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Diagnosis of myelodysplastic syndromes in Poland: Polish Adult Leukemia Group (PALG) 2021 recommendations

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Abstract

Myelodysplastic syndromes (MDS) are a heterogeneous group of neoplastic diseases of the hematopoietic cells manifested by ineffective hematopoiesis and a tendency to transform into acute myeloid leukemia. MDS should be considered in the differential diagnosis of cytopenia, especially in the elderly. This article presents the recommendations of MDS experts of the Polish Adult Leukemia Group (PALG) for the diagnosis of myelodysplastic syndromes. We present current classifications and prognostic indices, as well as diagnostic examinations recommended for MDS: cytological, histopathological, immunophenotypic, cytogenetic and molecular tests. The aim of the study is to implement up-to-date knowledge about myelodysplastic syndromes into routine clinical practice, from the diagnosis of cytopenia to the specific diagnosis and prognosis in MDS patients.

Key words: myelodysplastic syndromes, diagnosis, recommendations

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Introduction

Myelodysplastic syndromes (MDS) are neoplastic diseases with a variable clinical course originating from hematopoietic stem cells (HSCs). A characteristic feature of MDS is ineffective hematopoiesis manifested by dysplasia of bone marrow and peripheral blood cells, peripheral cytopenia, and an increased risk of transformation into acute myeloid leukemia (AML).

Epidemiology

It is estimated that the incidence rate of newly diagnosed MDS is 4.5/100,000/year. Usually the disease affects the elderly. The median adult age at diagnosis is 70–75 years, whilst according to the Polish MDS Registry it is 70 years [1, 2]. In the age bracket of 70–74, the incidence is 16.6/100,000/year; in the age bracket of 75–79 years it is 25.7/100,000/year; and this increases to over 36/100,000/year in people aged 80 and over [3]. MDS in children is very rare, with a median age at diagnosis of 6.8 years. In the population of people under 30 years, the incidence rate of newly diagnosed MDS is 0.1/100,000/year. Patients <50 years of age constitute 9% of all MDS cases. The disease is more prevalent among men, with a male to female ratio 1.1–1.4:1 and this ratio increases with age.

The number of MDS cases is probably underestimated due to the lack of a proper diagnosis of cytopenia in the elderly.

Clinical manifestation

The clinical manifestation of MDS is not characteristic, with symptoms most often resulting from cytopenia. There are features of anemia, thrombocytopenia, infections (usually bacterial and fungal) resulting from granulocytopenia and dysfunction of neutrophils. Hepato- and splenomegaly is rare. General symptoms (weight loss, fever, sweating) are also not common and occur in higher risk MDS patients or during leukemic transformation. Autoimmune diseases are detected in c.19–28% of MDS patients [4], and the most common include hypothyroidism (12%), rheumatoid arthritis (3%), autoimmune thrombocytopenia (3%), psoriasis (2%), ulcerative colitis (1%), and vasculitis (1%). Polymyalgia rheumatica (PMR), skin ulcers, iritis, myositis, peripheral neuropathy, Sweet's syndrome, and pericarditis are slightly less common. Pure red cell anemia (PRCA), large granular lymphocytic leukemia (LGL) and nocturnal paroxysmal hemoglobinuria (PNH) are associated with MDS and they are also found more often than in the general population.

It is worth adding that patients with MDS, especially after the age of 65, are more likely to develop cardiovascular events (CVE), including myocardial infarction, heart failure, and arrhythmia. Within three years of MDS diagnosis, CVE have occurred in 73.2% of patients, compared to 54.5% of 1.4 million people receiving medical services for other reasons (Medicare, USA) [5].

Diagnosis

The primary examination is complete blood count (CBC) with differential (features of dyshematopoiesis, percentage of blasts). The anemia is usually macrocytic, less commonly normocytic or microcytic, and the number of reticulocytes is usually not increased. Cytopenia is a prerequisite for MDS diagnosis. In the differential diagnosis of cytopenia, it is recommended to perform basic tests, such as: iron metabolism parameters, vitamin B_{12} and folic acid levels, direct antiglobulin test (DAT), renal and hepatic function, and exclusion of viral diseases [hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV)].

Another examination is a bone marrow aspiration with cytomorphological, histopathological, cytochemical (Prussian blue staining to detect sideroblasts) and cytogenetic tests.

Cytomorphological bone marrow examination is decisive in assessing the percentage of blasts and the features of dysplasia, both qualitatively and quantitatively [6]. The most common dysplastic features found in patients with MDS are set out in Table I. The coexistence of cytopenia with morphological changes typical for MDS or an increased percentage of blasts allow for an MDS diagnosis. Histopathology should be routinely performed in all patients, and is particularly helpful in assessing bone marrow cellularity, fibrosis, megakaryocyte dysplasia, atypical localization of immature precursors (ALIP), and blast rates in cases where cytomorphology is not fully reliable. In 80% of patients, there is increased bone marrow (BM) cellularity, while in the remaining 20%, BM is normo- or hypocellular.

The diagnosis of MDS is also possible in patients with no obvious signs of dysplasia or increased blast percentage, if specific cytogenetic changes are present, i.e. –7 or del(7q), del(5q), and (17q) or del(17p), –13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X) (q13), t(11; 16) (q23; p13.3), t(3; 21) (q26.2; q22.1), t(1; 3) (p36.3; q21.1), t(1; 3) (p36.3; q21.1), t(2; 11) (p21; q23), inv(3) (q21q26.2), t(3; 3) (q21; q26.2), t(6; 9) (p23; q34). Cytogenetic abnormalities such as +8, del (20q) and –Y are not considered specific for MDS. Molecular and immunophenotypic tests by flow cytometry are complementary and not mandatory. MDS diagnostic criteria are set out in Table II [7].

The initial diagnostic workup for MDS is set out in Table III, while Figure 1 shows MDS diagnostic algorithm.

Differential diagnosis

The first priority in the differential diagnosis of MDS is to exclude primary extramedullary causes of cytopenia,

Table I. Marrow dysplastic features

Erythroid lineage	Cell nucleus: • polyploid shapes • intranuclear bridges • internuclear bridges • tabs • multinuclear forms • megaloblastic forms • nuclear hypersegmentation • pyknosis Cytoplasm: • ring-shaped sideroblasts • vacuolization • uneven staining of cytoplasm • basophilic spotting • Howell-Jolly bodies (fragments of a disintegrated nucleus) • Pappenheimer bodies Asynchronous maturation of nucleus in relation to cytoplasm
Granulocyte lineage	Too small or too large precursor forms Cell nucleus: • atypical nuclear shape • biplane cell nuclei (pseudo Pelger-Huët) • nuclear hypersegmentation Cytoplasm: • reduction of cytoplasm granularity • irregular granularity distribution • pseudo-Chédiak-Higashi granules • Auer rods • vacuoles in cytoplasm Asynchronous maturation of nucleus in relation to cytoplasm
Megakaryocytic lineage	Micromegakaryocytes (7–15 µm) One or two-lobed cell nuclei Lack of synchronization between maturation of nucleus and cytoplasm Multinuclear forms Agranular or hypogranular platelets

other hematopoietic malignancies, as well as PRCA, PNH, or bone marrow metastases. In the case of a typical family or personal medical history, especially in younger people, congenital myeloid neoplasms should be excluded. The causes leading to cytopenia/dysplasia are set out in Table IV.

