BMJ Best Practice

Myelodysplastic syndrome

Straight to the point of care

Last updated: Oct 11, 2024

Table of Contents

Overview 3
- Summary 3
- Definition 3

Theory 4
- Epidemiology 4
- Aetiology 4
- Pathophysiology 5
- Classification 5
- Case history 8

Diagnosis 9
- Approach 9
- History and exam 12
- Risk factors 13
- Investigations 15
- Differentials 18
- Criteria 20

Management 23
- Approach 23
- Treatment algorithm overview 28
- Treatment algorithm 31
- Emerging 65
- Patient discussions 65

Follow up 66
- Monitoring 66
- Complications 67
- Prognosis 67

Guidelines 71
- Diagnostic guidelines 71
- Treatment guidelines 72

Online resources 73

References 74

Images 85

Disclaimer 87

Summary

Myelodysplastic syndrome or myelodysplastic neoplasm (MDS) is primarily a disease of older adults. It is often diagnosed incidentally in asymptomatic patients. Some patients present with symptoms of anaemia, leukopenia, and thrombocytopenia.

Diagnosis is confirmed if blood and bone marrow evaluation reveals cytopenias, morphological dysplasia, clonal cytogenetic abnormalities or molecular mutations, and blasts (classically <20%).

Supportive care is central to management and includes: red blood cell (RBC) transfusions with iron chelation support (for anaemia); platelet transfusions (for thrombocytopenia and bleeding); and anti-infective therapy (e.g., antibiotics).

Treatment is guided by risk assessment, disease type/characteristics, symptoms/severity of cytopenias, and erythropoietin levels. Treatment includes drug therapy (e.g., lenalidomide, erythropoiesis-stimulating agents, hypomethylating agents, luspatercept, imetelstat, immunosuppressive therapy [antithymocyte globulin], ivosidenib) and allogeneic stem cell transplantation (for select patients e.g., those with high-risk disease).

Patients may have a prolonged disease course (i.e., with anaemia, thrombocytopenia, neutropenia), or may progress rapidly to acute myeloid leukaemia (AML). Most deaths occur due to complications from MDS (e.g., infection) before progression to AML.

Definition

MDS is a heterogenous group of clonal haematopoietic neoplasms characterised by cytopenias (anaemia, neutropenia, and/or thrombocytopenia); significant bone marrow dysplasia; blasts in the peripheral blood and/or bone marrow (classically <20%); cytogenetic/genetic abnormalities (e.g., 5q deletion, SF3B1 mutation, TP53 mutation); and a predilection to progress to AML.[1] [2]

MDS can arise de novo or occur secondary to antecedent haematological malignancy or following exposure to chemotherapy or radiotherapy.[3]

Epidemiology

MDS occurs primarily in older adults; median age at diagnosis is 70-75 years.[9] [10] MDS is more common in males than in females (approximately 2:1).[10][11][12][13]

In the US, the incidence of MDS is approximately 4 per 100,000 (based on 2016-2020 data), which rises to approximately 40 per 100,000 in those aged ≥75 years.[13] Incidence in the UK and Europe appear to be similar to the US.[10]

The incidence of MDS is believed to be rising, in part due to an increase in the incidence of secondary MDS (e.g., following exposure to chemotherapy or radiotherapy) and an ageing population.[14] However, accurate data are difficult to obtain.

MDS in younger adults and children is relatively rare, and is often associated with congenital disorders (e.g., Down syndrome, Fanconi syndrome, Bloom syndrome).[15] [16] [17] [18]

In Asian countries, the average age at which patients are diagnosed is much younger than in other countries.[16] While the reason for this difference is unclear, chemical contamination and infectious causes in addition to ethnic differences may contribute.[19]

Aetiology

MDS can occur de novo or secondary to antecedent haematological malignancy or following exposure to chemotherapy or radiotherapy.[3] Most cases of MDS occur de novo, and the exact cause is unknown. However, a number of risk factors (genetic, environmental, and prior medical history) have been identified.

Chromosomal abnormalities

Chromosomal abnormalities are found in approximately 50% of patients with de novo MDS, and in as many as 90% of patients with MDS secondary to previous chemotherapy or radiotherapy.[20] [21] The most common chromosomal abnormalities include -5, del(5q), -7, del(7q), del(11q), del(12p), -17, del(17p), and del(20q), suggesting a role for tumour suppressor genes located on these chromosomes.[18] [22]

Genetic mutations

Somatic mutations are found in 80% to 90% of patients with MDS.[23] [24] [25] The most common mutations include DNMT3A, TET2, ASXL1, TP53, and SF3B1.[18] [23]

Congenital disorder

MDS in children and younger adults is often associated with congenital disorders.[18]

Risk of MDS is increased in those with inherited bone marrow failure syndromes (e.g., Fanconi anaemia, Diamond-Blackfan anaemia, Shwachman-Diamond syndrome, dyskeratosis congenita, severe congenital neutropenia [Kostmann syndrome]), Down syndrome (trisomy 21), ataxia telangiectasia, xeroderma pigmentosum, Bloom syndrome, glutathione transferase theta 1 (GSTT1) gene defect, and Li-Fraumeni syndrome.[15] [16] [18] [26] [27] [28] [29] [30]

Previous haematological disorders

Risk of MDS is increased in patients with previous haematological disorders, including aplastic anaemia and paroxysmal nocturnal haemoglobinuria.[18] [31]

Environmental exposures

Increased risk of MDS has been associated with exposure to tobacco and benzene.[32] [33] [34]

Previous exposure to chemotherapy or radiotherapy

Alkylating agents (e.g., chlorambucil, cyclophosphamide, melphalan), topoisomerase inhibitors (e.g., etoposide, teniposide), anthracyclines (e.g., doxorubicin, daunorubicin), and platinum agents (e.g., cisplatin, carboplatin) are associated with an increased risk for secondary MDS.[35] [36] [37]

Radiotherapy is associated with an increased risk for secondary MDS.[37] Radiotherapy combined with chemotherapy increases the risk compared with radiotherapy alone.[38] [39]

Autologous haematopoietic stem cell transplantation increases risk, but this is likely related to the use of chemotherapy for conditioning before transplantation.[40]

Pathophysiology

MDS is a heterogeneous group of clonal haematopoietic neoplasms that arise from a multipotent haematopoietic stem cell.[41] Sequential acquisition of somatic mutations in haematopoietic stem cells is thought to play a key role in the development and expansion of a malignant stem cell clone. The stem cell clone in MDS gives rise to intermediate cell types that are defective and susceptible to apoptosis, resulting in premature cell death in the bone marrow and ultimately cytopenias.

Dysregulation of the immune system and inflammatory signalling in MDS can result in abnormal haematopoiesis and unbalanced cell death and cell proliferation in the bone marrow, which may contribute to the pathogenesis of MDS.[42] [43]

Classification

The 5th edition of the World Health Organization (WHO) classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms[1]

The WHO classification introduces the term myelodysplastic neoplasms (MDS) to replace myelodysplastic syndromes. MDS is categorised based on defining genetic abnormalities or morphology.

MDS with defining genetic abnormalities

- MDS with low blasts and isolated 5q deletion (MDS-5q)
    - Blasts: <5% in bone marrow and <2% in peripheral blood
    - Cytogenetics: 5q deletion alone, or with one other abnormality other than monosomy 7 or 7q deletion.
- MDS with low blasts and SF3B1 mutation (MDS-SF3B1)
    - Blasts: <5% in bone marrow and <2% in peripheral blood

- Cytogenetics: absence of 5q deletion, monosomy 7, or complex karyotype
- Mutations: SF3B1 (≥15% ring sideroblasts may substitute for SF3B1 mutation).

- MDS with biallelic TP53 inactivation (MDS-biTP53)
  - Blasts: <20% in bone marrow and peripheral blood
  - Cytogenetics: usually complex
  - Mutations: two or more TP53 mutations, or one mutation with evidence of TP53 copy number loss or copy neutral loss of heterozygosity.

MDS, morphologically defined

- MDS with low blasts (MDS-LB)
  - Blasts: <5% in bone marrow and <2% in peripheral blood.
- MDS, hypoplastic (MDS-h)
  - Blasts: <5% in bone marrow and <2% in peripheral blood
  - Bone marrow cellularity ≤25% (age adjusted).
- MDS with increased blasts (MDS-IB)
  - MDS-IB1
    - Blasts: 5% to 9% in bone marrow or 2% to 4% in peripheral blood.
  - MDS-IB2
    - Blasts: 10% to 19% in bone marrow or 5% to 19% in peripheral blood or Auer rods.
  - MDS with fibrosis (MDS-f)
    - Blasts: 5% to 19% in bone marrow; 2% to 19% in peripheral blood.

International Consensus Classification (ICC) of myeloid neoplasms and acute leukaemias[2]

The ICC categorises MDS based on cytogenetic abnormalities, morphological dysplasia, or presence of excess blasts. The statement 'therapy-related' is added to specific classifications as a diagnostic qualifier if MDS is therapy related.

MDS with mutated SF3B1 (MDS-SF3B1)

- Dysplastic lineages: typically ≥1
- Cytopenias: ≥1
- Cytoses: 0
- Blasts: <5% in bone marrow; <2% in peripheral blood
- Cytogenetics**: any, except isolated del(5q), -7/del(7q), abn3q26.2, or complex
- Mutations: SF3B1 (≥10% variant allele frequency [VAF]), without multi-hit TP53, or RUNX1.

MDS with del(5q) [MDS-del(5q)]

- Dysplastic lineages: typically ≥1
- Cytopenias: ≥1
- Cytoses: thrombocytosis allowed
- Blasts*: <5% in bone marrow; <2% in peripheral blood
- Cytogenetics**: del(5q), with up to 1 additional, except -7/del(7q)

- Mutations: any, except multi-hit TP53.

MDS, not otherwise specified (NOS) without dysplasia

- Dysplastic lineages: 0
- Cytopenias: ≥1
- Cytoses: 0
- Blasts*: <5% in bone marrow; <2% in peripheral blood
- Cytogenetics**: -7/del(7q) or complex
- Mutations: any, except multi-hit TP53 or SF3B1 (≥10% VAF).

MDS, NOS with single lineage dysplasia

- Dysplastic lineages: 1
- Cytopenias: ≥1
- Cytoses: 0
- Blasts*: <5% in bone marrow; <2% in peripheral blood
- Cytogenetics**: any, except not meeting criteria for MDS-del(5q)
- Mutations: any, except multi-hit TP53; not meeting criteria for MDS-SF3B1.

MDS, NOS with multilineage dysplasia

- Dysplastic lineages: ≥2
- Cytopenias: ≥1
- Cytoses: 0
- Blasts*: <5% in bone marrow; <2% in peripheral blood
- Cytogenetics**: any, except not meeting criteria for MDS-del(5q)
- Mutations: any, except multi-hit TP53; not meeting criteria for MDS-SF3B1.

MDS with excess blasts (MDS-EB)

- Dysplastic lineages: typically ≥1
- Cytopenias: ≥1
- Cytoses: 0
- Blasts*: 5% to 9% in bone marrow; 2% to 9% in peripheral blood. For paediatric patients (aged <18 years), the blast thresholds for MDS-EB are 5% to 19% in bone marrow and 2% to 19% in peripheral blood, and the entity MDS/AML does not apply
- Cytogenetics**: any
- Mutations: any, except multi-hit TP53.

MDS/AML

- Dysplastic lineages: typically ≥1
- Cytopenias: ≥1
- Cytoses: 0
- Blasts: 10% to 19% in bone marrow or peripheral blood. For paediatric patients (aged <18 years), the blast thresholds for MDS-EB are 5% to 19% in bone marrow and 2% to 19% in peripheral blood, and the entity MDS/AML does not apply
- Cytogenetics**: any, except AML-defining cytogenetic abnormalities (see Acute myeloid leukaemia)
- Mutations: any, except NPM1, bZIP CEBPA, or TP53.

*Presence of 1% blasts in peripheral blood confirmed on two separate occasions also qualifies for MDS-EB.

**BCR::ABL1 rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

THEORY

Case history

Case history #1

A 70-year-old man presents with generalised fatigue that has slowly progressed over several months. On physical examination, the patient has pale mucous membranes and mild tachycardia. The remainder of the examination is unremarkable.

Other presentations

Patients are often asymptomatic at presentation, and MDS is diagnosed incidentally following routine laboratory tests. If symptoms develop they are usually non-specific and related to anaemia (e.g., weakness, fatigue, decreased exercise tolerance, light-headedness, angina).[4] Less common symptoms are those related to thrombocytopenia (e.g., easy bruising, bleeding) and neutropenia (e.g., infections).[5] Occasionally, MDS can present with autoimmune abnormalities, such as vasculitis, connective tissue disease, and inflammatory arthritis.[6] [7] [8]

Approach

Diagnosis of MDS requires a detailed medical history and physical examination, and pathological assessment of the peripheral blood and bone marrow.

MDS is a heterogeneous disease with varying presentations. Patients are often asymptomatic at presentation, and MDS is suspected following a routine blood test showing cytopenia (most commonly anaemia).[47] Some patients present with symptoms related to cytopenia (e.g., fatigue, infections, bruising).

History and physical examination

Median age at diagnosis is 70-75 years, but the disease can occur at any age and should be considered in younger patients who have had prior exposure to chemotherapy or radiotherapy, or who have a congenital disorder (e.g., Fanconi syndrome, Bloom syndrome, Down syndrome).[9] [10][15][16][18] [26] [27] [36][37] [48] [49]

History should include a careful assessment of prior exposure to chemotherapy and/or radiotherapy; prior infections or bleeding episodes; presence of comorbid conditions; family history of haematological disorders; nutritional status (nutrient deficiencies); alcohol use; and exposure to toxic chemicals.[11] [15]

A careful physical examination is required which may identify signs and symptoms related to cytopenias, such as pallor, fatigue, exercise intolerance, infections (usually bacterial), bruising, and bleeding (petechiae, purpura).

Autoimmune disorders (e.g., vasculitis, connective tissue disease, inflammatory arthritis) are reported in approximately 25% of MDS patients.[6] [7] [8]

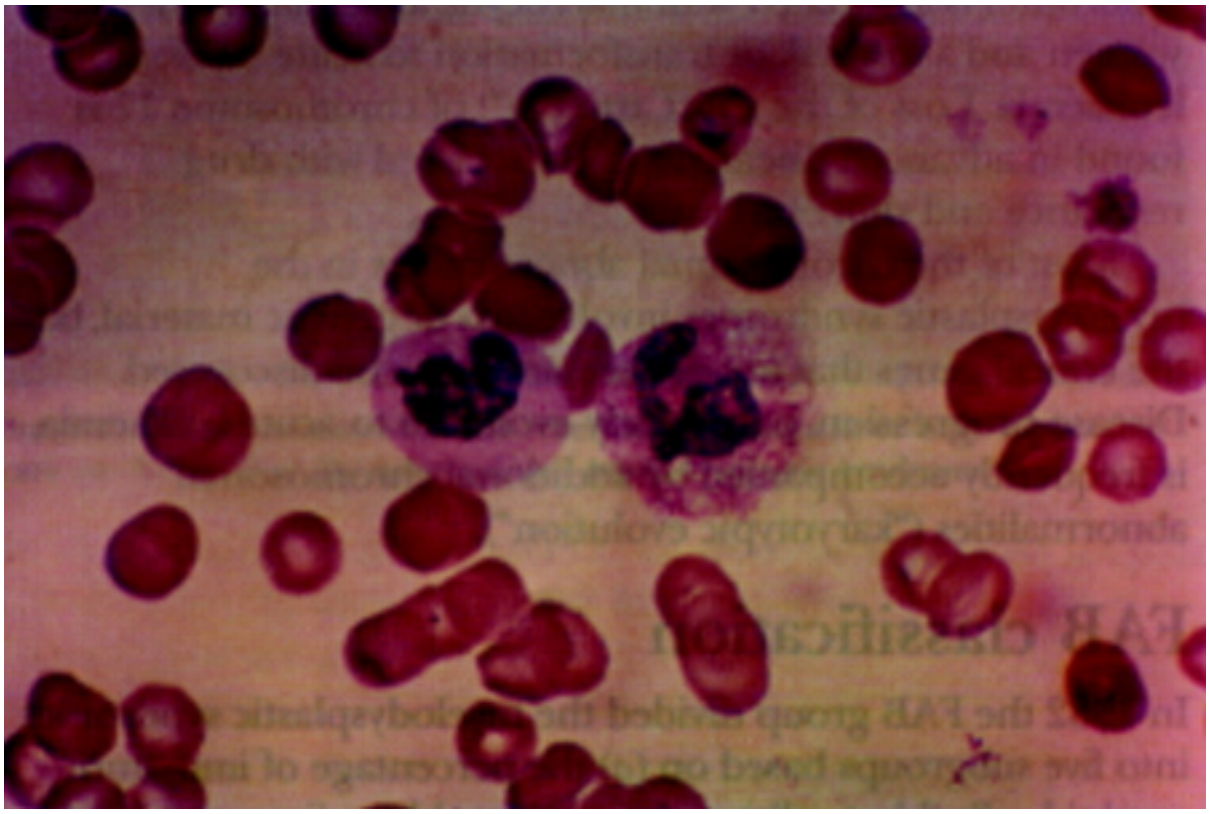
Splenomegaly, hepatomegaly, and lymphadenopathy rarely occur in MDS. They can occur in chronic myelomonocytic leukaemia (CMML), a myeloid neoplasm with pathological and molecular features that overlap with MDS.[1]

