals without cytopenias or morphologically diagnostic marrow dysplasia [5,6]. CHIP is associated with an increased risk of hematologic malignancy and cardiovascular events, linking hematologic clonal selection with systemic inflammation and vascular biology [5,7]. Clonal cytopenia of undetermined significance (CCUS) extends this concept, by coupling persistent cytopenias with clonal mutations, but without morphologic criteria for MDS. CCUS carries substantially higher risk of progression to a clinically recognizable myeloid disease

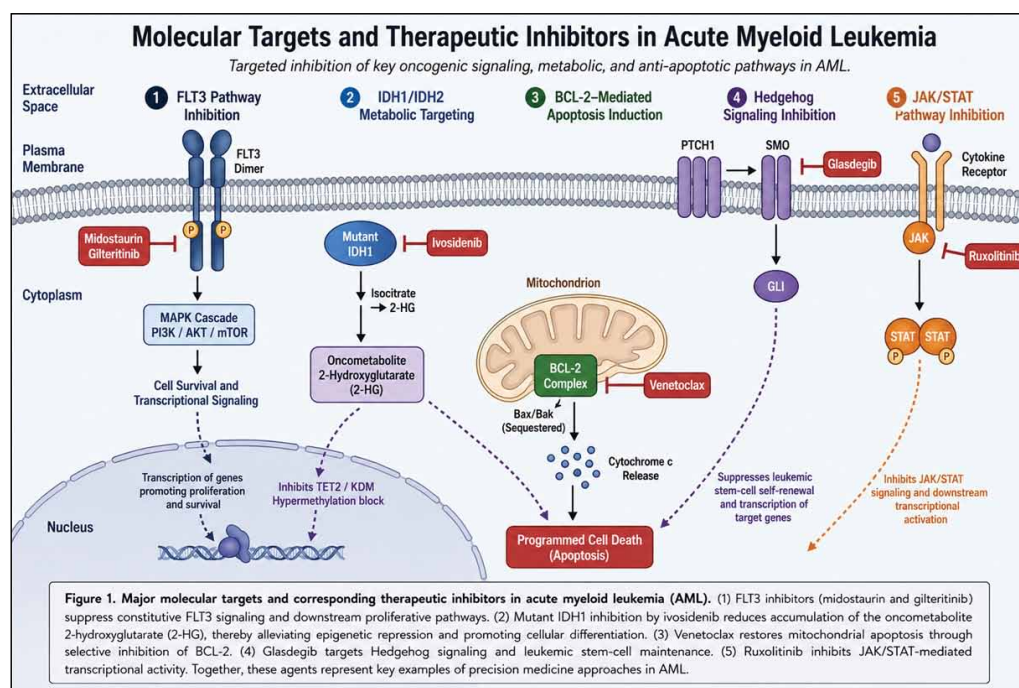


Figure 1. Major molecular targets and corresponding therapeutic inhibitors in acute myeloid leukemia.

Table 1. Pivotal phase 3 trials and selected investigational strategies in myeloid neoplasms.

Disease/ Setting	Trial (Phase)	Population	Intervention vs Control	Primary Endpoint	Key Result	Key Safety Signal	Ref
LR-MDS, TD, RS+	MEDALIST (III)	ESA-refractory	Luspatercept vs placebo	TI ≥ 8 weeks	38% vs 13%	Fatigue, GI AEs	[18]
LR-MDS, ESA-naïve	COMMANDS (III)	TD	Luspatercept vs epoetin alfa	TI + Hb↑	Superior TI & durability	Favorable safety	[19]
LR-MDS, post-ESA	IMerge (III)	TD, non-del(5q)	Imetelstat vs placebo	TI ≥ 8 weeks	40% vs 15%	Neutropenia, thrombocytopenia	[20]
HR-MDS	AZA-001 (III)	Untreated HR	Azacitidine vs CCR	OS	OS benefit	HMA-related cytopenias	[24]
HR-MDS/CMML	PANTHER (III)	Untreated HR	Pevonedistat + AZA vs AZA	EFS	NS	Manageable toxicity	[28]
ND AML (unfit)	VIALE-A (III)	Newly diagnosed	AZA + Ven vs AZA	OS	14.7 vs 9.6mo	Myelosuppression	[36]
ND AML IDH1-mut	AGILE (III)	Unfit	AZA + ivosidenib vs AZA	OS	24.0 vs 7.9 mo	Differentiation syndrome	[38]
R/R AML FLT3-mut	ADMIRAL (III)	Relapsed	Gilteritinib vs chemo	OS	OS 9.3 vs 5.6 mo	Cytopenias, QT	[40]
ND AML FLT3-ITD	QuANTUM-First (III)	Intensive	Quizartinib + "7+3" vs "7+3"	OS	31.9 vs 15.1 mo	QT prolongation	[41]
R/R AML	FF-10101 (I)	Post-FLT3i	Covalent FLT3 inhibitor	Safety	Early activity	Investigational	[42]
R/R KMT2A/NPM1	AUGMENT-101 (II)	Pretreated	Revumenib	CR/CRh	MRD-neg responses	Differentiation syndrome	[43,44]

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; CCR, conventional care regimens; CR/CRh, complete remission/complete remission with partial hematologic recovery; EFS, event-free survival; HR, higher risk; LR, lower risk; OS, overall survival; RS+, ring sideroblast-positive; TD, transfusion-dependent; TI, transfusion independence; VEN, venetoclax.

entity than CHIP, particularly when multiple mutations, high variant allele frequency, or high-risk lesions (e.g., TP53, spliceosome genes) are present [8,9]. Such pre-malignant states, like those two previously mentioned, are now central to clinical research: they enable risk modeling, biomarker discovery, and the design of early-intervention trials aimed at intercepting progression before overt neoplasia.

Genomics-integrated prognostic models

Risk stratification in MDS historically relied on IPSS-R, which uses marrow blasts, severity of cytopenias, and cytogenetics, as major prognostic parameters [10]. While clinically useful, IPSS-R does not formally incorporate somatic mutations, despite the clear prognostic significance of lesions, such as TP53, ASXL1, RUNX1, and SF3B1

mutations [11,12]. IPSS-M addresses this inadequacy, by integrating clinical variables, cytogenetics, and mutation data to redefine risk categories and improve discrimination, especially within the intermediate-risk groups, for which treatment decisions are most difficult [13]. This has catalyzed biologically-based clinical trial design, in which high-risk molecular features can drive eligibility, even at lower blast counts, and the identifiable endpoints increasingly incorporate molecular response and MRD. Beyond prognosis, somatic mutations are often not only predictive but also diagnostic: SF3B1 mutations correlate with the ring sideroblast phenotype and response to erythroid maturation strategies, whereas multi-hit TP53 defines a subset with inherent resistance to HMAs and poor outcomes with conventional approaches, including allogeneic transplantation [14,15].

Table 2. *Signal transduction pathways, molecular targets, and therapeutic agents in myeloid neoplasms.*

Pathway / Molecular Target	Role in Pathogenesis / Mechanism	Targeted Agent(s)	Development Stage & Status	Key Myeloid Neoplasm(s)	Ref
FLT3 Signaling	Constitutive activation of FLT3 tyrosine kinase receptors drives uncontrolled cell proliferation and survival pathways.	Gilteritinib, Quizartinib, Midostaurin	FDA-approved & widely available; used in combination with intensive chemo or as monotherapy.	FLT3-mutated AML	[40,41,62]
IDH1 / IDH2 Metabolic Pathway	Neomorphic mutations result in the abnormal production of the oncometabolite 2-hydroxyglutarate (2-HG), causing global DNA hypermethylation and differentiation arrest.	Ivosidenib (IDH1), Enasidenib (IDH2), Olutasidenib (IDH1)	FDA-approved & widely available; used as targeted monotherapy or in combination regimens.	IDH1/2-mutated AML / MDS	[38,39,53,63]
BCL-2 / Apoptotic Pathway	Overexpression of anti-apoptotic B-cell lymphoma 2 (BCL-2) allows leukemia blasts to evade apoptosis and resist chemotherapy.	Venetoclax	FDA-approved & widely available; standard of care when combined with hypomethylating agents.	Acute Myeloid Leukemia (AML) (unfit for intensive therapy)	[32,33,36,69]
JAK/STAT Pathway	Aberrant JAK2/STAT signaling leads to severe cytokine hypersensitivity, constitutional symptoms, and splenomegaly via uncontrolled myeloproliferation.	Ruxolitinib, Fedratinib, Pacritinib, Momelotinib	FDA-approved & widely available across multiple myelofibrosis sub-settings.	Myelofibrosis (Primary and Post-PV/ET), Post-MPN AML	[64]
Hedgehog Signaling Pathway	Aberrant activation of Smoothened (SMO) maintains leukemia stem cell self-renewal, drives disease progression, and mediates chemotherapy resistance.	Glasdegib	FDA-approved & available; combined with low-dose cytarabine (LDAC).	Newly diagnosed AML (elderly/unfit)	[66]
KMT2A (MLL) / Menin Complex	Chromosomal rearrangements or NPM1 mutations cause dysregulated HOX gene transcription, preventing proper myeloid differentiation.	Revumenib, Ziftomenib	Advanced Clinical Development / Newly Approved (Phase II/III); highly active targeted strategy.	Relapsed/Refractory KMT2A-rearranged or NPM1-mutated AML	[43–46,65]
Spliceosome Machinery	Somatic mutations in core splicing factors (SF3B1, SRSF2, U2AF1) impair mRNA splicing of vital hematopoietic genes, altering regular differentiation.	H3B-8800, Pladienolide B derivatives	Early-phase clinical trials (Phase I/II investigational therapies); targeting RNA-splicing modulation.	MDS, CMML, AML with spliceosome mutations	[61,67,68]
Epigenetic Regulation (DNA Methylation)	Somatic hypermethylation and chromatin alterations downregulate and silence critical tumor suppressor genes.	Azacitidine, Decitabine, Oral ASTX727 (decitabine/cedazuridine)	FDA-approved & standard backbone therapy for high-risk non-intensive regimens.	HR-MDS, CMML, AML	[24,36]

Lower-risk mds: targeting ineffective erythropoiesis

Clinical goals and the ESA benchmark

Lower-risk MDS (LR-MDS) is dominated by chronic anemia and transfusion dependence, with morbidity mainly driven by cytopenias, infections, iron overload, and reduced quality of life, rather than by an imminent leukemic transformation. ESAs remain the standard first-line treatment approach for many patients with low transfusion burden and low serum levels of endogenous erythropoietin; typical response rates are about 30–40%, with median durations often lasting less than two years. Responses are less likely to be observed in patients with high baseline levels of serum erythropoietin or in those with substantial transfusion needs [16,17]. These limitations have motivated biologically targeted approaches that aim for higher response rates, longer durability, and potential disease modification.

Luspatercept: Targeting late-stage erythroid maturation

Luspatercept is an erythroid maturation agent that modulates TGF- β superfamily signaling to enhance late-stage erythropoiesis. The phase 3 MEDALIST trial was a randomized, double-blind, placebo-controlled study, enrolling transfusion-dependent LR-MDS patients with ring sideroblasts, who were refractory to, or unlikely to respond to ESAs [18]. The primary endpoint red blood cell (RBC) transfusion independence (TI) for ≥ 8 weeks during weeks 1–24—was achieved by 38% with luspatercept versus 13% with placebo, and additional benefits were observed, such as in longer TI intervals and erythroid hematologic improvement [18]. Adverse events were generally manageable; fatigue, diarrhea, and musculoskeletal symptoms were common, and discontinuation rates were relatively low. Importantly, the trial validated that targeting erythroid maturation, rather than stimulation of earlier stages of erythropoiesis can meaningfully reduce transfusion dependence in a biologically defined patient subgroup.

