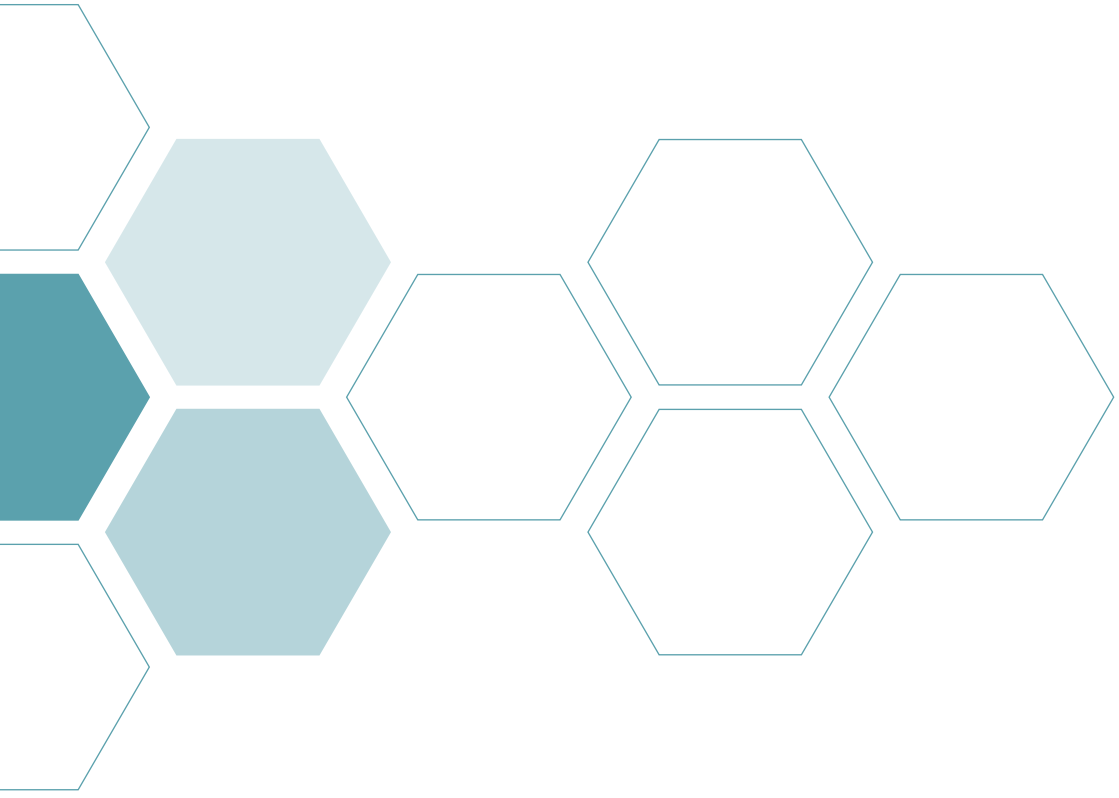
JOURNAL of MANAGED CARE MEDICINE

Vol. 28, No. 1, 2025

Educating Medical Directors of Employers, Health Plans and Provider Systems



FEATURED ARTICLES INCLUDE:

Innovations and Advancements in Sickle Cell Disease: Expert Guidance for Adapting Novel Treatments into Practice

Innovative Approaches in the Management of Acute Myeloid Leukemia: Managed Care Insights in an Evolving Treatment Landscape

Keeping Pace with Rapid Advancements in the Management of Hereditary Angioedema: Optimized Strategies in Managed Care Decision-Making

Editorial Review Board

JMCM

JOURNAL OF MANAGED CARE MEDICINE

4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
Thomas Morrow, MD

PUBLISHER
Jeremy Williams

ADVERTISING REPRESENTATIVE
Maria Sercia
American Medical Communications, Inc.
msercia@americanmedicalcomm.com
(267) 614-6809

JOURNAL MANAGEMENT
Douglas Murphy Communications
Richmond, Virginia
grant.murphy@douglasmurphy.com
(804) 387-7580

GRAPHIC DESIGN
Douglas Murphy Communications

Custom Article Reprints
High quality reprints of individual articles are available in print and electronic formats.
Contact Jeremy Williams,
jwilliams@namcp.org,
(804) 527-1905 for reprints.

ISSN: 1094-1525. The ***Journal of Managed Care Medicine*** is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: 15 Bridgehampton Place, Richmond, VA 23229; Tel (804) 387-7580. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 28, No. 1, 2025

TABLE OF CONTENTS

Innovations and Advancements in Sickle Cell Disease: Expert Guidance for Adapting Novel Treatments into Practice

Matthew M. Heeney, MD

This journal article is supported by educational grants from bluebird bio; Vertex Pharmaceuticals

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Sickle cell disease (SCD) is a hereditary blood disorder characterized by sickle-shaped red blood cells resulting in restricted blood flow and limited oxygen delivery to the body's tissues, leading to severe pain and organ damage. Sickle cell crises can lead to life-threatening disabilities and/or early death. Management of SCD is focused on preventing and treating pain episodes and other complications but the future is gene-based therapies for possible cures.

Key Points

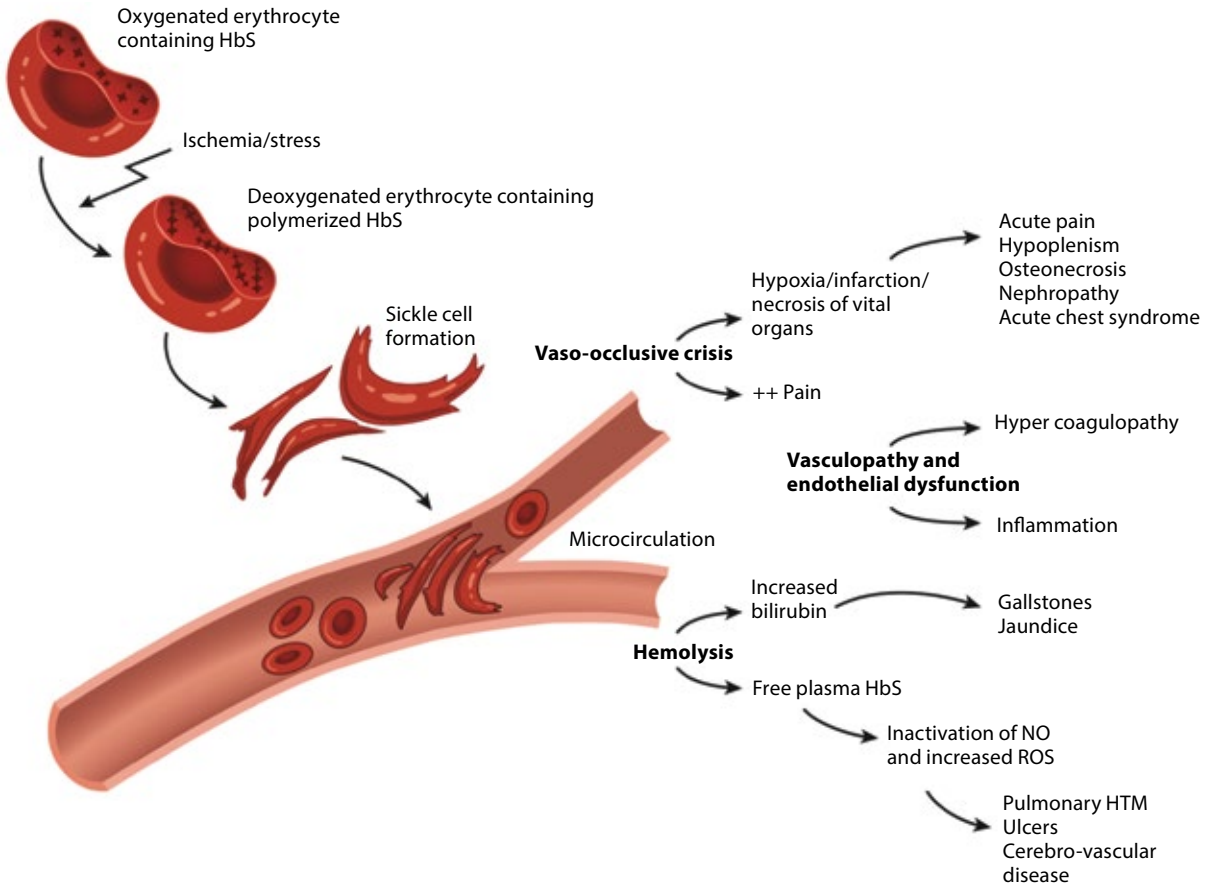
- SCD is a significant cause of morbidity and death.
- A few interventions such as universal newborn screening, childhood antibiotics, vaccines, and hydroxyurea have been shown to improve survival.
- Other disease-modifying treatments and potentially curative stem cell transplants and gene therapy are available.
- There are significant issues to be resolved with gene therapy including cost and durability of response.

SICKLE CELL DISEASE (SCD) IS A COMPLEX group of autosomal recessive inherited blood disorders associated with mutation in hemoglobin resulting in debilitating pain and complications that can affect every organ in the body. It is the most common single gene disorder in African Americans. More than 90 percent of those affected in the United States (U.S.) are non-Hispanic Blacks or African Americans, and an estimated 3 percent to 9 percent are Hispanic or Latino.[1] About one in 10 African Americans are heterozygous carriers (sickle cell trait) and one in 400 are homozygous SCD. Approximately 100,000 Americans are affected by SCD and about 2,200 babies with SCD are born annually. These new cases are detected by universal newborn screening.[2]

SCD is a global health problem. Seventy-five percent of global individuals with SCD live in Sub-Saharan Africa and as many as 80 percent of these individuals do not live to adulthood. Worldwide, 300,000 children with SCD are born annually.[3]

Those with sickle cell trait inherited one gene for sickle hemoglobin (HbS) and those with SCD inherited two HbS genes from their parents. A single amino acid substitution in hemoglobin of valine for glutamic acid produces HbS. Valine creates a hydrophobic surface when deoxygenated leading to non-covalent bonds form between βS proteins and formation of 14-stranded helical polymers. Polymerization leads to distortion of red blood cell (RBC) shape, damage to RBC membrane, abnormal RBC permeability, irreversible sickling, premature

Exhibit 1: Cascade of Events in Sickle Cell Disease



hemolysis (resulting in hemolytic anemia) and impairment of RBC flow resulting in tissue infarction. Exhibit 1 shows the consequences of the hemoglobin mutation and Exhibit 2 the acute and chronic complications of SCD.

The estimated life expectancy of those with SCD in the U.S. is more than 20 years shorter than the expected average.[1] Quality-adjusted life expectancy is more than 30 years shorter. Survival has improved over the years. The mean age at death for all SCD genotypes for 2010 through 2020 was 43 years (females: 44 years, males: 41 years) versus 39 years for 1999 through 2009 (females: 40 years, males: 38 years).[4]

Several measures are important for health maintenance in those with SCD and are where there are national guidelines. Clinical management guidelines for SCD are available from the American Society of Hematology (Cardiopulmonary and Kidney Disease [2019], Transfusion Support [2020], Cerebrovascular Disease [2020], Management of Acute and Chronic Pain [2020], Stem Cell Transplant [2021]; available at hematology.org), National Heart, Lung, and Blood Institute (2014, available at nhlbi.nih.gov/resources/evidence-based-management-sickle-cell-disease-expert-panel-report-2014), and the National Institute of Health (2017, available at nhlbi.nih.gov/sites/default/files/publications/04-2117.pdf).

Infection prevention is one area for preventing acute complications. Prophylactic therapy with oral penicillin from four months of age to five years old decreases the morbidity and mortality associated with pneumococcal septicemia. Children and adults with SCD should receive all recommended vaccinations, including an influenza vaccination.[5] People with SCD are considered high risk for certain infections and should follow a special vaccination schedule for haemophilus influenzae type b (Hib), pneumococcal, and meningococcal vaccines. Childhood survival has improved with newborn screening, oral penicillin, and vaccination and is now 96 to 98 percent for all SCD genotypes.

Stroke is another common cause of morbidity and mortality which needs to be prevented. Blood transfusions to reduce HbS levels to below 30

Exhibit 2: Clinical Manifestations

ACUTE	CHRONIC
Non Vaso-occlusive	• Cardiovascular: pulmonary hypertension, cardiomegaly
Bacteremia (encapsulated organisms)	• Renal: hyposthenuria, proteinuria
Cholecystitis / RUQ Syndrome	• Eyes: proliferative retinopathy
Aplastic Crisis	• Skin: leg ulcers
Vaso-occlusive	• Lungs: chronic lung disease
Pain crises	• Musculoskeletal: bone changes, osteonecrosis/avascular necrosis
Acute chest syndrome	• Central nervous system: developmental delays, learning disability
Cerebrovascular accident	
Dactylitis / Hand Foot Syndrome	
Hepatosplenic sequestration	
Priapism	

percent prevent strokes in children with high central nervous system blood flow. Transcranial doppler screening and transfusion have significantly reduced risk of stroke.[6]

Disease-modifying treatments of SCD are available. Fetal hemoglobin (HbF) induction is one therapeutic target. HbF has higher affinity for oxygen but not so great to be a problem in the adult patient. HbF can effectively replace adult hemoglobin (HbA) without adverse consequences and HbF blocks polymerization of HbS. HbF level in adults is subject to genetic control. Persistence of HbF in adults can be due to common genetic variation (minor differences) or rare genetic variation (large effects). Hydroxyurea, an antimetabolite chemotherapy agent, is used to enhance HbF in those with SCD and has been shown to extend the time to first and second painful SCD-related events and improves 10-year overall survival.[7,8] Hydroxyurea use is a standard of care for all patients with SCD. It is recommended that hydroxyurea be offered for infants nine months and older and adolescents, regardless of clinical severity, to reduce complications of SCD.[9]

Transfusion is a disease-modifying therapy for treatment and prevention of acute and chronic complications of SCD. Blood may be administered by simple transfusion, manual exchange, and automated red blood cell exchange. The main complications of transfusion are iron overload, alloimmunization, delayed hemolytic transfusion reactions, and transfusion-associated circulatory overload. Acute or episodic transfusion therapy is typically reserved for acute chest syndrome, splenic/hepatic sequestration, pre-operative, aplastic crisis, maternofetal complication, and multiorgan failure. The goal is to maximize oxygen-carrying capacity but post-transfusion Hb should not exceed 10 to 11 g/dL.[10] Phenotypically matched blood for minor antigens C, E and Kell is used and allo-sensitization should be reassessed one to three months after transfusion.

Oxidative stress damage is believed to be involved in the pathophysiology of SCD. L-glutamine, an amino acid, is a precursor for the synthesis of essential metabolic redox cofactors. L-glutamine utilization in SCD exceeds the body's ability to produce it and its depletion plays a role in oxidative stress. Oral therapy with L-glutamine has been shown to increase the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which reduces oxidative stress and could result in fewer episodes of sickle cell–related pain. An L-glutamine product was FDA approved for SCD in 2017 based on a study showing prolongation to pain events.[11]

One agent for SCD was withdrawn from the market in September 2024. Voxelotor was a an oral, once-daily therapy which increased hemoglobin's affinity for oxygen. It inhibited sickle hemoglobin polymerization and the resultant sickling and destruction of red blood cells. It was FDA approved in 2019 under an accelerated approval but subsequent

Exhibit 3: Summary of Disease Modifying Therapies

Treatment	MOA	Hemoglobin	Pain	Benefits	Disadvantages
Hydroxyurea 1998	Increase fetal hemoglobin	✓	✓	Oral, $	Daily, chemotherapy, inconsistently effective in adults
L-glutamine 2017	Decrease RBC oxidative stress	✓	✓	Oral, $$	Daily, large amount of powder needs to be taken (15 grams/day), noncompliance
Crizanlizumab 2019	P selectin blocker		✓	Monthly	Intravenous, $$$

data suggested excess vaso-occlusive events (VOE) and fatal events.[12]

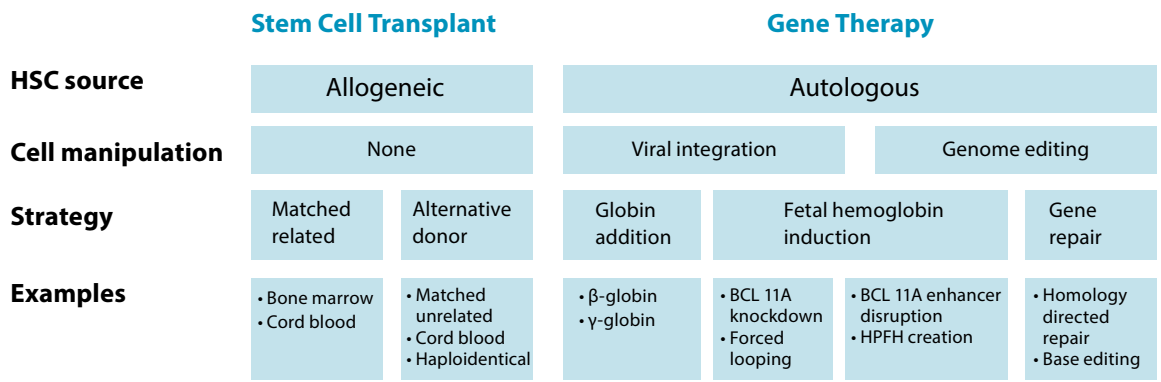
Crizanlizumab is an injectable monoclonal antibody that binds to P-selectin which blocks the interactions with P-selectin glycoprotein ligand-1 (PSGL-1) on white blood cells and endothelium which are "sticky" in SCD and contribute to VOE. It was FDA approved in 2019 to reduce the frequency of VOE in people aged 16 years and older who have sickle cell anemia. In the trial leading to FDA approval, crizanlizumab therapy resulted in a significantly lower rate of sickle cell-related pain crises than placebo and was associated with a low incidence of adverse events.[13] The most common side events include joint pain, nausea, back pain, fever, and abdominal pain. Exhibit 3 compares the disease-modifying therapies.

Investigational medications for SCD include oral erythrocyte pyruvate kinase activators (etavopivat, mitapivat). These agents are proposed to ameliorate sickling through multiple mechanisms, including reduction of 2,3-diphosphoglycerate. In addition, PKR activation increases adenosine triphosphate (ATP) produced via glycolytic flux, which helps preserve membrane integrity and RBC deformability. Mitapivat is already FDA approved for treating hemolytic anemia for adults with pyruvate kinase deficiency.

The future of SCD treatment is transformational therapies, of which some are already FDA approved and in use. These therapies are potentially curative approaches. The first is allogenic hematopoietic stem cell replacement, which has been in use since the late 1980s. There is now a 90 percent five-year event-free survival post-transplant.[14] The best outcomes are seen when transplant is done by age eight years. Graft versus host disease is still an issue for many patients which leads to significant morbidity. Finding a matched allogenic donor is limiting—there is only a one in six chance a sibling will be a match for a patient. Using alternative donors has become more common and also has had good success.

Gene therapies have been developed for SCD which eliminates some of the issues found with allogenic stem cell transplant such as requiring a donor and graft-versus-host disease because the patient's own cells are used and modified. It should be noted that gene therapies require stem cell mobilization and collection and conditioning chemotherapy before transplant of the modified cells. As shown in Exhibit 4, there are several ways the patient's cells can be manipulated for a potential cure. One approach is to add normal globin genes delivered by lentiviral infection of stem cells. Lovotibeglogene autotemcel (also called lentiglobin) consists of autologous transplantation of hematopoietic stem and progenitor cells transduced with the BB305 lentiviral vector encoding a modified β-globin gene, which produces an anti-sickling hemoglobin, HbAT87Q. In the trial that led to FDA approval, 88 percent of 34 patients who received this gene therapy did not experience any VOE and 94 percent did not have a severe VOE during a six to 18 months assessment period after transplant.[15] Patients had a median 40 percent of their hemoglobin as the modified HbAT87Q. The hemoglobin response was durable out to 60 months follow-up. Because gene therapy requires conditioning chemotherapy before the stem cell transplant, there are significant adverse events. With lentiglobin, most treatment-emergent adverse events occurred within one year and were known consequences of conditioning with busulfan. There were no cases of veno-occlusive liver disease, graft failure, or graft-versus-host disease. There were no vector-related complications, no insertional oncogenesis, or vector-mediated replication-competent lentivirus. There was one death, due to significant baseline SCD-related cardiopulmonary

Exhibit 4: Curative Approaches for SCD



disease but it was not considered related to procedure. A few cases of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), which was not thought to be related to the lentivirus but likely chemotherapy exposure, have been reported.[16,17]

BCL11A gene conditional knock-out (BCH-BB694) is an investigational gene therapy. Knocking out this gene increases HgF production and reduces sickling. A small Phase I clinical trial (NCT03282656), showed BCH-BB694 prevented SCD-associated complications.[18] The gene therapy was more effective at preventing red blood cell sickling than hydroxyurea.[19] BCH-BB694 is also being tested in up to 25 severe SCD patients, ages 13 to 40 years, in the Phase II GRASP trial (NCT05353647).

BCL11A can also be impacted by enhancer disruption. CRISPR/Cas9 gene editing uses an RNA sequence to target a specific/unique target DNA sequence. The Cas9 protein attached to the CRISPR induces a double strand DNA cut at the target sequence. When the DNA cut is repaired, insertions/deletions ("indels") disrupt and disable the target gene, which in this case is BCL11A. Exagamglogene autotemcel (exa-cel), which targets the erythroid-specific enhancer region of the BCL11A gene using a nonviral delivery method, is FDA approved to treat SCD and transfusion-dependent beta thalassemia.

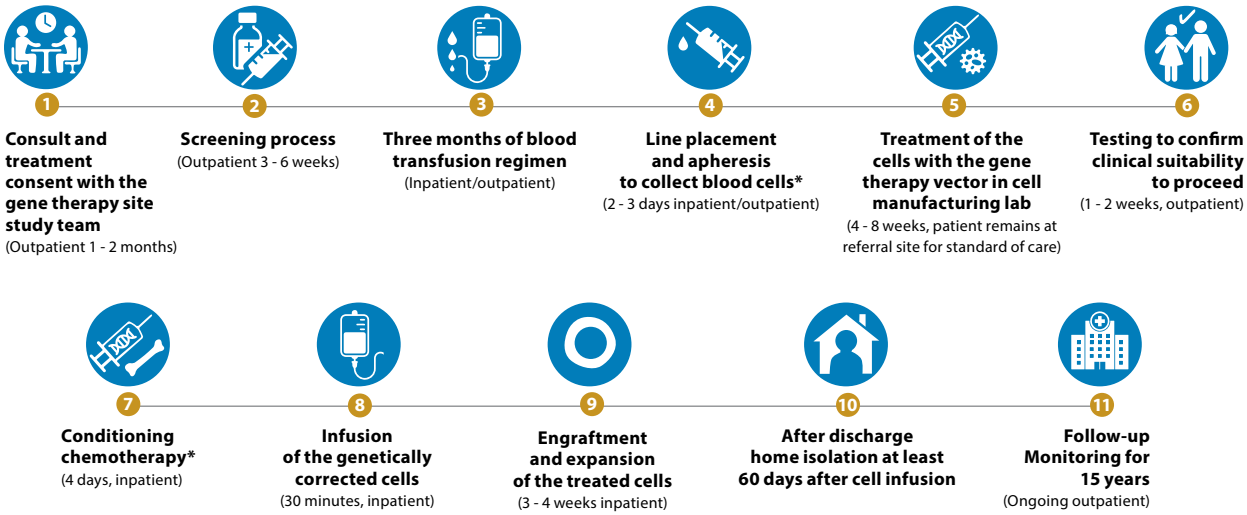
A Phase III, single-group, open-label study of exa-cel in patients 12 to 35 years of age with SCD who had had at least two severe VOE in each of the two years before screening led to FDA approval.[20] A total of 44 patients received exa-cel, and the median follow-up was 19.3 months (range, 0.8 to 48.1). Of the 30 patients who had sufficient follow-up to be evaluated, 97 percent were free from VOE for at least 12 consecutive months, and 100 percent were free from hospitalizations for VOE for at least 12 consecutive months ($p < 0.001$ for both comparisons against the null hypothesis of a 50% response). The safety profile of exa-cel was consistent with that of myeloablative busulfan conditioning and autologous transplantation.