Initial testing

The initial tests should be a full blood count (FBC) with differential, and a peripheral smear. The FBC will show one or more cytopenias (most commonly anaemia) that are sustained (e.g., >4 months).[11] [15] [16] Peripheral blood smear will show cytopenias and dysplasia (e.g., hypogranular and hypolobulated granulocytes [pseudo-Pelger-Huet anomaly]).[16]

Additional laboratory tests include reticulocyte count, red blood cell folate, serum vitamin B12, and iron studies (serum iron, total iron-binding capacity, ferritin).[11] [15][16] These should be carried out to exclude other causes of cytopenias. Reticulocyte count is often low in MDS.[50]

Testing for viral infection (e.g., HIV; hepatitis B, C, and E; cytomegalovirus; parvovirus) can be carried out if there are risk factors for prior exposure.[11] [15][16] HIV infection can cause dysplastic bone marrow changes that are similar to those seen in MDS.[51]



Blood film showing normal neutrophil (right) and dysplastic neutrophil with agranular cytoplasm and hypolobated nucleus

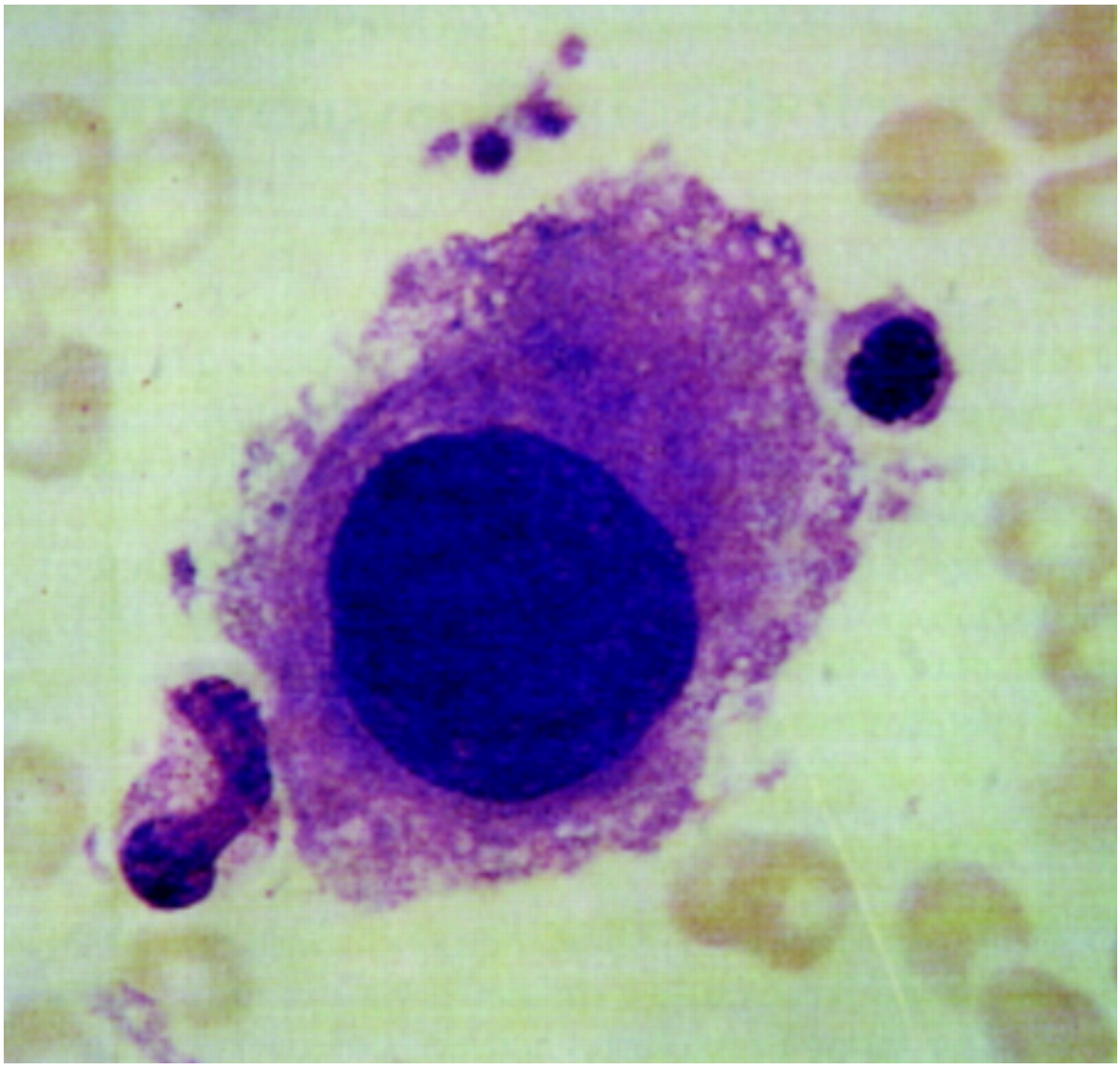
Image used with permission from BMJ 1997;314:883

Bone marrow evaluation

Bone marrow aspiration (with iron stain) and core biopsy are required for morphological, cytogenetic, mutational, and flow cytometric analyses.[15] [47] These investigations confirm the diagnosis of MDS, and guide risk stratification and management.[15] [47] [52]

A diagnosis of MDS can be made in a patient with persistent cytopenia in the presence of one of the following three criteria: significant bone marrow dysplasia (≥10% in one or more of three major bone marrow lineages); blasts in the peripheral blood and/or bone marrow (<20%); or a clonal cytogenetic abnormality or somatic mutation.[1] [2][11] Biological features are more important than a strict blast cut-off value.[15]

Patients with blasts ≥20% should be assessed for acute myeloid leukaemia. See Acute myeloid leukaemia .



Large mononuclear megakaryocyte in bone marrow of patient with MDS-del(5q)

Image used with permission from BMJ 1997;314:883

Genetic testing

Genetic testing for MDS-associated cytogenetic abnormalities (e.g., -5, del(5q), -7, del(7q), del(11q), del(12p), -17, del(17p), del(20q)) and somatic mutations (e.g., DNMT3A, TET2, ASXL1, TP53, SF3B1) informs the diagnosis and prognostic risk stratification.[11] [15] The presence of certain cytogenetic abnormalities or somatic mutations (e.g., -7/del(7q), del(5q), and SF3B1) may establish a diagnosis without dysplasia.[1] [2]

Genetic testing may be carried out on peripheral blood if bone marrow testing is not possible.

Patients with significant dysplasia who do not have a clonal cytogenetic abnormality or somatic mutation should undergo further evaluation to exclude a non-malignant cause of dysplasia.

Subsequent testing

Once a diagnosis is established, the following additional tests may be useful in certain situations.

- Serum erythropoietin levels: can be measured to guide treatment with erythropoiesis-stimulating agents.[15] [16] [53] Serum erythropoietin is usually elevated in MDS except in concurrent renal failure, in which case it is low.
- Lactate dehydrogenase: has prognostic value and can be measured to inform risk stratification and management.[15] [16] Elevated lactate dehydrogenase is associated with poorer outcomes.[54] [55]
- HLA typing: useful if the patient is a candidate for haematopoietic stem cell transplantation, or if extensive platelet transfusions are needed or anticipated.[53]
- Flow cytometry: can contribute to the diagnosis (by identifying dysplastic features and blasts) and prognostication. May be used (alongside STAT3 mutation testing) for the evaluation of a concurrent paroxysmal nocturnal haemoglobinuria clone, and possible large granular lymphocytic leukaemia.[3] [15]

History and exam

Key diagnostic factors

older age (common)

- MDS occurs primarily in older adults; median age at diagnosis is 70-75 years.[9] [10]
- MDS can occur at any age and should be considered in younger patients with prior exposure to chemotherapy or radiotherapy, or who have a congenital disorder.

fatigue (common)

- Usually related to anaemia, which is common on diagnosis.[56]
- Patients may be asymptomatic, with cytopenia an incidental finding during routine blood tests.

exercise intolerance (common)

- Symptom of anaemia, which is common on diagnosis.[56]
- Patients may be asymptomatic, with cytopenia an incidental finding during routine blood tests.

pallor (common)

- Associated with anaemia, which is common on diagnosis.[56]
- Patients may be asymptomatic, with cytopenia an incidental finding during routine blood tests.

bruising or bleeding (common)

- Bruising or bleeding (including petechiae and purpura) due to thrombocytopenia occurs in approximately 20% of patients.[56] This may become more prominent as disease progresses.
- Patients may be asymptomatic, with cytopenia an incidental finding during routine blood tests.

prior chemotherapy and/or radiotherapy (uncommon)

- MDS should be considered in younger patients who have had prior exposure to chemotherapy and/or radiotherapy.[35] [36] [37] [38] [39]

congenital disorder (uncommon)

- MDS should be considered in younger patients who have a congenital disorder, such as an inherited bone marrow failure syndrome (e.g., Fanconi anaemia, Diamond-Blackfan anaemia, Shwachman-

Diamond syndrome, dyskeratosis congenita, severe congenital neutropenia [Kostmann syndrome]), Down syndrome (trisomy 21), ataxia telangiectasia, xeroderma pigmentosum, Bloom syndrome, glutathione transferase theta 1 (GSTT1) gene defect, and Li-Fraumeni syndrome.[15] [16] [18] [26][27] [28] [29] [30]

bacterial infections (uncommon)

- Approximately 40% to 50% of MDS patients have neutropenia; only a subset has recurrent infections, usually bacterial.[3] [57]

Other diagnostic factors

presence of risk factors (uncommon)

- Key risk factors include: age >70 years; prior chemotherapy; prior radiotherapy; prior autologous haematopoietic stem cell transplantation; and congenital disorders.

autoimmune disorders (uncommon)

- Autoimmune disorders (e.g., vasculitis, connective tissue disease, inflammatory arthritis) are reported in approximately 25% of MDS patients.[6] [7] [8]

splenomegaly (uncommon)

- Rare in MDS. Can occur in chronic myelomonocytic leukaemia (CMML), a myeloid neoplasm with pathological and molecular features that overlap with MDS.[1]

hepatomegaly (uncommon)

- Rare in MDS. Can occur in chronic myelomonocytic leukaemia (CMML), a myeloid neoplasm with pathological and molecular features that overlap with MDS.[1]

lymphadenopathy (uncommon)

- Rare in MDS. Can occur in chronic myelomonocytic leukaemia (CMML), a myeloid neoplasm with pathological and molecular features that overlap with MDS.[1]

Risk factors

Strong

age >70 years

- MDS occurs primarily in older adults; median age at diagnosis is 70-75 years.[9] [10]
- MDS can occur at any age and should be considered in younger patients with prior exposure to chemotherapy or radiotherapy, or who have a congenital disorder.

prior chemotherapy

- Alkylating agents (e.g., chlorambucil, cyclophosphamide, melphalan), topoisomerase inhibitors (e.g., etoposide, teniposide), anthracyclines (e.g., doxorubicin, daunorubicin), and platinum agents (e.g., cisplatin, carboplatin) are associated with an increased risk for secondary MDS.[35] [36][37]

prior radiotherapy

- Radiotherapy is associated with an increased risk for secondary MDS.[37] Radiotherapy combined with chemotherapy increases the risk compared with radiotherapy alone.[38] [39]

prior autologous haematopoietic stem cell transplantation

- Likely to be related to DNA damage from chemotherapy agents (e.g., conditioning regimens) prior to autologous haematopoietic stem cell transplantation.[40]

congenital disorders

- MDS in children and younger adults is often associated with congenital disorders.[18]
- Risk of MDS is increased in those with inherited bone marrow failure syndromes (e.g., Fanconi anaemia, Diamond-Blackfan anaemia, Shwachman-Diamond syndrome, dyskeratosis congenita, severe congenital neutropenia [Kostmann syndrome]), Down syndrome (trisomy 21), ataxia telangiectasia, xeroderma pigmentosum, Bloom syndrome, glutathione transferase theta 1 (GSTT1) gene defect, and Li-Fraumeni syndrome.[15] [16] [18] [26] [27] [28] [29] [30]

Weak

tobacco

- A known mutagen.[32]

benzene

- Observational data suggest an increased risk of developing MDS following occupational exposure to benzene.[44] [45] Possible mechanisms include inducing apoptosis, altering the bone marrow micro-environment, and inducing immunological dysregulation.[46]

aplastic anaemia

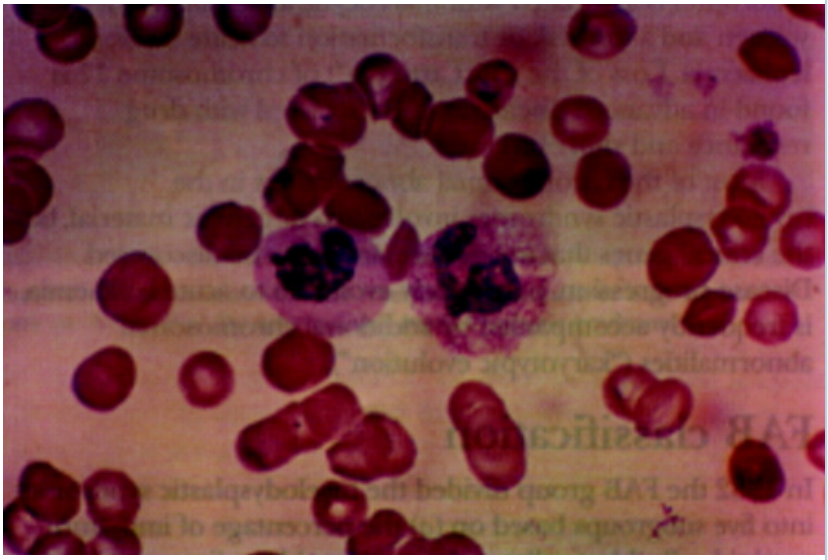
- Can transform into MDS.[18] [31]

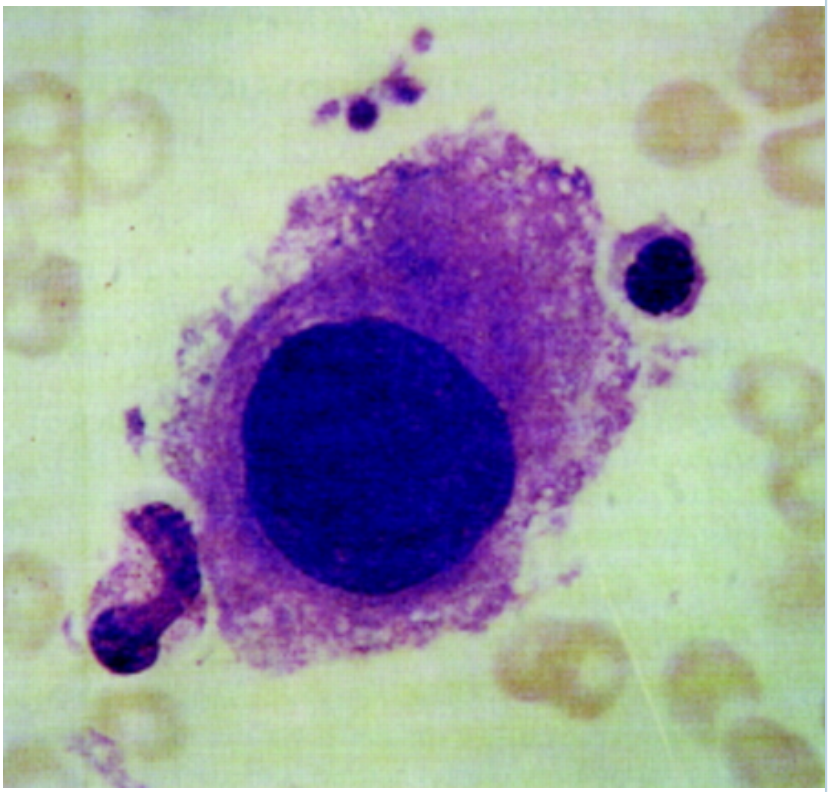
paroxysmal nocturnal haemoglobinuria (PNH)

- MDS clone can arise.[18] [31]

