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Best Practices in the Treatment and Management of Ovarian Cancer: Expert Managed Care Strategies on the Evolving Role of PARP Inhibitors

Assessing the Expanding Roles of Optimal Therapies and Technology in Pulmonary Arterial Hypertension Management

Patient Focused Treatment Decisions in the Management of Endometrial Cancer: Managed Care Insights on the Evolving Role of Immunotherapy

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Best Practices in the Treatment and Management of Ovarian Cancer: Expert Managed Care Strategies on the Evolving Role of PARP Inhibitors

Shannon N. Westin, MD, MPH

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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 introduction of PARP inhibitors has significantly changed the management of advanced ovarian cancer. These agents improve progression-free (PFS) survival when used as maintenance therapy after first-line platinum-based chemotherapy. The most benefit is for those who have genetic mutations that make the tumor more susceptible to PARP inhibition.

Key Points

- Disparities exist in genetic testing and treatment that have a clear impact on clinical outcomes.
- PARP inhibitors improve PFS in first-line maintenance.
- Adverse events are common but generally manageable.
- Patient counseling is key to maintaining therapy.

OVARIAN CANCER ACCOUNTS FOR 1 PERCENT of all cancers and is the second most common gynecologic cancer but it is the deadliest. In 2025, an estimated 20,890 cases of ovarian cancer will be diagnosed in the United States (U.S.) and 12,730 women will die from this cancer.[1] The rate of ovarian cancer has been declining in the U.S. since 1975 and part of this decline can be attributed to the use of oral contraceptives which reduce risk. Deaths from ovarian cancer have been slowly declining since 2003 and newer therapies are contributing to this decline. Five-year survival is now 51.6 percent (2015 to 2021 data).

Ovarian cancer is a subtle killer because its symptoms are very nonspecific including bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary urgency or frequency. Greater than 90 percent of women with ovarian cancer have these symptoms but they may be attributed to something else. In many cases, symptoms have been happening for years prior to diagnosis. Even at the early disease stages when cure rates are high, symptoms are occurring in 90 to 95 percent of women. Importantly, 55 percent of ovarian cancer cases are not detected until the disease has already metastasized.[1]

Exhibit 1 shows the typical course of a patient with advanced ovarian cancer. Surgery plus platinum-based chemotherapy is the first-line treatment in those with Stage III or IV disease which are the majority of cases at diagnosis. Other therapies to reduce risk of recurrence including the poly(adenosine

Exhibit 1: Typical Course of Advanced Ovarian Cancer

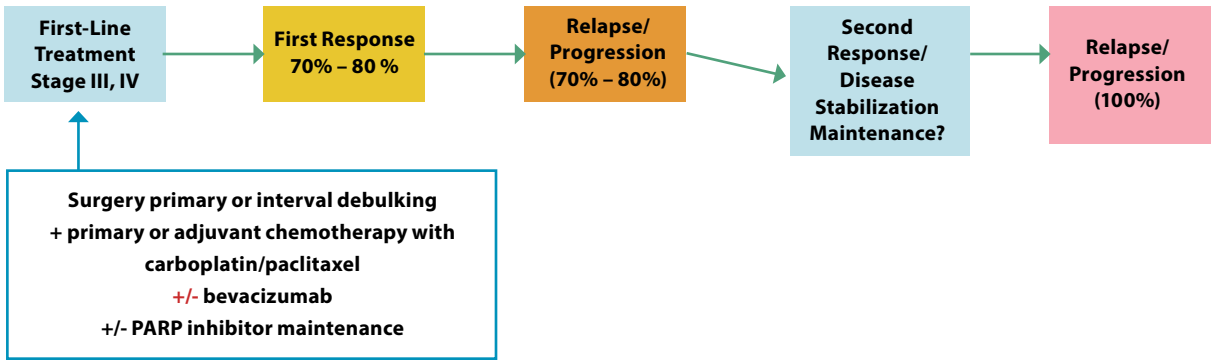
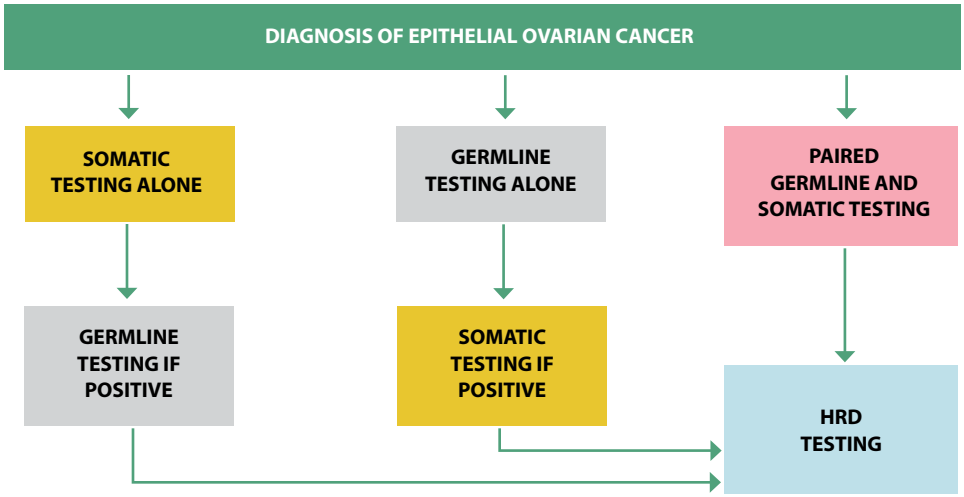


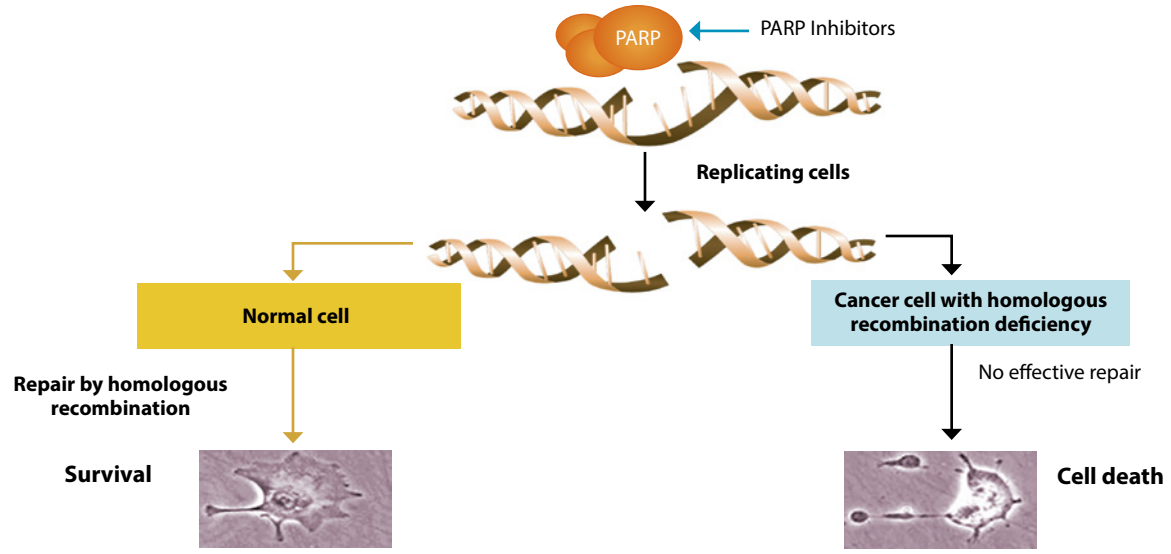
Exhibit 2: New Testing Paradigm for Ovarian Cancer



diphosphate [ADP]-ribose) polymerase (PARP) inhibitors and bevacizumab may be added on to first-line treatment. Generally, 70 to 80 percent of patients respond to first-line therapy and many will have no evidence of disease. Conversely, 20 to 30 percent will have primary resistance. Of those who respond to primary therapy, most will have a disease relapse and undergo multiple lines of therapy. In later lines of therapy, the selection of therapy will depend on many factors including whether the disease is still sensitive to platinum-based chemotherapy. Platinum-resistant disease is progression of disease less than six months after completion of platinum-based chemotherapy and has a poor prognosis.

Germline and somatic genomic testing have been incorporated into treatment selection. The National Comprehensive Cancer Network (NCCN), Society of Gynecology Oncology, and the American Society of Clinical Oncology all recommend germline testing of all women with ovarian cancer. The genomic panel will include breast cancer (BRCA) gene and homologous DNA repair deficiency (HRD) testing which both impact risk for cancer and indicate likely benefit from PARP inhibitors. Exhibit 2 outlines the testing paradigm for a woman newly diagnosed. There are pros and cons to each approach. With somatic testing alone, about 5 percent of patients with germline abnormalities are missed. Many clinicians either choose germline testing and then somatic if germline is positive or perform both upfront. With somatic testing, HRD testing can also be done.

Exhibit 3: PARP and Homologous Recombination Repair



From a managed care standpoint, it is important that people are genetically tested and then referred to genetic counseling which can identify other family members who should be tested. In one study, only 30 percent of patients completed recommended testing.[2] There are opportunities to improve testing rates because therapies may be being used in those who would not benefit or patients are not receiving a therapy which could improve their outcomes.

Another opportunity for managed care to improve outcomes is by referring patients with ovarian cancer to specialized and high-volume treatment centers which are associated with better survival outcomes.[3] With ovarian cancer, Black race is an independent predictor of mortality. The impact of race on mortality is mitigated, albeit not eliminated, in high-volume treatment centers.[4] In a study using the Surveillance, Epidemiology, and End Results–Medicare database, there was longer time from presentation to diagnosis in Hispanic women and non-Hispanic Black women with a lower likelihood of survival at five years after adjustment for time to diagnosis and treatment among non-Hispanic Black women (hazard ratio [HR] 1.15) compared with non-Hispanic White women.[5] Gynecologic oncology utilization was associated with improved overall ($p < 0.001$) and cancer specific ($p < 0.001$) survival despite a longer time from presentation to treatment ($p < 0.001$).[5]

Hospitalizations have an impact on overall cost of care in ovarian cancer. Factors associated with high-cost (defined as $55,447) hospitalizations in the elderly (defined as greater than 65 years) include open or extended procedures and non-elective admission.[6] Another study found a reduction in mean cost of hospitalization for cytoreductive surgery between 2010 and 2018, primarily because of decreased length of stay.[7] Most centers have instituted programs to promote earlier discharge. Surgical complexity, radical upper abdominal surgery, and postoperative complications are factors leading to increased costs.

Chemotherapy adverse events can also lead to hospitalizations and increased overall costs of care. One study found that 40 percent of those receiving outpatient chemotherapy had unplanned hospital admissions.[8] There was a significant difference in disease-free ($p = 0.01$) and overall survival ($p = 0.004$) for patients with unplanned admission after chemotherapy as compared to those without admission. There are patient populations at higher risk of unplanned admission who could use early intervention to prevent hospitalizations.

Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors are one of the revolutionary advances in ovarian cancer treatment. DNA single-strand breaks (SSBs) occur all the time in cells and PARP detects and repairs them. During the replication process unrepaired SSBs are converted into double-strand breaks (DSBs). These DSBs are repaired by homologous repair pathways. Exhibit 3 shows how PARP inhibitors contribute to cell death in cells with homologous repair deficiency (HRD). Loss-of-function genes involved in the HRD

Exhibit 4: PARP Inhibitor Maintenance Indications

Agent	Dose	Maintenance Indication
Olaparib	300 mg BID (2 x 150mg capsules)	*BRCA* mutated ovarian cancer after response to upfront treatment. HRD ovarian cancer after response to upfront treatment in combination with bevacizumab. Platinum-sensitive ovarian cancer after response to platinum-based treatment.
Rucaparib	600 mg BID (2 x 300mg tablets)	Platinum-sensitive *BRCA* mutated ovarian cancer after response to platinum-based treatment.
Niraparib	300 mg QD (3 x 100mg capsules)	Advanced ovarian cancer after response to upfront treatment. Platinum-sensitive *BRCA* mutated ovarian cancer after response to platinum-based treatment.

pathway can sensitize tumors to PARP inhibitors and platinum-based chemotherapy. HRD can be identified in different ways – the FDA-approved ways for use of PARP inhibitors in ovarian cancer are the use of polymerase chain reaction (PCR) or next generation sequencing for germline and somatic BRCA 1/2 gene mutations and next generation sequencing for both BRCA mutations and germline loss of heterozygosity (gLOH), a measure of HRD. [9]

Starting in 2014, PARP inhibitors (olaparib, niraparib, rucaparib) were FDA-approved for second-line or later treatment but these agents are no longer approved for this indication. Additional data after approval suggested they may increase risk of death so the indication was withdrawn.[10]

Maintenance therapy for two years after front-line chemotherapy has become the standard use of PARP inhibitors in ovarian cancer (Exhibit 4). Multiple trials have shown first-line maintenance provides the most benefit from PARP inhibitors with the best benefit seen in those patients with BRCA mutations. Benefit is also seen in those with HRD; there is a small benefit in those without HRD or BRCA mutations. Olaparib maintenance after complete or partial response to first-line chemotherapy in BRCA mutation positive patients led to a 70 percent reduction in risk of progression and the benefits continued even after patients stopped taking two years of maintenance.[11] At seven-year follow-up, the hazard ratio for OS was 0.55 (p = .0004) which was not statistically significant.[12] At seven years, 67.0 percent of olaparib patients versus 46.5 percent of placebo patients were alive, and 45.3 percent versus 20.6 percent respectively, were alive and had not received a subsequent treatment. Most clinicians consider about 50 percent of women who receive PARP inhibitor maintenance, cured.

Olaparib has also been studied in combination with bevacizumab after first-line surgery and platinum-based chemotherapy. Bevacizumab maintenance alone is also used to improve PFS. The combination provided the most benefit in those with HRD or BRCA mutation.[13] After a median follow-up of 22.9 months, the median PFS was 22.1 months with olaparib plus bevacizumab and 16.6 months with placebo plus bevacizumab (hazard ratio for disease progression or death, 0.59; $p < 0.001$). The hazard ratio (olaparib group versus placebo group) for disease progression or death was 0.33 in patients with tumors positive for HRD, including tumors that had BRCA mutations (median PFS, 37.2 versus 17.7 months), and 0.43 in patients with HRD-positive tumors that did not have BRCA mutations (median PFS, 28.1 versus 16.6 months). After a median follow-up of five years in the olaparib and placebo arms, respectively, OS was 73.2 percent versus 53.8 percent in the HRD/BRCA mutation group, 54.7 percent, and 44.2 percent in the HRD/No BRCA mutation

group, and 32.3 percent and 25.7 percent in the HR-proficient group.[14]

In a high risk for recurrence population, niraparib provided a clinically significant benefit in the HR-proficient subgroup with a 32 percent risk reduction in progression or death in addition to significant benefit in HRD subgroups.[15] The population in this trial either had Stage IV disease at diagnosis or residual disease after surgery which are both negative prognostic factors. At the six-year follow-up, in the overall population, the OS hazard ratio was 1.01 (p = 0.8834) for niraparib versus placebo.[16] In the HRD and HR-proficient populations, the OS hazard ratios were 0.95 and 0.93, respectively. Subsequent PARP inhibitor therapy was received by 11.7 percent and 15.8 percent of niraparib patients and 37.8 percent and 48.4 percent of placebo patients in the overall and HRD populations, respectively, which could impact the long-term survival results.

Rucaparib has also been compared to placebo for maintenance in an all-comers trial. Median PFS was 28.7 months with rucaparib versus 11.3 months with placebo in the HRD population (p = .0004) and 12.1 months versus 9.1 months in the HR-proficient population.[17]

Although the benefit of PARP inhibitor in HR-proficient populations is small, clinicians are hesitant not to institute maintenance because the recurrence rate for ovarian cancer is so high (70% or more). The choice is bevacizumab for 15 cycles or a PARP inhibitor for two years which requires a conversation between the clinician and patient about pros and cons of each.

Overall, the PFS benefit from PARP inhibitor maintenance is similar across all the agents. In the National Comprehensive Cancer Network (NCCN) Guidelines, the selection of agent will depend on whether bevacizumab was used, HRD/BRCA mutation status, and adverse event profiles.[18] For example, if no bevacizumab is used during primary therapy, a germline or somatic BRCA mutation is present, and the patient had a complete or partial response to chemotherapy, olaparib and niraparib are Category 1 recommended agents for maintenance. Rucaparib is a Category 2B recommendation. Additionally, PARP inhibitors are approved for second-line maintenance in the BRCA/HRD population with platinum-sensitive disease but the populations in the trials supporting this use had not been given a PARP inhibitor in the first-line setting. As with the treatment trials, there appears to be an increase in deaths in those who receive second-line or later maintenance with a PARP inhibitor but who do not have BRCA mutation or HRD.

Given comparable efficacy of the three agents available for ovarian cancer treatment, other characteristics will also inform choice including toxicities, drug on drug interactions, dosing schedule, pricing, insurance coverage, and special clinical situations (e.g., treatment of central nervous system disease). Niraparib crosses the blood brain barrier so it would be used in patients with brain metastases. Rucaparib and olaparib have more drug on drug interactions than niraparib.

Even though PARP inhibitors are "just a pill," there are adverse events and toxicities. Most toxicities are manageable. Nausea, vomiting, and other gastrointestinal adverse events are fairly common. Emetogenic potential for these agents is moderate-high risk (30% or more frequency of emesis). Antiemetic prophylaxis is recommended with an oral 5-HT3 antagonist (i.e., granisetron, ondansetron, or dolasetron). Patients can also be educated to eat smaller meals throughout the day and eat foods that are easy on the stomach. Fatigue can also occur and has a major impact on quality of life.

Adverse event monitoring should occur at least once a month during the first few cycles of therapy especially for anemia, thrombocytopenia, and neutropenia. Myelodysplastic syndrome or acute myeloid leukemia can occur with these agents but the incidence is low (0.5 – 1.4% of patients). Hematologic adverse events can be managed with dose reductions and medication interruptions. Other adverse events which may favor one agent over another are hypertension, elevated liver function tests, and elevated creatinine. Hypertension is more common with niraparib, elevated liver functions tests only occur with rucaparib, and olaparib can cause elevations in creatinine.

It is important to manage expectations of patients and caregivers to alleviate key symptoms so that therapy can continue uninterrupted. To maximize patient outcomes, it is important to prospectively anticipate adverse events and toxicities, utilize multidisciplinary resources for education and monitoring, maintain frequent contact with patients, and provide supportive measures prior to onset of toxicity.

Conclusion

Disparities exist in genetic testing and treatment that have a clear impact on clinical outcomes. Data support important clinical efficacy of PARP inhibitors in ovarian cancer in maintenance settings and first-line use is better. Adverse events are common but generally manageable. Patient counseling is key to maintaining therapy. Incorporating multidisciplinary staff into education can help keep patients on therapy.

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Assessing the Expanding Roles of Optimal Therapies and Technology in Pulmonary Arterial Hypertension Management

Richard N. Channick, MD

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

Summary

Patient prognosis with pulmonary arterial hypertension (PAH) has progressively improved in the current treatment era in which multiple medications are available. Median survival has significantly increased but PAH remains a fatal disease only curable by double lung transplant.

Key Points

- Proper treatment for PAH includes a thorough assessment of disease severity.
- Risk assessment tools should be used at baseline and at each follow-up visit.
- A pro-active approach to treatment modulation is important to maximize outcomes.
- In depth evaluation of right ventricle (RV) function should be done regularly.
- Treatment tolerability needs to be accessed at each visit.
- Active engagement of the patient in treatment decisions and collaboration with other specialties and PAH centers is important.

PULMONARY HYPERTENSION (PH) IS elevated pressure in the pulmonary vasculature. Different components can lead to PH including high pulmonary vascular resistance (PVR) due to loss of a cross-sectional area of vasculature or precapillary pulmonary hypertension, high cardiac output from hyperdynamic states, and high wedge pressure due to post-capillary PH. The five different clinical classification categories of PH are shown in Exhibit 1.[1]

PAH is a rare disease resulting in restricted blood flow through the pulmonary arterial circulation resulting in increased PVR which causes increased workload of the right ventricle and right heart failure and death. The hemodynamic definitions of PAH are mean pulmonary artery pressure (mPAP) of 20 mmHg or more, pulmonary artery wedge pressure (PAWP) of 15 mmHg or less, and PVR more than 2 Wood units.[1] The only way to diagnose PAH is through right heart catheterization.

PAH can be caused by various medications and substances. Stimulant use including amphetamine, methamphetamine, and cocaine is associated with development of PAH. About 30 percent of patients with PAH in one survey had methamphetamine use histories.[2] Dasatinib, a kinase inhibitor used to treat specific types of leukemia, is also associated with PAH.[3]

PAH remains challenging to diagnose and requires comprehensive assessment, including right heart catheterization. The symptoms are nonspecific and include shortness of breath, fatigue, and chest pain. Unfortunately, it can take up to three years for a patient to receive a diagnosis of PAH. Prompt and accurate diagnosis is key to instituting timely and appropriate therapy to improve symptoms and prognosis. Many PAH specialists see patients referred to them who have not had an adequate workup and are started on PAH therapies but really have some other reason for PH.

