

Beyond Morphology: Molecular Drivers, Updated Classifications, and Novel Therapeutics in Myelodysplastic Syndromes

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ABSTRACT

Background: Myelodysplastic syndromes/neoplasms (MDS) are clonal myeloid disorders characterized by ineffective hematopoiesis, cytopenias, and a variable risk of progression to acute myeloid leukemia (AML). Morphology remains central to diagnosis, but cytogenetic and molecular findings increasingly inform disease classification, prognosis, and treatment selection. **Review Approach:** This narrative review draws on a selective PubMed literature search covering 2008–2022 and on relevant classification and prognostic publications. **Conclusion:** MDS assessment requires integration of blood counts, peripheral-blood and bone-marrow morphology, cytogenetics, and molecular findings. The WHO fifth edition and the International Consensus Classification (ICC), both published in 2022, place greater emphasis on genetically defined entities, while prognostic tools such as IPSS-R and IPSS-M support risk assessment. Treatment remains dependent on disease risk, cytopenias, molecular features, patient fitness, and transplant eligibility.

Keywords: *Myelodysplastic syndromes; Molecular pathogenesis; WHO fifth edition; International Consensus Classification; Next-generation sequencing; IPSS-M; Risk stratification; Targeted therapy; Acute myeloid leukemia; Hematopoietic stem cell transplantation.*

INTRODUCTION

Myelodysplastic syndromes (MDS) are clonal/neoplastic haematopoietic stem cell (HSC) disorders, characterised by ineffective haematopoiesis leading to blood cytopenia of peripheral blood and progression to acute myeloid leukaemia (AML).¹ The term “myelodysplastic syndrome” was established in the 1980s and first used by the French-British-American working group in 1982 to encompass a group of cytopenic myeloid neoplasms.² MDS is distinguished from other non-neoplastic clonal myeloid proliferations by the presence of morphologic dysplasia making diagnosis of MDS a challenge because of the reason that cytopenias can have a large number of other causes. Hence there is an importance of integration of clinical features, peripheral blood morphology, bone marrow examination findings along with immunophenotyping and genetic analysis. This review focuses on the relationship between morphology, molecular findings, classification,

prognostic assessment, and treatment. It compares the broad aims of the WHO fifth edition and ICC frameworks and describes how genetic information can complement clinical risk assessment. It is a narrative synthesis, not a systematic review or a meta-analysis.

PATHOGENESIS

The pathophysiology is characterised by a multi-step process involving cytogenetic changes and/or gene mutations,³ abnormalities of the bone marrow microenvironment⁴ and widespread gene hypermethylation at advanced stages.^{5,6} MDS is recognized as a clonal disorder of stem cells. Defects within myeloid progenitors and bone marrow microenvironment have been found to contribute to abnormal apoptosis, accumulation of cells with mutated DNA and progression to acute myeloid leukemia. It can be described as: Initial genetic hit→ Clonal expansion→ Dysplastic hematopoiesis→

Microenvironment interactions→ Leukemic transformation.

ABNORMAL APOPTOSIS IN THE BONE MARROW

Apoptosis (programmed cell death) regulate the population of cells. The ratio of proapoptotic protein, e.g. p⁵³, Bax, etc. to antiapoptotic protein, e.g. BCL2 and BCLXL regulate the rate of apoptosis.⁷ TNFα is well recognized as a cytokine promoter of apoptosis in erythroid cells in early stages of MDS. Overall in early stage MDS, rate of apoptosis is high. Use of growth factors such as erythropoiesis stimulating agents and G-CSF has been shown to decrease rate of apoptosis.⁷

EPIGENETIC ALTERATIONS

The term epigenetics is the alterations of gene expression without altering the primary DNA sequence. The most studied epigenetic alterations in cancer are promoter hypermethylation and histone deacetylation. The role of promoter hypermethylation in low risk MDS is not well studied while in high risk MDS, hypermethylation of any of the tumor suppressor genes p15, HIC1, ER CDH1 is associated with adverse survival and increased risk of leukemia evolution.⁸

GENETIC ALTERATIONS-MDS

Requires multiple hits and to date no single genetic lesion has been shown to be sufficient for developing the disease. Mutated N-RAS is identified in 6-48% (higher in patients with increase blast counts) and it correlates with increased risk of AML evolution.⁹ The tumor suppressor gene TP53 is mutated in 8-14% of patients and is often associated with complex karyotype, resistance to chemotherapy and poor outcome. FLT3 mutations are found in < 1%, KIT mutation in 1.2% and MLL partial tandem duplications in 2.7% of MDS patients.¹⁰

IMMUNE MEDIATED:

A minority of MDS patients have hypocellular bone marrow and has a clear link to the HLA DR 15. Immunosuppressive therapy induces long lasting response in this subcategory.¹¹

Pathogenesis of 5q- syndrome-In 5q-syndrome commonly deleted segment is 31-32. There are 44 genes, out of which defect in RPS14 is found to be associated with block in erythroid maturation.¹² RPS 14 is a component of ribosomal 40s subunit, and interestingly another ribosomal gene RPS 19 is found to cause Diamond Blackfan anemia.

