Allogeneic Stem Cell Transplantation
Clinical Coverage Criteria

Overview

Stem cell transplantation, also known as hematopoietic stem cell transplantation, is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow, peripheral blood or umbilical cord blood for intravenous infusion.

In an allogeneic stem cell transplantation, also called hematopoietic cell transplantation (HCT), stem cells are donated to the patient from another person who is a genetically matched stem cell donor. This is usually a sibling with the same tissue type as the patient. Where no sibling is available, a search is made of donor registries to find a suitably matched unrelated stem cell donor. Allogeneic transplants can offer the best chance of curing a number of blood and bone marrow cancers and other diseases. They are complex procedures that carry significant risks. The complexities and risks may be increased even more with a mismatched donor or volunteer unrelated donor transplant. As such, allogeneic transplants are usually not suitable for all patients.

Two types of allogeneic HCT treatment plans available: myeloablative and non-myeloablative. Before a myeloablative allogeneic HCT, the patient receives a conditioning regimen of high-dose chemotherapy and, sometimes, radiation therapy. This conditioning regimen serves two purposes: (1) it destroys any remaining cancer cells in the body and (2) it weakens the patient's immune system to keep the body from rejecting the donated stem cells. When a transplant is successful, the donated stem cells move to the bone marrow where they will begin to produce new blood cells, including red blood cells, platelets and white blood cells. This process is called engraftment. One of the benefits of allogeneic HCT is that after the donated cells engraft in the patient, they create a new immune system that attacks any remaining cancer cells in the patient's body. This is called the graft-versus-tumor effect, and it may be even more important than the conditioning regimen that is administered to destroy the cancer cells. This benefit can only occur in allogeneic stem cell transplantation.

One complication of allogeneic HCT is that despite the treatment to suppress the immune system, the patient's body may reject the donated stem cells before they are able to engraft in the bone marrow. Another complication of allogeneic HCT is that the immune cells from the donor (the graft) may attack healthy cells in the patient's body (host). This is called graft-versus-host-disease (GVHD). GVHD can be mild, moderate or severe. There are treatments for GVHD, but in some patients, GVHD does not respond to treatment and can be fatal.

Myeloablative allogeneic HCT for patients who are older or have overall poor health are relatively uncommon. This is because the pre-transplant conditioning regimen is generally not well tolerated by such patients, especially those with poorly functioning internal organs. However, reduced intensity allogeneic stem cell transplants may be an appropriate treatment for some older or sicker patients. Reduced-intensity allogeneic transplants, sometimes called nonmyeloablative or mini-transplants, use lower, less toxic doses of chemotherapy and radiation than the conditioning regimen that is given before a standard myeloablative allogeneic HCT. Reduced-intensity allogeneic transplants may be an option for certain patients who are older, who have organ complications or who are otherwise not healthy or strong enough to undergo standard allogeneic transplantation.

Policy

This Policy applies to the following Fallon Health products:

☒ Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)

☒ MassHealth ACO
☒ NaviCare HMO SNP
☒ NaviCare SCO
☒ PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
☒ Community Care

Prior authorization is required for allogeneic stem cell transplants.

Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)
Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Medicare statutes and regulations do not have coverage criteria for allogeneic stem cell transplants. Medicare has an **NCD for Stem Cell Transplantation (110.23, formerly 110.8.1)**, Version Number 2, Effective Date of this Version 03/06/2024. Under NCD 110.23, allogeneic stem cell transplantation is covered:

- Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
- Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome

On March 6, 2024, CMS issued a final decision (**CAG-00415R**) to expand Medicare coverage for allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare beneficiaries with myelodysplastic syndromes (MDS) designated as high-risk or very high-risk with a score of ≥ 4.5 according to criteria specified by the International Prognostic Scoring System - Revised (IPSS-R). CMS also finalized coverage of additional risk designations and scoring systems. The final NCD includes patients with MDS designated as Intermediate-2 or high-risk with a score of ≥ 1.5 according to criteria specified by the International Prognostic Scoring System (IPSS) and patients with MDS designated as high-risk or very high-risk with a score of ≥ 0.5 according to criteria specified by the Molecular International Prognostic Scoring System (IPSS-M).

Additionally, allogeneic hematopoietic stem cell transplants are covered in the context of a clinical trial under **Coverage with Evidence Development** (CED):

- Allogeneic hematopoietic stem cell transplant for MDS
- Allogeneic hematopoietic stem cell transplant for multiple myeloma
- Allogeneic hematopoietic stem cell transplant for myelofibrosis
- Allogeneic hematopoietic stem cell transplant for sickle cell disease

Coverage of all other indications for stem cell transplantation not otherwise specified above as covered or non-covered will be made by local Medicare Administrative Contractors under section 1862(a)(1)(A).

In addition to the nationally covered indications for allogeneic stem cell transplantation, National Government Services, Inc., the Part A/B Medicare Administrative Carrier (MAC) with jurisdiction in our service area, has an LCD for Allogeneic Hematopoietic Cell Transplantation for Primary Refractory or Relapsed Hodgkin and Non-Hodgkin Lymphoma with B-cell or T-cell Origin (L39513) effective for services performed on or after 08/01/2023.

Link to: **NCD for Stem Cell Transplantation (110.23, formerly 110.8.1)**
Link to: **LCD for Allogeneic Hematopoietic Cell Transplantation for Primary Refractory or Relapsed Hodgkin and Non-Hodgkin Lymphoma with B-cell or T-cell Origin (L39513)**

Coverage for allogeneic stem cell transplantation for indications not otherwise specified in the NCD or LCD as covered or non-covered will be made by Fallon Health for Medicare Advantage members.

MassHealth ACO
Fallon Health follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

MassHealth does not have Guidelines for Medical Necessity Determination for allogeneic stem cell transplantation, therefore, Fallon Health Clinical Coverage Criteria are applicable (MassHealth website search 05/23/2024).

NaviCare HMO SNP, NaviCare SCO
For plan members enrolled in NaviCare, Fallon Health first follow's CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Fallon Health Clinical Coverage Criteria

Fallon Health considers allogeneic hematopoietic cell transplantation (HCT) medically necessary for the following indications when all criteria are met.

Acute Lymphoblastic Leukemia (ALL), Pediatric (per NCCN Guidelines Version 5.2024 Pediatric Acute Lymphoblastic Leukemia)

- B-Cell:
  - In first complete remission (CR1), with high risk of relapse
  - Induction failure (M3 marrow) after achieving MRD-negative status
  - CR 2: Consider based upon timing of relapse (or refractory disease) and leukemic phenotype
  - CR3
  - CNS Involvement at time of relapse
  - Medullary or extramedullary relapse
- T-Cell:
  - Induction failure (M3 marrow), after achieving MRD-negative status
  - MRD positivity (>0.1%) at completion of consolidation , after achieving MRD-negative status
  - Medullary or extramedullary relapse

Acute Lymphoblastic Leukemia (ALL), Adult

- In remission or relapsed or refractory
- Reduced intensity conditioning when the member is in complete marrow and extramedullary first or second remission
- Relapsing ALL after a prior autologous stem cell transplant

Acute Myeloid Leukemia (AML)
- In first complete remission with poor- to intermediate-risk
- Refractory/relapsed to standard chemotherapy but responsive to intensified chemotherapy
- Refractory/relapsed after autologous stem cell transplant but responsive to intensified chemotherapy
- Reduced intensity conditioning when the member is in complete marrow and extramedullary first or second remission

Chronic Myeloid Leukemia
- Using myeloablative
- With reduced intensity, with comorbidities

Juvenile Myelomonocytic Leukemia (JMML)
- At diagnosis using myeloablative
- Refractory/relapsed after first-line treatment with chemotherapy (e.g. azacitidine)
- Relapsed after a prior allogeneic HCT

Hodgkin's Lymphoma
- Primary refractory or relapsed, using either myeloablative or reduced-intensity conditioning

Non-Hodgkin Lymphomas
- Aggressive B-cell subtypes
    - Myeloablative conditioning or high dose chemotherapy
        - Salvage therapy for those who do not achieve complete remission after first-line treatment with a full course of standard-dose chemotherapy
        - Consolidate or achieve a complete remission during responding treatment of a relapse
        - In patients with diffuse large B-cell lymphoma, with an adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse, who are in their first complete remission
- Indolent B-cell subtypes
    - Salvage therapy for those who do not achieve complete remission after first-line treatment with a full course of standard-dose chemotherapy
    - Consolidate or achieve a complete remission during responding treatment of a relapse
- Mantle cell or mature T-cell lymphoma
    - Salvage therapy with myeloablative or reduced-intensity conditioning
- Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma(SLL) in patients with:
    - Non-response or early relapse (within 12 months) after purine analogue containing therapy
    - Relapse (within 24 months) after purine analogue combination therapy or treatment of similar efficacy (i.e., autologous stem cell transplantation)
    - p53 deletion/mutation (del 17p) requiring treatment

Myelofibrosis, including primary myelofibrosis (PMF) and essential thrombocythemia or polycythemia vera that has progressed to MF (secondary MF) (per NCCN Guidelines Version 1.2024 Myeloproliferative Neoplasms)
- At diagnosis for higher-risk, including:
    - MIPSS-70/MIPSS-70+ Version 2.0 ≥4
    - DIPSS-Plus >1
    - DIPSS >2
    - MYSEC-PM: ≥14
- For lower-risk disease, (MIPSS-70 ≤3, MIPSS-70+ Version 2.0 ≤3. DIPSS-Plus ≤1, DIPSS ≤2 or MYSEC-OM <14), allogeneic HCT may be considered for select patients with disease progression following first-line therapies (JAK Inhibitors, peginterferon alfa-a or hydroxyurea as clinically indicated)

Myelodysplastic Neoplasms (MDS) (per NCCN Guidelines Version 2.2024 Myelodysplastic Syndromes)
- At diagnosis for higher-risk, including:
    - IPSS Intermediate-2, High;

    - IPSS-R Intermediate, High, Very High; or
    - WPSS High, Very High
- For lower-risk disease (IPSS Low, Intermediate-1; IPSS-R Very Low, Low, Intermediate; or WPSS Very Low, Low, Intermediate), allogeneic HCT may be considered for select patients with disease progression/no response to recommended first-line therapies and without m*IDH1*.