Genomic editing to mimic hereditary persistence of fetal hemoglobin (HPFH) is also possible which increases fetal hemoglobin production. Renizgamglogene autogedtemcel (reni-cel) also use CRISPER/Cas9 and is investigational. In data presented at a professional meeting, but not yet published, of 28 patients, 27 were VOE free post-reni-cel infusion.[21] Reni-cel administration led to early, robust increases and sustained levels of total Hb and HbF, with a mean HbF percentage of 48.1 percent.

The last type of gene editing to discuss is gene repair. Using CRISPER, but without Cas9 that produces indels, individual edits of a base can be made. A deaminase enzyme is fused to the CRISPR protein. The deaminase converts the target base to the desired base (example C to T). Data from a Phase I/II trial with BEAM-101, a base edit of C to T in the BCL11A promoter site to mimic HPFH, was presented in December 2024 at an American Society of Hematology meeting.[22] All four patients experienced rapid and robust HbF induction by month one (> 60%) and corresponding HbS reduction (≤ 36%), which was sustained over time. Markers of hemolysis normalized or improved for all four patients. No VOE were reported by investigators post-treatment.

Shared decision-making is important in managing SCD. This is especially true with the advent of gene therapy and the unknowns related to long-term effects of these therapies. There is a long patient

Exhibit 5: Patient Journey for SCD Gene Therapy



**fertility preservation to occur prior to conditioning therapy.*

journey that leads to gene therapy (Exhibit 5) so patients need to understand the steps, alternatives (disease-modifying therapy, conventional stem cell transplant), the differences in the two available gene therapies, and whether clinical trial enrollment for an investigational gene therapy is an option. The patient informed consent process involves a psychologist evaluation, fertility preservation evaluation, and transplant physician consultation. Busulfan conditioning results in infertility in most patients so fertility preservation is even offered to prepubescent individuals. Financial considerations include cost of the gene therapy and insurance coverage, fertility preservation, travel to treatment site, lodging during treatment, and finally long-term follow-up.

The cost of gene therapy is enormous. Lovotibeglogene autotemcel is $3.1 million and exagamglogene autotemcel is $2.2 million. The patient selection and exclusion criteria for these therapies are not yet known and there are no labelling restrictions in the FDA approvals. About 25 percent of the U.S. SCD population (~25,000 people) may be eligible for transformative therapies based on the severity criteria used in the gene therapy clinical trials. Payers must confront the high cost and considerable clinical uncertainty of efficacy and durability. Three main gene therapy payment models have been proposed.[23] Amortization spreads the payments over time to reduce the initial budget impact. Risk spreading pools costs with other payers or caps costs based on expected volume to make budgets more predictable. Performance-based payments ties prices to patient- or population-level outcomes to address clinical uncertainty.

About 60 percent of SCD patients have Medicaid as a payer. The Centers for Medicare and Medicaid Services has proposed a Cell and Gene Therapy Access Model.[24] Under this model, the federal government will negotiate Outcome-Based Agreements, Value-Based Contracting, and Discounts with manufacturers on behalf of state Medicaid agencies. The state Medicaid agencies must agree to the negotiated prices and pledge to provide broad access to the therapies. Meaningful risk sharing tied to a claims-based metric that is directly correlated with clinical benefit and aligned with study endpoints over three years (VOE-related hospitalizations) will be included. If there are no in-state treatment centers, Medicaid agencies would pay for patients to receive the therapies in another state.

Conclusion

SCD is a significant cause of morbidity and death. A few interventions such as universal newborn screening, childhood antibiotics, vaccines, and hydroxyurea have been shown to improve survival. Other disease-modifying treatments and potentially curative stem cell transplants and gene therapy are available. Although gene therapy offers great hope for transforming the treatment of SCD, there are still significant issues to be determined including how to pay for gene therapy, the durability of these therapies, and whether they impact overall survival.

Matthew M. Heeney, MD is an Associate Chief of Hematology, Director of the Sickle Cell Program, and Orah S. Platt Chair in Hematology at the Boston Children's Hospital in Boston, MA.

References

1. CDC. Data and Statistics on Sickle Cell Disease. Available at cdc.gov/sickle-cell/data. Accessed 1/9/2025.
2. Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. *J Hematol Oncol.* 2022;15(1):20.
3. Piel FB, Hay SI, Gupta S, et al. Global burden of sickle cell anemia in children under five, 2010-2050: Modelling based on demographics, excess mortality, and interventions. *PLoS Med*. 2013;10(7):e1001484.
4. Karkoska K, McGann PT. Changing trends in sickle cell disease-related mortality in the United States over four decades. *Blood*. 2023;142 (Supplement 1):925.
5. Complications of SCD: Infection. Available at cdc.gov/sickle-cell/complications/complications-of-scd-infection.html. Accessed 1/9/2025.
6. Fullerton HJ, Adams RJ, Zhao S, Johnston SC. Declining stroke rates in Californian children with sickle cell disease. *Blood*. 2004;104(2):336-9.
7. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med*. 1995;332(20):1317-22.
8. Voskaridou E, Christoulas D, Bilalis A, et al. The effect of prolonged administration of hydroxyurea on morbidity and mortality in adult patients with sickle cell syndromes: results of a 17-year, single-center trial (LaSHS). *Blood*. 2010;115(12):2354-63.
9. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: Summary of the 2014 evidence-based report by expert panel members. *JAMA*. 2014;312(10):1033-48.
10. Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: Transfusion support. *Blood Adv*. 2020;4(2):327-55.
11. Niihara Y, Miller ST, Kanter J, et al. A Phase III trial of l-glutamine in sickle cell disease. *N Engl J Med*. 2018;379(3):226-35.
12. Pfizer Voluntarily Withdraws All Lots of Sickle Cell Disease Treatment OXBRYTA® (voxelotor) From Worldwide Markets. September 24, 2024. Available at pfizer.com/news/press-release/press-release-detail/pfizer-voluntarily-withdraws-all-lots-sickle-cell-disease. Accessed 1/9/2025.
13. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429-39.
14. Bernaudin F, Dalle JH, Bories D, et al. Long-term event-free survival, chimerism and fertility outcomes in 234 patients with sickle-cell anemia younger than 30 years after myeloablative conditioning and matched-sibling transplantation in France. *Haematologica*. 2020;105(1):91-101.
15. Kanter J, Walters MC, Krishnamurti L, et al. Biologic and clinical efficacy of lentiglobin for sickle cell disease. *N Engl J Med*. 2022;386(7):617-28.
16. Hsieh MM, Bonner M, Pierciey FJ, et al. Myelodysplastic syndrome unrelated to lentiviral vector in a patient treated with gene therapy for sickle cell disease. *Blood Adv*. 2020;4(9):2058-63.
17. ASH Clinical News. FDA Places Clinical Hold on LentiGlobin Gene Therapy Trials. 2021. Available at ashpublications.org/ashclinicalnews/news/5565/FDA-Places-Clinical-Hold-on-LentiGlobin-Gene. Accessed 1/9/2025.
18. Esrick EB, Lehmann LE, Biffi A, et al. Post-transcriptional genetic silencing of BCL11A to treat sickle cell disease. *N Engl J Med*. 2021;384(3):205-15.
19. De Souza, D.C., Hebert, N., Esrick, E.B. et al. Genetic reversal of the globin switch concurrently modulates both fetal and sickle hemoglobin and reduces red cell sickling. *Nat Commun*. 2023;14:5850.
20. Frangoul H, Locatelli F, Sharma A, et al. Exagamglogene autotemcel for severe sickle cell disease. *N Engl J Med*. 2024;390(18):1649-62.
21. Editas Medicine Reports Updated Clinical Data from the RUBY Trial of Reni-cel in Patients with Severe Sickle Cell Disease at the American Society of Hematology (ASH) Annual Meeting. Available at ir.editasmedicine.com/news-releases/news-release-details/editas-medicine-reports-updated-clinical-data-ruby-trial-reni. Accessed 1/9/2025.
22. Beam Therapeutics to Present Data Across Hematology Franchise, Including First Clinical Data for BEAM-101 in Sickle Cell Disease and ESCAPE Non-human Primate Data, at American Society of Hematology (ASH) Annual Meeting. Available at investors.beamtx.com/news-releases/news-release-details/beam-therapeutics-present-data-across-hematology-franchise. Accessed 1/9/2025.
23. Horrow C, Kesselheim AS. Confronting high costs and clinical uncertainty: Innovative Payment models for gene therapies. *Health Aff (Millwood).* 2023;42(11):1532-40.
24. CMS. Cell and Gene Therapy (CGT) Access Model. Available at cms.gov/priorities/innovation/innovation-models/cgt. Accessed 1/9/2025.

Innovative Approaches in the Management of Acute Myeloid Leukemia: Managed Care Insights in an Evolving Treatment Landscape

Jeffrey E. Lancet, MD

This journal article is supported by educational grants from Daiichi Sankyo; Jazz Pharmaceuticals; Syndax Pharmaceuticals

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

AML is the most common acute leukemia affecting adults, and its incidence increases with age. Fortunately for patients with AML many new treatments, which have shown improved efficacy and safety, have become available in the past several years. With so many recent new options available, and more to come, the treatment paradigm in AML has drastically changed, including options for patients with secondary AML.

Key Points

- New therapies for AML are improving outcomes and have shifted care toward the outpatient setting, especially for older adults.
- Unique toxicity profiles of the new medications and high acuity of AML patients require resources and excellent communication for optimal management in the community.
- The high cost of oral AML medications is a major challenge to cost containment.

ACUTE MYELOID LEUKEMIA (AML) IS THE most usual form of acute leukemia in adults with an estimated 28,800 cases in the United States (U.S.) in 2024.[1] Still, AML is rare overall, accounting for only about 1 percent of all cancers. The median age at diagnosis is 69 years and the five-year relative survival is 31.9 percent.

Traditionally, the approach to treating AML was to treat those who were in better physical shape with intensive chemotherapy for induction followed at remission by additional chemotherapy or allogenic stem cell transplant. Those who could not tolerate this regimen were given supportive care. Intensive curative intent chemotherapy regimens with or without a stem cell transplant remains the most effective option for those who can tolerate such therapy. The major changes in AML treatment have occurred for those who are unable to tolerate intensive therapy. Treatment today is selected based on patient and disease characteristics and a comprehensive genomic profile. AML is a very heterogenetic disease which provides many targets for oral therapies.

Several oral therapies have changed the treatment landscape for AML for those who are unable or unwilling to receive chemotherapy-based treatment and for those with specific mutations. Ten oral therapies have been approved since 2017, with one of these being approved in late 2024 (revumenib). Two of the newest agents target common mutations—FMS-like tyrosine kinase 3 (FLT3) mutation and isocitrate dehydrogenase 1 (IDH1) mutation. FLT3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation. FLT3 ITD mutations occur in 20 to 25 percent of AML cases and result in poor prognosis and high rates of relapse after treatment and FLT3 TKD mutations occur in 5 to 10 percent of cases.[2] Quizartinib, a

Exhibit 1: Toxicity Concerns with Oral Medications for AML

Drug	Important Toxicities
FLT3 inhibitors	Nausea and vomiting Prolonged QTc
IDH inhibitors	Differentiation syndrome QTc prolongation
Venetoclax	Severe myelosuppression Interactions with CYP3A4 inhibitors
Oral Azacitidine	Nausea, Vomiting Neutropenia/thrombocytopenia
Revumenib	Prolonged QTc Differentiation syndrome Interactions with CYP3A4 inhibitors

Exhibit 2: Costs of Oral Medications for AML

Drug	Average wholesale price
Midostaurin	$170.24 per 25 mg tablet
Gilteritinib	$300.00 per 40 mg tablet
Quizartinib	$575.00 per 17.7 mg tablet
Enasidenib	$1,029.79 per 100 mg tablet
Ivosidenib	$522.30 per 250 mg tablet
Venetoclax	$111.51 per 100 mg tablet
Glasdegib	$338.50 per 25 mg tablet
Azacitidine (oral)	$1,650.14 per 200 mg tablet
Revumenib	Cost not yet available (1/2025)

second generation FLT3 inhibitor which is more potent and more selective, is indicated for first-line treatment of FLT3 ITD positive AML. This agent and midostaurin, another first-line FLT3 inhibitor, improve survival in first-line treatment of AML.[3,4] Median overall survival (OS) with quizartinib for three years after the end of chemotherapy was 31.9 months versus 15.1 months for placebo (hazard ratio 0.78, $p = 0{\cdot}032$).[4] The presence of a FLT3 mutation is an indication for incorporation of FLT3 inhibitors with induction and consolidation chemotherapy in fit patients followed by the FLT3 inhibitor maintenance. Gilteritinib is another FLT3 inhibitor which is only approved for relapsed/refractory (R/R) AML. It does improve OS in the R/R setting compared to salvage chemotherapy (9.3 versus 5.6 months).[5] Gilteritinib is currently under study for newly diagnosed and R/R FLT3 mutated AML in combination with venetoclax and azacitidine.

Approximately 8 percent of patients with AML have an isocitrate dehydrogenase one (IDH1) mutation and 12 percent have an IDH2 mutation.[6] IDH is an enzyme in the citric acid cycle. Mutant IDH1 or IDH2 produces 2-hydroxyglutarate, an oncometabolite, which alters DNA methylation and leads to a block in cellular differentiation. Olutasidenib is the newest IDH1 inhibitor, joining ivosidenib. Olutasidenib is currently FDA approved for IDH1+ R/R AML where as ivosidenib is approved for newly diagnosed or R/R IDH1+ AML. Ivosidenib is effective in combination with azacitidine in newly diagnosed IDH1 mutated AML and improved median OS significantly over azacitidine alone (24.0 versus 7.9 months) in older patients who were not fit enough for even low-intensity chemotherapy.[7] Enasidenib is FDA approved for IDH2+ R/R AML.

The newest oral targeted therapy in AML is revumenib, the first in class menin inhibitor, which is FDA approved for R/R acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients aged 12 months and older. It works by disrupting the interaction between menin and KMT2A proteins, which prompts leukemia cells to differentiate into normal cells. In adult AML patients, KMT2A gene rearrangements are found in 3 percent of *de novo* AML and in 10 percent of therapy-related AML cases.[8] The prevalence is much higher in acute leukemias found in infants. Several other menin inhibitors are in development.

One of the most used oral agents in patients who are unfit for chemotherapy is venetoclax. Venetoclax promotes apoptosis by selectively inhibiting B cell lymphoma two (BCL-2). In AML, overexpression of BCL-2 enables cancer cells to evade apoptosis via sequestering proapoptotic proteins. Venetoclax selectively binds to BCL-2, thereby freeing proapoptotic proteins to initiate apoptosis. In combination with azacitidine, a hypomethylating agent used alone in the past, venetoclax significantly improves OS in first-line treatment of AML.[9] This combination has become

the standard of care first-line agent for many patients with newly diagnosed AML.

There are several issues with venetoclax use in AML. There is limited efficacy in p53 mutant AML. Efficacy in patients who develop AML but were treated with a hypomethylating agent for an antecedent hematological disorder is unclear. Lastly, venetoclax is a highly myelosuppressive medication administered in an outpatient setting which can lead to many adverse events.

In addition to being commonly used in combination with venetoclax, oral azacitidine is effective as maintenance therapy after achievement of complete response to first-line induction and consolidation therapy (first remission). In the maintenance setting, it improved OS compared to placebo (24.7 versus 14.8 months, respectively; $p < 0.001$).[10]

In addition to myelosuppressive issues with venetoclax and other agents, the other newer therapies for AML have some unique adverse events of which clinicians encountering patients with AML in the community need to be aware (Exhibit 1). For example, IDH inhibitors and menin inhibitors can cause differentiation syndrome (DS) which is a serious potentially fatal adverse event. These therapies can produce drug-induced differentiation of leukemic cells. Proliferation of differentiated leukemic cells can alter cytokine balance, leading to tissue damage and inflammation. Signs and symptoms of DS include unexplained fever, dyspnea, pleural or pericardial effusions, pulmonary infiltrates, hypoxia, and acute kidney injury. DS occurs in 10 to 15 percent patients treated with an IDH inhibitor and 32 percent of those treated with revumenib. The median time to DS is 30 days after starting therapy but can be much longer. Treatments are corticosteroids, supportive care, and holding the IDH inhibitors. Another example is QT prolongation syndrome with revumenib. Other usual adverse events of cancer treatment such as nausea, vomiting, thrombocytopenia, and neutropenia also commonly occur. Patients and clinicians need to understand the potential adverse events of these potent oral cancer treatments and how to manage these in the community.

Another area where treatment option improvement has occurred is with secondary AML. Secondary AML can develop from myelodysplastic syndrome (MDS), prior treatment of AML (tAML), or myeloproliferative neoplasms (MPNs). Mutations commonly seen in Secondary AML (sAML) include SRSF2, ZRSR2, SF3B1, ASXL1, BCOR, EZH2, U2AF1, and STAG2.[11] Secondary AML has a worse prognosis than *de novo* AML.

Liposome-encapsulated cytarabine and daunorubicin is a treatment option for secondary AML which was FDA approved in 2017. It was designed to provide optimal delivery of a specific ratio of cytarabine to daunorubicin (5:1), that has been shown to be synergistic *in vitro*. Compared to non-liposomal versions of the same two chemotherapies, the liposomal version produced significantly longer median OS, better remission rates, and improved opportunity for stem cell transplant in newly diagnosed secondary AML in those aged 60 to 75 years who were fit for chemotherapy.[12]

The new oral agents approved since 2017 have led to a paradigm shift from a binary choice of intense chemotherapy or supportive care to various options including intense chemotherapy with or without targeted agents, oral but potent therapies for those who only got supportive care in the past, and numerous options for relapsed/refractory disease. Much of AML care has shifted from hospitals to the home with the introduction of so many oral agents.

Challenges in this transition to primarily outpatient care are numerous. These include long travel distances from the primary treating center for patients, education of community-based oncologists in management of diseases with less familiarity, need for frequent visits to community oncologists, and resource strains (e.g., blood products). Transportation costs for patient/families, communication with tertiary specialists, and accessibility of medical records between primary treating center and community-based providers are all substantial issues to overcome. There are questions whether these challenges affect overall efficacy of the treatment regimens and negatively impact any potential cost savings.

The cost of care for chemotherapy treated AML patients is driven by inpatient costs.[13] Innovations such as liposomal cytarabine/daunorubicin, although more expensive than either agent alone, may improve cost effectiveness through improved efficacy or reduced adverse events. A budget impact analysis for a hypothetical one-million-member health plan, where 15.1 members would receive intensive induction for newly diagnosed secondary AML annually, found that induction treatment with daunorubicin-cytarabine liposome instead of a non-liposomal regimen would have a limited economic impact on the budget of commercial health plans and may result in cost offsets, particularly in patients who respond to therapy.[14]

Even without chemotherapy, treatment of AML can be costly. One study from 2018 found an average cost of $25,000 per month for care of older AML patients and this was when monthly medication costs were $450.[15] Assuming an average 10-month

life expectancy for AML patients over 60 years of age, who are the primary group for lower intensity therapy, this equates to a cost of $250,000 for AML care over the average life of a patient or an estimated $4.8 billion for all the older AML patients in the U.S.

The new oral medications are now the primary cost driver of AML care. Exhibit 2 shows the per unit average wholesale cost of the oral therapies but some of these require more than one dose daily. Annual costs can be almost $200,000. A few cost-effectiveness studies of the new therapies have been published. An analysis of midostaurin plus standard chemotherapy compared to chemotherapy alone in the treatment of newly diagnosed FLT3-mutated AML found midostaurin to be a cost-effective addition, from a U.S. third-party payer perspective.[16] In another analysis, venetoclax/azacitidine was compared to azacitidine alone for use in older, unfit people for first-line treatment from a U.S. third party perspective.[17] Over a lifetime horizon, venetoclax plus azacitidine versus azacitidine led to gains of 1.89 life years (LYs, 2.99 versus 1.10, respectively) and 1.45 quality adjusted life years (QALYs, 2.30 versus 0.84, respectively). Patients receiving venetoclax plus azacitidine incurred higher total lifetime costs ($250,486 versus $110,034). The combination was cost effective with incremental cost-effectiveness ratios (ICERs) for venetoclax plus azacitidine versus azacitidine at $74,141 per LY and $96,579 per QALY gained. Also, gilteritinib compared to chemotherapy for R/R FLT 3 mutated AML was found to be cost effective.[18] Ivosidenib in combination with azacitidine for newly diagnosed, older, or intensive chemotherapy-ineligible patients with IDH1-mutated AML was found to not be cost effective at current prices (ICER $252,782/QALY).[19]

In addition to the high acquisition costs of the medications, there are other barriers to cost savings in AML with the newer medications. Outpatient therapies are still complex and potent, which could lead to a higher risk of adverse events and hospitalizations amongst patients cared for by less experienced clinicians. AML remains a disease with very limited curative potential, but this is changing. As people live longer with the disease, they will accumulate financial toxicity from their therapies. Extremely high medication prices make it mandatory to manage patients appropriately such that any savings are not offset by increased hospitalization rates. Few treatment strategies currently employ discontinuation of oral or maintenance therapies—these therapies are continued until disease progression. There are no published studies of pathway utilization and clinical and financial outcomes in AML—these are needed. In addition, studies are needed on patient financial burden of the newer medications and the impact on therapeutic outcomes. There also needs to be comparative or real-world cost studies where two agents are available for a particular target (i.e., quizartinib versus midostaurin).

Conclusion

Multiple new therapies for AML are improving outcomes and have shifted care toward the outpatient setting, especially for older adults. Unique toxicity profiles for many of the new medications, along with high acuity of AML patients, require resources and excellent communication for optimal management in the community. The high cost of outpatient AML medications, especially as outcomes improve and patients live longer, provides a major challenge to cost containment. Future research should focus on patient financial burden of new oral AML medications and effects on outcomes.

Jeffrey E. Lancet, MD is Chair of the Department of Malignant Hematology at the Moffitt Cancer Center and a Professor of Oncologic Sciences at the University of South Florida in Tampa, FL.

References

1. National Cancer Institute. Cancer Stat Facts: Leukemia — Acute Myeloid Leukemia (AML). Available at seer.cancer.gov/statfacts/html/amyl.html. Accessed 1/6/2025.
2. Garcia JS, Stone RM. The development of FLT3 inhibitors in acute myeloid leukemia. *Hematol Oncol Clin North Am*. 2017;31(4):663-80.
3. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-64.
4. Erba HP, Montesinos P, Kim HJ, et al; QuANTUM-First Study Group. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukemia (QuANTUM-First): A randomized, double-blind, placebo-controlled, Phase III trial. *Lancet*. 2023;401(10388):1571-83.
5. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18): 1728-40.
6. Kayser S, Levis MJ. The clinical impact of the molecular landscape of acute myeloid leukemia. *Haematologica*. 2023;108(2):308-20.
7. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. *N Engl J Med*. 2022;386(16):151.
8. Vetro C, Haferlach T, Meggendorfer M, et al. Cytogenetic and molecular genetic characterization of KMT2A-PTD positive acute myeloid leukemia in comparison to KMT2A-rearranged acute myeloid leukemia. *Cancer Genet*. 2020;240:15-22.
9. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7): 617-29.
10. Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26): 2526-37.

11. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood*. 2015;125(9):1367-76.

12. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36(26):268492.

13. Huggar D, Knoth RL, Copher R, et al. Economic burden in U.S. patients with newly diagnosed acute myeloid leukemia receiving intensive induction chemotherapy. *Future Oncol*. 2022;18(32):3609-21.

14. Jensen IS, Wu E, Sacks NC, et al. Budget impact analysis of using daunorubicin-cytarabine liposome in patients with newly diagnosed therapy-related AML or AML and myelodysplasia-related changes. *Am Health Drug Benefits*. 2018;11(7):380-6.

15. Bell JA, Galaznik A, Farrelly E, et al. Economic burden of elderly patients with acute myeloid leukemia treated in routine clinical care in the United States. *Leuk Res*. 2018;71:27-33.

16. Stein E, Xie J, Duchesneau E, et al. Cost effectiveness of midostaurin in the treatment of newly diagnosed FLT3-mutated acute myeloid leukemia in the United States. *Pharmacoeconomics*. 2019;37(2):239-53.

17. Pratz KW, Chai X, Xie J, et al. Cost-effectiveness analysis of venetoclax in combination with azacitidine versus azacitidine monotherapy in patients with acute myeloid leukemia who are ineligible for intensive chemotherapy: From a U.S. third party payer perspective. *Pharmacoeconomics*. 2022;40(8):777-90.

18. Pandya BJ, Qi CZ, Garnham A, et al. Cost-effectiveness of gilteritinib for relapsed/refractory FLT3mut+ acute myeloid leukemia. *J Manag Care Spec Pharm*. 2021;27(10):1469-81.

19. Bewersdorf JP, Patel KK, Goshua G, et al. Cost-effectiveness of azacitidine and ivosidenib in newly diagnosed older, intensive chemotherapy-ineligible patients with IDH1-mutant acute myeloid leukemia. *Leuk Lymphoma*. 2023;64(2):454-61.

Keeping Pace with Rapid Advancements in the Management of Hereditary Angioedema: Optimized Strategies in Managed Care Decision-Making

William R. Lumry, MD

This journal article is supported by educational grants from CSL Behring; BioCryst

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Hereditary angioedema (HAE) is a debilitating, rare, potentially fatal disease. Patients require on-demand medications for treatment of HAE attacks to prevent death. Short- or long-term prophylactic treatment will also be required by many patients. Additional treatments are on the horizon which may improve the patient experience.

Key Points

- HAE is mediated through bradykinin.
- Type I and II HAE result from a deficiency of C1-INH.
- Effective treatments reduce bradykinin production or block a bradykinin receptor.
- HAE guidelines emphasize diagnosis, an individualized treatment plan, care for acute attacks, on-demand and prophylactic medications, and patient quality of life.

ANGIOEDEMA IS THE RESULT OF FLUID extravasation into deep dermis and subcutaneous tissues which is mediated by bradykinin or mast cell products such as histamine.[1] The clinical presentation of angioedema is non-pitting, localized swelling in the skin or mucosa. Onset happens in minutes to hours and the swelling frequently has an asymmetric distribution which is not in dependent areas. Angioedema has many causes including allergy to foods, medications, insect stings and/or bites; radiocontrast media; nonsteroidal anti-inflammatories; autoimmune diseases; angiotensin converting enzyme (ACE) inhibitors; heredity; and idiopathic.[2,3] An allergic reaction is the most common cause of angioedema. Effective treatment of angioedema relies on identifying the underlying cause, especially in life-threatening cases. Most cases result from mast cell product release—typically from an allergic reaction—but bradykinin-mediated angioedema results in a disproportionate number of deaths compared with other types of angioedema.[4] Mast cell-mediated cases are caused by release of mast cell mediators (histamine, leukotriene C4, prostaglandin D2, heparin) which increase vascular permeability. Ninety percent of these cases are associated with urticaria and/or pruritis. Bradykinin-mediated angioedema is mediated by generation of bradykinin and complement-derived mediators which increase vascular permeability but urticaria and pruritis are usually not present. Exhibit 1 compares mast cell-mediated and bradykinin-mediated angioedema.

Hereditary angioedema is a rare bradykinin mediated condition characterized by the presence of angioedema without urticaria with acute attacks that are sometimes preceded by prodromal symptoms.[5] It occurs in approximately one in 50,000 individuals in the United States (U.S.) and there are approximately 7,000 individuals affected in the U.S.

Most HAE cases are caused by complement (C1) esterase inhibitor (C1-INH) gene mutations which lead to deficiency (Type I) or dysfunction (Type II)

Exhibit 1: Characteristics of Major Types of Angioedema

	Mast-cell Mediated or Allergic	Bradykinin Mediated or Non-allergic
Onset	Minutes to hours	Hours
Urticaria	Yes	No
Pruritis	Yes	No
Pain/burning	No	May be present
Response to Epinephrine or Antihistamine	Yes	No
Response to steroids	Yes	No

in C1-INH. C1-INH inhibits all active enzymes of the bradykinin-forming cascade. With a C1-INH deficiency, bradykinin levels increase leading to endothelial cell leakage through vasodilatation and increased vascular permeability. Type I is most common accounting for 85 percent of cases and Type II accounts for 15 percent of cases.[5] HAE with normal C1-INH appears to occur in less than 1 percent of HAE cases and is more common in women than in men (10 to 1), whereas the Type I and II occur equally in women and men.[5-7] Several features of HAE with normal C1-INH suggest it is bradykinin-mediated similar to Type I and II.[6]

HAE can be quite severe, affecting the face, oropharynx(causingriskofasphyxiation),extremities, gastrointestinal system, and genitourinary tract. Depending on the location of swelling, HAE can be life-threatening or disabling. One-third of patients with HAE develop a prodromal non-itchy rash (erythema marginatum). HAE attacks increase in intensity over 24 hours, and typically resolve in two to four days without treatment. Notably, they are unresponsive to treatment with antihistamines, corticosteroids, or epinephrine. Attacks typically occur unpredictably and vary in frequency. The average angioedema attack frequency is one episode every two weeks. In most cases, a family history of HAE is identified.

Disease severity of HAE is highly variable between patients and within families with the same mutation. Disease severity is also variable over the course of a patient's lifetime. Women tend to have more severe disease and are usually over-represented in clinical trials (65%). There is no simple relationship between disease severity and C1-INH levels.

Symptoms of HAE typically begin in childhood and worsen during puberty. In 75 percent of cases there is a family history of HAE—HAE has an autosomal dominant inheritance pattern.[5] In the cases with no family history, *de novo* mutations cause HAE and these mutations subsequently follow an autosomal dominant inheritance pattern. There are no known ethnic or race differences in HAE rates.

Extremity attacks affect 96 percent of patients. These attacks are functionally disabling. Hand attacks cause difficulty in driving, typing, and other uses of the hands. Attacks on the feet impede walking and standing. Extremity attacks interfere with work and school but rarely result in hospitalization. Abdominal attacks occur in 93 percent of patients with HAE. These result in mild-to-severe colicky pain and vomiting. Constipation or diarrhea may occur. The attacks lead to functional intestinal obstruction. On examinations the patient can have a protuberant abdomen, tenderness, and rebound. Fluid loss may lead to hemoconcentration and hypovolemic shock. Because the symptoms of an HAE abdominal attack mimic surgical emergencies, misdiagnosis and unnecessary surgery can occur. Laryngeal attacks occur in 50 to 60 percent of patients and are the most common cause of death in those with HAE.[8] These attacks require acute medication and airway management. One survey found a 40 percent incidence of asphyxiation in untreated laryngeal attacks.[9]

Common triggers for HAE attacks include emotional or physical stress, minor trauma, surgery, infections such as colds or influenza, ACE inhibitors, and changes in estrogen levels (oral contraceptives, hormone replacement therapy).[10] Unfortunately, many HAE episodes have no known trigger.

Diagnosis requires suspicion of HAE. It should be considered in a patient with recurrent episodes of angioedema without concomitant urticaria or unexplained abdominal pain.[11] HAE should also be considered in those with a family history of

Exhibit 2: Overview of Current Diagnostic Tests for HAE[6,11]

HAE Types I and II	HAE with Normal C1 Inhibitor
C4 level:	**C4 and C1-INH level/function:**
Below low limit of normal 90% of time	Normal
C1-INH antigenic level:	Genetic testing useful for known 6 mutations
Type I: low	Next generation sequencing useful,
Type II: normal to elevated	but many mutations not yet identified
C1-INH function:	Trial of high dose H1/H2 blockers,
Type I: low	omalizumab, or HAE specific drugs
Type II: low	

angioedema or choking or throat swelling as a cause of sudden death. Diagnosis requires measurement of complement levels and C1-INH function and antigenic level and, if normal C1-INH, further genetic testing (Exhibit 2).[6,11] For those diagnosed with HAE, screening should be performed on all first-degree relatives. For normal C1-INH patients, a trial of high-dose H1 and H2 blockers, omalizumab, or HAE specific drugs can be done to determine if these patients are bradykinin or mast cell mediated. For managed care, it may be less expensive to do a three-month trial of omalizumab, an anti-IgE antibody indicated for asthma, chronic spontaneous urticaria, chronic rhinosinusitis with nasal polyps, and IgE mediated food allergies, to see if it is effective in stopping angioedema attacks as a diagnostic measure than to start HAE specific medications.

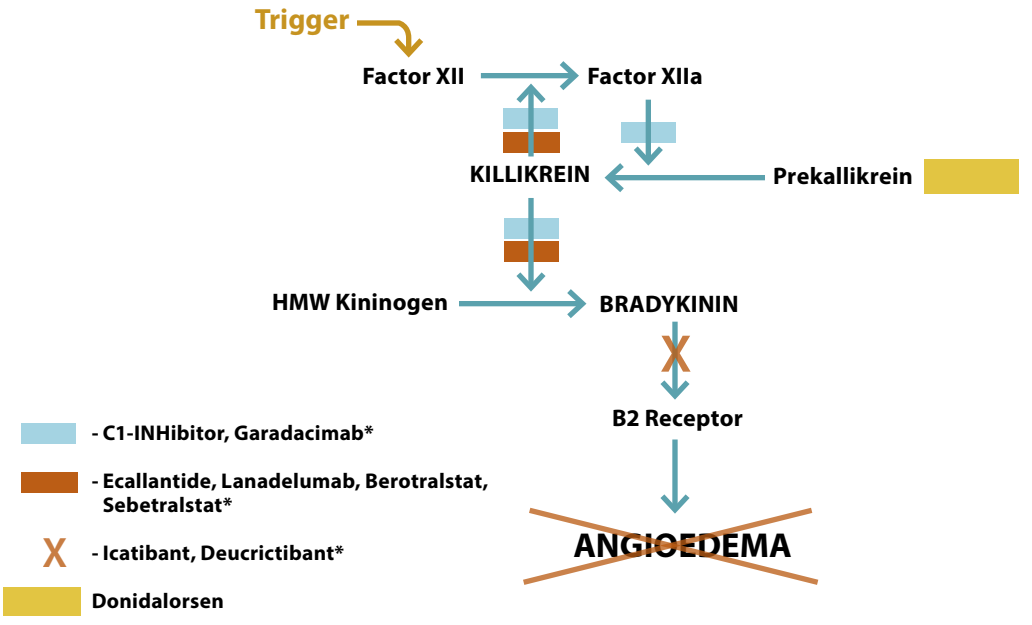
The therapeutic goals of HAE treatment are to return normalcy to life, reduce hospitalization and disability, and prevent death and excessive pain. The three treatment strategies for HAE include on demand medication to resolve angioedema symptoms as quickly as possible during an attack, short-term prophylaxis to prevent an attack when the patient will be exposed to a known trigger, and long-term prophylaxis to decrease the frequency and severity of ongoing attacks.[6,11] All patients need on demand treatment and many will also need long-term prophylaxis. HAE specialists recommend that all attacks be treated with on demand agents—about 70 percent of attacks in the U.S. are treated on demand. Some patients choose not to treat some attacks but an attack that starts only in the hand can progress to the larynx and potentially be fatal. Short-term prophylaxis should be prescribed for those with known triggers or before invasive procedures such as an endoscopy or dental treatment which might provoke an attack. Long-term prophylaxis is really where patient lives can be made better as it prevents attacks. Treatment for HAE must be individualized to provide optimal care and normalize health-related quality of life. Optimal management requires an individualized management plan and shared decision-making between the patient and clinician.

Exhibit 3 shows the targets for the FDA approved HAE treatments and some investigational agents. Plasma-derived (pd) and recombinant human (rh) C1-INH products are FDA approved for on-demand treatment of HAE attacks and supplement existing levels of C1-INH in Type I and II HAE. Both agents significantly reduce the time to symptom relief compared with placebo.[12,13] Plasma-derived C1-INH is approved for adult and pediatric patients and rhC1-INH is approved for adult and adolescent patients. Unfortunately, these products require intravenous or subcutaneous administration and have a short half-life of three to four days.

Ecallantide is a plasma kallikrein inhibitor FDA approved for on demand treatment of patients 12 years of age or more and given by subcutaneous injection. The benefit of ecallantide is apparent within two hours after dosing and is maintained 24 hours after dosing.[14] It is supposed to be given by a healthcare professional because of the potential for anaphylaxis (3 to 4%).

Icatibant is a bradykinin B2 receptor antagonist FDA approved for on demand treatment for adults 18 years of age or more.[15] Because this is self-

Exhibit 3: Treatment Targets in HAE



* Investigational

administered subcutaneously and does not have the risk of anaphylaxis as with ecallantide, it has become very commonly used. Because of icatibant, most patients are now treating themselves at home rather than seeking care at an emergency room.[16]

Long-term prophylactic treatments of HAE include pdC1-INH, lanadelumab, and berotralstat. Subcutaneous pdC1-INH given twice a week reduces monthly HAE attacks by 95 percent compared to placebo.[17] Lanadelumab, a monoclonal antibody given as a subcutaneous injection every two weeks, binds plasma kallikrein and inhibits its proteolytic activity thereby reducing monthly attack rate by 87 percent compared to placebo.[18] Berotralstat is a once daily oral plasma kallikrein inhibitor approved for patients 12 years of age or more which provides a significant reduction in attack rate (1.31 attacks per month; $p < .001$) relative to placebo (2.35 attacks per month).[19] It has also been shown to reduce attack rates a similar amount in those with normal C1-INH HAE.[20]

All patients should keep on-demand medication to treat two acute attacks at all times and treat all attacks as quickly as possible.[6,11] Some patients use or require two on-demand medications with different mechanisms of action. Short-term prophylaxis is administered when patients know they will experience known or potential triggers such as an oral/dental trauma, procedures requiring intubation, and invasive surgical procedures or medical procedures (upper or lower endoscopy). Short-term prophylaxis options include C1-INH concentrate, attenuated androgen therapy, or fresh frozen plasma. On demand therapy should also be available at the surgical or dental procedure site. For long-term prophylaxis, first-line medications for HAE Types I and II, include IV or subcutaneous C1-INH, berotralstat, and lanadelumab. Most patients are choosing to start with oral medication and if that is unsuccessful, then they will start one of the IV or subcutaneous agents. For normal C1-INH HAE, tranexamic acid or progestin-only medication can be considered for prophylaxis. First-line medications for on-demand and prophylactic treatment are also used in children even if they are not necessarily FDA approved for that age group. For women with HAE, avoidance of estrogen use is advised. C1-INH replacement is recommended in pregnant and lactating women.

Patients should have an action plan for acute attacks and short-term prophylaxis. Long-term prophylaxis treatment options should be discussed with every patient for potential inclusion in the management plan. The decision on when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient.[6] Physicians should help patients optimize their treatment plan, coordinate care, and provide

education about HAE. Importantly, on-demand therapy and long-term prophylaxis treatment of HAE change the burden of illness significantly and have been shown to improve quality of life.[21]

There is still room for improvement in HAE treatment. Factors that will improve treatment are agents with increased efficacy and safety, reduced treatment burden, and improved accessibility. Innovations that may improve HAE patient outcomes include more targeted oral medications, longer lasting prophylactic treatments including modified Fc region longer lasting monoclonal antibodies and RNA interference therapies, and gene therapies. Sebetralstat (oral plasma kallikrein inhibitor), deucrictibant (oral bradykinin receptor antagonist), garadacimab (Factor XIIa antagonist), donidalorsen (m-RNA anti-sense therapy which lowers prekallikrein production), and gene therapy are all under investigation for managing HAE and are showing good preliminary study results.

Garadacimab, sebetralstat, and donidalorsen have all been accepted for review by the FDA.[22-24] In a Phase III trial, sebetralstat, as an oral on-demand therapy, enabled patients to treat attacks early with a median time from attack onset to treatment of nine minutes, had a consistent safety and efficacy profile, and had a median time to beginning of symptom relief for laryngeal attacks of 1.3 hours.[25] Early intervention in an attack can help flatten the attack curve.

Donidalorsen would be a first-in-class RNA-targeted medicine for HAE, assuming approval. In a Phase III prophylactic trial, this injectable every four or eight weeks reduced attack rates.[26]

In 2023, the FDA accepted a Biologics License Application for garadacimab as a once-monthly prophylactic treatment for HAE. Garadacimab is a novel first-in-class, recombinant monoclonal antibody targeting activated FXII. By targeting FXIIa, garadacimab inhibits this cascade at the top as compared to HAE therapies that target downstream mediators. This agent has completed Phase III trials but is not yet FDA approved. In one trial, 62 percent of patients were attack free with every month dosing which compares favorably with lanadelumab every two weeks.[27]

Conclusion

HAE is mediated through bradykinin which is different from other types of angioedema. Clinicians need to consider HAE when encountering cases of angioedema. Type I and II HAE result from a deficiency of C1-INH function. HAE normal-C1INH is likely bradykinin-mediated, but definitive diagnostic tests are lacking. Most treatments reduce bradykinin production or block a bradykinin receptor, which reduces vasodilation and swelling. HAE guidelines emphasize diagnosis, an individualized treatment plan, care for acute attacks, on-demand and prophylactic medications, and patient quality of life. The availability of oral on-demand and prophylactic treatments will lower the burden of treatment.

William R. Lumry, MD is Clinical Professor of Internal Medicine at the University of Texas Southwestern Medical School, Medical Director at the AARA Research Center, and in private practice at Allergy and Asthma Specialists of Dallas, TX.

References

1. Angioedema. Available at my.clevelandclinic.org/health/diseases/22632-angioedema. Accessed 12/27/2024.
2. Cichon S, Martin L, Hennies HC, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema Type III. *Am J Hum Genet*. 2006;79(6):1098-104.
3. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(3 Suppl):S51-131.
4. Crochet J, Lepelley M, Yahiaoui N, et al. Bradykinin mechanism is the main responsible for death by isolated asphyxiating angioedema in France. *Clin Exp Allergy*. 2019;49(2):252-4.
5. U.S. Hereditary Angioedema Association. About Hereditary Angioedema. Available at haea.org. Accessed 12/27/2024.
6. Busse PJ, Christiansen SC, Riedl MA, et al. U.S. HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-50.e3.
7. Bork K. Hereditary angioedema with normal C1 inhibitor. *Immunol Allergy Clin North Am*. 2013;33(4):457-70.
8. Bork K, Hardt J, Schicketanz KH, Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. *Arch Intern Med*. 2003;163(10):1229-35.
9. Bork K, Siedlecki K, Bosch S, et al. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc*. 2000;75(4):349-54.
10. Angioedema News. Hereditary Angioedema Triggers. Available at angioedemanews.com/angioedema-triggers/. Accessed 12/27/2023.
11. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961-90.
12. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124(4):801-8.
13. Moldovan D, Bernstein JA, Cicardi M. Recombinant replacement therapy for hereditary angioedema due to C1 inhibitor deficiency. *Immunotherapy*. 2015;7(7):739-52.
14. Levy RJ, Lumry WR, McNeil DL, et al. EDEMA4: A Phase III, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104(6):523-9.
15. Lumry WR, Farkas H, Moldovan D, et al. Icatibant for multiple hereditary angioedema attacks across the controlled and open-label extension phases of FAST-3. *Int Arch Allergy Immunol*. 2015;168(1):44-55.

16. Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: Follow-up survey of U.S. physicians. *Ann Allergy Asthma Immunol.* 2021;126(3):264-72.

17. Longhurst H, Cicardi M, Craig T, et al; COMPACT Investigators. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med.* 2017;376(12):1131-40.

18. Banerji A, Riedl MA, Bernstein JA, et al; HELP Investigators. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: A randomized clinical trial. *JAMA.* 2018;320(20): 2108-21.

19. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled Phase III trial. *J Allergy Clin Immunol.* 2021;148(1): 164-72.e9.

20. BioCryst Presents New Real-world Data Showing Rapid, Substantial and Sustained HAE Attack Rate Reductions After Beginning ORLADEYO® (berotralstat) Treatment. February 23, 2024. Available at ir.biocryst.com/news-releases/news-release-details/biocryst-presents-new-real-world-data-showing-rapid-substantial. Accessed 12/27/2024.

21. Lumry WR, Weller K, Magerl M, et al; HELP Study Investigators. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. *Allergy.* 2021;76(4):1188-98.

22. KalVista Announces FDA Acceptance of New Drug Application for Sebetralstat for Oral On-Demand Treatment of Hereditary Angioedema. Sep 03, 2024. Available at ir.kalvista.com/news-releases/news-release-details/kalvista-announces-fda-acceptance-new-drug-application. Accessed 12/26/2024.

23. Ionis announces FDA acceptance of New Drug Application for donidalorsen for prophylactic treatment of HAE. November 4, 2024. Available at ir.ionis.com/news-releases/news-release-details/ionis-announces-fda-acceptance-new-drug-application-donidalorsen. Accessed 12/26/2024.

24. CSL's Garadacimab, a First-in-Class Factor XIIa Inhibitor, Receives FDA, and EMA Filing Acceptance. December 14, 2023. Available at newsroom.csl.com/2023-12-14-CSLs-Garadacimab,-a-First-in-Class-Factor-XIIa-Inhibitor,-Receives-FDA-and-EMA-Filing-Acceptance. Accessed 12/27/2024.

25. Riedl MA, Farkas H, Aygören-Pürsün E, et al. Oral sebetralstat for on-demand treatment of hereditary angioedema attacks. *Engl J Med.* 2024;391(1):32-43.

26. Riedl MA, Tachdjian R, Lumry WR, et al. Efficacy and safety of donidalorsen for hereditary angioedema. *N Engl J Med.* 2024;391(1):21-31.

27. Craig TJ, Reshef A, Li HH, et al. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): A global, multicenter, randomized, double-blind, placebo-controlled, Phase III trial. *Lancet.* 2023;401(10382):1079-90.

Targeting New Strategies in Narcolepsy and Idiopathic Hypersomnia: Novel Approaches to Diagnosis and Treatment

Anne Marie Morse, DO

This journal article is supported by educational grants from Jazz Pharmaceuticals; Avadel CNS Pharmaceuticals, LLC

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Central disorders of hypersomnolence can have various causes and presentations and have a major impact on those affected due to excessive daytime sleepiness. Medications which promote wakefulness are available for treatment but each has advantages and disadvantages. Individualized treatment plans need to be developed to achieve the best outcomes.