Investigations

1st test to order

Test	Result
FBC with differential • FBC will show one or more cytopenias (most commonly anaemia) that are sustained (e.g., >4 months).[11] [15][16] • Approximately 90% of MDS patients have anaemia.[58] [59] • Approximately 40% of patients have neutropenia.[3] [57] • Approximately 30% have thrombocytopenia.[3] [60]	**one or more cytopenias**
peripheral blood smear • Peripheral blood smear will show cytopenias (most commonly anaemia) and dysplasia.[16] • Anaemia is usually normochromic or macrocytic. • May see hypogranular and hypolobulated granulocytes (pseudo-Pelger-Huet anomaly).[61]  *Blood film showing normal neutrophil (right) and dysplastic neutrophil with agranular cytoplasm and hypolobated nucleus* *Image used with permission from BMJ 1997;314:883*	**cytopenias; normochromic or macrocytic red cells; dysplasia; hypogranular and hypolobulated granulocytes (pseudo-Pelger-Huet anomaly)**
reticulocyte count • Often low in MDS.[50] • Inadequate reticulocyte response for degree of anaemia; if an adequate response is present, other diagnoses are more likely.	**inappropriately normal or low**
red blood cell folate • Used to rule out folate deficiency as cause of anaemia.	**normal**
serum vitamin B12 • Used to rule out vitamin B12 deficiency as cause of anaemia.	**normal**
iron studies • Serum iron, total iron-binding capacity, ferritin used to rule out iron deficiency.	**normal**

Test	Result
bone marrow aspiration with iron stain • A diagnosis of MDS can be made in a patient with persistent cytopenia in the presence of one of the following three criteria: significant bone marrow dysplasia (≥10% in one or more of three major bone marrow lineages); blasts in the peripheral blood and/or bone marrow (<20%); or a clonal cytogenetic abnormality or somatic mutation.[1] [2][11] Biological features are more important than a strict blast cut-off value.[15] Patients with blasts ≥20% should be assessed for acute myeloid leukaemia. (See Acute myeloid leukaemia) • Prussian blue iron staining of bone marrow aspirate can show ringed sideroblasts - abnormal erythroid precursor cells that have granules around the nucleus. • May need to repeat to assess: transformation into AML; persistence of morphological abnormalities (as other conditions such as vitamin B12 deficiency and infections can cause transient dysplastic abnormalities). •  *Large mononuclear megakaryocyte in bone marrow of patient with MDS-del(5q)* *Image used with permission from BMJ 1997;314:883*	**dysplasia (≥10% in one or more of three major bone marrow lineages); ringed sideroblasts; bone marrow blasts (<20%)**
bone marrow core biopsy • Can assess overall bone marrow cellularity and architecture and help differentiate MDS from myeloproliferative disorder (reticulin deposits, fibrosis). Hypocellular marrow may be seen in some patients with MDS, but this is rare. • May need to repeat to assess: transformation into AML; persistence of morphological abnormalities (as other conditions such as vitamin B12 deficiency and infections can cause transient dysplastic abnormalities).	**usually hypercellular marrow; rarely hypocellular marrow**

Test	Result
genetic testing • Genetic testing for MDS-associated cytogenetic abnormalities (e.g., -5, del(5q), -7, del(7q), del(11q), del(12p), -17, del(17p), del(20q)) and somatic mutations (e.g., DNMT3A, TET2, ASXL1, TP53, SF3B1) informs the diagnosis and prognostic risk stratification.[11] [15] • The presence of certain cytogenetic abnormalities or somatic mutations (e.g., -7/del(7q), del(5q), or SF3B1) may establish a diagnosis without dysplasia.[1] [2] • Genetic testing may be carried out on peripheral blood if bone marrow testing is not possible. • Patients with significant dysplasia who do not have a clonal cytogenetic abnormality or somatic mutation should undergo further evaluation to exclude a non-malignant cause of dysplasia.	**MDS-associated cytogenetic abnormalities (e.g., -5, del(5q), -7, del(7q), del(11q), del(12p), -17, del(17p), del(20q)); MDS-associated somatic mutations (e.g., DNMT3A, TET2, ASXL1, TP53, SF3B1)**

Other tests to consider

Test	Result
viral serology • Testing for viral infection (e.g., HIV; hepatitis B, C, and E; cytomegalovirus; parvovirus) can be carried out if there are risk factors for prior exposure.[11] [15][16] • HIV infection can cause dysplastic bone marrow changes that are similar to those seen in MDS.[51]	**may be positive for viral infection**
serum erythropoietin • Serum erythropoietin levels can be measured to guide treatment with erythropoiesis-stimulating agents.[15] [16] [53] • Elevated in MDS except in concurrent renal failure, in which case it is low.	**elevated**
lactate dehydrogenase • Lactate dehydrogenase has prognostic value and can be measured to inform risk stratification and management.[15] [16] • Elevated lactate dehydrogenase is associated with poorer outcomes.[54] [55]	**varies**
HLA typing • Useful for candidates for haematopoietic stem cell transplantation, or those requiring extensive platelet transfusions.[53]	**varies**
flow cytometry • Can be performed on bone marrow samples to support a diagnosis of MDS (by identifying dysplastic features and blasts).[52] • May be used (alongside STAT3 mutation testing) for the evaluation of a concurrent paroxysmal nocturnal haemoglobinuria clone, and possible large granular lymphocytic leukaemia.[3] [15]	**dysplasia (≥10% in one or more of three major bone marrow lineages); bone marrow blasts (<20%)**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Aplastic anaemia	• May have history of medications that cause aplastic anaemia; otherwise, symptoms may be the same.	• The marrow is hypocellular for age, and precursors are morphologically normal. There is no clonal chromosomal abnormality.
HIV infection	• History of HIV infection or activities that increase the risk of contracting HIV.	• HIV testing is positive. • Bone marrow may show some dysplastic cells, with erythroid and granulocytic precursors and megakaryocytes, but this is not usually a persistent finding and will change on repeat aspirate or biopsy.
Other viral infections (e.g., parvovirus, CMV, or hepatitis)	• May have viral prodromal symptoms or other symptoms specific to individual viral infection (e.g., jaundice with hepatitis).	• Positive test for viral infection. • Marked erythroid hypoplasia and occasional giant erythroblasts noted in bone marrow in parvovirus infection. • Intranuclear inclusions may be noted in CMV infection.
Acute myeloid leukaemia	• More likely to have: symptomatic cytopenia and leukocytosis; complications such as tumour lysis syndrome or disseminated intravascular coagulopathy; hepatosplenomegaly; and lymphadenopathy.	• Blasts ≥20%. Presence of AML-defining chromosomal abnormalities, irrespective of blast count (e.g., t(15;17)(q24.1;q21.2)/PML::RARA; t(8;21)(q22;q22.1)/RUNX1::RUNX1T1; inv(16)(p13.1q22); t(16;16)(p13.1;q22)/CBFB::MYH11; t(9;11)(p21.3;q23.3)/MLLT3::KMT2A; t(6;9)(p22.3;q34.1)/DEK::NUP214; inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2.[1]
Vitamin B12 deficiency	• History may highlight the underlying cause (e.g., bariatric surgery). In severe cases of vitamin B12 deficiency, symptoms such as glossitis, paraesthesia, and symptoms of subacute combined degeneration of cord may be present.	• Macrocytic anaemia will be present unless there is an associated iron deficiency. • Peripheral blood smear shows megaloblastic changes. • Serum vitamin B12 levels are low.

Condition	Differentiating signs / symptoms	Differentiating tests
Folate deficiency	• History may highlight the underlying cause (e.g., use of methotrexate). • Painful swallowing, glossitis, and angular stomatitis may be present in patients with severe folate deficiency	• Macrocytic anaemia will be present unless there is an associated iron deficiency. • Peripheral blood smear shows megaloblastic changes. • Serum folate levels are low.
Myelofibrosis	• Splenomegaly is present in most patients. Some patients may have hepatomegaly.	• Bone marrow biopsy shows reticulin fibrosis.
Essential thrombocythaemia	• More commonly presents with vasomotor symptoms or complications from thrombosis or bleeding. • Livedo reticularis (a purplish mottled discolouration of the skin, usually on the legs, typically described as lacy or net-like in appearance) may be present.	• Elevated platelet count. • Bone marrow shows proliferation of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei, but does not show dysplasia. • Genetic testing may identify JAK2 V617F, CALR, or MPL mutations.
Large granular lymphocytic leukaemia (LGL)	• Splenomegaly and a history of autoimmune diseases may be present.	• Lymphocytosis is typical. • Large granular lymphocytes present on peripheral blood smear. • CD3+ cytotoxic T-cell clone present on flow cytometry. • Polymerase chain reaction may show T-cell receptor gene rearrangements in T-cell LGL.
Bone marrow toxicity secondary to azathioprine or cyclophosphamide	• May be undergoing treatment for lupus or rheumatoid arthritis.	• Reassess bone marrow aspirate for resolution of abnormalities after holding medication.
Bone marrow toxicity secondary to cytotoxic therapy (especially with alkylating drugs)	• History includes exposure to these medications.	• Reassess bone marrow aspirate for resolution of abnormalities after holding medication.
Heavy metal poisoning (particularly arsenic)	• History includes possible exposure, often occupational.	• Sideroblastic anaemia with no other marrow abnormalities and no abnormalities in other cell lines (normal platelets, WBC), abnormal heavy metal testing.

Criteria

Molecular International Prognostic Scoring System (IPSS-M) risk assessment[62]

A refined version of the IPSS and IPSS-R that combines somatic mutations (31 genes) with haematological and cytogenetic parameters to risk stratify patients with MDS. The IPSS-M classifies MDS patients into the following six risk groups based on a risk score derived from clinical (bone marrow blast percentage, platelet count, haemoglobin level), cytogenetic, and genetic prognostic factors:

- Very low risk (risk score: ≤-1.5)
- Low risk (risk score: >-1.5 to -0.5)
- Moderate low risk (risk score: >-0.5 to 0)
- Moderate high risk (risk score: >0 to 0.5)
- High risk (risk score: >0.5 to 1.5)
- Very high risk (risk score: >1.5).

The risk score and risk groups can be calculated using a web-based tool: [IPSS-M risk calculator] (https://mds-risk-model.com)

Revised International Prognostic Scoring System (IPSS-R) risk assessment[63]

A refined version of the IPSS, using a larger patient database (Revised IPSS [IPSS-R], n = 7012, IPSS, n = 816) for analysis. Multiple statistically weighted clinical features were used to generate prognostic indicators.

Bone marrow blasts

- ≤2% = 0 points
- >2% to 5% = 1 point
- 5% to 10% = 2 points
- >10% = 3 points.

Karyotype (cytogenetic testing)

- Very good risk: -Y, del(11q) = 0 points
- Good risk: normal, del(5q), del(12p), del(20q), double including del(5q) = 1 point
- Intermediate risk: del(7q), +8, +19, i(17q), any other single or double independent clones = 2 points
- Poor risk: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), or complex 3 abnormalities = 3 points
- Very poor risk: complex >3 abnormalities = 4 points.

Haemoglobin (g/dL)

- ≥10 = 0 points
- 8 to <10 = 1 point
- <8 = 1.5 points.

Platelets (x 10^9/L)

- ≥100 = 0 points
- 50 to <100 = 0.5 points
- <50 = 1 point.

Absolute neutrophil count (x 10^9/L)

- ≥0.8 = 0 points
- <0.8 = 0.5 points.

Total summed score:

<1.5 points = very low risk

>1.5 to 3.0 points = low risk

>3.0 to 4.5 points = intermediate risk

>4.5 to 6.0 points = high risk

>6 points = very high risk.

A web-based IPSS-R calculator tool is available. [MDS Foundation: Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes risk assessment calculator] (https://www.mds-foundation.org/ipss-r-calculator)

The World Health Organization Prognostic Scoring System (WPSS)[64]

Unlike prognostic scoring systems that predict outcomes based upon findings at diagnosis, the WPSS provides prognostic information for patients with myelodysplastic syndrome (MDS) at any time during the course of their disease.

The World Health Organization (WHO) category

- Refractory anaemia; refractory anaemia with ringed sideroblasts; MDS with isolated del(5q) and marrow blasts <5% = 0 points
- Refractory cytopenia with multilineage dysplasia; refractory cytopenia with multilineage dysplasia and ringed sideroblasts = 1 point
- Refractory anaemia with excess of blasts-1 = 2 points
- Refractory anaemia with excess of blasts-2 = 3 points.

The WHO classification for MDS was revised in 2016.[65] In the revised classification, the terms 'refractory anaemia' and 'refractory cytopenia' have been replaced with the term 'MDS'.

Karyotype (cytogenetic testing)

- Good risk: normal, -Y, del(5q), del(20q) = 0 points
- Intermediate risk: not classified as good risk or poor risk (other abnormalities) = 1 point
- Poor risk: complex (≥3 abnormalities), chromosome 7 anomalies = 2 points.

RBC transfusion requirement

- None = 0 points
- Regular = 1 point (transfusion dependency defined as having at least one RBC transfusion every 8 weeks over a period of 4 months).

Total summed score:

0 points = very low risk

1 point = low risk

2 points = intermediate risk

3-4 points = high risk

5-6 points = very high risk.

International Prognostic Scoring System (IPSS) risk assessment[66]

Scores for three domains (bone marrow blasts, karyotype, and peripheral blood cytopenias) are summed to give an overall score and assign a risk category; age (≤60 years) is also important.

Bone marrow blasts

- <5% = 0 points
- 5% to 10% = 0.5 points
- NA = 1 point
- 11% to 20% = 1.5 points
- 21% to 30% = 2 points.

Karyotype (cytogenetic testing)

- Good risk: normal, isolated-Y, isolated del(5q), or isolated del(20q) = 0 points
- Intermediate risk: all karyotypes not defined as good or poor = 0.5 points
- Poor risk: abnormal chromosome 7, or a complex karyotype (3 or more abnormalities) = 1 point.

Peripheral blood cytopenias

- 0 or 1 = 0 points
- 2 or 3 = 0.5 points.

Total summed score:

0 points = low risk

0.5 to 1.0 points = intermediate-1 (INT-1) risk

1.5 to 2.0 points = INT-2 risk

≥2.5 points = high risk.

Approach

Treatment for MDS is guided by risk assessment, disease type/characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms/severity of cytopenias, and erythropoietin levels (in patients with anaemia).[12] [15] Other important treatment considerations include patient age, performance status, comorbidities, and patient preference/goals.

Risk assessment informs treatment. The revised International Prognostic Scoring System (IPSS-R) is used to determine whether patients have lower-risk disease or higher-risk disease. See Criteria.

All patients should be encouraged to enrol in a clinical trial (if available and eligible), particularly those with higher-risk disease and those unresponsive to treatment.[12] [15]

Supportive care

Supportive care is central to management of MDS. All symptomatic patients (lower- or higher-risk) should receive supportive care as appropriate, which includes: red blood cell (RBC) transfusions with iron chelation support (for anaemia); platelet transfusions (for thrombocytopenia and bleeding); and anti-infective therapy (e.g., antibiotics).[12] [15]

Transfusions

RBC transfusion (with iron chelation therapy support if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, RBC transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

Platelet transfusions are recommended for thrombocytopenic bleeding.[15] Platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count is <10,000/microlitre.[15] Avoiding unnecessary platelet transfusions can improve quality of life and may reduce the risk of repeated suboptimal response to transfusion (platelet refractoriness).

All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic stem cell transplantation (SCT).[15]

Anti-infective therapy

Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.[15]

Allogeneic stem cell transplantation (SCT)

Allogeneic SCT is the only potentially curative therapy for MDS.[68]

Allogeneic SCT is recommended for patients with high-risk disease, if eligible.[15] It may be considered for select patients with lower-risk disease (e.g., intermediate risk according to IPSS-R with severe cytopenias; see Criteria).

Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15] [68] Many patients are unsuitable for allogeneic SCT because of advanced age, lack of a compatible donor (although becoming less common with use of haploidentical transplant), poor performance status, or comorbidities.

A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

Lower-risk disease: asymptomatic

Lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) is associated with a relatively low risk of progression to acute myeloid leukaemia (AML) or death.

Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

Patients with lower-risk disease who are asymptomatic can be monitored without treatment until symptoms, complications of cytopenias, or disease progression occur, or are likely to occur.[16]

Lower-risk disease: symptomatic anaemia

For treatment of symptomatic anaemia in lower-risk patients, the National Comprehensive Cancer Network (NCCN) recommends stratifying patients based on erythropoietin levels and the following disease type/characteristics:[15]

- MDS-5q, i.e., MDS with del(5q), with or without one other cytogenetic abnormality except those involving chromosome 7
- MDS-SF3B1, i.e., MDS with no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts ≥15% (or ≥5% with an SF3B1 mutation)
- MDS with no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts <15% (or <5% with an SF3B1 mutation). See Classification.