Exclusions

- Allogeneic stem cell transplant is considered experimental and therefore is not covered for the following conditions:
    - Mantle cell lymphoma to consolidate a first remission
    - Tandem transplants to treat patients with any stage, grade, or subtype of NHL
    - NK-cell lymphoma to consolidate a first remission
    - Waldenstrom macroglobulinemia

Summary of Evidence

Hematopoietic stem cell transplantation (HCT) using blood progenitor cells from the patient (autologous HCT), or a donor source (allogeneic HCT) has expanded to become a vital component of the therapeutic armamentarium against several life-threatening cancers and nonmalignant disorders. The clinical application of transplant has continued to grow, with over 22,000 HCTs performed in the United Stated in 2018. Key developments in conditioning strategies (development of reduced-intensity and nonmyeloablative conditioning), use of alternative donor source HCT (cord blood and haploidentical donors), emerging newer indications, and improvements in procedural technology and supportive care practices have safely expanded the applicability and utilization of HCTs. Participation in clinical research has played a pivotal role in advancing HCT over the years. Indeed, time trends data show significant improvements in overall survival (OS) and non-relapse mortality in recipients of HCT. The field of immune effector cell therapy (IECT) has also witnessed fruition of years of research, 2018 being a breakthrough year, with US Food and Drug Administration (FDA) approval of chimeric antigen receptor T cells (CAR-Ts) for relapsed/refractory B cell acute lymphoblastic leukemia in children and young adults and large B cell lymphoma in adults (Kanate et al., 2020).

Juvenile myelomonocytic leukemia

Juvenile myelomonocytic leukemia (JMML) is a rare myeloproliferative neoplasm of early childhood. Most patients carry either somatic or germline mutations of *PTPN11*, *KRAS*, *NRAS*, *CBL*, or *NF1* in their leukemic cells. These genetic aberrations are largely mutually exclusive and activate the RAS/mitogen-activated protein kinase pathway. For most patients, allogeneic hematopoietic stem cell transplantation (HCT) is the only curative therapy. Chemotherapy is employed as a bridge to HCT, except in few with less aggressive disease, in which chemotherapy alone can result in long term remission. *NRAS*-initiated JMML is heterogeneous and adequate management ranges from watchful waiting to allogeneic HCT. Upfront azacitidine in *KRAS* patients can achieve long-term remissions without HCT; if HCT is required, a less toxic preparative regimen is recommended. Germline *CBL* patients often experience spontaneous resolution of the leukemia or exhibit stable mixed chimerism after HCT. JMML driven by *PTPN11* or *NF1* is often rapidly progressive, requires swift HCT and may benefit from pretransplant therapy with azacitidine. Myeloablative conditioning is most commonly used with graft versus host disease (GVHD) prophylaxis tailored to the aggressiveness of the disease. Relapses are common even after HCT and a second HCT can salvage a third of these patients (Gupta et al., 2021; Mayerhofer et al., 2021).

The World Health Organization (WHO) classifies juvenile myelomonocytic leukemia (JMML) as a RAS pathway activation–driven myeloproliferative neoplasm (MPN) of early childhood (Khoury et al., 2022). The pathogenesis of JMML has been closely linked to activation of the RAS oncogene pathway, along with related syndromes. Syndromes and genetic features associated with an increased risk of developing JMML include the following:

- Neurofibromatosis type 1. Up to 14% of cases of JMML occur in children with NF1.

- Noonan syndrome. Noonan syndrome is usually inherited as an autosomal dominant condition but can also arise spontaneously. It is characterized by facial dysmorphism, short stature, webbed neck, and neurocognitive and cardiac abnormalities. Germline mutations in *PTPN11* are observed in children with Noonan syndrome and in children with JMML.
- Mutations in the *CBL* gene**.** *CBL* is an E3 ubiquitin-protein ligase that is involved in targeting proteins, particularly tyrosine kinases, for proteasomal degradation. Mutations in the *CBL* gene occur in 10% to 15% of JMML cases, with many of these cases occurring in children with germline *CBL* mutations. *CBL* germline mutations result in an autosomal dominant developmental disorder that is often characterized by impaired growth, developmental delay, cryptorchidism, and a predisposition to JMML. Some individuals with *CBL* germline mutations experience spontaneous regression of their JMML but develop vasculitis later in life, whereas patients with only somatic *CBL* mutations require therapy. JMML arising from germline mutations is clinically indistinguishable from JMML arising from somatic mutations, which necessitates studies of both normal and leukemic tissue. *CBL* mutations are nearly always mutually exclusive of *RAS* and *PTPN11* mutations.

A diagnosis of JMML can be made by combining clinical, laboratory, and molecular criteria. Updates to diagnostic criteria include: (1) exclusion of *KMT2A* rearrangements; (2) elimination of monosomy 7 as a cytogenetic criterion; and (3) emphasizing the significance of diagnostic molecular studies, particularly those aimed at demonstrating RAS pathway activation. The genetic background of JMML plays a major role in risk stratification and therapeutic approaches, with cases initiated by somatic mutations involving *PTPN11* and germline pathogenic variants associated with neurofibromatosis type 1 being the most aggressive types, while some cases associated with pathogenic germline *CBL* variants undergoing occasionally spontaneous remission (Khoury et al., 2022).

HCT currently offers the best chance of cure for most children with JMML. The European Working Group on Childhood Myelodysplastic Syndromes reported on outcomes of 100 transplant recipients at multiple centers treated with allogeneic HCT after a preparative regimen including busulfan, cyclophosphamide, and melphalan. Forty-eight and 52 children received transplants from an HLA-identical relative or an unrelated donor, respectively. The source of hematopoietic stem cells was bone marrow, peripheral blood, and cord blood in 79, 14, and 7 children, respectively. Splenectomy had been performed before HCT in 24 children. Thirteen patients died of transplantation-related causes, with the 5-year cumulative incidence of TRM being 13% (8% to 22%). The 5-year cumulative incidence of transplant-related mortality (TRM) for patients receiving transplants from either an HLA-identical sibling or an unrelated volunteer was 10% (5% to 24%) and 16% (8% to 30%), respectively (P = NS). The median time to treatment-related death was 2.7 months (range, 1 to 16). Thirty-four patients had hematologic relapse after transplantation, at a median time of 6 months (range, 2 to 36) after the allograft. Twenty-one children died due to disease progression at a median of 11 months after transplantation (range, 2 to 65). The 5-year cumulative incidence of relapse was 35%, with no significant difference between patients receiving transplants from either a relative or an unrelated donor The 5-year probability of event-free survival for children given HCT from either a relative or a unrelated donor was 55% and 49%, respectively (P = NS), with median observation time of patients alive being 40 months (range, 6 to 144). Overall, 66 children remain alive after HCT, the 5-year Kaplan Meier estimate of survival being 64% (54% to 74%). Fifty-three patients are alive in first complete remission after HCT, with a median observation time of 40 months (range, 6 to 144). The 5-year cumulative probability of EFS after the first allograft is 52% (42% to 62%) for the whole cohort of patients studied, being 55% (41% to 70%) and 49% (35% to 63%) for patients given HCT from either a relative or an unrelated donor, respectively (P = NS). Six patients are alive with disease, and 7 patients are alive in hematologic remission after a second allograft, which was performed in a total of 15 cases. Five of these 15 patients given a second transplantation died because of further disease recurrence, and 3 died due to transplantation-related complications. In 10 of the 15 children who received a second transplantation, the same donor used in the first HCT was used, and total body irradiation was added as part of the preparative regimen in 8 of these 15 patients. In multivariate analysis, age older than

4 years and female sex predicted poorer outcome. Results of this study compare favorably with previously published reports. Disease recurrence remains the major cause of treatment failure.

The use of reduced-intensity preparative regimens to decrease the adverse side effects of transplant have also been reported in small numbers of patients, generally for patient's ineligible for myeloablative HCT. The Children's Oncology Group conducted a randomized trial in children with JMML that compared a standard-intensity preparative regimen (busulfan/cyclophosphamide/melphalan) with a reduced-intensity regimen (busulfan/fludarabine). The trial closed to enrollment early when an interim analysis revealed a higher frequency of relapse/disease persistence (7 of 9 patients) in children who received the reduced-intensity regimen than in children who received the standard-intensity regimen (1 of 6 patients) (Dvorak et al., 2018).

Guidelines from the American Society for Transplantation and Cellular Therapy

Kanate et al., 2020 published updated recommendations from the American Society for Transplantation and Cellular Therapy (ASTCT) on indications for allogeneic hematopoietic stem cell transplantation (HCT) and immune effector cell therapy (IECT). Indications for HCT/IECT were categorized as (1) Standard of care, where indication is well defined and supported by evidence (S); (2) Standard of care, clinical evidence available, where large clinical trials and observational studies are not available but have been shown to be effective therapy (C); (3) Standard of care, rare indication, for rare diseases where demonstrated effectiveness exists but large clinical trials and observational studies are not feasible (R); (4) Developmental, for diseases where preclinical and/or early-phase clinical studies show HCT/IECT to be a promising treatment option (D); and (5) Not generally recommended, where available evidence does not support the routine use of HCT/IECT (N). The ASTCT will continue to periodically review these guidelines and update them as new evidence becomes available.

The ASTCT, formerly known as the American Society for Blood and Marrow Transplantation published guidelines regarding indications for autologous and allogeneic hematopoietic cell transplant in 2015 (Majhail et al., 2015) in response to a need identified by patients, transplant physicians, payers, and policymakers. Based on the recommendations of a task force consisting of clinical experts, payers, and

At the time it was also recognized that as the scientific field evolved and progressed, these guidelines would be updated to encompass new data.

Myelodysplastic syndromes	
Juvenile myelomonocytic leukemia	S

HCT is defined as an episode of care starting with a conditioning regimen and followed by hematopoietic progenitor cell infusion, derived from bone marrow, peripheral blood, or cord blood, and subsequent recovery.

Myelofibrosis

Myelofibrosis (MF) is a rare chronic BCR-ABL1 (breakpoint cluster region-Abelson murine leukemia viral oncogene homologue 1)-negative myeloproliferative neoplasm characterized by progressive bone marrow fibrosis, ineffective hematopoiesis, extramedullary hematopoiesis (EMH), splenomegaly consequent to extramedullary hematopoiesis, cytopenias, and an array of potentially debilitating abdominal and constitutional symptoms. The MF-associated consequences and medical complications often result in premature death from infection, thrombohemorrhagic events, cardiac or pulmonary failure, and leukemic transformation.

MF can be classified as primary or secondary to either polycythemia vera or essential thrombocytopenia. The current diagnostic criteria for primary myelofibrosis (PMF) were defined by the World Health Organization in 2016 and include clinical and laboratory features. There are two stages of development: initially a prefibrotic/ early stage, followed by an overt fibrotic stage (Arber et al., 2016). Progress over the last decade has enabled the incorporation of genetic information and specific morphologic features, for

both disease prognostication and determination of treatment response in myeloproliferative neoplasms. All myeloproliferative neoplasms feature the presence or absence of specific genetic markers in their diagnostic criteria according to the current WHO classification, underlining the importance of molecular studies. The molecular landscape of PMF shows one of the typical and disease-defining mutations in JAK2 (virtually always V617F), CALR encoding for calreticulin and MPL (myeloproliferative leukemia virus oncogene) encoding the thrombopoietin receptor. More than half of the cases (about 50–65%) show the JAK2 mutation in exon 14, followed by 25 to 30% with a CALR mutation and 8 to 10% with a MPL mutation (Nann and Fend, 2021). PMF is mostly a diagnosis of the sixth and seventh decade of life and the gender distribution is roughly even. About 15% of PV patients, and a small minority of patients with ET, show progression to a myelofibrotic phase, usually many years after primary diagnosis, called secondary myelofibrosis.