The COMMANDS study extended luspatercept into the frontline setting by head-to-head comparing luspatercept with epoetin alfa in ESA-naïve, transfusion-dependent LR-MDS [19]. In the primary analysis, luspatercept demonstrated superiority in the achievement of clinically meaningful transfusion independence, with hemoglobin improvement and longer response durability across relevant subgroups, including patients without ring sideroblasts, and those with low/normal

baseline serum erythropoietin levels [19]. These findings reframe first-line anemia management in lower-risk MDS patients: rather than viewing ESAs as default and luspatercept as second-line, a phenotype- and biology-informed approach can prioritize the durability of response and transfusion avoidance. Ongoing analyses focus on the identification of predictors of response (including SF3B1 mutational status), disease progression rates, and practical sequencing strategies.

Imetelstat: telomerase inhibition and a disease-modifying hypothesis

Imetelstat, a first-in-class telomerase inhibitor, represents a mechanistically distinct approach that targets clonal persistence, rather than erythroid maturation alone. The multinational, randomized, double-blind, placebo-controlled phase 3 IMerge trial enrolled transfusion-dependent LR-MDS patients without del(5q), who relapsed after, were refractory to, or were ineligible for treatment with ESAs [20]. The primary endpoint of TI ≥ 8 weeks was met by 40% of imetelstat-treated patients compared with 15% of those on placebo; a clinically important subset achieved TI ≥ 24 weeks, and median TI duration approximated one year in many reports [20]. The dominant toxicities were cytopenias (notably neutropenia and thrombocytopenia), necessitating careful monitoring, dose modifications, and strategies for infection prophylaxis, where appropriate. From a translational standpoint, IMerge is a notable study, because some responders showed reductions in mutation allele burden, raising the possibility that in this patient group telomere inhibition might induce partial disease modification. Whether telomerase inhibition can consistently suppress malignant clones, while allowing recovery of effective, non-clonal hematopoiesis remains an active research question, requiring longer follow-up, clonal architecture analyses, and integration of marrow and molecular response endpoints.

Other directions in LR-MDS

Additional anemia-directed strategies include hypoxia-inducible factor (HIF) prolyl hydroxylase inhibition (e.g., roxadustat), which increases endogenous erythropoietin signaling and iron utilization, induces the formation of agents, and modulates the inflammatory marrow microenvironment [21,22]. Safety signals (including thrombotic concerns) and heterogeneous efficacy underscore the need for biomarker-driven selection and the design of a robust phase 3 validation. A

broader, unifying direction is to re-conceptualize LR-MDS as a chronic clonal disorder of aging, with inflammatory contributions (“inflammaging”), where the therapeutic aim will remain the durable transfusion independence with minimal toxicity, while delaying disease progression [7,22].

Practical sequencing and response prediction

A central clinical question is how to sequence ESAs, luspatercept, and imetelstat, in a way that maximizes survival time, free of transfusions, while concurrently minimizing cumulative toxicity and clinic burden. While ESAs remain appropriate for patients with low transfusion needs and favorable baseline serum erythropoietin levels, the COMMANDS trial results suggest that transfusion-dependent patients—particularly those with ring sideroblasts and/or SF3B1 mutations—may benefit from earlier initiation of luspatercept, to achieve longer transfusion independence and to reduce transfusion-related iron overload [19]. In contrast, imetelstat is positioned at the second or third line of treatment, for patients who have failed, are ineligible for, or are unlikely to gain benefit from ESAs, and who require a strategy with the potential for longer durability, accepting the trade-off of higher rates of cytopenias and need for monitoring [20]. From a research standpoint, predictive biomarkers for response remain an urgent need. Candidate predictors include baseline transfusion burden, serum erythropoietin, ring sideroblast status, SF3B1 mutational status, and broader co-mutation patterns that may reflect stem-cell dominance versus lineage-restricted ineffective erythropoiesis [13–23]. Another practical direction is to study “switch” or “step-up” designs (e.g., early switch from ESA to luspatercept, based on predefined non-response criteria, or escalation to imetelstat in patients with short TI duration), with endpoints that capture patient-centered benefit, such as cumulative transfused units avoided, time to achievement of a hemoglobin level above a functional threshold, and validated quality-of-life instruments.

Higher-risk mds: combination strategies and transplant bridging

Backbone therapy and unmet need

For higher-risk MDS (HR-MDS), the management objectives are to delay AML transformation, prolong survival, and, where feasible, bridge to allogeneic stem cell transplantation. Azacitidine has demonstrated survival

benefit over conventional care regimens in the pivotal AZA-001 study and remains a backbone standard for non-transplant candidates [24]. Nevertheless, responses are often transient, and outcomes after HMA failure are poor, motivating intensive research into the design of rational combinations, molecular enrichment, and MRD-guided strategies [25,26].

Venetoclax plus azacitidine: depth versus tolerability

Given the biologic overlap between HR-MDS and AML, BCL-2 inhibition with venetoclax or other similar emerging compounds has been explored in combination with azacitidine. Early phase studies in untreated HR-MDS have reported high overall response rates, with meaningful complete remission rates and the potential to bridge some patients to transplantation [27]. However, translating higher response rates into improved overall survival is sometimes challenging, because profound myelosuppression, infections, and early mortality can offset benefit in frail patients. Current clinical research, therefore, emphasizes response-adaptive scheduling (shortened venetoclax exposure or tailoring its dose), optimized supportive care, and patient selection to maximize benefit, while minimizing infection-related complications.

Pevonedistat: a phase 3 lesson in translation

Pevonedistat inhibits NEDD8-activating enzymes, disrupting cullin-RING ligase activity and inducing proteotoxic stress in malignant cells. Although earlier studies suggested synergy with azacitidine, the phase 3 PANTHER trial (pevonedistat plus azacitidine vs azacitidine alone) did not meet its primary endpoint; outcomes numerically favored the combination in some analyses but without prespecified statistical significance [28]. These results have offered a lesson: the failure of the trial to reach its primary endpoint was methodological and biologic, namely, not all “add-on” combinations succeed in heterogeneous diseases, and future programs increasingly require biomarker-defined subgroups, mechanistic correlatives, and careful endpoint selection, beyond overall response rates alone.

Immune checkpoint modulation and the “cold marrow” problem

Checkpoint inhibition has proven less successful in MDS than in some solid tumors, probably reflecting the existence of an immunosuppressive marrow milieu, with complex myeloid and stromal interactions. TIM-3

blockade with sabatolimab was advanced through early studies, but the pivotal development of a phase-3 study has encountered major setbacks, highlighting the difficulty of translating checkpoint concepts to MDS without combination logic, predictive biomarkers, or targeting of innate immune pathways [29,30]. Current translational efforts increasingly focus on macrophage-controlled checkpoints, bispecific antibodies, and microenvironment reprogramming, rather than simply checkpoint modulatory monotherapy.

TP53-mutant HR-MDS: the central unmet need

TP53 mutations, especially multi-hit/biallelic alterations, define a high-risk subset, characterized by genomic instability, poor HMA responsiveness, high relapse risk after transplant, and short survival [14,15]. Eprenetapopt (APR-246), designed to restore wild-type p53 conformation, generated encouraging phase 2 trial results but failed to confirm benefit in later-stage testing, emphasizing allelic context and biologic complexity [31]. Research directions include exploiting DNA damage response vulnerabilities, integrating innate immune approaches, optimizing transplant strategies, and developing maintenance regimens that target residual TP53-mutant clones. These efforts represent a defining frontier for the next generation of HR-MDS therapeutics.

Optimizing combinations and transplant pathways

In HR-MDS, venetoclax plus azacitidine is often discussed as the currently most effective regimen available, through the lens of high response rates, but the critical clinical questions are durability of response, safety, and the ability of the patient to reach transplantation in adequate clinical condition. Early phase cohorts commonly included patients with excess blasts (often MDS-EB) and demonstrated rapid cytoreduction and measurable remissions [27]. It is important to note that the results of the venetoclax plus azacitidine (Ven-Aza) combination are highly compelling; if not superior in safety and tolerability to conventional anthracycline-based intensive chemotherapy regimens. Consequently, utilizing this combination even in patients with secondary AML arising from antecedent MDS (post-MDS AML) may significantly increase the proportion of patients who can successfully achieve a deep enough remission to proceed to allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, venetoclax-driven myelosuppression may be

profound in a population that already has limited hematopoietic reserve, and infectious complications can be frequent without careful schedule optimization and application of appropriate prophylaxis. Consequently, contemporary clinical trials increasingly explore shorter venetoclax exposure per cycle (for example, 7–14 days rather than 28 days), individualized cycle length and dose intensification based on count recovery, and standardized antimicrobial prophylaxis algorithms. Translational correlates focus on apoptotic priming, BCL-2 family adaptation (e.g., upregulation of MCL-1 or BCL-xL), and clonal selection as mechanisms of resistance [32,33]. The research direction is therefore not merely “add venetoclax,” but “engineer a deliverable and affordable regimen” where depth of response is achieved without unacceptable infection-related mortality.

Outcomes after HMA failure in HR-MDS are poor, with limited effective options and frequent progression to AML [25,26]. This has driven a methodological shift: trials in the post-HMA setting increasingly prioritize endpoints, such as overall response with transfusion improvement, time to AML transformation, and event-free survival, and they incorporate molecular response and MRD where feasible. In addition, studies increasingly stratify patients by TP53 allelic state and complex karyotype, because these features clearly dominate outcomes and can dilute efficacy signals, if not balanced or enriched [14,15]. Another direction is the development of maintenance treatment strategies after the achievement of an initial response (with HMAs, targeted agents, or immunomodulatory approaches) to prolong remission and delay clonal escape, particularly for patients not proceeding to transplant.

Allo-HSCT remains the only potentially curative therapy for many HR-MDS and AML patients, but transplant benefit is tightly linked to disease biology and depth of remission at transplantation. Achieving cytoreduction with acceptable toxicity is, therefore, a core research target, and not just a secondary consideration. Trials increasingly evaluate “bridge-to-transplant” endpoints (proportion transplanted, MRD status at transplant, non-relapse mortality, and relapse-free survival), rather than response rates alone. Conditioning regimen intensity and post-transplant maintenance are also active research areas. For example, in FLT3-mutated AML, post-transplant FLT3 inhibitor maintenance treatment has demonstrated a reduction in relapse rates in multiple studies and,

therefore, the general concept that molecularly targeted maintenance may be required to suppress residual disease after transplant has clearly been formed [34,35]. Extending this paradigm to other genotypes (IDH, menin-dependent programs, TP53) is a major translational goal, although robust data still remain limited for some patient subsets.

AML: targeted therapy era and response-adaptive strategy

Venetoclax-based therapy in older/unfit AML

The phase 3 VIALE-A trial established azacitidine plus venetoclax as standard therapy for newly diagnosed AML patients ineligible for intensive chemotherapy, demonstrating improved overall survival (median 14.7 vs 9.6 months), and higher composite complete remission rates, compared with azacitidine alone [36]. The regimen's major limitation is the induction of substantial myelosuppression and an increased infection risk. Contemporary practice and research increasingly use early marrow assessment and the time interval to blood count recovery, to individualize venetoclax duration (e.g., 14–21 days rather than 28 days) and to guide cycle timing, reflecting a broader shift toward response-adaptive dosing, rather than fixed-intensity protocols [37]. Ongoing studies explore triplets (azacitidine and venetoclax, plus targeted agents) and post-remission strategies, including transplant bridging and maintenance treatment regimens.