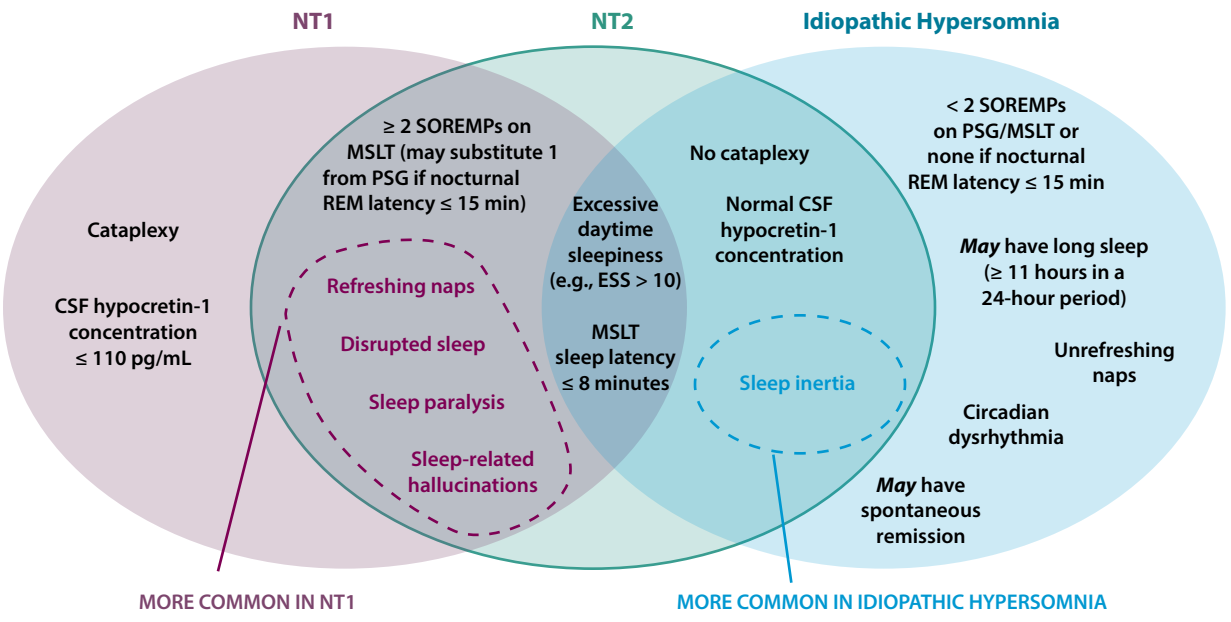
Key Points

- Narcolepsy and idiopathic hypersomnia are related overlapping entities that are unified by the presence of excessive daytime sleepiness.
- The burden of these disorders is far reaching and lifelong.
- Clinical guidelines offer a starting place for strategies to consider, but the patient should direct the personalized treatment plans for these disorders.
- These "invisible" conditions are costly and need comprehensive timely diagnosis management.
- Combination therapy is commonly required for management.

NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA (IH) are typically pediatric onset diagnoses but there can be significant delays in diagnosis. There is a bimodal peak for age at diagnosis of 15 and 36 years for narcolepsy.[1] Both affect about one in 2,000 people which is a similar rate to multiple sclerosis but the prevalence may be underestimated.[2] Both narcolepsy and IH, even when treated, cause significant social and economic burden, reduce quality of life, and affect the patient all day, every day. Both can result in poor school performance, compromised academic success, social isolation, family strain, embarrassment, disability, co-morbid psychiatric disease, and reduced earnings. A timely diagnosis is important because medical comorbidities can develop over time. Unfortunately, it can take 10 to 19 years from symptom onset to receive a diagnosis. Both can be misdiagnosed as insomnia, ADHD, depression, and obstructive sleep apnea.

Narcolepsy is a chronic neurologic disorder characterized by a decreased ability to regulate sleep-wake cycles characterized by excessive daytime sleepiness (EDS), rapid eye movement (REM)-related phenomena, and disturbed nocturnal sleep.[2] Patients can have continual background sleepiness, involuntary sleep episodes (sleep attacks), and wakeful sleepiness (automatic behavior, microsleeps). The REM-related phenomena include cataplexy (transient change in muscle tone) which

Exhibit 1: Overlap between Narcolepsy and Idiopathic Hypersomnia



NT1 = narcolepsy Type 1; NT2 = narcolepsy Type 2; CSF = cerebrospinal ;
ESS = Epworth Sleepiness scale; SOREMP = sleep onset rapid eye movement periods; MSLT = multiple sleep latency testing

Exhibit 2: Key Comorbidities with Narcolepsy[7,8]

Sleep Disorders	Mood Disorders	Pain-Related Disorders	Others
• Insomnia	• Anxiety	• Myalgia	• Vitamin D deficiency
• Obstructive sleep apnea	• Dysthymia	• Carpal Tunnel Syndrome	• Hypothyroidism
• Restless leg syndrome	• Depression	• Fibromyalgia	• Syncope
		• Migraine	• Diabetes
		• Chronic Pain Syndrome	• Obesity
			• Hyperlipidemia
			• Cardiovascular disease

occurs in about 60 percent of those with narcolepsy, hypnagogic hallucinations in 67 percent, and sleep paralysis in 64 percent.[3] The majority of people have partial cataplexy where their head drops, hands fall, or knees buckle rather than complete cataplexy where they fall down or slump out of a chair.[4] In children, cataplexy manifests as spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia without any obvious emotional triggers, which can be mistaken for seizures.[5]

Narcolepsy occurs as two types—Type 1 (with cataplexy) and Type 2 (without cataplexy, Exhibit 1). Type 1 is thought to be an immune-mediated disease where T cells cause destruction of hypocretin producing cells or there is an epigenetic silencing of these cells in the hypothalamus leading to hypocretin deficiency (cerebral spinal fluid [CSF] levels of hypocretin < 110 pg/mL).[6] Hypocretin (also known as orexin) is an important regulator of sleep/wake behavior but it also impacts every organ in the

Exhibit 3: 2021 AASM Clinical Practice Guideline (Adults)[14]

NARCOLEPSY			Outcomes Showing Clinically Significant Improvement			
Intervention	**Recommendation**	**FDA Approval**	**EDS**	**Cataplexy**	**Disease Severity**	**QoL**
Modafinil	Strong	EDS in narcolepsy or shift work sleep disorder (≥ 17 years)	x		x	x
Pitolisant	Strong	EDS or cataplexy in narcolepsy (≥ 6 years)	x	x	x	
Oxybate	Strong	EDS or cataplexy in narcolepsy (≥ 7 years) IH (adults, low sodium only)	x	x	x	
Solriamfetol	Strong	EDS in narcolepsy or OSA (adults)	x		x	x
Armodafinil	Conditional	EDS in narcolepsy, OSA, shift work sleep disorder(≥ 17 years)	x		x	
Dextro-amphetamine	Conditional	Narcolepsy, ADHD	x	x		
Methylphenidate	Conditional	ADHD (≥ 6 years)	x		x	

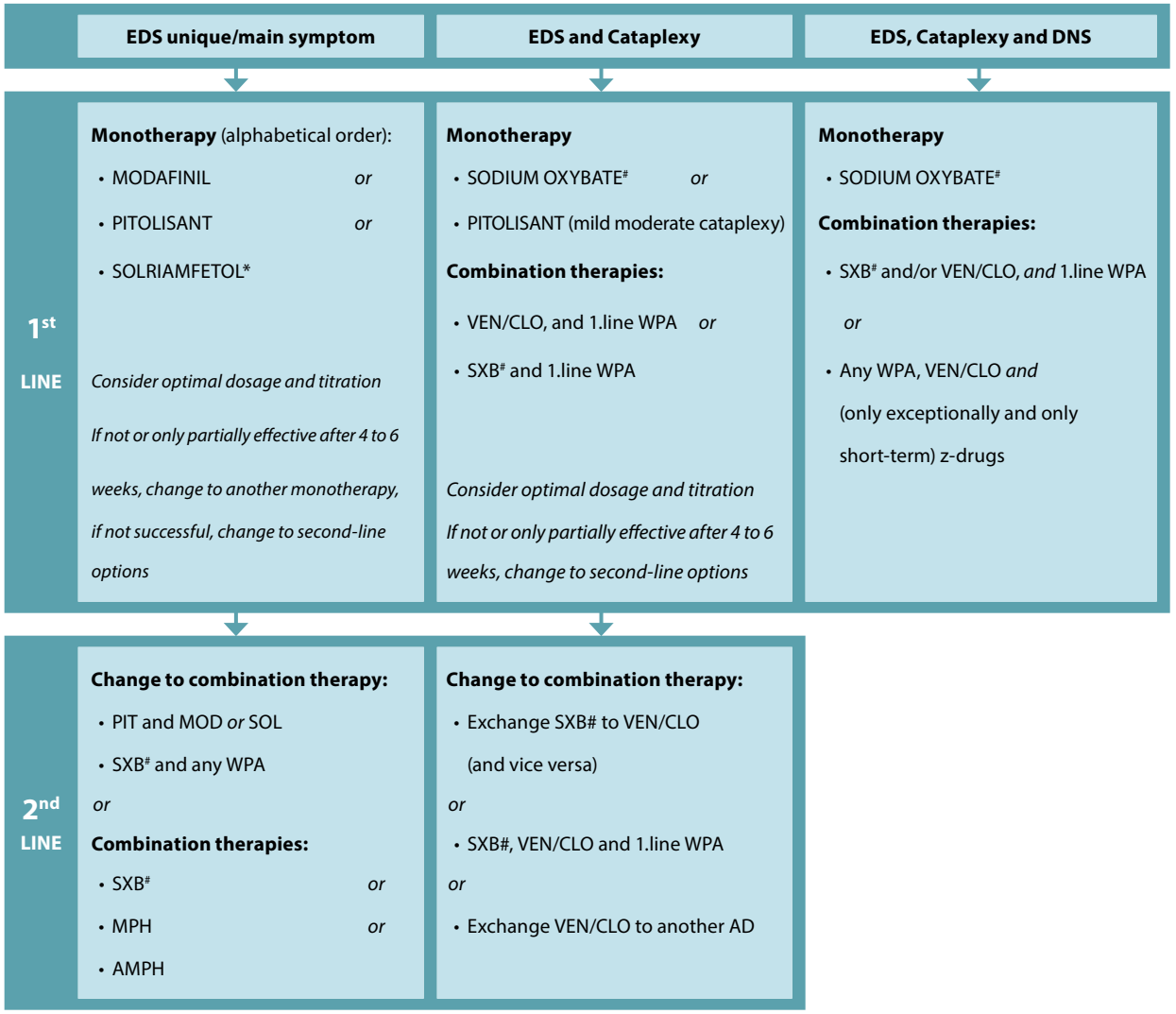
EDS = excessive daytime sleepiness; QoL = Quality of Life; OSA = obstructive sleep apnea.

body. Orexin deficiency leads to obesity, obstructive sleep apnea, diabetes, depression, pain syndromes, and other comorbidities (Exhibit 2).[7,8] Narcolepsy can also be primary or secondary. Primary is caused by autoimmunity or an unknown factor. Secondary can be caused by multiple sclerosis, traumatic brain injury, stroke, brain neoplasm, Prader Willi syndrome, Niemann Pick Type C disease, Parkinson's disease, and others which can cause defects in brain signals for sleep.

Idiopathic hypersomnia (IH), first identified in 1956, is characterized by long sleep duration (9 or more hours, typically 12 to 14), chronic daytime sleepiness, long prolonged and unrefreshing naps, sleep inertia, and daytime impairment.[9,10] Sleep inertia is prolonged difficulty waking with repeated returns to sleep, irritability, automatic behavior, and confusion. Patients may have difficulty concentrating or thinking clearly throughout the day (brain fog) which is distinct from EDS. The need to sleep can strike at any time, including while driving or working, which makes IH potentially dangerous as with narcolepsy. Unlike narcolepsy, naps are not refreshing for those with IH. IH typically arises in late adolescence or early adulthood and is more common in women. IH is not a deficiency of wakefulness similar to narcolepsy but is an overexaggeration of sleepiness. There is controversy whether narcolepsy and IH are separate diseases or different spectrum of same disease.

Symptoms of autonomic nervous system dysfunction are common in both narcolepsy and IH including gastroparesis symptoms, resting tachycardia, and orthostatic intolerance—autonomic dysfunction is much more common in IH.[11] Postural orthostatic tachycardia syndrome (POTS) is a dysautonomia characterized by increased sympathetic nervous system activation and orthostatic intolerance whose symptoms overlap with IH-related autonomic dysfunction. EDS is also common in POTS.[12] Both POTS and IH are associated with profound Ehlers-Danlos syndrome. Ehlers-Danlos syndrome is reported in 40 percent of POTS patients. A distinctive feature

Exhibit 4: European Guidelines and Expert Statements on the Management of Narcolepsy in Adults and Children



AD = Antidepressant; AMPH=Amphetamines; CLO = Clomipramine (low-dose); DNS = Disturbed nocturnal sleep; MOD = Modafinil; MPH = Methylphenidate; PIT = Pitolisant; SOL = Solriamfetol; SXB = Sodium Oxybate; VEN = Venlafaxine; WPA = wake-promoting agents (MOD, SOL, PIT, MPH AMPH); z-drugs = zopiclone, eszopiclone, zaleplon, zolpidem.
*Suggested from trials, few clinical experience; #Consider sleep apnea before starting with SXB

of POTS as compared to IH with autonomic dysfunction is that POTS patients also have poor sleep efficiency on polysomnography and some also complain of insomnia. The mechanism of autonomic dysfunction in IH are unclear but may be related to reduced physical activity or immune dysregulation.[12] Autonomic dysfunction makes treating IH complicated as many of the medications used to decrease sleepiness stimulate the autonomic nervous system which can make the patient's autonomic symptoms worse.

Diagnosing narcolepsy or IH requires eliminating other sleep disorders and Ehlers-Danlos/POTS. Narcolepsy can be diagnosed by symptoms of EDS and an average sleep latency of less than eight minutes and two or more sleep onset REM periods (SOREMPs) on multiple sleep latency testing (MSLT) or a SOREMP on nocturnal polysomnography (PSG).[6] A difference with Type 2 narcolepsy is CSF hypocretin levels are not deficient, however, spinal taps for hypocretin are not done frequently. The test results which suggest IH are, an average sleep latency of less than eight minutes and less than two SOREMPs on MSLT, 660 minutes or more of total

Exhibit 5: Approach to Treatment for IH[20]

EDS	Refractory EDS	Long Sleep Time	Morning Sleep Inertia	Nap Sleep Inertia (take prior to nap onset)	Brain Fog/Cognitive Complaints	Overall Burden of IH
Lower-sodium oxybate[a]	Lower-sodium oxybate[a]	Lower-sodium oxybate[a]	Lower-sodium oxybate[a]	Methylphenidate (IR)	Lower-sodium oxybate[a]	Lower-sodium oxybate[a]
Sodium oxybate	Sodium oxybate	Sodium oxybate	Sodium oxybate	Amphetamine (IR)	Modafinil	
Modafinil	Flumazenil		Methylphenidate (DR)	Modafinil		
Armodafinil	Clarithromycin		Transdermal methylphenidate (applied by bed partner or parent 2 h before waking time)			
Pitolisant						
Solriamfetol						
Methylphenidate (IR, LA, SR, CD, DR)						
Amphetamine (IR, ER, XR)						

CD = continuous delivery; DR = delayed release; EDS = excessive daytime sleepiness; ER = extended release; IH = idiopathic hypersomnia; LA = long acting; SR = sustained release; XR = extended release.
[a]Note: Lower sodium oxybates the only US Food and Drug Administration-approved medication for IH and is indicated for the overall burden with subjective evidence of improvement in day and night symptoms based on the Idiopathic Hypersomnia Severity Scale.

sleep time (TST) on average over one to two weeks on actigraphy, or 660 minutes or more of TST on 24-hour PSG.[6]

There are issues with using home sleep studies and MSLT for diagnosis. Home sleep studies were developed for identifying obstructive sleep apnea but most managed care plans require their use for narcolepsy and IH diagnosis. The MSLT was developed to test for narcolepsy Type 1 sleep attacks and has poor sensitivity for Type 2 and IH. The sensitivity of MSLT for IH is documented to be as low as 12 percent and approximately 40 percent or more IH patients have MSLT of more than eight minutes.[13] MSLT also has poor retest reliability with IH and narcolepsy Type 2.[13] Clinicians have to play an artificial game of repeating the MSLT in order to try and achieve a diagnosis of narcolepsy, especially in those with IH, to open up more treatment opportunities according to managed care policies which do not always match the known science. The 24-hour PSG has the best specificity for IH diagnosis but is rarely reimbursed by managed care.

Treating narcolepsy and IH is not just managing daytime sleepiness but also limiting the impact the disease has on quality of life, work/school, and social aspects of life. It is also reducing the risk from poor sleep. Poor sleep places people at higher risk for cardiovascular disease, cognitive decline and dementia, depression, hypertension, diabetes, hyperlipidemia, and obesity. Life-long cardiovascular disease risk has been shown to be related to sleep fragmentation which occurs in both these diseases. It takes a strategic alliance of many medical professions to manage the widely varied aspects of central sleep disorders.

Exhibit 3 shows the 2021 American Academy of Sleep Medicine guideline medication recommendations for managing narcolepsy.[14] For IH, the guidelines give modafinil a strong recommendation and a conditional recommendation for clarithromycin, methylphenidate, pitolisant, and oxybate. The only FDA-approved medication for IH is low-sodium oxybate which is discussed later. It is important to note that no currently available medication impacts all aspects of either disease when given as monotherapy.

There are gaps in our treatment landscape. One major gap is a lack of data for use of commonly used treatments such as amphetamines. There are very few comparative effectiveness studies of the

available treatments and standardized validated outcome measures are not used across studies. Outcome measures that reflect patient symptoms are needed. Additionally, the guidelines have not been updated since 2021, yet low-sodium oxybate and one daily dosing of extended release oxybate have been introduced since that time. In addition to these gaps and lack of guideline updates, many healthcare providers may not be comfortable and up-to-date with treating these patients. Other barriers are managed care policies which require trials of medications not even listed in the guidelines nor FDA approved, such as venlafaxine for cataplexy.

The European guidelines are more helpful at least for novice healthcare providers treating patients with narcolepsy because they are more prescriptive (Exhibit 4).[15] These guidelines also provide for combination therapy. In clinical experience, combination is frequently required to adequately control symptoms.

As noted previously, low-sodium oxybate is the only agent with an FDA-approved indication for IH—this indication was granted in 2023. The potential benefits of long-term low-sodium oxybate treatment of narcolepsy or IH include flexible optimization of dosing and regimen, improvement of quality of life and functioning, weight loss, and relative to sodium oxybate use health benefits of reduced sodium content. Trials have been published showing the effectiveness of low-sodium oxybate in both narcolepsy and IH and effectiveness and tolerance in transitioning from sodium oxybate to low-sodium oxybate.[16-19] Both forms of oxybate reduce EDS, cataplexy, and improve or normalize the Epworth Sleepiness Scale.

The three formulations of oxybate (twice nightly sodium oxybate, extended release once nightly sodium oxybate, and once or twice nightly low-sodium oxybate) have different pharmacokinetic profiles which allow customization of patient treatment depending on the pattern of nocturnal sleep disturbance. Many patients with IH can be treated with a single nightly dose of low-sodium oxybate. Across the patient's life, their needs may change so a formulation change may be necessary.

Normalization of the Epworth Sleepiness Scale can be seen in IH with once nightly dosing of low-sodium oxybate but is not typically seen with any of the other medications used for IH. Response to oxybate in IH is almost a diagnostic test. It allows realignment of the patient's circadian rhythm by increasing slow wave sleep. Being able to give time back to patients through effective medications which reduce their amount of sleep back into the normal seven-to-nine-hour range is a meaningful treatment response.

Each of the medication options for these diseases have limitations and adverse events. Common adverse events include headache, nausea, insomnia, and decrease appetite. All but pitolisant are controlled medications which have prescribing barriers. The oxybate products are only available through restrictive Risk Evaluation and Management Strategy (REMS) programs because of potential for abuse.

Initial steps to maximize outcomes in those with narcolepsy or IH include having patients keep a sleep/symptom diary and defining their goals for treatment. The sleep/symptom diary should also include how the symptoms disrupt their life, severity, cognitive/emotional state, and any other wellness concerns. All the pillars of wellness need to be considered when managing these patients. These pillars include mental, physical, spiritual, intellectual, social, financial, academic/occupational, and environmental well-being.

The approach to treating narcolepsy should be guided by patient desired outcomes. Combination therapy is typically the rule, and not the exception. It is important to treat beyond just the sleep-related symptoms and consider treatment and prevention of comorbidities. An approach for IH which focuses on primary symptoms is shown in Exhibit 5.[20]

The future treatment of narcolepsy and IH is an orexin agonist. Agents are now in Phase I to III trials. Danavorexton, ALKS 2680, YNT-185, and TAK-861 are some of the agents under investigation.

Conclusion

Central disorders of hypersomnolence can have various causes and presentations. The burden of these disorders is far reaching and lifelong. These "invisible" conditions are costly and need comprehensive timely diagnosis management. Combination therapy is commonly required for management. Overall, consideration of the whole person is required for optimal outcomes now and in the future.

Anne Marie Morse, DO is Director of Child Neurology and Pediatric Sleep Medicine at the Janet Weis Children's Hospital and an Associate Professor at the Geisinger Commonwealth College of Health Sciences in Mechanicsville, PA.

References

1. Latorre D, Sallusto F, Bassetti CLA, Kallweit U. Narcolepsy: A model interaction between immune system, nervous system, and sleep-wake regulation. *Semin Immunopathol.* 2022;44(5):611-23

2. American Academy of Sleep Medicine. Provider Fact Sheet. Narcolepsy. Available at aasm.org/wp-content/uploads/2022/07/ProviderFS-Narcolepsy.pdf. Accessed 1/23/2025.

3. Scammell TE. Narcolepsy. *N Engl J Med*. 2015;373(27):2654-62.

4. National Institute of Neurological Disorders and Stroke. Narcolepsy. Available at ninds.nih.gov/health-information/disorders/narcolepsy. Accessed 1/23/2025.

5. Ahmed I, Thorpy M. Clinical features, diagnosis, and treatment of narcolepsy. *Clin Chest Med.* 2010;31(2):371-81

6. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.

7. Lipford MC, Ip W, Awasthi S, et al. Demographic characteristics, and comorbidities of patients with narcolepsy: A propensity-matched cohort study. *Sleep Adv.* 2024;5(1):zpae067.

8. Cohen A, Mandrekar J, St Louis EK, et al. Comorbidities in a community sample of narcolepsy. *Sleep Med*. 2018;43:14-18.

9. Arnulf I, Dodet P, Leu-Semenescu S, Maranci JB. Idiopathic hypersomnia, and Kleine-Levin syndrome. *Rev Neurol (Paris).* 2023;179(7):741-54.

10. Dhillon K, Sankari A. Idiopathic Hypersomnia. 2023 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.

11. Miglis MG, Schneider L, Kim P, et al. Frequency and severity of autonomic symptoms in idiopathic hypersomnia. *J Clin Sleep Med*. 2020;16(5):749-56.

