Focus on Anemia, Suspect MDS:
A pocket guide to diagnosing MDS

Symptoms of MDS

Typical presenting symptoms of MDS are generally non-specific and usually differs, depending on the type of cytopenia[1,2]

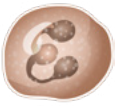
Most common symptoms of MDS

Anemia[1]

- Fatigue/weakness
- Shortness of breath
- Chest pains
- Headache
- Palpitations
- Pale skin
- Loss of appetite
- Cold extremities

Other symptoms of MDS

Neutropenia[1]



- Frequent infections
- Fever
- Mouth sores

Thrombocytopenia[1]

- Easy bruising
- Prolonged bleeding
- Petechiae

Criteria for MDS diagnosis

An International Working Group has recommended a diagnostic guideline to assist in providing consistent diagnosis of MDS[3]

Minimal prerequisites to establish MDS diagnosis[3,4]

≥ 1 unexplained cytopenia

+

Exclusion of other potential disorders as primary reason for dysplasia/cytopenia

The diagnosis of MDS also requires ≥ 1 of the following[3]:

1. ≥ 10% morphologic dysplasia in ≥ 1 of the 3 lineages of hematopoietic cells
2. A blast cell count of 5%-19%
3. A specific MDS-associated karyotype such as del(5q), del(20q), +8, or –7/del(7q)

Diagnosing MDS

There is no single diagnostic parameter for MDS; therefore, diagnosis requires a combination of clinical suspicion, laboratory tests, morphologic analysis, and cytogenetic/molecular evaluation[4-6]

Diagnostic workup for MDS[6,7]

	Diagnostic workflow		Diagnostic assessment
1	History and physical exam	→	Clinical suspicion of cytopenia
2	Peripheral blood count and peripheral blood smear	→	Cytopenia
3	**Screening tests to rule out non-malignant causes** **Anemia**: Exclude: GI bleeding, cardiac causes, inflammatory causes, and nutritional causes **Neutropenia**: Exclude: hypersplenism, autoimmune disorders, medication, toxic exposures **Thrombocytopenia**: Exclude: ITP, hypersplenism	→	Unexplained cytopenia
4	**Specialist referral and additional tests to rule out other non-malignant or malignant causes** • Bone marrow aspiration and biopsy • Somatic mutation analysis (gene sequencing) • Cytogenetics (karyotyping, FISH) • Immunophenotyping (flow cytometry)	→	MDS

Adapted from *Blood* and *Am J Med*.[6,7]

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Classification

Two updated classifications for MDS were developed in 2022: the WHO5 and the ICC for Myeloid Neoplasms and Acute Leukemia, which are overall similar but with some differences in diagnostic criteria and nomenclature[6,8]

Comparison of MDS classification according to WHO5 and ICC[6,8-10]

Bone marrow blasts	WHO5	ICC
No dysplasia	CCUS	CCUS/MDS-NOS without dysplasia
< 5%	MDS, hypoplastic	Not included
	MDS with LB	MDS-NOS with SLD, or with MLD
	MDS with LB and isolated 5q deletion	MDS with del(5q)
	MDS with LB and *SF3B1* mutation[a]	MDS with mutated *SF3B1*
5%-9%	MDS with IB1	MDS with EB
	MDS with fibrosis[b]	Not included
10%-19%	MDS with IB2	MDS/AML
	MDS with biallelic *TP53* inactivation[c]	MDS with mutated *TP53*[d] MDS/AML with mutated *TP53*[e]

[a]Detection of ≥ 15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts. [b]Bone marrow blasts: 5%-19%. [c]Bone marrow blasts: 0%-19%. [d]Bone marrow blasts: 0%-9%. [e]Bone marrow blasts: 10%-19%.

Adapted with permission from *Blood*.[6]

Risk stratification

The IPSS-R is the most commonly used risk stratification system in MDS, taking into account the degree of cytopenia, proportion of blasts in the bone marrow, and presence of cytogenetic abnormalities[2,11,12]

Recently, the IPSS-M was developed, which integrated information from 31 gene mutations in addition to the IPSS-R components[2,12,13]

Revised International Prognostic Scoring System (IPSS-R)[11]

Very low (≤ 1.5)	Low (> 1.5 to 3)	Intermediate (> 3 to 4.5)	High (> 4.5 to 6)	Very high (> 6)
19%	38%	20%	13%	10%
8.8	5.3	3.0	1.6	0.8

Median survival, years

Molecular International Prognostic Scoring System (IPSS-M)[13]

Very low (≤ –1.5)	Low (> –1.5 to –0.5)	Moderate low (> –0.5 to 0)	Moderate high (> 0 to 0.5)	High (> 0.5 to 1.5)	Very high (> 1.5)
14%	33%	11%	11%	14%	17%
10.6	6.0	4.6	2.8	1.7	1.0

Median survival, years

≈ 77% of patients are diagnosed with lower-risk MDS

CCUS, clonal cytopenia of unknown significance; del, deletion; EB, excess blasts; FISH, fluorescence in situ hybridization; GI, gastrointestinal; IB, increased blasts; ICC, International Consensus Classification; IPSS-M, Molecular International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; ITP, idiopathic thrombocytopenic purpura; LB, low blasts; MDS, myelodysplastic syndromes; MDS/AML, myelodysplastic syndromes/acute myeloid leukemia overlap; MDS-NOS, myelodysplastic syndrome-not otherwise specified; MLD, multilineage dysplasia; SLD, single-lineage dysplasia; WHO5, World Health Organization 5th edition.

References: 1. Referenced with permission from the NCCN Guidelines for Patients® for Myelodysplastic Syndromes, 2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 31, 2024. To view the most recent and complete version of the NCCN Guidelines for Patients, go online to NCCN.org/patientguidelines 2. Sekeres MA, Taylor J. *JAMA*. 2022;328:872-880. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myelodysplastic Syndromes V.2.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed May 30, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Weinberg OK, Hasserjian RP. *Semin Hematol*. 2019;56:15-21. 5. Barone P, Patel S. *Semin Diagn Pathol*. 2023;40:172-181. 6. Hasserjian RP et al. *Blood*. 2023;142:2247-2257. 7. Foran JM, Shammo JM. *Am J Med*. 2012;125(suppl):S6-S13. 8. Xu ML, Hasserjian RP. *Cancer J*. 2023;29:122-129. 9. Arber DA et al. *Blood*. 2022;140:1200-1228. 10. Khoury JD et al. *Leukemia*. 2022;36:1703-1719. 11. Greenberg PL et al. *Blood*. 2012;120:2454-2465. 12. Volpe VO et al. *Clin Lymphoma Myeloma Leuk*. 2023;23:168-177. 13. Bernard E et al. *NEJM Evid*. 2022;1. doi:10.1056/EVIDoa2200008.

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