IDH inhibition: differentiation therapy via metabolic correction

Mutations in IDH1 and IDH2 produce the oncometabolite 2-hydroxyglutarate, which impairs epigenetic regulation and blocks differentiation. In the AGILE trial, azacitidine plus ivosidenib (IDH-1 inhibitor) significantly improved outcomes in newly diagnosed IDH1-mutated AML patients unfit for intensive therapy, achieving a median overall survival of 24.0 months versus 7.9 months for azacitidine plus placebo [38]. Differentiation syndrome is an important class toxicity, requiring early recognition and corticosteroid management. Enasidenib, an IDH2 inhibitor, has demonstrated activity in relapsed/refractory IDH2-mutated AML with durable responses in a subset and similar differentiation-related toxicity patterns [39]. Current research evaluates combinations of IDH inhibitors with venetoclax or HMAs, mechanisms of resistance (including clonal evolution and second-site mutations), and sequencing strategies.

FLT3 inhibition: from salvage to frontline survival improvement

FLT3 mutations, particularly FLT3-ITD, confer proliferative signaling to the leukemic cell and poor prognosis to the patient, without targeted therapy. In relapsed/refractory FLT3-mutated AML, the ADMIRAL trial showed that the FLT3-inhibitor gilteritinib improved overall survival versus salvage chemotherapy (median 9.3 vs 5.6 months), with a tolerable safety profile that supports outpatient administration and transplant bridging [40]. In the frontline intensive setting, the QuANTUM-First trial demonstrated that adding quizartinib to standard induction and consolidation improved median overall survival (31.9 vs 15.1 months) in FLT3-ITD AML, establishing potent FLT3 inhibition as a practice-changing strategy [41]. Despite these advances, resistance remains common via the presence of insensitive TKD mutations, bypass signaling, and clonal selection. Next-generation approaches include covalent FLT3 inhibitors such as FF-10101, designed to retain activity against resistant kinase conformations and to be incorporated into rational combinations [42].

Menin inhibition: targeting transcriptional dependency in KMT2A and NPM1 AML

KMT2A-rearranged and NPM1-mutated AML share a leukemogenic transcriptional program, dependent on menin–KMT2A interaction. Menin inhibitors disrupt this dependency, promoting differentiation and loss of leukemic self-renewal. In the AUGMENT-101 program, revumenib demonstrated clinically meaningful remissions in heavily pretreated KMT2A/NPM1 acute leukemias, with MRD negativity in a substantial fraction of responders and differentiation syndrome as a characteristic, manageable toxicity [43,44]. These findings represent a novel and modern differentiation therapy concept beyond APL. Ziftomenib and other menin inhibitors are currently being developed, including combinations with venetoclax and HMAs, to increase the depth and durability of response and to mitigate resistance [45,46]. Key interpretational questions include the recognition of the optimal line of therapy, establishment of the appropriate biomarkers of sensitivity, and the prevention or inhibition of potentially emerging mechanisms of acquired resistance at the menin-binding interface.

MRD, clonal dynamics, and transplantation

MRD is increasingly incorporated into AML trials and clinical practice as a crucial endpoint, because MRD

negativity correlates with relapse risk and survival across treatment intensities [47,48]. Methods for its evaluation include multiparameter flow cytometry, quantitative PCR for selected lesions, and NGS-based detection of residual clones. MRD is also being explored as a trigger for post-remission therapy escalation, transplant referral, or maintenance. In MDS, MRD assessment is more challenging, due to lower blast burden and overlap with clonal hematopoiesis, but molecular monitoring (including TP53 allele burden) is increasingly used in transplant settings and clinical research [49]. A major direction for 2025–2030 is the standardization of MRD assays, thresholds, and the establishment of appropriate timepoints, to enable MRD-guided adaptive therapy as a validated strategy rather than an investigational tool.

AML: resistance biology and rational triplets

Mechanisms of resistance to venetoclax-based therapy

Despite high initial responses, relapse after venetoclax plus HMA is common, and resistance biology has become a dominant translational research field. Mechanisms include clonal evolution with acquisition or selection of RAS/MAPK pathway mutations, upregulation of alternative anti-apoptotic proteins (MCL-1, BCL-xL), changes in mitochondrial priming, and metabolic rewiring toward oxidative phosphorylation states less sensitive to BCL-2 blockade [32,33,50]. These insights motivate rational triplets, such as venetoclax plus HMA plus a targeted inhibitor (FLT3, IDH, or menin) to address both lineage/epigenetic programs and survival signaling. However, triplets increase myelosuppression and infectious risk, reinforcing the importance of response-adaptive scheduling and supportive care as integral components of a holistic therapeutic design.

Resistance to FLT3 and IDH inhibitors

Resistance to FLT3 inhibitors arises via secondary kinase-domain mutations, activation of parallel signaling (RAS/MAPK), and stromal protection. Combination regimens aim to suppress multiple escape routes, and next-generation inhibitors (including covalent agents) attempt to maintain activity against common resistance mutations [42,51]. IDH inhibitor resistance can involve second-site IDH mutations, isoform switching (IDH1 to IDH2 or vice versa), and selection of non-IDH-driven clones, highlighting the need for serial molecular monitoring and combination strategies that prevent outgrowth of alternative clones [52,53]. In this context,

MRD and clonal tracking are not merely prognostic; they are actionable tools for early detection of escape and timely therapeutic switching.

Menin inhibitor resistance and differentiation dynamics

Menin inhibitor therapy introduces distinctive response dynamics: differentiation programs that can occur without immediate cytotoxic clearance, and differentiation syndrome can mimic infection or inflammatory relapse. Clinical research, therefore, emphasizes the need for education and standardized management pathways, including the early administration of corticosteroids and supportive care, without unnecessary discontinuation when feasible [43,44]. Resistance mechanisms include mutations that disrupt drug binding, and adaptation of transcriptional programs. Combination strategies (menin inhibitor plus venetoclax/HMA, or with kinase inhibitors in selected contexts) are being evaluated to deepen remissions and reduce the probability of resistant clone emergence [46].

Preclinical and translational frontiers

Innate immune targeting: CD47 blockade

The CD47–SIRP α axis functions as a macrophage checkpoint, by delivering a “don’t eat me” signal to phagocytes. CD47 blockade aims to enhance macrophage-mediated clearance of malignant cells and has been investigated to enhance phagocytic signaling and immune activation [54,55]. While clinical development has been heterogeneous across programs, innate immune engagement remains a major translational direction, particularly for genomically high-risk disease, where classic cytotoxic strategies are inadequate.

Bispecific antibodies and redirected cytotoxicity

T-cell redirecting bispecific antibodies (e.g., CD123 $\times$ CD3 constructs) recruit cytotoxic lymphocytes to target myeloid blasts. Early-phase studies demonstrate activity in heavily pretreated AML, with cytokine release syndrome as an important toxicity requiring standardized mitigation and monitoring [56]. Translational research focuses on improving therapeutic windows, preventing antigen escape, combining with venetoclax/HMAs to reduce tumor burden, and identifying biomarkers predictive of durable benefit.

Cellular therapy: CAR-T and CAR-NK in AML

Adoptive cellular therapies face unique constraints in AML because many of the target antigens are shared

with normal hematopoietic progenitors (e.g., CD33, CD123), and consequently raising the risk of prolonged aplasia. Strategies in development include transient CAR expression, dual-target constructs, safety switches, and use as a bridge to transplant. CAR-NK platforms may reduce cytokine toxicity and enable “off-the-shelf” manufacturing, and are being explored as a potentially safer immunotherapeutic approach [57,58].

Targeting Epigenetic Networks and Inflammatory Signaling

Epigenetic dysregulation is central to MDS/AML biology. Beyond HMAs, next-generation epigenetic strategies aim to reprogram differentiation and restore therapeutic sensitivity. LSD1 inhibition is one such approach promoting differentiation and may synergize with HMAs or venetoclax in preclinical and early clinical settings [59].

Inflammatory signaling is another emerging target. Aberrant TLR/MyD88/IRAK pathway activation has been linked to subsets of MDS/AML, particularly those with spliceosome mutations that generate IRAK4 isoforms with oncogenic signaling. IRAK4 inhibition (e.g., with emavusertib) has shown encouraging early clinical signals and represents a compelling example of targeting leukemia-intrinsic signaling and the inflammatory microenvironment simultaneously [60,61]. These directions align with the broader recognition that inflammaging and innate immune dysregulation contribute to disease maintenance and therapy resistance [7,22]. Moreover, expanding beyond these classical kinase and metabolic cascades, next-generation therapeutic strategies in Table 2 focus heavily on epigenetic reprogramming and the targeting of aberrant bone marrow inflammatory microenvironments. Simultaneously, hyperactivated innate immune signaling is emerging as a critical therapeutic vulnerability.

Also, other pathways such as FLT3 signaling, where targeting the kinase cascade with midostaurin or gilteritinib remains a cornerstone of precision care [40,62]; the IDH1/IDH2 metabolic pathway, where reversing oncometabolite-induced differentiation blocks using ivosidenib or enasidenib has yielded durable clinical remissions; the BCL-2/Apoptotic pathway, where bypassing cellular survival networks via venetoclax combinations has re-established the global standard of care in unfit acute myeloid leukemia (AML) [39,63]; the JAK/STAT pathway, where downstream cascade inhibition with ruxolitinib has transformed myelofibrosis manage-

ment [64]; and the Hedgehog signaling pathway, where stem-cell-directed targeting via glasdegib has disrupted leukemia stem cell self-renewal.

Crucial therapeutic advancements are also occurring within KMT2A (MLL)/Menin Complex chromatin-remodeling networks, where menin inhibitors like revumenib disrupt oncogenic interactions to deliver deep, minimal residual disease (MRD)-negative remissions [43,44,65]. Beyond epigenetic regulation (DNA Methylation) targeted by conventional hypomethylating agents (HMAs), next-generation epigenetic strategies aim to actively reprogram differentiation and restore therapeutic sensitivity; lysine-specific demethylase 1 (LSD1) inhibition is one such approach, promoting differentiation and showing strong potential to synergize with HMAs or venetoclax in preclinical and early clinical settings. Concurrently, targeting hyperactivated innate immune signaling and the structural components of the core spliceosome machinery (such as with the splicing modulator H3B-8800) represents a highly critical therapeutic vulnerability. Aberrant TLR/MyD88/IRAK pathway activation has been fundamentally linked to subsets of MDS/AML, particularly those harboring somatic spliceosome mutations that preferentially drive the production of oncogenic, hypermorphic IRAK4 long isoforms [67,68].

Metabolic targeting beyond IDH

AML metabolism includes dependencies in oxidative phosphorylation, amino acid utilization, and mitochondrial integrity, which intersect with apoptotic priming and venetoclax sensitivity [32,69]. Emerging metabolic strategies include N-myristoyltransferase inhibition, which disrupts membrane localization and function of signaling proteins and has demonstrated preclinical anti-leukemia activity, motivating early translational development [70]. The prevailing research theme is combination logic: metabolic stressors may sensitize leukemia cells to apoptosis-inducing regimens or overcome resistance by collapsing adaptive metabolic states.

Artificial intelligence and implementation science

As treatment options expand, the challenge shifts from drug availability to optimal selection and drug combination, treatment sequencing, and supportive care. AI-assisted decision tools are being developed to integrate genomics, MRD kinetics, comorbidities, frailty, and prior toxicity into individualized recommendations.