12. Adra N, Reddy M, Attarian H, Sahni AS. Autonomic dysfunction in idiopathic hypersomnia: an overlooked association and potential management. *J Clin Sleep Med*. 2022;18(3):963-65.

13. Trotti LM. Twice is nice? Test-retest reliability of the Multiple Sleep Latency Test in the central disorders of hypersomnolence. *J Clin Sleep Med.* 2020;16(S1):17-18.

14. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: An American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2021;17(9):1881–93.

15. Bassetti CLA, Kallweit U, Vignatelli L, et al. European guideline, and expert statements on the management of narcolepsy in adults and children. *Eur J Neurol*. 2021;28(9):2815-30.

16. Morse AM, Dauvilliers Y, Arnulf I, et al. Long-term efficacy, and safety of low-sodium oxybate in an open-label extension period of a placebo-controlled, double-blind, randomized withdrawal study in adults with idiopathic hypersomnia. *J Clin Sleep Med.* 2023;19(10):1811-22.

17. Bae CJ, Zee PC, Leary EB, et al. Effectiveness and tolerability in people with narcolepsy transitioning from sodium oxybate to low-sodium oxybate: Data from the real-world TENOR study. *Sleep Med*. 2023;109:65-74.

18. Bogan RK, Foldvary-Schaefer N, Skowronski R, et al. Long-term safety and tolerability during a clinical trial and open-label extension of low-sodium oxybate in participants with narcolepsy with cataplexy. *CNS Drugs*. 2023;37(4):323-35.

19. Erman M, Emsellem H, Black J, et al. Correlation between the Epworth Sleepiness Scale and the Maintenance of Wakefulness Test in patients with narcolepsy participating in two clinical trials of sodium oxybate. *Sleep Med*. 2017;38:92-5.

20. Morse AM, Naik S. Idiopathic hypersomnia: Neurobiology, diagnosis, and management. *CNS Drugs*. 2023;37(4):305-22.

New Horizons in the Treatment and Management of Non-Small Cell Lung Cancer

Gary M. Owens, MD

This journal article is supported by educational grants from Merck Sharp & Dohme LLC; AstraZeneca; Daiichi Sankyo; Janssen Biotech, Inc.

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

The management of advanced non-small cell lung cancer continues to evolve with additional targeted therapy for specific genetic mutations that drive this cancer, antibody drug conjugates, and immunotherapy which utilizes the body's natural defense. These various options are used as monotherapy or in combinations which are becoming more complicated.

Key Points

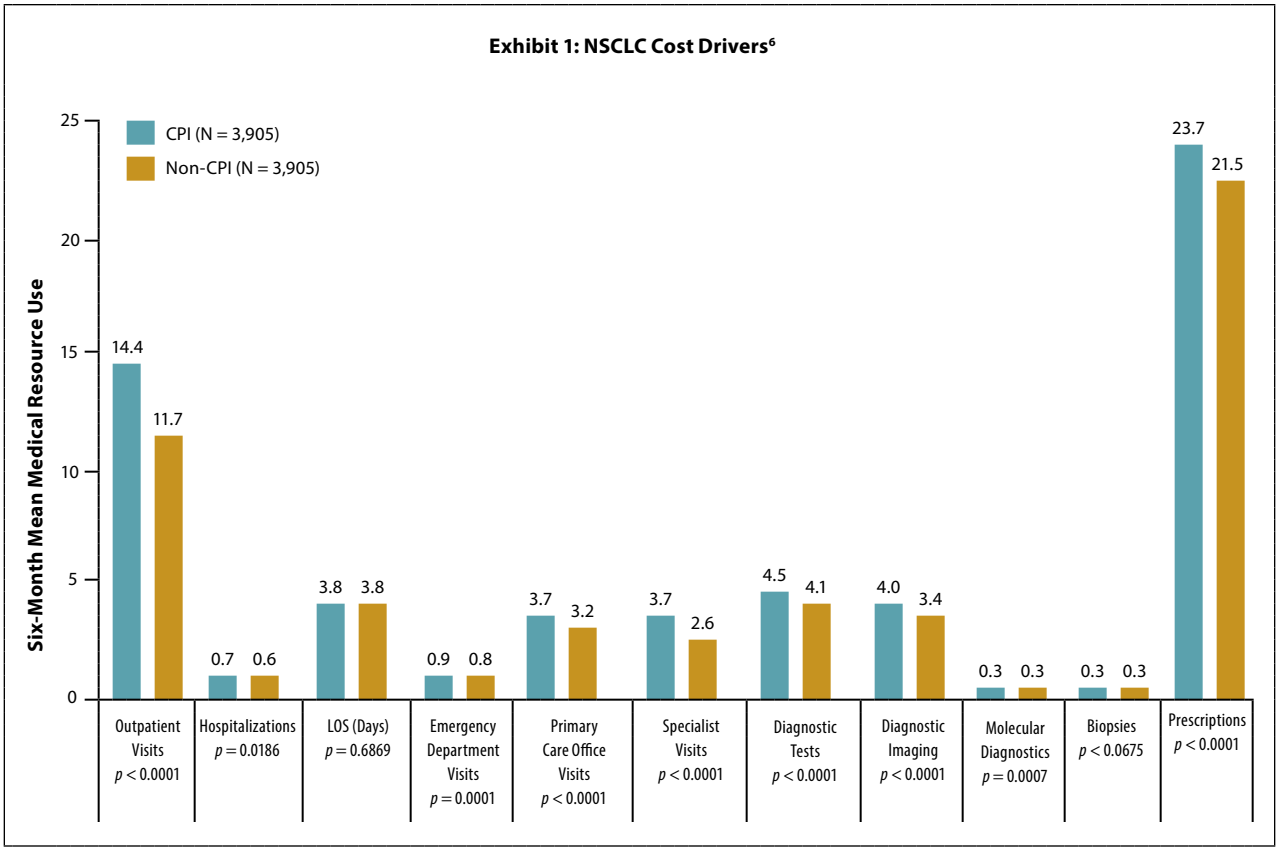
- Immunotherapy plus platinum-based chemotherapy doublets is standard first-line therapy in advanced NSCLC for those without actionable genetic mutations.
- Targeted therapy is first-line for those with actionable genetic mutations.
- A new combination is available for first-line treatment of those with EGFR mutations.
- Newer targets such as Trop2 are the future of treatment.

LUNG CANCER IS THE SECOND MOST common cancer in both men and women and the most common type is non-small cell lung cancer (NSCLC).[1,2] An estimated 226,650 new cases of lung cancer will be diagnosed and 124,730 deaths as a result of lung cancer will occur in the United States (U.S.) in 2025.[1] Lung cancer deaths have begun to decline in both men and women, reflecting a decrease in smoking, but lung cancer is still the leading cause of cancer deaths.

The costs of treating cancer have been increasing significantly for managed care and the patient economic burden associated with cancer care is substantial.[3,4] In 2020, lung cancer was the third most costly cancer.[5] With NSCLC, costs are driven primarily by outpatient visits and medications, especially for checkpoint inhibitor immunotherapy and targeted agents (Exhibit 1).[6] Although lung cancer is costly to treat, benefits for society are being shown. In one study, population-level mortality from NSCLC in the U.S. fell sharply from 2013 to 2016, and survival after diagnosis improved which was likely driven by targeted therapies.[7]

Despite improvements in survival, there may be patient financial consequences because of significant out-of-pocket expenses. Financial toxicity is the detrimental effect of the excess financial strain caused by the diagnosis of cancer on the well-being of patients and has become an important consideration in cancer care.[8]

Treatment options for NSCLC are numerous and selection of the most appropriate treatment requires molecular testing. Therapies targeted at molecular mutations have consistently demonstrated significantly improved outcomes for patients with NSCLC. Methods for screening NSCLC patients for driver mutations and other abnormalities are continually evolving and there is no single standard platform for testing. Features that make a platform clinically useful are fast turnaround time (two weeks or less), cost efficiency, ability to perform on clinically available samples, and semi-automation which



CPI = checkpoint inhibitor immunotherapy; LOS = length of stay

eliminates reliance upon a single operator.[9] The most common genetic mutations in NSCLC are KRAS (29%) and EGFR (19%)—see Exhibit 2.[9] These driver mutations create pathways for targeted therapy.

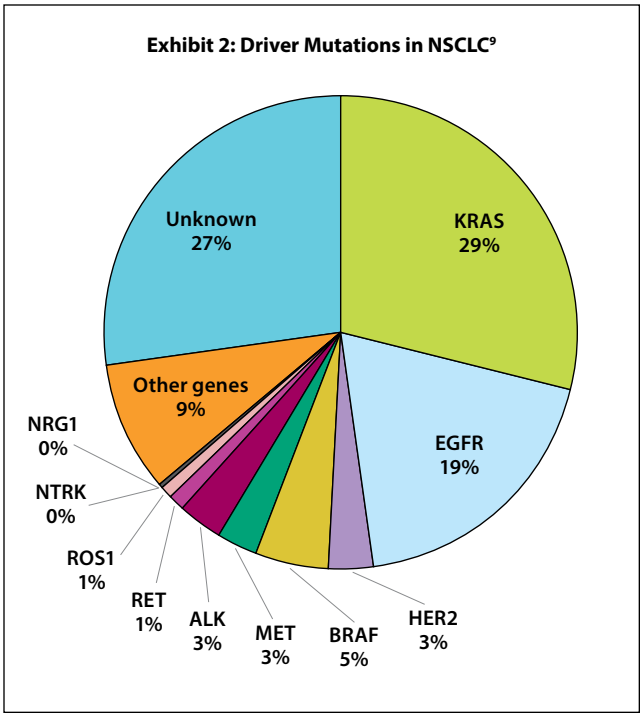
Driver mutations for which a targeted therapy inhibitor is available is one key factor in initial treatment selection for advanced NSCLC. Other key factors are the presence of programmed cell death ligand 1 (PD-L1) expression, a biomarker of immunotherapy efficacy in NSCLC; the extent of disease, including the number and sites of metastases; squamous versus nonsquamous histology; performance status, comorbidities, and brain or liver metastases.[10]

If a patient with advanced NSCLC is identified as having a targetable tumor mutation, then targeted therapy is the first-line treatment, except in case of certain mutations where chemotherapy is first-line.[10] If the patient has no targetable mutations, checkpoint inhibitor immunotherapy with or without chemotherapy and/or bevacizumab is the treatment option, depending on the expression of PD-L1.[10,11] Patients without contraindications to checkpoint inhibitor immunotherapy, good performance status, and PD-L1 expression of 50 percent or more are offered either monotherapy with a checkpoint inhibitor or a platinum-doublet chemotherapy plus a checkpoint inhibitor, depending on whether the disease is adenocarcinoma or squamous.

Pembrolizumab, atezolizumab, nivolumab/ipilimumab, cemiplimab, or tremelimumab/durvalumab are options in the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) Guidelines.[10,11] For patients with PD-L1 expression less than 50 percent, the combination of a platinum-doublet chemotherapy and a checkpoint inhibitor is standard. Choice of chemotherapy, for those receiving it, is again influenced by tumor histology.

Checkpoint inhibitor immunotherapy improves overall survival (OS) in NSCLC. For example, in the Keynote 189 study with pembrolizumab, five-year OS was improved by the addition of immunotherapy to chemotherapy (19.4% versus 11.3%).[12,13] Cemiplimab also improved median OS in the EMPOWER Lung III trial (22 versus 13 months).[14] Immunotherapy also improves progression-free survival (PFS) and overall response rates.

Because checkpoint inhibitor immunotherapy takes the brakes off the immune system, they produce a wide range of immune-mediated adverse events which must be monitored and managed to



avoid significant consequences. The most frequent immune-related adverse events (irAEs) are cutaneous and mimic several types of spontaneous skin disorders.[15] Most irAEs are classified as autoimmune conditions mediated by immunotherapy-activated CD8+ cytotoxic T.[15] Newer data on selected driver mutations (HER2, EGFR Exon20, and TROP2) are impacting treatment selection in selected patients. Human epidermal growth factor two (HER2) is a member of the human epidermal growth factor receptor, along with HER1 (also known as EGFR), HER3, and HER4. HER2 expression occurs in about 3 percent of NSCLC cases.[16] After the use of HER2-directed therapies in patients with breast cancer was studied, strategies targeting HER2 were studied in other tumor types, including NSCLC. HER2 gene mutation, gene amplification and protein overexpression alterations are found in NSCLC.[17] HER2 activation triggers the phosphorylation of tyrosine kinase residues and activates downstream tumorigenic signaling pathways.[18]

Fam trastuzumab deruxtecan (T-Dxd) is an antibody drug conjugate (ADC) composed of the anti-HER2 monoclonal antibody trastuzumab, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor, deruxtecan. In 2022, T-Dxd received accelerated approval from the FDA for adults with previously treated, unresectable or metastatic NSCLC. In the Phase II trial used for accelerated approval evaluating two doses (5.4 and 6.4 mg/kg) of T-Dxd, confirmed overall response rate was 49.0 percent and 56.0 percent and median duration of response was 16.8 months and not estimable, respectively.[19] Median treatment duration was 7.7 months (range, 0.7 to 20.8) with 5.4 mg/kg and 8.3 months (range, 0.7 to 20.3) with 6.4 mg/kg. Median OS of 19.5 months was seen in the 5.4 mg/kg dose groups.[20] The 5.4 mg/kg dose was better tolerated with fewer Grade 3 or higher drug-related treatment-emergent adverse events and is the recommended dose. The most common adverse events are nausea, vomiting, neutropenia, anemia, thrombocytopenia, lymphopenia, alopecia, and elevated liver function tests.

Classical activating mutations (exon 19 deletions and the L858R point mutation in exon 20) comprise 90 percent of EGFR mutations and are well defined as strong predictors for good clinical response to EGFR tyrosine kinase inhibitors (TKI).[21] EGFR exon 20 insertion mutation occurs in about 2 percent of NSCLC cases and is more commonly found in people who never smoked and also in Asian persons.[21] Rarer mutations including point mutations, deletions, insertions, and duplications occur within exons 18 – 25 of the EGFR gene in NSCLC and are associated with poor responses to EGFR TKI. Because of poor response to EGFR TKI, chemotherapy had been the preferred first-line treatment for advanced NSCLC patients harboring EGFR exon 20 insertion mutations. Amivantamab, a bispecific EGFR and MET receptor antibody, is available to target exon 20 insertion mutation and is FDA approved for both first-line treatment in combination with standard chemotherapy or as monotherapy for second-line treatment for patients with progression during or after first-line chemotherapy. In combination with carboplatin and pemetrexed, amivantamab improved PFS compared to chemotherapy alone (11.4 versus 6.7 months). OS data from this trial have not yet been reported.[22] The combination of amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC has been shown to improve median OS when compared to osimertinib.[23] Lazertinib is a brain-penetrant, irreversible EGFR TKI that targets the T790M mutation and activating EGFR mutations Ex19del and L858R, while sparing wild type-EGFR. The combination of amivantamab and lazertinib is now FDA approved for first-line therapy and is a Category 1 other recommended alternative to osimertinib in first-line treatment.[10]

A new area of treatment in some cancers is targeting trophoblast cell surface antigen (Trop2), a transmembrane glycoprotein calcium signal transducer. Trop2 mediates cell migration and anchorage-independent growth and is associated

with poor overall and disease-free survival in several types of solid tumors.[24] In lung cancer, Trop2 overexpression has been observed in up to 64 percent of adenocarcinomas and 75 percent of squamous cell carcinomas.[25] Trop2 overexpression is associated with reduced survival and a potential role in resistance to chemotherapy in NSCLC. Sacituzumab govitecan and datopotamab deruxtecan, two Trop-2-directed antibody and topoisomerase inhibitor ADC which are already FDA approved for metastatic breast cancer, have shown promising activity signals in NSCLC.[26] Additional larger trials are ongoing with these two ADC in NSCLC treatment.

Triple therapy with chemotherapy, immunotherapy, and targeting agents are likely to be the future of treating some types of NSCLC. Such combinations can be very expensive which is worrisome for managed care. Payers have seen projections that estimate the cost of combination therapy with personalized approaches in the range of $250,000 to over $1 million per year which is unsustainable. Payers are not the only ones involved as their employer customers are demanding action on escalating costs as well.

Current value assessments for novel therapies may need revision. Payers need to better define and understand the key aspects and attributes of personalized therapies that should be considered in any assessment of their value. Payers need to address evidence gaps in existing value frameworks given the unique properties of patient outcomes with personalized therapies. A better characterization of the benefit of personalized treatment will allow a more thorough assessment of its benefits and provide a template for the design of management programs and roadmaps for healthcare insurers to optimize coverage for patients with NSCLC.

One of the evidence gaps to address is the alternate stakeholder perspective. There needs to be more research emphasis on the societal perspective when considering treatment value. Cost-effectiveness analyses should include both quality of life year (QALY) and no QALY adjustment so that absolute mortality reductions can be easily reported for decision-makers. Another gap is to address outcomes that are important to patients, such as hope, which can help decision-makers compare medications within the same disease state.[27] More research is needed to quantify the value of hope to cancer patients. For a cancer patient, any innovation that can extend life (even at the same or worse quality of life) may give a patient a chance to live long enough for a new treatment to develop, and possibly even a cure.

Payers may need to leverage patient reported outcomes, real-world evidence, and other tools to expand the knowledge base and continuously improve patient outcomes from personalized approaches. From such analyses, payers and providers together must develop careful patient selection that ensures treatments are provided only to those patients most likely to benefit.

Conclusion

The treatment of NSCLC continues to change. In recent years immunotherapy, targeted therapy, and antibody drug conjugates have been added to the therapeutic possibilities. More agents such as those targeting TROP-2 are on the way. All the treatment options and substantial costs complicate fiscal management for this disease.

Gary M. Owens, MD is President of Gary Owens and Associates in Ocean View, DE.

References

1. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. *CA Cancer J Clin*. 2025 Jan 16.
2. American Cancer Society. Key Statistics for Lung Cancer. Available at cancer.org/cancer/types/lung-cancer/about/key-statistics.html. Accessed 1/19/2025.
3. Mariotto AB, Enewold L, Zhao J, Zeruto CA, Yabroff KR. Medical care costs associated with cancer survivorship in the United States. *Cancer Epidemiol Biomarkers Prev*. 2020;29(7):1304-12.
4. Yabroff KR, Mariotto A, Tangka F, et al. Annual Report to the Nation on the Status of Cancer, Part 2: Patient economic burden associated with cancer care. *J Natl Cancer Inst*. 2021;113(12):1670-82.
5. National Cancer Institute. Cancer Trends Progress Report. Financial Burden of Cancer Care. Available at progressreport.cancer.gov/after/economic burden. Accessed 1/19/2025.
6. Nesline MK, Knight T, Colman S, Patel K. Economic burden of checkpoint inhibitor immunotherapy for the treatment of non-small cell lung cancer in US clinical practice. *Clin Ther*. 2020;42(9):1682-98.e7.
7. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med*. 2020;383(7):640-9.
8. Desai A, Gyawali B. Financial toxicity of cancer treatment: Moving the discussion from acknowledgement of the problem to identifying solutions. *EClinicalMedicine*. 2020;20:100269.
9. Chevallier M, Borgeaud M, Addeo A, Friedlaender A. Oncogenic driver mutations in non-small cell lung cancer: Past, present, and future. *World J Clin Oncol*. 2021;12(4):217-37.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 3.2025. Available at nccn.org. Accessed 1/19/2025.
11. Singh N, Jaiyesimi IA, Ismaila N, et al. Therapy for Stage IV non-small-cell lung cancer without driver alterations: ASCO Living Guideline, Version 2023.3. *J Clin Oncol*. 2024;41(11):e23-e43.
12. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-92.
13. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes

from the Phase III KEYNOTE-189 study. *J Clin Oncol*. 2023;41:1992-8.

14. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: A randomized, controlled, double-blind Phase III trial. *Nat Med*. 2022;28:2374-80.
15. Okiyama N, Tanaka R. Immune-related adverse events in various organs caused by immune checkpoint inhibitors. *Allergol Int*. 2022;71(2):169-78.
16. Friedlaender A, Perol M, Banna GL, et al. Oncogenic alterations in advanced NSCLC: A molecular super-highway. *Biomark Res*. 2024;12(1):24.
17. Li BT, Ross DS, Aisner DL, et al. HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers. *J Thorac Oncol*. 2016;11(3):414-9.
18. Reyes A, Pharaon R, Mohanty A, Massarelli E. Arising novel agents in lung cancer: Are bispecifics and ADCs the new paradigm? *Cancers (Basel)*. 2023;15(12):3162.
19. Goto K, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small-cell lung cancer: Primary results from the randomized, Phase II DESTINY-Lung02 trial. *J Clin Oncol*. 2023;41(31):4852-63.
20. Goto K, Goto Y, Kubo T, et al. Trastuzumab deruxtecan in patients with HER2-mutant metastatic non-small-cell lung cancer: Primary results from the randomized, Phase II DESTINY-Lung02 Trial. *J Clin Oncol*. 2023;41(31):4852-63.
21. Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. *Semin Cancer Biol*. 2020;61:167-79.
22. Zhou C, Tang K-J, Cho BC, et al. Amivantamab plus chemotherapy in NSCLC with EGFR exon 20 insertions. *N Engl J Med*. 2023;389(22):2039-51.
23. Cho BC, Lu S, Felip E, et al. Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. *N Engl J Med*. 2024;391(16):1486-98.
24. Li Z, Jiang X, Zhang W. TROP2 overexpression promotes proliferation and invasion of lung adenocarcinoma cells. *Biochem Biophys Res Commun*. 2016;470(1):197-204.
25. Wang X, Long M, Dong K, et al. Chemotherapy agents-induced immune-resistance in lung cancer cells could be reversed by trop-2 inhibition in vitro and in vivo by interaction with MAPK signaling pathway. *Cancer Biol Ther*. 2013;14(12):1123-32.
26. Parisi C, Mahjoubi L, Gazzah A, Barlesi F. TROP-2 directed antibody-drug conjugates (ADCs): The revolution of smart drug delivery in advanced non-small cell lung cancer (NSCLC). *Cancer Treat Rev*. 2023;118:102572.
27. Kaufman HL, Atkins MB, Subedi P, et al. The promise of immuno-oncology: Implications for defining the value of cancer treatment. *J Immunother Cancer*. 2019;7(1):129.

New Horizons in HIV Prevention and Management: Navigating ART and PrEP Managed Care Decision-Making for Optimized Outcomes

Mary W. Montgomery, MD

This journal article is supported by educational grants from Gilead Sciences; ViiV Healthcare

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

The new horizon in HIV management is long-acting injectables for both prevention and treatment. New treatments, such as injectables, are needed to help patients take their medications, become virally suppressed to prevent transmission, and stay suppressed to help end the HIV epidemic.

Key Points

- There continue to be wide gaps in who receives PrEP.
- Prescribers of PrEP need to be expanded (primary care providers, pharmacists, etc.).
- Injectable cabotegravir is a great PrEP option.
- For those who struggle taking oral medications, long-acting injectable therapy is a good option.
- Barriers to prescribing long-acting injectable therapy need to be reduced.

THE RATE OF NEW HIV DIAGNOSES IN THE United States (U.S.) has declined 12 percent from 2018 to 2022 with 31,800 new cases in 2022.[1] In 2022, an estimated 1.2 million Americans were infected and only 87 percent of them knew they were infected.