MDS-5q with erythropoietin levels ≤500 IU/L

- Lenalidomide (preferred) or an erythropoiesis-stimulating agent (ESA; e.g., epoetin alfa, darbepoetin alfa) is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-5q and erythropoietin levels ≤500 IU/L.[15] Patients who fail to respond (i.e., no improvement in haemoglobin or no reduction in RBC transfusion requirement) to an ESA prescribed first-line can be considered for lenalidomide therapy, if absolute neutrophil count is >500/microlitre and platelet count is >50,000/microlitre.[15]
- If there is no response to initial treatment with lenalidomide or an ESA, a clinical trial or treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine) is recommended.[15]
- If there is no response to (or there is intolerance of) treatment with hypomethylating agents, patients can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15]

MDS-5q with erythropoietin levels >500 IU/L

- Lenalidomide is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-5q and erythropoietin levels >500 IU/L.[15] Patients with erythropoietin levels >500 IU/L are unlikely to benefit from treatment with ESAs.[69]
- If there is no response to initial treatment, a clinical trial or treatment with a hypomethylating agent is recommended.[15]
- If there is no response to (or there is intolerance of) treatment with hypomethylating agents, these patients can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15]

MDS-SF3B1 with erythropoietin levels ≤500 IU/L

- Luspatercept is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-SF3B1 and erythropoietin levels ≤500 IU/L.[15] [70]
- If there is no response to initial treatment, imetelstat or an ESA is recommended.[15] Granulocyte colony-stimulating factor (G-CSF; e.g., filgrastim) may be combined with an ESA to treat anaemia. Evidence suggests that G-CSF may improve the erythroid response rate of ESAs.[71] A validated decision model has been developed for predicting erythroid responses to ESAs plus G-CSF based on erythropoietin level and number of previous RBC transfusions.[72]
- If there is no response to treatment with imetelstat or ESAs (with or without G-CSF), patients can be considered for a clinical trial (if available and eligible) or treatment with a hypomethylating agent.[15]
- Patients who do not respond to (or are intolerant of) treatment with hypomethylating agents can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15] Patients who do not respond to ivosidenib can be considered for a clinical trial or allogeneic SCT.[15]

MDS-SF3B1 with erythropoietin levels >500 IU/L

- Luspatercept or imetelstat is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-SF3B1 and erythropoietin levels >500 IU/L.[15] [70]
- Lenalidomide can be considered if there is no response to initial treatment with luspatercept or imetelstat.[15]
- If there is no response to treatment with lenalidomide, patients should be considered for a clinical trial or treatment with a hypomethylating agent.[15]
- Patients who do not respond to (or are intolerant of) treatment with hypomethylating agents can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15] Patients who do not respond to ivosidenib can be considered for a clinical trial or allogeneic SCT.[15]

MDS with no del(5q) with ring sideroblasts <15% with erythropoietin levels ≤500 IU/L

- An ESA alone or luspatercept is recommended for initial treatment of symptomatic anaemia in lower-risk patients with no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) and erythropoietin levels ≤500 IU/L.[15] [73] Patients who fail to respond (i.e., no improvement in haemoglobin or no reduction in RBC transfusion requirement) to an ESA prescribed first-line can be considered for luspatercept therapy.[15]
- G-CSF or lenalidomide may be combined with an ESA if there is no response to initial treatment with an ESA alone or luspatercept.[15] [71] [72] Imetelstat or lenalidomide alone can also be considered if there is no response to initial treatment in these patients.
- Patients who do not respond to treatment with an ESA (with or without G-CSF or lenalidomide) or imetelstat can be considered for a clinical trial or treatment with a hypomethylating agent.[15]

- If there is no response to (or there is intolerance of) treatment with hypomethylating agents, patients can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15] Patients who do not respond to ivosidenib can be considered for a clinical trial or allogeneic SCT.[15]

MDS with no del(5q) with ring sideroblasts <15% with erythropoietin levels >500 IU/L

- Patients with MDS who have no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) and erythropoietin levels >500 IU/L should be evaluated for suitability for immunosuppressive therapy (IST). Patients who are likely to respond to IST (e.g., those with hypocellular bone marrow) can be treated with IST comprising antithymocyte globulin (ATG) with or without ciclosporin.[15] [74] Eltrombopag may be combined with IST. A corticosteroid should be given alongside ATG to prevent serum sickness.
- IST may be effective in patients aged ≤60 years with ≤5% marrow blasts, or in those who have the following features: HLA-DR15 positivity; paroxysmal nocturnal haemoglobinuria (PNH) clone; or STAT-3 mutant T-cell clone. However, the evidence is mixed.[74] [75] [76] [77] [78]
- Patients who are unlikely to respond to IST, or who are unresponsive to initial treatment with IST, can be considered for a clinical trial, or treatment with a hypomethylating agent or imetelstat.[15] [74] Lenalidomide may also be considered if absolute neutrophil count is >500/microlitre and platelet count is >50,000/microlitre.[15]
- If there is no response to (or there is intolerance of) treatment with hypomethylating agents, imetelstat, or lenalidomide, patients can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15]

Lower-risk disease: clinically relevant thrombocytopenia or neutropenia (without symptomatic anaemia)

A clinical trial or a hypomethylating agent is recommended for initial treatment of patients with lower-risk disease who have clinically relevant thrombocytopenia or neutropenia (without symptomatic anaemia).[15]

Patients likely to respond to IST (e.g., those with hypocellular bone marrow) can be considered for initial treatment with ATG plus ciclosporin (with or without eltrombopag).[15] [74] Eltrombopag alone can be considered for treatment of severe or life-threatening thrombocytopenia in lower-risk patients.[15]

A hypomethylating agent (if not previously used) or ivosidenib (if patients have IDH1 mutations) can be considered if there is disease progression or no response to initial treatment of clinically relevant thrombocytopenia or neutropenia in lower-risk patients.[15] Romiplostim can be considered for treatment of severe or refractory thrombocytopenia.[15] [79] Patients who do not have IDH1 mutations should be considered for a clinical trial or allogeneic SCT.[15]

Higher-risk disease

Patients with higher-risk disease (e.g., intermediate, high, or very high risk according to IPSS-R) have a poor prognosis (relatively increased risk of progression to AML or death).[12] [15]

Treatment for higher-risk disease is focused on delaying progression and prolonging survival, reducing symptoms and complications, and improving quality of life.

Higher-risk patients should be promptly referred for allogeneic SCT evaluation.[12] [80] [81] Patients should be encouraged to enrol in a clinical trial (if available and eligible), especially if they have poor prognostic markers (e.g., TP53 mutations).

Higher-risk disease: transplant candidate

Higher-risk patients may undergo immediate allogeneic SCT if suitable (e.g., based on age, performance status, comorbidities, patient preference, and donor availability).[12] [15]

Pre-transplant cytoreduction (debulking) using chemotherapy or hypomethylating agents is recommended to reduce marrow blasts to <5% in patients with high tumour burden.[12] [15] [53]

Ivosidenib can be used for cytoreduction if there is no response to chemotherapy or hypomethylating agents, and the patient has IDH1 mutations.[15] Cytoreduction may reduce the risk of post-transplant relapse. However, this has not yet been confirmed by prospective clinical trials.

Higher-risk disease: non-transplant candidate

Higher-risk patients who are unsuitable for allogeneic SCT can be considered for a clinical trial or initial treatment with a hypomethylating agent.[12] [15] [82] Azacitidine improves overall survival in higher-risk patients compared with supportive care and chemotherapy.[83] A survival benefit with decitabine has not been shown in phase 3 trials, but a US-based registry study suggested similar survival to azacitidine.[84]

Oral decitabine/cedazuridine may be used instead of intravenous decitabine based on patient preference and convenience. In patients with higher-risk disease, treatment with a hypomethylating agent should continue until the patient stops responding or treatment becomes intolerable.

Patients who do not respond to initial treatment with a hypomethylating agent can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial if they do not have IDH1 mutations.[15]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
lower-risk disease: asymptomatic		
	1st	**observation**
lower-risk disease: MDS-5q (del(5q) ± one other cytogenetic abnormality except those involving chromosome 7) with symptomatic anaemia		
▪ **with erythropoietin levels ≤500 IU/L**	**1st**	**lenalidomide or erythropoiesis-stimulating agent (ESA)**
	plus	**supportive care**
	2nd	**clinical trial or hypomethylating agent**
	plus	**supportive care**
	3rd	**ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**
	plus	**supportive care**
▪ **with erythropoietin levels >500 IU/L**	**1st**	**lenalidomide**
	plus	**supportive care**
	2nd	**clinical trial or hypomethylating agent**
	plus	**supportive care**
	3rd	**ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**
	plus	**supportive care**
lower-risk disease: MDS-SF3B1 (no del(5q) ± other cytogenetic abnormalities with ring sideroblasts ≥15% [or ≥5% with an SF3B1 mutation]) with symptomatic anaemia		
▪ **with erythropoietin levels ≤500 IU/L**	**1st**	**luspatercept**
	plus	**supportive care**
	2nd	**imetelstat; or erythropoiesis-stimulating agent (ESA) ± granulocyte colony-stimulating factor (G-CSF)**

Acute (summary)

	plus	supportive care
	3rd	clinical trial or hypomethylating agent
	plus	supportive care
	4th	ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)
	plus	supportive care
■ with erythropoietin levels >500 IU/L	1st	luspatercept or imetelstat
	plus	supportive care
	2nd	lenalidomide
	plus	supportive care
	3rd	clinical trial or hypomethylating agent
	plus	supportive care
	4th	ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)
	plus	supportive care
lower-risk disease: no del(5q) with ring sideroblasts <15% (or <5% with an SF3B1 mutation) with symptomatic anaemia		
■ with erythropoietin levels ≤500 IU/L	1st	erythropoiesis-stimulating agent (ESA) alone or luspatercept
	plus	supportive care
	2nd	erythropoiesis-stimulating agent (ESA) ± granulocyte colony-stimulating factor (G-CSF) or lenalidomide; or imetelstat; or lenalidomide alone
	plus	supportive care
	3rd	clinical trial or hypomethylating agent
	plus	supportive care
	4th	ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)
	plus	supportive care
■ with erythropoietin levels >500 IU/L and likely to respond to immunosuppressive therapy	1st	antithymocyte globulin (ATG) ± ciclosporin ± eltrombopag

Acute (summary)		
	plus	supportive care
	2nd	clinical trial or hypomethylating agent or imetelstat or lenalidomide
	plus	supportive care
	3rd	ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)
	plus	supportive care
with erythropoietin levels >500 IU/L and unlikely to respond to immunosuppressive therapy	1st	clinical trial or hypomethylating agent or imetelstat or lenalidomide
	plus	supportive care
	2nd	ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)
	plus	supportive care
lower-risk disease: with clinically relevant thrombocytopenia or neutropenia (without symptomatic anaemia)		
	1st	clinical trial; or hypomethylating agent; or antithymocyte globulin (ATG) + ciclosporin ± eltrombopag; or eltrombopag alone
	plus	supportive care
	2nd	hypomethylating agent or ivosidenib or romiplostim or clinical trial or allogeneic stem cell transplantation (SCT)
	plus	supportive care
higher-risk disease: transplant candidate		
	1st	allogeneic stem cell transplant (SCT)
	plus	supportive care
higher-risk disease: non-transplant candidate		
	1st	clinical trial or hypomethylating agent
	plus	supportive care
	2nd	ivosidenib or clinical trial
	plus	supportive care

MANAGEMENT

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

lower-risk disease: asymptomatic

1st **observation**

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic Scoring System [IPSS-R]), disease type/characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» Patients with lower-risk disease who are asymptomatic can be monitored without treatment until symptoms, complications with cytopenias, or disease progression occur, or are likely to occur.[16]

lower-risk disease: MDS-5q (del(5q) ± one other cytogenetic abnormality except those involving chromosome 7) with symptomatic anaemia

with erythropoietin levels ≤500 IU/L

1st **lenalidomide or erythropoiesis-stimulating agent (ESA)**

Primary options

» lenalidomide

OR

» epoetin alfa

OR

» darbepoetin alfa

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic Scoring System [IPSS-R]), disease type/characteristics (e.g., cytogenetic abnormalities,

MANAGEMENT

Acute

ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» Lenalidomide (preferred) or an ESA (e.g., epoetin alfa, darbepoetin alfa) is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-5q (i.e., MDS with del(5q), with or without one other cytogenetic abnormality except those involving chromosome 7) and erythropoietin levels ≤500 IU/L.[15]

» Patients who fail to respond (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) to an ESA prescribed first-line can be considered for lenalidomide therapy, if absolute neutrophil count is >500/microlitre and platelet count is >50,000/microlitre.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **clinical trial or hypomethylating agent**

Primary options

» azacitidine

MANAGEMENT

Acute

OR

» decitabine

OR

» decitabine/cedazuridine

» A clinical trial or treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine) is recommended if there is no response to initial treatment with lenalidomide or an ESA (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) in patients with MDS-5q who have symptomatic anaemia and erythropoietin levels ≤500 IU/L.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

3rd **ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**

Primary options

» ivosidenib

» Patients with MDS-5q and symptomatic anaemia and erythropoietin levels ≤500 IU/L who do not respond to (or are intolerant of) treatment with hypomethylating agents can be treated with ivosidenib if they have IDH1 mutations.[15]

» Patients who do not have IDH1 mutations should be considered for a clinical trial (if

Acute

available and eligible) or allogeneic SCT (for select patients).[15]

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15] [68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.[15]

with erythropoietin levels >500 IU/L **1st** **lenalidomide**

Primary options

» lenalidomide

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic

MANAGEMENT

Acute

Scoring System [IPSS-R]), disease type/ characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» Lenalidomide is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-5q (i.e., MDS with del(5q), with or without one other cytogenetic abnormality except those involving chromosome 7) and erythropoietin levels >500 IU/L.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **clinical trial or hypomethylating agent**

Primary options

» azacitidine

OR

» decitabine

OR

Acute

» decitabine/cedazuridine

» A clinical trial or treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine) is recommended if there is no response to initial treatment with lenalidomide (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) in patients with MDS-5q who have symptomatic anaemia and erythropoietin levels >500 IU/L.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy (consult local hospital guidelines).[15]

3rd **ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**

Primary options

» ivosidenib

» Patients with MDS-5q and symptomatic anaemia and erythropoietin levels >500 IU/L who do not respond to (or are intolerant of) treatment with hypomethylating agents can be treated with ivosidenib if they have IDH1 mutations.[15]

» Patients who do not have IDH1 mutations should be considered for a clinical trial (if available and eligible) or allogeneic SCT (for select patients).[15]

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

Acute

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15] [68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67]However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.

lower-risk disease: MDS-SF3B1 (no del(5q) ± other cytogenetic abnormalities with ring sideroblasts ≥15% [or ≥5% with an SF3B1 mutation]) with symptomatic anaemia

- **with erythropoietin levels ≤500 IU/L** — **1st** **luspatercept**

Primary options

» luspatercept

Acute

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic Scoring System [IPSS-R]), disease type/characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» Luspatercept is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-SF3B1 (i.e., MDS with no del(5q) with or without other cytogenetic abnormalities with ring sideroblasts ≥15% [or ≥5% with an SF3B1 mutation]) and erythropoietin levels ≤500 IU/L.[15] [70]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **imetelstat; or erythropoiesis-stimulating agent (ESA) ± granulocyte colony-stimulating factor (G-CSF)**

Primary options

» imetelstat

OR

Acute

» epoetin alfa

OR

» darbepoetin alfa

OR

» epoetin alfa
-and-
» filgrastim

OR

» darbepoetin alfa
-and-
» filgrastim

» Imetelstat or an ESA (e.g., epoetin alfa, darbepoetin alfa) is recommended if there is no response to initial treatment with luspatercept (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) in patients with MDS-SF3B1 who have symptomatic anaemia and erythropoietin levels ≤500 IU/L.[15]

» G-CSF (e.g., filgrastim) may be combined with an ESA to treat anaemia. Evidence suggests that G-CSF may improve the erythroid response rate of ESAs.[71] A validated decision model has been developed for predicting erythroid responses to ESAs plus G-CSF based on erythropoietin level and number of previous red blood cell (RBC) transfusions.[72]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be

Acute

individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

3rd **clinical trial or hypomethylating agent**

Primary options

» azacitidine

Secondary options

» decitabine

OR

» decitabine/cedazuridine

» Patients with MDS-SF3B1 and symptomatic anaemia and erythropoietin levels ≤500 IU/L who do not respond to treatment with imetelstat or ESAs (with or without G-CSF) can be considered for a clinical trial (if available and eligible) or treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine).[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) are recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

4th **ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**

MANAGEMENT

Acute

Primary options

» ivosidenib

» Patients with MDS-SF3B1 and symptomatic anaemia and erythropoietin levels ≤500 IU/L who do not respond to (or are intolerant of) third-line treatment with hypomethylating agents can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15]

» Patients who do not respond to ivosidenib can be considered for a clinical trial or allogeneic SCT.[15]