Early studies suggest the potential utility of AI in risk stratification and outcome prediction, but prospective validation is required before routine adoption [71,72]. Implementation research—ensuring timely molecular testing, standardized MRD workflows, infection mitigation protocols, and multidisciplinary care pathways—will be as important as pharmacologic innovation in translating trial advances into population-level outcome improvements.

Therapy-related and secondary myeloid neoplasms: a distinct translational priority

Therapy-related myeloid neoplasms (t-MN), including therapy-related MDS/AML and many secondary AMLs evolving from antecedent hematologic disorders, are enriched for adverse genetics such as TP53 mutations, complex karyotype, and epigenetic driver combinations that reflect prior genotoxic stress and clonal selection [73,74]. Clinically, these diseases have inferior responses to conventional chemotherapy and high relapse rates, making them a proving ground for biology-first strategies. Current research emphasizes the importance of early molecular identification, avoidance of ineffective cytotoxic escalation in biologically refractory subsets, and prioritization of transplant pathways when feasible. Translationally, t-MN highlights the importance of clonal evolution: relapses frequently arise from pre-existing minor clones or from CHIP-like clones that survive therapy and later acquire additional hits [75,76]. This biology supports longitudinal NGS monitoring and motivates maintenance strategies that suppress residual high-risk clones after remission or transplant. It also reinforces the need for prevention research in high-risk CHIP/CCUS populations exposed to chemotherapy or radiation, where interception could have substantial public health impact.

Patient-centered outcomes as co-primary research targets

As therapies prolong survival and shift treatment into chronic management, patient-reported outcomes (PROs) and functional measures are increasingly incorporated into trials, particularly in LR-MDS where anemia and transfusion burden drive daily well-being. Future studies should routinely measure fatigue, physical functioning, reduced in-hospital stay and transfusion-related time costs, and should report clinically meaningful hemoglobin thresholds, rather than laboratory change alone. Incorporating PROs alongside molecular

and MRD endpoints will help ensure that precision therapy improves not only survival curves but also lived experience.

CONCLUSION

Research in myeloid neoplasms is converging on a precision framework built on molecular disease definition, mechanism-native therapy, and response-adaptive clinical strategy. Classification systems that integrate genomics have moved the field beyond morphology and have enabled trials and treatment pathways centered on biologically coherent entities [3,4]. In lower-risk MDS, luspatercept validated late-stage erythroid maturation as a therapeutic lever and, in COMMANDS, demonstrated superiority over epoetin alfa, for clinically meaningful transfusion independence and durability, particularly in biologically aligned phenotypes [18,19]. Imetelstat introduced telomerase inhibition as an anemia-directed strategy, with unexpectedly durable freedom of transfusion in ESA-refractory patients, and with molecular signals that raise a credible hypothesis of partial disease modification in selected responders [20]. Together, these developments move lower-risk MDS care from just a symptom-control approach, toward a durable, biology-informed intervention.

In higher-risk MDS and AML, venetoclax-based regimens and genotype-specific targeted therapies have established a new standard: deep remissions are achievable without default reliance on intensive chemotherapy, but benefit is contingent on deliverability and safety. VIALE-A transformed outcomes in older/unfit AML, while AGILE demonstrated that molecular selection (IDH1 mutation) can yield survival gains exceeding many non-targeted approaches [36,38]. In FLT3-ITD AML, QuANTUM-First showed that potent driver suppression integrated into intensive therapy can double median overall survival, and gilteritinib remains a cornerstone in relapsed disease and transplant bridging [40,41]. Menin inhibition has opened a modern differentiation-therapy paradigm for KMT2A-rearranged and NPM1-mutated AML, with MRD negativity among responders and a distinctive, manageable toxicity profile, centered on differentiation syndrome [43,44]. Across these examples, the most practice-changing trials combine a clear biologic rationale, clinically meaningful endpoints, and feasible toxicity management, an overarching message reinforced by Table 1.

At the same time, the field has become more rigorous about what constitutes meaningful benefit. Phase

3 disappointments, such as the PANTHER trial, underscore that response rate signals are insufficient if they do not translate into survival advantage, transplant readiness, or patient-centered improvements, and they highlight the need for biomarker-enriched designs and mechanistic correlatives in heterogeneous diseases [28]. MRD has emerged as a critical integrator of biology and clinical decision-making, offering a pathway toward response-adaptive therapy intensity, transplant timing, and maintenance strategies, provided appropriate assays and decision thresholds are standardized and prospectively validated [47,48].

The largest unmet needs remain concentrated in genomically adverse and therapy-resistant subsets—most notably TP53 multi-hit MDS/AML, therapy-related myeloid neoplasms, and post-venetoclax relapse. Addressing these will likely require multi-pronged strategies that combine DNA damage response vulnerabilities, innate immune engagement, and rational combinations that prevent clonal escape rather than merely deepen initial response. Translational pipelines in innate immunity (CD47 blockade), bispecific antibodies, and cellular therapies are advancing, with the central challenge being leukemia selectivity while preserving normal hematopoiesis [54–58]. Epigenetic reprogramming, inflammatory pathway inhibition (e.g., IRAK4), and emerging metabolic strategies further diversify the research landscape and may become essential components of therapy in resistant biology [59–61,69,70].

Finally, precision medicine in myeloid neoplasms will depend as much on implementation as invention. As therapeutic options multiply, clinicians face complex sequencing decisions that must integrate genomics, MRD kinetics, frailty, infection risk, and access to transplantation. AI-supported decision tools may help operationalize this complexity, but only if they are validated prospectively and embedded within robust care pathways that ensure timely molecular testing and standardized supportive care. The next decade is therefore poised to be defined not simply by more drugs, but by coherent, biology-driven therapeutic pathways—built around early molecular diagnosis, MRD-guided adaptation, and mechanistically justified combinations—that improve survival while preserving quality of life across the spectrum of myeloid neoplasms.

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REFERENCES

1. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209–21.
2. Haferlach T, Nagata Y, Grossmann V, Okuno Y, Bacher U, Nagae G, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia*. 2014;28(2):241–7.
3. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200–28.
4. Khoury JD, Solary E, Abal O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703–19.
5. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488–98.
6. Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med*. 2014;371(26):2477–87.
7. Bick AG, Weinstock JS, Nandakumar SK, Fulco CP, Bao EL, Zekavat SM, et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. *Nature*. 2020;586(7831):763–8.
8. Steensma DP. Clinical consequences of clonal hematopoiesis of indeterminate potential. *Blood Adv*. 2018;2(22):3404–10.
9. Malcovati L, Galli A, Travaglino E, Ambaglio I, Rizzo E, Molteni E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. *Blood*. 2017;129(25):3371–8.
10. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised International Prognostic Scoring System for Myelodysplastic Syndromes. *Blood*. 2012;120(12):2454–65.
11. Bejar R, Stevenson KE, Caghey BA, Abdel-Wahab O, Steensma DP, Galili N, et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol*. 2012;30(27):3376–82.
12. Haferlach T. Molecular genetics in myelodysplastic syndromes. *Leuk Res*. 2012;36(12):1459–62.
13. Bernard E, Tuechler H, Greenberg PL, Hasserjian RP, Arango Ossa JE, Nannya Y, et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndromes. *NEJM Evid*. 2022;1(7):EVIDoa2200008.
14. Bernard E, Nannya Y, Hasserjian RP, Devlin SM, Tuechler H, Medina-Martinez JS, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med*. 2020;26(10):1549–56.

15. Molica M. Challenges and emerging therapeutic strategies for TP53-mutated acute myeloid leukemia: still disappointing findings? *Expert Rev Hematol*. 2025;18(1):1–4.
16. Park S, Grabar S, Kelaidi C, Beyne-Rauzy O, Picard F, Bardet V, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. *Blood*. 2008;111(2):574–82.
17. Molteni A, Riva M, Greco R, Nichelatti M, Ravano E, Marbello L, et al. Verifying Hellström-Lindberg score as predictive tool for response to erythropoietin therapy according to the “International Working Group” criteria, in anemic patients affected by myelodysplastic syndrome: a monocentric experience. *Int J Hematol*. 2013;97(4):472–9.
18. Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382(2):140–51.
19. Della Porta MG, Garcia-Manero G, Santini V, Zeidan AM, Komrokji RS, Shortt J, et al. Luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naïve, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): primary analysis of a phase 3, open-label, randomised, controlled trial. *Lancet Haematol*. 2024;11(9):e646–58.
20. Platzbecker U, Santini V, Fenaux P, Sekeres MA, Savona MR, Madanat YF, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;403(10423):249–60.
21. Henry DH, Glaspy J, Harrup R, Mittelman M, Zhou A, Carraway HE, et al. Roxadustat for the treatment of anemia in patients with lower-risk myelodysplastic syndrome: open-label, dose-selection, lead-in stage of a phase 3 study. *Am J Hematol*. 2022;97(2):174–84.
22. BarreYRO L, Chlon TM, Starczynowski DT. Chronic immune response dysregulation in MDS pathogenesis. *Blood*. 2018;132(15):1553–60.
23. Nakajima H. Molecular pathogenesis and treatment of myelodysplastic syndromes. *Intern Med*. 2021;60(1):15–23.
24. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10(3):223–32.
25. Prébet T, Gore SD, Esterni B, Gardin C, Itzykson R, Thepot S, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol*. 2011;29(24):3322–7.
26. Zeidan AM, Kharfan-Dabaja MA, Komrokji RS. Beyond hypomethylating agents failure in patients with myelodysplastic syndromes. *Curr Opin Hematol*. 2014;21(2):123–30.
27. Zeidan AM, Borate U, Pollyea DA, Brunner AM, Roncolato F, Garcia JS, et al. A phase 1b study of venetoclax and azacitidine combination in patients with relapsed or refractory myelodysplastic syndromes. *Am J Hematol*. 2023;98(2):272–81.
28. Adès L, Girshova L, Doronin VA, Díez-Campelo M, Valcárcel D, Kambhampati S, et al. Pevonedistat plus azacitidine vs azacitidine alone in higher-risk MDS/chronic myelomonocytic leukemia or low-blast-percentage AML. *Blood Adv*. 2022;6(17):5132–45.
29. Brunner AM, Esteve J, Porkka K, Knapper S, Traer E, Scholl S, et al. Phase Ib study of sabatolimab (MBG453), a novel immunotherapy targeting TIM-3 antibody, in combination with decitabine or azacitidine in high- or very high-risk myelodysplastic syndromes. *Am J Hematol*. 2024;99(2):E32–6.
30. Abaza Y, Zeidan AM. Immune checkpoint inhibition in acute myeloid leukemia and myelodysplastic syndromes. *Cells*. 2022;11(14):2249.
31. Sallman DA, DeZern AE, Garcia-Manero G, Steensma DP, Roboz GJ, Sekeres MA, et al. Eprenetapopt (APR-246) and azacitidine in TP53-mutant myelodysplastic syndromes. *J Clin Oncol*. 2021;39(14):1584–94.
32. Pollyea DA, Amaya M, Strati P, Konopleva MY. Venetoclax for AML: changing the treatment paradigm. *Blood Adv*. 2019;3(24):4326–35.
33. Bhatt S, Pioso MS, Olesinski EA, Yilma B, Ryan JA, Mashaka T, et al. Reduced mitochondrial apoptotic priming drives resistance to BH3 mimetics in acute myeloid leukemia. *Cancer Cell*. 2020;38(6):872–90.e6.
34. Xuan L, Wang Y, Yang K, Shao R, Huang F, Fan Z, et al. Sorafenib maintenance after allogeneic haemopoietic stem-cell transplantation in patients with FLT3-ITD acute myeloid leukaemia: long-term follow-up of an open-label, multicentre, randomised, phase 3 trial. *Lancet Haematol*. 2023;10(8):e600–11.
35. Murdock HM, Ho VT, Garcia JS. Innovations in conditioning and post-transplant maintenance in AML: genomically informed revelations on the graft-versus-leukemia effect. *Front Immunol*. 2024;15:1359113.
36. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617–29.
37. Pollyea DA, Pratz K, Letai A, Jonas BA, Wei AH, Pullarkat V, et al. Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: long term follow-up from a phase 1b study. *Am J Hematol*. 2021;96(2):208–17.
38. Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):1519–31.
39. Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130(6):722–31.
40. Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728–40.
41. Erba HP, Montesinos P, Kim HJ, Patkowska E, Vrhovac R, Žák P, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10388):1571–83.