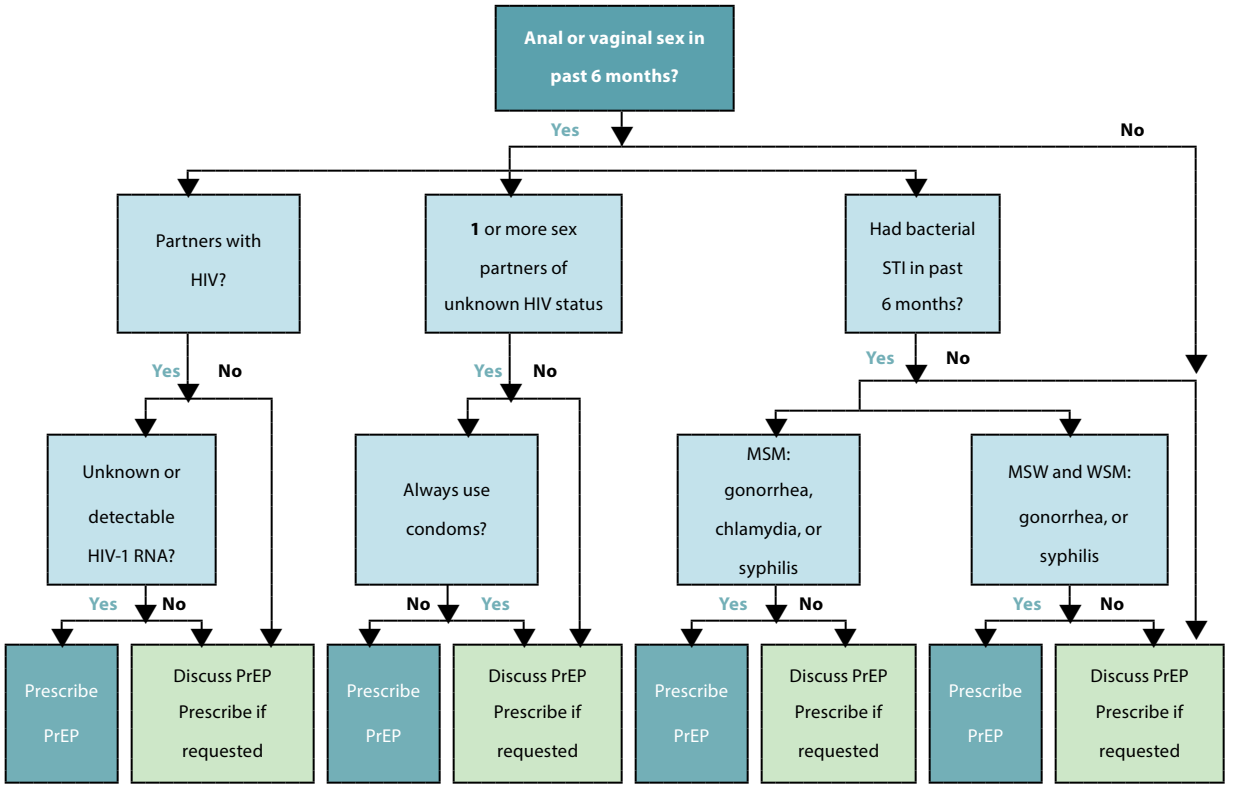
Most new HIV diagnoses are in the south (49%), among men (81%), among Black/African American or Hispanic/Latino groups (72%), and those with male-to-male sexual contact (MSM, 67%). Black/African American MSM have a one in three lifetime risk of acquiring HIV and Hispanic/Latino MSM have a one in five lifetime risk compared to a one in 15 risk for whites.[2] HIV stigma, homophobia, poverty, and barriers to healthcare access continue to drive the disparity in HIV diagnoses.

Improving these disparities and preventing new HIV diagnoses requires removing barriers to HIV testing, getting pre-exposure prophylaxis (PrEP) to those who most need it, and providing access and support for HIV treatment. Remember that HIV treatment is also prevention—those who are on medication who have viral suppression are not infectious. Some states such as New York have been making a push for easier HIV testing but this needs to be done nationally.

Many patients at risk of HIV are not getting PrEP. Of the 1.2 million people in the U.S. at risk for HIV infection, only 36 percent received PrEP in 2022.[3] "The Ending", the HIV Epidemic initiative has a goal of 50 percent of those eligible to be on PrEP by 2025. PrEP coverage varies widely across the U.S.—only New York state met the 50 percent goal in 2021. The best PrEP coverage is among at-risk whites (78%) and lowest among at-risk Black/African Americans (11%).

One barrier to PrEP prescription by healthcare providers is a perception of it being complicated. It does not need to be prescribed by infectious disease or HIV specialists. Since PrEP is akin to contraception, we can take a lesson from contraception care with

Exhibit 1: PrEP Pathway[4]



STI = sexually transmitted infection; MSM = male-to-male sex; MSW = men who have sex with women; WSM = women who have sex with men

expansion of contraception care services beyond gynecology providers to family medicine, internal medicine, pediatricians, and pharmacists increased access to and prescription of contraception. Thirty states and the District of Columbia allow pharmacists to prescribe contraceptives. Expanding prescribers can expand PrEP prescription and this may be especially important in more rural areas. Pharmacists have authority to independently prescribe PrEP in 12 states.

All sexually active adults and adolescents should be informed about PrEP for prevention of HIV acquisition and it should be provided to anyone who requests it.[4] Exhibit 1 shows the pathway for prescribing and discussing.[4] The three very effective options for PrEP include oral emtricitabine (FTC) 200 mg in combination with tenofovir disoproxil fumarate (TDF) 300 mg (TDF/FTC) daily, oral emtricitabine (FTC) 200 mg in combination with tenofovir disoproxil fumarate (TDF) 300 mg (TDF/FTC) daily, and intramuscular cabotegravir (CAB) 600 mg every two months. Two studies of IM cabotegravir found it to be superior to TDF/FTC because IM injection protects for two months without relying on patient daily adherence.[5,6] Exhibit 2 shows the options for PrEP by risk group.[4,7,8] On demand PrEP is an alternative to daily oral medication or every two-month injections. PrEP 2-1-1 starts by taking two tablets between two and 24 hours before sex. After sex, a tablet is taken 24 hours and 48 hours after the first dose. On demand PrEP has not been FDA approved but has been studied and shown to be an effective HIV prevention choice for MSM. PrEP medication absorbs slower into vaginal tissue than anal tissue, so on demand use is not an effective option for vaginal sex. All three types of PrEP are well tolerated, with adverse events that are usually mild-to-moderate, manageable, and temporary. In selecting agents, TAF/FTC is best for those with reduced kidney function (CrCl < 60) or osteoporosis. An HIV test is required before prescription of PrEP.

The PrEP options are expensive ($1,900 to $2,000 per month) but most insurance plans and state Medicaid cover PrEP. Under the Affordable Care Act, PrEP must be free under almost all health insurance plans. If patients do not have insurance or have a

Exhibit 2: Risk Groups and Recommended PrEP[4,7,8,]

Risk Group*†	Daily FTC/TDF	On-Demand (2:1:1) FTC/TDF	Daily FTC/TAF	Injectable CAB
Men who have sex with men	FDA approved, guideline recommended	Off label, IAS-USA and WHO guideline recommended	FDA approved, guideline recommended	FDA approved, guideline recommended
Transgender women				
Cisgender men†		Off label, IAS-USA guideline recommended		
Cisgender women		Off label, not recommended (unless risk from anal sex only)	Off label, not recommended (unless risk from anal sex only)	FDA approved, guideline recommended (except in pregnancy)
Transgender men				

*For people who inject drugs, sexual risk should be assessed and considered. CDC guidelines state that people who inject drugs are likely to benefit from any FDA-approved medication for PrEP with or without a sexual risk indication.
†Includes other gender identifies where HIV could be acquired through vaginal sex.

high copayment, options include pharmaceutical company co-pay assistance programs, the Patient Advocate Foundation (patientadvocate.org), and some state programs.

The huge issue in HIV treatment is stigma. Even patients who are undetectable and who will not die from their disease, HIV infection causes significant impact on patient quality of life. It impacts a patient's dating life, self-esteem, and their relationships. There are patients who have been diagnosed for 30 years but have never told anyone about their infection. Those with HIV need to understand that being undetectable means they will not pass along the infection and this relieves much of a patient's anxiety about the disease.

In terms of HIV treatment, even though there are many available antiretroviral treatments (ART), only a few combinations are frequently used for initial therapy.[9] Close to 95 percent of new therapy starts are with the one tablet a day regimen of bictegravir/tenofovir alafenamide/emtricitabine. There are uses for the other available medications because of comorbidities, adverse events, or drug resistance.

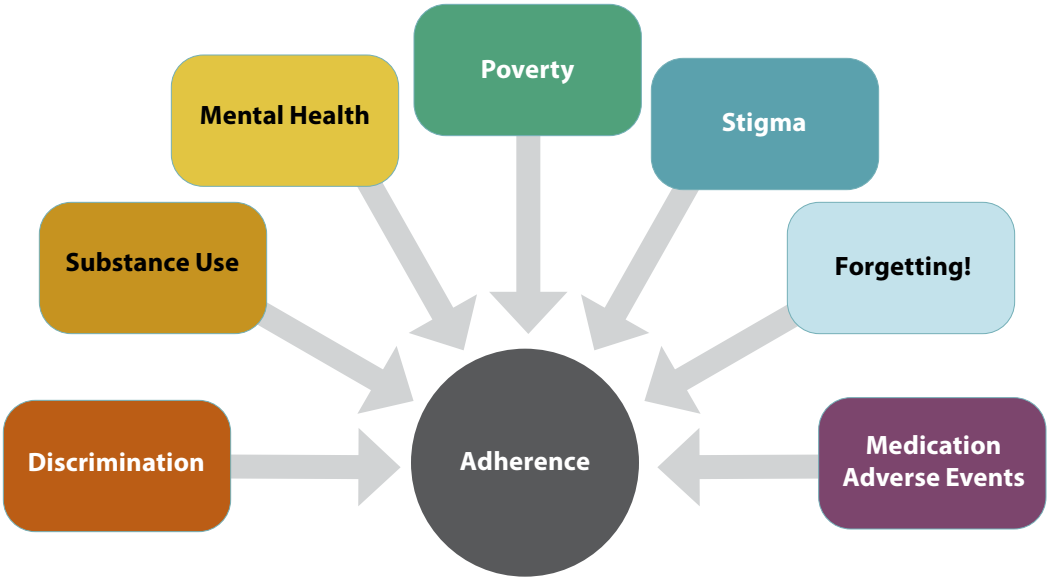
Viral suppression requires good adherence of around 90 percent of prescribed doses but there are many obstacles to patients being adherent with a daily regimen (Exhibit 3). Some red flags for potential nonadherence include denial and fear of HIV, misinformation, distrust of the medical establishment, fear of medications, low self-esteem, mental illness, unstructured and chaotic lifestyles, lack of support, lack of housing, abusive relationships, inconsistent access to care or health insurance, and risk of inadvertent parental disclosure. In the clinic, clinicians can assess adherence using non-stigmatizing language and ask about support systems that could help (friends, family). They can discuss tools that the patient could use (pill boxes, apps, text message reminders) and provide resources for daily directly observed therapy.

The newest advance in HIV treatment is long-acting injectable antiretrovirals. Intramuscular cabotegravir and rilpivirine (CAB + RPV) are now available for every one- or two-month injections. Each agent requires a separate injection into the gluteal muscles. Optimal candidates for injectable therapy are those who are virologically suppressed on an oral regimen for at least three to six months, engaged with their healthcare, and agree to make frequent clinic visits.

Contraindications include certain types of viral resistance, prior virologic failure, or chronic hepatitis B infection (active or occult). Most patients prefer the two-month regimen instead of a monthly clinic visit. A healthcare provider must provide these injections. Injection site reactions are common, but most are mild (Grade 1 or 2) and can be treated with over-the-counter pain relievers or hot or cold packs.

The long-acting injectable combination was initially studied in those already virally suppressed

Exhibit 3: Barriers to Adherence



with good adherence. The Latitude study examines the use in patients who struggle to take medications and/or come to visits. Preliminary data from this trial was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in March 2024.[10] In this Phase III open-label trial, participants received comprehensive and incentivized adherence support while taking guideline-recommended three-drug regimen oral ART, including dolutegravir and bictegravir-based regimens, to achieve viral suppression. Those who achieved viral suppression were eligible to randomize, to staying on oral standard of care (SOC) regimens or switch to long-acting injectable cabotegravir plus rilpivirine (LA CAB+RPV), dosed monthly. During the randomized phase of the study, 146 participants received monthly LA CAB+RPV and 148 continued on SOC. The primary endpoint was a comparison of regimen failure, defined as a combination of virologic failures and regimen discontinuations, between arms. Twenty-four percent of participants on LA CAB+RPV experienced regimen failure compared to 38.5 percent on SOC. Key secondary endpoints of virologic failure (7.2% versus 25.4%) and treatment-related failure (9.6% versus 26.2%) favored the LA-ART regimen. The safety monitoring board stopped this study early due to superior efficacy of LA CAB+RPV in secondary endpoints. The participants in this trial were primarily Black/African Americans with high viral loads but preserved CD4 levels at the start of the trial. This study has not yet been published.

The International Antiviral Society–USA updated their treatment recommendations for the use of LA CAB+RPV in 2024.[11] When supported by intensive follow-up and case management services, injectable LA CAB+RPV may be considered for people with viremia who meet certain criteria when no other treatment options are effective due to a patient's persistent inability to take oral ART. These patients need to be unable to take oral ART consistently despite extensive efforts and clinical support, have a considerable risk of HIV disease progression (CD4+ cell count < 200/µL or history of AIDS-defining complications), and the virus is susceptible to both CAB and RPV. If applicable, patients should also be referred for treatment of substance use disorder and/or mental illness.

There are patients who have difficulty coming for every one- or two-month injection visits. In a few places there are now services which will provide in home injection of LA CAB+RPV. Continued innovation is needed to make treatment adherence better. There is a self-injected product and an every six-month injectable under study.

The monthly cost of LA CAB+RPV is similar to bictegravir/tenofovir alafenamide/emtricitabine. Getting LA CAB+RPV reimbursed can often be a headache for providers. For insurance plans, coverage can either be seen as pharmacy or medical

benefit. If a pharmacy benefit, prior authorization is often required which adds a lot of paperwork and roadblocks. If under the medical benefit, clinics must buy the product upfront and then bill the insurance provider, which is not financially possible for many clinics. If the patient has no insurance, they can access through the manufacturer Patient Assistance Program. If the insurance provider denies this therapy, the manufacturer will cover the therapy for one year.

Conclusion

There continue to be wide gaps in who receives PrEP, so prescribers of PrEP need to be expanded (primary care providers, pharmacists, etc.) if the U.S. is going to reach goals of ending the HIV epidemic. Injectable cabotegravir is a great PrEP option for those at risk for HIV infection. For those who struggle to take oral medications, long-acting injectable therapy is a good option and barriers to prescribing them need to be reduced. To end the HIV epidemic, the healthcare community must be creative both with prevention and treatment options because there is no one size that fits all approach.

Mary W. Montgomery, MD is an Associate Physician in the Division of Infectious Diseases at the Brigham and Women's Hospital and an Instructor in Medicine at Harvard Medical School in Boston, MA.

References

1. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2018–2022. *HIV Surveillance Supplemental Report*. 2024; 29 (No.1).
2. Singh S Hu X, Hess K, Iqbal K. Estimating Lifetime Risk of a Diagnosis of HIV Infection Among MSM: United States, 2017-2021. Conference on Retroviruses and Opportunistic Infections 2024. Denver, CO. Abstract 193.
3. Centers for Disease Control and Prevention. Core indicators for monitoring the Ending the HIV Epidemic initiative (preliminary data): National HIV Surveillance System data reported through June 2023; and preexposure prophylaxis (PrEP) data reported through March 2023. *HIV Surveillance Data Tables*. 2023;4(3).
4. U.S. Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2021 Update: A Clinical Practice Guideline. Centers for Disease Control and Prevention.
5. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med*. 2021;385(7):595-608.
6. Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: Results from HPTN 084, a Phase III, randomized clinical trial. *Lancet*. 2022;399(10337):1779-89.
7. Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 Recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2023;329(1):63-84.
8. What's the 2+1+1? July 2019. Technical Brief. Event-Driven Oral Pre-Exposure Prophylaxis to Prevent HIV For Men Who Have Sex with Men: Update to Who's Recommendation on Oral Prep. Available at iris.who.int/bitstream/handle/10665/325955/WHO-CDS-HIV-19.8-eng.pdf?ua=1. Accessed 2/6/2025.
9. DHHS Guidelines. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. May 2023.
10. ViiV Healthcare announces interim data at CROI indicating superior efficacy of long-acting injectable HIV treatment Cabenuva (cabotegravir + rilpivirine) compared to daily oral therapy in individuals living with HIV who have adherence challenge. March 6 2024. Press Release. Available at gsk.com/media/11024/latitude-croi-global-press-release.pdf. Accessed 2/6/2025.
11. Sax PE, Thompson MA, Saag MS, et al. Updated treatment recommendation on use of cabotegravir and rilpivirine for people with HIV from the IAS-USA Guidelines Panel. *JAMA*. 2024;331(12):1060-1.

Casting Light on the Burden and Unmet Need of Psoriasis: A Targeted Approach to Optimizing Treatment and Improving Outcomes

Gary M. Owens, MD

This journal article is supported by educational grants from Dermavant Sciences; Sun Pharmaceutical Industries; Bristol Myers Squibb

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Psoriasis is a complex, chronic, immune-mediated inflammatory disease that affects approximately seven million people in the United States. Although many patients' disease can be controlled with topical therapy, those with moderate-to-severe disease will require systemic therapy with biologics or oral small molecules.

Key Points

- Treatment of psoriasis requires personalization.
- Newer topical, biologic, and oral small molecule medications provide additional treatment options especially for difficult to treat patients.
- Management of therapy costs requires new approaches.

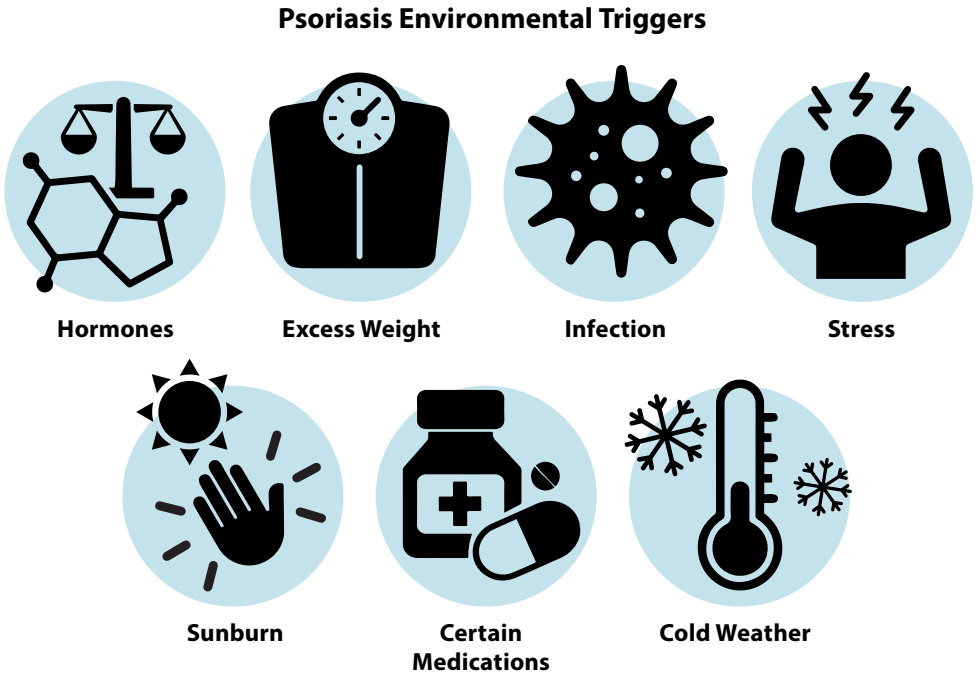
PSORIASIS, AS A CHRONIC AUTOIMMUNE inflammatory disease, is much more than just a skin disease—it also manifests in joints and other organs. Psoriasis can present at any age but the two peak age groups are 20 to 30 and 50 to 60 years of age. As psoriasis is a body wide inflammatory disease and those affected are more likely to have associated co-morbidities including cardiovascular disease, psoriatic arthritis, obesity, diabetes, hypertension, and cancer. Depression is also more likely. Those with psoriasis are 58 percent more likely to have a major cardiac event and 43 percent more likely to have a cerebrovascular event.[1]

The prevalence of psoriasis in the United States (U.S.) population 20 years of age or older is 3.0 percent. Prevalence has not changed significantly over the past decade. Psoriasis is one of the most common immune-mediated diseases affecting adults in the U.S., affecting approximately 7.55 million adults aged 20 years or older.[2]

Psoriasis tends to occur in cycles where it can flare up for weeks or months, or it can subside into periods of remission where symptoms are gone or significantly reduced. Some triggers are shown in Exhibit 1.[3] There are five major forms of psoriasis—plaque, guttate, pustular (generalized and localized), inverse, and erythrodermic.[4] Plaque psoriasis is the most common type. Severity ranges from mild (< 3% of body surface area affected) to moderate (3 to 10%) to severe (> 10%). The National Psoriasis Foundation defines moderate-to-severe disease as patients with BSA greater than 3 percent or patients with a BSA of less than 3 percent who have face, genital, palm, or sole involvement, or those with psoriasis causing severe impact on quality of life.[4]

The pathogenesis of this disease is not completely understood. The epidermis is infiltrated by a large number of activated T cells, which are capable of

Exhibit 1: Psoriasis Triggers[3]



inducing keratinocyte proliferation.[5] Epidermal hyperplasia leads to an accelerated cell turnover rate, leading altered keratinocyte differentiation. A ramped-up, deregulated inflammatory process ensues with large production of various cytokines (e.g., tumor necrosis factor alpha [TNF-α], interferon [IFN], interleukin[IL]-12). T-cell hyperactivity and the resulting proinflammatory mediators (in this case IL-17 and -23) play a significant role in the pathogenesis of psoriasis.