Pre-MDS states

Some healthy people have somatic mutations/cytogenetic abnormalities typical for myeloid neoplasms. The lack of cytopenia and other features of MDS allows for the diagnosis of clonal hematopoiesis with indeterminate potential (CHIP). In the case of cytopenia without other features of MDS or dysplasia without cytopenia and other features of MDS, idiopathic cytopenia of undetermined significance (ICUS) and idiopathic dysplasia of undetermined significance (IDUS) are diagnosed, respectively. On the other hand, if cytopenia is revealed without a detectable cause and molecular or cytogenetic abnormalities specific for MDS, a clonal cytopenia of undetermined significance (CCUS) should be diagnosed [8].

It has not been determined whether the acquired mutations in CHIP are the result of aging or an early stage of cancer. Some patients may develop MDS in the future (0.5–1%/year). In people with CHIP, especially with mutations in epigenetic factors, an increased incidence of coexistent cardiovascular diseases has been found. The differential diagnosis of CHIP, CCUS, IDUS, and ICUS conditions is set out in Table V.

Principles of cytogenetic testing in MDS

According to the current criteria for the diagnosis of MDS, cytogenetic testing is still one of the basic diagnostic and prognostic examinations.

Considering cytogenetic abnormalities, only the deletion of the long arm of chromosome 5 defines a distinct histoclinical entity — MDS with an isolated 5q deletion. In the current World Health Organization (WHO) classification, the scope of the concept of 'isolated' has been extended; this category still includes del(5q) as the only aberration, but also del(5q) with one additional aberration, other than the unfavorable chromosome 7 aberrations, e.g. del(7q) and monosomy 7 (–7) [9]. Classic cytogenetic testing in MDS should be performed before commencement of any treatment, because, for example, treatment with steroids may inhibit cell division and make it impossible to put the right diagnosis. The sample should be bone marrow, as there may be an insufficient number of CD34+ cells in the peripheral blood. The culture of the marrow cells of patients suffering from MDS is a short-term, 24- or 48-hour culture without mitogen (stimulator of cell proliferation). Chromosomes are analyzed after G-banding by trypsin with Giemsa (GTG) staining. In MDS, as a rule, at least 20 metaphases are analyzed. If it is difficult to obtain 20 metaphases, a few cells with a clonal aberration are sufficient to determine the result (clonal aberration is defined as the presence of a given trisomy or a structural aberration in at least two cells, or a given monosomy in at least three cells). On the other hand, the lack of aberration does not allow the completion of the test before the analysis of 20 cells. In about half of the karyotypes, chromosomal aberrations are found, most often –5/del (5q), –7/del(7q), +8, del(20q), –Y. The most common abnormalities are set out in Table VI [10].

Table II. Minimal diagnostic criteria of myelodysplatic syndrome (MDS)

MDS can be diagnosed when both preliminary criteria (A) and at least one criterion B are met

A. Preliminary criteria (both must be met)

1. Persistent (≥4 months) peripheral blood cytopenia* affecting ≥1 cell lineage: erythroid, neutrophilic, megakaryocytic (in the case of excess blasts or cytogenetic changes associated with MDS, the diagnosis can be made immediately)
2. Exclusion of other causes of cytopenia/dysplasia**

B. MDS-specific criteria (major; at least one must be met)

1. Dysplasia in ≥10% of cells of a given cell lineage: erythroid, neutrophilic, megakaryocytic***
2. In at least 15% ring-shaped sideroblasts or ≥5% ring-shaped sideroblasts with *SF3B1* mutation
3. From 5% to 19% myeloblasts in bone marrow cytology (or 2–19% myeloblasts in peripheral blood)
4. Typical chromosome abnormalities confirmed by conventional cytogenetics or FISH****

C. Additional criteria — for patients meeting both criteria A but no criteria B, in the case of typical clinical manifestation, e.g. transfusion-dependent macrocytic anemia ≥2 additional criteria (C) must be met in order to diagnose MDS. Regular bone marrow biopsies may allow the final diagnosis

1. Abnormalities in the histological examination and/or immunohistochemistry of trepanobioptates supporting the diagnosis of MDS***
2. Abnormalities in the immunophenotypic test of bone marrow cells, in the form of numerous aberrant MDS phenotypes that indicate the monoclonal nature of erythroid and/or myeloid lineages
3. Proof of the clonality of myeloid lineage cells confirmed in a molecular test by finding somatic mutations typical for MDS*****

*Cytopenia defined as values below the specific reference ranges in a given laboratory; **in rare cases, MDS may coexist with other causes of cytopenia; ***examples: clusters of atypical localization of immature precursors (ALIP), clusters of CD34+ blasts, immunohistochemically confirmed dysplastic micromegakaryocytes (≥10% dysplastic megakaryocytes); ****chromosome abnormalities typical of MDS, e.g. del(5q), –7 indicate the diagnosis of MDS even in the absence of morphological changes; *****the presence of numerous typical mutations (e.g. *SF3B1*) increases the likelihood of MDS diagnosis or the development of MDS in future; FISH — fluorescence *in situ* hybridization

The 5q deletion covering the 5q31 (*EGR1*)–5q33.1 (*RPS14*) region and appearing alone or accompanied by a single additional aberration defined above is associated with a favorable prognosis.

Older men may experience a loss of the Y chromosome unrelated to MDS. Therefore, in this group, –Y is assigned to MDS when it occurs in more than 70% of metaphases, while in younger men the threshold is 30%. A complex karyotype (at least three independent autosomal chromosome aberrations, i.e. autosomes) is always unfavorable. It is often accompanied by the loss of ≥1 copy of *TP53* gene or its mutation. The monosomal karyotype (at least two autosomal monosomies or at least one autosomal monosomy and at least one autosome structural aberration) is always unfavorable, and according to some authors it is worse than the complex karyotype.

If metaphasal plates are not obtained, or the number of metaphasal planes obtained, which also does not contain clonal aberrations, is suboptimal (<20), or they are unreadable, FISH with the MDS probe panel [for –5/del(5q), –7/del(7q), +8, del(17p)/*TP53*, del(20q), and possibly –Y] should be performed. Some of these probes can be used together, which speeds up FISH diagnostics. In total, 100–200 interphasic nuclei are routinely analyzed under fluorescence microscopy. It is believed that FISH detects cytogenetic abnormalities in 15% of patients with normal karyotype tested using the classical method [11].

Immunophenotyping

The WHO classification of hematopoietic neoplasms indicates that flow cytometry (FC) is not a sufficient diagnostic method for MDS in the absence of definitive cytomorphological and/or cytogenetic criteria. However, it points out that the aberrant immunophenotypic features show a strong correlation with this diagnosis [12].

Immunophenotype abnormalities described as typical MDS are shown in 6.4% of cytopenia cases without marked dysplasia in cytological examination, however, around one third of these cases present with typical cytogenetic changes.