42. Levis M, Perl A, Schiller G, Fathi AT, Roboz G, Wang ES, et al. A phase 1 study of the irreversible FLT3 inhibitor FF-10101 in relapsed or refractory acute myeloid leukemia. *Blood Adv.* 2024;8(10):2527–35.
43. Issa GC, Aldoss I, Thirman MJ, DiPersio J, Arellano M, Blachly JS, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *J Clin Oncol.* 2025;43(1):75–84.
44. Arellano ML, Thirman MJ, DiPersio JF, Heiblig M, Stein EM, Schuh AC, et al. Menin inhibition with revumenib for NPM1-mutated relapsed or refractory acute myeloid leukemia: the AUGMENT-101 study. *Blood.* 2025;146(9):1065–77.
45. Wang ES, Montesinos P, Foran J, Erba H, Rodríguez-Arbolí E, Fedorov K, et al. Ziftomenib in relapsed or refractory NPM1-mutated AML. *J Clin Oncol.* 2025;43(31):3381–90.
46. Issa GC, Cai SF, Bataller A, Kantarjian HM, Stein EM. Combination strategies with menin inhibitors for acute leukemia. *Blood Cancer Discov.* 2025;6(6):547–60.
47. Schuurhuis GJ, Heuser M, Freeman S, Béné MC, Buccisano F, Cloos J, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood.* 2018;131(12):1275–91.
48. Short NJ, Zhou S, Fu C, Berry DA, Walter RB, Freeman SD, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncol.* 2020;6(12):1890–9.
49. Platzbecker U, Kubasch AS, Homer-Bouthiette C, Prebet T. Current challenges and unmet medical needs in myelodysplastic syndromes. *Leukemia.* 2021;35(8):2182–98.
50. Shlush LI, Mitchell A, Heisler L, Abelson S, Ng SW, Trotman-Grant A, et al. Tracing the origins of relapse in acute myeloid leukaemia to stem cells. *Nature.* 2017;547(7661):104–8.
51. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence: molecular targets for therapy. *Leukemia.* 2019;33(2):299–312.
52. Amatangelo MD, Quek L, Shih A, Stein EM, Roshal M, David MD, et al. Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. *Blood.* 2017;130(6):732–41.
53. Intlekofer AM, Shih AH, Wang B, Nazir A, Rustenburg AS, Albanese SK, et al. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. *Nature.* 2018;559(7712):125–9.
54. Chao MP, Alizadeh AA, Tang C, Jan M, Weissman-Tsukamoto R, Zhao F, et al. Therapeutic antibody targeting of CD47 eliminates human acute lymphoblastic leukemia. *Cancer Res.* 2011;71(4):1374–84.
55. Advani R, Flinn I, Popplewell L, Forero A, Bartlett NL, Ghosh N, et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. *N Engl J Med.* 2018;379(18):1711–21.
56. Uy GL, Aldoss I, Foster MC, Sayre PH, Wieduwilt MJ, Advani AS, et al. Flotetuzumab as salvage immunotherapy for refractory acute myeloid leukemia. *Blood.* 2021;137(6):751–62.
57. Zugasti I, Espinosa-Aroca L, Fidyk K, Mulens-Arias V, Diaz-Beya M, Juan M, et al. CAR-T cell therapy for cancer: current challenges and future directions. *Signal Transduct Target Ther.* 2025;10(1):210.
58. Rezvani K, Rouse R, Liu E, Shpall E. Engineering natural killer cells for cancer immunotherapy. *Mol Ther.* 2017;25(8):1769–81.
59. Hartung EE, Singh K, Berg T. LSD1 inhibition modulates transcription factor networks in myeloid malignancies. *Front Oncol.* 2023;13:1149754.
60. Parrondo RD, Iqbal M, Von Roemeling R, Von Roemeling C, Tun HW. IRAK-4 inhibition: emavusertib for the treatment of lymphoid and myeloid malignancies. *Front Immunol.* 2023;14:1239082.
61. Chesnais V, Kosmider O, Damm F, Itzykson R, Bernard OA, Solary E, et al. Spliceosome mutations in myelodysplastic syndromes and chronic myelomonocytic leukemia. *Onco-target.* 2012;3(11):1284–93.
62. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med.* 2017;377(5):454–64.
63. DiNardo CD, Stein EM, De Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med.* 2018;378(25):2386–98.
64. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799–807.
65. Issa GC, Aldoss I, DiPersio J, Cuglievan B, Stone R, Arellano M, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. *Nature.* 2023;615(7954):920–4.
66. Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia.* 2019;33(2):379–89.
67. Smith MA, Choudhary GS, Pellagatti A, Choi I, Bolanos LC, Bhagat TD, et al. U2AF1 mutations induce oncogenic IRAK4 isoforms and activate innate immune pathways in myeloid malignancies. *Nat Cell Biol.* 2019;21(5):640–50.
68. Pellagatti A, Boulwood J. Hyperactivation of NF-κB signaling in splicing factor mutant myelodysplastic syndromes and therapeutic approaches. *Adv Biol Regul.* 2025;95:101055.
69. Konopleva M, Pollyea DA, Potluri J, Chyla B, Hogdal L, Busman T, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov.* 2016;6(10):1106–17.
70. Gamma J, Beauchamp E, Liu Q, Iyer A, Yap M, Zak Z, et al. Targeting N-myristoylation for adult acute myeloid leukemia therapy. *Blood.* 2022;140(Suppl 1):3088–9.
71. Eckardt JN, Walter W, Middeke JM, Haferlach T. Artificial intelligence for risk assessment and outcome prediction in malignant haematology. *Br J Haematol.* 2026;208(1):25–38.
72. Tsamesidis I, Drillis G, Varlamis S, Smaragdaki N, Klonizakis P, Dimou M, et al. Novel approaches to the management of myelodysplastic syndromes: the roles of artificial intelligence and oxidative stress biomarkers. *Hematol Rep.* 2026;18(3):33.
73. Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, Allen

- SL, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood*. 2015;125(9):1367–76.
74. Fianchi L, Criscuolo M, Fabiani E, Falconi G, Maraglini AME, Voso MT, et al. Therapy-related myeloid neoplasms: clinical perspectives. *Onco Targets Ther*. 2018;11:5909–15.
75. Yan C, Richard MA, Gibson CJ, He J, Bosworth A, Crossman DK, et al. Clonal hematopoiesis and therapy-related myeloid neoplasms after autologous transplant for Hodgkin lymphoma. *J Clin Oncol*. 2024;42(20):2415–24.
76. Coombs CC, Zehir A, Devlin SM, Kishtagari A, Syed A, Jonsson P, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and

associated with adverse clinical outcomes. *Cell Stem Cell*. 2017;21(3):374–82.e4.

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Understanding Pleural Effusion and Chylothorax: Clinical Features and Therapeutic Approaches

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Abstract

Pleural effusion is defined as the abnormal accumulation of fluid within the pleural space and represents a common clinical manifestation of diverse cardiopulmonary, infectious, inflammatory, systemic, and malignant disorders. Its development reflects an imbalance between pleural fluid production and reabsorption.

Key words: *Pleural effusion; chylothorax; pleural fluid; pseudochylothorax*

Pleura Anatomy – Innervation – Pleural fluid – Pleural effusion

Lungs are separated from the chest wall by a continuous fibrous mesothelial membrane (serous membrane) that is divided into two layers, parietal pleura and visceral pleura, with the hilum being the transition point. The visceral pleura overlies the lung surface, and the parietal pleura overlies the chest wall. The parietal pleura is further divided into cervical, costal, mediastinal and peripheral pleura based on the underlying structures. This subdivision of the parietal pleura is of utmost importance since each part has distinct somatic innervation, leading to radiation of pain to different neighbouring structures of the same somatic innervation. More specifically, the cervical pleura is innervated by the first thoracic spinal nerve, the costal pleura by the overlying thoracic nerves, the mediastinal pleura by the phrenic nerve, and the peripheral diaphragmatic pleura by the lower six thoracic nerves. On the other

hand, the visceral pleura adheres to the lungs and is only innervated by autonomic fibres leading to an absence of pain sensation [1].

The space between the two layers of the pleura is filled with a small amount of fluid, approximately 0.2–0.3 ml/kg per pleural cavity (10–20 ml for a 70kg human per pleural space). The presence of a small amount of pleural fluid plays a crucial role in immune surveillance and facilitates movement between the two layers of the pleura during respiration acting as a natural lubricant. It is continuously produced at a rate of 0.01 ml/kg/h, by the systemic circulation, arising from the thoracic pleura into the pleural space with a net driving force of +5 cm H₂O. This driving force is the result of the difference between the oncotic and hydrostatic pressures of the systemic and pulmonary circulations. Drainage of the pleural fluid is managed through the lymphatics of parietal pleura which end up draining into the right thoracic or the left thoracic duct. Drainage rate can reach a maximum of 0.3 to 0.4 ml/kg/h [1–3]. More specifically, the thoracic duct is responsible for the lymphatic drainage of the entire body except for the right sides of the head and neck, the right side of the thorax and pleural space, and the right upper extremity, which are drained by the right lymphatic duct [4].

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As far as the composition of pleural fluid is concerned it generally contains a normal number of cells, approximately 1.7×10^3 white blood cells per microliter, of which 75% are macrophages, 23% lymphocytes, 1% neutrophils (slightly higher in smokers), 0% eosinophils and 1% to 2% mesothelial cells. Moreover, it contains a small amount of protein, which is less than 1.5 g/dl and is primarily composed of albumin [1,5].

MATERIALS AND METHODS

This narrative review was conducted following a PubMed search using the keywords “pleural effusion,” “pleural fluid,” “pseudochylothorax” and “chylothorax,” limited to English-language publications through February 2026. Twenty-nine relevant articles, including clinical studies, reviews, and guideline-based publications, were selected for analysis.

Mechanisms of Fluid Accumulation

Pleural effusion is the abnormal accumulation of pleural fluid due to local or systemic pathologies that lead to changes in the dynamic balance and equilibrium within the chest cavity [1]. This pathological fluid accumulation is generally the result of an imbalance between the rate of production and the rate of reabsorption of pleural fluid. The underlying pathology affecting the production of fluid may be either systemic or local, and it affects the oncotic and/or hydrostatic pressure or the integrity of the pleura (Table 1). As far as disruption of drainage is concerned, the underlying pathologic mechanisms affect the removal of fluid and

mainly disrupt the flow of the lymphatic vessels or lead to increased central venous pressure, which indirectly leads to lymphatic fluid accumulation [2].