Exhibit 1: Clinical Classification of Pulmonary Hypertension[1]

1. Pulmonary Arterial Hypertension (PAH)

- 1.1 Idiopathic PAH (IPAH)
- 1.2 Heritable PAH
  - 1.2.1 BMPR2
  - 1.2.2 Unknown
- 1.3 Associated with drugs and toxins
- 1.4 Associated PAH
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
- 1.6 Persistent pulmonary hypertension of the newborn (PPHN)

2. PH associated with left heart disease

- 2.1 Heart failure
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction
  - 2.1.3 cardiomyopathies with specific aetiologies
- 2.2 Valvular heart disease
  - 2.2.1 aortic valve disease
  - 2.2.2 mitral valve disease
  - 2.2.3 mixed valvular disease
- 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH associated with lung disease and/or hypoxia

- 3.1 COPD and/or emphysema
- 3.2 Interstitial lung disease
- 3.3 Combined pulmonary fibrosis and emphysema
- 3.4 Other parenchymal lung diseases
- 3.5 Nonparenchymal restrictive disease
  - 3.5.1 hypoventilation syndromes
  - 3.5.2 pneumonectomy
- 3.6 Hypoxia without lung disease (e.g. high altitude)
- 3.7 Developmental lung disease

4. PH associated with pulmonary artery obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5. PH with unclear or multifactorial mechanisms

- 5.1 Hematologic disorders
- 5.2 Systemic disorders; sarcoidosis; pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1
- 5.3 Metabolic disorders
- 5.4 Chronic renal failure with or without hemodialysis
- 5.5 Pulmonary tumor thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis
- 5.7 Complex congenital heart disease

In the past there was little that could be done for a patient with PAH but now there are numerous FDA-approved therapies. Despite advances in treatment, PAH is still a fatal disease. From a United States registry using modern treatment era data (2015 to 2020 enrollment), the one- , two- , and three-year mortality was 8 percent, 16 percent and 21 percent, respectively.[4] When stratified into low-, intermediate-, and high-risk PAH, the mortality at one, two, and three years was 1 percent, 4 to 6 percent, and 7 to 11 percent for low risk; 7 to 8 percent, 11 to 16 percent, and 18 to 20 percent for intermediate risk; and 12 to 19 percent, 22 to 38 percent, and 28 to 55 percent for high risk, respectively. Historical survival was 2.5 years from diagnosis. Five-year survival is now about 70 percent of patients.[5]

Risk stratification plays an essential role in prediction of prognosis and the management of patients with PAH. A four-stratum risk assessment model based on functional class, six-minute walk distance, B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide (BNP/NT-proBNP) levels, and hemodynamic measures is used to classify patients as low, intermediate-low, intermediate-high,

Exhibit 2: PAH Treatments

Oral Therapy				Subcutaneous Injection	Inhaled Therapy	Continuous Parenteral Therapy
Endothelin	**Nitric Oxide**		**Prostacyclin**	**Activin**	**Prostacyclin**	
ERA	**PDE-5 Inhibitors**	**sGC Stimulator**				
Ambrisentan	Sildenafil	Riociguat	Treprostinil	Activin inhibitor Sotatercept	Iloprost	Epoprostenol
Bosentan	Tadalafil		Selexipag		Treprostinil	RTS-Epoprostenol
Macitentan						Treprostinil (SC or IV)

ERA = Endothelin receptor antagonist; PDE-5 = phosphodiesterase; sGC = Soluble guanylate cyclase; RTS = room temperature stable; SC = subcutaneous; IV = intravenous
A combination tadalafil and macitentan product was FDA-approved in 2024

and high risk of death at baseline.[6] Risk stratification is also done after therapy is started and frequently thereafter to improve prognosis and outcomes. The goal of therapy is to get the patient to a low-risk status and maintain that status. Because PAH is typically a progressive disease, repeated risk stratification is necessary to ensure appropriate therapy is given over time.

Treatment development in PAH treatment is a wonderful example of translational research. Learning about the cellular pathophysiology of PAH has led directly to development of targeted therapies. Treatment for PAH currently targets four pathways that are disrupted leading to increased vascular tone (endothelin, nitric oxide, prostacyclin) and increased vascular proliferation (activin). Treatment targeting the activin pathway is a new option. Exhibit 2 shows the available medications by pathway and administration route. Therapy is chosen based on risk for death using risk assessment tools, right ventricle function on imaging, hemodynamics, natriuretic biomarkers, route of administration, comorbidities, and patient factors such as age, quality of life, and support system.

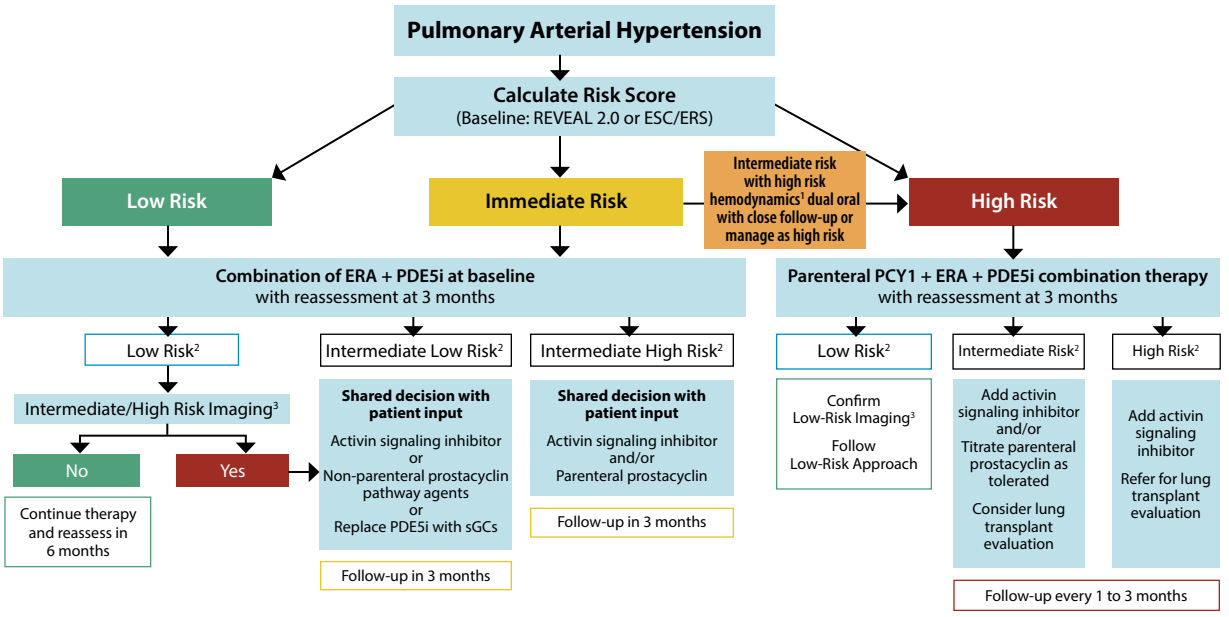
Unfortunately, many patients do not achieve low-risk status on treatment. One trial found that greater than 50 percent of patients were intermediate risk at follow-up after starting therapy.[7] Trials have shown that achieving and maintaining low-risk status significantly improves survival.[8] One major way to improve outcomes in this population is to increase or add medications according to the treatment guidelines to lower a given patient's risk.

The prostacyclin pathway agents have been shown to improve six-minute walk time, symptoms, biomarkers, and in the case of epoprostenol and selexipag, survival and time to first morbidity or mortality event, respectively. Selexipag and one formulation of treprostinil are oral agents. The others must be given by continuous parenteral infusion or inhalation, which can be difficult for the patient to manage and with which to be adherent. Selected adverse events of this class include flushing, headache, dizziness, and syncope. Carefully titrating the dose of prostacyclin agents can make these agents more tolerable.

The nitric oxide pathway agents provide benefits on six-minute walk time, symptoms, hemodynamics, and delay of clinical worsening. Selected adverse events include nosebleeds, headache, dyspepsia, flushing, diarrhea, and visual changes. Phosphodiesterase (PDE) inhibitors sildenafil and tadalafil are contraindicated with use of nitrates. Riociguat, a soluble guanylate cyclase (sGC) stimulator, is contraindicated in pregnancy, with use of nitrates or nitric oxide donors in any form, or with use of sildenafil or tadalafil.

The endothelin receptor antagonists (ERA) have also been shown to improve six-minute walk time, symptoms, and delay clinical worsening or disease progression. Nasal congestion, edema that may require diuretic adjustment, and anemia are common

Exhibit 3: Proposed PAH Treatment Algorithm[13]



1. High risk hemodynamics as defined in the ESC/ERS guidelines.
2. Follow-up risk assessment: Reveal 2.0 Lite or ESC/ERS 4-strata.
3. Imaging risk: Suggest referring to the risk table in the 2022 ESC/ERS guidelines. In patients with intermediate and high-risk imaging parameters should be considered for further escalation of therapy.

**Among patients not able to tolerate therapies as indicated above alternative approaches can be adopted as an individual approach.*

Parenteral PCY (prostacyclin) refers to both intravenous and subcutaneous delivery.

adverse events. Bosentan can cause abnormal hepatic function so liver function tests must be monitored. This class of agents is teratogenic. Women must use dual contraceptive methods (hormonal plus barrier).

Sotatercept is an activin signaling inhibitor which acts as a ligand trap for members of the transforming growth factor β (TGF-β) superfamily, thus restoring balance between the growth-promoting activin growth differentiation factor pathway and the growth-inhibiting bone morphogenetic protein (BMP) pathway.[9] It is an antiproliferative agent. In a Phase III trial, adults with PAH who were receiving stable background therapy randomly received subcutaneous sotatercept or placebo every three weeks for 24 weeks.[10] The patients in this trial had long standing PAH (approximately 10 years) and 60 percent were on three classes of therapies. Sotatercept resulted in a greater improvement in exercise capacity, as measured by six-minute walk distance, than placebo (median change from baseline at week 24, 34.4 meters versus 1.0 meter). Among high-risk adults with PAH who were receiving the maximum tolerated dose of background therapy, addition of sotatercept resulted in a lower risk of a composite of death from any cause, lung transplantation, or hospitalization (24 hours and more) for worsening PAH than placebo (17.4% sotatercept group versus 54.7% in placebo group, $p < 0.001$).[11] Adverse events with sotatercept included epistaxis, dizziness, telangiectasia, increased hemoglobin levels, thrombocytopenia, and increased blood pressure. Hemoglobin and platelet monitoring is needed and dual contraception methods for women are required. This therapy works on the pathogenesis of the disease unlike the already approved therapies that work downstream to minimize the impact of PAH-related changes in the lung vasculature. Starting an agent that targets pathogenesis of PAH may be able to prevent heart failure and the need for complicated parenteral therapies and lung transplant. Additional antiproliferative therapies are under investigation.

The PAH treatment guidelines recommend initial dual therapy with ERA and PDE for those at low or intermediate risk and triple therapy (ERA/PDE plus subcutaneous or intravenous prostacyclin) for those with high-risk disease with risk reassessment at three months.[1] The newly approved single tablet daily combination of macitentan and tadalafil may help improve patient adherence with initial combination therapy.[12] This product is available as macitentan 10 mg and tadalafil 20 mg or macitentan 10 mg and tadalafil 40 mg.

Exhibit 3 shows a proposed treatment algorithm which incorporates the use of the new activin inhibitor.[13] It also incorporates the use of cardiac imaging to move patients among risk categories. In addition to frequent monitoring to assess patient improvement/risk status, adverse events and medication tolerability should be monitored at each visit. Managing adverse events is another way to improve patient adherence with therapy.

The awareness of the importance of RV function in PAH has increased considerably since right heart failure is the predominant cause of death in PAH patients.[14] Given its wide availability and reduced cost, echocardiography is of paramount importance in the evaluation of the right heart in PAH during therapy instead of repeating right heart catheterization. The most commonly used echocardiography indices in PAH patients are right atrial area, tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (RV FAC), eccentricity index, and RV longitudinal systolic strain (RV LSS). RV function can be used to move patients to more aggressive treatment.

Other therapeutic interventions for PAH include supervised exercise programs, supplemental oxygen, and diuretics. Depression can be an issue in those with PAH so periodic assessment and treatment if necessary are important. Double lung transplant is curative for PAH.

Enrollment in clinical trials should also be encouraged.

Conclusion

Proper treatment for PAH includes a thorough assessment of disease severity. Risk assessment tools should be used at baseline and at each follow-up visit. A pro-active approach to treatment modulation (initiation, escalation, switches, additions) is important to maximize outcomes. In depth evaluation of RV function should be done regularly. Treatment tolerability also needs to be accessed at each visit. Patients should be actively engaged in treatment decisions. Because this is a rare disease, collaboration with other specialties and PAH centers is important.

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Patient Focused Treatment Decisions in the Management of Endometrial Cancer: Managed Care Insights on the Evolving Role of Immunotherapy

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Summary

Similar to many other cancers, immunotherapy is transforming the endometrial cancer treatment landscape. The first-line treatment strategy for advanced or recurrent disease has changed to incorporate immunotherapy rather than waiting until second-line or later treatment.

Key Points

- Immunotherapy in combination with standard first-line chemotherapy is the standard of care for advanced or recurrent disease.
- This combination has demonstrated significant improvement in PFS, particularly in dMMR patient population.
- A survival benefit has been shown in the dMMR population with dostarlimab.

IN THE UNITED STATES (U.S.), ENDOMETRIAL cancer is, overall, the fourth most common cancer for women and the most common gynecologic cancer. The incidence of endometrial cancer has been increasing by more than 1 percent per year since the mid-2000s; the rate increased by 0.6 percent per year in White women and 2 to 3 percent per year in women of all other racial and ethnic groups[1] The American Cancer Society estimates about 69,120 new cases of cancer of the uterus will be diagnosed in 2025 and 13,860 women will die from this cancer.[1] Excess weight is a major risk factor with each increase in body mass index of 5 kg/m^2 significantly increasing a woman's risk of endometrial cancer.[2,3] Thus, the U.S. obesity epidemic is the major cause of endometrial cancer case increases.

Endometrial cancers have traditionally been divided into less aggressive estrogen-dependent type I and the less common, clinically aggressive, estrogen-independent type II. Type II cancers are rarer histologic subtypes, such as serous, clear cell, carcinosarcoma and undifferentiated/ dedifferentiated. No matter what stage at diagnosis, type I survival rates are better because type II cancers account for a disproportionate amount of endometrial cancer mortality (75%).[4]

In addition to survival differences based on type, there are racial/ethnic differences in survival regardless of initial stage at presentation. Black women have poorer survival at every stage of diagnosis, regardless of histologic subtype compared with non-Hispanic white women.

The percentage differences in survival range from 6 percent risk difference for local-stage low-grade endometrioid cancers to 59 percent lower survival for distant-stage clear-cell cancers.[5] There are also differences in stage at diagnosis, guideline concordant care, and surgical treatment based on race. With the *status quo*, 39.1 percent of black

Exhibit 1: Clinical implications of Molecular Testing

Molecular Classification's Roles	
Prognostic Factor	Estimate PFS and OS according to molecular class
Risk Assessment	More objective attribution to a specific risk class
Predictive Factor	Identification of patients who may be more sensitive to different treatment options
Genetic Screening	Identification of patients with gene mutations which increase risk of other cancers (i.e., Lynch syndrome) prompting familial testing

compared to 19.8 percent of white women die within five-years, a 19.3 percent absolute difference.[6] Equalizing surgery rates would decrease the absolute difference in survival to 17.7 percent and equal stage at diagnosis would lower the difference to 12.9 percent. When both stage at diagnosis and rates of surgery are equal for Black and White women, the absolute difference in five-year survival between races would be 11.6 percent.

How clinicians address post-menopausal bleeding, a common symptom of endometrial cancer, could be one reason for differences in care. Transvaginal ultrasound to measure the thickness of the endometrium is a common starting point but the use of transvaginal ultrasound can lead to missed cases in those with fibroids. Fibroids, which are more common in Black women, can distort the quality of ultrasound images. Black women more often have high-risk cancer types that may cause less thickening of the endometrium than low-risk types. Transvaginal ultrasound can miss as many as 50 percent of cases in Black women and result in an eight-fold higher frequency of false negative results than reported for the general population.[7] Additionally, Black women have a higher risk for non-guideline adherent work-up.[8]

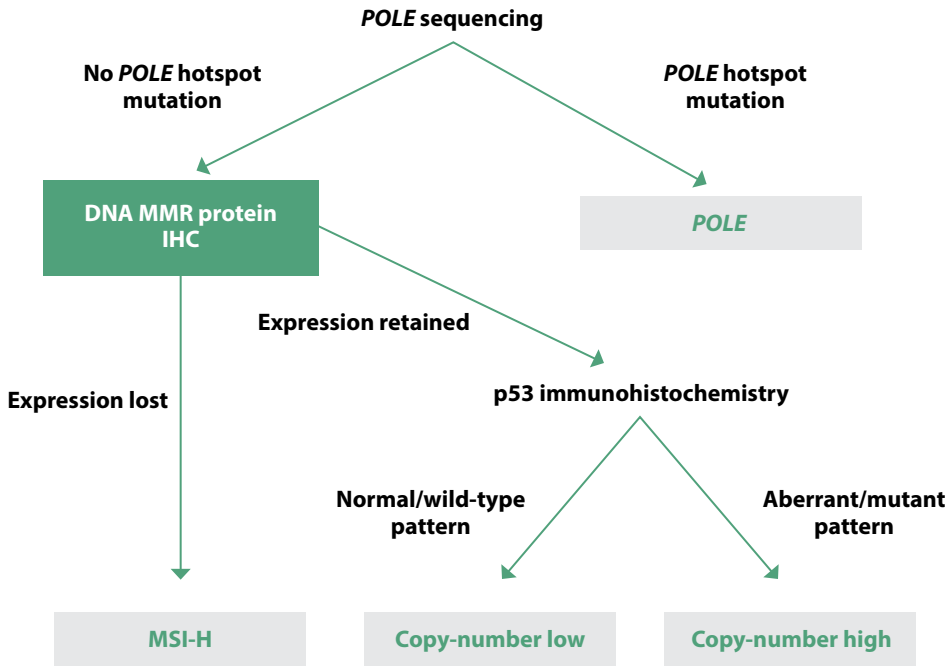
There are many barriers to a timely diagnosis of endometrial cancer in women seeking an answer for post-menopausal bleeding. Beyond failure of providing guideline directed diagnosis and relying too much on ultrasound, poor provider communication, misattribution of symptoms to another gynecologic or non-gynecologic disease, insurance/financial issues, and healthcare structural issues are all common barriers. Clinicians and managed care need to work together to overcome these barriers.

Treatment modalities for endometrial cancer include surgery, chemotherapy, hormone therapy, radiation, and targeted therapy. Most women will require surgical treatment when diagnosed. Adjuvant systemic therapy is used after surgical therapy in Stage II – IV disease. Until recently, the standard systemic therapy regimen has been carboplatin and paclitaxel chemotherapy. In those with uterine serous carcinomas which overexpress HER2, trastuzumab has been added to the chemotherapy regimen.

As with many other cancers, it is now recognized that there are four clinically significant molecular subgroups with different clinical prognoses:

- polymerase-epsilon (POLE) mutated
- microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) high
- copy-number low
- copy-number high.[9]

Exhibit 2: NCCN Guidelines® Biomarker Testing Recommendations for Endometrial Carcinoma[11]



Tumors which are POLE or MSI-H/dMMR are ultra-mutated and hyper-mutated, respectively. POLE occurs in about 4 percent of cases and results in the lowest mortality rate of the four subtypes. MSI-H/dMMR occurs in about 40 percent of cases. Those with this subtype have a higher rate of distant recurrence and lower relapse-free survival compared to those with proficient MMR (pMMR).[10] Copy-number high is P53 aberrant endometrial cancer, which is mostly serous histology, accounts for 19 percent of high-grade endometrioid carcinomas, and results in the highest mortality. Endometrial cancer without POLE mutations, MSI-H/dMMR, or P53 mutations is classified as a non-specific molecular profile (NSMP) subtype, accounting for approximately 50 percent of endometrial cancers. Its molecular characteristics include low-cell mutation and low-copy number variation, and its histological subtype is mostly low-grade endometrial carcinoma. These subtypes can be used for prognosis, staging, and treatment selection; additionally, molecular testing also plays a role in genetic screening (Exhibit 1). At a minimum, endometrial cancer specialists are testing for MSI-H/dMMR because there are treatment implications. Exhibit 2 shows the current National Comprehensive Cancer Network (NCCN) diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinoma.[11]

The International Federation of Obstetrics and Gynecology (FIGO) staging guidelines from 2023 use the presence of these subtypes for staging of patients.[12] FIGO recommends complete molecular classification in all endometrial carcinomas and as potential influencing factors of adjuvant or systemic treatment decisions. If the molecular subtype is known, this is recorded in the FIGO stage by the addition of "m" for molecular classification, and a subscript indicating the specific molecular subtype. When molecular classification reveals P53 or POLE status in Stage I and II disease, this results in upstaging or downstaging of the disease, respectively, because of the prognostic implications of the subtypes.

