Guidelines for standardized diagnostic and prognostic procedures in adult myelodysplastic syndromes

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Diagnostic workup of suspected MDS

The diagnosis of MDS rests largely on morphological findings of bone marrow dysplasia in patients with clinical evidence of impaired hematopoiesis manifested by different combinations of anemia, leukopenia, neutropenia and thrombocytopenia. The diagnostic criteria aim to distinguish MDS from reactive causes of cytopenia and dysplasia as well as from other clonal stem cell disorders. However, if multilineage dysplasia, chromosomal aberrations, and proof of clonality are absent, this distinction could be difficult.

Patient history and examination
This should include family history, prior chemotherapy, irradiation, radioimmunotherapy, radioiodine, occupational or hobby exposure, especially benzene, concomitant medication including "alternative medication", alcohol intake, smoking, tendency for bleeding/bruising and infection, and a complete physical examination including spleen size.

Blood tests

- WBC, full differential count including erythrocyte morphology, hemoglobin, platelet count, red blood cell indices (MCV), and reticulocyte count. For dysplasia see below, under bone marrow analysis.
- RBC-folate/S-folic acid, cobalamin, iron, TIBC, ferritin, LDH, bilirubin, haptoglobin, DAT (Coombs test), ALAT, ASAT, Alkaline phosphatase, Albumin, Uric acid, Creatinine, S-erythropoietin, S- protein electrophoresis (S-immunoglobulins), B2 microglobulin, Thyroid function tests.
- Anti-HIV, anti-Parvovirus B19 (hypoplastic MDS), CMV-test. HBAg and anti-HCV in transfusion dependent patients.
- PNH clone, HLA DR15 desirable in low-risk MDS without sideroblasts.
- JAK2 analysis in RARS-T may give additional information, but will not influence prognostic assessment or treatment.
- Exclude thalassemia / hemoglobinopathy.

Bone marrow analysis:
A diagnosis of MDS often requires repeated bone marrow examinations a few weeks or months, or even years apart in order to firmly establish the diagnosis and to identify cases with rapid disease progression. For evaluation of bone marrow morphology and dysplasia in blood and bone marrow, follow guidelines in the WHO 2008 classification. An initial biopsy is essential to make a diagnosis according to WHO. Optimal investigations during follow-up bone marrow analyses should be planned on an individual basis.

- Bone marrow aspirate + biopsy + peripheral blood smear.
- A good quality diagnostic bone marrow analysis includes marrow aspirate (MGG / equivalent and iron staining) and a bone marrow biopsy either decalcified / paraffin embedded or plastic embedded. Degree of fibrosis should be estimated. Staining should include Haematoxylin-Eosin / equivalent, iron staining, Peroxidase-Staining (Auer rods, MPO deficiency).
- At least 500 cells in bone marrow smears, 200 cells in blood smears and 25 megakaryocytes should be evaluated. Moreover, at least 100 erythroblasts should be evaluated. An optimal staining of blood and marrow slides prepared from freshly drawn aspirates is important for evaluation of dysplasia.

- For significant dysplasia, dysplastic features should be present in at least 10% of the nucleated cells in the lineage in consideration. For description of dysplastic features, se WHO 2008, page 90.
- A cytogenetic analysis of bone marrow aspirate should be done in all cases, at least 25 metaphases, whenever possible, and described according to International System recommendations. FISH analysis may be helpful to clarify complex aberrations or to detect monosomy 7. Screening FISH (5q-, -7, +8) from peripheral blood may be performed in case of dry tap and in case this may influence management of the patient.
- By flow cytometry, emerging pathological CD34 and or CD117 positive populations are suggestive of transformation. Multiple aberrant features (≥3) in maturation patterns of erythroid and myeloid lineage are highly specific for MDS, single aberrancies are not diagnostic. The role of flow cytometry is not yet established in the diagnostic work-up of MDS, but the ELN work package for flow cytometry will soon finalize a consensus document, after which these guidelines will be updated.

Differential diagnosis

The diagnosis of MDS may be difficult, in particular in patients with less than 5% bone marrow blasts and only one cytopenia. No single morphologic finding is diagnostic for MDS and it is important to keep in mind that MDS often remains a diagnosis of exclusion. For this reason, thorough work-up to rule out the possible differential diagnoses below is recommended. Most often, cases in which the diagnosis is uncertain are fairly asymptomatic, and should not be diagnosed with MDS too early, but should be subject to follow-up as "possible MDS".