DIAGNOSTICS: PATHOLOGY AND HEMATOLOGY

Diagnosis is a multidisciplinary integration, no single test suffices. The diagnosis of MDS requires a combination of several different tests which includes the presence of at least 1 cytopenia: hemoglobin [Hb]

in females: <12 g/dL; Hb in males: <13 g/dL; platelets, <150 × 10⁹/L; and/or absolute neutrophil count <1.8 × 10⁹/L).^{13,14} The presence of morphologic dysplasia affecting at least 10% of cells in at least 1 hematopoietic (erythroid, granulocytic, or megakaryocytic) lineage is also mandatory, with only rare exception made for certain genetic abnormalities considered to be MDS-defining in the International Consensus Classification (ICC) and revised fourth edition World Health Organization Classification (WHO) systems.¹³ Ironically the morphologic dysplasia in hematopoietic cells has not been found to be specific for MDS and can be found in other myeloid neoplasms as well as many reactive conditions.¹⁵ Hence it becomes imperative to integrate the morphological findings with immunophenotyping data and genetic studies and then to interpret the final results with correlation of the clinical presentation, as well as blood count abnormalities. AML cases with blast percentage of ≥20% in blood or bone marrow as well as certain AML-defining genetic abnormalities^{13,14} excludes MDS and supports a diagnosis of AML. In addition an elevation of monocytes (≥0.5 × 10⁹/L and ≥ 10% of leukocytes), platelets (≥450 × 10⁹/L, in the absence of isolated del(5q) or inv (3)/t(3;3) cytogenetic aberrations), or leukocytes (≥13 × 10⁹/L) is suggestive of an alternative diagnosis in support of MDS/myeloproliferative neoplasm.

PERIPHERAL BLOOD FINDINGS

- Granulocytes: A full differential count of at least 200 nucleated peripheral blood leukocytes must be performed to quantify the proportion of blasts as well as monocytes. Signs of dysplasia include Pseudo Pelger-Huet cells, abnormal chromatin clumping, hypo-/degranulation, left shift.
- Platelets: Giant platelets, anisocytosis of platelets
- Red cells: Anisocytosis, poikilocytosis, dimorphic erythrocytes, polychromasia, megalocytes, basophilic stippling, presence of nucleated erythroid precursors, tear drop cells, ovalocytes, fragmentocytes/schistocytes, basophilic stippling, nucleated precursors, dimorphic populations, megaloblastic cells, anisocytosis, and poikilocytosis.

BONE MARROW MORPHOLOGY (Aspirate/Biopsy)

It is important to count at least 500 nucleated cells and quantify blasts, including any promonocytes, which are regarded as blast equivalents and 25 megakaryocytes and at least 100 erythroblasts should be evaluated.¹⁶ Granulocytic, erythrocytic, and megakaryocytic cells should be evaluated for dysplastic changes: a lineage is considered to be dysplastic if at least 10% of cells in that line age manifest cytologic dysplasia. The biopsy

can also reveal alternate pathologies that simulate MDS in their clinical presentation or may occur concomitantly with MDS, such as tumor metastases, granulomas, multiple myeloma, systemic mastocytosis, and lymphomas.

- **Cellularity of the marrow:** Typically hypercellularity, rarely hypocellularity.
- **Erythropoiesis:** Megaloblastoid changes, multinuclearity, nuclear budding, non-round nuclei, karyorrhexis, nuclear bridges, atypical mitoses, sideroblastosis, ring sideroblasts, periodic acid-Schiff-positive red cell precursors.
- **Megakaryopoiesis:** Micromegakaryocytes, mononuclear megakaryocytes, dumbbell-shaped nuclei, hypersegmentation, multinuclearity with multiple isolated nuclei.
- **Granulocytopoiesis:** Left shift, increased medullary blast count, Auer rods or Auer bodies, hypo-/degranulation, pseudo-Pelger cells, nuclear anomalies (e.g. hypersegmentation, abnormal chromatin clumping), deficiency of myeloperoxidase, increase and morphological abnormality of monocytes.
- **Blast quantification:** can be done by immunohistochemistry (CD34) as well as identification of specific cell types (e.g. micromegakaryocytes)

FLOW CYTOMETRY, CYTOGENETICS & MOLECULAR GENETIC TESTING

Flow cytometry can be helpful for quantification of CD34 and CD117 positive progenitor cells along with identification of clonal B cell/abnormal T cell population which can help to rule out alternative diagnoses. Karyotyping has emerged as the most widely used method for calculating the chromosomal abnormalities (numerical/structural). Molecular genetic testing includes detection of driver somatic mutation and germ line mutation detected by targeted NGS testing can be helpful to show mutation patterns (minimum VAF levels of 10%) having high predictive value for diagnosis whereas absence of any driver mutation has a negative predictive value.

Most frequent somatic mutations seen in MDS/MD:^{17,18}

- Epigenetic regulators and chromatin-remodelling factors-TET2 ASXL1 DNMT3A IDH1/2
- Pre-mRNA splicing factors-SF3B1 SRSF2 U2AF1
- Transcription factors-RUNX1 TP53
- Signalling molecules-NRAS/KRAS
- Cohesin complex-STAG2.