The European LeukemiaNet (ELN) Working Group for Flow Cytometry in MDS (IMDSFlow) proposed guidelines for the use of this method in the integrated diagnosis of MDS [13]. For screening purposes, a mini-panel (so-called Ogata score) with four parameters (one point for each) can be used [12]:

- increased CD34+ progenitors rate among all BM nucleated cells (>2%);
- reduced CD34+/CD19+ and/or CD34+ CD10+ B-cell precursors rates among all CD34+ cells;
- altered expression of CD45 on myeloblasts relative to lymphocytes (≤4 or ≥7.8);
- reduced granularity (SSC, side scatter channel) on granulocytes in relation to lymphocytes (≤6).

A total score of ≥2 points allows the diagnosis of low-risk MDS with a specificity of 92–98%. The disadvantage

Table III. Diagnostic tests used in myelodysplatic syndrome (MDS)

Test	Material/assessment recommendations	Purpose	
CBC (differential)	Peripheral blood	Cytopenia and dysplasia of one or more cell lineages Assessment of blasts rate	Required
Bone marrow aspiration biopsy	Bone marrow Assessment of at least 500 cells	Assessment of bone marrow cellularity and E:M lineage ratio Assessment of blasts rate — percentage of nucleated cells regardless of dominant erythroid lineage Dysplasia of one or more hematopoietic cell lineages	Required
	Ring-shaped sideroblasts — Prussian blue staining Assessment of 100 erythroblasts	Assessment of ring sideroblasts rate	Required in LR-MDS
Bone marrow aspiration biopsy (histopathology)	Biopsy ≥1 cm (formalin) • IHC minimal panel: CD34+, CD117/KIT, CD42b or CD61, tryptase • Additional panel: CD3, CD14, CD20	Assessment of BM cellularity, blasts rate and dysplasia features	Required
Cytogenetic analysis	Bone marrow (heparin) ≥5 mL Blood — conditionally, in absence of BM material	Detection of acquired chromosomal abnormalities that may allow establishment of final diagnosis and prognosis	Required
FISH	Bone marrow/peripheral blood	Detection of targeted abnormalities in the case of failure of standard cytogenetic method	Recommended
Flow cytometry — immunophenotyping	Bone marrow (EDTA) ≥2 mL	Detection of abnormalities in erythroid lineage, immature cells of myeloid lineage, mature granulocytes, monocytes, immature and mature cells of lymphoid lineage	Recommended
Molecular testing	Bone marrow (EDTA) ≥2–5 mL	Detection of somatic mutations	Recommended
	Skin, hair follicles	Detection of somatic mutations	Recommended

BM — bone marrow; CBC — complete blood count; EDTA — ethylenediaminetetraacetic acid; FISH — fluorescence *in situ* hybridization; IHC — immunohistochemistry; LR-MDS — low-risk MDS

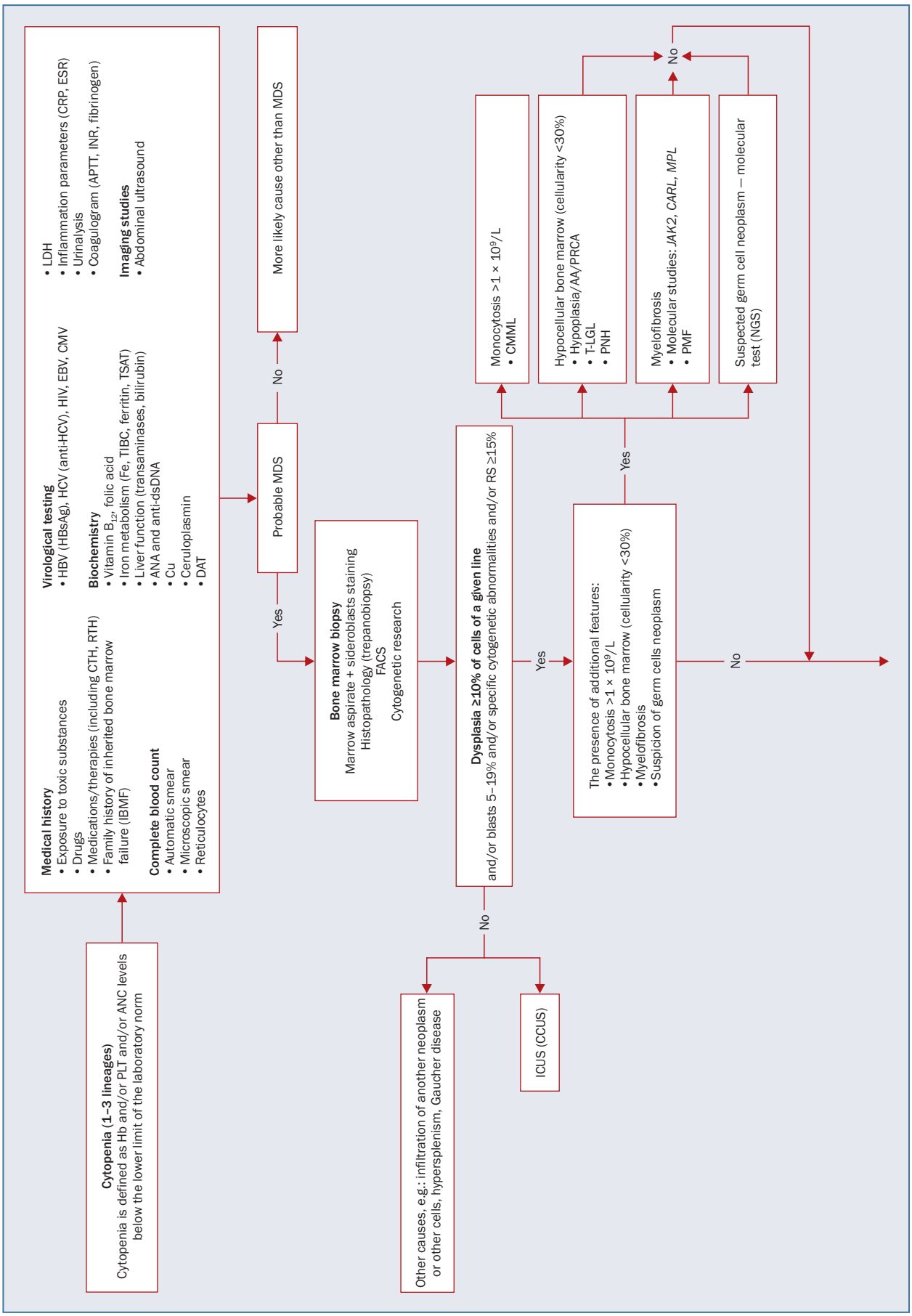
of the panel is the low sensitivity (44–71%) resulting, among others, from reduced blasts rate due to peripheral blood contamination in bone marrow aspirate sample. Reduction in the B-cell progenitors rate is sometimes found in the elderly, and MDS blasts may aberrantly fail to express CD34 [14].

In conclusion, flow cytometry testing in the diagnosis of MDS is useful:

- in cases of cytopenia without marked dysplasia and cytogenetic/molecular changes. The abnormalities found in FC may then indicate MDS or, in their absence, another cause of detected abnormalities;
- in MDS patients with single-lineage dysplasia in cytology examination, and with alterations of other lineages in FC. These changes may have a prognostic value or suggest incorrect classification of MDS (re-assessment of dysplasia in lineage disturbed in FC is strongly recommended).