Treatment is moving into molecular based therapy. The MSI-H/dMMR subtype is the one area for which there are specific treatments. This subtype identifies patients with high-intermediate risk endometrioid endometrial cancer at highest risk of recurrence after primary treatment.[10] Because of the sensitivity of tumors with MSI-H/dMMR to the effects of immunotherapy due to high mutational burden, checkpoint inhibitors have been

studied in this subtype of endometrial cancer and provide progression-free survival (PFS) benefits. Pembrolizumab, dostarlimab, and durvalumab are the checkpoint inhibitors which have FDA indications for endometrial cancer.

Checkpoint immunotherapy initially transformed the management of recurrent endometrial cancer post-platinum chemotherapy. The NCCN Guidelines include biomarker directed therapy options for recurrent disease after prior platinum-based therapy including neoadjuvant and adjuvant use.[11] For tumor mutation burden high (TMB-H) and MSI-H/dMMR tumors, pembrolizumab monotherapy is an option and for MSI-H/dMMR tumors, dostarlimab monotherapy is an option.[13-15] For pMMR tumors, the combination of lenvatinib and pembrolizumab has been shown to improve PFS.[16] For patients who can still receive platinum-based chemotherapy at recurrence, pembrolizumab, dostarlimab, or durvalumab (only dMMR tumors) can be added to carboplatin/paclitaxel for Stage II-IV tumors. Pembrolizumab is not recommended for carcinosarcoma because this type of tumor was not included in the studies.

The next evolution in therapy was to use immunotherapy with first-line chemotherapy in stages where surgery was not an option. The combination of immunotherapy with chemotherapy may work synergistically by leveraging rapid tumor response, enhancing immunogenic cell death, and reducing immunosuppression in the tumor microenvironment.[17] Checkpoint immunotherapy agents can be added to carboplatin/paclitaxel for first-line chemotherapy or adjuvant therapy after surgery. In women with Stage III or IV or recurrent endometrial cancer, the addition of pembrolizumab to standard chemotherapy was beneficial in improving PFS compared to chemotherapy alone in patients with and without dMMR. In the 12-month analysis of this study, Kaplan-Meier estimates of PFS in the dMMR cohort were 74 percent in the pembrolizumab group and 38 percent in the placebo group (hazard ratio [HR] for progression or death, 0.30; $p < 0.001$).[18] In the pMMR cohort, median PFS was 13.1 months with pembrolizumab and 8.7 months with placebo (HR, 0.54; $p < 0.001$). While not as beneficial in the pMMR group, many clinicians still consider use of immunotherapy with chemotherapy and it is recommended by the NCCN Guidelines.

In a similar primary advanced or recurrent disease patient population, dostarlimab plus carboplatin/paclitaxel significantly increased PFS with a substantial benefit in the MSI-H/dMMR population compared to carboplatin/paclitaxel alone. In the MSI-H/dMMR population, estimated PFS at 24 months was 61.4 percent in the dostarlimab group and 15.7 in the placebo group (HR for progression or death, 0.28; $p < 0.001$).[19] In the overall population, PFS at 24 months was 36.1 percent in the dostarlimab group and 18.1 percent in the placebo group (HR, 0.64; $p < 0.001$). Overall survival (OS) at 24 months was 71.3 percent with dostarlimab and 56.0 percent with placebo. The OS at 24 months in the dMMR group was 83.3 percent versus 58.7 percent and in the pMMR was 67.7 percent versus 55.1 percent. Patients with carcinosarcoma were included in this trial which is why the NCCN Guidelines recommend dostarlimab in this population.[11] In this trial dostarlimab was given as maintenance therapy for up to three years after the end of chemotherapy.

Durvalumab was studied in combination with carboplatin/paclitaxel in newly diagnosed advanced or recurrent endometrial cancer. This trial included several arms; carboplatin/paclitaxel plus durvalumab placebo followed by placebo maintenance (control arm); carboplatin/paclitaxel plus durvalumab followed by maintenance durvalumab plus olaparib placebo (durvalumab arm); or carboplatin/paclitaxel plus durvalumab followed by maintenance durvalumab plus olaparib (durvalumab plus olaparib arm). Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, was included in this trial because it may improve outcomes, especially in pMMR disease. In the intention-to-treat population, a statistically significant PFS benefit was observed in the durvalumab (HR, 0.71; $p = .003$) and durvalumab plus olaparib arms (HR, 0.55; $p < .0001$) versus control.[20] Prespecified, exploratory subgroup analyses showed PFS benefit in dMMR (HR [durvalumab versus control], 0.42; HR [durvalumab plus olaparib versus control], 0.41) and pMMR subgroups (HR [durvalumab versus control], 0.77; HR [durvalumab plus olaparib versus control] 0.57); and in PD-L1-positive subgroups (HR [durvalumab versus control], 0.63; HR [durvalumab plus olaparib versus control], 0.42). Interim OS results (maturity approximately 28%) were supportive of the primary outcomes (durvalumab versus control: HR, 0.77; $p = .120$; durvalumab plus olaparib versus control: HR, 0.59; $p = .003$). In the dMMR subgroup, median PFS was not reached (NR) versus 7.0 months for durvalumab versus control, and median PFS was 31.8 versus 7.0 months for durvalumab plus olaparib versus control.

Based on these trials, the new standard of care for first-line treatment of advanced or recurrent disease is the combination of platinum-based chemotherapy and checkpoint immunotherapy. The NCCN Guidelines list the combination

of carboplatin/paclitaxel/pembrolizumab or dostarlimab or durvalumab as Category 1 preferred regimens for primary or adjuvant treatment of advanced (Stage III to IV) disease.[11] The exceptions are no pembrolizumab for carcinosarcoma and durvalumab only for dMMR tumors. The use of durvalumab only in dMMR tumors is based on the durvalumab study presented above and the FDA approval.[11] PARP inhibitor addition to the standard regimen is not currently recommended.

A study evaluating treatment patterns, healthcare resource use and healthcare costs among newly diagnosed U.S. patients with endometrial cancer found that newly diagnosed patients generally receive guideline-recommended treatment.[21] For 2016 to 2018 data, mean per-patient per-month costs per-line of therapy (LOT) were US$14,601 for pre-treatment, $6,859 for LOT1, $10,649 for LOT2, and $9,206 for LOT3 and beyond. With recent changes in the treatment guidelines recommending earlier use of immunotherapy will result in the monthly cost being higher. Treating patients more aggressively with immunotherapy/chemotherapy combinations in first-line therapy will hopefully reduce the number of patients requiring later-lines of therapy.

Conclusion

Improving outcomes, reducing disparities, and reducing costs require increasing provider awareness and patient education. Early referral and access to a gynecologic oncologist for appropriate treatment selection, surgical intervention, and surgical staging will decrease the number of patients needing more than one line of treatment. Immunotherapy should be used in combination with standard first-line chemotherapy for advanced or recurrent disease because this combination has demonstrated significant improvement in PFS, particularly in the dMMR patient population where a survival benefit was also observed with dostarlimab.

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Navigating Treatment Advances for Prostate Cancer: Integrating the Latest Evidence-Based Approaches for Optimal Health Outcomes

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Summary

The management of prostate cancer has evolved based on the biology of disease which changes over time in response to therapy. The treatment of prostate cancer is now rather complicated because of all the possible options.

Key Points

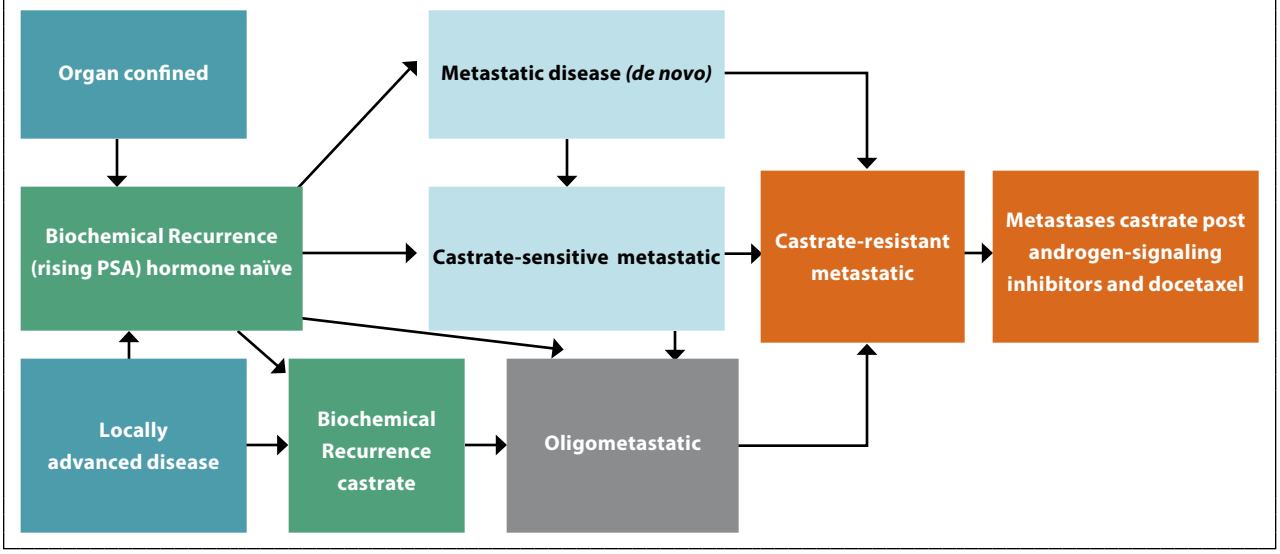
- The movement of therapies into earlier stages of disease complicates metastatic disease management.
- The impact of next generation imaging is significant and challenging given limited prospective evidence to guide disease management.
- Optimal management of patients is expertise dependent and needs to be multidisciplinary.

PRIOR TO 2000, THOSE WITH PROSTATE cancer were typically diagnosed once the disease was widespread. Common treatments were radical removal of the prostate, bilateral orchiectomy, and chemotherapy. Patients survived 12 to 18 months before becoming castration resistant and died within a year of becoming resistant. How prostate cancer is managed has evolved significantly. With more data we now know that the clinical states of prostate cancer across the spectrum of disease are different and respond to treatment differently; additionally, there is significant heterogeneity within each state (Exhibit 1).[1] The various disease states and heterogeneity in addition to the impact of various treatments on the biology of the disease and new imaging techniques which identify disease early make treatment much more complicated than in the past.

Some additional definitions are important. Prostate cancer with biochemical failure is a detectable, rising prostate specific antigen (PSA) post definitive local therapy. Non-metastatic castration-resistant prostate cancer (nmCRPC) has no evidence of metastatic disease on conventional imaging, testosterone level ≤ 50 ng/dL, and rising PSA. Metastatic castration-sensitive prostate cancer (mCSPC) is metastatic disease on imaging with a non-castrate testosterone level (> 50 ng/dL). Metastatic castration-resistant prostate cancer (mCRPC) is metastatic disease on imaging, testosterone ≤ 50 ng/dL, and rising PSA or new metastases on imaging.

Integration of more sensitive imaging has complicated the management of prostate cancer. It is important to note that all the FDA-approved medications and level one evidence from therapeutic prostate cancer trials utilized conventional CT bone scans. The newer, more sensitive imaging technique of prostate-specific membrane antigen-positron emission tomography (PSMA-PET) was only used in clinical trials to support use of lutetium Lu 177

Exhibit 1: The Clinical States of Prostate Cancer[1]



vipivotide tetraxetan, which is discussed later, in metastatic disease. PSMA can be overexpressed in metastatic prostate cancer relative to normal tissue and is present in more than 80 percent of men with metastatic disease.[2,3] PSMA-PET is FDA-approved for assessment of patients with PSA failure or high risk clinically localized disease or for determining PSMA expression status for therapy with lutetium Lu 177 vipivotide tetraxetan but it is being used in a much broader context than these approved indications. Earlier detection of PSMS positive prostate cancer metastases may not translate into benefit from earlier therapeutic intervention but may be applied irrespective of the lack of data. Earlier detection could result in "aborting" planned curative intent therapies without data. Earlier detection may result in more therapy earlier with the potential for more toxicity without benefit. Overall, we do not know if using more sensitive imaging improves overall survival. Some current clinical trials of prostate cancer treatments are combining PSMA-PET and another sensitive test (FDG-PET which identifies the 10 percent of patients with no PSMA) with conventional imaging.

Which clinician who cares for the patient is another complicator of prostate cancer treatment. Prostate cancer, especially advanced disease, is the only solid tumor managed by a village of clinicians. This includes community urologists, academic urologists, urologists in large urology group practices, medical oncologists, urologic medical oncologists, nuclear medicine specialists, and radiation oncologists. In absence of clear data supporting a specific therapy sequence, which type of clinician a patient sees will impact what treatment they receive.

Locally advanced disease is a common presentation of prostate cancer because of PSA screening programs. High-risk prostate cancer accounts for approximately 10 percent of localized disease.[4] High-risk features are PSA greater than 20 ng/ml, Gleason score of 8 to 10 (measure of tumor aggressiveness), and tumor extension beyond the prostate capsule on one or both sides or invasion into the seminal vesicles.[5] Patients with localized high-risk disease have an increased risk of biochemical recurrence (rising PSA), metastases, and death from prostate cancer. Treatment intensification which involves the addition of androgen receptor pathway inhibitors (ARPI, abiraterone, enzalutamide, apalutamide, darolutamide) to standard androgen deprivation therapy (ADT) with or without radiation therapy has been shown to improve metastases-free survival (MFS) and overall survival (OS) and is now the standard of care for nonmetastatic prostate cancer with high-risk features.[6]

About 30 percent of patients following radical prostatectomy and 30 to 50 percent of males treated with radiation therapy will experience biochemical recurrence within 10 years of definitive local therapy.[7,8] There can be a lot of anxiety related to rising PSA which may mean recurrent disease but it may not. Most men who develop biochemical recurrence do not die of prostate cancer.

The EMBARK trial studied patients who had high-risk biochemical recurrence in nmCSPC with a PSA doubling time of nine months or less.[9] Enzalutamide

Exhibit 2: Median Overall Survival Improvement with FDA-Approved Agents in mCRPC Clinical Trials[21-30]

Agent	Median OS Improvement in Months
Docetaxel	2.4
Cabazitaxel	2.4
Sipuleucel-T	4.1
Abiraterone	4.6
Enzalutamide	4.8
Radium-223	3.6
Olaparib	3.4
Rucaparib	3.8 (rPFS), 2 (OS)
Lu 177 Vipivotide	44

rPFS = radiologic progression-free survival

daily plus leuprolide every 12 weeks (combination group), placebo plus leuprolide (leuprolide-alone group), or enzalutamide (monotherapy group) were compared. At five years, MFS was 87.3 percent in the combination group, 71.4 percent in the leuprolide-alone group, and 80.0 percent in the monotherapy group. With respect to MFS, enzalutamide plus leuprolide was superior to leuprolide alone (hazard ratio for metastasis or death, 0.42; $p < 0.001$); enzalutamide monotherapy was also superior to leuprolide alone (hazard ratio for metastasis or death, 0.63; $p = 0.005$). Enzalutamide monotherapy is being used in large group urology practices in high-risk biochemical recurrence patients but not in community urology or oncology settings. The use of enzalutamide does increase cardiovascular morbidity in the older male population who have prostate cancer; clinicians must balance out the risk of prostate cancer death versus adverse impact of treatment. Clinicians do not have an effective way to identify which patients with biochemical failure and fast doubling time are more likely to do worse with their disease.

For patients with nmCRPC (based on conventional imaging) who have been treated with hormonal therapy and still have a rising PSA, the combination of ADT and ARPI has been shown to improve MFS by about 23 months.[10-12] In clinical practice most patients with nmCRPC do not get treated with this combination. With next generation imaging, many of these patients will be shown to have low volume metastatic disease which means they have mCRPC and will be treated as such.

Combining ADT with docetaxel or second-generation hormone treatment (ARPI, abiraterone, apalutamide, or enzalutamide) improves outcomes in newly diagnosed mCSPC. Triple therapy with ADT, docetaxel, and ARPI provides the longest overall median survival over ADT alone, ADT plus docetaxel, and ADT plus abiraterone.[13-18] ADT intensification (i.e., using multiple androgen targeting agents) improves survival by almost two years in high-volume mCSPC. This was paradigm shifting in managing advanced prostate cancer and is now the standard of care for newly diagnosed mCSPC. The improved survival in the mCSPC setting is significantly better than the survival effect of the many agents FDA-approved for the mCRPC setting (2.4 to 4 months). Unfortunately based on retrospective data, the use of triple therapy regimens is not being used in the community urology or oncology setting in the United States for those with mCSPC despite the evidence of improved survival.[19,20] Up to two-thirds of patients are not receiving intensification. These therapies are well tolerated but not all patients will be appropriate candidates. The main reason for low rates of triple therapy use appears to be the clinician the patient sees for care. Overall, the number one thing which could move the needle in improving care and impacting overall survival in advanced prostate cancer is applying data that already exists. Managed care can have a role in identifying clinicians who may not be using the most up-to-date regimens and educating these individuals.

Even once prostate cancer is castrate resistant, targeting the androgen receptor is still important. Treatments for mCRPC include chemotherapy (docetaxel, cabazitaxel), ARPI, radium-223 for symptomatic bone metastases, lutetium Lu 177 vipivotide tetraxetan for prostate-specific membrane antigen (PSMA)-positive metastases, immunotherapy for a small number of patients (sipuleucel-T for selected patients or pembrolizumab for tumors with microsatellite instability high or deficient mismatch repair), poly ADP-ribose polymerase (PARP) inhibitors for tumors with homologous recombination repair (HRR) deficiency, and combination therapy with PARP and ARPI. No data exists on the best sequencing of these agents partly because of heterogeneity of the disease, how prostate cancer is treated by so many different specialists, and in the past, a lack of appropriate active comparator in clinical trials, which is beginning to change. The choice of first-line treatment for mCRPC depends on many factors, including prior systemic treatments,

site and extent of disease involvement, comorbidities, presence or absence of symptoms, genomics, and which clinician the patient sees. The earlier use of intensified ADT for mCSPC will have a major impact on therapeutic options in the mCRPC setting. The care goals for patients with mCRPC are to improve overall survival and maintain quality of life.

Exhibit 2 shows the median OS with FDA-approved monotherapies for mCRPC.[21-30] Chemotherapy for mCRPC is still relevant. Despite a modest impact on OS, docetaxel and cabazitaxel remain extremely active medications with significant palliative activity.

In selecting therapy for prostate cancer treatment, there is an evolving impact of genomics. Numerous guidelines support standard of care genomic testing for all patients with metastatic prostate cancer but unfortunately genomic testing is not as widely used as it should be. Targetable mutations may be either germline or somatic (tumor) and somatic DNA testing results may change over time due to the genetic instability of tumor DNA and these changes are identified by serial tumor or liquid biopsies.[31] Twenty-three percent of mCRPC cases have somatic DNA repair alterations and 11.8 percent of men have germline DNA repair defects such as BRCA mutations.[32] There is a high rate of DNA repair defects in those who are diagnosed with *de novo* metastatic disease (i.e., already metastatic at initial diagnosis) which tends to be a more aggressive disease. Germline genetic testing for newly appreciated mCSPC and mCRPC are guideline supported. Those with an HRR gene mutation (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) who have been treated previously with androgen receptor-directed therapy can receive a PARP inhibitor. Immunotherapy with pembrolizumab is also an option for those who have received prior docetaxel and androgen receptor-directed therapy and who have microsatellite high, deficient mismatch repair, or high tumor mutational burden.

PARP inhibitors are a therapy choice for some patients. PARP inhibitors, compared to physician choice ARPI therapy have been shown to improve OS in mCRPC. In a study of olaparib, the improved OS was in those BRCA1, BRCA2, or ATM mutations (19.1 versus 14.7 months) and in the overall population with and without those mutations (17.3 versus 14.0 months).[27] Rucaparib improved radiologic PFS when compared to physician choice of therapy (docetaxel or ARPI) in mCRPC patients with BRCA1, BRCA2 or ATM mutations but did not statistically improve OS (23.2 versus 21.2 months).[28,29] Olaparib and rucaparib are both FDA-approved as monotherapy for mCRPC with these mutations. Olaparib is the standard of care in BRCA positive post ARPI mCRPC. Most clinicians who manage mCRPC will only use PARP monotherapy in the setting of BRCA mutations since this is where the most benefit is seen rather than with other mutations. PARP inhibitors can be difficult for patients to tolerate, especially in the late metastatic disease stage, because of anemia, thrombocytopenia, and progressive fatigue. Ideally, they would be used earlier in the metastatic disease course but this requires doing genomic testing early.