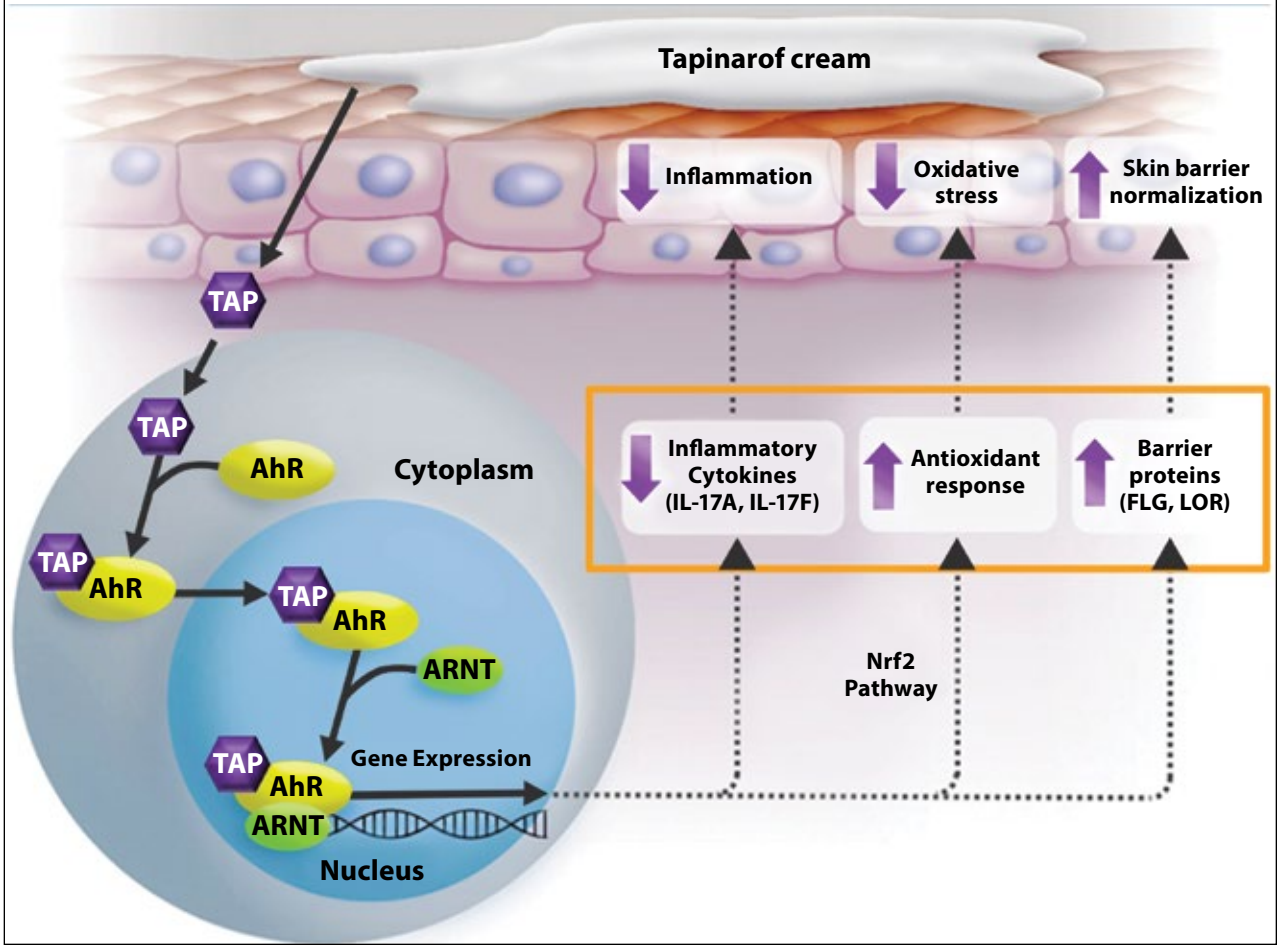
Treatment of psoriasis can be complex because patients present with a broad spectrum of symptoms and severity. A variety of treatment options are available and must be tailored to the patient's needs. The goals of treatment are to gain initial rapid control of the disease, maintain the patient in long-term remission and avoid relapse, avoid adverse events as much as possible, and improve the patient's quality of life[6]. Although many patients, particularly those with the limited form of the disease, may be treated with topical therapy, those with extensive (moderate-to-severe) psoriasis require phototherapy or systemic therapy to adequately suppress the systemic, immunopathogenic process.[4]

Topical corticosteroids are the mainstay of treatment for mild and limited psoriasis. Vitamin D analogs are frequently used in patients with lesions resistant to topical corticosteroid therapy or with lesions on the face or exposed areas where thinning of the skin from corticosteroids would pose cosmetic problems. Keratolytic agents are used to remove scale, to smooth the skin, and to treat hyperkeratosis. Aqueous gel formulations of retinoids may also be used and avoid the issue of disease worsening if the therapy is withdrawn which can occur with corticosteroids.

Tapinarof is a steroid-free option for topical treatment which was FDA approved in 2022 for mild-to-severe psoriasis. The efficacy of tapinarof in psoriasis is attributed to its specific binding and activation of aryl hydrocarbon receptor, a ligand-dependent transcription factor, leading to the downregulation of proinflammatory cytokines, including IL-17, and regulation of skin barrier protein expression (i.e., filaggrin and loricrin) to promote skin barrier normalization (Exhibit 2).[7]

In two Phase III trials, a physicians global assessment (PGA) score response occurred in 35.4 percent of the patients in the tapinarof group and in 6.0 percent of those in the vehicle group in trial I and in 40.2 percent and 6.3 percent, respectively, in trial II ($p < 0.001$ for both comparisons) at 12 weeks of once daily application.[8] Psoriasis area severity index 75 percent disease clearance (PASI-75) occurred in 36.7 percent and 47.6 percent of those treated with tapinarof compared to 10.2 percent and 6.9 percent

Exhibit 2: Tapinarof Mechanism of Action[7]

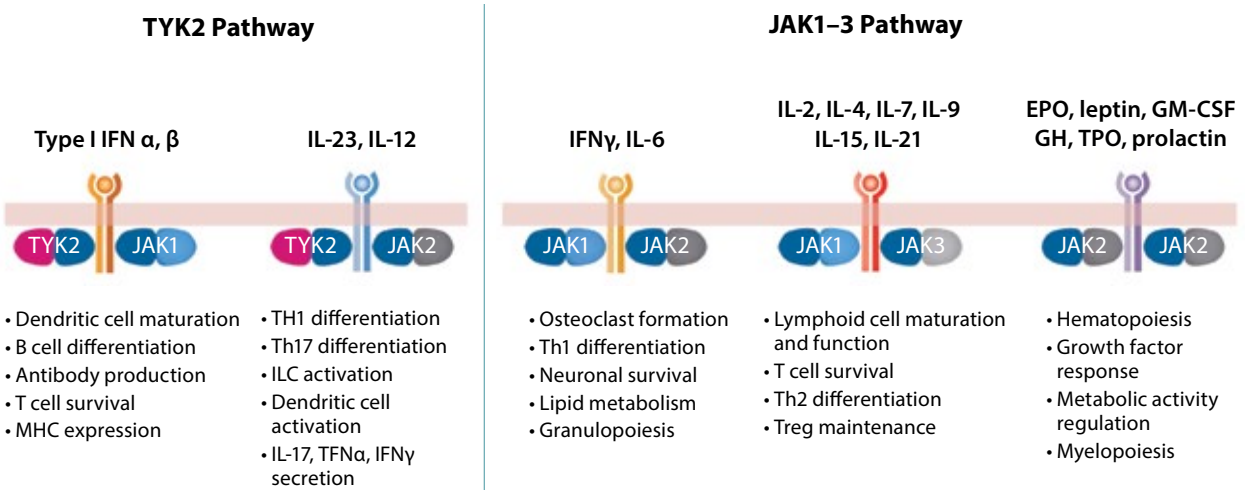


of vehicle group. Another Phase III trial evaluated long-term safety, efficacy, remittive effect, durability of response, and tolerability of tapinarof in those who responded in the 12-week trials. After 40 total weeks of therapy, 40.9 percent of patients achieved complete disease clearance (PGA = 0), and 58.2 percent entering with PGA 2 or greater achieved PGA of 0 or 1. At the end of 40 weeks, tapinarof was stopped and patient disease was monitored. The mean duration of off therapy remittive effect for patients achieving PGA 0 was 130.1 days. Folliculitis, contact dermatitis, headache, and pruritus are the most common adverse events with this agent.

If a patient has disease that cannot be controlled topically, biologics are an option. FDA-approved injectable biologics include TNF inhibitors (certolizumab, etanercept, adalimumab, infliximab, golimumab), a T cell inhibitor (abatacept), IL-17 inhibitors (bimekizumab, secukinumab, brodalumab, ixekizumab), IL-23 inhibitors (tildrakizumab, risankizumab, guselkumab), and an IL-12/23 inhibitor (ustekinumab).

A newer biologic for use in psoriasis, tildrakizumab was FDA approved in 2018 for moderate-to-severe psoriasis. It is dosed as a 100 mg injection at weeks zero, four, and every 12 weeks thereafter and should only be administered by a healthcare provider. This is an option for patients who need a biologic but prefer not to self-inject or those who have adherence issues and require some supervision. Every 12-week long-term dosing results in fewer annual injections than most other biologics except risankizumab. Approval was based on the data from two randomized Phase III trials comparing it to placebo and etanercept.[10] In the first trial, at week 12, 64 percent in the tildrakizumab group achieved PASI 75, compared with 6 percent in the placebo group ($p < 0{\cdot}0001$ for comparisons of both tildrakizumab groups versus placebo). Fifty-eight percent achieved PGA responses, compared with 7 percent in the

Exhibit 3: TYK-2 Inhibitor versus JAK Inhibitors[13]



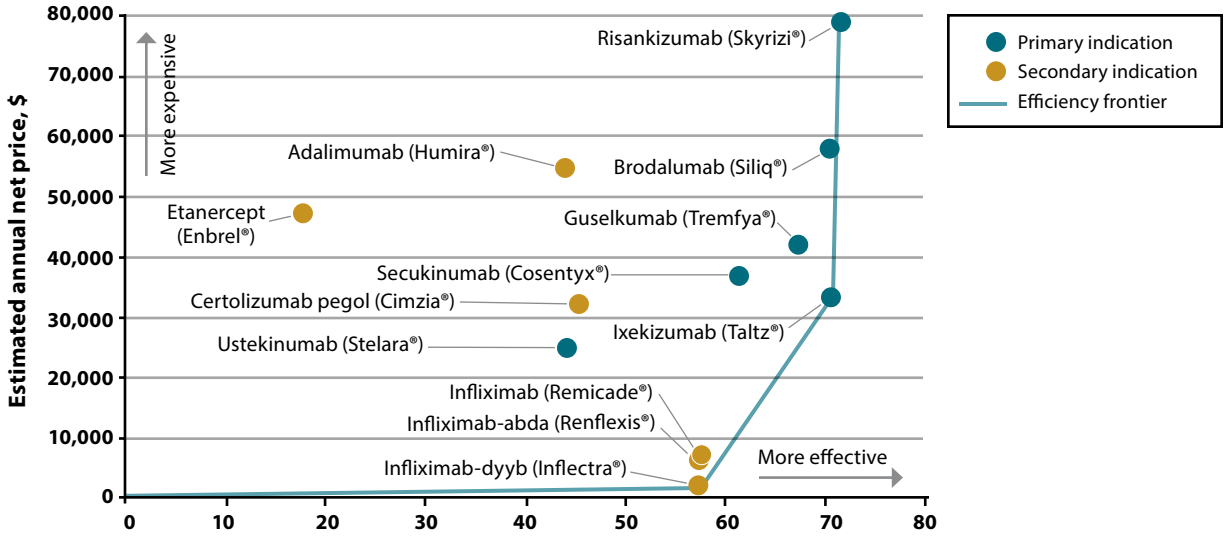
EPO = erythropoietin; GH = growth hormone;
GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon;
IL = interleukin; ILC = innate lymphoid cell; JAK = Janus kinase;
MHC = major histocompatibility complex; Th = T helper; TNF = tumor necrosis factor;
TPO = thrombopoietin; Treg = regulatory T cell; TYK = tyrosine kinase

placebo group ($p < 0.0001$ for comparisons of both tildrakizumab groups versus placebo). The second trial, at week 12, 61 percent in the tildrakizumab group achieved PASI 75, compared with 6 percent in the placebo group and 48 percent in the etanercept group ($p < 0.0001$ for comparisons of tildrakizumab versus placebo; $p = 0.0010$ for 100 mg versus etanercept). Fifty-nine percent achieved a PGA response, compared with 4 percent and 48 percent, respectively ($p < 0.0001$ vs placebo; $p = 0.0663$ versus etanercept). Tildrakizumab maintains efficacy and a favorable safety profile over five years in patients with psoriasis.[11]

Because moderate-to-severe chronic plaque psoriasis may be difficult to control with current agents, more therapies are needed. Also, more effective oral therapies as an alternative to injectable biologics are needed. A first in class oral selective tyrosine kinase 2 (TYK-2) inhibitor, deucravacitinib, was FDA approved in 2022 for moderate-to-severe psoriasis. It selectively binds to the regulatory domain of TYK2, which inhibits the signaling of cytokines involved in psoriasis. TYK2 is a Janus Kinas (JAK) enzyme that is coded by the TYK2 gene and constitutively expressed in immune cells. Mutations and polymorphisms in TYK2 impact IL-23, IFN-α/β, and IL-6,10,12 immune-mediated signaling, and are associated with an altered risk for psoriasis and other immune-related diseases.[12] As shown in Exhibit 3, TYK2 inhibitors have different down-stream impact from JAK inhibitors, which are FDA approved for rheumatoid arthritis, myelofibrosis, and chronic obstructive lung disease.[13] Higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with a JAK inhibitor compared to those treated with TNF inhibitors in RA patients. It is not known if TYK2 inhibitors cause the same issues but it seems less likely because of the lack of overlap with the JAK 1 to 3 pathways.

In one Phase III trial, at week 16, response rates were significantly higher with deucravacitinib versus placebo or apremilast (an oral small molecule phosphodiesterase 4 inhibitor) for PASI-75 (58.4% versus 12.7% versus 35.1%; $p < 0.0001$) and PGA 0/1 (53.6% versus 7.2% versus 32.1%; $p < 0.0001$).[14] Efficacy improved beyond week 16 with 69.3 percent of those treated with deucravacitinib achieving PASI-75 and was maintained through week 52. Equivalent results were seen in a second identically designed Phase III trial.[15] Adverse event rates with deucravacitinib in these trials were similar to those with placebo and apremilast. Safety and efficacy data

Exhibit 4: Efficiency Fronter for Psoriasis Biologics[20]



out to three years of therapy have been published or presented at professional meetings and show sustained efficacy without significant additional toxicities.[16,17] The most common adverse events of deucravacitinib are upper respiratory infections, herpes zoster, canker sores, folliculitis, and acne. Serious infections and lymphoma can occur because of the immunosuppressive effects of this agent. Rhabdomyolysis is another rare adverse event.

Specialty drug management is providing significant financial challenges for managed care. In 2023 specialty spend grew by 11.7 percent while traditional spend grew 7.3 percent on an invoice price basis and accounted for 51 percent of total spending.[18] Biologics, especially those for immunologic diseases like psoriasis, are a large part of specialty spend.

The psoriasis market size has grown rapidly in recent years because of the many new medication approvals. It is expected to grow from $26.56 billion in 2024 to $29.5 billion in 2025 at a compound annual growth rate (CAGR) of 11.1 percent.[19] The market is expected to continue to grow to $42.34 billion by 2029. The growth in the forecast period can be attributed to additional regulatory approvals, patient preferences, aging population, increased awareness, and introduction of novel therapies.[19] Use of combination therapies such as a biologic with a small molecule for better disease control is an emerging trend in the psoriasis market.

To combat the rising costs of psoriasis treatment, managed care looks to many different avenues. Management strategies currently used include step therapy through most effective agents, prior authorization, preferred biological agents, limited prescribing to appropriate specialists, managing site of service and guideline-based management when available. Coverage and formulary decisions must always be evidence-based.

One strategy proposed in a recent paper is an efficiency frontier (EF) approach to better align prices with the clinical efficacy of biologic medications for plaque psoriasis.[20] The authors of this paper noted the U.S. lacks a systematic approach for aligning drug prices with clinical benefit, and traditional cost-effectiveness analysis faces political obstacles due to the use of quality-adjusted life-years. EFs were constructed based on each biologic's efficacy, measured using the PASI-90 response rate and annual treatment cost as of January 2023—costs were net of estimated manufacturer rebates. Prices based on the EF were compared with traditional CEA-based prices calculated by the Institute for Clinical and Economic Review at a threshold of $150,000 per quality-adjusted life-year gained. Among 13 biologics, PASI 90 response rates ranged from 17.9 percent (etanercept) to 71.6 percent (risankizumab). U.S. net annual treatment costs ranged from $1,664 (infliximab-dyyb – a biosimilar) to $79,277 (risankizumab). Tildrakizumab was not included in this analysis. The U.S. spends more than three times as much on these biologics compared to selected peer countries. In this analysis, three medications

were considered cost effective based on the U.S. EF, (the most cost-effective, nondominated treatments) including infliximab-dyyb (PASI 90: 57.4 percent; annual cost: $1,664), ixekizumab (PASI 90: 70.8%; annual cost: $33,004), and risankizumab (PASI 90: 71.6%; annual cost: $79,277)—see Exhibit 4.[20] U.S. prices for the other psoriasis biologics would need to be reduced by a median of 71 percent (31% to 95%) to align with those estimated using the EF. Except for risankizumab, the EF-based prices were lower than the prices based on traditional CEA.

Conclusion

Psoriasis is a complex disease to manage, but the goal should be for a patient-centered treatment that reduces disease burden, improves quality-of-life, and addresses the risks of systemic complications and comorbid conditions. Newer agents which are very effective but also safe may be options for patients with uncontrolled disease. Because of the high cost of the biologics and oral small molecules, managed care must find a way to control costs while providing the right agent for the right patient.

Gary M. Owens, MD is President of Gary Owens and Associates in Ocean View, DE.

References

1. National Psoriasis Foundation. Related Conditions. Available at psoriasis.org/about-psoriasis/related-conditions. Accessed 1/16/2025.
2. Armstrong AW, Mehta MD, Schupp CW, et al. Psoriasis prevalence in adults in the United States. *JAMA Dermatol*. 2021;157(8):940-6.
3. Barhum L. Is Psoriasis Hereditary? Yes, but genes alone are not enough. Available at verywellhealth.com/is-psoriasis-hereditary-5191433. Accessed 1/16/2025.
4. National Psoriasis Foundation. Pocket Guide to Psoriasis and Psoriatic Arthritis. 2023. Available at psoriasis.org. Accessed 1/16/2025.
5. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis*. 2005;64(Suppl 2):ii30-6.
6. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. 2021;84(2):432-70.
7. Bissonnette R, Stein Gold L, Rubenstein DS, et al. Tapinarof in the treatment of psoriasis: A review of the unique mechanism of action of a novel therapeutic aryl hydrocarbon receptor-modulating agent. *J Am Acad Dermatol*. 2021;84(4):1059-67.
8. Lebwohl MG, Stein Gold L, Strober B, et al. Phase III trials of tapinarof cream for plaque psoriasis. *N Engl J Med*. 2021;385(24):2219-29.
9. Strober B, Stein Gold L, Bissonnette R, et al. One-year safety and efficacy of tapinarof cream for the treatment of plaque psoriasis: Results from the PSOARING 3 trial. *J Am Acad Dermatol*. 2022;87(4):800-6.
10. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): Results from two randomized controlled, Phase III trials. *Lancet*. 2017;390(10091):276-88.
11. Fernandez AP, Dauden E, Gerdes S, et al. Tildrakizumab efficacy and safety in patients with psoriasis and concomitant metabolic syndrome: post hoc analysis of 5-year data from reSURFACE 1 and reSURFACE 2. *J Eur Acad Dermatol Venereol*. 2022;36(10):1774-83.
12. Muromoto R, Oritani K, Matsuda T. Current understanding of the role of tyrosine kinase 2 signaling in immune responses. *World J Biol Chem*. 2022;13(1):1-14.
13. Gooderham MJ, Hong HC, Litvinov IV. Selective TYK2 inhibition in the treatment of moderate to severe chronic plaque psoriasis. *Skin Therapy Letter*. 2022;27:6.
14. Armstrong AW, Gooderham M, Warren RB, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled Phase III POETYK PSO-1 trial. *J Am Acad Dermatol*. 2023;88(1):29-39.
15. Strober B, Thaçi D, Sofen H, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, Phase III program for evaluation of TYK2 inhibitor psoriasis second trial. *J Am Acad Dermatol*. 2023;88(1):40-51.
16. Lebwohl M, Warren RB, Sofen H, et al. Deucravacitinib in plaque psoriasis: 2-year safety and efficacy results from the Phase III POETYK trials. *Br J Dermatol*. 2024;190(5):668-79.
17. Stein Gold L, et al. Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, in plaque psoriasis: 3-year Psoriasis Area and Severity Index (PASI) outcomes in the long-term extension of the Phase III POETYK PSO-1 and PSO-2 trials. Presentation (Poster #51091) at the American Academy of Dermatology (AAD) 2024 Annual Meeting. March 2024
18. Biggs S, Long D. Insights Into the 2023 U.S. Pharmaceutical Market. Biologics growth continues to outpace other products. Available at iqvia.com/locations/united-states/blogs/2023/07/insights-into-the-2023-us-pharmaceutical-market. Accessed 1/16/2025.
19. Psoriasis Global Market Report 2025. Available at thebusinessresearchcompany.com/report/psoriasis-drugs-global-market-report. Accessed 1/16/2025.
20. Egilman AC, Kesselheim AS, Avorn J, et al. Use of efficiency frontiers to align prices and clinical benefits of biologic therapies for plaque psoriasis. *JAMA Dermatol*. 2024;160(4):409-16.

Navigating an Increasingly Complex Treatment Paradigm in the Management of Heart Failure: Managed Care Insights for Optimized Clinical and Economic Outcomes

Michael Miller, MD, FACC, FAHA

This journal article is supported by educational grants from Merck Sharp & Dohme LLC; Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Heart failure (HF) is a common condition resulting in an estimated $39 billion in costs in the United States (U.S.) each year. Fortunately for HF patients, new therapeutic options have entered the paradigm over the past few years with the potential to improve clinical and economic outcomes for the patient, the system, and HF with preserved ejection fraction. There is still much that could be done to benefit those with HF such as improving patient and clinician adherence with guideline-directed medical therapy (GDMT).

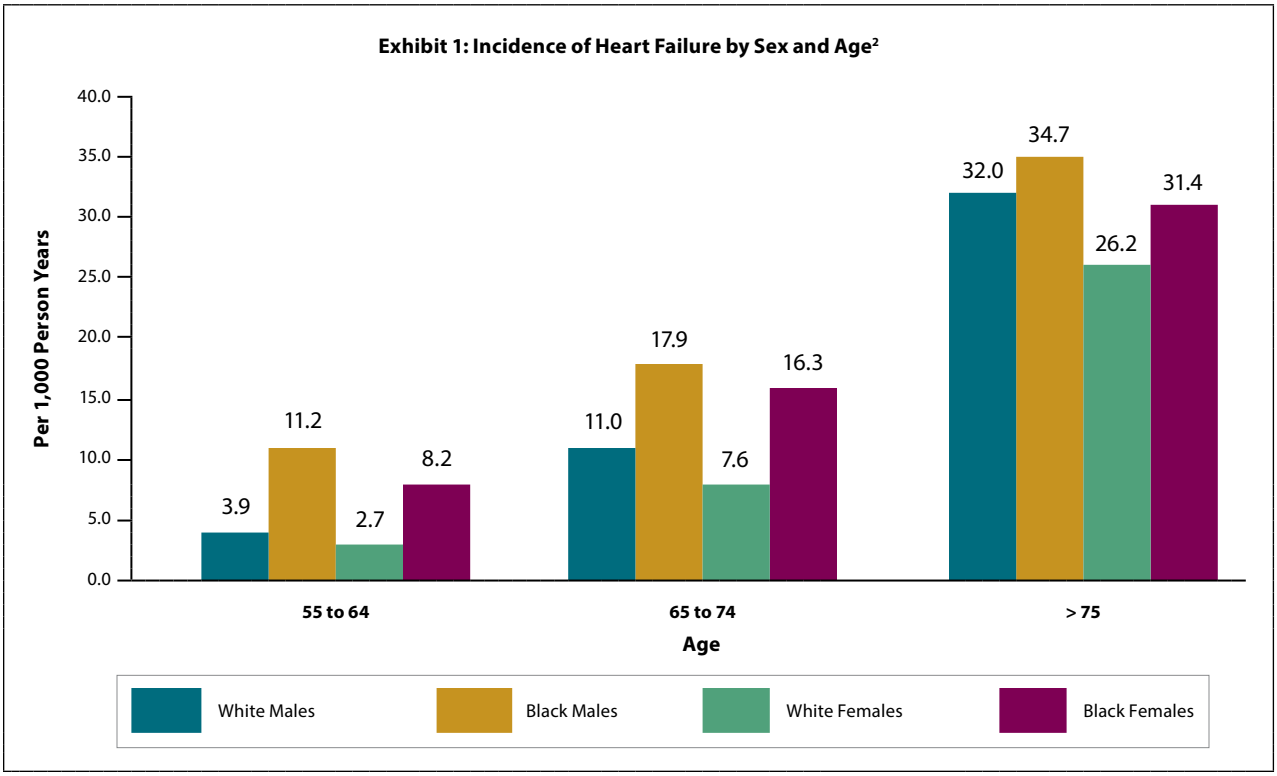
Key Points

- Managed care can play a significant role in improving access to and utilization of guideline-directed medications for HF.
- Optimization of GDMT is important through the use of foundational medication classes and appropriate target doses.
- Patients with multiple HF hospital admissions should be referred to a multidisciplinary disease management program.