JAK-2 inhibitors alleviate many symptoms and even possibly increase survival, but they are not considered curative. Allogeneic hematopoietic stem cell transplant (HCT), with an overall cure rate of 30-65%, remains the only curative treatment for primary MF (Robin et al., 2019). Critical questions in the management of MF are which patients may benefit from allogenic HCT and when the transplant should be carried out. Powerful prognostic tools have been developed that assist clinicians in patient counseling and therapeutic decision making. The International Prognostic Scoring System (IPSS) is a clinic-based model to assess prognosis at the time of diagnosis (Cervantes et al., 2009). The Dynamic IPSS (DIPSS) was designed to track changes in prognosis related to changes in scoring parameters over time and can be applied at any time during the disease course (Passamonti et al., 2010). The DIPSS defines 4 risk categories—low, intermediate (int)-1, int-2, and high—which can be assigned on the basis of the instantaneous values of hemoglobin, white blood cell count (WBC), circulating blasts, constitutional symptoms, and patient age during follow-up. IPSS- and DIPSS-independent risk factors for overall survival (OS) in PMF were subsequently identified: they included unfavorable karyotype, the need for red cell transfusion, and a platelet count < 100×10^9. Accordingly, DIPSS was modified into DIPSS-Plus (Gangat et al., 2011). More recently, MIPSS-70 (Guglielmelli et al., 2018) and MIPSS-70+ Version 2.0 (Tefferi et al., 2018) were developed, which include mutational analysis.

Survival of patients with PMF can be predicted using one of those models, and thus eligibility for a transplant procedure. However eligibility must also include transplant related variables, such as patients age up to 70-75 years, a good performance status, low transfusion burden, absence of a massive splenomegaly and portal hypertension and donor type. Older patients also tend to have one or more comorbidities which may increase the risk of transplant related mortality or even preclude a transplant (Bacigalupo et al., 2021).

Kröger et al., 2015 analyzed outcomes in 438 patients <65 years who received allogenic SCT (n = 190) or conventional therapies (n = 248) using the Dynamic International Prognostic Scoring System (DIPSS). Among patients with low risk per the DIPSS model, the relative risk of death after allogeneic HCT versus those treated with other modalities was 5.6 (95% CI, 1.7-19; P = .0051); for intermediate-1 risk it was 1.6 (95% CI, 0.79-3.2; P = .19), for intermediate-2 risk, 0.55 (95% CI, 0.36-0.83; P = .005), and for high risk, 0.37 (95% CI, 0.21-0.66; P = .0007). Thus, patients with intermediate-2 or high-risk PMF clearly benefit from allogenic SCT.

NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms, Version 1.2024.

The diagnosis of primary myelofibrosis (PMF) is based on WHO 2022 criteria (Khoury et al., 2022). WHO 2022 criteria are the same as WHO 2016 criteria (Swerdlow et al., 2016). The WHO criteria describe two stages of development: an early/profibrotic stage (pre-PMF), followed by an overt fibrotic stage (overt PMF). The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations.

PROGNOSTIC SCORING SYSTEMS

For primary myelofibrosis (PMF), MIPPS-70 (Guglielmelli et al., 2018) or MIPSS-70+ Version 2 (Tefferi et al., 2018) are the preferred methods of prognostic risk stratification. If molecular testing is not available, then DIPSS-Plus. If recent karyotyping is not available, then DIPSS.

For secondary myelofibrosis (post-PV or post-ET), the Myelofibrosis Secondary to PV And ET-Prognostic Model (MYSEC-PM) is recommended for risk stratification (Passamonti et al., 2017).

NCCN stratifies myelofibrosis into Higher-risk and Lower-risk.

Higher-risk myelofibrosis is defined as:
- MIPSS-70: ≥4
- MIPSS-70+ Version 2.0: ≥4
- DIPSS-Plus: >1
- DIPSS: >2
- MYSEC-PM: ≥14

Lower-risk myelofibrosis is defined as:
- MIPSS-70: ≤3
- MIPSS-70+ Version 2.0: ≤3
- DIPSS-Plus: ≤1
- DIPSS: ≤2
- MYSEC-PM: <14

Online calculator for DIPSS score can be found at https://qxmd.com/calculate/calculator_187/dipss-prognosis-inmyelofibrosis

Online calculator for DIPSS-PLUS score can be found at https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis

Online calculator for MIPSS-70 can be found at http://www.mipss70score.it/

Online calculator for MIPSS-70+ Version 2.0 can be found at http://www.mipss70score.it/

Online calculator for MYSEC-PM can be found at http://mysec-pm.eu/

RECOMMENDATIONS

Allogeneic HCT is recommended for the treatment for higher-risk patients with platelets <50 x 10^9/L who are transplant candidates (MF-2).

For lower-risk patients, allogeneic transplant is not recommended as a first-line treatment. Allogeneic HCT may be considered for select patients with disease progression following first-line therapy (JAK Inhibitors, peginterferon alfa-2a or hydroxyurea as clinically indicated) (MF-1).

Guidelines from the American Society for Transplantation and Cellular Therapy

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The ASTCT, formerly known as the American Society for Blood and Marrow Transplantation published guidelines regarding indications for autologous and allogeneic hematopoietic cell transplant in 2015 (Majhail et al., 2015) in response to a need identified by patients, transplant physicians, payers, and policymakers. Based on the recommendations of a task force consisting of clinical experts, payers, and

At the time it was also recognized that as the scientific field evolved and progressed, these guidelines would be updated to encompass new data.

Myelofibrosis	
Primary, low risk	C
Primary, intermediate/high risk	C
Secondary	C

HCT is defined as an episode of care starting with a conditioning regimen and followed by hematopoietic progenitor cell infusion, derived from bone marrow, peripheral blood, or cord blood, and subsequent recovery.

The optimal timing for referral for HCT has been described in Recommended Timing for Transplant Consultation, published jointly by the ASTCT and NMDP (formerly known as the National Marrow Donor Program and Be The Match), available at https://bethematchclinical.org/). For myeloproliferative neoplasms, including primary myelofibrosis (PMF) and essential thrombocythemia or polycythemia vera that has progressed to MF (secondary MF):

High-resolution HLA typing and referral to HCT consultation is recommended at diagnosis for all patients with:

- DIPSS or DIPSS Plus Intermediate-1 (INT-1) or higher
- MIPSS70/MIPSS 70 plus version 2.0 intermediate-risk or higher
- Cytopenic subtype
- Young age
- High-risk features including high-risk mutations (*ASXL1, TP53*), triple negative (lack of a driver mutation such as *JAK2, MPL* or *CALR*)
- Patients failing JAK inhibitor therapy

HCT is recommended upfront for patients with:

- DIPSS or DIPSS Plus Intermediate-2 (INT-2) and high-risk disease
- MIPSS-70/MIPSS-70+ Version 2.0 high-risk disease
- Patients with DIPSS INT-1 or MIPSS70/MIPSS 70 plus version 2.0 intermediate-risk, cytopenic subtype, young age, high-risk features, including high-risk mutations (*ASXL1, TP53*), triple negative (lack of a driver mutation such as *JAK2, MPL*, or *CALR*) and those failing JAK inhibitor therapy should be considered for upfront HCT balancing patient preferences and clinical trial options.

Revised Management Recommendations from European LeukemiaNet

Over the last few years, significant progress has been made in a number of areas of Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-neg MPNs), i.e., polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). A panel of 23 experts were selected for their expertise in research and clinical practice in Philadelphia chromosome negative myeloproliferative neoplasms (Ph-neg MPNs). The goal was to produce consensus-based recommendations in the areas where no scientific evidence is available, and evidence-based recommendations when controlled clinical trials were available. This document updates the recommendations on the management of Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-neg MPNs) published in 2011 by the European LeukemiaNet (ELN) consortium (Barbui et al., 2018).

DIAGNOSIS

- In all three categories of Ph-neg MPNs, i.e., PV, ET, and MF, strict adherence to the 2016 revised WHO diagnostic criteria is recommended.
- Bone marrow biopsy is a necessary diagnostic test in any patient suspected of a Ph-neg MPN, with the exception of patients with PV with a hemoglobin greater than 18.5 g/dl in males and greater than 16.5 g/dl in females.

- Peripheral blood or bone marrow screening for driver mutations, i.e., JAK2V617F, CALR, and MPL, is recommended in any patient who may have a Ph-neg MPN.
- JAK2V617F should be the first test in patients suspected of any of the three diseases; in the case of JAK2V617F negativity, CALR and MPL, in that order, should then be tested in ET and MF, while JAK2 exon 12 should be tested in those JAK2V617F negative patients suspected of PV.
- Search for complementary clonal markers, such as ASXL1, EZH2, IDH1/IDH2, and SRSF2 is recommended in patients who tested negative for the three driver mutations and have bone marrow features and a clinical phenotype consistent with MF.
- There was no consensus concerning the search of additional clonal markers such as TP53, TET2, DNMT3A, and CBL in MF, and no consensus concerning the need for searching for complementary clonal markers in ET. Thus, this decision should follow individual institutional preference.

RISK STRATIFICATION

- In MF, the IPSS, based on hematological and clinical variables, is the recommended prognostic system and should be scored in all patients at diagnosis.
- There is increasing evidence that integration of IPSS with additional genetic information, i.e., cytogenetics and molecular parameters, allows a more detailed individualized prognostic classification.
- The Panel agreed that a complete genetic assessment should be encouraged in all patients for the prognostic assessment at diagnosis. However, the Panel also claimed that failure to perform a full genetic characterization at the time of diagnosis is acceptable in clinical practice.
- DIPSS, based on hematological and clinical variables, or DIPSS-plus, based on hematological, clinical and cytogenetic variables, are the recommended systems for prognostic re-assessment during the disease course.
- Molecular assessment during the course of the disease (at least ASXL1 mutation) is recommended for therapeutic decisions in selected MF patients, such as to decide a transplant in those who have an intermediate-1 risk category according to the DIPSS/DIPSS-plus score.

MANAGEMENT OF MYELOFIBROSIS

Asymptomatic patients with low- or intermediate-1 risk disease

There is no evidence to support the value of disease-modifying therapy in patients with IPSS/DIPSS/DIPSS-plus low or intermediate-1 risk disease. However, some of these patients might require palliative therapy for anemia, splenomegaly, or constitutional symptoms, as recommended in the previous guidelines

Observation alone for IPSS/DIPSS/DIPSS-plus low- or intermediate-1 MF risk patients who lack significant symptoms, and who do not display significant anemia (hemoglobin < 10 g/dl), splenomegaly (palpable spleen size > 10 cm), leukocytosis (leukocyte count > 25 × 109/l) or marked thrombocytosis (platelet count > 1000 × 109/l).