There is preclinical data that suggests increased synthetic lethality of tumor cells when PARP inhibition is combined with ARPI. Thus, PARP inhibitors have been studied in combination with ARPI for mCRPC. The combination of olaparib with abiraterone as first-line therapy in mCRPC regardless of HRR mutation status led to a 34 percent risk reduction of progression or death and 8.2 month improvement in imaging based PFS.[33] Similar results were seen with the combination of niraparib and abiraterone which reduced risk of progression or death by 47 percent in those with BRCA 1 or 2 mutation.[34] Both trials reported significant imaging based PFS benefit, but the OS data did not show a benefit. A randomized, double-blind, Phase III trial of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line therapy in men with asymptomatic or mildly symptomatic mCRPC receiving ongoing ADT also resulted in clinically meaningful and statistically significant improvement in imaging-based PFS with talazoparib versus enzalutamide.[35] Subjects in this trial may have had previous treatment (docetaxel or abiraterone, or both) in the castration-sensitive setting. The final OS results of this trial showed a statistically significant and clinically meaningful improvement in survival with the addition of talazoparib to first-line enzalutamide, both in patients with HRR-deficient mCRPC and in all-comers (45.8 versus 37.0 months, $p < 0.022$).[36] Overall survival favored talazoparib plus enzalutamide over enzalutamide plus placebo in HRR-deficient patients (HR 0.55; $p = 0.0035$) and to a lesser extent in HRR-non-deficient or unknown patients (HR 0.88; $p = 0.22$). The population studied in these combination therapy trials is not the future state of mCRPC as more patients over time will have ADT intensification in the non-metastatic and mCSPC setting.

The combination of talazoparib with enzalutamide, olaparib with abiraterone, and niraparib with abiraterone are currently FDA-approved. The talazoparib combination is approved for HRR mCRPC whereas olaparib and niraparib combinations are only approved for BRCA mutated mCRPC. The broader FDA approval of talazoparib plus enzalutamide

as compared to olaparib/abiraterone or niraparib/abiraterone is a consequence of study design and not better outcomes. There is not going to be a large uptake of these combinations because most clinicians who practice evidence-based medicine and use ADT intensification will have already used ARPI in their patients in earlier stages. Those who have not adopted the current standard of care of ADT intensification are also unlikely to adopt PARP/ARPI combination. A study is ongoing evaluating talazoparib and enzalutamide earlier in mCSPC which may produce practice changing results.

Radium-223 dichloride (radium-223), an alpha emitter, selectively targets bone metastases with alpha particles. It is an option in mCRPC with symptomatic bone metastases and no visceral metastatic disease. It led to a 30 percent reduction in risk of death and 34 percent reduction in risk of significant skeletal events.[26] This therapy has also been studied in combination with enzalutamide, in a non-intensified population, and was shown to improve OS.[37] Radium-223 is not typically used by community urology or oncology because it requires involvement of radiation oncology and the combination would not be used in those who have received earlier therapy intensification.

The newest therapy for mCRPC is a radiopharmaceutical, lutetium Lu 177 vipivotide tetraxetan which was FDA-approved in February 2022. It is indicated for the treatment of men with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy. The active moiety, the radionuclide lutetium-177, is linked to a moiety that binds to PSMA. Upon binding to PSMA expressing cells, beta emission from lutetium-177 delivers radiation to the cells, as well as to surrounding cells, and induced DNA damage leads to cell death. The trial that led to FDA approval found that lutetium Lu 177 vipivotide tetraxetan plus standard care compared to standard care (which was an ARPI) significantly prolonged both imaging-based progression-free survival (PFS, 8.7 versus 3.4 months; $p < 0.001$) and overall survival (OS, 15.3 versus 11.3 months; $p < 0.001$).[30] Another trial compared this radiopharmaceutical to a change in ARPI in taxane-naïve patients with PSMA-positive mCRPC who had progressed once on a previous ARPI. Cross-over of therapy was allowed and 57 percent assigned to the ARPI change group crossed over to receive lutetium Lu 177 vipivotide tetraxetan. At a median follow-up of 24 months, median radiographic progression-free survival was 11.6 months in the lutetium Lu 177 vipivotide tetraxetan group versus 5.59 months in the ARPI change group (HR 0·49).[38] OS data are not final but appear similar between the two treatments. The use of this therapy is likely to increase in large group practices that have radiation oncology included. This therapy will not be used by community practitioners for similar reasons due to lack of Radium-223 use.

Overall, management of metastatic prostate cancer is increasingly impacted by therapy administered "earlier" in the disease process. The androgen receptor remains the holy grail throughout the disease continuum because the receptor is overexpressed and mutated. There is no standard sequence of therapeutic agents. The role of PARP inhibitors in metastatic disease continues to evolve.

Conclusion

Prostate cancer is an extremely heterogenous disease in its biology and clinical manifestations. The impact of next generation imaging will be significant and challenging given the limited prospective evidence to guide management. The movement of therapies into earlier stages of disease complicates advanced disease management. Optimal management of patients is not specialty dependent, its expertise dependent. Since uptake of new data, new imaging, genomics, and therapeutics is more optimal with interdisciplinary care, it should be encouraged for prostate cancer management.

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Best Practices in the Diagnosis and Management of Hereditary Angioedema: Managed Care Considerations for Optimized Clinical and Economic Outcomes

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Summary

Hereditary angioedema (HAE), a rare, lifelong, disabling, and potentially life-threatening condition, is caused by a deficiency of C1 esterase inhibitor. It is important that HAE be recognized, diagnosed, and treated. Available treatments manage acute attacks and prevent future attacks. Various patient factors impact treatment selection.

Key Points

- Life without interference from HAE should be the goal for all patients.
- Reducing hospitalizations, disability, prevention of death, and excessive pain are important outcomes of treatment.
- Every patient must have an acute HAE treatment plan.
- Long-term prophylactic treatment is considered on an individual basis.
- Newer therapies are highly effective and tolerable treatment options.
- Quality of life must be considered carefully when evaluating efficacy of the treatment plan.
- Collaboration is necessary to optimize access to effective HAE treatments.

ANGIOEDEMA IS ALARMING TO PEOPLE and is a common reason people seek care at emergency rooms. One rare type of angioedema is hereditary angioedema (HAE). HAE has a prevalence of one in 50,000, can be difficult to diagnose, and is frequently misdiagnosed.

Diagnosis of HAE requires excluding other causes of angioedema including IgE-mediated allergies (foods, medications, insect stings), non-IgE mediated radiocontrast media allergy, chronic spontaneous urticaria/angioedema, physical urticaria/angioedema, idiopathic angioedema, and angiotensin converting enzyme inhibitor (ACE-I), nonsteroidal anti-inflammatory, or aspirin induced angioedema.[1,2] About 50 percent of patients with HAE have previously had their conditions misdiagnosed, most commonly as allergic angioedema or appendicitis.[3] The median delay in diagnosis is 10 years. The challenge of getting an HAE diagnosis is that it is a rare condition with variable symptoms similar to more common conditions. Clinician's thinking of the diagnosis is often the greatest obstacle because clinicians often "see" through a highly specialized lens or specific time interval. Misdiagnosis results in marked delays in receiving the correct diagnosis, during which time patients cannot access effective, lifesaving treatment and this may result in unnecessary surgeries or even death.[4]

HAE attacks are characterized by non-itching angioedema (Exhibit 1). Attacks can be quite severe, affecting the face, oropharynx (causing risk of

Exhibit 1: Clinical Features of Hereditary Angioedema

- Angioedema **without** urticaria.
- Angioedema often quite severe.
  - Face, oropharynx, extremities, gastrointestinal system, genitourinary tract.
- Prolonged attacks.
  - Increasing intensity over 24 hours, resolve in 2-4 days.
  - Unresponsive to therapy with antihistamines, corticosteroids, or epinephrine.
- Attacks occur unpredictably and are of varying frequency.
- Frequently worsened by estrogen-containing oral contraceptives, hormone replacement therapy.
- Often precipitated by trauma or stress.
- Frequent positive family history.

asphyxiation), extremities, gastrointestinal system, and genitourinary tract. These attacks have a rapid onset from minutes to hours, increase in intensity over 24 hours, and typically resolve in two to four days without treatment. Importantly, HAE attacks are not an allergic process and thus are unresponsive to treatment with antihistamines, corticosteroids, or epinephrine.

The skin and abdomen are the most common locations for HAE attacks followed by the larynx.[5] With abdominal attacks, mild-to-severe pain, abdominal distension, tenderness, and vomiting occur. The symptoms can mimic other abdominal conditions, resulting in misdiagnosis and unnecessary surgery. Airway angioedema can cause death. In one survey, 1.3 percent of diagnosed patients died from asphyxiation and more importantly 31 percent of those undiagnosed also died.[6] All patients need to be educated on the possibility of airway attacks and how to manage them.

Attacks typically occur unpredictably and vary in frequency. Although there are several known triggers of attacks, only about 40 percent of individuals with HAE can identify the cause of an episode.[4] Common triggers include estrogen-containing oral contraceptives, hormone replacement therapy, emotional stress, physical trauma from accident or dental or surgical procedures, and infections. In most cases, a family history of HAE is identified.

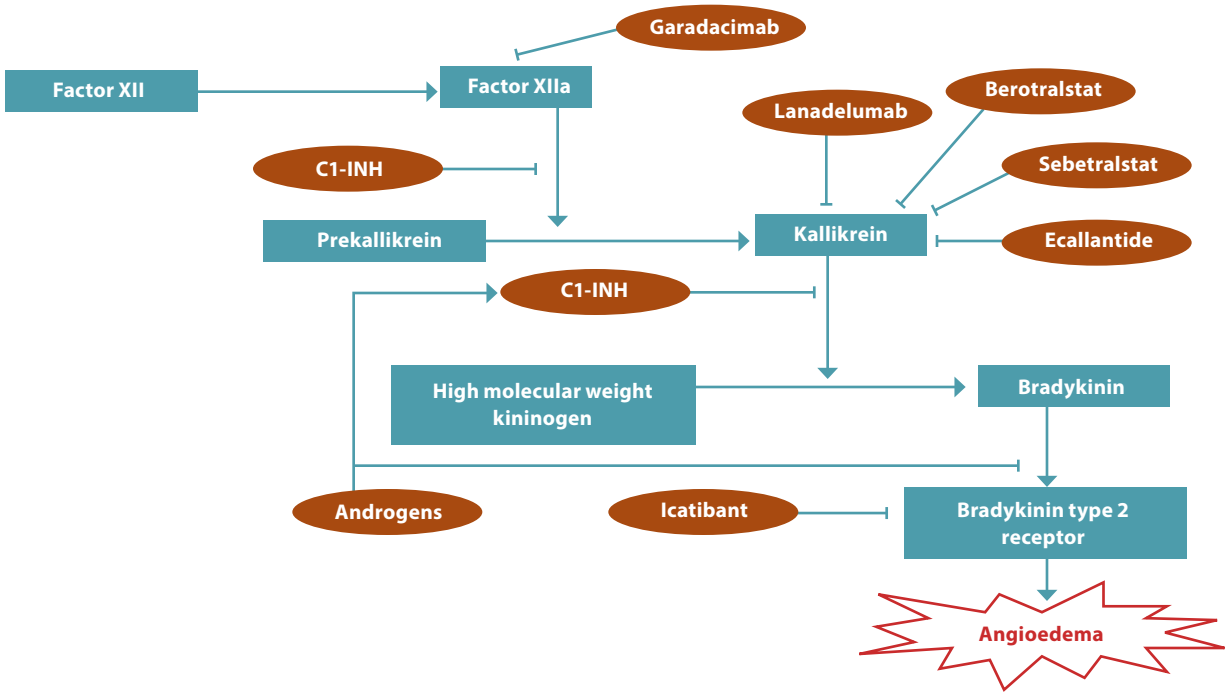
Type 1 and Type 2 HAE are autosomal dominant diseases caused by C1 inhibitor (C1INH) gene mutations which lead to deficiency in or dysfunctional C1INH.[7] Over 800 unique mutations in SERPING1 have been identified which lead to issues with C1INH. C1INH inhibits all active enzymes of the bradykinin-forming cascade. With a C1INH deficiency, bradykinin levels increase and bradykinin causes endothelial cell fluid extravasation through vasodilatation and increased vascular permeability.[8]

HAE is diagnosed with C1INH functional assays. Type 1 HAE accounts for about 85 percent of cases and has low C4 level, C1INH antigenic level, and C1INH antigenic function. Type 2 HAE accounts for close to 15 percent of cases and has normal C1INH antigenic level but low C4 level and C1INH antigenic function. There are rare cases of C1INH normal HAE which can be especially difficult to diagnose using functional assays. There is much work going on to use genetic mutation studies and various biomarkers to diagnose these patients.[9,10] Families of those diagnosed with HAE should be screened for the disease.

The therapeutic goals of HAE treatment are to return normalcy to life, reduce hospitalization and disability, and prevent death and excessive pain. Evidence-based guidelines are available to support therapeutic evaluations—these guidelines are in the process of being updated.[1,11,12] The three treatment strategies for HAE include on-demand 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.[11] All patients need on-demand treatment and many will also need long-term prophylaxis. Short-term prophylaxis should be prescribed for those with known triggers. Treatment for HAE must be individualized to provide optimal care and normalize quality of life.

Since 2009 there have been dramatic advances in available treatments for HAE for both acute attack

Exhibit 2: Current HAE Therapies



treatment and prophylaxis. The available agents target bradykinin production or effects in several ways (Exhibit 2). Because newer agents have better safety and efficacy data, older therapies including androgens and tranexamic acid are no longer used first-line except for the case of tranexamic acid for long-term prophylaxis which may be beneficial in some with C1INH normal HAE.[12] Androgens cause significant adverse events including hypertension, diabetes, hypercholesterolemia, and liver disease. The challenge for HAE specialists is how to use the numerous agents efficiently and effectively to optimize treatment to the individual patient.

Five agents are available for acute treatment of an attack:

- intravenous plasma-derived C1INH
- intravenous recombinant C1INH
- subcutaneous ecallantide (kallikrein inhibitor)
- subcutaneous icatibant (bradykinin-2 receptor antagonist)
- oral sebetralstat (kallikrein inhibitor, Exhibit 3).

Sebetralstat was newly approved by the FDA in July 2025. Only icatibant and sebetralstat are FDA-labeled for self-administration during an attack. Treatment of early symptoms of an HAE attack with any licensed therapy results in milder symptoms and shorter duration of attack compared with later treatment.[13] All acute therapies have been shown to be well-tolerated, with minimal risk of serious adverse events. All HAE attacks are considered for on-demand treatment and any attack affecting or potentially affecting the upper airway must be treated.[11] HAE attacks should be treated as early as possible and patients or caregivers should be taught how to give the medication. Not having to travel to a hospital speeds recovery from an attack. All patients must have on hand sufficient medication for on-demand treatment of two attacks and must always carry on-demand medication. Importantly, few hospitals have acute medications stocked as HAE is rare. Because these agents are dispensed by specialty pharmacies, deliveries can take time, and policies which allow sufficient on-demand medications are important. All patients who are provided with icatibant or the intravenous agents must be taught to self-administer the medication. Patients must also be educated not to "save" on-demand medication just in case an attack worsens and treat as soon as possible.

Prophylactic treatments for HAE help patients prevent and reduce the frequency and severity of attacks and need for on-demand treatment (Exhibit 4). All currently available prophylactic agents are associated with breakthrough attacks; therefore, an acute treatment plan is essential for every patient when on prophylactic agents. Patients may also need additional prophylaxis before surgical procedures or

Exhibit 3: HAE Acute Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages
Plasma-derived C1-INH	• Infectious risk • Potential infusion reactions	• Needs IV access • Dependent on plasma supply	• Extensive clinical experience • Relatively long half-life
Recombinant C1-INH	• Potential hypersensitivity	• Needs IV access	• No human virus risk • Scalable supply
Ecallantide	• Allergic reactions • Antibody formation	• Requires administration by a healthcare provider (3% to 4% risk of anaphylaxis)	• No infectious risk • Subcutaneous administration
Icatibant	• Local injection reactions		• No infectious risk • Stable at room temperature • Subcutaneous administration
Sebetralstat	• None	• Dosage reduction required with hepatic dysfunction and certain concomitant medications	• Oral administration • Ages 12 and older

other known triggers. The guidelines recommend use of the lowest effective dose.[11]

Subcutaneous administration of C1INH is a significant advancement in therapy over intravenous administration because it does not require intravenous access which can become an issue with patients over time. It is effective in reducing attacks by about 90 percent compared to placebo in adults, adolescents, and children.[14,15] Subcutaneous administration also reduces need for on-demand treatment. In one trial, the need for rescue medication was reduced from 5.55 uses per month in the placebo group to 1.13 uses per month in the 40-IU dose group and from 3.89 uses in the placebo group to 0.32 uses per month in the 60-IU dose group.[14] Prophylactic subcutaneous C1INH improves patient quality of life compared with on demand alone treatment.[16]

Lanadelumab, which targets plasma kallikrein, was approved in the United States (U.S.) in 2018 as the first monoclonal antibody indicated for prophylactic treatment of HAE. Subcutaneous lanadelumab for 26 weeks significantly reduced the attack rate in adults by approximately 78 percent and improved quality of life compared with placebo.[17] In children, the mean attack rate during treatment decreased by 94.8 percent from baseline (1.84 ± 1.53 to 0.08 ± 0.17 attacks/month), and 76.2 percent of patients were attack-free.[18] It is given every two to four weeks as a subcutaneous injection and is approved for ages two years and older.

Berotralstat is an oral, once daily, plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years and older. Berotralstat demonstrated an overall 44 percent reduction in attack rate relative to placebo.[19] The responder analysis of this trial showed that 50 percent of the patients had at least a 70 percent reduction in attacks and 25 percent had over 90 percent reduction. The dose of this agent needs to be reduced for moderate or severe hepatic impairment and may need adjustment in patients with persistent gastrointestinal adverse events. Because this is the only oral option, there is much patient interest in using this agent.

In 2025, garadacimab was FDA-approved for prophylaxis in adult and pediatric patients aged 12 years and older. It is an activated Factor XII (FXIIa) inhibitor self-administered as a subcutaneous injection. An initial loading dose of 400 mg (two 200 mg injections) is followed by a maintenance dosage of 200 mg once monthly. In the pivotal, multicenter, randomized, double-blind, placebo-controlled, Phase III trial, patients (aged 12 years or more) with Type I or Type II hereditary angioedema across seven countries (Canada, Germany, Hungary, Israel, Japan, the Netherlands, and the USA) were

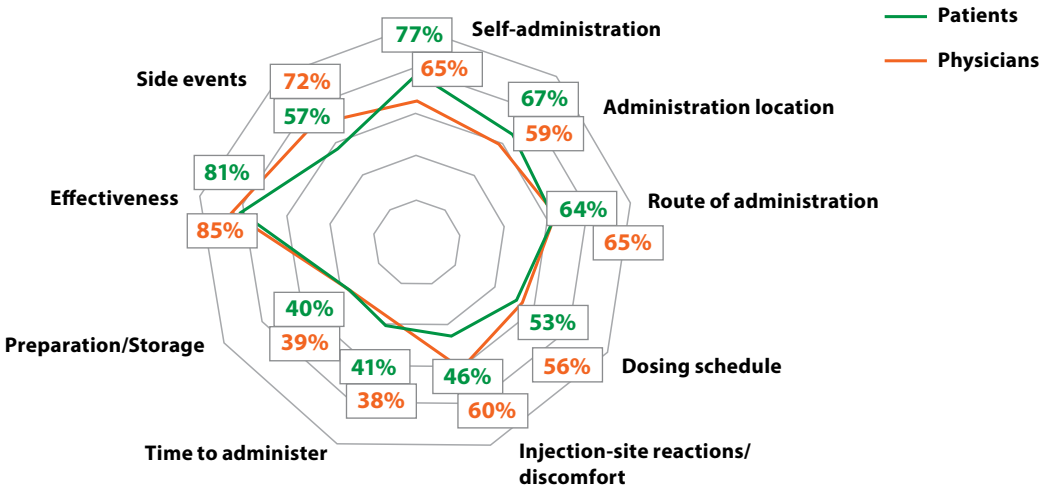
Exhibit 4: HAE Prophylactic Therapies

Drug	Mechanism	Potential Safety Concerns	Disadvantages	Advantages
Plasma-derived nanofiltered C1INH (intravenous)	Inactivation and consumption of C1 inhibitor	• Infectious risk • Infusion reactions • Thrombosis	• Needs IV access • Dependent on plasma supply • Twice a week infusion	• Extensive clinical experience • Long half-life
Plasma-derived nanofiltered C1INH (subcutaneous)	Inactivation and consumption of C1-INH	• Infectious risk • Infusion reactions • Thrombosis	• Dependent on plasma supply	• Improved steady-state C1INH levels • No IV access required
Lanadelumab	Monoclonal antibody; binds plasma kallikrein and inhibits its proteolytic activity	• Unknown safety in pregnancy • Anti-drug antibodies/ hypersensitivity	• Injection site reactions	• No human virus risk • Subcutaneous administration • Less frequent dosing • Ages 2 and older
Berotralstat	Plasma kallikrein inhibitor	• Abdominal pain, vomiting, diarrhea	• Dosage adjustments for moderate or severe hepatic impairment and persistent gastrointestinal adverse events	• Oral administration
Garadacimab	Activated Factor XII inhibitor	• Unknown safety in pregnancy	• Injection site reactions	• Monthly administration • Self-injection
Danazol	Unknown	• Hepatic toxicity, elevated LDL, weight gain, hypertension • Virilization, amenorrhea • Psychological effects	• Contraindicated in pregnancy, lactation, children, cancer	• Oral administration
Tranexamic acid	Inhibits activation of plasminogen and activity of plasmin	• Thrombosis, myalgias, abdominal pain, diarrhea	• Inferior efficacy compared to other agents • Off-label for HAE	• Oral administration

included. Randomly assigned patients received a 400 mg loading dose of subcutaneous garadacimab as two 200 mg injections or volume-matched placebo on day one of the treatment period, followed by five additional self-administered (or caregiver-administered) monthly doses of 200 mg subcutaneous garadacimab or volume-matched placebo for a total of six months of treatment. Of 65 eligible patients with Type I or Type II hereditary angioedema, 39 were randomly assigned to garadacimab and 26 to placebo. During the six-month treatment period the mean number of investigator-confirmed hereditary angioedema attacks per month was significantly lower in the garadacimab group (0.27) than in the placebo group (2.01; $p < 0{\cdot}0001$), corresponding to a percentage difference in means of 87 percent.[20] In an interim analysis of a long-term open-label extension of trial including Phase II and Phase III trial subjects, mean HAE attack rate decreased by 95 percent from the run-in period and 60 percent of patients were attack-free.[21] The most common treatment-emergent adverse events were injection site reactions. FXIIa inhibition was not associated with an increased risk of bleeding or thromboembolic events.