- B12 / folate deficiency/ S-EPO
- Recent cytotoxic therapy
- Drug-induced cytopenias
- Chronic liver disease
- Excessive alcohol intake
- Exposure to heavy metals, e.g. lead, arsenic, or copper deficiency
- HIV infection
- Anemia of chronic disorders (infection, inflammation, cancer)
- Rare anemias, such as congenital dyserythropoietic anemia
- Autoimmune cytopenia
- Other hemopoietic stem cell disorders incl. acute myeloid leukaemia, myeloproliferative disorders, aplastic anemia, paroxysmal nocturnal hemoglobinuria, and LGL leukemia.

Idiopathic Cytopenia of Undetermined Significance (ICUS)

Patients with maintained (>6 months) cytopenias of one or more myeloid lineages (erythroid, neutrophil and megakaryocytic), which do not meet the (minimal) criteria for MDS and cannot be explained by any other hematologic or non-hematologic disease may be considered as ICUS. In some of patients, the type of cytopenia (e.g., transfusion-dependent macrocytic anemia) may point to the potential existence of an underlying MDS or an MDS pre-phase.

Classifications

The European LeukemiaNet recommends classification according to WHO only, where a revised version was published in Sept. 2008. For historical reasons and since some may still classify according to FAB, the FAB classification is still included below.

WHO 2008 classification of MDS

Peripheral blood and bone marrow findings in myelodysplastic syndromes

Disease	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage dysplasia (RCUD) Refractory anaemia (RA) Refractory neutropenia (RN) Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia[1] No or rare blasts (<1%)	Unilineage dysplasia; ≥ 10% of the cells of the affected lineage are dysplastic <5% blasts <15% of the erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia only ≥ 15% of erythroid precursors are ring sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1%)[2] No Auer rods <1x10^9/l monocytes	Dysplasia in ≥ 10% of cells in two or more myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts No Auer rods ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenia(s) <5% blasts No Auer rods <1x10^9/l monocytes	Unilineage or multilineage dysplasia 5-9% blasts[2] No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5-19% blasts Auer rods ±[3] <1x10^9/l monocytes	Unilineage or multilineage dysplasia 10-19% blasts Auer rods±
Myelodysplastic syndrome – unclassified (MDS-U)	Cytopenias ≤ 1% blasts[2]	a) Dysplasia in less than 10% but typical cytogenetic abnormality b) RCUD/RCMD with 1% blasts in peripheral blood c) RCUD with pancytopenia
MDS associated with isolated del(5q)	Anaemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No auer rods

[1] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U

[2] If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB-1. If the marrow myeloblast percentage is <5% and there are 1% myeloblasts in the blood, the case should be classified as MDS-U.

[3] Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2

Note: Therapy-associated MDS and MDS/MPN should classified in the category "therapy-associated myeloid malignancies"

WHO 2008 classification of myelodysplastic/myeloproliferative neoplasms

Disease	Blood findings	Bone marrow findings
Chronic myelomonocytic leukaemia (CMML) (CMML-1; <5% blasts in PB, <10% in BM, CMML-2; ≥5% blasts in PB, ≥10% in BM)	Peripheral blood monocytosis > $1x10^9$/l No BCR/ABL-1 fusion gene <20% blasts	Dysplasia in one or more myeloid lineage[1] <20% blasts. Blasts include myeloblasts, monoblasts and promonocytes. No rearrangement of PDGFRα or PDGFRβ
Atypical chronic myeloid leukaemia, BCR-ABL1 negative (aCML)	Leukocytosis, neutrophilia Neutrophilic dysplasia Neutrophil precursors ≥10% of leukocytes Blasts <20% No BCR-ABL1 fusion gene No rearrangement of PDGFRα or PDGFRβ Minimal basophilia Monocytes < 10% of leukocytes	Neutrophil dysplasia with or without dysplastic lineages <20% blasts
Juvenile myelomonocytic leukaemia (JMML)	Peripheral blood monocytosis >$1x10^9$/l <20% blasts Usually WBC > $10x10^9$/l	<20% blasts Evidence of clonality
Myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN)	Mixed MDS and MPN features No prior diagnosis of MDS or MPN No history of recent growth factor or cytotoxic therapy to explain MDS or MPN features No BCR-ABL1 fusion gene of rearrangements of PDGFRα or PDGFRβ	Mixed MDS and MPN features <20% blasts
[1]Refractory anaemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) (provisional entity)[2]	Persistent thrombocytosis >$450x10^9$/l Anaemia BCR-ABL1 negative Cases with t(3;3)(q21;q26), inv(#)(q21q26) and isolated del(5q) are excluded	Morphologic features of RARS; ≥ 15% of erythroid precursors are ring sideroblast Abnormal megakaryocytes similar to those observed in BCR-ABL1 negative MPN 50% JAK2 mutations in RARS-T with plt>600.