If cytoreductive treatment for the reduction of leukocytosis or thrombocytosis is indicated, the first-line drug of choice is hydroxyurea.

Allogeneic stem cell transplantation

The Panel recommends considering allogeneic HCT for patients with IPSS/DIPSS/DIPSS plus high or intermediate-2 risk.

The Panel also recommends considering an allogeneic HCT for transplant-eligible patients with IPSS/DIPSS/DIPSS-Plus intermediate-1 risk score, who present with either refractory, transfusion-dependent anemia, a percentage of blasts in peripheral blood > 2% in at least two repeated manual measurements, adverse cytogenetics, or high-risk mutations, such as such as ASXL1, EZH2, IDH1/IDH2, SRSF2. In this situation, the transplant procedure should be performed in a controlled setting (registries, clinical trial).

Acute Lymphoblastic Leukemia (Pediatric)

Adapted from National Cancer Institute (NCI) Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®)

Incidence

Acute Lymphoblastic Leukemia (ALL), the most common cancer diagnosed in children, represents approximately 25% of cancer diagnoses among children younger than 15 years. A sharp peak in ALL incidence is observed among children aged 1 to 4 years, with rates decreasing by age 10 years. The incidence of ALL among children aged 1 to 4 years is approximately four-fold greater than that for infants and for children aged 10 years and older. Childhood ALL originates in the T and B lymphoblasts in tissues with hematopoietic progenitor cells, such as the bone marrow and thymus.

Overall Prognosis

Among children with ALL, approximately 98% attain remission. Approximately 85% of patients aged 1 to 18 years with newly diagnosed ALL treated on current regimens are expected to be long-term event-free survivors, with more than 90% of patients alive at 5 years. In addition, the excess risk of death associated with the leukemia diagnosis had decreased such that the mortality rate of the surviving patients at 6 to 7 years after diagnosis was similar to that of the general population.

Cytogenetic and genomic findings combined with minimal residual disease (MRD) results can define subsets of ALL with event-free survival (EFS) rates exceeding 95% and, conversely, subsets with EFS rates of 50% or lower.

The World Health Organization (WHO) 5th Edition classifies childhood ALL into B-Cell Lymphoblastic Leukemias/Lymphomas and T-Lymphoblastic Leukemia/Lymphoma (Alaggio et al., 2022). The genomics of childhood ALL has been extensively investigated, and multiple distinctive subtypes have been defined on the basis of cytogenetic and molecular characterizations, each with its own pattern of clinical and prognostic characteristics. In recognition of the clinical significance of many of these genomic alterations, the 5th Edition Revision of the WHO Classification of Hematolymphoid Tumours (Allaggio et al., 2022) classifies B-ALL based on genomic subtypes:

- B-lymphoblastic leukemia/lymphoma, NOS.
- B-lymphoblastic leukemia/lymphoma with high hyperdiploidy.
- B-lymphoblastic leukemia/lymphoma with hypodiploidy.
- B-lymphoblastic leukemia/lymphoma with iAMP21.
- B-lymphoblastic leukemia/lymphoma with BCR::ABL1 fusion.
- B-lymphoblastic leukemia/lymphoma with BCR::ABL1-like features.
- B-lymphoblastic leukemia/lymphoma with KMT2A rearrangement.
- B-lymphoblastic leukemia/lymphoma with ETV6::RUNX1 fusion.
- B-lymphoblastic leukemia/lymphoma with ETV6::RUNX1-like features.
- B-lymphoblastic leukemia/lymphoma with TCF3::PBX1 fusion.
- B-lymphoblastic leukemia/lymphoma with IGH::IL3 fusion.
- B-lymphoblastic leukemia/lymphoma with TCF3::HLF fusion.
- B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities.

Pediatric T-ALL is characterized by genomic alterations leading to activation of transcriptional programs related to T-cell development and by a high frequency of cases (approximately 60%) with variants in NOTCH1 and/or FBXW7 that result in activation of the NOTCH1 pathway. Cytogenetic abnormalities common in B-ALL (e.g., hyperdiploidy, 51–65 chromosomes) are rare in T-ALL. Pediatric T-ALL cases are divided into 10 molecular subtypes based on their RNA expression and gene variant status. pediatric T-ALL cases are divided into 10 molecular subtypes based on their RNA expression and gene variant status.

Risk-Based Treatment Assignment

Children with ALL are usually treated according to risk groups defined by both clinical and laboratory features. The intensity of treatment required for cure varies substantially among subsets of children with ALL. Risk-based treatment assignment is used in children with ALL so that patients with favorable clinical and biological features who are likely to have a very good outcome with modest therapy can be spared

more intensive and toxic treatment, while a more aggressive, potentially more toxic therapeutic approach is reserved for patients with a lower probability of long-term survival.

Certain ALL study groups, such as the Children's Oncology Group, use a more- or less-intensive induction regimen based on a subset of pretreatment factors, while other groups give a similar induction regimen to all patients.

Factors used by the Children's Oncology Group to determine the intensity of induction include the following:

- Immunophenotype
- The presence or absence of extramedullary disease
- Steroid pretreatment
- The presence or absence of Down syndrome
- The National Cancer Institute (NCI) risk group classification

The National Cancer Institute (NCI) risk group classification for B-ALL stratifies risk according to age and white blood cell (WBC) count, as follows:

- Standard risk: WBC count less than 50,000/μL and age 1 to younger than 10 years.
- High risk: WBC count 50,000/μL or greater and/or age 10 years or older.

All study groups modify the intensity of postinduction therapy on the basis of a variety of prognostic factors, including NCI risk group, immunophenotype, early response determinations, and cytogenetics and genomic alterations. Detection of the BCR::ABL1 fusion (i.e., BCR::ABL1-positive ALL) leads to immediate changes in induction therapy, including the addition of a tyrosine kinase inhibitor, such as imatinib or dasatinib.

Risk-based treatment assignment requires the availability of prognostic factors that reliably predict outcome. For children with ALL, a number of factors have demonstrated prognostic value, some of which are described below. Factors affecting prognosis are grouped into the following three categories:

- Patient and clinical disease characteristics - Patient and clinical disease characteristics affecting prognosis include the following:
  - Age at diagnosis
  - WBC count at diagnosis
  - Central nervous system (CNS) involvement at diagnosis
  - Testicular involvement at diagnosis
  - Down syndrome (trisomy 21)
  - Sex
  - Race and ethnicity
  - Weight at diagnosis and during treatment
- Leukemic characteristics – Leukemic cell characteristics affecting prognosis include the following:
  - Immunophenotype
  - Cytogenetics/genomic alterations
- Response to initial treatment - The rapidity with which leukemia cells are eliminated after initiation of treatment and the level of residual disease at the end of induction are associated with long-term outcome. Because treatment response is influenced by the drug sensitivity of leukemic cells and host pharmacodynamics and pharmacogenomics, early response has strong prognostic significance. Various ways of evaluating the leukemia cell response to treatment have been used, including the following:
  - MRD determination in bone marrow at the end of induction and end of consolidation
  - Day 7 and day 14 bone marrow responses
  - Peripheral blood response to steroid prophase
  - Peripheral blood response to multiagent induction therapy
  - Peripheral blood MRD before end of induction (day 8, day 15)
  - Persistent leukemia at the end of induction (induction failure)

For a detailed discussion of each of these factors affecting prognosis, go to the Prognostic Factors Affecting Risk-Based Treatment section in Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®).

Treatment Option Overview for Childhood ALL

Phases of Therapy

Treatment for children with acute lymphoblastic leukemia (ALL) is typically divided into the following phases:

1. Remission induction chemotherapy (at the time of diagnosis).
2. Postinduction therapy (after achieving complete remission).
    - Consolidation/intensification therapy.
    - Maintenance therapy.

Risk-based treatment assignment is an important therapeutic strategy for children with ALL. This approach allows children who historically have a very good outcome to be treated with less intensive therapy and to be spared more toxic treatments, while children with a historically lower probability of long-term survival receive more intensive therapy that may increase their chance of cure. For more information about clinical and laboratory features that have shown prognostic value, see the Risk-Based Treatment Assignment section in Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®).

Treatment options for newly diagnosed ALL

Standard Induction Treatment Options for Newly Diagnosed ALL

Standard treatment options for newly diagnosed childhood acute lymphoblastic leukemia (ALL) include the following:

1. Chemotherapy.

Remission induction chemotherapy

The goal of the first phase of therapy (remission induction) is to induce a complete remission (CR). This induction phase typically lasts 4 weeks. Overall, approximately 98% of patients with newly diagnosed B-ALL achieve CR by the end of this phase, with somewhat lower rates in infants and in noninfant patients with T-ALL or high presenting leukocyte counts.

Induction chemotherapy typically consists of the following drugs, with or without an anthracycline (either doxorubicin or daunorubicin):

- Vincristine.
- Corticosteroid (either prednisone or dexamethasone).
- Asparaginase
- Intrathecal chemotherapy.

The Children's Oncology Group protocols administer a three-drug induction (vincristine, corticosteroid, and pegaspargase) to National Cancer Institute (NCI) standard-risk B-ALL patients and a four-drug induction (vincristine, corticosteroid, and pegaspargase plus anthracycline) to NCI high-risk B-ALL and all T-ALL patients. Other groups use a four-drug induction for all patients.

Response to remission induction chemotherapy

More than 95% of children with newly diagnosed ALL will achieve a CR within the first 4 weeks of treatment. Of those who fail to achieve CR within the first 4 weeks, approximately one-half will experience a toxic death during the induction phase (usually caused by infection) and the other half will have resistant disease (persistent morphological leukemia).

Remission is classically defined as an end-induction bone marrow examination by routine microscopic cytomorphology with fewer than 5% lymphoblasts at the end of induction (M1). The Ponte de Legno consortium includes approximately 15 large national and international cooperative groups devoted to the study and treatment of childhood ALL. This group published a consensus definition of complete remission, as follows:

- Achievement of minimal residual disease (MRD) levels of less than 1% and/or M1 cytomorphology.
    - MRD is the gold standard and takes precedence over cytomorphology.

- MRD is determined by either flow cytometry or polymerase chain reaction techniques.
- Resolution of extramedullary disease assessed no earlier than the end of induction.

Most patients with persistence of morphologically detectable leukemia at the end of the 4-week induction phase have a poor prognosis and may benefit from an allogeneic hematopoietic stem cell transplant (HCT) once CR is achieved.

Standard postinduction treatment options for childhood ALL

Standard treatment options for consolidation/intensification and maintenance therapy (postinduction therapy) include the following:

1. Chemotherapy.

CNS-directed therapy is provided during premaintenance chemotherapy by all groups. Some protocols provide ongoing intrathecal chemotherapy during maintenance, while do not. For specific information about CNS therapy to prevent CNS relapse in children with ALL who are receiving postinduction therapy, see the CNS-Directed Therapy for Childhood ALL section.