The treatment guidelines recommend that patients be evaluated for long-term prophylaxis at every visit.[1,11] The disease can change over time so the patient may need more or less medication. Disease burden and patient preference should be taken into consideration when considering prophylaxis. The guidelines recommend C1INH (intravenous or subcutaneous), lanadelumab, or berotralstat as

Exhibit 5: Patients and Physicians: Important Factors in Selecting HAE Prophylactic Therapy[23]



first-line long-term prophylaxis and androgens as second-line.[11] Garadacimab is not yet included in the guidelines but will likely be considered first-line. The guidelines recommend modification of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease and treatment.

Management plans need to be individualized to lessen the burden of illness, aim to provide patients with HAE a normal quality of life, and consider treatment burden.[1,11] Overall, acute treatment and prophylaxis should be selected considering unique patient factors such as frequency of attacks, rapidity of attack progression, location of attacks (i.e., laryngeal), access to medical care, history of frequent hospitalization, treatment complications, and quality of life. Medication factors to consider include efficacy, safety, cost, route of administration, and patient preference/tolerability. The treatment plan needs to be assessed at least biannually and sometimes more often.

HAE is associated with significant and multifaceted disease burden.[4,22] Many contributing factors include debilitating, painful, dangerous, and unpredictable symptoms; challenges in diagnosis; lack of access to effective treatment; and treatment burden. HAE also increases risk of depression, anxiety, and loss of productivity. Patients can lose significant amounts of work and school time. The disease has an impact on the quality of life between angioedema episodes which has not always been considered by clinicians. Unpredictability of the disease is stressful, limits educational/employment opportunities, causes disruption of social activities, and causes negative impact on family relationships. A higher frequency of attacks is associated with a higher burden of disease (physical, psychological, social). Overall, HAE results in significant humanistic burden across physical and mental health domains and negatively impacts productivity and quality of life.

One survey found that physicians and patients were not always aligned on how treatment choices affect patients' lives, which may mean that there are opportunities for enhanced patient-physician dialog and shared decision-making in HAE management in the U.S.[23] The differences were most apparent for side events, injection site reactions, self-administration, and location of administration (home versus while out and about versus medical setting, Exhibit 5).[23] One patient survey found that patients have significant anxiety around needing to take their HAE medications, significant injection fatigue, and high rates of worry about the demanding nature of their treatment.[24]

Once on a treatment plan, clinicians need to assess whether a patient's disease is being controlled where the patient feels they have control, can do life activities, and are able to be adherent with their medications. Clinicians need to ask about activities in the patient's life that they are not doing or not doing well but that they would like to be doing. There are objective HAE specific disease control and quality of life tools which clinicians can use to measure efficacy and benefit of therapy.[25,26] Studies show that those on prophylactic therapy have reduced disease burden compared to those who get

on-demand treatment only.[27,28] Home treatment of attacks has largely replaced emergency room treatment which can significantly reduce costs and disease burden.

Donidalorsen, a subcutaneous injection antisense oligonucleotide to reduce pre-kallikrein expression, has been submitted to the FDA for approval with a decision expected in August 2025. Other agents are being investigated for HAE. Deucrictibant, an oral bradykinin B2 receptor antagonist, is in Phase III trials. NTLA-2002, an *in vivo* gene-editing therapy based on clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9, targets the gene encoding kallikrein B1 (KLKB1), with the goal of lifelong control of attacks after a single dose. A Phase III trial with this agent started in early 2025.

Conclusion

Life without interference from HAE should be the goal for all patients. Reducing hospitalizations and disability and prevention of death and excessive pain are important outcomes of treatment. Quality of life must be considered carefully when evaluating efficacy of the treatment plan. Continued collaboration among providers and managed care is necessary to optimize access to effective HAE treatments.

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Overcoming Barriers to Adult Immunizations: Practical Strategies for Improved Outcomes in Suboptimal Vaccination Practices

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Summary

Vaccination has been shown to reduce morbidity and mortality but there are significant gaps in coverage rates for many vaccines. Given the rise in vaccine hesitancy in the United States, a concerted effort is needed to increase rates.

Key Points

- Optimizing rates of vaccinations in adults has the potential to achieve reductions in morbidity and mortality.
- The recommended age for pneumococcal vaccination has been lowered to 50 years of age.
- HPV vaccine is recommended for selected adults who were not vaccinated as children.

THE 2025 ADULT IMMUNIZATION SCHEDULE for the United States (U.S.) includes updated recommendations for several vaccines (Exhibit 1).[1] Gaps in vaccination coverage for selected vaccines in U.S. adults from the National Immunization Surveys in 2014 and 2022 are shown in Exhibit 2.[2,3] Vaccines which are the focus of this update are pneumococcal and human virus papillomavirus (HPV) vaccines as examples of areas where there is significant disease burden and a need for additional vaccine uptake.

Illness caused by streptococcus pneumoniae is associated with high morbidity and mortality, particularly in children less than five years of age, adults over 50 years of age, and individuals with underlying medical conditions.[4] Pneumococcal disease results in over 150,000 hospitalizations annually. There are two clinical presentations. With non-invasive disease, non-bacteremic pneumonia, otitis media, and sinusitis occur all of which usually can be treated on an outpatient basis. Invasive pneumococcal disease (IPD) includes meningitis, bacteremia, and bacteremic pneumonia which require hospitalization. The incidence of and mortality rate from IPD increases with age and comorbid medical conditions (heart disease, diabetes, and lung disease).[5] Heart disease leads to a four- to 10-fold increase in risk for IPD compared to healthy person of the same age. Lung disease and diabetes result in a three- to six-fold increased risk.

One hundred pneumococcal serotypes have been identified; however, most infections are caused by a subset of serotypes. Exhibit 3 shows the serotypes included in the FDA-approved vaccines. One dose of 15-valent pneumococcal conjugate vaccine (PCV15), 20-valent (PCV20), or 21-valent (PCV21) is recommended for anyone aged over 50 years.[1] The recommended age for universal vaccination was reduced from age 65 to 50 years in 2024.[6] Key considerations supporting lowering the age-based recommendation to age 50 years were a relatively high burden of pneumococcal disease in adults aged 50 to 64 years, particularly among those with risk conditions; potential for improved vaccine uptake through an age-based recommendation, which is easier to implement compared with the prior risk-based recommendation; potential to reduce

Exhibit 1: Recommended Adult Immunization Schedule by Age Group in the United States, 2025[1]

Vaccine	19 to 26 years	27 to 49 years	50 to 64 years	65 years and greater
COVID-19	1 or more doses of 2024 - 2025 vaccine (see notes)			2 or more doses of 2024-25 vaccine (see notes)
Influenza inactivated (IIV3, ccIV3) **Influenza recombinant** (RIV3)	1 dose annually			1 dose annually (HD-IIv3, RIV3, or allV3 preferred)
Influenza inactivated (allV3; HD-IIV3) **Influenza recombinant** (RIV3)	Solid organ transplant (see notes)			
Influenza live, attenuated (LAIV3)	1 dose annually			
Respiratory syncytial virus (RSV)	Seasonal administration during pregnancy (see notes)		60 through 74 years (see notes)	75 years or more
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born 1957 or later)			For healthcare personnel (see notes)
Varicella (Var)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PCV21, PPSV23)			See Notes	
				See Notes
Hepatitis A (HepA)	2, 3, or 4 doses depending on vaccine			
Hepatitis (HepB)	2, 3, or 4 doses depending on vaccine		or condition	
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication (see notes for booster recommendations)			
Meningococcal B (MenB)	19 through 23 years	2 or 3 doses depending on vaccine and indications (see notes for booster recommendations)		
Haemophilus influenzaetype b (Hib)	1 or 3 doses depending on indication			
Mpox	2 doses			
Inactivated poliovirus (IPV)	Complete 3-dose series if incompletely vaccinated. Self-report of previous doses acceptable (see notes)			

Recommended vaccination for adults who meet age requirement lack documentation of vaccination, or lack evidence of immunity.

Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision-making

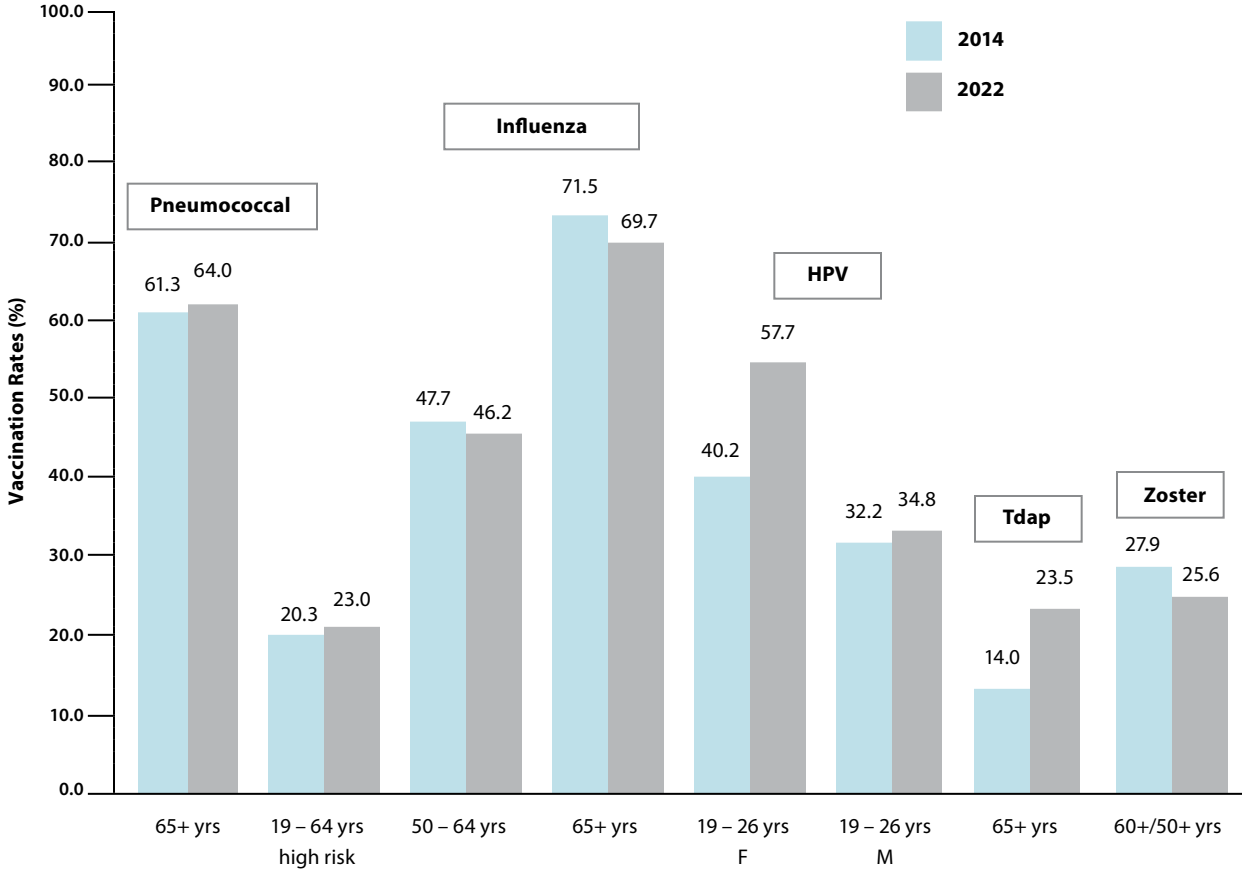
No Guidance/ Not Applicable

Age-based recs

Risk-based recs

Shared clinical decision-making

Exhibit 2: Vaccination Coverage, U.S. Adults, National Immunization Survey, 2014 and 2022[2,3]



pneumococcal disease incidence in demographic groups experiencing the highest burden (health equity); and projected health benefits from economic models despite increased net costs.

The PCV21 vaccine is the newest formulation and was approved in 2024. By including different serotype than the PCV20 vaccine, it provides increased coverage for serotypes leading to IPD; 85 percent of cases in those aged 65 and older would be covered compared to 54 percent with PCV20.[7] This vaccine has comparable safety to the earlier pneumococcal vaccines.

If PCV15 is used for initial vaccination, one dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) should be given at least one year after the PCV15 dose. A minimum interval of eight weeks can be used for adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak. Adults aged 19 to 49 with certain underlying medical conditions or other risk factors should also receive vaccination. If the patient has received a prior pneumococcal vaccination, the guidelines provide specifics on which vaccine to use and the recommended doses depending on the patient's age. Because of the number of pneumococcal vaccines and prior availability of other vaccines with lower serotype content, determining which vaccine is appropriate in which patients can be complicated. The PneumoRecs VaxAdvisor application can be a helpful point-of-care tool for vaccine providers.

As noted in Exhibit 2, 64 percent of U.S. adults aged 65 and older have been vaccinated against pneumococcus.[3] Rates in those aged 50 to 64 are even lower. The 2022 Behavioral Risk Factor Surveillance System data showed that only 37 percent of adults aged 50 to 64 years with a risk-based vaccination recommendation received a pneumococcal vaccine.[8] Coverage rates vary among states and among various racial groups. Overall, there is work to be done to increase rates of pneumococcal vaccination.

Another vaccine for which uptake increases would have a significant healthcare impact is HPV.

Exhibit 3: Serotypes Included in Adult Pneumococcal Vaccines

	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	22F	23F	8	10A	11A	12F	15B	2	9N	17F	20	15C	16F	23A	24F	31	33B	35B
PCV15																														
PCV20																														
PPSV23																														
PCV21																														

PCV15 = 15-valent pneumococcal conjugate vaccine
PCV20 = 20-valent pneumococcal conjugate vaccine
PCV21 = 21-valent pneumococcal conjugate vaccine
PPSV23 = 23-valent pneumococcal polysaccharide vaccine

It is the most common sexually transmitted disease in the U.S.[9] Seventy-nine million Americans are already infected and 14 million new infections occur annually. About half of the new infections occur among people aged 15 to 24 years. Almost all sexually active men and women will be infected at some point in their lives and most will be unaware of infection. About 90 percent of HPV infections are cleared by the immune system within two years. The issue is with persistent infection which causes precancer or cancer years later. Immunocompromised people have higher rates of HPV acquisition and progression to cancer.

Each year in the U.S., about 47,984 new cases of cancer are found in parts of the body where HPV is often found (26,280 among females, and 21,704 among males). HPV causes about 37,800 of these cancers.[10] HPV infection with oncogenic subtypes is responsible for more than 90 percent of anal and cervical cancers, 70 percent of vaginal and vulvar cancers, 60 percent of penile cancers, and 70 percent of oropharyngeal cancers.[11-14] Exhibit 4 shows which HPV subtypes are associated with which diseases.

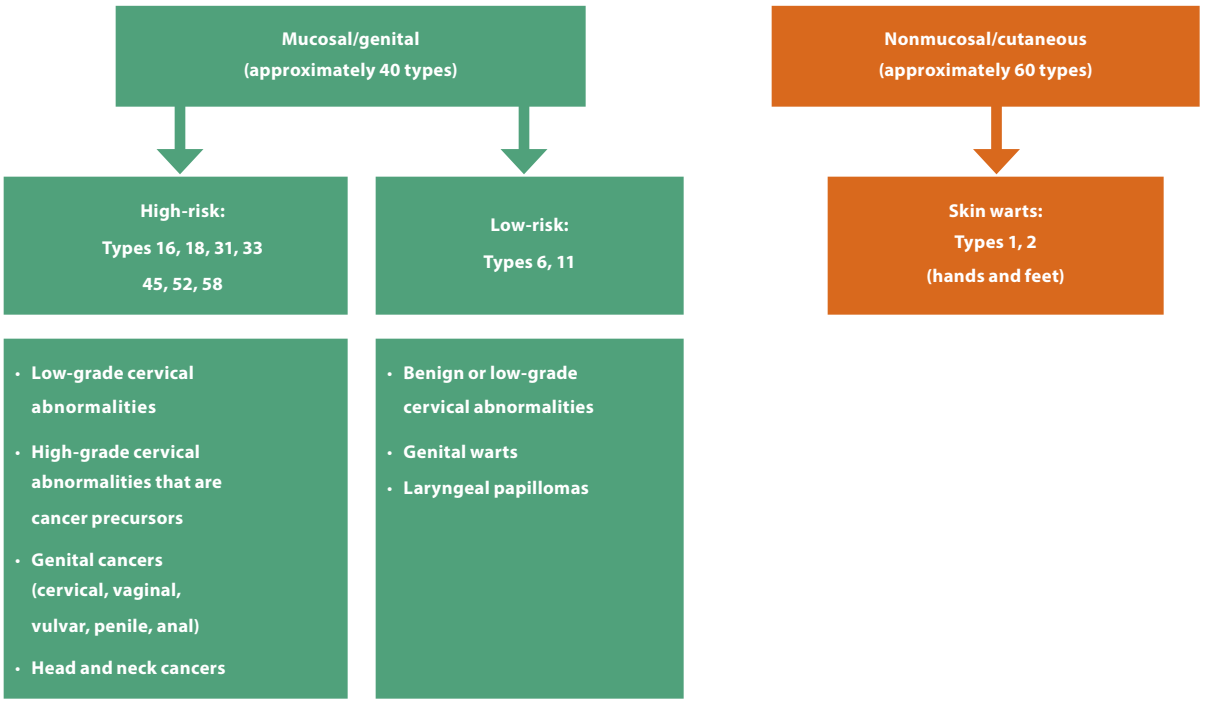
HPV exposure can occur with any type of skin-to-skin contact. Intercourse is not necessary to become infected. Infection from fomites is possible but unlikely. There are different age-specific HPV prevalence patterns in females and males. Females have a decreased prevalence at older ages whereas men have no decline in prevalence out to age 59. Rates in women decline after age 24.[15] Relevance of infections acquired at older ages is unknown. There appears to be a bimodal distribution of oral cases of HPV with peaks in the mid-20s and mid-50s for both genders.[16] High-risk oral HPV prevalence is higher among men (7.3%) than in women (1.4%) but infected men can transfer oral HPV to uninfected women.