[1] If myelodysplasia minimal or absent, CML can still be diagnosed if the other requirements are met and there is an acquired clonal cytogenetic or molecular geneticabnormalityBicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U

[2] If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB-1. If the marrow myeloblast percentage is <5% and there are 1% myeloblasts in the blood, the case should be classified as MDS-U.

[3]Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB-2

FAB-classification of MDS

(Bennett et al, 1982)

It is no longer recommended to use the FAB classification for newly diagnosed patients.
The FAB classification remains in the guidelines mainly for patients who were diagnosed prior to implementation of the WHO 2001 classification.

Type	Blasts in BM	Blasts in blood	Ringsiderobl. in BM	Monocytes in blood
RA	<5%	<1%	<15%	<1 x 10^9/l
RARS	<5%	<1%	>15%	<1 x 10^9/l
RAEB	5-20%	<5%	+/-	<1 x 10^9/l
CMML	0-20%	<5%	+/-	>1 x 10^9/l
RAEB-t	21-29%	<30%	+/-	<1 x 10^9/l
AML	≥30%	≥30%	+/-	

AML after a well-established phase of MDS is classified as MDS-AML

Prognosis

IPSS for MDS (International Prognostic Scoring System) (Greenberg et al, 1997)

The IPSS is based on a multivariate analysis of a largely untreated patient population of 816 patients used to evaluate the prognosis of newly diagnosed MDS patients.

Risk group	**Score**	**Median survival** (years)	**Time to AML transformation** (for 25% in years)
Low risk	0	5.7	9.4
INT-1	0.5-1.0	3.5	3.3
INT-2	1.5-2.0	1.2	1.1
High risk	≥2.5	0.4	0.2

Score value

Prognostic variable	**0**	**0.5**	**1**	**1.5**	**2**
BM blasts (%)	<5	5-10	-	11-20	21-30
Karyotype°	Good	Intermed.	Poor		
Cytopenias*	0/1	2/3			

° Good: normal, isolated-Y, del(5q), or del(20q). Poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies. Intermediate: other abnormalities.
* Cut-off values for cytopenia. Hemoglobin <100 g/l, ANC <1.8 x 10^9/l, platelets <100 x 10^9/l.

Low risk vs High risk MDS

In daily clinical practice, MDS is divided into so-called ”low risk” MDS encompassing IPSS low risk and INT-1, whereas ”high risk” includes IPSS INT-2 and high risk. This separation is practical since it reflects the different treatment strategies in the two groups.

WPSS

This updated scoring system includes combines the WHO classification with information about transfusion need. This score suggests that patients with unilineage erythroid dysplasia and no stable transfusion need have a prognosis comparable to the average population. Irrespective of the risk group defined by blast percentage and cytogenetic profile, presence of a transfusion need implicated a worse prognosis. This score has been evaluated by a couple of studies and the guidelines suggest that it should be incorporated into prospective clinical registries and studies for further validation.

WPSS risk group	**Score**	**Median survival Italian cohort (months)**	**Median survival German cohort (months)**
Very low	0	103	141
Low	1	72	66
Intermediate	2	40	48
High	3-4	21	26
Very high	5-6	12	9

Variable	0	1	2	3
WHO category	RA, RARS, isolated 5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	
Transfusion requirement†	No	Regular		

*Good: normal, −Y, del(5q), del(20q); poor: complex (≥ 3 abnormalities) or chromosome 7 anomalies; and intermediate: other abnormalities.

†At least 1 RBC transfusion every 8 weeks over a period of 4 months.

Recommendation for diagnosis and prognosis of MDS

- All patients should be classified according to the WHO 2008 classification
- All patients should be risk stratified according to IPSS.
- Prospective registries and clinical studies should include stratification according to WPSS
- MDS should be reported to National Cancer registries, if such registries exist, and to MDS specific registries, if applicable
- Please note that for patients with AML and 20-29% marrow blasts, MDS specific treatment may be indicated both in adults and in children.

Follow up of patients with MDS

We recommend that all newly diagnosed patients are evaluated at a centre with specific hematological competence. Patients should undergo regular follow-up including blood tests. If a patient is considered to be a candidate for therapeutic intervention at disease progression or in case of planned clinical studies, control visits including regular bone marrow analysis ± cytogenetic analysis are recommended. The frequency of these controls depends on the therapeutic option, and should be relatively short, 3 months, if SCT is an option.

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APPENDIX

Table 1.

A) Levels of evidence

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports and/or clinical experiences of respected authorities

B) Grades of recommendation

Grade	Evidence level	Recommendation
A	Ia, Ib	Required: At least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required: Availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C	IV	Required: Evidence obtained from expert committee reports or opinions and /or clinical experiences of respected authorities. Indicates absence of directly applicable studies of good quality