Germ line mutations (eg, CEBPA, GATA2, RUNX1, and TP53) can be detected by routine somatic NGS panels with VAF in the germ line range (40%-60%) can help in confirming that the mutation is germ line by testing of nonhematopoietic cells. Rare germ line

mutations may present with VAF levels <40% (variant allele frequency).^{19,20}

CLASSIFICATION: WHO FIFTH EDITION AND INTERNATIONAL CONSENSUS CLASSIFICATION

MDS has historically been subdivided into several subtypes by classification schemes, the most recent of which are the International Consensus Classification and World Health Organization Classification (fifth edition), both published in 2022. The aim of MDS classification is to identify entities with shared genetic alteration and molecular pathogenesis and to incorporate morphologic features (bone marrow and blood blast percentage, degree of dysplasia, ring sideroblasts, bone marrow fibrosis, and bone marrow hypocellularity) and separation of 3 entities defined by genetics: isolated del(5q) cytogenetic abnormality, SF3B1 mutation, and TP53 mutation /wild type. Current diagnostic criteria establish a precise level of morphologic dysplasia (10% dysplastic cells) and maturation impairment (20% blasts) that separate MDS from non-neoplastic clonal hematopoiesis and AML, respectively.^{13,14}

New Systems:

A. WHO 2022 classification(5th Edition)

It has introduced the term myelodysplastic neoplasm to replace myelodysplastic syndromes, for emphasizing their neoplastic nature and harmonizing terminology with MPN. MDS entities are now grouped as those having defining genetic abnormalities and those that are morphologically defined. The recommended threshold for dysplasia has been kept 10% for all lineages and the distinction between single lineage and multilineage dysplasia is now considered optional. The updated MDS classification scheme and the incorporation of CCUS in the classification obviates the need for “NOS” or “unclassifiable” attributes. Specifically, MDS, unclassifiable, which was present in the prior edition, is removed.⁴⁴

MDS with Defining Genetic Abnormalities

Myelodysplastic neoplasms with defining genetic abnormalities are grouped together and include: MDS with low blasts and isolated 5q deletion (MDS-5q), MDS with low blasts and SF3B1 mutation (MDS-SF3B1), and MDS with biallelic TP53 inactivation (MDS-biTP53). The latter supersedes MDS-5q and MDS-SF3B1. WHO 2022 introduced two new MDS entities, defined by SF3B1 mutation and multi-hit TP53 mutation, expanding the role of genetics in MDS classification. SF3B1-mutated and del(5q) MDS exhibit relatively indolent clinical behavior and lack increased blasts, whereas TP53 mutated MDS is a highly aggressive disease characterized by genetic instability and a rapidly progressive course. Recent studies have identified MDS-SF3B1 as a distinct disease type that includes over 90% of MDS with ≥5%

ring sideroblasts²². The term MDS with low blasts and ring sideroblasts is retained as an acceptable alternative to be used for cases with wild-type SF3B1 and $\geq 15\%$ ring sideroblasts. This permits inclusion of rare MDS cases harbouring driver mutations in other RNA splicing components. Pathogenic TP53 alterations of any type (sequence variations, segmental deletions and copy neutral loss of heterozygosity) are detected in 7-11% of MDS.^{23,24,25} Among these, about two-thirds of patients have multiple TP53 hits (multi-hit), consistent with biallelic TP53 alterations²³. Biallelic TP53 (biTP53) alterations may consist of multiple mutations or mutation with concurrent deletion of the other allele. This “multi-hit” mutational status results in a neoplastic clone that lacks any residual wild-type p53 protein. Clinical detection of biallelic TP53 alterations is based on sequencing analysis (covering at least exons 4 to 11)^{23,26}, often coupled with a technique to detect copy number status, usually fluorescence in situ hybridization with a probe set specific for the TP53 locus on 17p13.1 and/or array techniques (e.g., comparative genomic hybridization or single nucleotide polymorphism arrays).²⁷ A TP53 VAF $\geq 50\%$ may be regarded as presumptive (not definitive) evidence of copy loss on the trans allele or copy neutral loss of heterozygosity when a constitutional TP53 variant can be ruled out. When two or more TP53 mutations are detected, they usually affect both alleles²³ and can be considered a multi-hit status. Over 90% of patients with MDS-biTP53 have complex, mostly very complex (>3), karyotype^{23,24} and thus are regarded as very high risk in IPSS-R³³.

MDS, Morphologically Defined

Hypoplastic MDS (MDS-h) is listed as a distinct MDS type in this edition. Long recognized as having distinctive features, MDS-h is associated with a T-cell mediated immune attack on haematopoietic stem and progenitor cells, along with oligoclonal expansion of CD8+cytotoxic T-cells overproducing IFN γ and/or TNF α . Several features overlap across the triad of MDS-h, paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia (AA).^{28,29,30}

MDS AND AML

The boundary between MDS and AML is vague, but the 20% blast cut off to define AML is retained to minimise the risk of overtreatment. A balanced approach has been adopted by eliminating blast cut offs for most AML types with defining genetic alterations but retaining a 20% blast cut off to delineate MDS from AML.