The 9-valent recombinant HPV vaccine, which replaced an earlier 4-valent version, is FDA-approved for females nine through 45 years of age for the prevention of cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; cervical, vulvar, vaginal, and anal precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11. It is also FDA-approved for males nine through 45 years of age for the prevention of anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58; anal precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV types 6 and 11. The vaccine has been shown to be 93 to 99 percent effective in women depending on the clinical endpoint used with the efficacy in men being lower.[17] HPV vaccination has been shown to provide herd protection as well.[18]

There are disparities in HPV vaccination among mid-adults (27 to 45 year old) in the U.S. Data from the 2019 National Health Interview Survey (NHIS), found that only 15.5 percent of this age group had initiated HPV vaccine (compared to 58% for females and 35% for males, ages 19 to 26).[19] Females were 3.5 times more likely to report HPV vaccination. Non-Hispanic Black people were more likely to report HPV whereas Hispanics were less likely. There was decreased odds of HPV vaccination among less educated individuals compared to individuals who graduated college or more.

Routine HPV vaccination is recommended for both males and females ages 11 to 12 years, but it can start at ages nine or 10.[20] If the series is started before age 15 only two doses at zero and six months are needed whereas, if series is started at 15 years of age or older three doses are needed at zero, two, and six months. Importantly for the adult population, catch-up vaccination is recommended for everyone

Exhibit 4: HPV Types and Disease Association



through age 26 years, if not adequately vaccinated when younger. The guidelines recommend shared clinical decision-making for deciding to vaccinate adults aged 27 through 45 years.[21] HPV vaccination of people in this age range provides less benefit, for several reasons, including that more people in this age range have already been exposed to HPV.

Significant benefit from the HPV vaccination has been shown. The HPV vaccine has been shown to reduce the risk of HPV infection with the serotypes included in the vaccine and precancerous cervical changes related to prolonged infections. Since 2006 when the vaccine was first introduced, infections with HPV types that cause most HPV cancers and genital warts among teen girls have dropped 88 percent.[22] Among young adult women, infections have dropped 81 percent. Among vaccinated women, the percentage of cervical precancers caused by the HPV types most often linked to cervical cancer has dropped by 40 percent. It also reduces the risk of invasive cervical cancer especially when given prior to age 17 years.[23] Australia is one country which has achieved high vaccination coverage across both men and women. A modeling study found that if high-coverage vaccination and recommended HPV screening is maintained, at an elimination threshold of four new cases per 100,000 women annually, cervical cancer could be eliminated as a public health problem in Australia by 2066.[24] The U.S. has a long ways to go in eliminating cervical cancer through the use of HPV vaccination.

Vaccine hesitancy has been growing steadily in the U.S. In a 2024 survey, 24 percent of those who met the guidelines for a pneumococcal vaccine said they did not plan to be vaccinated. The top reasons cited for not getting vaccinated were concern about adverse events from the vaccine (41%), concerns about getting sick from the vaccine (32%), and distrust of vaccines in general (32%).[25] This survey also found that healthcare professionals are the primary and most trusted source of information about vaccines. Seventy-five percent of U.S. adults in this survey trusted doctors, nurses, and pharmacists "a great deal or a lot." Slightly more than one-half (55%) trusted the CDC and 51 percent trusted state and local health departments "a great deal or a lot".

Combating vaccine hesitancy requires providers to make a clear confident recommendation to patients about appropriate vaccines and discuss patient concerns and questions. Clinicians can consider using a "pro-social" approach by encouraging voluntary actions that benefit others by suggesting that a patient picture the positive effects on family, friends, and neighbors of getting a vaccine.[26] Most people are decent and compassionate and will follow along.

Ways to improve adult immunization rates beyond strong professional recommendations include reminder/recall systems for patients, prompts/system alerts for clinicians, clinician performance feedback, and standing vaccine orders. Medical offices and pharmacies can utilize educational materials to promote patient engagement in these preventive services. Managed care organizations can send educational materials to targeted subgroups of patients encouraging completion of recommended adult vaccines and can encourage vaccination focused quality improvement activities within offices and health systems.

Conclusion

Pneumococcal disease is associated with advancing age and medical co-morbidities. HPV is ubiquitous and chronic persistent HPV infection with oncogenic HPV types is linked with anogenital and oropharyngeal cancers and precancers. Optimizing rates of vaccination against both pneumococcal disease and HPV has the potential to achieve reductions in morbidity and mortality.

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Improving Outcomes and Integrating Evidence-Based Treatment Approaches for Psoriasis

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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 psoriasis has changed significantly over time but the numerous medications now available can make treatment selection challenging. Treatment selection depends on the disease severity and presence of psoriatic arthritis among other factors. Patients with mild disease can be treated topically but those with moderate-to-severe disease require systemic therapy.

Key Points

- Multiple effective treatment options are available.
- The primary goals of treatment include clearing the skin, reducing signs and symptoms of joint pain, minimizing adverse events, addressing comorbidities, and enhancing patient quality of life.
- Patient preference should be considered when selecting therapy.
- Psoriasis patients should be screened for joint involvement.

PSORIASIS IS A CHRONIC RELAPSING immune-mediated inflammatory disease characterized by psoriatic plaques which are graded on erythema, induration, and desquamation (scaling).[1] It is a systemic disease affecting multiple parts of the body. Psoriasis causes significant clinical, social, emotional, and economic burden and has multiple associated comorbidities. The estimated costs of psoriasis are 1.6 to 3.2 billion dollars annually.

Psoriasis affects 3 percent of the population with 7.5 million Americans affected.[2] Two million of those have moderate-to-severe disease which requires more aggressive treatment than mild disease. There are about 150,000 newly diagnosed cases per year in the United States. It affects males and females equally and impacts all races and socioeconomic groups.

There is bimodal age of onset in the second or third decade of life and a second peak incidence after 50 years of age. Onset prior to 15 years of age may indicate more severe, resistant disease. Up to 33 percent of patients report a family history of psoriasis.

A range of factors can trigger or exacerbate psoriasis, such as stress, infections, physical trauma, and medications. Medications reported to be an issue include lithium, beta-adrenergic blockers, anti-malarias, nonsteroidal anti-inflammatories, interferon, and gold. Although not recommended for psoriasis treatment, systemic steroids given for another reason can cause a rebound in disease when discontinued.

Plaque psoriasis is the most common type of psoriasis, accounting for 80 percent of all psoriasis cases. Eczema, drug eruption, and tinea corporis need to be ruled out when diagnosing plaque psoriasis. Guttate psoriasis appears as small droplets of psoriatic lesions. It is frequently the first manifestation of psoriasis, often precipitated

Exhibit 1: CASPAR Criteria for Diagnosing Psoriatic Arthritis[4]

Established Inflammatory Articular Disease (joint, spine, or entheseal) with three or more of the following		
1. Psoriasis	(a) Current	Psoriatic skin or scalp disease present today as judged by a qualified health professional.
	(b) History	A history of psoriasis that may be obtained from patient, or qualified health professional.
	(c) Family History	A history of psoriasis in a first or second degree relative according to patient report.
2. Nail changes		Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination.
3. A negative test for RF		By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range.
4. **Dactylitis**	(a) Current	Swelling of an entire digit.
	(b) History	A history of dactylitis recorded by a qualified health professional.
5.Radiological evidence of juxta-articular new bone formation		Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain x-rays of hand or foot.

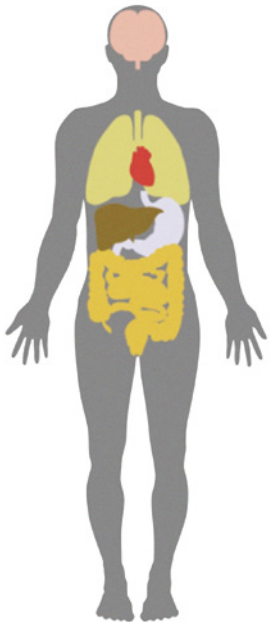
by group A beta-hemolytic streptococcus throat infection, and commonly develops into plaque psoriasis. The differential diagnosis for guttate includes pityriasis rosea, drug eruption, and secondary syphilis. Inverse psoriasis is found in the flexural (intertriginous areas) of the body. Intertrigo and necrolytic migratory erythema need to be ruled out. Palmer planter psoriasis is where the palms and soles of feet are affected by scaly plaques and these can be pustular. Planter palmer psoriasis can be very debilitating if the patient cannot use their hands or feet. It is the predominant manifestation of psoriasis in 5 to 10 percent of cases. Here, dyshidrotic eczema and keratoderma need to be ruled out.

Two types of psoriasis, generalized pustular psoriasis and erythrodermic psoriasis, can be medical emergencies. The differential for pustular psoriasis is acute generalized exanthematous pustulosis, pemphigus variants (such as IgA pemphigus and pemphigus foliaceus), dermatitis herpetiformis, and impetigo. The differential diagnosis for erythrodermic psoriasis includes drug eruption, cutaneous T cell lymphoma, and pityriasis rubra pilaris. Both pustular and erythrodermic can be precipitated by systemic steroids or acute withdrawal of psoriasis treatment.

Up to 30 percent of patients with psoriasis develop psoriatic arthritis (PsA), usually 10 to 15 years after onset of psoriasis.[3] Onset is most common between ages of 30 and 50 years. Earlier onset is associated with poorer prognosis. The frequency of psoriatic arthritis increases with disease severity and duration. In most cases (75%), psoriasis precedes arthritis. In 15 percent of cases, psoriasis and arthritis have synchronous onset and in 10 percent of cases arthritis precedes psoriasis.

Manifestations associated with PsA include nail changes, dactylitis, enthesitis, and spondylitis. Nail changes including pitting and dystrophy can occur with psoriasis and are difficult to treat. These changes occur in up to 50 percent of patients with psoriasis and are associated with psoriatic arthritis.

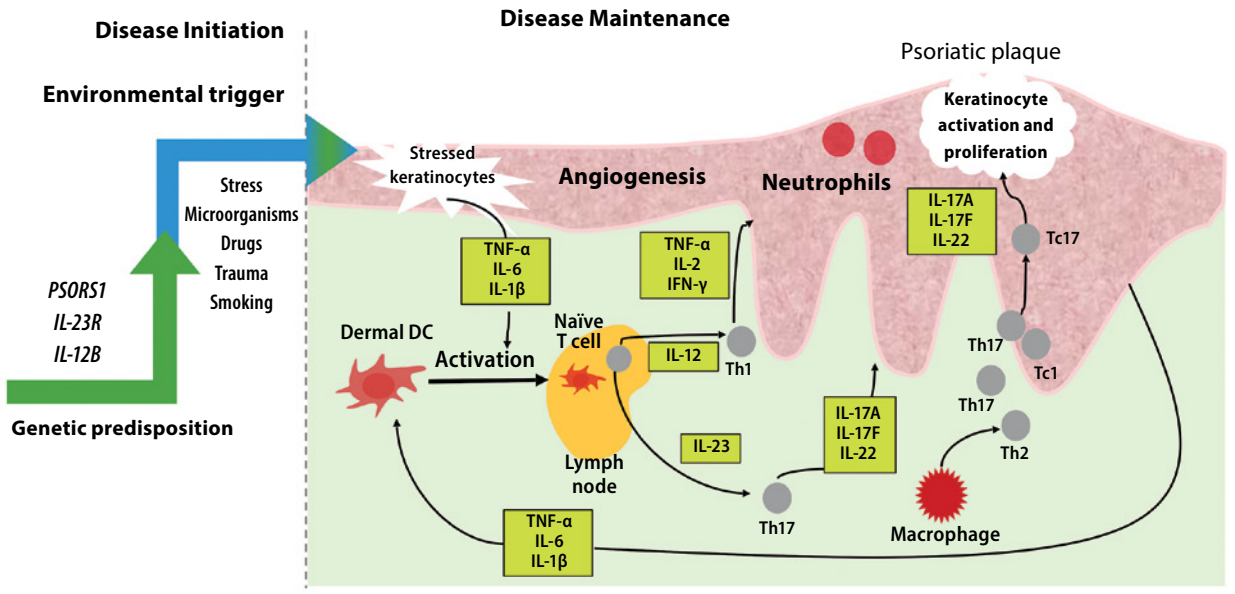
Exhibit 2: Individuals with Psoriasis are at Risk of Developing Other Chronic Comorbid Conditions[5,6]



Depression/Anxiety	↑ risk of poor self-esteem, psychological stress, and anxiety due to their psoriasis
Cardiovascular Disease	39% ↑ risk of CV mortality 70% ↑ risk of MI 56% ↑ risk of MI
Obesity	346% ↑ risk (mild psoriasis) 123% ↑ risk (severe)
Metabolic Syndrome	22% ↑ risk (mild) 98% ↑ risk (severe)
Diabetes	14% ↑ risk (mild) 46% ↑ risk (severe)
Psoriatic Arthritis	↑ 30% of patients 10 to 15 years after onset of psoriasis

CV = cardiovascular; MI = myocardial infarction

Exhibit 3: Immunopathogenesis of Chronic Plaque Psoriasis[7,8]



DC = dendritic cell; PSORS1 = psoriasis susceptibility 1; IL = interleukin; TNF = tumor necrosis factor

Significant nail changes which are unsightly can cause quality of life changes. Dactylitis is diffuse swelling of a digit and is one of the cardinal features of PsA, occurring in up to 40 percent of patients. The feet are affected more than hands. Dactylitis involved digits show significant radiographic damage. Enthesitis (inflammation at the regions at which a tendon, ligament, or joint capsule attaches to bone) is another hallmark feature of PsA. Common sites are Achilles, bottom of feet (plantar fasciitis), and knees. The pathogenesis of enthesitis has yet to be fully elucidated. Isolated peripheral enthesitis may

Exhibit 4: Biologic and Oral Agents Approved for Psoriasis and Psoriatic Arthritis

Type	Generic Name	Psoriasis and/or Psoriatic Arthritis
TNF-alpha Inhibitor	Etanercept	PsO and PsA
	Adalimumab	PsO and PsA
	Infliximab	PsO and PsA
	Certolizumab pegol	PsO and PsA
IL-12/23 Inhibitor	Ustekinumab	PsO and PsA
IL-17A Inhibitor	Secukinumab	PsO and PsA
	Ixekizumab	PsO and PsA
IL-17A/IL-17F inhibitor	Bimekizumab	PsO and PsA
IL-17 Receptor Inhibitor	Brodalumab	PsO
PDE4 Inhibitor	Apremilast	PsO and PsA
Tyk2 Inhibitor	Deucravacitinib	PsO
IL-23 Inhibitor	Guselkumab	PsO and PsA
	Tildrakizumab	PsO
	Risankizumab	PsO

be the only rheumatologic sign of PsA in a subset of patients. Spondylitis causes low back pain and morning stiffness. The axial spine may be involved in 20 to 40 percent of PsA cases. The frequency increases to 51 percent with long-term follow-up. HLA-B27 is associated with 40 to 50 percent of cases in Caucasians and there is a male predominance. The Classification of Psoriatic Arthritis (CASPER) criteria for diagnosing PsA is shown in Exhibit 1.[4] Importantly, like rheumatoid arthritis, PsA causes joint destruction and disability.

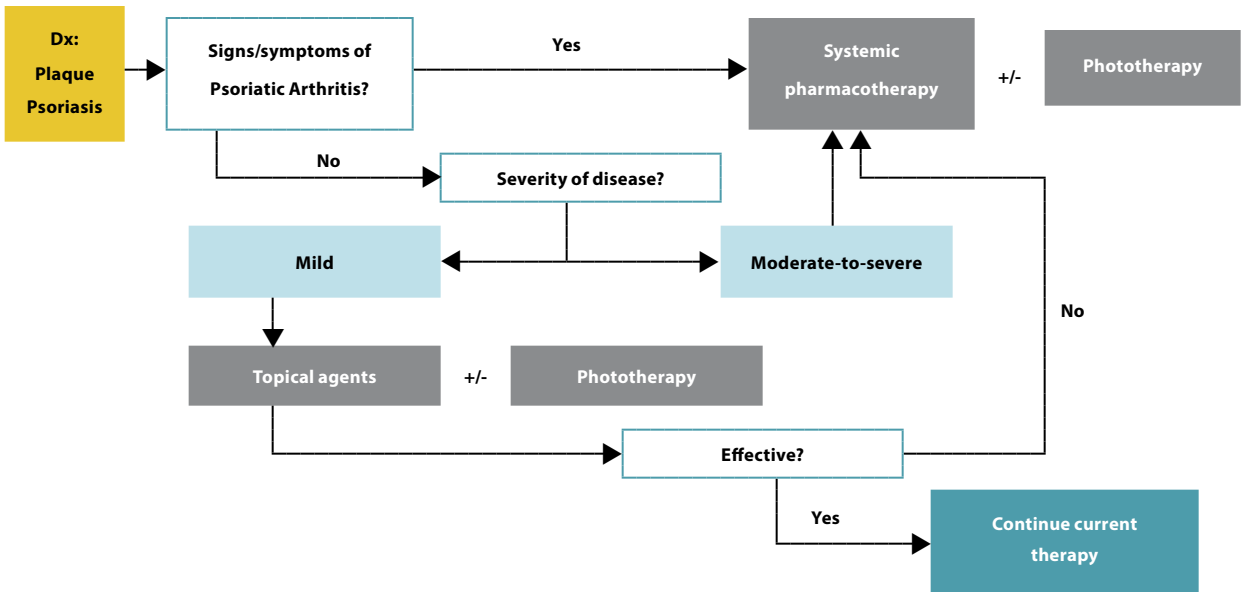
Psoriasis is not just a skin disease—it is a systemic inflammatory disease. Because of this, patients are at risk for various comorbidities beyond PsA including cardiovascular and diabetes (Exhibit 2).[5,6] Because it is a visible skin condition, patients have a higher rate of depression and anxiety.

Three cytokines have been implicated in the pathogenesis of psoriasis. These are tumor necrosis factor (TNF) alpha, interleukin (IL)-23, and IL-17 (Exhibit 3).[7,8] Each of these are targeted by approved therapies.

Severity of psoriasis is determined by the amount of body surface area (BSA) affected. Mild is 1 to 3 percent of BSA, moderate is 3 to 10 percent, and severe is more than 10 percent. To illustrate this, think of one palm equal to 1 percent BSA. Location also determines severity. Psoriasis that affects scalp, hands and feet, and groin and other skin folds can be especially debilitating. Psoriasis Area Severity Index (PASI) is a measure used in clinical trials and by some clinicians to assess severity. PASI has a score scale of 0 to 72 and rates various regions of the body on erythema, induration, and scaling. A PASI score of 12 or above is moderate-to-severe. Studies use PASI 75 (75% reduction in score from baseline), PASI 90, and PASI 100. Studies also use improvement in investigator global assessment (IGA) or physician's global assessment (PGA) which scores the body as 0 (clear) to 4 (severe) percentage reduction in affected BSA, and itch reduction to determine medication efficacy.

Mild-to-moderate psoriasis can be controlled with topical medications and/or phototherapy. Topical options include moisturizers, corticosteroids, calcipotriene, tazarotene, roflumilast (phosphodiesterase-4 inhibitor), and tapinarof (aryl hydrocarbon receptor agonist). Biologics are more efficacious and have a higher benefit-to-risk ratio in the treatment of moderate-to-severe disease. The IL-17 and IL-23 targeting agents appear to be more effective in clearing psoriasis when using PASI 75, 90, and 100 rates compared to the TNF and IL-12/23 agents.[9] Risankizumab, bimekizumab, guselkumab,

Exhibit 5: Use Disease Severity to Guide Treatment Selection[1,15-19]



ixekizumab, and secukinumab are the most used biologics due to superior efficacy and for some prolonged dosing intervals (every 2 to 3 months). The IL-17 targeting agents are preferred for PsA by most clinicians based on efficacy to treat both skin and joints. Beyond biologics, two oral systemic therapies are also available; apremilast, an oral phosphodiesterase-4 inhibitor, and deucravacitinib, an oral tyrosine kinase 2 (TYK2) inhibitor. Exhibit 4 shows which agents are FDA-approved for psoriasis and PsA.

Deucravacitinib, the first-in-class TYK2 inhibitor, was FDA-approved for moderate-to-severe plaque psoriasis in 2022. TYK2 mediates IL-23, IL-12, and type 1 interferon driven responses but not cytokine responses driven by other kinases which should reduce off-target events which can be seen with JAK inhibitors.[10] It was studied in two Phase III trials compared to placebo and apremilast. In the 52-week, double-blinded, Phase III POETYK PSO-1 trial, response rates at week 16 were significantly higher with deucravacitinib versus placebo or apremilast for PASI 75 (58.4% versus 12.7% versus 35.1%; $p < .0001$) and PGA 0 or 1 (53.6% versus 7.2% versus 32.1%; $p < .0001$).[11] Efficacy improved beyond week 16 and was maintained through week 52. PASI 90 was a secondary endpoint but again the rates achieved were higher with deucravacitinib versus apremilast (42.2% versus 22.0% at 24 weeks, $p < 0.0001$). The PSO-2 trial produced similar results.[12] In patients who received continuous deucravacitinib (n = 513) in PSO-1, PSO-2, and other long-term extensions from Phase II trials, clinical and patient-reported outcome rates were well maintained from year one through year four (e.g., PASI 90, 1 year, 45.6%, 4 years, 47.5%).[12] About 20 percent of patients maintained PASI 100 through four years. Infections, elevation of triglycerides, herpes simplex activation, folliculitis, and acne are some of the more commonly reported adverse events of deucravacitinib. It does have a warning label about malignancies including lymphomas (which were observed in clinical trials), elevations of creatinine phosphokinase and rhabdomyolysis. Patients should be tested for tuberculosis and receive any needed live vaccines before starting therapy.