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15] [68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered

Acute

when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.

with erythropoietin levels >500 IU/L — **1st** — **luspatercept or imetelstat**

Primary options

» luspatercept

OR

» imetelstat

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic Scoring System [IPSS-R]), disease type/characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» Luspatercept or imetelstat is recommended for initial treatment of symptomatic anaemia in lower-risk patients with MDS-SF3B1 (i.e., MDS with no del(5q) with or without other cytogenetic abnormalities with ring sideroblasts ≥15% or [≥5% with an SF3B1 mutation] and erythropoietin levels >500 IU/L.[15] [70]

» See local specialist protocol for dosing guidelines.

plus — **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

Acute

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **lenalidomide**

Primary options

» lenalidomide

» Lenalidomide can be considered if there is no response to initial treatment with luspatercept or imetelstat (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) in patients with MDS-SF3B1 who have symptomatic anaemia and erythropoietin levels >500 IU/L.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

3rd **clinical trial or hypomethylating agent**

Primary options

» azacitidine

Secondary options

» decitabine

Acute

OR

» decitabine/cedazuridine

» Patients with MDS-SF3B1 and symptomatic anaemia and erythropoietin levels >500 IU/L who do not respond to treatment with lenalidomide should be considered for a clinical trial (if available and eligible) or treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine).[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

4th **ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**

Primary options

» ivosidenib

» Patients with MDS-SF3B1 and symptomatic anaemia and erythropoietin levels >500 IU/L who do not respond to (or are intolerant of) third-line treatment with hypomethylating agents can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15]

» Patients who do not respond to ivosidenib can be considered for a clinical trial or allogeneic SCT.[15]

Acute

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15] [68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic stem cell transplantation.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic stem cell transplantation should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.

lower-risk disease: no del(5q) with ring sideroblasts <15% (or <5% with an SF3B1 mutation) with symptomatic anaemia

with erythropoietin levels ≤500 IU/L **1st** **erythropoiesis-stimulating agent (ESA) alone or luspatercept**

Acute

Primary options

» epoetin alfa

OR

» darbepoetin alfa

OR

» luspatercept

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic Scoring System [IPSS-R]), disease type/characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» An ESA alone (e.g., epoetin alfa, darbepoetin alfa) or luspatercept is recommended for initial treatment of symptomatic anaemia in lower-risk patients with no del(5q) with or without other cytogenetic abnormalities and ring sideroblasts <15% (or <5% with an SF3B1 mutation) and erythropoietin levels ≤500 IU/L.[15] [73]

» Patients who fail to respond (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) to an ESA prescribed first-line can be considered for luspatercept therapy.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

Acute

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **erythropoiesis-stimulating agent (ESA) ± granulocyte colony-stimulating factor (G-CSF) or lenalidomide; or imetelstat; or lenalidomide alone**

Primary options

» epoetin alfa

OR

» darbepoetin alfa

OR

» epoetin alfa
-and-
» filgrastim

OR

» epoetin alfa
-and-
» lenalidomide

OR

» darbepoetin alfa
-and-
» filgrastim

OR

» darbepoetin alfa
-and-
» lenalidomide

OR

» imetelstat

OR

» lenalidomide

Acute

» G-CSF (e.g., filgrastim) or lenalidomide may be combined with an ESA if there is no response to initial treatment with an ESA alone or luspatercept (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) in patients with no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) who have symptomatic anaemia and erythropoietin levels ≤500 IU/L.[15]

» Imetelstat or lenalidomide alone can also be considered if there is no response to initial treatment in these patients.

» Evidence suggests that G-CSF may improve the erythroid response rate of ESAs.[71] A validated decision model has been developed for predicting erythroid responses to ESAs plus G-CSF based on erythropoietin level and number of previous red blood cell transfusions.[72]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of an\emia or to return the patient to a safe h \emoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

3rd **clinical trial or hypomethylating agent**

Primary options

» azacitidine

Secondary options

» decitabine

OR

MANAGEMENT

Acute

» decitabine/cedazuridine

» Patients with no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) with symptomatic anaemia and erythropoietin levels ≤500 IU/L who do not respond to treatment with an ESA (with or without G-CSF or lenalidomide) or imetelstat can be considered for a clinical trial (if available and eligible) or treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine).[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic aneamia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

4th **ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**

Primary options

» ivosidenib

» Patients with no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) with symptomatic anaemia and erythropoietin levels ≤500 IU/L who do not respond to (or are intolerant of) third-line treatment with hypomethylating agents can be treated with ivosidenib if they have IDH1 mutations, or considered for a clinical trial or allogeneic SCT if they do not have IDH1 mutations.[15]

» Patients who do not respond to ivosidenib can be considered for a clinical trial or allogeneic SCT.[15]

Acute

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15] [68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.

with erythropoietin levels >500 IU/L and likely to respond to immunosuppressive therapy

1st **antithymocyte globulin (ATG) ± ciclosporin ± eltrombopag**

Primary options

» lymphocyte immunoglobulin, anti-thymocyte globulin (equine)
-and-
» prednisolone

OR

Acute

» lymphocyte immunoglobulin, anti-thymocyte globulin (equine)
-and-
» prednisolone
-and-
» ciclosporin

OR

» lymphocyte immunoglobulin, anti-thymocyte globulin (equine)
-and-
» prednisolone
-and-
» eltrombopag

OR

» lymphocyte immunoglobulin, anti-thymocyte globulin (equine)
-and-
» prednisolone
-and-
» ciclosporin
-and-
» eltrombopag

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic Scoring System [IPSS-R]), disease type/characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» Lower-risk patients with no del(5q) with or without other cytogenetic abnormalities and ring sideroblasts <15% (or <5% with an SF3B1 mutation) who have symptomatic anaemia and erythropoietin levels >500 IU/L should be evaluated for suitability for immunosuppressive therapy (IST).

» Patients who are likely to respond to IST (e.g., those with hypocellular bone marrow) can be treated with IST comprising antithymocyte globulin (ATG) with or without ciclosporin.[15]

Acute

[74] Eltrombopag may be combined with IST. A corticosteroid (e.g., prednisolone) should be given alongside ATG to prevent serum sickness.

» IST may be effective in patients aged ≤60 years with ≤5% marrow blasts, or in those who have the following features: HLA-DR15 positivity; paroxysmal nocturnal haemoglobinuria (PNH) clone; or STAT-3 mutant T-cell clone. However, the evidence is mixed.[74] [75] [76] [77] [78]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **clinical trial or hypomethylating agent or imetelstat or lenalidomide**

Primary options

» azacitidine

OR

» imetelstat

Secondary options

» decitabine

OR

» decitabine/cedazuridine

Tertiary options

» lenalidomide

MANAGEMENT

Acute

» A clinical trial (if available) or treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine) or imetelstat is recommended if there is no response to initial treatment with IST (i.e., no improvement in haemoglobin or no reduction in red blood cell transfusion requirement) in patients with no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) who have symptomatic anaemia and erythropoietin levels >500 IU/L.[15]

» Lenalidomide may also be considered if absolute neutrophil count is >500/microlitre and platelet count is >50,000/microlitre.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

3rd **ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**

Primary options

» ivosidenib

» Patients with no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) and symptomatic anaemia and erythropoietin levels >500 IU/L who do not respond to (or are intolerant of) treatment with hypomethylating agents, imetelstat, or lenalidomide can be treated with ivosidenib if they have IDH1 mutations.[15]

Acute

» Patients who do not have IDH1 mutations should be considered for a clinical trial (if available and eligible) or allogeneic SCT (for select patients).[15]

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15][68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.

with erythropoietin levels >500 IU/L and unlikely to respond to immunosuppressive therapy

1st **clinical trial or hypomethylating agent or imetelstat or lenalidomide**

Primary options

» azacitidine

Acute

OR

» imetelstat

Secondary options

» decitabine

OR

» decitabine/cedazuridine

Tertiary options

» lenalidomide

» Treatment is based on risk assessment (e.g., using the Revised International Prognostic Scoring System [IPSS-R]), disease type/characteristics (e.g., cytogenetic abnormalities, ring sideroblasts), symptoms, and erythropoietin levels (in patients with anaemia).[12] [15]

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to IPSS-R) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» Lower-risk patients with no del(5q) with or without other cytogenetic abnormalities and ring sideroblasts <15% (or <5% with an SF3B1 mutation) who have symptomatic anaemia and erythropoietin levels >500 IU/L should be evaluated for suitability for immunosuppressive therapy (IST).

» Patient who are unlikely to respond to IST (e.g., those without hypocellular bone marrow) can be considered for a clinical trial (if available and eligible) or initial treatment with a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine) or imetelstat.[15] [74]

» Lenalidomide may also be considered if absolute neutrophil count is >500/microlitre and platelet count is >50,000/microlitre.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Acute

Treatment recommended for ALL patients in selected patient group

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **ivosidenib or clinical trial or allogeneic stem cell transplantation (SCT)**

Primary options

» ivosidenib

» Patients with no del(5q) and ring sideroblasts <15% (or <5% with an SF3B1 mutation) and symptomatic anaemia and erythropoietin levels >500 IU/L who do not respond to (or are intolerant of) initial treatment with hypomethylating agents, imetelstat, or lenalidomide can be treated with ivosidenib if they have IDH1 mutations.

» Patients who do not have IDH1 mutations should be considered for a clinical trial (if available and eligible) or allogeneic SCT (for select patients).[15]

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15][68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

Acute

	plus	**supportive care** Treatment recommended for ALL patients in selected patient group » Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level. » RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels. » All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15] » Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15] » Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.
lower-risk disease: with clinically relevant thrombocytopenia or neutropenia (without symptomatic anaemia)		
	1st	**clinical trial; or hypomethylating agent; or antithymocyte globulin (ATG) + ciclosporin ± eltrombopag; or eltrombopag alone** **Primary options** » azacitidine **OR** » decitabine **OR** » decitabine/cedazuridine **OR** » lymphocyte immunoglobulin, anti-thymocyte globulin (equine)

Acute

-and-
» prednisolone
-and-
» ciclosporin

OR

» lymphocyte immunoglobulin, anti-thymocyte globulin (equine)
-and-
» prednisolone
-and-
» ciclosporin
-and-
» eltrombopag

OR

» eltrombopag

» Patients with lower-risk disease (e.g., very-low, low, or intermediate risk according to the Revised International Prognostic Scoring System [IPSS-R]) have a relatively low risk of progression to acute myeloid leukaemia (AML) and death.

» Treatment for lower-risk disease is focused on improving quality of life by reducing symptoms, reducing transfusion need, and preventing complications associated with cytopenias.

» A clinical trial or a hypomethylating agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine) is recommended for initial treatment of patients with lower-risk disease who have clinically relevant thrombocytopenia or neutropenia (without symptomatic anaemia).[15]

» Patients likely to respond to immunosuppressive therapy (IST; e.g., those with hypocellular bone marrow) can be considered for initial treatment with ATG plus ciclosporin (with or without eltrombopag).[15] [74]

» IST may be effective in patients aged ≤60 years with ≤5% marrow blasts, or in those who have the following features: HLA-DR15 positivity; paroxysmal nocturnal haemoglobinuria (PNH) clone; or STAT-3 mutant T-cell clone. However, the evidence is mixed.[74] [75] [76] [77] [78]

» Eltrombopag alone can be considered for treatment of severe or life-threatening thrombocytopenia in lower-risk patients.[15]

Acute

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Platelet transfusions are recommended for thrombocytopenic bleeding.[15] Platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count is <10,000/microlitre.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **hypomethylating agent or ivosidenib or romiplostim or clinical trial or allogeneic stem cell transplantation (SCT)**

Primary options

» azacitidine

OR

» decitabine

OR

» decitabine/cedazuridine

OR

» ivosidenib

Secondary options

» romiplostim

» A hypomethylating agent (if not previously used) or ivosidenib (if patients have IDH1 mutations) can be considered if there is disease progression or no response to initial treatment of clinically relevant thrombocytopenia or neutropenia in lower-risk patients.[15]

» Romiplostim can be considered for treatment of severe or refractory thrombocytopenia.[15] [79]

» Patients who do not have IDH1 mutations should be considered for a clinical trial (if available and eligible) or allogeneic SCT (for select patients).[15]

Acute

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» Patients should be assessed for suitability for allogeneic SCT and referred for transplant evaluation as early as possible following diagnosis.[12] [15][68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» Platelet transfusions are recommended for thrombocytopenic bleeding.[15] Platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count is <10,000/microlitre.[15]

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.

higher-risk disease: transplant candidate

1st **allogeneic stem cell transplant (SCT)**

» Patients with higher-risk disease (e.g., intermediate, high, or very-high risk according to the Revised International Prognostic Scoring System [IPSS-R]) have a poor prognosis (relatively increased risk of progression to acute myeloid leukaemia [AML] or death).[12] [15]

» Treatment for higher-risk patients is focused on delaying progression and prolonging survival, reducing symptoms and complications, and improving quality of life.

Acute

» Higher-risk patients should be promptly referred for allogeneic SCT evaluation.[12] [80] [81] Patients should be encouraged to enrol in a clinical trial (if available and eligible), especially if they have poor prognostic markers (e.g., TP53 mutations).

» Higher-risk patients may undergo immediate allogeneic SCT if suitable (e.g., based on age, performance status, comorbidities, patient preference, and donor availability).[12] [15]

» Pre-transplant cytoreduction (debulking) using chemotherapy or hypomethylating agents (azacitidine, decitabine, decitabine/cedazuridine) is recommended to reduce marrow blasts to <5% in patients with high tumour burden.[12] [15] [53]

» Ivosidenib can be used for cytoreduction if there is no response to chemotherapy or hypomethylating agents, and the patient has IDH1 mutations.[15] Cytoreduction may reduce the risk of post-transplant relapse. However, this has not yet been confirmed by prospective clinical trials.

» Allogeneic SCT is the only potentially curative therapy for MDS.[68]

» A matched sibling donor, unrelated donor, haploidentical donor, or cord blood donor can be used for allogeneic SCT.[68] Standard or reduced-intensity conditioning regimens may be considered.[68]

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All symptomatic patients should receive supportive care as appropriate.

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Platelet transfusions are recommended for thrombocytopenic bleeding.[15] Platelet

Acute

transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count is <10,000/microlitre.[15]

» All transfused blood products should be irradiated before use in patients who are potential candidates for allogeneic SCT.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

» Patients who have undergone allogeneic SCT should receive antibiotic prophylaxis alongside post-transplant immunosuppressive regimens used to manage graft-versus-host disease.

higher-risk disease: non-transplant candidate

1st **clinical trial or hypomethylating agent**

Primary options

» azacitidine

Secondary options

» decitabine

OR

» decitabine/cedazuridine

» Patients with higher-risk disease (e.g., intermediate, high, or very-high risk according to the Revised International Prognostic Scoring System [IPSS-R]) have a poor prognosis (relatively increased risk of progression to acute myeloid leukaemia [AML] or death).[12] [15]

» Treatment for higher-risk patients is focused on delaying progression and prolonging survival, reducing symptoms and complications, and improving quality of life.

» Higher-risk patients should be promptly referred for allogeneic stem cell transplantation (SCT) evaluation.[12] [80] [81] Patients should also be encouraged to enrol in a clinical trial (if available and eligible), especially if they have poor prognostic markers (e.g., TP53 mutations).

» Higher-risk patients who are unsuitable for allogeneic SCT can be considered for a clinical trial or initial treatment with a hypomethylating

Acute

agent (azacitidine [preferred]; decitabine; or decitabine/cedazuridine).[12] [15] [82]

» Azacitidine improves overall survival in higher-risk patients compared with supportive care and chemotherapy.[83] A survival benefit with decitabine has not been shown in phase 3 trials, but a US-based registry study suggested similar survival to azacitidine.[84]

» In patients with higher-risk disease, treatment with a hypomethylating agent should continue until the patient stops responding or treatment becomes intolerable.

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All symptomatic patients should receive supportive care as appropriate.

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Platelet transfusions are recommended for thrombocytopenic bleeding.[15] Platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count is <10,000/microlitre.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

2nd **ivosidenib or clinical trial**

Primary options

» ivosidenib

» Patients with higher-risk disease who do not respond to initial treatment with a hypomethylating agent can be treated with

Acute

ivosidenib if they have IDH1 mutations, or considered for a clinical trial if they do not have IDH1 mutations.[15]

» See local specialist protocol for dosing guidelines.

plus **supportive care**

Treatment recommended for ALL patients in selected patient group

» All symptomatic patients should receive supportive care as appropriate.

» Red blood cell (RBC) transfusion (with iron chelation therapy supported if needed) is recommended for symptomatic anaemia.[15] Patients should be transfused with the minimum number of units necessary to relieve symptoms of anaemia or to return the patient to a safe haemoglobin level.