Consolidation/intensification therapy

Once CR has been achieved, systemic treatment in conjunction with CNS-directed therapy follows. The intensity of the postinduction chemotherapy varies considerably depending on risk group assignment, but all patients receive some form of intensification after the achievement of CR and before beginning maintenance therapy.

The most commonly used intensification schema is the BFM backbone. This therapeutic backbone, first introduced by the BFM clinical trials group, includes the following:

1. An initial consolidation (referred to as induction IB) immediately after the initial induction phase. This phase includes intrathecal therapy, cyclophosphamide, low-dose cytarabine, and mercaptopurine. An interim maintenance phase, which includes intrathecal therapy and four doses of high-dose methotrexate (typically 5 g/m2) with leucovorin rescue.
2. Reinduction (or delayed intensification), which typically includes agents and schedules similar to those used during the induction and initial consolidation phases.
3. Maintenance, typically consisting of daily mercaptopurine (6-MP), weekly low-dose methotrexate, and sometimes, intermittent administration of vincristine and a corticosteroid, as well as continued intrathecal therapy.

<u>Standard-risk ALL</u>

In children with low- and standard-risk B-ALL, there has been an attempt to limit exposure to drugs such as anthracyclines and alkylating agents that may be associated with an increased risk of late toxic effects. The Children's Oncology Group regimen for standard-risk B-ALL postinduction therapy can be delivered in the outpatient setting and has multiple favorable characteristics, including low-intensity 4-week consolidation, limited anthracycline (75 mg/m2) and alkylator exposure (1 gm/m2), only two doses of pegaspargase, and interim maintenance phases consisting of escalating doses of methotrexate (without leucovorin rescue) rather than high-dose IV methotrexate.

The prognostic impact of end-induction and/or consolidation MRD has influenced the treatment of patients originally diagnosed as NCI standard risk. Multiple studies have demonstrated that higher levels of end-induction MRD are associated with poorer prognosis. Augmenting therapy has been shown to improve the outcome in standard-risk patients with elevated MRD levels at the end of induction. Patients with NCI standard-risk B-ALL with high-risk features (including increased end-of-induction MRD levels as well as CNS2 status at diagnosis, and/or unfavorable genetics) are treated with more intensified therapy.

<u>High-risk ALL</u>

In high-risk patients, a number of different approaches have been used with comparable efficacy. Treatment for high-risk patients is generally more intensive than that for standard-risk patients and typically includes higher cumulative doses of multiple agents, including anthracyclines and/or alkylating agents. Higher doses of these agents increase the risk of both short-term and long-term toxicities, and many clinical trials have focused on reducing the side effects of these intensified regimens.

Very high-risk ALL

Approximately 10% to 20% of patients with ALL are classified as very high risk, including the following:

- Infants younger than 1 year, especially if there is a KMT2A gene rearrangement present. For more information about infants with ALL, see the Infants With ALL section.
- Patients with adverse cytogenetic abnormalities, including BCR::ABL1, TCF3::HLF, KMT2A gene rearrangements, and low hypodiploidy (<44 chromosomes).
- Patients who achieve CR but have a slow early response to initial therapy, including those with a high absolute blast count after a 7-day steroid prophase, and patients with high MRD levels at the end of induction (week 4) or later time points (e.g., week 12).
- Patients who have morphologically persistent disease after the first 4 weeks of therapy (induction failure), even if they later achieve CR.

Patients with very high-risk features have been treated with multiple cycles of intensive chemotherapy during the consolidation phase. These additional cycles often include agents not typically used in frontline ALL regimens for standard-risk and high-risk patients, such as high-dose cytarabine, ifosfamide, and etoposide. However, even with this intensified approach, reported long-term EFS rates range from 30% to 50% for some of these very high-risk subsets. On some clinical trials, very high-risk patients have also been considered candidates for allogeneic HCT in first CR.

Maintenance therapy

Backbone of maintenance therapy

The backbone of maintenance therapy in most protocols includes daily oral mercaptopurine and weekly oral or parenteral methotrexate. On many protocols, intrathecal chemotherapy for CNS sanctuary therapy is continued during maintenance therapy. Also, vincristine/steroid pulses during maintenance are used by some groups but not others. It is imperative to carefully monitor children on maintenance therapy for both drug-related toxicity and for compliance with the oral chemotherapy agents used during maintenance therapy.

Duration of maintenance therapy

Maintenance chemotherapy generally continues for 2 to 3 years of continuous CR.

Nonadherence to treatment with mercaptopurine during maintenance therapy is associated with a significant risk of relapse.

Central Nervous System (CNS)-Directed Therapy for Childhood ALL

At diagnosis, approximately 3% of patients have CNS3 disease (defined as cerebrospinal fluid [CSF] specimen with ≥5 white blood cells [WBC]/μL with lymphoblasts and/or the presence of cranial nerve palsies). However, unless specific therapy is directed toward the CNS, most children will eventually develop overt CNS leukemia whether or not lymphoblasts were detected in the spinal fluid at initial diagnosis. Therefore, all children with ALL should receive systemic combination chemotherapy together with some form of CNS prophylaxis.

Because the CNS is a sanctuary site (i.e., an anatomical space that is poorly penetrated by many of the systemically administered chemotherapy agents typically used to treat ALL), specific CNS-directed therapies must be instituted early in treatment to eliminate clinically evident CNS disease at diagnosis and to prevent CNS relapse in all patients. Historically, survival rates for children with ALL improved dramatically after CNS-directed therapies were added to treatment regimens.

Standard treatment options for CNS-directed therapy include the following:

1. Intrathecal chemotherapy.
2. CNS-directed systemic chemotherapy.
3. Cranial radiation therapy.

All of these treatment modalities have a role in the treatment and prevention of CNS leukemia. The combination of intrathecal chemotherapy plus CNS-directed systemic chemotherapy is standard. Cranial radiation is reserved for select situations.

The type of CNS-therapy that is used is based on a patient's risk of CNS-relapse, with higher-risk patients receiving more intensive treatments.

For a detailed discussion of each of these factors affecting prognosis, go to the Central Nervous System (CNS)-Directed Therapy for Childhood ALL section in Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®).

Postinduction Treatment for Specific ALL Subgroups

T-ALL

Historically, patients with T-ALL have had a worse prognosis than children with B-ALL.

Treatment options for T-ALL

Treatment options for T-ALL include the following:

1. Chemotherapy with or without prophylactic cranial radiation therapy.

Infants With ALL

Infant ALL is uncommon, representing approximately 2% to 4% of cases of childhood ALL. Because of their distinctive biological characteristics and their high risk of leukemia recurrence, infants with ALL are treated on protocols specifically designed for this patient population. Common therapeutic themes of the intensive chemotherapy regimens used to treat infants with ALL are the inclusion of postinduction intensification courses with high doses of cytarabine and methotrexate.

Adolescents and Young Adults With ALL

Adolescents and young adults with ALL have been recognized as high risk for decades. Outcomes for this age group are inferior in almost all studies of treatment compared with children younger than 10 years. The reasons for this difference include more frequent presentation of adverse prognostic factors at diagnosis, including the following:

- T-cell immunophenotype.
- *BCR*::*ABL1* and *BCR*::*ABL1*-like disease.
- Lower incidence of favorable cytogenetic abnormalities.

In addition to more frequent adverse prognostic factors, patients in this age group have higher rates of treatment-related mortality and nonadherence to therapy.

Treatment options for adolescents and young adults with ALL

Studies from the United States and France were among the first to identify the difference in outcome based on treatment regimens. Other studies have confirmed that older adolescent and young adult patients fare better on pediatric rather than adult regimens.

Given the relatively favorable outcome that can be obtained in these patients with chemotherapy regimens used for high-risk pediatric ALL, there is no role for the routine use of allogeneic HCT for adolescents and young adults with ALL in first remission.

Children With Down Syndrome

Approximately 2% to 3% of childhood ALL cases occur in children with Down syndrome. ALL in pediatric patients with Down syndrome is characterized by a lower incidence of both favorable (e.g., ETV6::RUNX1 and high hyperdiploidy with favorable trisomies) and unfavorable (e.g., BCR::ABL1, KMT2A rearrangements, low hypodiploidy, t(9;22)(q34;q11.2) or t(4;11)(q21;q23)) biology and a near absence of T-cell phenotype.

Patients with Down syndrome have an increased risk of developing toxicities from treatment, including infections, mucositis, and seizures. In some studies, outcomes of children with Down syndrome and ALL have been reported to be inferior, although in other studies, patients with Down syndrome appeared to fare as well as those without Down syndrome. Inferior outcomes for patients with Down syndrome, when observed, are related to both an increased risk of relapse, as well as increased frequency of treatment-related mortality.

Because of the well-established increase in toxicity experienced by patients with Down syndrome, some ALL protocols (such as those of the Children's Oncology Group) have de-intensified risk-based treatment for patients with Down syndrome and ALL to minimize exposure to the morbid components of therapy. While this treatment reduction strategy reduces the frequency and severity of toxicities, its impact on antileukemic outcomes is not yet known.

BCR::*ABL1*-positive (Philadelphia Chromosome-positive) ALL

BCR::*ABL1*-positive (Philadelphia chromosome–positive [Ph+]) ALL is seen in about 3% of pediatric ALL cases, increases in adolescence, and is seen in 15% to 25% of adults. In the past, this subtype of ALL has been recognized as extremely difficult to treat, and patients had a poor outcome. In 2000, an international pediatric leukemia group reported a 7-year EFS rate of 25%, with an OS rate of 36%. In 2010, the same group reported a 7-year EFS rate of 31% and an OS rate of 44% in patients with *BCR*::*ABL1* ALL treated without tyrosine kinase inhibitors. Treatment of this subgroup has evolved, from an initial emphasis on aggressive chemotherapy, to allogeneic HCT in first CR as the standard of care, and currently to combination therapy using chemotherapy plus a TKI, with only a small number of patients allocated to allogeneic HCT in first CR.

Treatment of relapsed childhood ALL

The prognosis for a child with ALL whose disease recurs depends on multiple factors. The following two important risk factors after first relapse of childhood ALL are key to determining prognosis and treatment approach:

- Site of relapse.
- Time from diagnosis to relapse.

Other prognostic factors include the following:

- Patient characteristics (e.g., age and peripheral blast count at time of relapse).
- Risk group classification at initial diagnosis.
- Response to reinduction therapy.
- Cytogenetics/genomic alterations.
- Immunophenotype.

For a detailed discussion of these prognostic factors, see the Prognostic Factors After First Relapse of Childhood ALL section, under Treatment of Relapsed Childhood ALL in Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®).