Childhood myelodysplastic neoplasms

Childhood MDS has been defined as a clonal haematopoietic stem cell neoplasm arising in children and adolescents (<18 years of age) leading to ineffective haematopoiesis, cytopenia, and risk of progression to AML. This category is considered to be biologically distinct from that seen in adults. JMML, myeloid proliferations associated with Down syndrome, and MDS post cytotoxic therapy are excluded from this group and belong elsewhere in the classification.^{31,32} Childhood MDS with low blasts (cMDS-LB) replaces the former term “refractory cytopenia of childhood (RCC)”. It includes two subtypes: childhood MDS with low blasts, hypocellular; and, childhood MDS with low blasts, not otherwise specified (NOS). Approximately 80% of cases show hypocellular bone marrow with features similar to severe aplastic anemia and other bone marrow failure syndromes, requiring close morphologic examination to evaluate the distribution, maturation, and presence of dysplasia in haematopoietic lineages.³³ Some cytogenetic findings such with an increased risk of progression to AML and typically treated with haematopoietic stem cell transplantation, while cases with normal karyotype or trisomy 8 can have an indolent course. Childhood MDS with increased blasts (cMDS-IB) is defined as having $\geq 5\%$ blasts in the bone marrow or $\geq 2\%$ blasts in the peripheral blood. The genetic landscape of cMDS-IB and cMDS-LB is similar, and they both differ from MDS arising in adults. Acquired cytogenetic abnormalities and RAS-pathway mutations are more common in cMDS-IB compared to cMDS-LB.^{34,35}

Table 1: WHO 2022 Classification and defining features of myelodysplastic neoplasms (MDS).

	BLASTS	CYTOGENETICS	MUTATIONS
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	$<5\%$ BM and $<2\%$ PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and SF3B1 mutation (MDS-SF3B1)		Absence of 5q deletion, monosomy7, or complex karyotype	SF3B1
MDS with biallelic TP53 inactivation (MDS-biTP53)	$<20\%$ BM and PB	Usually complex	Two or more TP53 mutations, or 1 mutation with evidence of TP53 copy number loss or cn LOH
MDS, morphologically defined			

MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic b (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10–19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

a Detection of $\geq 15\%$ ring sideroblasts may substitute for SF3B1 mutation. Acceptable related terminology : MDS with low blasts and ring sideroblasts.

b By definition, $\leq 25\%$ bone marrow cellularity, age adjusted. BM bone marrow, PB peripheral blood, cn LOH copy neutral loss of heterozygosity⁴⁴

B. International Consensus classification (ICC) 2022

It also reduced the absolute monocyte count defining chronic myelomonocytic leukemia (CMML) from $1 \times 10^9/L$ to $0.5 \times 10^9/L$, which will result in some cases previously classified as MDS to be classified as CMML in the current schemes. For practical purposes and minimizing confusion it has been strongly recommended that all diagnosticians shall provide both ICC and WHO5 classifications in diagnostic reports and in the clinical record, particularly when there are differences.

For therapy-related cases ICC 2022 the previous category of “therapy-related myeloid neoplasms was recommended to subclassify these cases similar to other MDS similar to WHO 2022 but retained the term “therapy-related”^{13,14}.

Table 2: International consensus classification(ICC)

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with del 5q	<5% BM and <2% PB	Isolated del(5q), or with up to 1 other abnormality other than &/del(7q)	Any, except multi-hit TP53
MDS with mutated SF3B1	<5% BM and <2% PB	No isolated del(5q), -7/del(7q), abn3q26.2, or complex	SF3B1 (10%VAF), without multi-hit TP53, or RUNX1
MDS with mutated TP53	0-9% BM and blood		Multi-hit TP53, or TP53 mutation (VAF >10%) and complex karyotype
MDS, Morphologically defined			
MDS, NOS, no dysplasia	<5% BM and <2% PB	-7/del(7q) or complex	Any, except multi-hit TP53 or SF3B1(>10%VAF)
MDS, NOS Single lineage dysplasia Multilineage dysplasia	<5% BM and <2% PB	Any, except meeting criteria for MDS-del(5q)	Any, except multi-hit TP53 or SF3B1(>10%VAF)
MDS with excess blasts(MDS-EB)	5-9%BM 2-9%PB	Any	Any, except multi-hit TP53
MDS/AML	10-19% BM or PB	Any, except AML-defining	Any, except NPM1, bZIP, CEPBA or TP53

Table 3: Showing Comparative MDS classification

WHO revised fourth edition	WHO fifth edition	ICC
MDS with RS (most <i>SF3B1</i> -mutated cases)	MDS with LB and <i>SF3B1</i> mutation	MDS with mutated <i>SF3B1</i>
MDS with RS (<i>SF3B1</i> wild-type cases)	MDS with LB and RS	Not included
MDS with isolated del(5q)	MDS with LB and isolated 5q deletion	MDS with del(5q)
MDS with SLD	MDS with LB	MDS-NOS with SLD
MDS with MLD	MDS with LB	MDS-NOS with MLD
MDS, unclassifiable (most cases)	CCUS	MDS-NOS without dysplasia
Not included	MDS, hypoplastic	Not included
MDS with EB1	MDS with IB1	MDS with EB
MDS with EB2	MDS with IB2	MDS/AML
Not included	MDS with fibrosis	Not included
Not included	MDS with bi-allelic <i>TP53</i> inactivation	MDS and MDS/AML with mutated <i>TP53</i>

CCUS, clonal cytopenia of undetermined significance; EB, excess blasts; IB, increased blasts; LB, low blasts; MLD, multilineage dysplasia; NOS, not otherwise specified; RS, ring sideroblasts; SLD, single lineage dysplasia. In addition it reduced the absolute monocyte count defining chronic myelomonocytic leukemia (CMML) from $1 \times 10^9/L$ to $0.5 \times 10^9/L$, which will result in some cases previously classified as MDS to be classified as CMML in the current schemes under the group “myelodysplastic/myeloproliferative neoplasms”.

MYELOYDYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS

This category of myeloid neoplasms is defined by overlapping pathologic and molecular features of MDS and MPN, often manifesting clinically with various combinations of cytopenias and cytoses. The definition of cytopenias is the same as that for MDS. The classification includes major revisions in the diagnostic criteria of CMML and terminology changes for other MDS/MPN types.

- Chronic myelomonocytic leukaemia
- Myelodysplastic/myeloproliferative neoplasm with neutrophilia
- Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis
- Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

CHRONIC MYELOMONOCYTIC LEUKAEMIA DIAGNOSTIC CRITERIA,

Chronic myelomonocytic leukaemia (CMML), which is characterized by sustained peripheral blood monocytosis and various combinations of somatic mutations involving epigenetic regulation, spliceosome, and signal transduction genes. Diagnostic criteria are revised to include prerequisite and supporting criteria. (Table 4)

The first prerequisite criterion is persistent absolute ($\geq 0.5 \times 10^9/L$) and relative ($\geq 10\%$) peripheral blood monocytosis. Namely, the cutoff for absolute monocytosis is lowered from $1.0 \times 10^9/L$ to $0.5 \times 10^9/L$ to incorporate cases formerly referred to as oligomonocytic CMML.^{36,37,38} To enhance diagnostic accuracy when absolute monocytosis is $\geq 0.5 \times 10^9/L$ but $< 1.0 \times 10^9/L$, detection of one of more clonal cytogenetic or molecular abnormality and documentation of dysplasia in at least one lineage are required.^{39,40} Two disease subtypes with salient clinical and genetic features are now formally recognized based on WBC: myelodysplastic CMML (MD-CMML) (WBC $< 13 \times 10^9/L$) and myeloproliferative CMML (MP-CMML) (WBC $\geq 13 \times 10^9/L$). MP-CMML is commonly associated with activating RAS pathway mutations and adverse clinical outcomes⁴¹. The blast-based subgroup of CMML-0 ($< 2\%$ blasts in blood and $< 5\%$ blasts in bone marrow) introduced in the previous edition has been eliminated in view of evidence that its addition provides no or limited prognostic significance.^{42,43}

Table 4: Diagnostic criteria of chronic myelomonocytic leukaemia.^{36,37,38}

Prerequisite criteria
1.Persistent absolute ($\geq 0.5 \times 10^9/L$) and relative ($\geq 10\%$) peripheral blood monocytosis.
2.Blasts constitute $< 20\%$ of the cells in the peripheral blood and bone marrow. ^a
3.Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.
4.Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.
Supporting criteria
1.Dysplasia involving ≥ 1 myeloid lineages.
2.Acquired clonal cytogenetic or molecular abnormality.
3.Abnormal partitioning of peripheral blood monocyte subsets. ^e
Requirements for diagnosis
- Pre-requisite criteria must be present in all cases
- If monocytosis is $\geq 1 \times 10^9/L$: one or more supporting criteria must be met.
- If monocytosis is ≥ 0.5 and $< 1 \times 10^9/L$: supporting criteria 1 and 2 must be met.
Sub-typing criteria
-Myelodysplastic CMML(MD-CMML): WBC $< 13 \times 10^9/L$
-Myeloproliferative CMML(MP-CMML): WBC $\geq 13 \times 10^9/L$
Sub-grouping criteria (based on percentage of blasts and promonocytes)
CMML-1: $< 5\%$ in peripheral blood and $< 10\%$ in bone marrow
CMML-2: 5–19% in peripheral blood and 10-19% in bone marrow

a Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes

d Morphologic dysplasia should be present in $\geq 10\%$ of cells of a haematopoietic lineage in the bone marrow

e Based on detection of increased classical monocytes ($> 94\%$) in the absence of known active auto immune diseases and/or systemic inflammatory syndromes⁴⁴

ATYPICAL CHRONIC MYELOID LEUKAEMIA: is renamed MDS/MPN with neutrophilia, and other terminology updates Diagnostic criteria for other MDS/MPN types were largely unchanged. The term MDS/MPN with neutrophilia replaces the term atypical CML. This change underscores the MDS/MPN nature of the disease and avoids potential confusion with CML. MDS/MPN with ring sideroblasts and thrombocytosis is redefined based on SF3B1 mutation and renamed MDS/MPN with SF3B1 mutation and thrombocytosis. The term MDS/MPN with ring sideroblasts and thrombocytosis has been retained as an acceptable term to be used for cases with wild-type SF3B1 and $\geq 15\%$ ring sideroblasts. MDS/MPN, unclassifiable is now termed MDS/MPN, not otherwise specified; this is in line with an intentional effort to remove the paradoxical qualifier “unclassifiable” from the entire classification. For therapy-related cases WHO 2022 the previous category of “therapy-related myeloid neoplasms was recommended to subclassify these cases similar to

other MDS but introduced the term “postcytotoxic therapy”.