Symptoms – Signs - Imaging modalities

Pleural effusion is characterized by a wide range of signs and symptoms varying from asymptomatic disease to exertional breathlessness or dyspnoea and orthopnoea at rest and moderate to profound hypoxemia and tachypnoea with the underlying pathophysiology being vague [6].

Based on the PLEASE study, one of the largest prospective studies regarding pleural effusion signs and symptoms pre- and post- drainage, reducing the space-occupying or mass effect of pleural effusion appears to be an important contributor to improved breathlessness irrespective of lung re-expansion. Notably, in the PLEASE study, lung volumes, heart rate and respiratory rate underwent only modest absolute changes after drainage, whereas the ipsilateral diaphragm showed more obvious changes in shape and movement, possibly due to its more compressible/distortable nature. Abnormalities in diaphragm movement were common, and their presence, in addition to baseline level of breathlessness, were independent predictors of the likelihood of symptom relief after fluid drainage [7]. Another smaller study by Estenne et al. suggested that relief of dyspnoea following thoracentesis results primarily from a reduction in the size of the thoracic cage, which allows the inspiratory muscles to operate on a more advantageous portion of their length-tension curve. This is because only small

Table 1. Mechanisms of pleural fluid accumulation.

Pleural fluid accumulation mechanisms
Increased production rate
With normal integrity of the endothelial and mesothelial membranes.
• Raised capillary hydrostatic pressure (e.g. congestive heart failure)
• Raised intrathoracic sub-atmospheric pressure (e.g. atelectasis)
• Low capillary oncotic pressure as in hypoalbuminemia (e.g. cirrhosis, nephrotic syndrome, malnutrition)
With disrupted permeability of the endothelial membrane.
• Local disruption of pleural integrity (e.g. pneumonia, pulmonary embolism, cancer)
Extrapulmonary pathology (e.g. hepatic hydrothorax)
Low reabsorption rate
Disrupted integrity of lymphatic vessels at the level of the stomata or along their course (e.g. cancer, thoracic duct rupture)
Increased Central Venous Pressure.

and inconsistent changes in pulmonary mechanics were observed and could not explain the immediate and remarkable relief of dyspnoea noted by the patients. In contrast, an invariable shift of the minimal (inspiratory) pleural pressure -volume curve resulted in generated pressures by the inspiratory muscles being markedly more negative at any comparable lung volume [8].

Moreover, symptoms like cough, fever, and systemic signs also depend on the underlying cause of the effusion. Rare though it may be, effusions can attain sizes significant enough to induce hemodynamic changes, imitating tamponade. Of note, patients suffering from pleural inflammation called pleurisy may complain of sharp, severe, localized crescendo-decrescendo pain with inhalation and exhalation or while coughing. However, the characteristic pleuritic pain is expected to subside when pleural effusion develops while constant pain is a hallmark of malignant diseases such as mesothelioma that may not subside even after pleural effusion accumulation [2,9].

Physical examination findings like intercostal space fullness and percussion dullness are appreciated in large effusions. Auscultation reveals decreased breath sounds and absence of tactile and vocal fremitus over the area of the effusion. Before pleural effusion formation, pleural rubs may be auscultated and are often mistaken for coarse crackles, indicating active pleurisy. Based on a systematic review by Camilla L Wong *et al.*, among the different examination maneuvers of conventional percussion, auscultatory percussion, breath sounds, chest expansion, tactile vocal fremitus, vocal resonance, crackles, and pleural friction rub, conventional percussion was most accurate for diagnosing pleural effusion (summary positive likelihood ratio, 8.7; 95% confidence interval, 2.2-33.8), while the absence of reduced tactile vocal fremitus made pleural effusion less likely (negative likelihood ratio, 0.21; 95% confidence interval, 0.12-0.37) [2,9].

Regarding the imaging modalities for pleural effusion detection, chest radiography (CXR), computed tomography (CT) and ultrasound (US) are the most common and useful options. More specifically, standing lateral view chest X-ray can detect small effusions of 50 ml, while standing posterior - anterior view (PA) chest X-ray can detect effusions of 200-300 ml. In both cases, guiding points are vague costophrenic angles. Lateral decubitus chest X-ray is regarded as the most useful X-ray in detecting pleural effusions even as low as 15-50 ml with a sensitivity of 96 % and a specificity

of 99% [10–12]. Based on a recent systematic review point of care ultrasound (POCUS) seems to have a higher diagnostic accuracy in identification of pleural effusion (as small as 20ml) as a screening tool compared to radiography with a sensitivity of 94% and a specificity of 97 % even in the hands of inexperienced users. It can also be superior to CT in cases of septated effusions identifying the multiple distinct, walled-off compartments or pockets and even guiding thoracentesis [11,13].

Finally, regarding the use of CT scan, it can detect effusions lower than 15 ml, identify a possible empyema or a septated effusion and also characterize nearby structures such as the lung parenchyma and lymph nodes. In that way it helps differential diagnosis, clarifying the possible underlying cause and describing the extent of it. A 2024 retrospective analysis assessed the diagnostic accuracy of CT in differentiation of transudate from exudate pleural effusions based on pleural effusion Hounsfield Units (HU) and pleural fluid to blood HU ratio. It showed that exudates had significantly higher CT values and pleural fluid to blood CT ratio than those with transudates. More specifically with a cut-off value of 10.81 HU, the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CT value were 0.85, 88.89%, 68.90%, 43.96%, and 95.76%, respectively. The optimum cut-off value for PF to blood CT value ratio was 0.27 with AUC of 0.86, yielding a sensitivity of 61.11%, specificity of 86.36%, PPV of 78.57%, and NPV of 73.08%. As a result, CT value and PF to blood CT value ratio showed good differential abilities in predicting transudates from exudates, which may help to avoid unnecessary thoracentesis [14].

Thoracentesis

To alleviate symptoms (therapeutic thoracentesis), differentiate exudate from transudate effusions and guide therapeutic decisions, fluid can be drained from the chest cavity via the minimally invasive technique of thoracentesis. In this procedure, a 20g needle is inserted in the intercostal space on the upper border of the lower rib to avoid the intercostal neurovascular bundle, typically between the sixth and eighth intercostal space in the midaxillary line if the patient is supine or the posterior mid-scapular line if the patient is seated. In cases where US guidance is used (ideally), the insertion point is usually 1-2 intercostal spaces lower than the upper limit of the effusion but not lower than the 9th rib. When performed with appropriate technique and

precautions, it carries a low risk of complications like pneumothorax (5-10%), hemothorax (1%) re-expansion pulmonary oedema (in therapeutic thoracocentesis where >1.5lt of fluid is drained) and spleen or liver laceration. As a result, post procedure CXR is not routinely indicated [3,13,15].

Contraindications for thoracocentesis are coagulation disorders, specifically a platelet count <50,000 / μ L or INR > 2 and local active dermal infection or cellulitis. Intubated patients are a relevant contraindication where thoracocentesis should only be performed when pleural fluid thickness is >15mm in >3 consecutive intercostal spaces [15].

Indications for thoracocentesis are the presence of a newly diagnosed pleural effusion larger than 1cm in the CXR decubitus view and over 1cm thickness in the US. However, small bilateral effusions in patients with decompensated heart failure, cirrhosis, or kidney failure with no underlying fever, chest pain or effusion asymmetry, are likely transudative and do not require diagnostic thoracocentesis. In these cases, diuresis for up to 48h can be performed leading to resolution of up to 75% of these effusions. In cases where the effusion does not resolve, a diagnostic thoracocentesis is prompted [3,16].

Moreover, parapneumonic effusions occurring as a complication of bacterial pneumonia, lung abscess, or bronchiectasis should be tapped as soon as possible to distinguish complicated from uncomplicated ones and to guide therapeutic decisions. More specifically, complicated parapneumonic effusions are characterized by positive Gram stain or positive culture or pH of pleural fluid < 7.2 or glucose of pleural fluid less than 60 mg/dl or LDH > 1000 IU/L and are in need of drainage with thoracostomy for resolution and not only antibiotic therapy. A special subcategory of complicated parapneumonic effusions is empyema, also known as pyothorax or purulent pleuritis, and it is characterized by a pleural effusion with the gross appearance of frank pus that also needs tube thoracostomy in addition to antibiotic therapy. Also, uncomplicated parapneumonic effusions that exceed 1/2 of the hemithorax should also be managed with tube thoracostomy to avoid organization [3,17,18].

Therapeutic thoracocentesis should also be performed in cases of haemothorax drainage, for symptomatic (dyspnoea, hypoxemia) pleural effusions of more than 300 ml and pre-pleurodesis. In all cases of tube thoracostomy, one should always avoid immediate

drainage of >1.5lt of fluid because of the possibility of re-expansion pulmonary edema which is characterised by the early sign of persistent cough post drainage [15].

Pleural fluid work up

In cases of diagnostic thoracocentesis at least 20-30 ml of pleural fluid should be drained and sent to the laboratory. The analysis of pleural aspirate should routinely include a Gram stain, differential cell count, culture, cytology (at least 60ml), protein levels, l-lactate dehydrogenase, and pH. The appearance of the fluid (bloody, clear, straw, turbid, purulent, milky) is also helpful in the diagnostic algorithm. Additional tests, such as tuberculosis (TB) screening with Ziehl-Neelsen stain and culture for common bacteria, Mycobacterium Tuberculosis and nontuberculous (NTM) mycobacteria, should be considered based on individual patient risk factors and regional prevalence [15,19].

Special pleural fluid values to keep in mind are:

- A ratio of pleural fluid Hct / blood Hct >50 %: Indicates hemothorax.
- NT pro-BNP of pleural fluid $\geq$ 1500 pg/ml has 91% Se and 93% Sp for congestive heart failure [20]
- ADA of pleural fluid: <40 exclude TB, >70 suggest TB
- Pleural fluid glucose <60mg/dl or pleural fluid glucose/ serum glucose < 0.5: Malignancy, TB pleuritis, Rheumatoid arthritis, Infection, Systemic Lupus Erythematosus
- High Pleural fluid amylase: Indicative of pancreatic disease or esophageal rupture
- Triglycerides >110mg/dL indicate chylothorax
- Pleural fluid cr / Serum cr >1 indicate urothorax
- Pleural fluid Lymphocytes in CBC >50%: Malignant effusion (Lymphomain 50% of cases), TB pleuritis, Sarcoidosis, Rheumatoid arthritis
- Pleural fluid Eosinophils in CBC > 10%: Drugs, Eosinophilic granulomatosis with polyangiitis, parasites, Pulmonary embolism, Malignancy [15].

Differentiating exudate from transudate pleural effusion and differential diagnosis.

Differentiating an exudate from a transudate pleural effusion by performing a pleural tap remains the standard of care for further differential diagnosis and therapeutic management keeping in mind that the leading causes of pleural effusion in adults are heart failure, infection, malignancy, and pulmonary embolism [16,21].

Transudate effusions mainly account for accumulation of fluid with intact vessels due to either high hy-

drostatic pressure in the pulmonary vessels such as in congestive heart failure, or systemic low oncotic pressure such as nephrotic syndrome, cirrhosis or malnutrition. Both groups can be managed with diuresis and do not require an extensive differential workup.

On the other hand, exudate effusions account for a wide spectrum of underlying pathologies and are the result of increased protein permeability in the capillaries or lymph vessels due to local pathologies, causing an increase in pleural fluid protein concentration. The main causes of exudate effusions are infections, such as pneumonia, metastatic or local malignancy with lung cancer, breast cancer, and lymphoma being the most frequent ones, granulomatous diseases such as tuberculosis or sarcoidosis, collagen vascular diseases and other less frequent causes such as chylothorax. In 20 % of cases the aetiology remains unclear.