Molecular testing in MDS

Thanks to the use of techniques based on next-generation gene sequencing, molecular disorders in the course of MDS have been found in c.80–90% of patients. Some of them have been shown to occur in MDS with a specific phenotype, but the most important observations concern the significance of the mutations for survival prognosis and transformation into AML, as well as treatment response. So


Cytopenia (1–3 lineages)
Cytopenia is defined as Hb and/or PLT and/or ANC levels below the lower limit of the laboratory norm
Medical history
• Exposure to toxic substances
• Drugs
• Medications/therapies (including CTH, RTH)
• Family history of inherited bone marrow failure (IBMF)
Complete blood count
• Automatic smear
• Microscopic smear
• Reticulocytes
Virological testing
• HBV (HBsAg), HCV (anti-HCV), HIV, EBV, CMV
Biochemistry
• Vitamin B12, folic acid
• Iron metabolism (Fe, TIBC, ferritin, TSAT)
• Liver function (transaminases, bilirubin)
• ANA and anti-dsDNA
• Cu
• Ceruloplasmin
• DAT
• LDH
• Inflammation parameters (CRP, ESR)
• Urinalysis
• Coagulogram (APTT, INR, fibrinogen)
Imaging studies
• Abdominal ultrasound
Probable MDS
Yes
No
More likely cause other than MDS
Bone marrow biopsy
Marrow aspirate + sideroblasts staining
Histopathology (trepanobiopsy)
FACS
Cytogenetic research
Dysplasia ≥10% of cells of a given line
and/or blasts 5–19% and/or specific cytogenetic abnormalities and/or RS ≥15%
No
Other causes, e.g.: infiltration of another neoplasm or other cells, hypersplenism, Gaucher disease
ICUS (CCUS)
Yes
The presence of additional features:
• Monocytosis >1 × 10⁹/L
• Hypocellular bone marrow (cellularity <30%)
• Myelofibrosis
• Suspicion of germ cells neoplasm
No
Yes
Monocytosis >1 × 10⁹/L
• CMML
Hypocellular bone marrow (cellularity <30%)
• Hypoplasia/AA/PRCA
• T-LGL
• PNH
Myelofibrosis
• Molecular studies: JAK2, CARL, MPL
• PMF
Suspected germ cell neoplasm — molecular test (NGS)
No

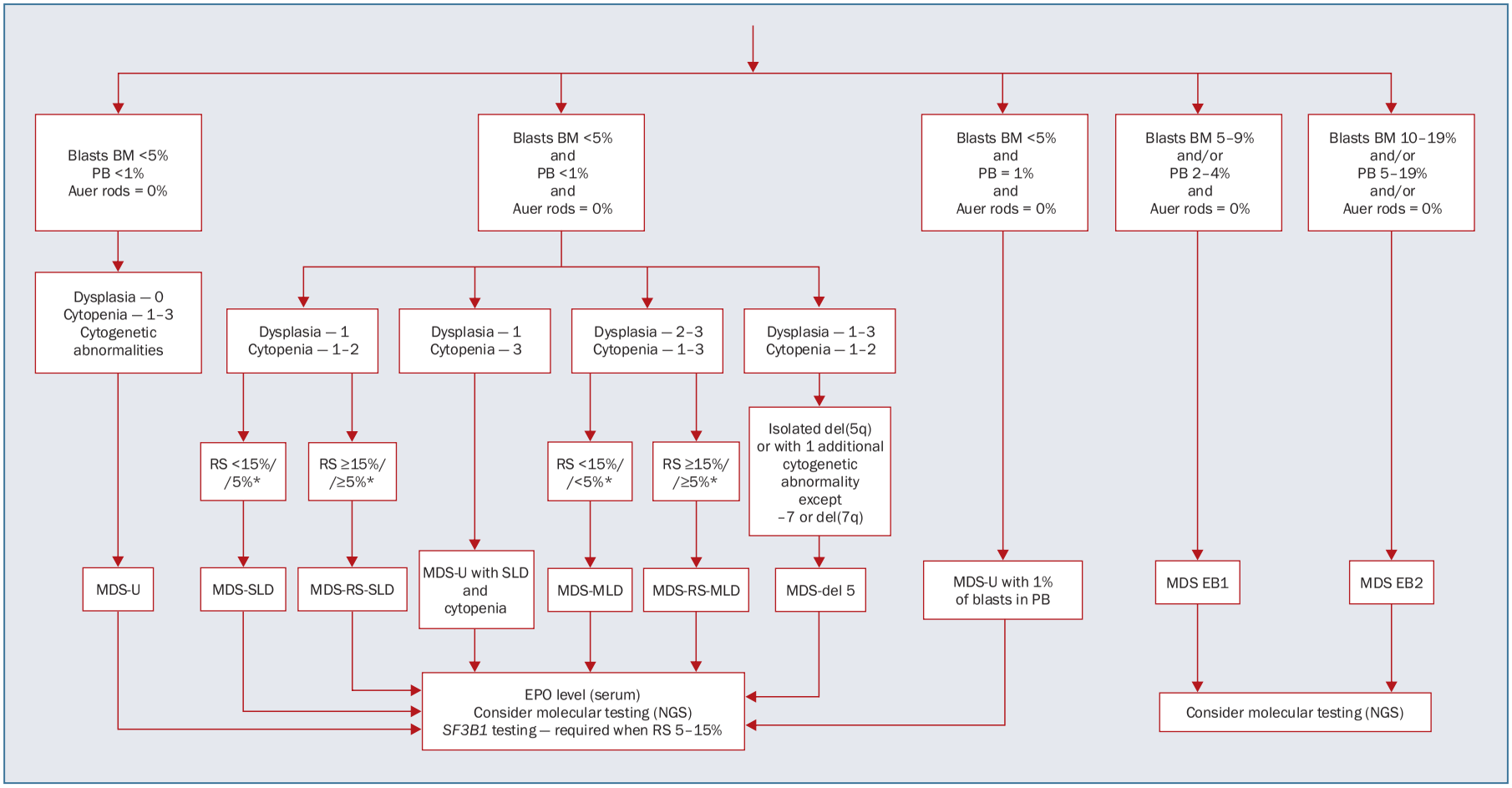


Figure 1. Diagnostic algorithm of myelodysplatic syndromes (MDS); *if mutation *SF3B1* (splicing factor 3b subunit 1) is present; AA — aplastic anemia; ANA — anti-nuclear antibodies; ANC — absolute neutrophil count; anti-dsDNA — anti-double stranded DNA; anti-HCV — anti-hepatitis C virus test; APTT — activated partial thromboplastin time; BM — bone marrow; CCUS — clonal cytopenia of undetermined significance; CTH — chemotherapy; CMML — chronic myelomonocytic leukemia; CMV — citomegalovirus; CRP — C-reactive protein; EB — excess blasts; EBV — Epstein-Bárr virus; EPO — erythropoietin; ESR — erythrocyte sedimentation rate; FACS — fluorescence-activated cell sorting; Hb — hemoglobin; HBsAg — hepatitis B surface antigen; HBV — hepatitis B virus; HCV — hepatitis C virus; HIV — human immonodeficiency virus; ICUS — idiopathic cytopenia of undetermined significance; INR — international normalized ratio; LDH — lactate dehydrogenase; MDS-del 5 — multilineage dysplasia; NGS — next-generation sequencing; PB — peripheral blood; PLT — platelets; PMF — primary myelofibrsis; PNH — nocturnal paroxysmal hemoglobinuria; PRCA — pure red cell leukemia; RS — ring sideroblasts; RTH — radiotherapy; SLD — single lineage dysplasia; TIBC — total iron-binding capacity; T-LGL — T-cell large granular lymphocytic leukemia; TSAT — transferrin saturation; U — unclassified