The first agent specifically for generalized pustular psoriasis (GPP), which is rare but life threatening, was FDA-approved in 2022. Spesolimab is an interleukin-36 receptor antagonist. In a Phase II trial 53 patients, with a GPP flare, were randomized on a 2:1 ratio to receive a single 900-mg intravenous dose of spesolimab or placebo and then two additional open-label doses given.[13] The primary endpoint was a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub score of 0 (range, 0 [no visible pustules] to 4 [severe pustulation]) at the end of week one. At baseline, 46 percent, and 39 percent of the patients in the spesolimab group and placebo group had a GPPGA pustulation sub-score of 3, and 37 percent and 33 percent respectively, had a pustulation sub-score of 4. At the end of week one, 54 percent in the

spesolimab group had a pustulation sub-score of 0 compared to 6 percent of placebo group ($p < 0.001$). In the GPP treatment trial, 92 subjects were assigned to receive spesolimab (30 high dose, 31 medium dose, and 31 low dose) subcutaneous injection every four weeks and 31 to placebo.[14] By week 48, 23 percent in the low-dose spesolimab group, 29 percent in the medium-dose, 10 percent in the high-dose, and 52 percent in the placebo group had a GPP flair. High-dose spesolimab (300 mg every 4 weeks) was significantly superior versus placebo on the primary outcome of time to GPP flare (hazard ratio = 0.16, $p = 0.0005$). This agent is given by subcutaneous injection 300 mg every 4 weeks for GPP treatment. If used for a flare, it is given as a 900 mg intravenous infusion. If flare symptoms persist, an additional intravenous dose can be given one week later.

In selecting an agent for plaque psoriasis or PsA, the severity of the disease is typically most important in choosing between topical and systemic therapy (Exhibit 5).[1, 15-19] Patient preference, comorbidities, current medications, adherence history, and insurance coverage also play a part in choosing individual agents. The potential adverse events of a given class of agents and dosing schedule of medication are also considerations. Importantly, patients need to understand that the oral agents for psoriasis are potent immune suppressants and have risks similar to the injectable biologics. Not all psoriasis patients respond to any one class of agent, thus finding an effective therapy can take time. Patient perception of response to therapy can influence physician definition of an inadequate response.

Additional agents are on the horizon. Zasocitinib and ESK-001 are other oral TYK2 inhibitors in Phase III trials. Icotrokinra is an oral IL-23 receptor blocker which would obviate the need for subcutaneous injections as with the current IL-23 agents. Two Phase III trials have been completed. Published trials with these three agents have been very positive with low rates of serious adverse events.

Conclusion

Multiple treatment options are now available. The primary goals of treatment include clearing the skin, reducing signs and symptoms of joint pain, minimizing adverse events, addressing comorbidities, and enhancing patient quality of life. Patient preference should be considered when selecting therapy. Dermatologists should screen for joint involvement in their psoriasis patients and collaborate with rheumatologists to adequately manage both skin and joint involvement over the long-term.

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Optimizing Outcomes in Sickle Cell Disease: Exploring the Latest Advances in Treatment Strategies

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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 that leads to restricted blood flow and limited oxygen delivery to the body's tissues, leading to severe pain and organ damage. Management of SCD has focused on preventing and treating pain episodes and other complications but new gene-based therapies offer possible cures.

Key Points

- SCD has a complex pathophysiology including both hemolytic anemia and vaso-occlusion.
- There are currently three approved therapies and two gene therapy options with more to come.
- Clinicians need to discuss all therapies including pros and cons with patients and their families.
- Clinicians should be advocating for multidisciplinary support for the patient.

SICKLE CELL DISEASE (SCD) IS A GROUP OF inherited red blood cell (RBC) disorders where there is polymerization of sickle mutated hemoglobin upon deoxygenation that leads to a "sickled" RBC shape, hemolysis, vaso-occlusive crises, pain, and chronic organ damage from vaso-occlusion.[1-3] SCD is caused by a point mutation in the β-globin gene changing glutamic acid to valine. It is the most common single gene disorder in African Americans. More than 90 percent of those affected in the United States are non-Hispanic Black or African American, and an estimated 3 percent to 9 percent are Hispanic or Latino. SCD is usually diagnosed through newborn screening tests and affects about 100,000 Americans. Exhibit 1 shows the different types of SCD.[1-3] Hemoglobin SS (HgbSS) is the most common and severe type, caused by inheriting two copies of the abnormal hemoglobin S (HgbS) gene.

Developments since the mid-1970s have improved patient management and survival (Exhibit 2).[4-6] Although the SCD field has come a long way with survivorship, it is still not enough. The average life expectancy with SCD is still 20 to 30 years shorter compared to those without SCD.[7]

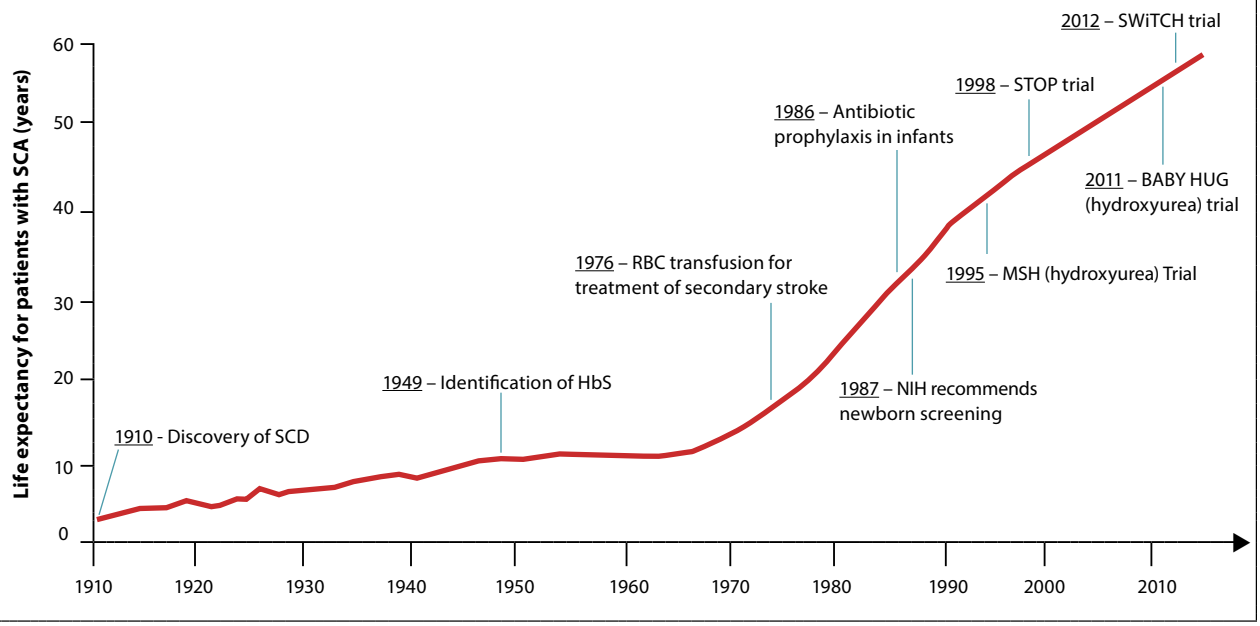
Treatment options for SCD include transfusions, hydroxyurea, L-glutamine, crizanlizumab, bone marrow transplant, and gene therapy (exagamglogene autotemcel and lovotibeglogene autotemcel). Exhibit 3 illustrates where in the disease process each therapy works. Clinical trials are also important for continuing to advance treatment.

Transfusions dilute the amount of sickled RBCs that are present in the blood. Episodic transfusions are used to manage acute stroke, symptomatic anemia, acute chest syndrome, multiorgan failure, and surgery preparation. Regular, chronic transfusions

Exhibit 1: Types of Sickle Cell Disease[1-3]

Type	% of Patients	Gene from Parent 1	Gene from Parent 2
Hemoglobin SS	65%	Hemoglobin S	Hemoglobin S
Hemoglobin SC	25%	Hemoglobin S	Hemoglobin C
Hemoglobin Sβ+	7%	Hemoglobin S	Beta-plus thalassemia
Hemoglobin Sβ^0	3%	Hemoglobin S	Beta-zero thalassemia

Exhibit 2: Recent Developments Have Greatly Improved Patient Management and Survival[4-6]

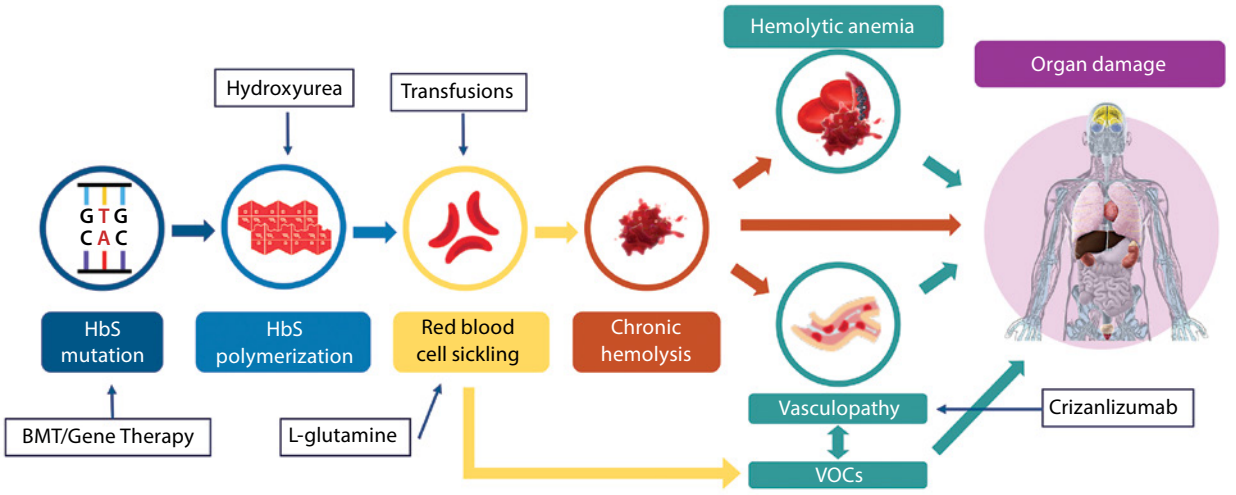


are standard of care for stroke prevention. Other indications for chronic transfusions in those with SCD which have more soft data to support use are recurrent acute chest syndrome not helped by hydroxyurea, frequent acute pain, recurrent splenic sequestration, leg ulcers, progressive organ failure (hepatic, renal, cardiac, and pulmonary), priapism, and complicated pregnancy. Blood transfusions have benefits of reduced central nervous system injury, reduced pulmonary damage, and reduced cardiac abnormalities.[8-10] Unfortunately, transfusions have risks including alloimmunization, immune reactions, blood hyperviscosity, organ complications, iron overload, and infections.[11,12] Chronic transfusions, which are given monthly, are also inconvenient for patients and use significant healthcare resources.

Hydroxyurea indirectly reduces HbS polymerization through induction of non-polymerizing fetal hemoglobin (HbF) expression. HbF holds onto oxygen and does not sickle. Treatment with hydroxyurea improves clinical outcomes compared to placebo by reducing the annual rate of painful vaso-occlusive crises (VOC) by about 45 percent and reducing hospitalization rates.[13] Despite being a good medication, hydroxyurea is not enough to adequately manage SCD over the patient's lifetime. Many patients continue to experience crises and organ damage and have reduced life expectancy.[14] Adverse events include oral, nail, and cutaneous pigmentation; oral mucositis; and patchy hair loss. It also causes fertility issues in males (oligospermia, azoospermia). These adverse events can lead to discontinuation.

Hydroxyurea should be started in hemoglobin SS and Sβ^0 patients at nine months of age.[15] It should be considered for the other two types of SCD. Use of hydroxyurea requires weeks to months for fetal

Exhibit 3: SCD Pathophysiology and Where Treatments Work



HbS = sickle hemoglobin; VOC = vaso-occlusive crisis; BMT = bone marrow transplant

hemoglobin to significantly increase. Adherence is important for patient benefits and it is important for patients to take it daily and not consistently miss doses.[16]

L-glutamine is an antioxidant which reduces oxidative stress in the RBC. It is indicated in those five years of age and older to reduce SCD complications. It is given as 5 to 15 grams (1 to 3 packets) twice per day. The dose twice a day, the volume of medication, and grittiness of the powder can lead to adherence issues or therapy discontinuation. It causes headaches, nausea, abdominal pain, and constipation. The benefits of l-glutamine are similar to hydroxyurea with a 45 percent reduction in VOC.[17]

Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin, a cellular adhesion molecule that is expressed on the endothelium and activated platelets, and plays a significant role in vaso-occlusion in SCD. P-selectin has been called sticky factor and its inhibition reduces the adhesion of sickled RBC. In a Phase II trial, it reduced VOC by about 45 percent.[18] The FDA-approved indication is to reduce frequency of VOC in patients aged 16 and older. It can be given with hydroxyurea. It is administered as an intravenous infusion over 30 minutes once a month. Adverse events include nausea, abdominal pain, body aches, and low-grade fever. Many clinicians are using this agent less often because a Phase III trial (STAND) showed no significant difference in annualized VOC efficacy between crizanlizumab and placebo.[19] Clinicians do use crizanlizumab off-label to treat SCD-related priapism.

Voxelotor, a HgS polymerization inhibitor, is no longer available. It was granted accelerated approval by the FDA in 2019 but was voluntarily withdrawn from market by the manufacturer in September 2024. The withdrawal was due to an increased rate of VOC and deaths in post-marketing and real-world registry studies.[20]

Bone marrow transplant (BMT) is potentially curative option but also has many issues. For individuals with SCD undergoing hematopoietic stem cell transplantation (HSCT) using HLA-matched sibling donors and either myeloablative or reduced intensity chemotherapy conditioning regimens, the five-year event-free and overall survival is high at 91 percent and 93 percent, respectively.[21] Issues with BMT include limited availability of HLA-matched sibling donors in the SCD population, the need for chemotherapy conditioning and subsequent malignancy risk, the need for immunosuppressants post-transplant, and graft versus host disease.

Gene therapy bypasses some of the issues with BMT. With gene therapy, the patient's bone marrow is erased with chemotherapy as with a BMT but the replacement bone marrow has its own cells which have been modified. Thus, post therapy immune suppression is not needed and graft versus host disease is not an issue. The two approved gene therapies use different methods. Exagamglogene autotemcel uses CRISPR/Cas9 gene-editing technology to increase fetal hemoglobin production and lovotibeglogene autotemcel uses addition of a modified, anti-sickling gene which leads to production of Hgb-

T87Q. This modified hemoglobin has an amino acid substitution (threonine to glutamine at position 87) that inhibits the sickling of RBC. The process for gene therapy begins with a discussion about appropriateness of the therapy—gene therapy is currently only used for those with the most severe disease. Once determined to be appropriate, the patient must receive transfusions to calm the SCD and then stem cells are harvested. The stem cells are then sent to laboratory for modification. The patient then undergoes chemotherapy before infusion of the gene therapy. With gene therapy, modified Hgb levels increase 40 to 45 percent, overall Hgb levels stabilize at 11 to 11.5 g/dL, and there is a 95 percent decrease in VOC.[22,23] Because the current gene therapy requires chemotherapy as preparation, there is a potential risk of myelodysplastic syndrome (MDS) and malignancies.

Two oral pyruvate kinase (PK) activators, mitapivat and etavopivat, are in trials for SCD. PK activators bind to and activate the PK enzyme in RBC. This activation increases the rate of glycolysis, leading to higher levels of ATP, the main energy currency for cells. The increased ATP helps RBC maintain their membrane and function correctly, which improves their survival and reduces hemolysis. In SCD, PK activators diminish sickling by decreasing 2,3-diphosphoglycerate. Mitapivat is already FDA-approved to treat hemolytic anemia in adults with PK deficiency. In a one-year pilot Phase II study in SCD, sustained improvement in Hgb level (mean increase, 1.1 ± 0.7 g/dL; p = .0014) was seen, which was accompanied by decreases in markers of hemolysis. In addition, the annualized rate of VOC reduced significantly from a historic baseline of 1.33 ± 1.32 to 0.64 ± 0.87 (p = .0489).[24] In a global, Phase II/III, double-blind, randomized, placebo-controlled trial (RISE UP), the 12 week Phase II part of the study has been completed and reported.[25] Patients aged 16 years or older with a confirmed diagnosis of SCD (any genotype), baseline hemoglobin of 5.5 to 10.5 g/dL, and two to 10 sickle cell pain crises within 12 months were randomly assigned 1:1:1 to receive oral mitapivat 50 mg, 100 mg, or placebo twice daily. Over 12 weeks, a statistically significant hemoglobin response rate versus placebo was shown in both treatment groups (46% in the mitapivat 50 mg group and 50% in the mitapivat 100 mg group, versus 4% in the placebo group; two-sided p = 0·0003 and p = 0·0001, respectively). VOC data was not reported. Mitapivat was generally well tolerated. Grade 3 or worse adverse events occurred in 12 percent, 19 percent, and 7 percent patients, respectively. No serious or Grade 3 or worse adverse events were considered treatment related and there were no treatment-related deaths. The most common Grade 3 or worse adverse events were infections and infestations which were considered non-treatment related. Headaches and mild transaminase elevations are the most common adverse events. The Phase III trial of mitapivat has completed enrollment with topline results expected to be reported in late 2025. A Phase I, 12-week trial of etavopivat reported a mean maximal increase in Hg of 1.6 g/dL [range, 0.8-2.8]).[26]

Numerous other agents are in ongoing clinical trials. This includes osivelotor (an oral regulator of HbS), inclacumab (injectable monoclonal antibody against P-selectin like crizanlizumab), fetal hemoglobin inducers, and other gene therapies. One gene therapy being studied is being done without chemotherapy.

SCD is complex and requires specialist management, especially in severe disease. Achieving optimal outcomes requires educating the patient about SCD so the patient can advocate for themselves when they encounter clinicians who are not familiar with SCD. For example, all SCD patients need to know the signs and symptoms of stroke which require them to seek emergent care. The patient needs to be educated to tell emergency room clinicians that they need an exchange transfusion in the situation of a stroke. Selecting appropriate therapy requires shared decision-making with the patient and family and reviewing the pros and cons of each possible treatment. Patients need to be taught self-management skills including early signs of complications, managing pain, and preventing triggers. Patients need to be regularly assessed for depression, anxiety, and chronic stress which are common among those with SCD given the unpredictable and major pain that can occur. Patients with SCD seeking care in emergency rooms may encounter clinicians assuming they have drug seeking behavior. Patients need individualized pain plans which can be given to all caregivers. Clinicians can encourage support from family, friends, and SCD communities to help with adherence and emotional well-being. Many families will need help accessing resources such as insurance navigation, assistance programs, and patient advocacy groups. Appropriate management of SCD over the lifetime requires coordination across disciplines including hematology, primary care, and the various specialists needed to manage chronic complications of SCD.

As noted previously, adherence with medication is needed for optimal outcomes. Simplified treatment regimens, reminder systems, caregiver support, and behavioral intervention are all helpful. For young people with SCD, the integration of technology such as texting which is tied into the electronic medical

record is one way to improve care. Telemedicine is another way to improve care for those who may not be near an SCD specialist.

Economic obstacles, transportation difficulties, and insufficient provider knowledge about acute crises and chronic organ complications of SCD can lead to disparities in health outcomes.[27] Sickle cell disease day hospitals that handle non-complicated VOC can reduce the burden on emergency rooms and keep patients out of the hospital.[28] Unfortunately, these are not widespread. Some health systems have hired hospitalists to address high utilizer patients who in many places are those with SCD. The patients get to know the hospitalist and it has been shown to save money for health systems.

Conclusion

SCD has a complex pathophysiology including both hemolytic anemia and vaso-occlusion due to polymerization. There are currently three approved therapies and two gene therapy options with more to come. Clinicians need to discuss all therapies including pros/cons with patients and their families. Clinicians should be advocating for multidisciplinary support for the patient.

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Optimizing Care of Patients with Hemophilia: Maximizing the Potential of Emerging Treatments

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Summary

To optimize outcomes for those with hemophilia, appropriate prophylactic treatments for the patient's lifetime and adherence support are required. Tremendous improvements in hemophilia treatment including extended half-life factors, non-factor rebalancing therapies, and gene therapy have been developed to address the major unmet needs in this devastating disease. Minimal disease consequences now occur in those with hemophilia who are started on therapy as children.