OLD SYSTEMS

In the last 20 years, different MDS classification and prognostic scoring systems have been proposed¹ French-American-British (FAB) classification was recommended in early and as modified by the World Health Organization (WHO) followed by who 2008 classification system. The WHO 2016 classification system uses percentages of blasts in bone marrow, ring sideroblasts and dysplastic changes to differentiate MDS subtypes. The International Prognostic Scoring System (IPSS) is based on a multivariate to evaluate the prognosis. MDS was classified according to the World Health Organization (WHO) criteria⁴⁵ with prognosis established by the international prognostic scoring system (IPSS)⁴⁶ or rather, its revised version (IPSS-R).⁴⁷ Prognosis was based on the marrow blast percentage, number and extent of cytopenias, and cytogenetic abnormalities, which are grouped in the IPSS-R.^{46,47}

Table 5: Comparative WHO 2008 and WHO 2016 classification⁴⁸

2008 WHO classification	2016 WHO classification
Refractory cytopenia with unilineage dysplasia (RCUD) encompassing refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT)	MDS with single lineage dysplasia (MDS-SLD)
Refractory cytopenia with multilineage dysplasia (RCMD)	MDS with multilineage dysplasia (MDS-MLD)
Refractory anemia with ringed sideroblasts (RARS)	MDS with ring sideroblasts (MDS-RS)

	MDS-RS with single lineage dysplasia (MDS-RS-SLD)
	MDS-RS with multilineage dysplasia (MDS-RS-MLD)
Myelodysplastic syndrome associated with isolated del(5q)	MDS with isolated del(5q)
	MDS with excess blasts (MDS-EB)
Refractory anemia with excess blasts-1 (RAEB-1)	MDS-EB-1
Refractory anemia with excess blasts-2 (RAEB-2)	MDS-EB-2
Myelodysplastic syndrome, unclassified (MDS-U)	MDS, unclassifiable (MDS-U)
	With 1% blood blasts
	With single lineage dysplasia and pancytopenia
	Based on defining cytogenetic abnormality
Refractory cytopenia of childhood	Refractory cytopenia of childhood

RISK STRATIFICATION

Risk stratification was used previously for “risk-based grouping”. The Revised International Prognostic Scoring System (IPSS-R) was used which was based on blast percentage, ring sideroblasts, and number of lineages with dysplasia. The cornerstone tool used 5 variables to calculate a score:- Very low, low, intermediate, high, very high.

The International Prognostic Scoring System–Revised (IPSS-R), developed by the International Working Group for Prognosis in MDS (IWG-PM), has been followed by proposing the IPSS-Molecular (IPSS-M) model. IPSS-M Risk Score is categorized into:

- Clinical
 - Bone marrow blasts—%
 - Platelets, 250— $\times 10^9/l$
 - Hemoglobin—g/dl
- Cytogenetic
 - IPSS-R cytogenetic category
- Gene mutations (17variables,16genes)
 - TP53 multihit, MLL PTD, FLT3 ITD+TKD, SF3B15q, NPM1, RUNX1, NRAS, ETV6, IDH2, CBL, EZH2, U2AF1, SRSF2, DNMT3A, ASXL1, KRAS, SF3B1a
- Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)
 - IPSS-M Risk Category is further sub grouped into discrete six-category risk schema into: very low, low, moderate low, moderate high, high, very high. Patients with lower-risk MDS are primarily candidates for treatments aimed at ameliorating cytopenias and improving quality of life, while patients with higher-risk MDS are considered for therapies capable of altering the natural disease course and prolonging survival (e.g., hypomethylating agents and allogeneic transplantation). Molecular testing is not yet routine globally because of cost, infrastructure, and reimbursement considerations. The IPSS-M provides a focused list of 31 genes that can be prioritized as centers set up their routine diagnostics for even more precise prognostication.⁴⁹ Regarding prognostication the IPSS-M has superseded older models, using

genetic data to provide a more precise risk estimate, directly impacting clinical decisions regarding therapy intensity and timing of transplant.

Despite all the classification system and diagnostic criterias some cytopenias can remain unexplained even after a vigorous workup. In cases having the absence of diagnostic criteria, a persistent unexplained cytopenia are grouped into “non-clonal cytopenia” either idiopathic cytopenia of undetermined significance (ICUS) or clonal cytopenia of undetermined significance (CCUS) until diagnostic criteria for a myeloid neoplasm are met.⁵⁰

MDS exists on a continuum. The arbitrary 20% blast threshold for AML is increasingly challenged. The biological journey from CHIP→CCUS→MDS→AML is a seamless spectrum of clonal evolution, demanding a flexible, biology driven approach.