HEART FAILURE (HF) IS A SIGNIFICANT public health issue in the U.S. which affects about 6.7 million adults and the prevalence is expected to rise to 8.5 million Americans by 2030.[1] The lifetime risk of HF has increased to 24 percent—approximately one in four persons will develop HF in their lifetime. As shown in Exhibit 1, the incidence of HF varies by gender, age, and race.[2] Approximately 33 percent of the U.S. adult population without known symptomatic HF is at-risk for HF (Stage A HF) and 24 to 34 percent have pre-HF (Stage B HF).[1]

HF results in significant financial impact. The total direct medical cost in the U.S. is estimated to be approximately $39.2 billion annually.[3] This cost is expected to increase to over $70 billion by 2030.[4] More Medicare dollars are spent on HF than any other disease. Factors contributing to HF-related hospitalizations and total cost include concomitant diseases of hypertension (72% of patients), coronary artery disease (56%), diabetes (48%), chronic kidney disease (47%), and atrial fibrillation (43%).

HF can occur with reduced left ventricular ejection fraction (LVEF) (HFrEF), preserved LVEF (HFpEF), or mildly reduced LVEF (HFmrEF).[5] Reduced LVEF is defined as an EF less than 50 percent. HFrEF is defined as EF less than 40 percent and HFmrEf as EF between 41 to 49 percent. Those with HFpEF have an EF greater than 50 percent. Prominent risk factors for HFpEF include hypertension, obesity, diabetes, atrial fibrillation, and metabolic syndrome whereas coronary artery disease is a prominent risk factor for HFrEF (Exhibit 2).



HFpEf is very different from HFrEF. In those with preserved EF, there is concentric thickening of the heart musculature which leads to impaired relaxation and filling of the heart chambers. In those with reduced EF, there is dilation of the heart which leads to impaired contraction of the muscle. HFrEF is more common in men and in those with coronary artery disease. HFpEF is more common in older women but is becoming more common in younger people due to obesity. Signs and symptoms of each type of HF are similar except an extra heart sound (S3) and cardiomegaly are less common with HFpEF.[6] Hospital admissions related to HF are higher for HFrEF and HFmrEF. Five-year mortality is similar across types at 75 percent.[7] Life expectancy with HF is greatly reduced compared to those without HF.

It is not all doom and gloom. If patients are treated with appropriate therapies and are adherent with those therapies, they can have improved outcomes. Reduced and preserved HF are treated differently. Guideline directed medical therapy (GDMT) for HFrEF includes four foundational medications initially—an angiotensin receptor-neprilysin inhibitor (ARNI, sacubitril/valsartan) or angiotensin converting enzyme inhibitor (ACE-I, e.g., lisinopril) or angiotensin receptor blocker (ARB, e.g., losartan), a beta-blocker (e.g., metoprolol), a mineralocorticoid receptor antagonist (MRA, e.g., spironolactone, eplerenone), and a sodium/glucose cotransporter 2 inhibitor (SGLT2, e.g., empagliflozin, canagliflozin, dapagliflozin).[5,8] The regimen may also include a diuretic as needed. Additional therapies may be added after the four foundational medications are established.

The SGLT2 inhibitor class, which increases renal excretion of glucose, was originally developed for and FDA approved to treat type 2 diabetes (T2D). Large-scale cardiovascular outcomes trials, which are required by the FDA for any new agents for T2D, found that these agents reduce risk of primary and secondary hospitalization due to HF and cardiovascular death, even in diverse subsets of patients with T2D regardless of cardiovascular disease history. Independent of glucose control, SGLT2 inhibitors exert pleiotropic metabolic and direct cardioprotective and nephroprotective effects which help explain the cardiovascular benefits.[9] SGLT2 inhibition also reduces inflammation, oxidative stress, fibrosis, intraglomerular hypertension, and sympathetic nervous system activation, and may improve mitochondrial function and myocardial efficiency. This class also increases sodium excretion which reduces blood pressure, preserves renal function, and leads to modest weight loss.[10]

Trials with SGLT2 inhibitors were also done in patients without T2D. Data from the Study to Evaluate the Effect of Dapagliflozin on the Incidence

Exhibit 2: Risk Factors for Heart Failure

Major 'traditional' Risk Factors	Additional Risk Factors	Medications and Toxins
Older age	Sleep disordered breathing	Cardiotoxic chemotherapies
Male sex	Chronic kidney disease	Cocaine, amphetamines
Black race	Albuminuria	Excess alcohol
Coronary artery disease	IGF-1, TNF-alpha, IL-6, CRP elevation*	Thiazolidinediones
Hypertension, left ventricular hypertrophy	Lower socioeconomic status	NSAIDs
Obesity	Dietary patterns	
Diabetes, metabolic syndrome	Sedentary lifestyle, low physical activity	
Smoking	Psychological stress	
Valvular heart disease	Family history/genetics	

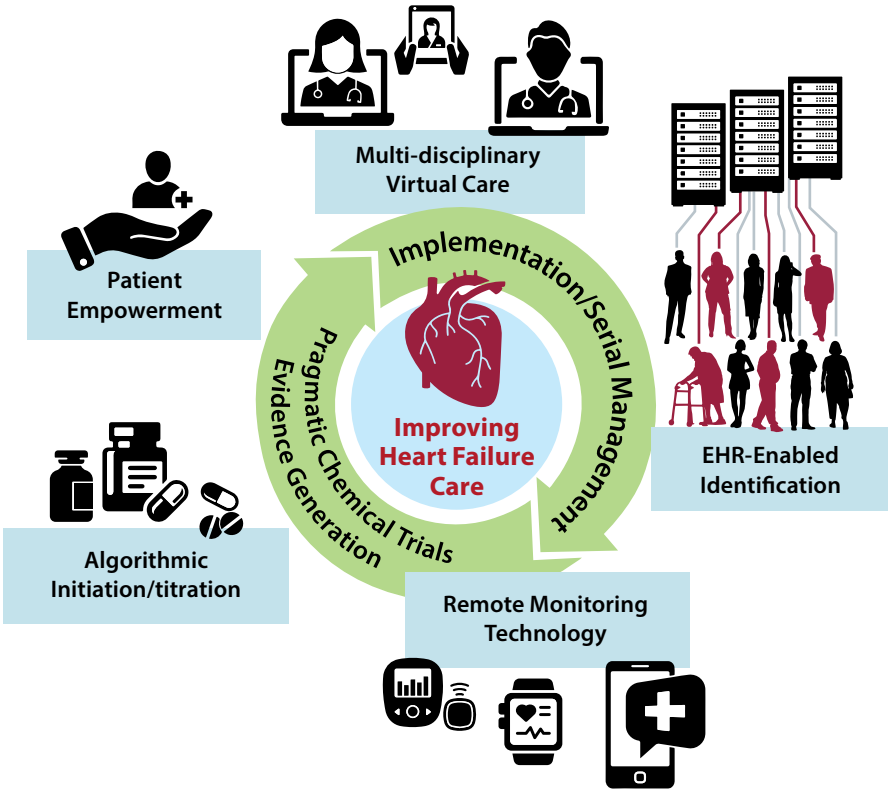
*Evidence of a pro-inflammatory state

of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR – Reduced) have demonstrated the positive clinical impact of SGLT2 inhibition in patients with HFrEF both with and without T2D.[11,12] These data have led to the FDA approval of dapagliflozin and empagliflozin to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure, irrespective of T2D status.

Vericiguat, an oral soluble guanylate cyclase (sGC) stimulator, increases sGC activity to improve myocardial and vascular function. In the heart, vericiguat therapy leads to a decrease in progressive myocardial stiffening and thickening, decrease in ventricular remodeling, and decrease in fibrosis. In the vasculature, there is then decreased arterial constriction and vascular stiffness. A Phase III trial compared vericiguat, at a target dose of 10 mg, with placebo in 5,050 patients with HFrEF (ejection fraction less than 45%) on top of GDMT.[13] The included patients had to have had a HF-related hospitalization or need of IV diuretic therapy in the past six months, making it a particularly high-risk and vulnerable patient population. The primary endpoint was the first occurrence of cardiovascular death or hospitalization for HF. Mortality following hospitalization for patients with HF is as high as 30 percent within one year.[14,15] Over a median follow up of 10.8 months, the primary endpoint occurred less frequently with vericiguat than with placebo (35.5% versus 38.5%, $p = 0.02$).[13] The number needed to treat with vericiguat to prevent death or hospitalization for HF from this trial was 24. This agent is now FDA approved to reduce the risk of cardiovascular death and HF hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and EF less than 45 percent. Patients in this trial were older, more symptomatic (up to 40% NYHA III-IV class), had higher N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) levels, and were more vulnerable since 84 percent had been hospitalized for heart failure in the previous six months.[16] Vericiguat may be a drug of choice in the highest risk patients with recent or recurrent hospitalizations despite full background medication. The drug has also shown safety in patients with reduced renal function.

The American College of Cardiology/American Heart Association/Heart Failure Society of American guidelines for managing heart failure were updated in 2022. Foundational medications recommended for HFrEF (ARNI/ACE-I/ARB, beta blocker, SGLT2, and as needed diuretic) may be started simultaneously at initial, low doses.[5] Alternatively, these medications may be started sequentially, with

Exhibit 3: Strategies for Improving Prescription of Guideline Directed Medical Therapy for Heart Failure[21]



sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target doses as tolerated. The guidelines recommend ARNI over ACE-I or ARB alone in NYHA II-III, if possible, and the guidelines note that this choice of therapy provides economic value. In patients with symptomatic chronic HFrEF, an SGLT2 inhibitor is recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of T2D, and also provides economic value. In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, vericiguat may be considered.

The treatment of HFpEF is different from HFrEF. Firstly, it is important to treat hypertension aggressively and according to guidelines.[5] Volume management with diuretics is essential for controlling symptoms and improving quality of life. SGLT2 inhibitors are now first-line for most patients. The guidelines note that in patients with HFpEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality. Over a median of 26.2 months, empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF in patients with HFpEF, regardless of the presence or absence of diabetes. The primary outcome, cardiovascular death, or HF hospitalization, for empagliflozin compared to placebo was 13.8 percent versus 17.1 percent ($p < 0.001$).[17] The benefit was primarily driven by a reduction in HF hospitalizations, not mortality. Over a median of 2.5 years, dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with HFmrEF and HFpEF—again it did not matter whether the patient had diabetes or not.[18] About 45 percent of those in the dapagliflozin trial had type 2 diabetes.

Other treatments are also beneficial for HFpEF. An exercise program is important because exercise significantly improves exercise capacity, quality of life, and overall function by addressing the underlying issues of impaired skeletal muscle oxygen use and systemic factors that contribute to exercise intolerance in this condition. Sacubitril/valsartan may be considered in selected patients with HFpEF to decrease hospitalizations, particularly among patients with LVEF on the lower

end of the spectrum.[5] The glucagon like peptide one (GLP-1) agonist semaglutide has been studied in patients with HFpEF and obesity in one trial, which found that weight loss from this agent reduced HF symptoms and physical limitations, and led to greater improvements in exercise function.[19]

About 20 to 25 percent of hospitalized patients with HF will end up back in the hospital within 30 days of discharge and about 50 percent will be re-admitted within six months. Several factors have been identified which led to readmissions. Patient-related factors include nonadherence with dietary restrictions, medications, fluid restriction, severity of illness, and comorbidities. Comorbidities associated with worsening HF and hospital re-admission include iron deficiency anemia, chronic kidney disease (CKD), diabetes, pulmonary disease, and depression. Patients with CKD may not be eligible for some of the main HF agents—vericiguat appears to be safe with severe CKD. Treatment of comorbidities with certain medications can also worsen HF. For example, nonsteroidal anti-inflammatories used to manage joint pain can worsen HF symptoms and fluid overload and reduce kidney function. Inadequate patient and family education and nonadherence with management guidelines are clinician-related factors leading to hospital re-admission. Healthcare system-related factors include inadequate discharge and transitional care planning and lack of appropriate follow-up.

Unfortunately, few patients with HF receive GDMT. In a registry trial of 3,518 patients, 27 percent, 33 percent, and 67 percent of eligible patients were not prescribed ACE-I/ARB/ARNI, beta-blocker, and MRA therapy, respectively.[20] When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%). Among patients eligible for all classes of medication, 1 percent were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA. Exhibit 3 highlights some strategies for improving prescription of GDMT.[21]

In addition to ensuring that patients with HF are on appropriate GDMT to maximize therapeutic outcomes, managed care should have a role in helping patients be adherent with their oftentimes complicated medication regimens. Interventions to improve medication adherence among HF patients have significant effects on reducing readmissions and decreasing mortality.[22] High-risk patients, particularly those with multiple or recent HF hospital admission, should be referred to a multi-disciplinary disease management program to reduce readmission. Patient-centered discharge instructions for transitional care and a follow-up appointment within seven days of discharge are also important.

Conclusion

Managed care can play a significant role in improving access to and utilization of guideline-directed medications for HF. Optimization of GDMT is important through the use of foundational medication classes and appropriate target doses. Patients with multiple HF hospital admissions should be referred to a multidisciplinary disease management program.

Michael Miller, MD, FACC, FAHA is a Cardiologist and Professor of Medicine at the University of Pennsylvania and Chief of Medicine at the Corporal Michael J. Crescenz VA Medical Center in Philadelphia, PA.

References

1. Bozkurt B, Ahmad T, Alexander KM, et al. Heart failure epidemiology and outcomes statistics: A report of the Heart Failure Society of America. *J Card Fail.* 2023;29(10):1412-51.

2. Virani SS, Alonso A, Benjamin EJ, et el. Heart Disease and Stroke Statistics-2020 Update: A report from the American Heart Association. *Circulation.* 2020;141(9):e139-e596.

3. Heidenreich PA, Fonarow GC, Opsha Y, et al. Economic issues in heart failure in the United States. *J Card Fail.* 2022;28(3):453-66.

4. Wei C, Heidenreich PA, Sandhu AT. The economics of heart failure care. *Prog Cardiovasc Dis.* 2024;82:90-101.

5. Heidenreich PA, Bozkurt B, Aguilar D, 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. *Circulation.* 2022;145(18):e895-e1032.

6. McMurray JJ, Carson PE, Komajda M, et al Heart failure with preserved ejection fraction: Clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail.* 2008;10(2):149-56.

7. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol.* 2017;70(20):2476-86.

8. Patel J, Rassekh N, Fonarow GC, et al. Guideline-directed medical therapy for the treatment of heart failure with reduced ejection fraction. *Drugs.* 2023;83(9):747-59.

9. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75(4):422-34.

10. Wilcox CS. Antihypertensive and renal mechanisms of SGLT2 (sodium-glucose linked transporter 2) inhibitors. *Hypertension.* 2020;75(4):894-901.

11. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381: 1995-2008.

12. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383:1413-24.

13. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2020;382(20):1883-93.

14. Loehr LR, Rosamond WD, Chang PP, et al. Heart failure incidence and

survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008;101:1016-22.

15. Hollenberg SM, Warner Stevenson L, Ahmad T, et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized with Heart Failure: A report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2019;74(15):1966-2011.
16. Coats AJS, Tolppanen H. Drug treatment of heart failure with reduced ejection fraction: Defining the role of vericiguat. *Drugs*. 2021;81(14): 1599-604.
17. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-61.
18. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387(12):1089-98.
19. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 2023;389(12):1069-84.
20. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF Registry. *J Am Coll Cardiol*. 2018;72(4):351-66.
21. Brooksbank JA, Faulkenberg KD, Tang WHW, Martyn T. Novel strategies to improve prescription of guideline-directed medical therapy in heart failure. *Curr Treat Options Cardiovasc Med*. 2023;25(5):93-110.
22. Ruppar TM, Cooper PS, Mehr DR, et al. Medication adherence interventions improve heart failure mortality and readmission rates: Systematic review and meta-analysis of controlled trials. *J Am Heart Assoc*. 2016;5(6):e002606.

Notes

2025 CORPORATE PARTNERS

PLATINUM

AbbVie
Daiichi Sankyo
Gilead Sciences
Medtronic
Menarini Silicon Biosystems
Nevro Corporation
Pfizer Biopharmaceuticals Group
Takeda Pharmaceuticals
Verrica Pharmaceuticals

GOLD

Aveo Oncology
Bristol Myers Squibb
Boston Scientific Corporation
BridgeBio
C2N Diagnostics
CVRx
DJO / Enovis
Ferring Pharmaceuticals, Inc.
Foundation Medicine
GE Healthcare
Genentech
Jazz Pharmaceuticals
Lantheus Medical Imaging
Lucid Diagnostics
Mitsubishi Tanabe Pharma America
Pharmacosmos
Recor Medical
Sumitomo Pharma America, Inc
Theranica
ViiV Healthcare

SILVER

Ambry Genetics
BillionToOne
Biodesix
CareDx
CorMedix, Inc.
Currax Pharmaceuticals, Inc.
Exagen, Inc.
EyePoint Pharmaceuticals
HepQuant
Intercept Pharmaceuticals, Inc.
Koya Medical, Inc.
LivaNova
Lynx DX
Mindera Health
Myriad Genetic Laboratories
Nalu Medical
Ocular Therapeutix
Otsuka America Pharmaceuticals
Pacira Pharmaceuticals
Podimetrics, Inc.
Pyros Pharmaceuticals, Inc.
Sobi – North America
SPR Therapeutics
Syndax Pharmaceuticals, Inc.
Veracyte

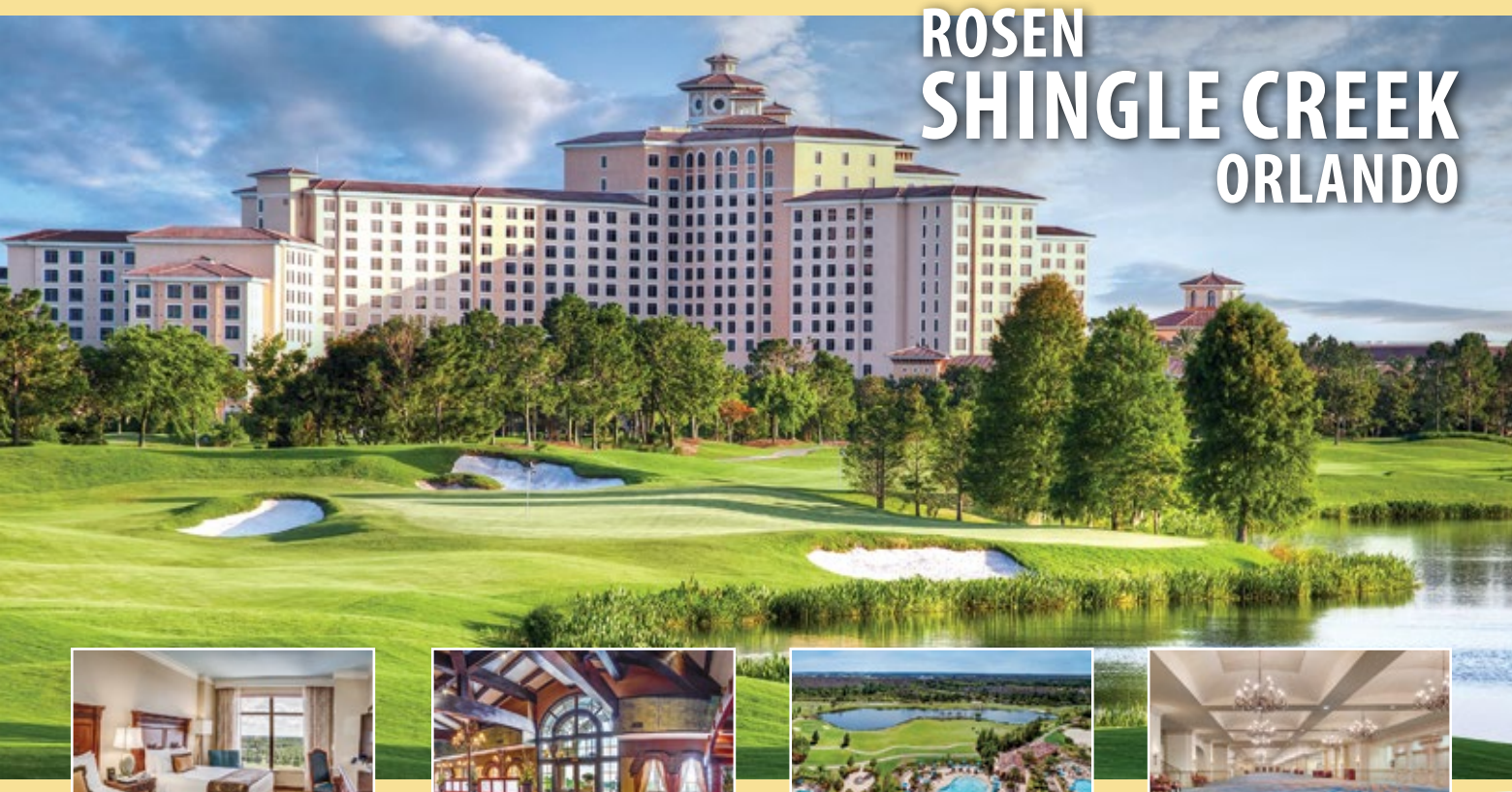
NAMCP
MEDICAL DIRECTORS INSTITUTE

For more information about Corporate Partnership with NAMCP, please call 804-527-1905.

MEDICAL DIRECTORS, PHYSICIANS, NURSES, ADMINISTRATORS, AND OTHER HEALTHCARE PROFESSIONALS

2025 SPRING MANAGED CARE FORUM

APRIL 24-25 | ROSEN SHINGLE CREEK | ORLANDO



photos by Rosen Shingle Creek®

POPULATION HEALTH MANAGEMENT, BUSINESS, ONCOLOGY AND GENOMICS, BIOTECH AND EMERGING MEDICAL TECHNOLOGIES TRACKS

CME/CEU/NCPD CREDITS AVAILABLE

PRESENTED BY:

NAMCP
WHERE MEDICAL DIRECTORS TRANSFORM KNOWLEDGE INTO IMPROVED OUTCOMES

AAIHDS

AAMCN
American Association of Managed Care Nurses

Contact Jeremy Williams at jwilliams@namcp.org for more information.