» RBC transfusions are usually warranted if haemoglobin falls below 7 g/dL or 8 g/dL.[12] [67] However, transfusions should be individualised because symptomatic anaemia may occur at higher haemoglobin levels.

» Platelet transfusions are recommended for thrombocytopenic bleeding.[15] Platelet transfusions should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count is <10,000/microlitre.[15]

» Antibiotics are recommended for bacterial infections and prophylaxis may be considered when starting patients on therapy; consult local guidance.[15]

Emerging

Venetoclax

Early studies of venetoclax (a B-cell lymphoma-2 [BCL-2] protein inhibitor) combined with azacitidine in patients with untreated or relapsed/refractory higher-risk MDS have shown promising results.[85] [86] The US Food and Drug Administration (FDA) has granted orphan drug designation and breakthrough therapy designation for venetoclax in combination with azacitidine for the treatment of patients with previously untreated higher-risk MDS.

Enasidenib

Enasidenib, an isocitrate dehydrogenase 2 (IDH2) inhibitor, is being investigated in MDS patients with IDH mutations. A phase 2 study is ongoing.[87]

Eltanexor

Eltanexor (a second-generation, oral selective inhibitor of nuclear export) has shown promise in a phase 1/2 open-label study of patients with higher-risk MDS refractory to hypomethylating agents.[88] The FDA has granted orphan drug designation and fast-track designation for eltanexor as monotherapy for the treatment of patients with relapsed or refractory intermediate-, high-, or very-high-risk MDS. The European Medicines Agency (EMA) has granted orphan drug designation to eltanexor for the treatment of MDS.

Tamibarotene

Tamibarotene (an oral selective retinoic acid receptor alpha [RARA] agonist) has been granted orphan drug designation and fast-track designation by the FDA for the treatment of higher-risk MDS. The EMA has also granted orphan drug designation to tamibarotene for the treatment of MDS. Tamibarotene is currently being evaluated in a phase 3 clinical trial of patients with newly diagnosed RARA-positive higher-risk MDS (in combination with azacitidine).[89] [90]

Magrolimab

Magrolimab (an anti-CD47 monoclonal antibody) has been granted orphan drug designation and breakthrough designation by the FDA for the treatment of newly diagnosed MDS. The EMA has also granted orphan drug designation to magrolimab for the treatment of MDS. Interim analysis of a phase 3 randomised clinical trial of magrolimab plus azacitidine versus azacitidine plus placebo in untreated higher-risk MDS demonstrated futility and increased risk of death.[91] [92] The trial has been discontinued, and the FDA has placed all magrolimab MDS and acute myeloid leukaemia studies on hold.

Patient discussions

Patients should be advised that a fever ≥38.3ºC (101°F) requires urgent evaluation in the accident and emergency department or urgent care if their usual provider is not available. This is true even in the absence of significant neutropenia, as neutrophils can be dysfunctional. Bleeding precautions should be advised if platelet counts have been low.

Vaccination

Patients with MDS are at increased risk of infections.[57] [97] Non-live vaccines are recommended, according to age, comorbidities, and local guidelines, particularly against influenza and *Streptococcus pneumoniae* .[98] [99]

FOLLOW UP

Monitoring

Monitoring

A full blood count should be checked routinely to monitor levels of red blood cells (RBCs), white blood cells, and platelets. The interval between testing varies based on the patient's symptoms.

Patients who require regular transfusion should be assessed for iron chelation therapy. Iron chelation therapy can improve event-free survival and should be considered for patients with a favourable prognosis with:[12] [15][16] [96]

- High transfusion burden (e.g., 15 or more RBC transfusions)
- Serum ferritin levels exceeding 1000 micrograms/L on repeat measurements.

Candidates for allogeneic stem cell transplantation should receive early chelation therapy.[16]

Complications

Complications	Timeframe	Likelihood
iron overload	**long term**	**medium**
Liver and other organ abnormalities can result from haemochromatosis secondary to multiple transfusions.[95] This may develop over an extended period of time, depending on the frequency of blood transfusions, but may be prevented by the use of iron chelation therapy. Patients who require regular transfusion should be assessed for iron chelation therapy. Iron chelation therapy can improve event-free survival and should be considered for patients with a favourable prognosis with high transfusion burden (e.g., 15 or more RBC transfusions); serum ferritin levels exceeding 1000 micrograms/L on repeat measurements.[12] [15] [16] [96] Candidates for allogeneic stem cell transplantation should receive early chelation therapy.[16]		
infection	**variable**	**high**
Neutropenia and neutrophil dysfunction predispose to recurrent infections. Bacterial infections are the principal cause of death in patients with MDS.[5] Treatment is broad-spectrum antibiotics when these patients are febrile. Growth factor support with granulocyte-colony stimulating factor (G-CSF; e.g., filgrastim) may improve neutrophil counts but does not improve long-term survival. G-CSF may be considered in patients with recurrent infections, but is not routinely recommended (including for infection prophylaxis).[15]		
bleeding	**variable**	**medium**
Bleeding complications are possible due to thrombocytopenia and functional defects of platelets. Platelet transfusion may be considered if there is bleeding, or if platelet count is less than 10×10^9/L, or before planned procedures (e.g., if platelet count is less than 50×10^9/L before major surgery).[94]		
progression to acute myeloid leukaemia (AML)	**variable**	**medium**
Once patients develop ≥20% undifferentiated blasts in the bone marrow, they are considered to have progressed to acute myeloid leukaemia (AML).[65] AML arising from MDS is usually refractory to standard therapy for MDS. Patients with secondary AML who are treated with chemotherapy regimens used for de novo AML may achieve remission but usually relapse quickly; allogeneic stem cell transplantation is recommended in eligible patients. Clinical trial enrolment is appropriate if a patient with secondary AML wishes treatment and can tolerate therapy.		

Prognosis

Patients aged under 60 years have a better survival rate than older patients. Specific prognostic criteria were defined by the International Prognostic Scoring System (IPSS) working group in 1997 after a multivariate analysis of 816 patients with de novo MDS who were treated primarily with supportive care.[66] The IPSS uses three factors (number of cytopenias [1, 2, or 3], percentage marrow blasts [<5, 5% to 10%, 11% to 20%, or 21% to 30%], and cytogenetic abnormalities [good-, intermediate-, or poor-risk karyotype]) to categorise patients into four overall risk groups for AML progression or death: low-, intermediate-1 (INT-1), INT-2, and high-risk disease. For older patients, overall median survival by risk group ranges from less

than 6 months for high-risk patients to 5.7 years for low-risk patients.[66] Secondary MDS has a poorer prognosis.[3] Chromosome 5q31 deletion (del(5q)), monosomy 7, 11q23, and TP53 mutations all have a poor prognosis.[93]

One of the major drawbacks of the 1997 IPSS is that it included patients with 21% to 30% blasts in the bone marrow, a group that is classified as having AML in the WHO classification.[65] Another limitation is that the number of cytogenetic subgroups in the intermediate karyotype risk category is large, and the actual prognostic significance of these is diverse. Nonetheless, the IPSS serves as a useful guide when discussing prognosis with patients and families.

Revised International Prognostic Scoring System (IPSS-R)[63]

The IPSS-R was developed to address some of the drawbacks of the IPSS. This IPSS-R scoring system includes five variables:

- Bone marrow blast percentage:
  - ≤2 (0 points)
  - >2 to <5 (1 point)
  - 5-10 (2 points)
  - >10 (3 points).
- Karyotype:
  - Very good (0 points): deletion Y or del(11q)
  - Good (1 point): normal karyotype, del (5q), del(12p), del (20q), a double abnormality, including del(5q)
  - Intermediate (2 points): deletion 7q, +8, +19, i(17q), and any other single or double independent clones
  - Poor (3 points): deletion 7, inv(3)/t(3q)/del(3q), double abnormalities including -7/del(7q), or three abnormalities
  - Very poor (4 points): complex karyotype (≥3 abnormalities).
- Haemoglobin level:
  - ≥10 g/dL (0 points)
  - 8 to <10 g/dL (1 point)
  - <8 g/dL (1.5 points).
- Platelet count:
  - ≥100,000/microlitre (0 points)
  - 50,000 to 100,000/microlitre (0.5 points)
  - <50,000/microlitre (1 point).
- Absolute neutrophil count:
  - ≥800/microlitre (0 points)
  - <800/microlitre (0.5 points).

The IPSS-R score is calculated by adding each of these five values, and is divided into five groups based on the risk of AML development and overall survival. The IPSS-R was first validated in a set of 7012 patients with primary MDS. The five risk groups are:

- Very low risk: ≤1.5
- Low risk: >1.5 to 3.0
- Intermediate risk: >3.0 to 4.5

- High risk: >4.5 to 6.0
- Very high risk: >6.

Median survival (without treatment) for the IPSS-R risk groups are:

- Very low risk: 8.8 years
- Low risk: 5.3 years
- Intermediate risk: 3 years
- High risk: 1.6 years
- Very high risk: 0.8 years.

Time to 25% AML evolution for the IPSS-R risk groups are:

- Very low risk: not reached
- Low risk: 10.8 years
- Intermediate risk: 3.2 years
- High risk: 1.4 years
- Very high risk: 0.7 years.

Molecular International Prognostic Scoring System (IPSS-M)[62]

The IPSS-M is a refined version of the IPSS and IPSS-R that combines somatic mutations (of 31 genes) with haematological and cytogenetic parameters to risk stratify patients with MDS. The IPSS-M classifies MDS patients into the following six risk groups based on a risk score derived from clinical (bone marrow blast percentage, platelet count, haemoglobin level), cytogenetic, and genetic prognostic factors (calculated using a web-based tool: [IPSS-M risk calculator] (https://mds-risk-model.com)):

- Very low risk (risk score: ≤-1.5)
- Low risk (risk score: >-1.5 to -0.5)
- Moderate low risk (risk score: >-0.5 to 0)
- Moderate high risk (risk score: >0 to 0.5)
- High risk (risk score: >0.5 to 1.5)
- Very high risk (risk score: >1.5).

Median overall survival for the IPSS-M risk groups are:

- Very low risk: 10.6 years
- Low risk: 6.0 years
- Moderate low risk: 4.6 years
- Moderate high risk: 2.8 years
- High risk: 1.7 years
- Very high risk: 1.0 years.

Risk of transformation to AML by 1, 2, and 4 years for the IPSS-M risk groups are:

- Very low risk: 0%, 1.2%, and 2.8%, respectively
- Low risk: 1.7%, 3.4%, and 5.1%, respectively
- Moderate low risk: 4.9%, 8.8%, and 11.4%, respectively
- Moderate high risk: 9.5%, 14%, and 18.9%, respectively
- High risk: 14.3%, 21.2%, and 29.2%, respectively
- Very high risk: 28.2%, 38.6%, and 42.8%, respectively.

Risk of death without AML by 1, 2, and 4 years for the IPSS-M risk groups are:

- Very low risk: 2.2%, 7%, and 15.9%, respectively
- Low risk: 8.5%, 16.2%, and 29.5%, respectively
- Moderate low risk: 12%, 19.8%, and 33.6%, respectively

FOLLOW UP

- Moderate high risk: 18%, 31.1%, and 51.1%, respectively
- High risk: 19.3%, 39.8%, and 54.2%, respectively
- Very high risk: 30.6%, 45.6%, and 51.3%, respectively.

Diagnostic guidelines

United Kingdom

British Society for Haematology guidelines for the diagnosis and evaluation of prognosis of adult myelodysplastic syndromes (https://b-s-h.org.uk/guidelines/?category=Haemato-oncology&fromdate=&todate=)

Published by: British Society for Haematology **Last published:** 2021

Good practice papers: the use of genetic tests to diagnose and manage patients with myeloproliferative and myeloproliferative/myelodysplastic neoplasms, and related disorders (https://b-s-h.org.uk/guidelines/?position-paper=false&gpp=true&addenda=false&audio=false&search=#guideline-filters__select__status)

Published by: British Society for Haematology **Last published:** 2021

Europe

Guidelines for the diagnosis and treatment of myelodysplastic syndrome and chronic myelomonocytic leukemia (10th update) (https://nmds.org/index.php/guidelines)

Published by: Nordic MDS Group **Last published:** 2021

Myelodysplastic syndromes (https://www.esmo.org/guidelines/guidelines-by-topic/haematological-malignancies?page=2)

Published by: European Society for Medical Oncology **Last published:** 2020

North America

NCCN clinical practice guidelines in oncology: myelodysplastic syndromes (https://www.nccn.org/guidelines/category_1)

Published by: National Comprehensive Cancer Network **Last published:** 2024

Asia

Guidelines for treating iron overload in myelodysplastic syndromes: a Taiwan consensus statement (https://pubmed.ncbi.nlm.nih.gov/24924953)

Published by: Hematology Society of Taiwan **Last published:** 2014

Treatment guidelines

United Kingdom

British Society for Haematology guidelines for the management of adult myelodysplastic syndromes (https://b-s-h.org.uk/guidelines/?category=Haemato-oncology&fromdate=&todate=)

Published by: British Society for Haematology **Last published:** 2021

Europe

Guidelines for the diagnosis and treatment of myelodysplastic syndrome and chronic myelomonocytic leukemia (10th update) (https://nmds.org/index.php/guidelines)

Published by: Nordic MDS Group **Last published:** 2021

Myelodysplastic syndromes (https://www.esmo.org/guidelines/guidelines-by-topic/haematological-malignancies?page=2)

Published by: European Society for Medical Oncology **Last published:** 2020

North America

NCCN clinical practice guidelines in oncology: myelodysplastic syndromes (https://www.nccn.org/guidelines/category_1)

Published by: National Comprehensive Cancer Network **Last published:** 2024

Asia

Guidelines for treating iron overload in myelodysplastic syndromes: a Taiwan consensus statement (https://pubmed.ncbi.nlm.nih.gov/24924953)

Published by: Hematology Society of Taiwan **Last published:** 2014

Online resources

1. IPSS-M risk calculator (https://mds-risk-model.com) *(external link)*

2. MDS Foundation: Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes risk assessment calculator (https://www.mds-foundation.org/ipss-r-calculator) *(external link)*

Key articles

- Killick SB, Wiseman DH, Quek L, et al. British Society for Haematology guidelines for the diagnosis and evaluation of prognosis of adult myelodysplastic syndromes. Br J Haematol. 2021 Jul;194(2):282-93. Full text (https://onlinelibrary.wiley.com/doi/10.1111/bjh.17621) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34137023?tool=bestpractice.bmj.com)
- Killick SB, Ingram W, Culligan D, et al. British Society for Haematology guidelines for the management of adult myelodysplastic syndromes. Br J Haematol. 2021 Jul;194(2):267-81. Full text (https://onlinelibrary.wiley.com/doi/10.1111/bjh.17612) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34180045?tool=bestpractice.bmj.com)
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: myelodysplastic syndromes [internet publication]. Full text (https://www.nccn.org/guidelines/category_1)
- Fenaux P, Haase D, Santini V, et al; ESMO Guidelines Committee. Myelodysplastic syndromes: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021 Feb;32(2):142-56. Full text (https://www.annalsofoncology.org/article/S0923-7534(20)43129-1/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33221366?tool=bestpractice.bmj.com)

References

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022 Jul;36(7):1703-19. Full text (https://www.doi.org/10.1038/s41375-022-01613-1) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35732831?tool=bestpractice.bmj.com)
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022 Sep 15;140(11):1200-28. Full text (https://www.doi.org/10.1182/blood.2022015850) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35767897?tool=bestpractice.bmj.com)
3. Steensma DP, Bennett JM. The myelodysplastic syndromes: diagnosis and treatment. Mayo Clin Proc. 2006 Jan;81(1):104-30. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16438486?tool=bestpractice.bmj.com)
4. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. Cancer. 2005 Aug 15;104(4):788-93. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15973668?tool=bestpractice.bmj.com)
5. Pomeroy C, Oken MM, Rydell RE, et al. Infection in the myelodysplastic syndromes. Am J Med. 1991 Mar;90(3):338-44. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2003516?tool=bestpractice.bmj.com)

6. Wolach O, Stone R. Autoimmunity and inflammation in myelodysplastic syndromes. Acta Haematol. 2016;136(2):108-17. Full text (https://www.doi.org/10.1159/000446062) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27337745?tool=bestpractice.bmj.com)

7. Komrokji RS, Kulasekararaj A, Al Ali NH, et al. Autoimmune diseases and myelodysplastic syndromes. Am J Hematol. 2016 May;91(5):E280-3. Full text (https://www.doi.org/10.1002/ajh.24333) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26875020?tool=bestpractice.bmj.com)

8. Enright H, Jacobs HS, Vercellotti G, et al. Paraneoplastic autoimmune phenomena in patients with myelodysplastic syndromes: response to immunosuppressive therapy. Br J Haematol. 1995 Oct;91(2):403-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8547082?tool=bestpractice.bmj.com)