Standard treatment options for first bone marrow relapse of childhood ALL

Standard treatment options for first bone marrow relapse include the following:

1. Reinduction chemotherapy.
2. Post-reinduction therapy for patients achieving a second CR.

Reinduction chemotherapy

Initial treatment of relapse consists of reinduction therapy to achieve a second CR. Using either a four-drug reinduction regimen (similar to that administered to newly diagnosed high-risk patients) or an alternative regimen including high-dose methotrexate and high-dose cytarabine, approximately 85% of patients with a marrow relapse achieve a second CR at the end of the first month of treatment. Patients with early marrow relapses have a lower rate of achieving a morphological second CR (approximately 70%) than do those with late marrow relapses (approximately 95%).

Patients with relapsed T-ALL have much lower rates of achieving second CR with standard reinduction regimens than do patients with B-cell phenotype.

Reinduction failure is a poor prognostic factor, but subsequent attempts to obtain remission can be successful and lead to survival after HCT, especially if MRD becomes low or nondetectable. Approaches have traditionally included the use of drug combinations distinct from the first attempt at treatment. These regimens often contain newer agents under investigation in clinical trials. Although survival is progressively less likely after each attempt, two to four additional attempts are often pursued, with diminishing levels of success measured after each attempt. Because studies of chimeric antigen receptor (CAR) T cells, blinatumomab, and inotuzumab have been shown to lead to high rates of remission in multiply relapsed and chemotherapy-refractory B-ALL patients, trials testing these agents after initial relapse are underway.

Post-reinduction therapy for patients achieving a second complete remission

Early-relapsing B-ALL

For B-ALL patients with an early marrow relapse, allogeneic transplant from an HLA-identical sibling or matched unrelated donor that is performed in second remission has been reported in most studies to result in higher leukemia-free survival (LFS) than a chemotherapy approach. However, even with transplant, the survival rate for patients with early marrow relapse is less than 50%. After initial reinduction chemotherapy, the use of blinatumomab instead of intensive cytotoxic chemotherapy as pre-HCT consolidation has been shown to be associated with superior outcomes.

Late-relapsing B-ALL

Previous studies of late marrow relapse in patients with B-ALL showed that a primary chemotherapy approach after achievement of second CR resulted in survival rates of approximately 50%, and it was not clear whether allogeneic HCT was associated with a superior cure rate. Subsequent data have shown that the presence of end-reinduction MRD identifies patients with a high risk of ensuing relapse if treated with chemotherapy alone (no allogeneic HCT) in second CR. A number of studies have shown that patients with a late marrow relapse who have high end-reinduction MRD have better outcomes if they receive an allogeneic HCT in second CR after achieving low or nondetectable MRD status.

***BCR::ABL1* (Philadelphia chromosome–positive [Ph+]) ALL**

There is limited information regarding the treatment of patients with relapsed BCR::ABL1 ALL in the era of tyrosine kinase inhibitors (TKIs).

T-ALL

For patients with T-ALL who achieve remission after bone marrow relapse, outcomes with post-reinduction chemotherapy alone have generally been poor, and these patients are usually treated with allogeneic HCT in second CR, regardless of time to relapse. At 3 years, the OS rate after allogeneic transplant for T-ALL in second remission was reported to be 48%, and the DFS rate was 46%.

Treatment options for second and subsequent bone marrow relapse

Although there are no studies directly comparing chemotherapy with allogeneic HCT for patients in third or subsequent CR, because cure with chemotherapy alone is rare, transplant has generally been considered a reasonable approach for those achieving remission. Long-term survival for ALL patients after a second relapse is particularly poor, in the range of less than 10% to 20%. One of the main reasons

for this is failure to obtain a third remission. Numerous attempts at novel combination approaches have resulted in only about 40% of children in second relapse achieving remission.

For multiply relapsed patients who achieve CR, allogeneic HCT has been shown to cure 20% to 35%, with failures occurring because of high rates of relapse and transplant-related mortality.

Given the poor outcomes for multiply relapsed B-ALL patients who are treated with chemotherapy followed by allogeneic HCT, CAR T-cell therapy has come to be used as standard in this population and has resulted in high rates of remission and improved survival (although direct comparative trials are lacking).

Immune therapies such as blinatumomab and inotuzumab have been used in this population and have improved rates of remission, which has then often led to cure when followed by HCT. Comparative studies of immune and cell therapy approaches have yet to be performed in this population, so data to inform optimal approaches to first therapy or sequence of therapies are lacking.

Hematopoietic Stem Cell Transplant for First and Subsequent Bone Marrow Relapse

Components of the transplant process - An expert panel review of indications for allogeneic HCT was published in 2012 (Oliansky et al., 2012). Components of the transplant process that have been shown to be important in improving or predicting outcome of HCT for children with ALL include the following:

- Total-body irradiation (TBI)-containing transplant preparative regimens.
- MRD detection just before transplant.
- MRD detection posttransplant.
- Donor type and HLA match.
- Role of GVHD/graft-versus-leukemia (GVL) in ALL and immune modulation after transplant to prevent relapse.

An analysis from the Center for International Blood & Marrow Transplant Research (CIBMTR) examined pretransplant variables to create a model for predicting LFS posttransplant in pediatric patients (aged <18 years). All patients were first transplant recipients who had myeloablative conditioning, and all stem cells sources were included. For patients with ALL, the predictors associated with lower LFS included age younger than 2 years, second CR or higher, MRD positivity (only in second CR, not in first CR), and presence of morphologically detectable disease at time of transplant. A scale was established to stratify patients on the basis of risk factors to predict survival. The 5-year LFS rate was 68% for the low-risk group, 51% for the intermediate-risk group, and 33% for the high-risk group (Qayed et al., 2021).

Guidelines from the American Society for Transplantation and Cellular Therapy

Kanate et al., 2020 published updated recommendations from the American Society for Transplantation and Cellular Therapy (ASTCT) on indications for allogeneic hematopoietic stem cell transplantation (HCT) and immune effector cell therapy (IECT). Indications for HCT/IECT were categorized as (1) Standard of care, where indication is well defined and supported by evidence (S); (2) Standard of care, clinical evidence available, where large clinical trials and observational studies are not available but have been shown to be effective therapy (C); (3) Standard of care, rare indication, for rare diseases where demonstrated effectiveness exists but large clinical trials and observational studies are not feasible (R); (4) Developmental, for diseases where preclinical and/or early-phase clinical studies show HCT/IECT to be a promising treatment option (D); and (5) Not generally recommended, where available evidence does not support the routine use of HCT/IECT (N). The ASTCT will continue to periodically review these guidelines and update them as new evidence becomes available.

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patient advocates, the monograph aimed to provide evidence-based guidance for indications for HCT. At the time it was also recognized that as the scientific field evolved and progressed, these guidelines would be updated to encompass new data.

Acute Lymphoblastic Lymphoma (Pediatric)	
CR1, standard risk	N
CR1, high risk	S
CR2	S
CR3+	C
Not in remission	C

HCT is defined as an episode of care starting with a conditioning regimen and followed by hematopoietic progenitor cell infusion, derived from bone marrow, peripheral blood, or cord blood, and subsequent recovery.

The optimal timing for referral for HCT has been described in Recommended Timing for Transplant Consultation, published jointly by the ASTCT and NMDP (formerly known as the National Marrow Donor Program and Be The Match), available at https://bethematchclinical.org/).

Additionally, the NMDP and the ASTCT have jointly developed guidelines for transplant consultation and referral timing based on disease characteristics, available at: https://bethematchclinical.org/transplant-indications-and-outcomes/disease-specific-indications-and-outcomes/. The National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN Guidelines®) were consulted when developing these guidelines.

For Acute Lymphoblastic Leukemia (ALL) - Pediatric

Transplant Consultation Guidelines: Acute Lymphoblastic Leukemia (ALL) - Age <15 years

- Infant at diagnosis
  - unfavorable genetics
  - age <3 months with any WBC, or <6 months with WBC>300,000 at presentation
- Primary induction failure
- Presence of measurable (also known as minimal) residual disease after initial therapy
- High/very high-risk CR1, including:
  - Philadelphia chromosome positive slow-TKI responders or with IKZF1 deletions; Philadelphia-like
  - iAMP21
  - 11q23 rearrangement
- First relapse
- CR2 and beyond, if not previously evaluated
- Chimeric Antigen Receptor Therapy (CAR-T)

Transplant Consultation Guidelines: Acute Lymphoblastic Leukemia (ALL) - Age 15-39 Years

- Primary induction failure
- Presence of measurable (also known as minimal) residual disease after initial therapy
- High/very high-risk CR1 including:
  - Philadelphia chromosome positive or Philadelphia-like
  - iAMP21
  - 11q23 rearrangement
- B-cell with poor-risk cytogenetics
- First relapse
- CR2 and beyond, if not previously evaluated

NCCN Clinical Practice Guidelines in Oncology: Pediatric Acute Lymphoblastic Leukemia, Version 5.2024 April 3, 2024.

NCCN Guidelines distinguish four treatment paths for pediatric ALL:

- B-ALL Ph-negative or Ph-like
- B-ALL Ph-positive
- T-ALL
- Infant ALL

Standard and high risk criteria are consistent with NCI:
- Standard risk: WBC count less than 50,000/µL, ≥ 1 year to < 10 years.
- High risk: WBC count 50,000/µL, < 1 year or ≥ 10 years.

The pediatric ALL panel considers “pediatric” to include any patient aged ≤18 years, and certain adolescent and young adult patients >18 years of age. Practice patterns vary with regard to adolescent and young adult patients from center to center in terms of whether patients with ALL are treated primarily by pediatric or adult oncologists. This guideline is intended to apply to adolescent and young adult patients treated in a pediatric oncology setting, and this may include patients up to age 30 years. The NCCN Guidelines for Acute Lymphoblastic Leukemia are intended to apply to adolescent and young adult patients treated in an adult oncology setting.

Minimal Residual Disease (MDR) in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow. The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used.

Allogeneic HCT has demonstrated improved clinical outcomes in pediatric patients with ALL with evidence of certain high-risk features and/or persistent disease. In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, cord blood, or haploidentical donor). Both total body irradiation (TBI) and non-TBI–containing regimens have been used in HCT for children and young adults with ALL. Randomized controlled trials indicate that TBI is superior to non-TBI–containing regimens for children with ALL. Non-TBI–containing regimens are currently under investigation. The benefit of allogeneic HCT in infants with ALL is controversial, although some studies have demonstrated a role in patients with high-risk disease with *KMT2A* rearrangements and other poor-risk factors. Based on the data, it is reasonable to consider HCT in first remission (CR1) for certain patients as described in the HCT sections throughout the discussion.

See Principles of Hematopoietic Cell Transplant:
- Indications for HCT (B-Cell) in First Remission
- Indications for HCT (B-Cell) in Non-First Remission Settings
- Indications for HCT (T-Cell)

Myelodysplastic Neoplasms

The MDS are a collection of myeloid malignancies characterized by one or more peripheral blood cytopenias. Diagnosis and disease stratification are based on multiple factors that may include clinical data, The major clinical problems in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). The division between MDS and AML is a continued area of debate. In addition, there are complications that may arise from chronic transfusions, treatment toxicity, and in some cases, secondary phenomena such as systemic inflammatory conditions. The management of MDS is complicated by the generally advanced age of the patients. MDS occur predominantly in older patients (usually older than 60 years), with a median age at diagnosis of approximately 70 years.