In cases of exudate effusions, a broad work up should follow the thoracentesis in order to clarify the underlying pathology and plan therapeutic approach [1,10,21,22] (Table 2).

The best-known and most widely used criteria to differentiate transudative from exudative pleural effusions are Light's criteria that exhibit high sensitivity (98%) in detecting exudative pleural effusions but relatively low specificity (80%) leading to misleading results as far as transudates are concerned characterizing them as exudates especially in cases where prior diuretic therapy has occurred [1,23,24].

Based on Light's criteria, to consider an effusion as exudate, at least one of the following criteria must be satisfied:

- Pleural fluid protein/serum fluid protein ratio > 0.5,
- Pleural fluid lactate dehydrogenase (LDH)/serum fluid LDH ratio > 0.6,
- Pleural fluid LDH > 2/3 the upper limit of normal serum LDH" (Figure 1).

When high suspicion of transudate effusion is present and Light's criteria indicate an exudate effusion the serum pleural effusion albumin gradient (SPAG) or serum pleural effusion protein gradient (SPPG) can be used as a tool. More specifically SPAG (= serum albumin – pleural albumin) > 1.2g/dl or SPPG (=serum protein – pleural protein) > 3.1 g/dl indicates a transudate effusion [1].

Other potential criteria that can be easily used and show a higher specificity identifying an exudate effusion compared to Light's are the Heffner's criteria, which are based on the pleural fluid cholesterol only and without the need for serum values. More specifically, with a cut off value of 45 mg/dl higher values indicate exudate effusions with a reported sensitivity and specificity of 94% and 100%, respectively [25,26].

Another potential way to differentiate exudate from transudate pleural effusions especially in cases where LDH, or protein are not easily available, is the pleural fluid serum bilirubin ratio. Exudates tend to have a greater mean bilirubin ratio compared to transudates. Based on a cross-sectional study in 2018 with a cut-off

Table 2. Causes of transudate and exudate effusions [21]. Causes indicated with * can cause both types of effusion.

TRANSUDATE EFFUSION	EXUDATE EFFUSION	
Congestive Heart Failure	Parapneumonic effusion	Rheumatoid arthritis
Cirrhosis	Atypical pneumonia	Systemic Lupus Erythematosus
Pulmonary embolism*	TB pleuritis	Amyloidosis*
Atelectasia	Nocardiosis/Actinomycosis	Sjogren syndrome
Nephrotic syndrome	Sepsis	Granulomatosis with polyangiitis
Malnutrition	Primary and secondary cancer	Eosinophilic granulomatosis with polyangiitis
Peritoneal dialysis	Meigs syndrome	Systemic sclerosis
Iatrogenic	Yellow nail syndrome	Dressler syndrome
Myxoedema*	Lymphangiomatosis	Asbestosis
Sarcoidosis*	Familial Mediterranean Fever	Chylothorax
Superior Vena Cava syndrome	Pancreatitis	Haemothorax
Constrictive pericarditis	Esophageal rupture	Drug induced
Liver Failure	Uremic pleuritis	Post Actinotherapy

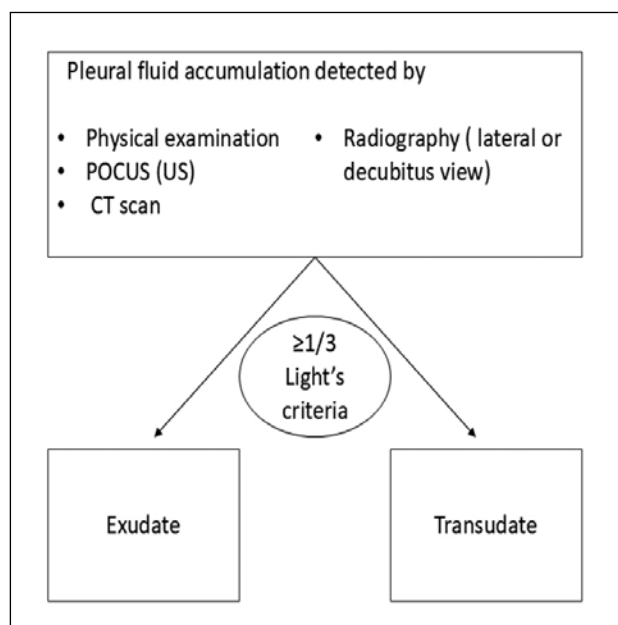


Figure 1. Pleural effusion types..

point of 0.6, the sensitivity, specificity, positive predictive value and negative predictive value were respectively 88.00%, 93.00%, 97.00% & 75.00%, while back in 1990 Meisel et al. revealed the sensitivity of 96% and specificity of 83% [27,28].

Chylothorax

The accumulation of chyle in the pleural space, also known as chylothorax, is a rare but highly morbid cause of exudate pleural effusion. Biochemical analysis of the pleural fluid is necessary for the diagnosis and requires triglyceride levels >110 mg/dl with concomitant cholesterol levels <200 mg/dl, while in cases where levels of triglycerides are less than 55mg/dl the diagnosis is excluded. Based on literature a pleural fluid triglyceride of >110 mg·dL⁻¹ has a 1% chance of being non-chylous and a triglyceride of <50 mg·dL⁻¹ has a 5% chance of being chylous. In borderline cases with high clinical suspicion for chylothorax where pleural fluid triglyceride levels are between 55 and 110mg/dl, such as in cases of malnutrition, the diagnosis can be made with the use of lipoprotein electrophoresis for the detection of chylomicrons in the pleural fluid. As far as the typical gross milky appearance of the fluid is concerned it is seen in only one third of patients. Therefore, the gross appearance is neither sensitive nor specific enough to diagnose a chylothorax, as similar appearances may also

be observed in conditions such as pseudochylothorax and pleural infection/empyema. Centrifugation may help in differentiating chylothorax from empyema as in cases of empyema it clears suspended leukocytes and debris leading to a clear supernatant [29–32].

Pathophysiology of Chylothorax

Chyle is transported *via* the major and minor thoracic duct into systemic circulation. It is composed of interstitial fluid, fluid from the lymphatic system and fluid originating from the intestines which is therefore rich in lymphocytes, immunoglobulins, proteins, lipids, fat soluble vitamins and electrolytes. The loss of this protein-rich, calorie-rich fluid, in cases of chylous leak, can cause serious complications including dehydration, malnutrition and immunosuppression [33].

The anatomical course of the major thoracic duct is complex with considerable variation; therefore, development of chylothorax is dependent on the site and level of the thoracic duct defect.

Causes of chylothorax are mainly traumatic and less frequently non-traumatic. Traumatic chylothorax can be subdivided into iatrogenic, such as after thoracic surgeries or after placement of a central subclavian line or a pacemaker, and non-iatrogenic, caused by external injuries or sudden physical strain. Non-traumatic chylothorax on the other hand, is associated with a wide variety of causes but malignancy remains the major one. Specifically, potential pathologies that directly invade the lymphatic ducts, such as lymphoma and mainly non-Hodgkin lymphoma (in 70% of cases) can cause non-traumatic chylothorax. Another potential mechanism is high hydrostatic pressure inside the lymphatics due to direct obstruction of the thoracic duct or indirectly through increased central venous pressure. Such direct or indirect causes are malignancies, a retrosternal goiter, right heart failure, mediastinal lymph node enlargement, such as in tuberculosis, lymphangioleiomyomatosis, histoplasmosis, sarcoidosis, subclavian vein thrombosis, or superior vena cava obstruction. Interestingly, chylous ascites can also lead to chylothorax through translocation of chyle via pores of the diaphragm. In up to 9% of cases, the etiology remains unknown (termed idiopathic chylothorax) [29,30,34]. However, before jumping to conclusions it is of paramount importance to consider drug-induced chylothorax as part of the differential diagnosis. For example, Chen, Bojiang et al. reported a phenomni-

cally exceptionally rare case of chylothorax induced by Dasatinib, which is a tyrosine kinase inhibitor used for the treatment of BCR-ABL-positive chronic myeloid leukaemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL) [35].

Therapeutic approach of chylothorax comprises conservative and invasive choices. The main therapeutic target is to reduce the production and flow of chyle by minimizing long-chain triglyceride (LCT) intake. This type of triglycerides is absorbed by the lymphatic vessels from the interstitial fluid after being converted to chylomicrons within the enterocytes and transported to the systemic circulation via the thoracic duct in the form of chyle.

In order to manage that, a very low-fat diet comprising mainly medium-chain triglycerides (MCT) that consist of saturated fatty acids of 8 to 12 carbon length is preferred. Medium-chain triglycerides are absorbed directly into the portal circulation without micelle formation thus bypassing the lymphatic system and not contributing to chyle production. Another potential solution is the nil-by-mouth approach and the use of parenteral nutrition. The goal is to allow the thoracic duct leak to heal while preventing malnutrition, for a period of 2–4 weeks. While on fat-modified diets, one must take into consideration the potential essential fatty acid deficiency that results when there is insufficient dietary intake of linoleic acid and alpha-linolenic acid from restricted dietary fat consumption. This is because the human body is unable to synthesize linoleic acid and alpha-linolenic acid due to the lack of enzymes that can introduce and nervous double bonds beyond the Δ^9 site. These essential fatty acids are necessary for healthy cell membrane formation, cholesterol metabolism, blood clotting, as well as proper brain and nervous system development. To prevent this, 2–4% of total calories should arise from linoleic acid and 0.2–1% from alpha-linolenic acid [33,36,37].

Another conservative way to reduce the production of chyle is via the administration of somatostatin analogues (SSAs) like octreotide, or α -adrenergic agonists such as midodrine. Both reduce the production of chyle by the small intestine, reducing its motility and the hepatic and visceral blood flow. Somatostatin analogues should be used when conservative dietary measures fail [36,38].

Regarding invasive therapeutic choices, drainage of the chylous effusion with a chest tube (tube thoracotomy) or catheter may be necessary for symptom relief

in parallel with the pharmaceutical approach [30]. In cases where the conservative management fails and for example pleural fluid drainage continues to exceed 1 L/d, surgical thoracic duct ligation or embolization is usually recommended [30].

Pseudochylothorax

Finally, a pathological entity worth mentioning is pseudochylothorax, which can mimic and must be differentiated from chylothorax. It is the result of a chronic persistent exudative pleural effusion that gradually becomes enriched with cholesterol, also termed cholesterol effusion (Table 3). Chronic tuberculous effusion, chronic pneumothorax, rheumatoid effusion, chronic haemothorax and incompletely drained empyema are among common causes of pseudochylothorax. These effusions have the same milky appearance as chylothorax but are differentiated in the pleural fluid analysis since they are characterized by higher levels of cholesterol (>200mg/dl), lower levels of triglycerides (<50mg/dl) and absence of chylomicrons compared to chylothorax [31]. Finally another tool to distinguish between pseudochylothorax and chylothorax, is a fluid to serum cholesterol ratio <1 and triglyceride ratio >1 which is characteristic for chylothorax [39] (Figure 2).

CONCLUSION

When dealing with a pleural effusion, a well-structured and concise approach should always be the primary goal. A combination of the patient's history, physical examination, clinical suspicion regarding the potential underlying etiology and use of POCUS to guide thoracocentesis is mandatory to differentiate exudative from transudative effusions and establish a therapeutic approach. Due to the diverse etiological factors and patient characteristics associated with pleural effusion, individualized management strategies are recommended especially in cases of rare entities such as chylothorax and pseudochylothorax where

Table 3. Chylothorax and pseudochylothorax differences.