Table IV. Differential diagnosis of cytopenia/dysplasia

Diagnosis	Bone marrow/morphology		Other tests (serum)
Vitamin B_{12} deficiency	Megaloid forms of erythroid and granulocytic lineages, irregular shapes of erythroblast nuclei, Howell-Jolly bodies, neutrophil nucleus hypersegmentation, macrocytosis, pancytopenia, decreased number of reticulocytes, hypercellular cell bone marrow		↓ vitamin B_{12} ↓ holotranscobalamin ↑ methylmalonic acid (MMA) ↑ homocysteine ↑ LDH ↑ bilirubin
Folic acid deficiency	Similar to vitamin B_{12} deficiency		↓ folic acid ↑ homocysteine MMA in normal range
Eating syndromes	Anorexia	Hypocellular bone marrow, possible 'gelatinous transformation' of bone marrow and/or cell necrosis, more numerous histiocytes, peripheral blood acanthocytes, anemia, leukopenia, less often thrombocytopenia	↑ cholesterol ↑ ALT ↓ Mg, Zn, P, K, Na ↓ estrogen, testosterone ↓ fT3, fT4
	Copper deficiency	Pancytopenia, vacuolization of cytoplasm of erythroid and granulocytic lineages, ring-shaped sideroblasts	↓ Cu
Exposure to heavy metals (including lead Pb, Hg, Cd, As)	Hypocellular bone marrow, ring-shaped sideroblasts, pancytopenia, basophilic spotting		↑ Pb, Hg, Cd, As
Alcohol abuse	Vacuolization of cytoplasm of erythroid and granulocytic lineages, ring-shaped sideroblasts, hyperplasia of erythroid lineage, hypocellular bone marrow, macrocytosis, pancytopenia, symptoms resolve after alcohol withdrawal;stomatocytes, acanthocytes are present in liver cirrhosis		↑ serum Fe ↑ GGTP
Cytostatics	Most cytostatics	After higher doses — hypoplasia Regeneration of megakaryocytic and erythroid lineages usually precedes regeneration of granulocytic lineage After low doses — megaloblastic regeneration, dyserythropoiesis	
	Hydroxyurea, cyclophosphamide, methotrexate, azathioprine	Macrocytosis	
Anticonvulsants, antithyroid drugs, antibiotics		Bone marrow hypoplasia, dysplasia of granulocytic and megakaryocytic lineages, mono-, duo-, pancytopenia	
Isoniazid, linezolid		Sideroblastic anemia	
Trimethoprim/sulfamethoxazole, tacrolimus, mycophenolate mofetil, azathioprine		Hypersegmentation of neutrophil nuclei, dyserythropoiesis	
Steroids		Granulocytic dysplasia with high doses of corticosteroids (resolves 1–4 weeks after discontinuation) ↑ neutrophils, ↓ lymphocytes	
G-CSF		Granulocyte lineage: toxic granules, 'left shift', vacuolization of cytoplasm, abnormal lobulization of neutrophil nuclei, ↑ neutrophils	

→

Table IV (cont.). Differential diagnosis of cytopenia/dysplasia

Diagnosis	Bone marrow/morphology		Other tests (serum)
Infections	HIV	Dysplasia (especially aggravated during antiretroviral therapy), megaloblastic reaction, cytopenia, macrocytosis	Serological tests, PCR
	Parvovirus B19	Hypoplasia of erythroid lineage, presence of single, giant basophils	PCR — parvovirus B19
	HBV, HCV	Lymphocyte clusters, reactive plasmocytes, dyserythropoiesis, cytopenia (more often thrombocytopenia and anemia)	↑ bilirubin ↑ AST, ALT, ALP, INR Serological tests, PCR
	EBV, CMV	Possible cytopenias, monocytoid cells, activated lymphocytes, possible development of HLH, NHL	Serological tests, PCR
	Leishmaniasis	Pancytopenia, dysplasia, fibrosis, hemophagocytosis, iron deposits	
	Bacterial	Neutrophils: toxic granules, Doehle bodies	↑ CRP, culture
	Tuberculosis	Cytopenias (mainly anemia), numerous macrophages, granular lymphocytes, granulomas in bone marrow	Culture, PCR
Autoimmune diseases	SLE, RA	Erythroid and megakaryocytic lineage dysplasia, cytopenia	Antinuclear antibodies, rheumatoid factor, ↑ ESR
	Autoimmune hemolytic anemia (AIHA)	Anemia, slight erythroid lineage dysplasia	Positive DAT, ↑ bilirubin, ↑ LDH, ↓ haptoglobin
	Primary immune thrombocytopenia (ITP)	Possible dysplasia of megakaryocytic lineage (micromegakaryocytes) ↑ MPV ↑ PDW, giant platelets	Antiplatelet antibodies
	Autoimmune neutropenia (including Felty's syndrome)	Neutropenia, possible dysplasia, possible T-cell clone	Anti-neutrophilic antibodies, splenomegaly, rheumatoid factor
	Hypothyroidism (Hashimoto's disease)	Possibility of erythroid lineage hypoplasia, anemia, macrocytosis, ↓ reticulocytes	TSH, fT3, fT4, anti-TG antibodies, anti-TPO antibodies
Chronic idiopathic neutropenia		Normal bone marrow or hypoplasia of granulocytic lineage, possible lymphopenia	
Post-transplant	Liver	Possible trilinear dysplasia, macrocytosis of erythrocytes	
	allo-HCT	Hypoplastic bone marrow, dyserythropoiesis, risk of t-MDS/t-AML	
Aplastic anemia		Hypocellular bone marrow, mainly lymphocytes present, anemia, duo- or pancytopenia, ↓ reticulocytes	
HLH		Cytopenia, hemophagocytosis and to a lesser extent dysplasia	↑ ferritin, TG ↓ fibrinogen ↑ sCD25 Imaging tests — splenomegaly
PNH		Cytopenia, hypo-/normocellular bone marrow	FACS: ↓ FLAER, CD 55, CD59 on granulocytes, monocytes and erythrocytes, ↑ bilirubin
LGL		Neutropenia, pancytopenia, possibility of hypoplastic bone marrow, infiltration of clonal T or NK lymphocytes in bone marrow, granular lymphocytes in peripheral blood	Possibility of a positive rheumatoid factor, imaging tests: splenomegaly
Congenital bone marrow failure syndromes (e.g. Fanconi anemia)		Cytopenias	Typical genetic abnormalities