The initial evaluation of patients with suspected MDS requires careful assessment of the peripheral blood smear and blood counts, marrow morphology, cytogenetics, duration of abnormal blood counts, other potential causes of cytopenias, and concomitant illnesses.

MDS is defined by dysplasia (≥10% for any hematopoietic lineage) and cytopenia(s). In general, clinical evidence should indicate that the blood count abnormality is chronic in duration (typically ≥2–4 months) and not explained by drug, toxin, or comorbid condition.

Although the diagnostic criteria allow for categorization of patients with MDS, the highly variable clinical outcomes within these subgroups indicate prognostic limitations. Prognostic scoring systems include the International Prognostic Scoring System (IPSS), revised as the IPSS-R, and the WHO Prognostic Scoring System (WPSS).

- IPSS is based upon the percent of blasts in bone, karyotype, and cytopenias (Greenberg et al., 1997). In the model it stratifies patients into four risk groups (Low, Intermediate-1, Intermediate-2, and High). Its current application is limited to the time of MDS diagnosis.
- IPSS-R is similar to the original IPSS scoring system, but the revised model incorporates a larger number of cytogenetic abnormalities, better accounts for the severity of cytopenias and establishes a lower cutoff for ANC and assigns greater weight to cytogenetic abnormalities than to blast percentage (Greenberg et al. 2012). This results in more accurate prognostic information. IPSS-R was derived from patients who primarily received supportive care and is intended for use only at the time of diagnosis. IPSS-R stratifies MDS patients into five categories: Very low, Low, Intermediate, High, and Very high-risk. Patients with IPSS-R score of <4.5 are said to have "low-risk" disease, while those with a score 4.5 or greater have "high-risk" disease (Greenberg et al. 2012). The American Society of Clinical Oncology (ASCO) considers IPSS-R the gold standard in risk assessment tools for MDS (Haider et al. 2017).
- IPSS-M is the newest MDS prognosis scoring system that combines genomic profiling with hematologic and cytogenetic parameters.
- WPSS is based on a time-dependent regression model and permits dynamic estimation of survival and risk of AML transformation at multiple time points during the natural course of MDS. The system uses three components: WHO diagnostic classification, karyotype, and transfusion needs. Based on these factors WPSS stratifies patients into five risk groups: Very Low, Low, Intermediate, High, and Very High.

The 5th Edition of the World Health Classification (Khoury et al., 2022) introduces the term myelodysplastic neoplasms (abbreviated MDS) to replace myelodysplastic syndromes. MDS entities are now grouped as those having defining genetic abnormalities and those that are morphologically defined. Cytopenia definitions include Hb <13 g/dL in males and <12 g/dL in females for anemia, absolute neutrophil count <1.8 $\times 10^9$/L for leukopenia, and platelets <150 $\times$ 10^9/L for thrombocytopenia.

Classification and defining features of myelodysplastic neoplasms (MDS) according to World Health Organization (WHO) 2022

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q), previously MDS-del(5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and SF3B1 mutation [a] (MDS-SF3B1), previously MDS with ring sideroblasts (MDS-RS)		Absence of 5q deletion, monosomy 7, or complex karyotype	SF3B1
MDS with biallelic TP53 inactivation (MDS-biTP53)	<20% BM and PB	Usually complex	Two or more TP53 mutations, or 1 mutation with evidence of TP53 copy number loss or cnLOH
MDS, morphologically defined			

MDS with low blasts (MDS-LB), previously MDS with single lineage dysplasia (MDS-SLD) and MDS with multilineage dysplasia (MDS-MLD)	<5% BM and <2% PB		
MDS, hypoplastic (MDS-h) [b]			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

(adapted from Khoury et al., 2022)

[a] Detection of ≥15% ring sideroblasts may substitute for SF3B1 mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b] By definition, ≤25% bone marrow cellularity, age adjusted.

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Myelodysplastic Syndromes	
Low/intermediate-1 risk	C
Intermediate-2/high risk	S

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The optimal timing for referral for HCT has been described in Recommended Timing for Transplant Consultation, published jointly by the ASTCT and NMDP (formerly known as the National Marrow Donor Program and Be The Match), available at https://bethematchclinical.org/).

Additionally, the NMDP and the ASTCT have jointly developed guidelines for transplant consultation and referral timing based on disease characteristics, available at: https://bethematchclinical.org/transplant-indications-and-outcomes/disease-specific-indications-and-outcomes/. The National Comprehensive Cancer Network Clinical Practice Guidelines (NCCN Guidelines®) were consulted when developing these guidelines.

Transplant Consultation Guidelines: Myelodysplastic Syndromes – Adult

- Any intermediate or high IPSS or IPSS-R score
- Any MDS with poor prognostic features including:
  - Treatment-related MDS
  - Refractory cytopenias
  - Adverse cytogenetics and molecular features
  - Transfusion dependence
  - Failure of hypomethylating agents or chemotherapy
  - Moderate to severe marrow fibrosis

Pediatric Myelodysplastic Syndromes

- At diagnosis for all subtypes

NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes, Version 2.2024 - May 22, 2024.

For the MDS therapeutic algorithm, all patients should receive relevant supportive care. Following that, NCCN Guidelines stratify patients with MDS into two risk groups:

- Lower-Risk Disease (IPSS Low, Intermediate-1; IPSS-R Very Low, Low, Intermediate; or WPSS Very Low, Low, Intermediate)
- Higher-Risk Disease (IPSS Intermediate-2, High; IPSS-R Intermediate, High, Very High; or WPSS High, Very High)

Patients with IPSS-R intermediate risk may be treated as lower risk if their score is ≤3.5 versus higher risk if their score is >3.5.202 In addition, patients with intermediate-risk disease that does not respond to therapy for lower-risk disease would be eligible to receive therapy for higher-risk MDS.

PROGNOSTIC SCORING SYSTEMS

The IPSS or IPSS-R risk categories are used in the initial planning of therapeutic options, because they provide a risk-based patient evaluation. In addition, factors such as patient age, performance status, and presence of comorbidities have a major influence on the patient's ability to tolerate certain intensive treatments and play a major role in selecting the optimal management strategy. The WPSS provides dynamic estimation of prognosis at any time during the course of MDS.

International Prognostic Scoring System (IPSS) - IPSS should be used for initial prognostic and planning purposes. The IPSS for primary MDS emerged from deliberations of the International MDS Risk Analysis Workshop. To develop the IPSS for MDS, relative risk scores for each significant variable (marrow blast percentage, cytogenetic subgroup, and number of cytopenias) were generated. By combining the risk scores for the three major variables, patients were stratified into four distinctive risk groups in terms of both survival and AML evolution: low, intermediate (int)-1, int-2, and high. When either cytopenias or cytogenetic subtypes were omitted from the classification, discrimination among the four subgroups was much less precise. Both for survival and AML evolution, the IPSS showed statistically greater prognostic discriminating power than earlier classification methods (Greenberg et al., 1997).

Revised International Prognostic Scoring System (IPSS-R) – The IPSS-R, which was derived from an analysis of a large dataset from multiple international institutions, refined the original IPSS by incorporating the following into the prognostic model: more detailed cytogenetic subgroups, separate subgroups within the "marrow blasts <5%" group, and a depth of cytopenias measurement defined with cutoffs for hemoglobin levels, platelet counts, and neutrophil counts. In the IPSS-R, the cytogenetic

subgroups comprise five risk groups (vs. three in the original IPSS) The IPSS-R defines five risk groups (very low, low, intermediate, high, and very high) versus the four groups in the initial IPSS based on a cytogenetic scoring system for MDS published in 2012. The predictive value of the IPSS-R was validated in a number of independent studies based on registry data, including studies that evaluated outcomes for patients treated with hypomethylation agents (Greenberg et al., 2012).

WHO-Based Prognostic Scoring System (WPSS) – The WPSS, which combines WHO type, cytogenetic abnormalities, and the presence (or absence) of severe anemia, defined as hemoglobin levels <9 g/dL for males and <8 g/dL for females, is another prognostic tool for MDS. As compared with the four groups defined by the IPSS, the WPSS classifies patients into five risk groups differing in both survival and risk of AML. The five risk groups are: very low, low, intermediate, high, and very high (Malcovate et al., 2011).

International Prognostic Scoring System Molecular (IPSS-M) - The IPSS-M is a prognostic model that takes into account blood counts, marrow blasts, IPSS-R cytogenetic risk categories, 16 main effect genes, and 15 residual genes and provides times estimates for OS, LFS, and AML transformation. IPSS-M classifies patients into six risk categories (very low, low, moderate low, moderate high, high, very high). The IPSS-M may have a role in clinical decision-making but requires confirmatory evidence to help assess its efficacy (Bernard et al., 2022).

Online calculator for IPSS can be found at https://qxmd.com/calculate/calculator_123/mds-international-prognostic-scoring-system-ipss

IPSS-R calculator tool https://www.mds-foundation.org/ipss-r-calculator/

IPSS-M Web calculator: https://mds-risk-model.com

Online calculator for WPSS can be found at https://qxmd.com/calculate/calculator_143/mds-who-classification-based-prognostic-scoring-system-wpss

Therapy for Higher-Risk Disease (IPSS Intermediate-2, High; IPSS-R Intermediate, High, Very High; or WPSS High, Very High)
Treatment for higher-risk disease is dependent on whether patients are possible candidates for intensive therapy (e.g., allogeneic HCT, intensive chemotherapy). Clinical features relevant for this determination include patient age (including patients up to 75 years of age), performance status, absence of major comorbid conditions, psychosocial status, patient preference, and availability of a suitable donor and caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant. The patient's personal preference for type of therapy needs particular consideration. Regardless, supportive care should be provided for all patients.

For patients who are transplant candidates, an HLA-matched sibling or HLA-matched unrelated donor can be considered. Results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas reduced-intensity conditioning for HCT is generally the strategy in older individuals.

For patients who relapse after allogenic HCT or have no response, the Panel recommends repeat molecular testing to identify targetable mutations. In patients with disease relapse after a prolonged remission following the first transplant or with no response, a second transplant or donor lymphocyte infusion immuno-based therapy may be considered. Enrollment in a clinical trial or HMAs (AzaC, decitabine, oral decitabine and cedazuridine) are also options. If there is no response to treatment or the disease relapses, enrollment in a clinical trial or supportive care is recommended.

Therapy for Lower-Risk Disease (IPSS Low, Intermediate-1; IPSS-R Very Low, Low, Intermediate; or WPSS Very Low, Low, Intermediate)

Regarding the therapeutic options for patients with lower-risk MDS with clinically significant cytopenias, the NCCN Guidelines Panel recommends stratifying these patients into several groups.