Characteristics	Chylothorax	Pseudochylothorax
Appearance	Milky	Milky
Triglycerides	>110mg/dl	<50mg/dl
Cholesterol	<200mg/dl	>200mg/dl
Chylomicrons	Present	Absent

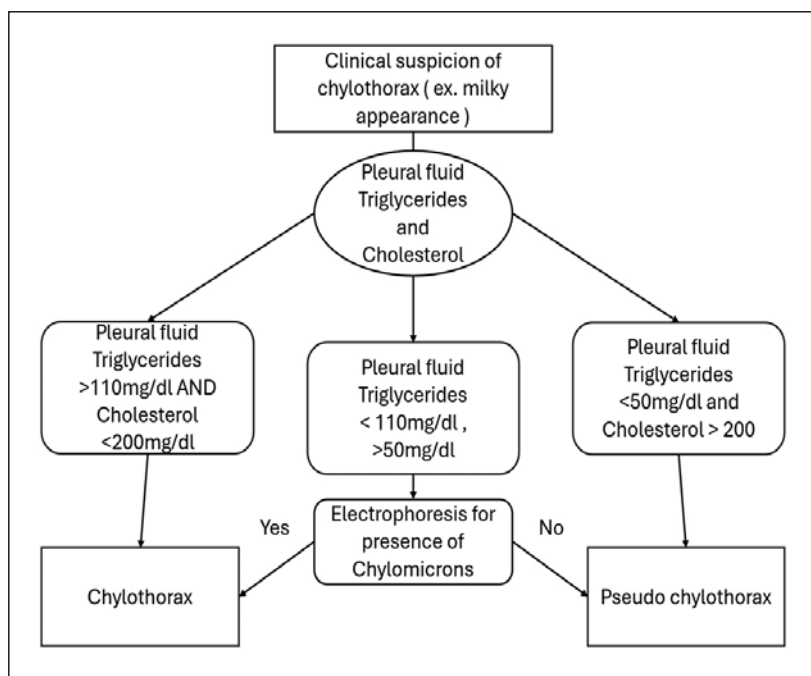


Figure 2. Chylothorax work up.

clinical suspicion and a well-established differential diagnosis are of paramount importance for addressing the underlying clinical entity.

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REFERENCES

1. D'Agostino HP, Edens MA. Physiology, Pleural Fluid. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK513353/>
2. Krishna R, Antoine MH, Alahmadi MH, Rudrappa M. Pleural Effusion. [Updated 2024 Aug 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK448189/>
3. Feller-Kopman D, Light R. Pleural Disease. N Engl J Med. 2018;378(8):740–51. doi:10.1056/NEJMr1403503
4. Ilahi M, St Lucia K, Ilahi TB. Anatomy, Thorax, Thoracic Duct. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK513227/>.
5. DeBiasi EM, Feller-Kopman D. Anatomy and Applied Physiology of the Pleural Space. Clin Chest Med. 2021;42(4):567–76. doi:10.1016/j.ccm.2021.08.005
6. Iyer NP, Reddy CB, Wahidi MM, Lewis SZ, Diekemper RL, Feller-Kopman D, et al. Indwelling Pleural Catheter versus Pleurodesis for Malignant Pleural Effusions. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2019;16(1):124–31. doi:10.1513/AnnalsATS.201807-495OC
7. Muruganandan S, Azzopardi M, Thomas R, Fitzgerald DB, Kuok YJ, Cheah HM, et al. The Pleural Effusion And Symptom Evaluation (PLEASE) study of breathlessness in patients with a symptomatic pleural effusion. Eur Respir J. 2020;55(5):1900980. doi:10.1183/13993003.00980-2019
8. Estenne M, Yernault JC, De Troyer A. Mechanism of relief of dyspnea after thoracentesis in patients with large pleural effusions. Am J Med. 1983;74(5):813–9. doi:10.1016/0002-9343(83)91072-0
9. Wong CL, Holroyd-Leduc J, Straus SE. Does This Patient Have a Pleural Effusion? JAMA. 2009;301(3):309–17. doi:10.1001/jama.2008.937
10. Karkhanis V, Joshi J. Pleural effusion: diagnosis, treatment, and management. Open Access Emerg Med. 2012;4:31–52. doi:10.2147/OAEM.S29942
11. Yousefifard M, Baikpour M, Ghelichkhani P, Asady H, Shahsavari Nia K, Moghadas Jafari A, et al. Screening Performance Characteristic of Ultrasonography and Radiography in Detection of Pleural Effusion; a Meta-Analysis. Emerg (Tehran). 2016;4(1):1–10.
12. Zaki HA, Albaroudi B, Shaban EE, Shaban A, Elgassim M, Almarri ND, et al. Advancement in pleura effusion diagnosis:

- a systematic review and meta-analysis of point-of-care ultrasound versus radiographic thoracic imaging. *Ultrasound J*. 2024;16(1):3. doi:10.1186/s13089-023-00356-z
13. Sikora K, Perera P, Mailhot T, Mandavia D. Ultrasound for the Detection of Pleural Effusions and Guidance of the Thoracentesis Procedure. *ISRN Emerg Med*. 2012;2012(1):1–10. doi:10.5402/2012/676524
 14. Zhang Y, Zhang Y, Wang W, Feng X, Guo J, Chen B, et al. Diagnostic accuracy of thoracic CT to differentiate transudative from exudative pleural effusion prior to thoracentesis. *Respir Res*. 2024;25(1):53. doi:10.1186/s12931-024-02681-w
 15. Wiederhold BD, Sharma S, O'Rourke MC. Thoracentesis. [Updated 2024 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441866/>
 16. Shen-Wagner J, Gamble C, MacGilvray P. Pleural Effusion: Diagnostic Approach in Adults. *Am Fam Physician*. 2023;108(5):464–75.
 17. Light RW. A New Classification of Parapneumonic Effusions and Empyema. *Chest*. 1995;108(2):299–301. doi:10.1378/chest.108.2.299
 18. Colice GL, Curtis A, Deslauriers J, Heffner J, Light R, Littenberg B, et al. Medical and Surgical Treatment of Parapneumonic Effusions. *Chest*. 2000;118(4):1158–71. doi:10.1378/chest.118.4.1158
 19. Wu H, Khosla R, Rohatgi PK, Chauhan SS, Paal E, Chen W. The minimum volume of pleural fluid required to diagnose malignant pleural effusion: A retrospective study. *Lung India*. 2017;34(1):34–7. doi:10.4103/0970-2113.197120
 20. Porcel JM, Vives M, Cao G, Esquerda A, Rubio M, Rivas MC. Measurement of pro-brain natriuretic peptide in pleural fluid for the diagnosis of pleural effusions due to heart failure. *Am J Med*. 2004;116(6):417–20. doi:10.1016/j.amjmed.2003.11.008
 21. Jany B, Welte T. Pleural Effusion in Adults—Etiology, Diagnosis, and Treatment. *Dtsch Arztebl Int*. 2019;116(21):377–86. doi:10.3238/arztebl.2019.0377
 22. Antony VB. DRUG-INDUCED PLEURAL DISEASE. *Clin Chest Med*. 1998;19(2):331–40. doi:10.1016/S0272-5231(05)70080-0
 23. Sharma K, Fultariya L, Reddy Mallimala P, Shah K, Sharma V. Comparison of the Efficacy of Light's Criteria With Serum-Effusion Albumin Gradient and Pleural Effusion Glucose. *Cureus*. 2023;15(8):e43319. doi:10.7759/cureus.43319
 24. Romero-Candeira S, Fernández C, Martín C, Sánchez-Paya J, Hernández L. Influence of diuretics on the concentration of proteins and other components of pleural transudates in patients with heart failure. *Am J Med*. 2001;110(9):681–6. doi:10.1016/S0002-9343(01)00726-4
 25. Devkota KC, Hamal S, Panta P. Comparison of Heffner Criteria and Light Criteria in Differentiating Exudative and Transudative Pleural Effusion. *Nepal Med Coll J*. 2020;22(3):141–5. doi:10.3126/nmcj.v22i3.32638
 26. Gautam S, K C SR, Bhattarai B, K C G, Adhikari G, Gyawali P, et al. Diagnostic value of pleural cholesterol in differentiating exudative and transudative pleural effusion. *Ann Med Surg (Lond)*. 2022;82:104479. doi:10.1016/j.amsu.2022.104479
 27. Agrawal P, Shrestha TM, Prasad PN, Aacharya RP, Gupta P. Pleural Fluid Serum Bilirubin Ratio for Differentiating Exudative and Transudative Effusions. *JNMA J Nepal Med Assoc*. 2018;56(211):662–5.
 28. Meisel S, Shamiss A, Thaler M, Nussinovitch N, Rosenthal T. Pleural Fluid to Serum Bilirubin Concentration Ratio for the Separation of Transudates from Exudates. *Chest*. 1990;98(1):141–4. doi:10.1378/chest.98.1.141
 29. Ur Rehman K, Sivakumar P. Non-traumatic chylothorax: diagnostic and therapeutic strategies. *Breathe*. 2022;18(2):210163. doi:10.1183/20734735.0163-2021
 30. Bhatnagar M, Fisher A, Ramsaroop S, Carter A, Pippard B. Chylothorax: pathophysiology, diagnosis, and management—a comprehensive review. *J Thorac Dis*. 2024;16(2):1645–61. doi:10.21037/jtd-23-1636
 31. McGrath EE, Blades Z, Anderson PB. Chylothorax: Aetiology, diagnosis and therapeutic options. *Respir Med*. 2010;104(1):1–8. doi:10.1016/j.rmed.2009.08.010
 32. Maldonado F, Hawkins FJ, Daniels CE, Doerr CH, Decker PA, Ryu JH. Pleural Fluid Characteristics of Chylothorax. *Mayo Clin Proc*. 2009;84(2):129–33. doi:10.4065/84.2.129
 33. Bibby AC, Maskell NA. Nutritional management in chyle leaks and chylous effusions. *Br J Community Nurs*. 2014;19(Suppl 11):S6–8. doi:10.12968/bjcn.2014.19.Sup11.S6
 34. Gary P, Giannios M, Ryu J, Flynn S. Chylothorax as a complication of Waldenström macroglobulinaemia with a patient's perspective. *BMJ Case Rep*. 2021;14(5):e241707. doi:10.1136/bcr-2021-241707
 35. Chen B, Wu Z, Wang Q, Li W, Cheng D. Dasatinib-induced chylothorax: report of a case and review of the literature. *Invest New Drugs*. 2020;38(5):1627–32. doi:10.1007/s10637-020-00932-3
 36. Fogg KL, Trauth A, Horsley M, Vichayavilas P, Winder M, Bailly DK, et al. Nutritional management of postoperative chylothorax in children with CHD. *Cardiol Young*. 2023;33(9):1663–71. doi:10.1017/S1047951122003109
 37. Agrawal A, Chaddha U, Shojaaee S, Nadolski G, Liberman M, Lee YCG, et al. Multidisciplinary management of adult patients with chylothorax: a consensus statement. *Eur Respir J*. 2024;64(5):2400470. doi:10.1183/13993003.00470-2024
 38. Sharkey AJ, Rao JN. The successful use of octreotide in the treatment of traumatic chylothorax. *Tex Heart Inst J*. 2012;39(3):428–30.
 39. Nair SK, Petko M, Hayward MP. Aetiology and management of chylothorax in adults. *Eur J Cardiothorac Surg*. 2007;32(2):362–9. doi:10.1016/j.ejcts.2007.04.024.

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