- Cytopenic causes of non-clonal type includes diseases like Chronic liver diseases, excessive alcohol intake, drug induced cytopenia, cytotoxic therapy related, B12/folate deficiency, autoimmune cytopenia, anemia of chronic disorders, parasitic manifestation (hypersplenism in malaria and leishmaniasis), human immunodeficiency virus infection (HIV), other stem cell disorder.
- Idiopathic cytopenia of uncertain significance (ICUS)
- Idiopathic dysplasia of unknown significance (IDUS)
- Clonal cytopenia of undetermined significance (CCUS)
- Clonal hematopoiesis of indeterminate potential (CHIP)

Table 6: ICUS

Mild cytopenia for at least 4 months
(haemoglobin < 11.0g/dl, neutropenia < 1500/ml, thrombocytopenia < 100000/ml)
No or only mild (< 10%) marrow dysplasia
Marrow blasts < 5%
No clonal cytogenetic or molecular markers
Exclusion of other diseases

Table 7: IDUS

No significant cytopenia (i.e. hemoglobin 11g/dl, Neutrophils 1500/ml and platelets 100000/ml)
Marked dysplasia in > 10% of neutrophilic and/or Erythroid and/or megakaryocytes lineages
Marrow blasts < 5%
No clonal cytogenetic or molecular markers

Table 8: CHIP

No significant cytopenia
No or only mild (< 10%) dysplasia
Marrow blasts < 5%
Presence of one or more MDS-related mutation(s)
Clonality defined by mutation of myeloid disorder associated genes (including particularly DNMT3A, ASXL1, TET2, JAK2 and TP53 genes), with a VAF of between 2% and 30%.

Table 9: CCUS

- Cytopenia for at least 4 months (hemoglobin < 11.0g/dl and/or neutropenia < 1500/ml and/or thrombocytopenia < 100000/ml)
- No or only mild (< 10%) marrow dysplasia
- Marrow blasts < 5%
- Presence of one or more MDS-related mutation(s)
- Clonality defined by mutation of myeloid disorder associated genes (including particularly DNMT3A, ASXL1, TET2, JAK2 and TP53 genes), with a VAF of between 2% and 30%

RECENT DEVELOPMENTS AND FUTURE DIRECTIONS

MOLECULAR DIAGNOSTICS AND INTEGRATED MODELS

Next Generation Sequencing (NGS) has revolutionized the diagnosis, prognostication and management of MDS, moving it from a morphologically defined syndrome to a molecularly-characterized neoplasm. It has become a standard of care integrated into the diagnostic workup suspected MDS.

- It has a utility in differentiating clonal MDS from non-clonal causes of cytopenia. The presence of a typical MDS-associated mutation with a high variant allele frequency (VAF) supports a clonal process.
- It can be helpful in defining specific entities by identifying certain mutations even with lower dysplasia thresholds.
- Identifying clonal hematopoiesis (CHIP/CCUS) in patients with cytopenias but insufficient dysplasia for MDS diagnosis, placing them on pre-MDS spectrum.
- Prognostic stratification by the Molecular International Prognostic Scoring System (IPSS-M) incorporates

data from up to 31 genes (plus blasts, cytogenetics, cytopenias). It has been helpful in reclassification in about 30% of patients compared to the older IPSS-R with half upgraded and half downgraded in risk. In addition it provides a more precise estimate of survival and AML progression risk.

- Some mutations have been linked with prognostic implications and grouped as:
 - ❖ Adverse: TP53 (multi-hit especially poor), FLT3, ASXL1, RUNX1, U2AF1(Q157), EZH2, STAG2.
 - ❖ Neutral/Favourable: SF3B1 (sole mutation in low-blast disease correlates with better outcome and ring sideroblasts), TET2, DNMT3A (often seen in CHIP).
- Therapeutic Guidance and Target identification:
 - Informing treatment choice: In del(5q) MDS it can help in confirming eligibility for lenalidomide.
 - RS-positive MDS-SF3B1 mutation predicts higher response to luspatercept.
 - Higher risk MDS with presence of TP53 mutations especially with complex karyotype,

indicates poor response to standard hypomethylating agents (HMAs) and can steer towards early transplant consideration.

- By identifying actionable targets it helps in directing patients to targeted therapy trials or approved agents for overlapping AML indications: IDH1/IDH2 mutations (ivosidenib, enasidenib), FLT3 mutations-FLT3 inhibitors, NPM1/BCOR help assess AML-like features.
- Serial NGS can track clonal evolution and emergence of new often more aggressive subclones which herald progression or transformation to AML. In addition changes in VAFs in response to treatment and therapy related clonal selection can be detected. VAF provide an estimate of clonal burden.
- Limitations: cannot detect all structural variants or copy-number changes and must be paired with karyotyping and FISH.
- In future NGS can play a role in monitoring minimal residual disease (MRD) in the form of trackable markers after treatment and prediction of relapse. The knowledge at molecular level has a tremendous utility in monitoring, early intervention and designing intelligent, personalized therapeutic regimens that can alter the natural history of disease by targeting the underlying malignant clone along its evolution.
- Current role of NGS is embedded in clinical practice for diagnosis, risk stratification and therapeutic decision making

TREATMENT: SUPPORTIVE CARE AND RISK-ADAPTED MANAGEMENT

Therapy is becoming Risk and Biology Adapted.