- Symptomatic anemia with del(5q), alone or with one other cytogenetic abnormality (except those involving chromosome 7). A clinical trial or consideration of HCT for select patients* are recommended for those without m*IDH1*.

  * Select patients = sEPO ≤500 mU/mL with no response to lenalidomide or ESA with poor probability to respond to IST and no response within 6 cycles of azacitidine or 4 cycles of decitabine or oral decitabine and cedazuridine or lenalidomide or intolerance and no *mIDH1*.

- Symptomatic anemia with no del(5q), alone or with one other cytogenetic abnormalities are categorized on the basis of ring sideroblasts percentage and sEPO levels. A clinical trial or consideration of HCT for select patients* are recommended for those without m*IDH1*.

  * Select patients = Serum EPO >500 mU/ml, poor probability to respond to IST, no response within 6 cycles of azacitidine or 4 cycles of decitabine or oral decitabine and cedazuridine or lenalidomide or intolerance and no *mIDH1.*

- Symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts <15% (or ring sideroblasts <5% with an *SF3B1* mutation) and sEPO levels >500 mU/mL. A clinical trial or consideration of HCT for select patients* are recommended for those without m*IDH1*.

  * Select patients = Serum EPO > 500 mU/ml, poor probability to respond to IST, no response within 6 cycles of azacitidine or 4 cycles of decitabine or oral decitabine and cedazuridine or lenalidomide or intolerance and no m*IDH1*.

- Without symptomatic anemia with clinically relevant thrombocytopenia or neutropenia. In the absence of m*IDH1*, clinical trial as well as consideration of allogeneic HCT in select patients* with lower-risk MDS (IPSS int-1, IPSS-R, and WPSS intermediate MDS) with severe cytopenias are recommended.

  * Select patients = disease progression /no response within 3-6 months of Azacitidine or Decitabine or oral decitabine and cedazuridine.

Analysis of Evidence (Rational for Determination)

In the early era of bone marrow transplantation, allogeneic HCT was mostly performed for patients with late-stage leukemia or aplastic anemia after failure of all conventional treatments. Owing to advances in donor selection, HLA typing, conditioning regimens and supportive care, the indications for allogeneic HCT have grown dramatically since this time. In addition to the constantly expanding list of indications, there has been a trend towards performing allogeneic HCT earlier in the course of the disease rather than employing this approach as a rescue attempt in the late or end stages of disease progression. This shift in practice was based on studies that revealed that transplant outcomes are highly dependent upon timing. One of the most significant developments in allogeneic HCT has been the development and proliferation of reduced-intensity conditioning regimens. These regimens have been feasible and effective, particularly for older adults. Graft versus host disease (GVHD) remains a major challenge; efforts to reduce GVHD while preserving graft-versus-tumor effects remain an ongoing focus of research.

Allogeneic HCT is the only curative treatment for myelodysplastic syndromes (MDS). Because of the older age of patients with MDS, transplantation has generally been reserved for patients with higher risk MDS or MDS transforming to AML. The best results have been obtained in relatively younger patients, who are earlier in their disease course and have not received any prior therapy.

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

CPT code 38204 is a Medicare Physician Fee Schedule Status Indicator “B” code which means payment is always bundled (not separately reimbursed).

CPT codes 38207-38215 and S2140, S2142 and S2150 are all Medicare Status “I” codes, and therefore, are not valid for Medicare or Medicare Advantage use.

CPT codes 38204, 38207-38215, and S2140, S2142 and S2150 are nonpayable per MassHealth Physician Manual Subchapter 6 (eff 1-1-2024).

CPT codes 38207-38215, and S2140, S2142 and S2150 are nonpayable for Community Care members. CPT code 38204 is not separately reimbursed for Community Care members.

CPT code	Description
38204	Management of recipient hematopoietic cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion with harvest, T cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38242	Allogeneic lymphocyte infusions
38243	HPC boost

CPT 38205 (Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic)

Physicians may separately report collection of blood-derived hematopoietic progenitor cells when the transplant takes place in the outpatient hospital setting. Collection of blood-derived hematopoietic progenitor cells (CPT 38205) is reported by the transplant hospital under revenue code 0815 when the transplant takes place in the inpatient hospital setting.

Acquisition Charges for Allogeneic Stem Cell Transplants

Acquisition charges for allogeneic stem cell transplants include, but are not limited to, charges for the costs of the following services:

- Registry fees from a national donor registry described in 42 U.S.C. 274k, if applicable, for stem cells from an unrelated donor;
- Tissue typing of donor and recipient;
- Donor evaluation;
- Physician pre-admission/pre-procedure donor evaluation services;
- Costs associated with harvesting procedure (e.g., general routine and special care services, procedure/operating room and other ancillary services, apheresis services, etc.);
- Post-operative/post-procedure evaluation of donor; and
- Preparation and processing of stem cells.

Acquisition charges for stem cell transplants apply only to allogeneic transplants, for which stem cells are obtained from a donor (other than the recipient himself or herself).The hospital bills and shows acquisition charges for allogeneic stem cell transplants based on the status of the patient (i.e., inpatient or outpatient) when the transplant is furnished.

90.3.1 - Allogeneic for Stem Cell Transplantation

Effective for cost reporting periods beginning on or after October 1, 2020, a subsection (d) hospital that furnishes an allogeneic hematopoietic stem cell transplant to an individual during such a period, payment to such hospital for hematopoietic stem cell acquisition shall be made on a reasonable cost basis.

(*Subsection (d) hospitals are acute care hospitals that are paid under the Inpatient Prospective Payment System. Subsection (d) hospitals exclude the following types of hospitals: children's, inpatient psychiatric, long-term care, rehabilitation hospitals and the 11 Prospective-Payment System Exempt cancer hospitals*.)

When the allogeneic stem cell transplant occurs in the inpatient setting, allogeneic bone marrow/stem cell acquisition charges shall be billed using revenue code 0815. Revenue code 0815 (Allogeneic Stem Cell Acquisition/Donor Services) charges should include all services required to acquire stem cells from a donor, as defined above. Effective for discharges occurring on or after October 1, 2021, such charges are not considered for the IPPS outlier calculation when billed for an allogeneic stem cell transplant. On the recipient's transplant bill, the hospital reports the acquisition charges, cost report days, and utilization days for the donor's hospital stay (if applicable) and/or charges for other encounters in which the stem cells were obtained from the donor. The donor is covered for medically necessary inpatient hospital days of care or outpatient care provided in connection with the allogeneic stem cell transplant under Part A. Expenses incurred for complications are paid only if they are directly and immediately attributable to the stem cell donation procedure. The hospital reports the acquisition charges on the billing form for the recipient, as described in the first paragraph of this section. It does not charge the donor's days of care against the recipient's utilization record. For cost reporting purposes, it includes the covered donor days and charges as Medicare days and charges.

The transplant hospital keeps an itemized statement that identifies the services furnished in collecting allogeneic hematopoietic stem cells including all invoices or statements for purchased services for all donors and their service charges. Records must be for the person receiving the service (donor or recipient). Beginning October 1, 2020, for all donor sources, the hospital must identify the prospective recipient and include the recipient's Medicare beneficiary identification number. These charges will be reflected in the transplant hospital's stem cell/bone marrow acquisition cost center. For allogeneic stem cell acquisition services in cases that do not result in transplant, due to death of the intended recipient or other causes, hospitals include the costs associated with the acquisition services on the Medicare cost report. The hospital shows charges for the transplant itself in revenue center code 0362 or another appropriate cost center. The hospital shows charges for acquiring allogeneic hematopoietic stem cells for transplant in revenue code 0815.

231.11 - Billing for Allogeneic Stem Cell Transplants

Payment for allogeneic hematopoietic stem cell acquisition services continues to be included in the OPPS APC payment when the transplant occurs in the outpatient setting. When the allogeneic stem cell transplant occurs in the outpatient setting, the hospital identifies stem cell acquisition charges for allogeneic bone marrow/stem cell transplants separately in FL 42 of Form CMS-1450 (or electronic equivalent) by using revenue code 0815 (Other Organ Acquisition). Revenue code 0815 charges should include all services required to acquire stem cells from a donor, as defined above, and should be reported on the same claim as the transplant procedure in order to be appropriately packaged for payment purposes.

The transplant hospital keeps an itemized statement that identifies the services furnished, the charges, the person receiving the service (donor/recipient), and whether this is a potential transplant donor or recipient. These charges will be reflected in the transplant hospital's stem cell/bone marrow acquisition cost center. For allogeneic stem cell acquisition services in cases that do not result in transplant, due to death of the intended recipient or other causes, hospitals include the costs associated with the acquisition services on the Medicare cost report. In the case of an allogeneic transplant in the hospital outpatient setting, the hospital reports the transplant itself with the appropriate CPT code, and a charge under revenue center code 0362 or another appropriate cost center. Selection of the cost center is up to the hospital.

Sources:

Medicare Claims Processing Manual, Chapter 3 – Inpatient Hospital Billing, Section 90.3.1 - Allogeneic for Stem Cell Transplantation.

Transmittal 10402CP Change to the Payment of Allogeneic Stem Cell Acquisition Services

MLN Matters: MM11729 Revised Change to the Payment of Allogeneic Stem Cell Acquisition Services

Medicare Claims Processing Manual Chapter 4 – Part B Hospital, 231.11 - Billing for Allogeneic Stem Cell Transplants.

Medicare Claims Processing Manual, Chapter 32, Section 90 – Stem Cell Transplantation

Medicare Claims Processing Manual Transmittal 3556, dated July 1, 2016 (Change Request 9620) updated Chapter 32, Section 90 – Stem Cell Transplantation, effective for claims with dates of service on and after January 27, 2016, to include instructions for billing allogeneic hematopoietic stem cell transplantation (HCT) for treatment of multiple myeloma, myelofibrosis, and sickle cell disease provided in the context of a Medicare-approved clinical study meeting specific criteria under the Coverage with Evidence Development (CED) paradigm. CR9620 also clarifies the appropriate ICD-10-CM diagnosis codes for allogeneic HCT for treatment of myelodysplastic syndromes (MDS) (MLN Matters Number: MM9620). Additional ICD-10 codes may apply, see NCD 110.23 for details.

Claims for allogeneic stem cell transplantation pursuant to Coverage with Evidence Development (CED) in the context of a CMS-approved clinical trial should be billed with:

- Clinical Trial ICD-10-CM diagnosis code - Z00.6, along with the appropriate ICD-10 CM diagnosis code
- Condition Code 30 – Qualifying Clinical Trial
- Value Code D4 – Clinical Trial Number
- Q0 modifier

Refer to Fallon Health Clinical Trials Payment Policy for additional information on billing for clinical trials.

References

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Policy history

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Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully-insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.