→

Table IV (cont.). Differential diagnosis of cytopenia/dysplasia

Diagnosis	Bone marrow/morphology	Other tests (serum)
Other hematopoietic malignancies (aCML, PMF, CMML)	1–3 linear dysplasia, fibrosis, anemia, thrombocytopenia Monocytosis >1 × 10^9/L (CMML) or immature forms of granulocyte lineage >10% peripheral blood WBC (aCML) or erythroblasts (PMF)	*JAK2* V617F, *MPL*, *CALR* genes mutations imaging tests — spleno- and/or hepatomegaly
Congenital sideroblastic anemia (e.g. XLSA)	Erythroid lineage dysplasia, ring-shaped sideroblasts, Pappenheimer bodies, ↓ MCV	Typical genetic abnormalities (e.g. *ALAS2* gene mutation) ↑ ferritin, hepatosplenomegaly

↓ — reduced value; ↑ — increased value; aCML — atypical chronic myeloid leukemia; ALAS2 — aminolaevulinic acid synthetase 2; allo-HCT — allogeneic hematopoietic cell transplantation; anti-TG — anti-thyroglobulin antibodies; ALP — alkaline phosphatase; ALT — alanine aminotransferase; anti-TPO — anti-thyreoperoxidase antibodies; As — arsenic; AST — aspartate aminotransferase; CD — cadmium; CMML — chronic myelomonocytic leukemia; Cu — cuprum; DAT — direct antiglobulin test; ESR — erythrocyte sedimentation rate; FACS — flow cytometric immunophenotypic testing; Fe —ferrum; FLAER — alexa 488 proaerolysin variant; fT3 — free triiodothyronine; fT4 — free thyroxine; G-CSF — granulocyte colony-stimulating factor; GGTP — gamma-glutamyltranspeptidase; Hg — mercury; HIV — human immonodeficiency virus; HLH — hemophagocytic lymphohistiocytosis; INR — international normalized ratio; ITP — primary immune thrombocytopenia; K — potassium; LDH — lactate dehydrogenase; LGL — large granular lymphocytic leukemia; line E — erythroid lineage; line G — granulocytic lineage; line M — megakaryocytic lineage; MCV — mean corpuscular volume; Mg — magnesium; MMA — methylmalonic acid; MPV — mean platelet volume; Na — calcium; NAIH — autoimmune hemolytic anemia; P — phosphorus; Pb — plumbum; PCR — polymerase chain reaction; PDW — platelet distribution width; PMF — primary myelofibrosis; PNH — paroxysmal nocturnal hemoglobinuria; RA — rheumatoid arthritis; sCD25 — soluble interleukin 2 receptor; SLE — systemic lupus erythematosus; TG — triglycerides; t-MDS/t-AML — therapy-related MDS/therapy-related AML; XLSA — X-linked sideroblastic anemia; TSH — thyroid-stimulating hormone; Zn — zinc

Table V. Pre-myelodysplatic syndrome (MDS) conditions

Idiopathic cytopenia of undetermined significance (ICUS)	Idiopathic dysplasia of undetermined significance (IDUS)	
Cytopenia (s) in CBC* No apparent causes of cytopenia Failure to meet criteria for MDS diagnosis No genetic abnormalities typical for MDS** Absence or presence of dysplasia in <10% of cells of a given hematopoietic lineage <5% blasts***	No cytopenia in CBC Failure to meet criteria for MDS diagnosis No genetic abnormalities typical of MDS** Dysplasia features in ≥10% of cells of a given hematopoietic lineage <5% blasts***	ICUS + IDUS — pre-MDS conditions without genetic abnormalities typical of MDS
Clonal cytopenia of undetermined significance (CCUS)	**Clonal hematopoiesis of indeterminate potential (CHIP)**	
Cytopenia (s) in CBC* No apparent causes of cytopenia Failure to meet criteria for MDS diagnosis Genetic abnormalities typical for MDS (one or more)** Absence or presence of dysplasia in <10% of cells of a given hematopoietic lineage <5% blasts***	No cytopenia in CBC Failure to meet criteria for MDS diagnosis Genetic abnormalities typical for MDS (one or more)** Dysplasia features in <10% of cells of a given hematopoietic lineage <5% blasts***	CCUS + CHIP — pre-MDS conditions with genetic abnormalities typical of MDS
ICUS + CCUS — pre-MDS conditions with cytopenias	IDUS + CHIP — pre-MDS conditions without cytopenias	

*Any grade cytopenia lasting more than four months after excluding other causes; **abnormalities identified by G-banding by trypsin with Giemsa (GTG) cytogenetics, fluorescence *in situ* hybridization (FISH) or by molecular biology. In the case of sequencing methods, a variant allele frequency (VAF) of at least 2% is considered to be diagnostic for pre-MDS conditions; for diagnosis of MDS, VAF should be ≥10%; ***blasts found in peripheral blood and/or bone marrow smears; CBC — complete blood count

Table VI. Commonest cytogenetic abnormalities in myelodysplatic syndrome patients (acc. to Schanz et al. [10])

Cytogenetic abnormalities	Incidence [%]
Single abnormalities:	
• del(5q)	6.4
• +8	4.7
• –Y	2.2
• del(20q)	1.7
• –7	1.6
• del(11q)	0.7
• del(12p)	0.6
• del(7q)	0.5
• i(17q)	0.4
• +19	0.4
• inv(3)/t(3q)/del(3q)	0.4
• +21	0.3
• der(1;7)	0.3
• –13/del(13q)	0.3
• –21	0.3
• –X	0.3
• Other single	5.8
Double abnormalities:	
• including del(5q)	1.6
• including –7/del(7q)	1.2
• including other abnormalities	3.4
Complex abnormalities:	
• 3 aberrations	2.1
• >3 aberrations	7.0
Independent clones	0.9
Clonal evolution	13.4

far, the occurrence of sequence variants has been demonstrated in as many as 181 genes, but only in 79 of them was it repeatable [15]. Two of the largest studies, involving a total of 1,682 patients, tested 104–111 genes and significant mutations were found in 43–47 genes [16, 17].

The most common mutations in MDS are detected in genes responsible for the following functions:

- **pre-mRNA splicing.** Sequence variants in *SF3B1* (splicing factor 3b subunit 1), *SRSF2* (serine and arginine rich splicing factor 2), *U2AF1* (U2 small nuclear RNA auxiliary factor 1) and *ZRSR2* (zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2) genes are among the most frequently reported disorders regulating splicing in MDS. They are found in almost 70% of patients, and are the most specific for MDS. *SF3B1* is the only gene whose sequence variants are included in the 2016 WHO revised classification, as well as in the 2020 proposal for a new MDS subtype with the *SF3B1* mutation [18]. The sequence variants in *SF3B1* gene is closely related to the presence of ring sideroblasts and is helpful in defining the myelodysplastic syndrome with ring sideroblasts (MDS-RS) subtype classification. Alterations of *SF3B1* gene occur proportionally more frequently in lower-risk patients according to the Revised International Prognostic Scoring System (IPSS-R). Sequence variants in *SRSF2* gene are indicative of an unfavorable course of MDS, with an increased risk of leukemic transformation;
- **epigenetic DNA modification.** Sequence variants in *TET2* (ten eleven translocation-2) gene are found quite frequently, in 19–25% of MDS cases, but are also present in other myeloid neoplasms. The presence of mutation predicts a good response to azacytidine, which, however, is not associated with an increase in survival time. Sequence variants in the DNMT3A (DNA-methyltransferase 3 alpha) gene occur mainly in elderly patients with a frequency of 3–8% in MDS. They are found in all of the marrow cells. The presence of mutation is associated with shorter survival;
- **chromatin modification.** Sequence variants in *ASXL1* (associated sex combs-like 1) gene are among the more frequent molecular changes in MDS, occurring in 15–20% of patients. Their presence in MDS adversely affects overall survival and is associated with a higher probability of transformation into AML. Sequence variants in *EZH2* (enhancer of zeste homolog 2) gene occur in 5–10% of myelodysplastic syndromes and are a marker of a poor prognosis;
- **DNA repair (*ATM, DLRE1C, FANCL, BRCC3*)**, as well as
- **cohesive complex (*CTCF, RAD21, STAG2, SMAC1A*);**
- ***RAS* signaling pathway (*KRAS, NRAS, CBL, NF1, PTPN11*);**
- **transcription factors (*RUNX1, GATA, TP53, CEBPA, BCOR, NCOR, PHF6, ETV6*).** Sequence variants in *TP53* gene (tumor protein 53) occur in 5–14% of higher risk MDS according to IPSS-R and in 27% of t-MDS cases. Their presence is associated with a poor survival prognosis. The presence of sequence variants in *TP53* gene in MDS with del (5q) results in lower lenalidomide efficacy and rapid transformation to AML in this group of patients. Bernard et al. [19] showed that an unfavorable prognosis concerns patients with a biallelic *TP53* mutation, usually the dominant clone. On the other hand, patients with the monoallelic *TP53* mutation, which usually occurs within the subclone, do not have a significantly worse prognosis compared to patients without *TP53* mutation [19]. Sequence variants in *RUNX1* (runt-related transcription factor 1) gene are found in approximately 10–15% of MDS cases, usually in advanced disease, and adversely affect overall survival. They are more common in secondary MDS (22–50%) and often coexist with *RAS* gene mutations;

Table VII. 2016 World Health Organization (WHO) classification of myelodysplastic syndromes (source [9])

Entity		Number of dysplastic lineages	Cytopenias*	Ring sideroblasts [%]	Blasts in bone marrow (BM) and peripheral blood (PB) [%]
MDS with single lineage dysplasia, MDS-SLD		1	1 or 2	<15/<5**	BM <5, PB <1, without Auer rods
MDS with multilineage dysplasia, MDS-MLD		2 or 3	1–3	<15/<5**	BM <5, PB <1, without Auer rods
MDS with ring sideroblasts (MDS-R)	MDS-RS-SLD	1	1 or 2	≥15/≥5**	BM <5, PB <1, without Auer rods
	MDS-RS-MLD	2 or 3	1–3	≥15/≥5**	BM <5, PB <1, without Auer rods
MDS with isolated del(5q)***		1–3	1–2	None or any	BM <5, PB <1, without Auer rods
MDS with excess blasts-MDS-EB	MDS-EB1	0–3	1–3	None or any	BM 5–9 or PB 2–4, without Auer rods
	MDS-EB2	0–3	1–3	None or any	BM 10–19 or PB 5–19 or Auer rods
MDS unclassifiable, MDS-U	With 1% blasts in PB	1–3	1–3	None or any	BM <5, PB = 1 without Auer rods
	Pancytopenia with unilineage dysplasia	1	3	None or any	BM <5, PB <1, without Auer rods
	Without dysplasia with a cytogenetic alteration defining MDS****	0	1–3	None or any	BM <5, PB <1, without Auer rods
	Del (5q) and pancytopenia	1–3	3	None or any	BM <5, PB <1,without Auer rods
Refractory cytopenia of childhood		1–3	1–3	None	BM <5, PB <2

*Cytopenias are defined as follows: hemoglobin (Hb) <10.0 g/dL, platelet count <100 × 10^9/L, absolute neutrophil count <1.8 × 10^9/L. Myelodysplatic syndrome (MDS) can rarely present with mild anemia or thrombocytopenia above the indicated values. Peripheral blood monocytes <1 × 10^9/L; **presence of *SF3B1* gene mutation; ***presence of cytogenetic del (5) abnormalities ± additional aberration without chromosome 7 abnormalities; ****presence of typical cytogenetic abnormalities; BM — bone marrow; PB — peripheral blood

- **signal transduction factors (*JAK2, FLT3, KIT, MLP, GNAS*).** In more than 10% of patients, sequence variants are found in six genes: *TET2*, *SF3B1*, *ASXL1*, *SRSF2*, *DNMT3A* and *RUNX1*, in 8–12% of patients in two genes *U2AF1* and *TP53,* and in 5–10% of patients in four genes: *EZH2*, *ZRSR2*, *STAG2*, *NRAS*.

WHO classification 2016, 2020

In the current modification of the 2016 classification, all types of syndromes are preceded by the name MDS [9] (*see* Table VII). Specific subtype without excess blasts and 5q deletion is primarily determined by the number of dysplastic cell lineages, and not by cytopenia.

Based on the data of 3,479 patients, of whom 795 had *SF3B1* gene mutation, an additional group of experts of the International Working Group for the Prognosis of MDS (IWG PM) proposed in 2020 to distinguish a new MDS subtype, i.e. MDS with *SF3B1* mutation (Table VIII). The authors showed that the presence of *SF3B1* gene mutation without ring sideroblasts (RS) had significant prognostic value. Patients with refractory anemia with ring sideroblasts (RARS) or refractory cytopenia with multilineage dysplasia (RCMD-RS) subtype with the *SF3B1* mutation live statistically significantly longer than patients with RARS or RCMD without *SF3B1* mutation. The effect of *SF3B1* mutation on survival is significant only in the group with blasts rate <5% in BM and <1% in peripheral blood without deletion 5q, monosomy 7 and chromosome 3 disorders, as well as in patients without *EZH2* and *RUNX1* mutations [18].

Congenital myeloid neoplasms

Myeloid neoplasms in which the predisposing genetic defect is inherited or arises *de novo* at an early stage of embryogenesis and is present in all (including terminal) cells in the body are known as myeloid neoplasms with germline predisposition (MNGP) or hereditary myeloid malignancy syndromes (HMMSs). Most often they concern genes such as: *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *SRP72*, and *SAMD9*. The exact frequency of these diseases is unknown, but it is estimated that they affect 1–5% of myeloid neoplasms. MNGP/HMMS can occur in as isolated abnormality or with concomitant diseases (including other neoplasms — lymphoid or solid tumors) or as part of complex syndromes [20–22].