9. Sekeres MA, Taylor J. Diagnosis and treatment of myelodysplastic syndromes: a review. JAMA. 2022 Sep 6;328(9):872-80. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36066514?tool=bestpractice.bmj.com)

10. Roman E, Smith A, Appleton S, et al. Myeloid malignancies in the real-world: occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004-15. Cancer Epidemiol. 2016 Jun;42:186-98. Full text (https://www.sciencedirect.com/science/article/pii/S1877782116300364) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27090942?tool=bestpractice.bmj.com)

11. Killick SB, Wiseman DH, Quek L, et al. British Society for Haematology guidelines for the diagnosis and evaluation of prognosis of adult myelodysplastic syndromes. Br J Haematol. 2021 Jul;194(2):282-93. Full text (https://onlinelibrary.wiley.com/doi/10.1111/bjh.17621) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34137023?tool=bestpractice.bmj.com)

12. Killick SB, Ingram W, Culligan D, et al. British Society for Haematology guidelines for the management of adult myelodysplastic syndromes. Br J Haematol. 2021 Jul;194(2):267-81. Full text (https://onlinelibrary.wiley.com/doi/10.1111/bjh.17612) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34180045?tool=bestpractice.bmj.com)

13. National Cancer Institute; Surveillance, Epidemiology, and End Results program (SEER). SEER*Explorer: an interactive website for SEER cancer statistics. Apr 2023 [internet publication]. Full text (https://seer.cancer.gov/statistics-network/explorer)

14. Ma X. Epidemiology of myelodysplastic syndromes. Am J Med. 2012 Jul;125(7 suppl):S2-5. Full text (https://www.doi.org/10.1016/j.amjmed.2012.04.014) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22735748?tool=bestpractice.bmj.com)

15. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: myelodysplastic syndromes [internet publication]. Full text (https://www.nccn.org/guidelines/category_1)

16. Fenaux P, Haase D, Santini V, et al; ESMO Guidelines Committee. Myelodysplastic syndromes: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021 Feb;32(2):142-56. Full text (https://www.annalsofoncology.org/article/S0923-7534(20)43129-1/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33221366?tool=bestpractice.bmj.com)

17. Xavier AC, Kutny M, Costa LJ. Incidence and outcomes of paediatric myelodysplastic syndrome in the United States. Br J Haematol. 2018 Mar;180(6):898-901. Full text (https://www.doi.org/10.1111/bjh.14460) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28240841?tool=bestpractice.bmj.com)

18. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. Nat Rev Cancer. 2017 Jan;17(1):5-19. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27834397?tool=bestpractice.bmj.com)

19. Chen B, Zhao WL, Jin J, et al. Clinical and cytogenetic features of 508 Chinese patients with myelodysplastic syndrome and comparison with those in Western countries. Leukemia. 2005 May;19(5):767-75. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15759035?tool=bestpractice.bmj.com)

20. Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. Blood. 2007 Dec 15;110(13):4385-95. Full text (https://www.doi.org/10.1182/blood-2007-03-082404) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17726160?tool=bestpractice.bmj.com)

21. Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood. 2003 Jul 1;102(1):43-52. Full text (https://www.doi.org/10.1182/blood-2002-11-3343) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12623843?tool=bestpractice.bmj.com)

22. Saygin C, Godley LA. Genetics of Myelodysplastic Syndromes. Cancers (Basel). 2021 Jul;13(14):3380. Full text (https://www.doi.org/10.3390/cancers13143380) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34298596?tool=bestpractice.bmj.com)

23. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013 Nov;122(22):3616-27; quiz 3699. Full text (https://www.doi.org/10.1182/blood-2013-08-518886) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24030381?tool=bestpractice.bmj.com)

24. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014 Feb;28(2):241-7. Full text (https://www.doi.org/10.1038/leu.2013.336) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24220272?tool=bestpractice.bmj.com)

25. Wang SA, Ok CY, Kim AS, et al. Myelodysplastic syndromes with no somatic mutations detected by next-generation sequencing display similar features to myelodysplastic syndromes with detectable mutations. Am J Hematol. 2021 Nov;96(11):E420-3. Full text (https://www.doi.org/10.1002/ajh.26325) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34416041?tool=bestpractice.bmj.com)

26. Oetjen KA, Levoska MA, Tamura D, et al. Predisposition to hematologic malignancies in patients with xeroderma pigmentosum. Haematologica. 2020 Apr;105(4):e144-6. Full text (https://www.doi.org/10.3324/haematol.2019.223370) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31439674?tool=bestpractice.bmj.com)

27. Aktas D, Koc A, Boduroglu K, et al. Myelodysplastic syndrome associated with monosomy 7 in a child with Bloom syndrome. Cancer Genet Cytogenet. 2000 Jan;116(1):44-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10616531?tool=bestpractice.bmj.com)

28. Sutton JF, Stacey M, Kearns WG, et al. Increased risk for aplastic anemia and myelodysplastic syndrome in individuals lacking glutathione S-transferase genes. Pediatr Blood Cancer. 2004 Feb;42(2):122-6. Full text (https://www.doi.org/10.1002/pbc.10479) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14752874?tool=bestpractice.bmj.com)

29. Chen H, Sandler DP, Taylor JA, et al. Increased risk for myelodysplastic syndromes in individuals with glutathione transferase theta 1 (GSTT1) gene defect. Lancet. 1996 Feb 3;347(8997):295-7. Full text (https://www.doi.org/10.1016/s0140-6736(96)90468-7) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8569364?tool=bestpractice.bmj.com)

30. Dutzmann CM, Spix C, Popp I, et al. Cancer in children with Fanconi anemia and ataxia-telangiectasia - a nationwide register-based cohort study in Germany. J Clin Oncol. 2022 Jan;40(1):32-9. Full text (https://www.doi.org/10.1200/JCO.21.01495) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34597127?tool=bestpractice.bmj.com)

31. Sun L, Babushok DV. Secondary myelodysplastic syndrome and leukemia in acquired aplastic anemia and paroxysmal nocturnal hemoglobinuria. Blood. 2020 Jul 2;136(1):36-49. Full text (https://www.doi.org/10.1182/blood.2019000940) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32430502?tool=bestpractice.bmj.com)

32. Tong H, Hu C, Yin X, et al. A meta-analysis of the relationship between cigarette smoking and incidence of myelodysplastic syndromes. PLoS One. 2013;8(6):e67537. Full text (https://www.doi.org/10.1371/journal.pone.0067537) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23805315?tool=bestpractice.bmj.com)

33. Schnatter AR, Glass DC, Tang G, et al. Myelodysplastic syndrome and benzene exposure among petroleum workers: an international pooled analysis. J Natl Cancer Inst. 2012 Nov;104(22):1724-37. Full text (https://www.doi.org/10.1093/jnci/djs411) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23111193?tool=bestpractice.bmj.com)

34. Mundt KA, Dell LD, Boffetta P, et al. The importance of evaluating specific myeloid malignancies in epidemiological studies of environmental carcinogens. BMC Cancer. 2021 Mar;21(1):227. Full text (https://www.doi.org/10.1186/s12885-021-07908-3) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33676443?tool=bestpractice.bmj.com)

35. Morton LM, Dores GM, Schonfeld SJ, et al. Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. JAMA Oncol. 2019 Mar;5(3):318-25. Full text (https://www.doi.org/10.1001/jamaoncol.2018.5625) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30570657?tool=bestpractice.bmj.com)

36. Sill H, Olipitz W, Zebisch A, et al. Therapy-related myeloid neoplasms: pathobiology and clinical characteristics. Br J Pharmacol. 2011 Feb;162(4):792-805. Full text (https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/j.1476-5381.2010.01100.x) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21039422?tool=bestpractice.bmj.com)

REFERENCES

37. Kaplan H, Malmgren J, De Roos AJ. Risk of myelodysplastic syndrome and acute myeloid leukemia post radiation treatment for breast cancer: a population-based study. Breast Cancer Res Treat. 2013 Feb;137(3):863-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23274844?tool=bestpractice.bmj.com)

38. Kaplan HG, Malmgren JA, Atwood MK. Increased incidence of myelodysplastic syndrome and acute myeloid leukemia following breast cancer treatment with radiation alone or combined with chemotherapy: a registry cohort analysis 1990-2005. BMC Cancer. 2011 Jun 21;11:260. Full text (https://www.doi.org/10.1186/1471-2407-11-260) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21693006?tool=bestpractice.bmj.com)

39. Leone G, Pagano L, Ben-Yehuda D, et al. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica. 2007 Oct;92(10):1389-98. Full text (https://www.doi.org/10.3324/haematol.11034) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17768113?tool=bestpractice.bmj.com)

40. Stone RM, Neuberg D, Soiffer R, et al. Myelodysplastic syndrome as a late complication following autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol. 1994 Dec;12(12):2535-42. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7989927?tool=bestpractice.bmj.com)

41. Janssen JW, Buschle M, Layton M, et al. Clonal analysis of myelodysplastic syndromes: evidence of multipotent stem cell origin. Blood. 1989 Jan;73(1):248-54. Full text (https://www.sciencedirect.com/science/article/pii/S0006497120804546?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2562924?tool=bestpractice.bmj.com)

42. Gañán-Gómez I, Wei Y, Starczynowski DT, et al. Deregulation of innate immune and inflammatory signaling in myelodysplastic syndromes. Leukemia. 2015 Jul;29(7):1458-69. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25761935?tool=bestpractice.bmj.com)

43. Zhan D, Park CY. Stem cells in the myelodysplastic syndromes. Front Aging. 2021;2:719010. Full text (https://www.doi.org/10.3389/fragi.2021.719010) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35822030?tool=bestpractice.bmj.com)

44. Linet MS, Gilbert ES, Vermeulen R, et al; Chinese Center for Disease Control and Prevention - US National Cancer Institute Benzene Study Group. Benzene exposure response and risk of myeloid neoplasms in Chinese workers: a multicenter case-cohort study. J Natl Cancer Inst. 2019 May 1;111(5):465-74. Full text (https://academic.oup.com/jnci/article/111/5/465/5232202) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30520970?tool=bestpractice.bmj.com)

45. Yarosh R, Roesler MA, Murray T, et al. Risk factors for de novo and therapy-related myelodysplastic syndromes (MDS). Cancer Causes Control. 2021 Mar;32(3):241-50. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7878335) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33392905?tool=bestpractice.bmj.com)

46. West RR, Stafford DA, Farrow A, et al. Occupational and environmental exposures and myelodysplasia: a case-control study. Leuk Res. 1995 Feb;19(2):127-39. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7869741?tool=bestpractice.bmj.com)

47. Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 Aug;98(8):1307-25. Full text (https://www.doi.org/10.1002/ajh.26984) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37288607?tool=bestpractice.bmj.com)

48. Sallman DA, Padron E. Myelodysplasia in younger adults: outlier or unique molecular entity? Haematologica. 2017 Jun;102(6):967-8. Full text (https://www.doi.org/10.3324/haematol.2017.165993) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28566339?tool=bestpractice.bmj.com)

49. Hirsch CM, Przychodzen BP, Radivoyevitch T, et al. Molecular features of early onset adult myelodysplastic syndrome. Haematologica. 2017 Jun;102(6):1028-34. Full text (https://www.doi.org/10.3324/haematol.2016.159772) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28255022?tool=bestpractice.bmj.com)

50. Juneja SK, Imbert M, Jouault H, et al. Haematological features of primary myelodysplastic syndromes (PMDS) at initial presentation: a study of 118 cases. J Clin Pathol. 1983 Oct;36(10):1129-35. Full text (https://jcp.bmj.com/content/jclinpath/36/10/1129.full.pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6619310?tool=bestpractice.bmj.com)

51. Katsarou O, Terpos E, Patsouris E, et al. Myelodysplastic features in patients with long-term HIV infection and haemophilia. Haemophilia. 2001 Jan;7(1):47-52. Full text (https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2516.2001.00445.x?sid=nlm%3Apubmed) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11136381?tool=bestpractice.bmj.com)

52. van de Loosdrecht AA, Kern W, Porwit A, et al. Clinical application of flow cytometry in patients with unexplained cytopenia and suspected myelodysplastic syndrome: a report of the European LeukemiaNet International MDS-Flow Cytometry Working Group. Cytometry B Clin Cytom. 2023 Jan;104(1):77-86. Full text (https://onlinelibrary.wiley.com/doi/10.1002/cyto.b.22044) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34897979?tool=bestpractice.bmj.com)

53. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017 Mar 30;129(13):1753-62. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5524528) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28096091?tool=bestpractice.bmj.com)

54. Wimazal F, Sperr WR, Kundi M, et al. Prognostic value of lactate dehydrogenase activity in myelodysplastic syndromes. Leuk Res. 2001 Apr;25(4):287-94. Full text (https://www.doi.org/10.1016/s0145-2126(00)00140-5) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11248325?tool=bestpractice.bmj.com)

55. Germing U, Hildebrandt B, Pfeilstöcker M, et al. Refinement of the international prognostic scoring system (IPSS) by including LDH as an additional prognostic variable to improve risk assessment in patients with primary myelodysplastic syndromes (MDS). Leukemia. 2005 Dec;19(12):2223-31. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16193087?tool=bestpractice.bmj.com)

56. Sanz GF, Sanz MA, Vallespí T, et al. Two regression models and a scoring system for predicting survival and planning treatment in myelodysplastic syndromes: a multivariate analysis of prognostic factors in 370 patients. Blood. 1989 Jul;74(1):395-408. Full text (https://www.sciencedirect.com/

science/article/pii/S0006497120773684) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2752119?tool=bestpractice.bmj.com)

57. Toma A, Fenaux P, Dreyfus F, et al. Infections in myelodysplastic syndromes. Haematologica. 2012 Oct;97(10):1459-70. Full text (https://haematologica.org/article/view/6430) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22733024?tool=bestpractice.bmj.com)

58. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol. 2005 Oct 20;23(30):7594-603. Full text (https://www.doi.org/10.1200/JCO.2005.01.7038) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16186598?tool=bestpractice.bmj.com)

59. Carraway HE, Saygin C. Therapy for lower-risk MDS. Hematology Am Soc Hematol Educ Program. 2020 Dec;2020(1):426-33. Full text (https://www.doi.org/10.1182/hematology.2020000127) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33275714?tool=bestpractice.bmj.com)

60. Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia. 2008 Mar;22(3):538-43. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18079733?tool=bestpractice.bmj.com)

61. Heaney ML, Golde DW. Myelodysplasia. N Engl J Med. 1999 May 27;340(21):1649-60. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10341278?tool=bestpractice.bmj.com)

62. Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evid. 2022;1(7). Full text (https://evidence.nejm.org/doi/pdf/10.1056/EVIDoa2200008)

63. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012 Sep 20;120(12):2454-65. Full text (https://ashpublications.org/blood/article/120/12/2454/30571/Revised-International-Prognostic-Scoring-System) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22740453?tool=bestpractice.bmj.com)

64. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007 Aug 10;25(23):3503-10. Full text (https://ascopubs.org/doi/10.1200/JCO.2006.08.5696) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17687155?tool=bestpractice.bmj.com)

65. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. Full text (https://ashpublications.org/blood/article/127/20/2391/35255/The-2016-revision-to-the-World-Health-Organization) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27069254?tool=bestpractice.bmj.com)

66. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997 Mar 15;89(6):2079-88. [Erratum in: Blood. 1998;91:1100.] Full text (https://ashpublications.org/blood/article/89/6/2079/139148/International-Scoring-System-for-Evaluating) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9058730?tool=bestpractice.bmj.com)

67. Mo A, McQuilten ZK, Wood EM, et al. Red cell transfusion thresholds in myelodysplastic syndromes: a clinician survey to inform future clinical trials. Intern Med J. 2017 Jun;47(6):695-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28580745?tool=bestpractice.bmj.com)

68. DeFilipp Z, Ciurea SO, Cutler C, et al. Hematopoietic cell transplantation in the management of myelodysplastic syndrome: an evidence-based review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. Transplant Cell Ther. 2023 Feb;29(2):71-81. Full text (https://www.sciencedirect.com/science/article/pii/S2666636722017821?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36436780?tool=bestpractice.bmj.com)

69. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol. 2019 May 20;37(15):1336-51. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30969847?tool=bestpractice.bmj.com)

70. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020 Jan 9;382(2):140-51. Full text (https://www.nejm.org/doi/10.1056/NEJMoa1908892) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31914241?tool=bestpractice.bmj.com)

71. Hellström-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol. 1997 Nov;99(2):344-51. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9375752?tool=bestpractice.bmj.com)

72. Hellström-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol. 2003 Mar;120(6):1037-46. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12648074?tool=bestpractice.bmj.com)

73. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023 Jul 29;402(10399):373-85. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37311468?tool=bestpractice.bmj.com)

74. Stahl M, DeVeaux M, de Witte T, et al. The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort. Blood Adv. 2018 Jul;2(14):1765-72. Full text (https://www.doi.org/10.1182/bloodadvances.2018019414) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30037803?tool=bestpractice.bmj.com)