Key Points

- Hemophilic arthropathy is the most significant complication of hemophilia.
- Inhibitor development is the most serious complication of factor replacement.
- Non-factor rebalancing therapies are the future of hemophilia treatment.
- Gene therapy is a potential cure for hemophilia and is now available.
- Hemophilia Treatment Center expertise and resources can optimize care.

HEMOPHILIA, WHICH REFERS TO deficiencies of factors VIII and IX, is an X-linked recessive hereditary disorder that classically affects males due to the presence of only one X chromosome in males. Hemophilia A (factor VIII deficiency) occurs in one in 5,000 males and hemophilia B (factor IX deficiency) in one in 20,000 males.[1,2] Importantly, 30 percent of patients have no known family history. Heterozygous females (i.e., carriers) can be symptomatic. Historically, they were called symptomatic carriers but are now referred to by their level of factor as mild or moderate hemophilia. Severe hemophilia can occur also in females because of skewed lyonization, also known as X-chromosome inactivation. When a female carrier of hemophilia experiences skewed lyonization, the X chromosome carrying the normal gene is preferentially inactivated and the X chromosome with the mutated gene is active.

Hemophilia is classified as mild, moderate, or severe based on factor activity which determines bleeding risk (Exhibit 1).[1,2] Severe disease is usually diagnosed early in life because of spontaneous bleeding or bleeding at birth or with activity such as crawling whereas mild may not be diagnosed until abnormal bleeding occurs after major injuries, surgery, or tooth extractions.

Bleeding and its consequences are the major risk of hemophilia. Without proper treatment, recurrent bleeding into joints results in crippling arthropathy. Hemophilic arthropathy is currently the most significant complication of hemophilia. Intramuscular, gastrointestinal, and intracranial bleeds can be limb- and life-threatening. Flexion contractures, chronic pain, muscle atrophy, compartment syndrome, and neurologic impairment can occur because of bleeding into joints and muscles. It is important to note that with hemophilia, particularly severe disease, bleeding can occur in any part of the body.

Hemophilia causes significant financial burden. For example, in patients with severe hemophilia A, the yearly cost using real-world American Thrombosis and Hemostasis Network (ATHN)

Exhibit 1: Categorizing Severity of Hemophilia A and B[1,2]

Severity	Factor Activity	Symptoms	Inhibitor Risk	Usual Age of Diagnosis
Severe	< 1%	Frequent spontaneous bleeding; abnormal bleeding after minor injuries, surgery, or tooth extractions.	~ 25% in FVIII ~ 5% in FIX	Age ≤ 2 years
Moderate	1% to 5%	Spontaneous bleeding is rare; abnormal bleeding after minor injuries, surgery, or tooth extractions.	~ 1% to 2%	Age < 5 to 6 years
Mild	> 5% to 35%	No spontaneous bleeding; abnormal bleeding after major injuries, surgery, or tooth extractions.	Rare	Often later in life, depending on hemostatic challenges

data was estimated to be $613,220 to $934,301, depending on the type of factor replacement used and the presence of inhibitors (neutralizing antibodies against factor), using 2013 to 2019 data.[3] Inhibitors are the most important complication of factor replacement. The rate of antibodies is higher in those with severe hemophilia because of higher amounts of factor exposure. In this study, those with inhibitors had more frequent healthcare visits, had the shortest interval between doses of prophylaxis, had the highest rate of treatment discontinuation, and had higher average doses of factor replacement. Patients without inhibitors were the opposite and most could manage their disease without significant healthcare utilization. Those with severe disease and inhibitors are a target population that would benefit from a specific care management model. Targeting the population of those with hemophilia and inhibitors is the area towards which many of the novel therapies are working.

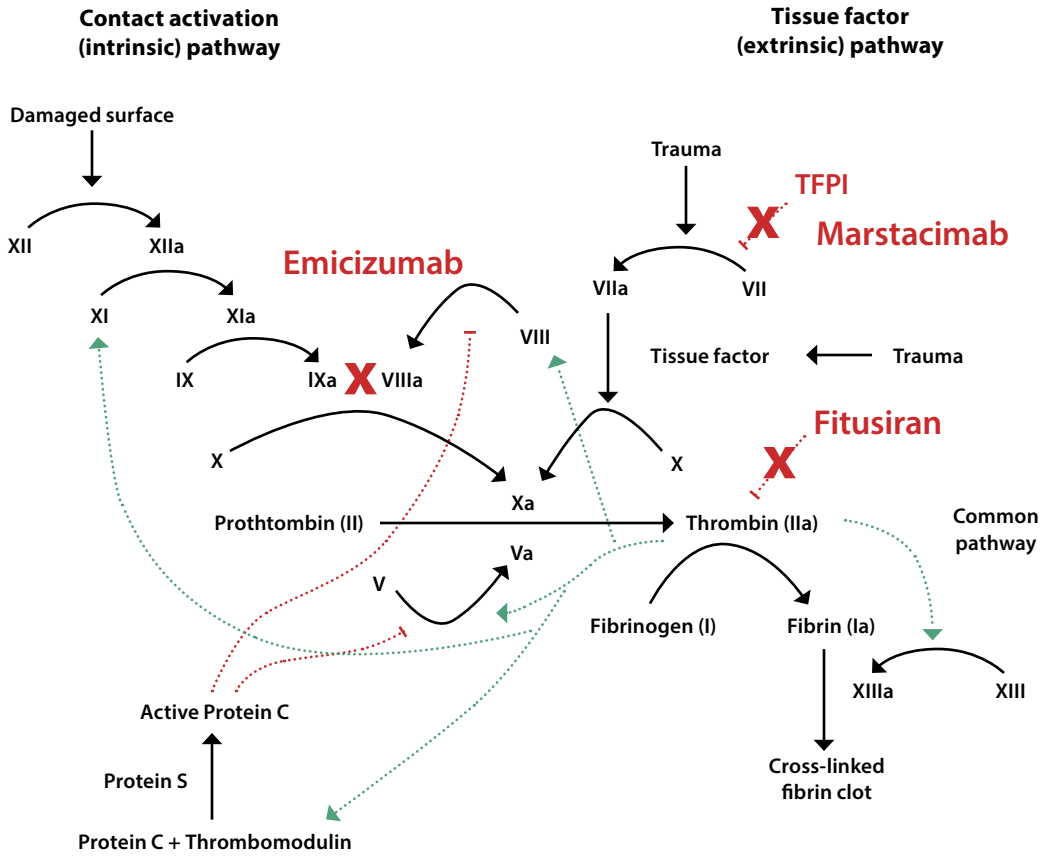
As with hemophilia A, the annual costs for hemophilia B are also significant. One study found annual total healthcare costs per patient increased with increasing severity (mean ± SD: mild, $80 811 ± $284 313; moderate, $137 455 ± $222 021; moderate-severe, $251 619 ± $576 886; severe, $632 088 ± $501 270).[4] The risk of inhibitors to factor IX is much lower than the risk with hemophilia A.

Financial burden with either type of hemophilia also comes from loss of time from work for oneself or children's treatment.[5] How factor replacement is given can also impact financial burden. Factor replacement can be given on demand (for bleeds, before procedures, etc.) or prophylactically. Those who receive prophylaxis have fewer emergency room visits, hospitalizations, and bleeding episodes—they also have shorter lengths of hospital stays.[5]

Use of prophylaxis from an early age is one way to reduce complications of the disease and reduce long-term costs such as the need for joint replacement. Prophylaxis from 30 months of age compared with episodic treatment in severe hemophilia A was shown in one trial (Joint Outcome Study, JOS) to significantly reduce the rate of hemophilic arthropathy by age six.[6] When the boys reached six years of age, 93 percent of those in the prophylaxis group and 55 percent of those in the episodic-therapy group were considered to have normal index-joint structure on MRI ($p = 0.006$). A continuation of JOS evaluated early versus delayed prophylaxis effects on long-term joint health, following participants to age 18 years in an observational, partially retrospective study. Thirty-seven of 65 participants of JOS study enrolled, including 15 randomized to prophylaxis at mean age 1.3 years ("early prophylaxis"); 18 initially randomized to episodic treatment, starting "delayed prophylaxis" at mean age 7.5 years; and four with high-titer inhibitors. At 18 years old, MRI osteochondral damage was found in 77 percent of those on delayed and 35 percent of those on early prophylaxis for an odds ratio of bone damage, in the delayed versus early prophylaxis group, of 6.3 ($p = .02$).[7] Annualized bleeding rates were higher with delayed prophylaxis (mean plus or minus standard deviation, 10.6 ± 6.6 versus 3.5 ± 2.1; $p < .001$), including when only comparing time periods on prophylaxis (6.2 ± 5.3 versus 3.3 ± 1.9; $p < .05$). In severe hemophilia A, early initiation of prophylaxis provided continued protection against joint damage throughout childhood compared with delayed initiation, but early prophylaxis was not sufficient to fully prevent damage because bleeds still occurred.

The standard of care is to initiate prophylaxis as soon as possible. This allows affected children to be physically active to strengthen joints and for general

Exhibit 2: Non-Factor Products Mechanism of Action



health. Adequately treating patients with severe hemophilia who play sports may require intensive factor replacement therapy. The goal of prophylaxis is a factor trough of 1 to 2 percent. Traditionally, recombinant factor VIII was given three times a week and factor IX twice a week, based on the half-life of the products. This is an intense regimen for parents or children to self-infuse peripherally or via a central venous catheter with its concomitant infection risk. Additionally, adolescence and adulthood are times when non-adherence with factor replacement can be a major issue.

The bioengineered extended half-life factor products (rEHL) are a major improvement in reducing treatment burden over earlier plasma derived factor products. They are all still given intravenously, but they are given less frequently than traditional factor therapy. They provide higher factor levels throughout the dosing interval, thus are more effective at preventing bleeds and joint disease. The most effective is efanesoctocog alfa, FDA-approved in 2023 and given once weekly, where children have 40 percent factor levels at day three and adults at day four.

Novel non-factor therapies for hemophilia have been developed which address many of the unmet needs in hemophilia treatment. These include improved efficacy, reduced treatment burden, improved adherence, and most significantly, improved outcomes for inhibitor patients.

The non-factor products (marstacimab, fitusiran, emicizumab) are called balancing agents because they shift the clotting cascade towards clotting (Exhibit 2). They are all given subcutaneously and most of them less frequently than factor therapy. These can be used in patients with inhibitors and therefore may be more effective at preventing joint disease in that population. Prior to approval of these agents, those with inhibitors were treated with immune tolerance induction (through frequent injections of clotting factor VIII or IX concentrates) to eradicate inhibitors and bypassing agents (such

as recombinant activated clotting factor VII and activated prothrombin complex concentrates) for the prevention and treatment of bleeding episodes. The biggest concern with the non-factor agents is tipping the balance too far into clotting and causing thromboembolic events.

Emicizumab was the first non-factor product approved by the FDA (2017). It is a bispecific factor IXa- and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients—ages newborn and older—with hemophilia A with or without factor VIII inhibitors. It is given every one to four weeks. Studied in seven trials, it is effective in reducing annualized bleeding rates in adults and children.[8] Fifty-six to 77 percent of patients had zero bleeds, depending on the patient population. For a newborn with hemophilia A, this agent could be started in the delivery room; unfortunately, hospitals do not stock it for this purpose, thus it begins as soon as insurance approves coverage, which can be from four to six weeks.

Marstacimab is a tissue factor pathway inhibitor (TFPI) antagonist. It was FDA-approved in 2024 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A or hemophilia B without inhibitors. After a loading dose, this agent is given once a week by subcutaneous injection. In the Phase III BASIS study, adolescents, and adults with severe hemophilia A or moderately-severe to severe hemophilia B received once-weekly subcutaneous 150 mg marstacimab for 12 months. Weekly subcutaneous marstacimab reduced annualized bleeding rates compared with prior on-demand or routine prophylaxis therapy.[9] There were no deaths or thromboembolic events related to treatment.

Approved in 2025, fitusiran is an antithrombin-directed small interfering ribonucleic acid (siRNA) indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors. By targeting antithrombin, the goal is to rebalance hemostasis in people with hemophilia A or hemophilia B, regardless of inhibitor status. This agent is given once every two months. Antithrombin levels must be monitored during therapy. This agent has been studied in both those with and without inhibitors. In the inhibitor study, mean annualized bleeding rate was significantly lower in the fitusiran prophylaxis group (1.7) than in the bypassing agents on-demand group (18.1), corresponding to a 90.8 percent reduction in favor of fitusiran prophylaxis ($p < 0.0001$).[10] Sixty-six percent of the fitusiran group had had zero treated bleeds versus one (5%) in the bypassing agents on-demand group. The most frequent treatment-emergent adverse event in the fitusiran group was increased alanine aminotransferase in 32 percent of 41 participants in the safety population. Suspected or confirmed thromboembolic events were reported in two participants in the fitusiran prophylaxis group. No deaths were reported. Comparable results of a 90 percent reduction in bleeding rates compared with on-demand therapy with factor replacement ($p < 0.0001$) was seen in the non-inhibitor trial; median annualized bleeding rate was 0.0 in the fitusiran group.[11] No thromboembolic events were reported in this trial and 19 percent had liver function test elevations. A third trial of this agent included those with hemophilia A or B, aged 12 years or more with or without inhibitors with prior bypass agent or clotting factor prophylaxis. Estimated mean annualized bleeding rates were substantially reduced with fitusiran by 79.7 percent ($p = .0021$) and 46.4 percent ($p = .0598$) compared with bypass agents and factor prophylaxis, respectively.[12] Forty-one participants (63.1%) experienced 0 treated bleeds with fitusiran compared to 11 (16.9%) with bypass agents/factor prophylaxis. Two participants experienced suspected or confirmed thromboembolic events with fitusiran and 25.4 percent had elevated liver function tests.

Gene therapy is also now available for severe hemophilia. Ideally, it will be a single infusion correcting the genetic absence of factor VIII or factor IX permanently. Long-term follow-up data will be needed to show whether gene therapy is a cure for hemophilia. FDA-approved gene therapies for adults include valoctocogene roxaparvovec for hemophilia A, etranacogene dezaparvovec for hemophilia B, and fidanacogene elaparvovec for hemophilia B. Valoctocogene roxaparvovec delivers a B-domain-deleted factor VIII coding sequence with an adeno-associated virus vector to prevent bleeding in persons with severe hemophilia A. In a study out to two years after this gene therapy, the mean annualized treated bleeding rate decreased by 84.5 percent from baseline ($p < 0.001$) among the participants.[13] From week 76 onward, the trajectory of the transgene-derived factor VIII activity showed first-order elimination kinetics; the model-estimated typical half-life of the transgene-derived factor VIII production system was 123 weeks (95% confidence interval, 84 to 232). The risk of joint bleeding was estimated among the trial participants; at a transgene-derived factor VIII level of 5 IU per deciliter measured with chromogenic assay, the

Exhibit 3: Adherence Barriers[19]

- **Patient-related factors**
  - Health beliefs
  - Age
- **Condition-related factors**
  - Frequency of bleeding
- **Treatment-related factors**
  - Venous access
  - Dosing regimen
  - Cost
  - Perceived costs
- **Healthcare system factors**
  - Access to hemophilia-treatment center
  - Insurance
- **Socioeconomic factors**
  - Language
  - Acculturation
  - Health literacy
  - Balancing the child's care with other family and social needs
- **Illness perception**
  - Influences adherence to treatment plan
  - Negative view = defiance/denial
  - Positive view = higher perception of control

authors expected that participants would have 1.0 episode of joint bleeding per year. At two-year post-infusion, no new safety signals had emerged and no new serious adverse events related to treatment had occurred. The patients in this trial required very little factor replacement over the course of the trial; there was a 98.2 percent decline in amount. At three years after gene therapy in the original 17 recipients, factor levels were still a mean of 16.81. With this hemophilia A gene therapy, the patient is essentially being converted from severe to mild disease.

With etranacogene dezaparvovec for hemophilia B, the annualized bleeding rate decreased from 4.19 during the lead-in period with factor replacement to 1.51 during months seven through 18 after treatment, for a rate ratio of 0.36 ($p < 0.001$), demonstrating noninferiority and superiority of etranacogene dezaparvovec as compared with factor IX prophylaxis.[14] Factor IX activity had increased from baseline by a least-squares mean of 36.2 percentage points at six months and 34.3 percentage points at 18 months after treatment. Usage of factor IX concentrate decreased by a mean of 248,825 international units per year per participant in the post-treatment period ($p < 0.001$ for all three comparisons).

Fidanacogene elaparvovec is an adeno-associated virus gene-therapy vector for hemophilia B containing a high-activity human factor IX variant. In the Phase III trial of this agent, the annualized rate of bleeding for all bleeding episodes decreased by 71 percent, from 4.42 at baseline to 1.28 after gene therapy, a treatment difference of -3.15 episodes ($p = 0.008$).[15] At 15 months, the mean factor IX activity was 26.9 percent (median, 22.9%; range, 1.9 to 119.0) compared to less than 2 percent, which was the study entry criteria. In a multi-year follow-up of 14 subjects from the Phase I and IIa trials, mean factor IX activity was in the mild hemophilia range; the mean annualized bleeding rate was less than one, and 10 participants had no treated bleeding episodes.[16] Surveillance liver ultrasounds obtained from year one onward showed no evidence of cancer but showed steatosis in four participants who had weight gain and elevated aminotransferase levels (maximum alanine aminotransferase level, 77 U per liter). One participant with a history of hepatitis C, hepatitis B, human immunodeficiency virus infection, and an elevated body-mass index had progression of underlying advanced liver fibrosis. A total of 13 surgical procedures, unrelated to the gene therapy administration, were performed in 8 participants; exogenous factor IX was administered for 10 procedures, and no associated unexpected bleeding complications occurred. The major adverse event with hemophilia gene therapy is elevated ALT which may require corticosteroid treatment. Most patients can taper off the steroids by 30 weeks after the therapy infusion.

Although gene therapy costs over $3 million, in the long-term it may be cost effective. Prophylaxis can cost $300,000 to $400,000 annually. A cost-effectiveness analysis of hemophilia B gene therapy for severe disease was conducted before FDA approval and known pricing. It utilized a time horizon from 18 years old until death from the perspective of a third-party payer in the United States. Gene therapy was cost-effective compared to on-demand factor IX replacement and primary factor IX prophylaxis, using either standard or extended half-life products, considering a $150,000/quality-adjusted life-year threshold.[17] The price for gene therapy was assumed to be $2 million in the base-case scenario.

The future of hemophilia treatment for most patients is novel therapies. Efanesoctocog alfa is a bioengineered extended half-life product that will likely replace all the other factor VIII concentrates. Most factor therapies for both hemophilia A and B are being replaced by non-factor therapies. Non-factor rebalancing agents offer a subcutaneous option for both hemophilia A and B patients and those with and without inhibitors. Gene therapy is already available for both hemophilia A and B; however, it is restricted to adults (18 and older) who meet specified eligibility criteria. It has the potential to provide long-term bleed protection without the need for any prophylaxis treatment. It may be a long time before gene therapy receives approval for children and may never be approved given the risk of liver damage.

Determining treatment selection in prophylaxis depends on physical activity level, infusion or injection schedule, and trough factor levels. Physical activity should be encouraged. With prophylaxis, there is no difference between high- and low-impact sports in bleeding rates. The goal of factor replacement is factor troughs of 1 to 2 percent; factor goals will be much higher for those who participate in sports. Other selection factors include patient age, cost, insurance coverage, how the therapy is delivered, individual pharmacokinetic elimination of factor, immunogenicity, infectious risk, and adherence. A pharmacokinetic-based approach to prophylaxis is necessary to achieve optimal protection.[18]

Adherence can be a major issue, especially with adolescents. Non-adherence in those under 18 years of age is highest in the 13 to 18 age group where the patient may be handling their own medications rather than a parent directly giving the medication. Poor adherence leads to more bleeding and missed days of school. Longer acting factor products and non-factor therapies are helping but there are still issues and barriers. Clinicians must identify the barriers for an individual and educate the patient and caregivers on the importance of adherence and how to overcome barriers (Exhibit 3).[19]

The best way to ensure optimal outcomes is for all those with hemophilia to be treated in a Hemophilia Treatment Center (HTC) The 140 HTCs in the United States are centers of excellence which offer comprehensive care for treatment of persons with bleeding disorders. Their comprehensive care model is recognized as specialized preventative care. These centers have social workers, support groups, transition of care programs for childhood to adult care, and other benefits. Mortality is decreased by 40 percent in patients using a comprehensive HTC.

Conclusion

Overall, hemophilic arthropathy is the most significant complication of hemophilia. Inhibitor development is the most serious complication of factor replacement. Non-factor rebalancing therapies and gene therapy are the future of hemophilia treatment. Gene therapy is a potential cure for hemophilia. Hemophilia Treatment Center expertise and resources can optimize care and are the best places for those with moderate-to-severe disease to receive care.

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Notes

Notes

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