The possibility of MNGP/HMMS should always be considered in patients with MDS and the following features:

Table VIII. Myelodysplatic syndromes (MDS) with *SF3B1* gene mutation: International Working Group (IWG) 2020 diagnostic criteria (source [18])

Peripheral blood cytopenia defined as reduction of parameters below laboratory standards in at least one cell lineage: erythroid, neutrophil and platelets
Presence of somatic mutation of *SF3B1* gene
Isolated erythroid or multilineage dysplasia*
Blasts in bone marrow <5% and in peripheral blood <1%
Failure to meet criteria for diagnosis of other diseases: MDS with isolated 5q deletion, MDS/MPN-RS-T and other MDS/MPN as well as primary myelofibrosis and other myeloproliferative neoplasms according to WHO 2016 classification
Normal karyotype or cytogenetic abnormalities with exception of: del(5q), chromosome 7 monosomy, inv(3) or 3q26 abnormalities, composite karyotype (≥3 abnormalities)
Coexistence of other somatic mutations except RUNX1 and/or EZH2**

*Presence of ring sideroblasts is not required; **presence of *JAK2* V617F, *CALR* or *MPL* mutation strongly suggests MDS/MPN-RS-T (a myelodysplastic/myeloproliferative neoplasm with an excess of ring sideroblasts and thrombocythemia); WHO — World Health Organization

- clinical symptoms or other diseases suggesting one of the congenital syndromes [20];
- ≥2 cases of MDS/AML in a family;
- ≥2 cases of aplastic anemia/unexplained cytopenia in a family;
- congenital syndrome diagnosed in relative;
- pathogenic mutation in the gene associated with congenital myeloid neoplasms, in particular:
  - *CEBPA* biallelic mutation (10% of cases have a germinal mutation),
  - *GATA2* mutation and/or chromosome 7 monosomy in a very young individual (most cases affect children and adolescents),
  - *RUNX1* mutation,
  - *DDX41* mutation;
- patients with and/or family history of multiple cancers (with the exception of chronic lymphocytic leukemia);
- related bone marrow donor of a patient with diagnosed congenital syndrome.

In addition, the possible presence of MNGP/HMMS should always be considered if:

- unexplained cytopenias are found;
- there are difficulties with hematopoietic cells mobilization.

Testing procedure for suspected MNGP

Testing of germline DNA from fibroblast cultures obtained by skin biopsy is the gold standard for MNGP/HMMS diagnostics. Other sources of DNA used include:

- skin cells examined immediately after skin specimen collection (no culture);
- hair follicles, nails (small amount of material);
- buccal swab/saliva (material quick and easy to collect, but possible contamination with blood and cancer cells).

Germinal DNA testing should also be performed in relatives and potential related donors of hematopoietic cells. In this situation, fibroblast culture is also the gold standard.

Prognostic factors

Prognostic and predictive scores for MDS patients have been published, including responses to immunosuppressive therapy, responses to treatment with erythropoiesis stimulating proteins or intensive chemotherapy. The most important is the International Prognostic Scoring System (IPSS) published in 1997 by Greenberg et al. and its modified 2012 version known as IPSS-R (see Table IX) [23, 24]. The International Prognostic Scoring System (IPSS) index stratifies patients depending on BM blasts percentage, cytogenetic abnormalities, and the number of peripheral blood cytopenia. IPSS risk stratification correlates with overall survival and transformation time to acute myeloid leukemia. The IPSS index is of significant clinical importance as it helps to qualify patients for a given type of treatment. The modified IPSS-R International Scoring System based on the analysis of data from 7,012 patients introduces five cytogenetic groups (with 18 subgroups of karyotype variants) and new, more detailed ranges for BM blasts rate, hemoglobin concentration, and the number of platelets and neutrophils. A limitation of the discussed indices is the lack of consideration of patient-related factors such as age, general condition and comorbidities. These factors are particularly important in qualifying for allotransplantation of hematopoietic cells. Della Porta et al. [25] have developed an index of comorbidities specific for MDS patients.

In 2005, Malcovati et al. [26] demonstrated that the dependence on red blood cell (RBC) transfusion assessed at any time point during the disease (defined as the necessity to transfuse ≥1 RBC within 8 weeks) is an important factor associated with shorter survival. Adverse prognostic factors in patients with MDS also include: increased ferritin and LDH and hypoalbuminemia. In recent years, much attention has been paid to molecular studies in MDS patients, which have been discussed in detail above. Bejar et al. [27] showed that the presence of a mutation of at least one of the following genes: *TP53*, *EZH2*, *ETV6*, *RUNX1* or *ASXL1* causes the patient to move to the next prognostically less favorable group according to IPSS. This is of particular importance in low-risk patients according to IPSS, as it allows to qualify them earlier for more aggressive treatment [27]. It seems that the implementation of molecular test results in MDS prognostic indices is an inevitable process, and additional research is still ongoing.

Table IX. Prognostic indices used in patients with myelodysplastic syndromes (sources [23, 24])

International Prognostic Scoring System (IPSS)					
Score	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Blasts in BM (%)	<5	5–10	–	11–20	21–30
Karyotype	Normal; –Y del(5q) del(20q)	Other abnormalities	Complex (≥3 abnormalities) chromosome 7 aberrations	–	–
Cytopenias*	0–1	2–3	–	–	–
Risk groups					
Low	Intermediate-1	Intermediate-2		High	
0 points	0.5–1 points	1.5–2 points		≥2.5 points	
Median overall survival					
Low risk	Intermediate-1	Intermediate-2		High	
5.7 years	3.5 years	1.2 years		0.4 years	
Mean time to transformation into AML (25% of the group)					
Low risk	Intermediate-1	Intermediate-2		High	
9.4 years	3.3 years	1.1 years		0.2 years	

Revised International Prognostic Scoring System (IPSS-R)							
Score	**0**	**0.5**	**1**	**1,5**	**2**	**3**	**4**
Karyotype	–Y del(11q)		Normal del(5q) del(12p) del(20q) 2 abnormalities including del(5q)		del(7q) +8 +19 i(17q) others (1 abnormality) others (2 abnormalities)	–7 inv(3) t(3q) del(3q) 2 abnormalities (including –7/del(7q) 3 abnormalities	>3 abnormalities
Blasts in BM [%]	≤2		>2–<5		5–10	>10	
Hemoglobin [g/dL]	≥10		8–<10	<8			
Platelets [× 10^9/L]	≥100	50–<100	<50				
Neutrophils (×10^9/L)	≥0.8	<0.8					

Risk groups				
Very low	Low	Intermediate	High	Very high
≤1.5 points	>1.5–3.0 points	>3.0–4.5 points	>4.5–6.0 points	>6.0 points
Proportion of patients at specified risk				
Very low	Low	Intermediate	High	Very high
19%	38%	20%	13%	10%

→

Table IX (cont.). Prognostic indices used in patients with myelodysplastic syndromes (sources [23, 24])

Revised International Prognostic Scoring System (IPSS-R)				
Median overall survival				
Very low risk	Low risk	Indirect risk	High risk	Very high risk
8.8 years	5.3 years	3 years	1.6 years	0.8 years
Mean time to transformation into AML (25% of group)				
Very low risk	Low risk	Intermediate risk	High risk	Very high risk
NR	10.8 years	3.2 years	1.4 years	0.73 years

*Hemoglobin (Hb) <10 g/dL; neutrophils <1,8 × 10^9/L; platelets <100 × 10^9/L; AML — acute myeloid leukemia; BM — bone marrow; IPSS — International Prognostic Scoring System; NR — not reached

Authors' contributions

Conception and design: KM, JDT. Manuscript writing, final approval of the manuscript: all authors.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to Biomedical journals.

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