75. Sloand EM, Wu CO, Greenberg P, et al. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. J Clin Oncol. 2008 May;26(15):2505-11. Full text (https://www.doi.org/10.1200/JCO.2007.11.9214) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18413642?tool=bestpractice.bmj.com)

76. Sauntharajah Y, Nakamura R, Wesley R, et al. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. Blood. 2003

Oct;102(8):3025-7. Full text (https://www.doi.org/10.1182/blood-2002-11-3325) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12829603?tool=bestpractice.bmj.com)

77. Parikh AR, Olnes MJ, Barrett AJ. Immunomodulatory treatment of myelodysplastic syndromes: antithymocyte globulin, cyclosporine, and alemtuzumab. Semin Hematol. 2012 Oct;49(4):304-11. Full text (https://www.doi.org/10.1053/j.seminhematol.2012.07.004) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23079060?tool=bestpractice.bmj.com)

78. Saunthararajah Y, Nakamura R, Nam JM, et al. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. Blood. 2002 Sep 1;100(5):1570-4. Full text (https://www.sciencedirect.com/science/article/pii/S0006497120592367?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12176872?tool=bestpractice.bmj.com)

79. Oliva EN, Alati C, Santini V, et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. Lancet Haematol. 2017 Mar;4(3):e127-36. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28162984?tool=bestpractice.bmj.com)

80. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004 Jul 15;104(2):579-85. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15039286?tool=bestpractice.bmj.com)

81. Oliansky DM, Antin JH, Bennett JM, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. Biol Blood Marrow Transplant. 2009 Feb;15(2):137-72. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19167676?tool=bestpractice.bmj.com)

82. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood. 2011 Oct 6;118(14):3765-76. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21753188?tool=bestpractice.bmj.com)

83. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009 Mar;10(3):223-32. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4086808) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19230772?tool=bestpractice.bmj.com)

84. Zeidan AM, Davidoff AJ, Long JB, et al. Comparative clinical effectiveness of azacitidine versus decitabine in older patients with myelodysplastic syndromes. Br J Haematol. 2016 Dec;175(5):829-40. Full text (https://www.doi.org/10.1111/bjh.14305) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27650975?tool=bestpractice.bmj.com)

85. Wei AH, Garcia JS, Borate U, et al. A phase 1b study evaluating the safety and efficacy of venetoclax in combination with azacitidine in treatment-naïve patients with higher-risk myelodysplastic

syndrome. Blood. 2019;134(1 suppl):568. Full text (https://ashpublications.org/blood/article/134/Supplement_1/568/426368/A-Phase-1b-Study-Evaluating-the-Safety-and)

86. Zeidan AM, Borate U, Pollyea DA, et al. A phase 1b study of venetoclax and azacitidine combination in patients with relapsed or refractory myelodysplastic syndromes. Am J Hematol. 2023 Feb;98(2):272-81. Full text (https://www.doi.org/10.1002/ajh.26771) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36309981?tool=bestpractice.bmj.com)

87. DiNardo CD, Venugopal S, Lachowiez C, et al. Targeted therapy with the mutant IDH2 inhibitor enasidenib for high-risk IDH2-mutant myelodysplastic syndrome. Blood Adv. 2023 Jun 13;7(11):2378-87. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10220255) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35973199?tool=bestpractice.bmj.com)

88. Lee S, Mohan S, Knupp J, et al. Oral eltanexor treatment of patients with higher-risk myelodysplastic syndrome refractory to hypomethylating agents. J Hematol Oncol. 2022 Aug;15(1):103. Full text (https://jhoonline.biomedcentral.com/articles/10.1186/s13045-022-01319-y) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35922861?tool=bestpractice.bmj.com)

89. ClinicalTrials.gov. Tamibarotene plus azacitidine in participants with newly diagnosed RARA-positive higher-risk myelodysplastic syndrome. Mar 2024 [internet publication]. Full text (https://clinicaltrials.gov/ct2/show/NCT04797780)

90. Dezern AE, Marconi G, Deeren D, et al. A randomized, double-blind, placebo-controlled study of tamibarotene/azacitidine versus placebo/azacitidine in newly diagnosed adult patients selected for RARA+ HR-MDS (SELECT-MDS-1). Paper presented at: 2022 American Society of Clinical Oncology Annual Meeting. 3-7 Jun 2022. Chicago, IL/virtual. Hematologic malignancies - leukemia, myelodysplastic syndromes, and allotransplant. Meeting abstract TPS7075. J Clin Oncol. 2022;40(16 Suppl):TPS7075. Full text (https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.TPS7075)

91. ClinicalTrials.gov. Magrolimab + azacitidine versus azacitidine + placebo in untreated participants with myelodysplastic syndrome (MDS) (ENHANCE). Jun 2024 [internet publication]. Full text (https://clinicaltrials.gov/ct2/show/NCT04313881)

92. Garcia-Manero G, Daver NG, Xu J, et al. Magrolimab + azacitidine versus azacitidine + placebo in untreated higher risk (HR) myelodysplastic syndrome (MDS): the phase 3, randomized, ENHANCE study. Paper presented at: 2021 American Society of Clinical Oncology Annual Meeting. 4-8 Jun 2021. Virtual. Hematologic malignancies - leukemia, myelodysplastic syndromes, and allotransplant. Meeting abstract TPS7055. J Clin Oncol. 2021;39(15 Suppl):TPS7055. Full text (https://ascopubs.org/doi/10.1200/JCO.2021.39.15_suppl.TPS7055)

93. Haider M, Duncavage EJ, Afaneh KF, et al. New insight into the biology, risk stratification, and targeted treatment of myelodysplastic syndromes. Am Soc Clin Oncol Educ Book. 2018 Oct 29;37:480-94. Full text (https://ascopubs.org/doi/10.1200/EDBK_175397) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28561687?tool=bestpractice.bmj.com)

94. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2018 Jan;36(3):283-99.

Full text (https://www.doi.org/10.1200/JCO.2017.76.1734) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29182495?tool=bestpractice.bmj.com)

95. Jensen PD, Heickendorff L, Pedersen B, et al. The effect of iron chelation on haemopoiesis in MDS patients with transfusional iron overload. Br J Haematol. 1996 Aug;94(2):288-99. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8759889?tool=bestpractice.bmj.com)

96. Angelucci E, Li J, Greenberg P, et al. Iron chelation in transfusion-dependent patients with low- to intermediate-1-risk myelodysplastic syndromes: a randomized trial. Ann Intern Med. 2020 Apr;172(8):513-22. Full text (https://www.doi.org/10.7326/M19-0916) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32203980?tool=bestpractice.bmj.com)

97. Radsak M, Platzbecker U, Schmidt CS, et al. Infectious complications in patients with myelodysplastic syndromes: a review of the literature with emphasis on patients treated with 5-azacitidine. Eur J Haematol. 2017 Aug;99(2):112-8. Full text (https://onlinelibrary.wiley.com/doi/10.1111/ejh.12883) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28321924?tool=bestpractice.bmj.com)

98. Mikulska M, Cesaro S, de Lavallade H, et al; European Conference on Infections in Leukaemia group. Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 2019 Jun;19(6):e188-99. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30744964?tool=bestpractice.bmj.com)

99. Centers for Disease Control and Prevention. ACIP vaccine recommendations and guidelines: vaccine-specific recommendations. Jul 2024 [internet publication]. Full text (https://www.cdc.gov/acip-recs/hcp/vaccine-specific)

Images

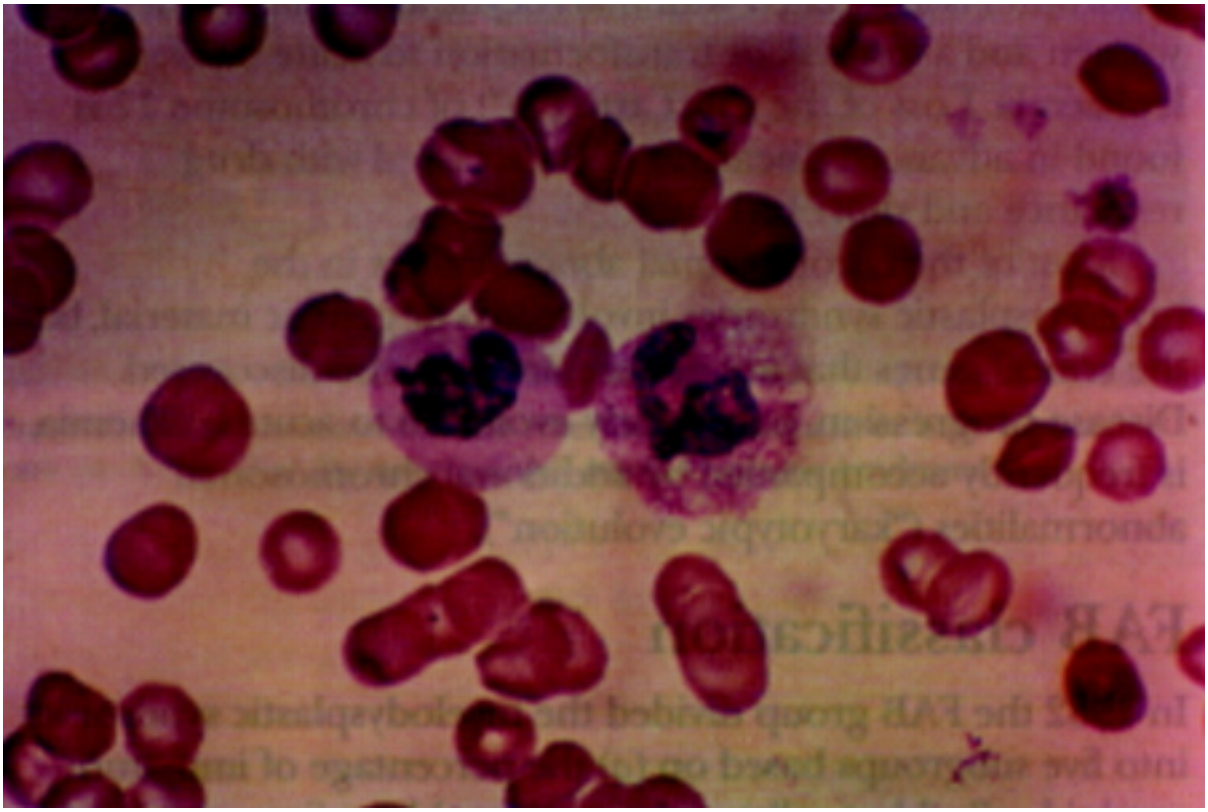


Figure 1: Blood film showing normal neutrophil (right) and dysplastic neutrophil with agranular cytoplasm and hypolobated nucleus

Image used with permission from BMJ 1997;314:883

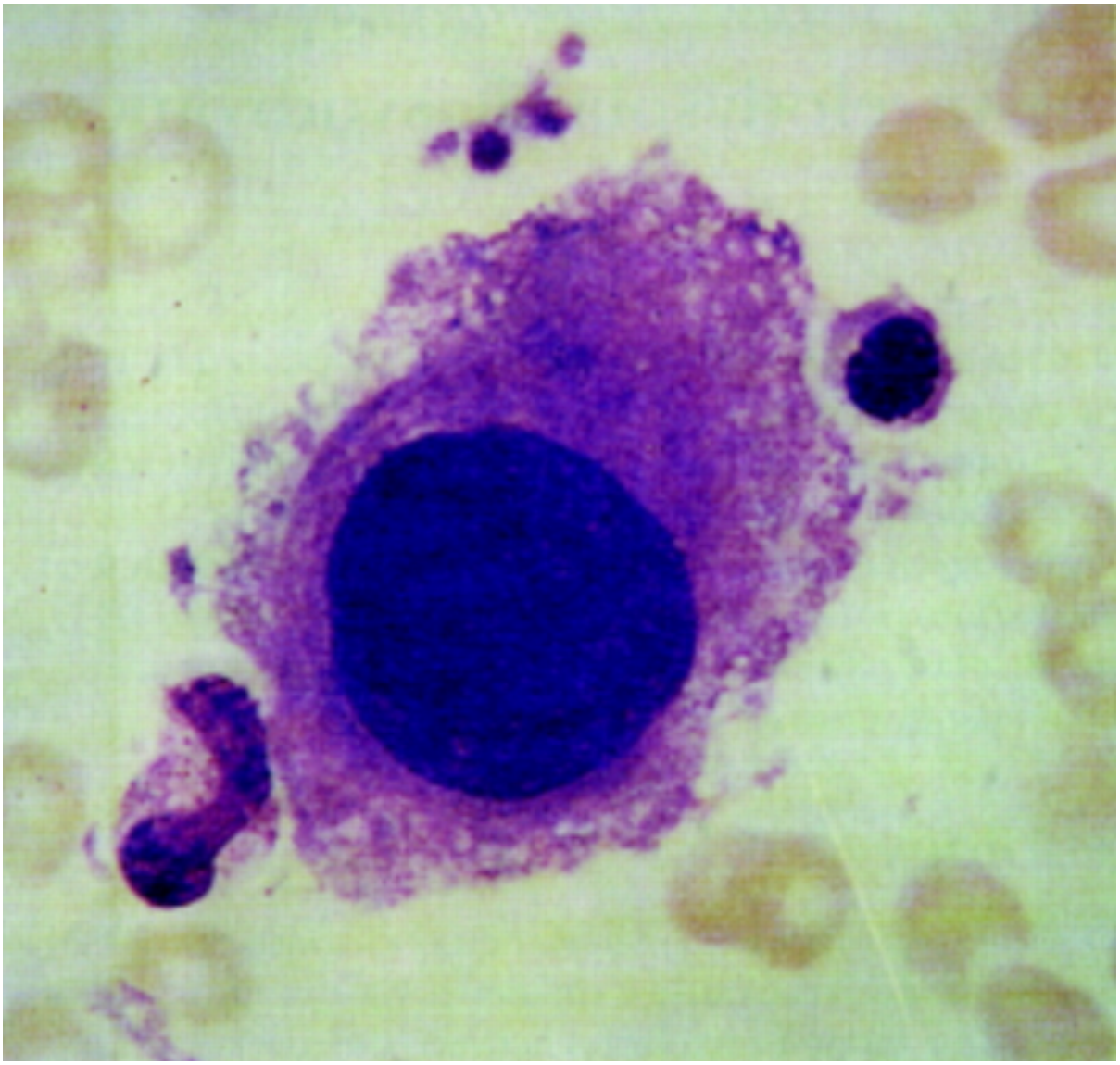


Figure 2: Large mononuclear megakaryocyte in bone marrow of patient with MDS-del(5q)

Image used with permission from BMJ 1997;314:883

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

DISCLAIMER

Contributors:

// Authors:

Vijaya Raj Bhatt, MBBS, MS

Associate Professor
Section Leader, Malignant Hematology, University of Nebraska Medical Center Division of Hematology-Oncology, Nebraska, NE
DISCLOSURES: VRB has participated in a Safety Monitoring Committee for Protagonist Therapeutics and served as an Associate Editor for the journal Current Problems in Cancer. He has received consulting fees from Taiho, Sanofi, Imugene, Genentech, Incyte, Servier Pharmaceuticals, and AbbVie; research funding (institutional) from MEI Pharma, Actinium Pharmaceutical, Sanofi, AbbVie, Pfizer, Incyte, Jazz, and NMDP; and drug support (institutional) from Chimerix for a trial.

Prajwal Dhakal, MBBS

Clinical Assistant Professor of Internal Medicine-Hematology, Oncology, and Blood and Marrow Transplantation
University of Iowa, Iowa City, IA
DISCLOSURES: PPD has been reimbursed by the Aplastic Anemia and MDS International Foundation for presenting on the topic 'High-risk MDS: non-transplant therapies, current therapies, and clinical trials' in a patient and family conference. PD has received consulting fees from AbbVie pharmaceuticals.

// Acknowledgements:

Dr Vijaya Raj Bhatt and Dr Prajwal Dhakal would like to gratefully acknowledge Professor Apar Kishor Ganti and Associate Professor Alissa Marr, previous contributors to this topic.
DISCLOSURES: AKG has received research support from Amgen, Apexigen, Bristol-Myers Squibb, Janssen, Merck, New Link Genetics, Pfizer, and Takeda Oncology. AKG has been reimbursed for consulting work for AbbVie and Genentech. None of the grants or payments relate to work involving myelodysplastic syndrome. AM declares that she has no competing interests.

// Peer Reviewers:

David P. Steensma, MD, FACP

Associate Professor of Medicine (Hematology) and Oncology
Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN
DISCLOSURES: DPS declares that he has no competing interests.

Adrian C. Newland, BA, MB, BCh, MA, FRCP, FRCPath

Professor of Haematology
Queen Mary University, London, UK
DISCLOSURES: ACN declares that he has no competing interests.