- Lower-risk MDS: Focus is on improving cytopenias and quality of life (ESAs, luspatercept for RS+, lenalidomide for del 5q).
- Higher-Risk MDS: Goal is to alter natural history and delay AML transformation (HMAs, venetoclax combinations, clinical trials, allo-SCT)
- Precision Medicine is a reality for subsets (IDH, FLT3 inhibitors, TP53 focused strategies)

The treatment for MDS includes:

- Observation of blood cell counts
- Transfusions and iron chelation therapy (drugs which removes excess iron in the body)
- Erythropoiesis-stimulating agents and other growth factors:
- Erythropoietin (EPO), & Growth Factors- epoetin alfa, darbepoetin alfa, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF),
- Antithymocyte globulin (ATG) therapy

- Drug therapy- azacytidine, decitabine, lenalidomide, imatinib mesylate
- Chemotherapy- cytarabine (cytosine arabinoside, ara-C) idarubicin, daunorubicin, mitoxantrone.

EMERGING AND INVESTIGATIONAL THERAPIES

Targeted treatments (such as splicing modulators and TP53 reactivators^{51,52})

- I. Targeting the ineffective Erythropoiesis Pathway
- II. Hypomethylating agents (HMA) Developments:
- III. Immune and microenvironment Targeting:
- IV. Precision Medicine Approaches

Evolving Understanding of MDS/AML Continuum : Platelet Growth Factors-Romiplostim and eltrombopag are agents being investigated. The following list includes examples of drug combinations and single-agent drugs under study. Clofarabine is a drug approved to treat childhood relapsed or refractory acute lymphoblastic leukemia (ALL). It is being studied when given in combination with AML-type chemotherapy. Rigosertib, a drug that increases MDS cell death, is being studied with intermediate-1-, intermediate-2- or high-risk patients as a single agent. It is also being studied in phase 3 trials with early data suggesting effectiveness in patients whose MDS has stopped responding to other drugs. Ezatiostat, a glutathione S-transferase P1-1 inhibitor that activates the Jun-kinase pathway is being studied in lower-risk, transfusion-dependent patients as a single agent. Valproic acid, a histone deacetylase (HDAC) inhibitor, is being studied in combination with decitabine. Vorinostat, a histone deacetylase (HDAC) inhibitor, is being studied in combination with azacitidine. Azacitidine, in combination with lenalidomide, is being studied for higher-risk or transfusion-dependent patients.

Allogeneic Stem Cell Transplantation (allo-SCT)- Allogeneic stem cell transplantation is a high-risk procedure. It is largely limited to patients with high-risk MDS because of its significant death rates.

DIAGNOSTIC CHALLENGES AND FUTURE DIRECTIONS

- I. Distinguishing MDS from CHIP/CCUS and non-clonal cytopenias
- II. The role of the microenvironment
- III. Artificial Intelligence (AI)
- IV. Minimal Residual Disease (MRD)

The treatment landscape is rapidly moving beyond supportive care and hypomethylating agents. In this era of mechanism based therapy, agents having specific targeted pathways like ineffective erythropoiesis (luspatercept) and immune evasion, alongside a growing arsenal of targeted drugs for molecular

subsets. Looking forward, the challenges will involve earlier intervention in pre-malignant states and leveraging MRD monitoring and AI driven diagnostics. The relentless progress in unraveling the biology of MDS continues to translate into tangible hope for improved patient outcomes and quality of life.

Strengths

This review provides an integrated overview of myelodysplastic syndromes (MDS), covering their morphological features, molecular pathogenesis, diagnostic approaches, updated classification systems, prognostic assessment, and therapeutic strategies. A major strength is the discussion of the WHO fifth edition and International Consensus Classification (ICC), highlighting the increasing importance of genetically defined MDS entities. The review also explains the clinical relevance of molecular testing, including next-generation sequencing and the IPSS-M prognostic model, in disease classification and risk assessment. Furthermore, it discusses risk-adapted treatment approaches, emerging targeted therapies, and potential future applications of molecular monitoring, offering a broad perspective on the evolving diagnosis and management of MDS.

Limitations

This review has certain limitations. It is a narrative review based on a selective literature search rather than a systematic review or meta-analysis; therefore, the literature selection process may not have captured all relevant studies. The stated literature search covers the period from 2008 to 2022, which limits the inclusion of more recent evidence on molecular classification, prognostic models, and therapeutic developments. In addition, differences between the WHO and ICC classification systems may complicate direct comparisons across studies. The discussion of emerging therapies and future applications is descriptive, and the clinical effectiveness of some investigational approaches requires further validation through well-designed clinical trials.

CONCLUSION

MDS is best understood through an integrated assessment of clinical findings, peripheral-blood and bone-marrow morphology, cytogenetics, and molecular alterations. The WHO fifth edition and ICC provide complementary frameworks, and their differences should be described explicitly when classifying genetically defined disease. IPSS-R and IPSS-M can inform prognosis, but treatment decisions also depend on cytopenias, transfusion needs, comorbidities, molecular findings, patient preferences, and transplant eligibility. The review's literature search ends in 2022; its classification and treatment sections therefore require an updated search before the manuscript is presented as a current account of clinical practice.

Declarations

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ABBREVIATIONS

- CCUS, clonal cytopenias of uncertain significance;
- CHIP, clonal hematopoiesis of indeterminate potential;
- ICUS, idiopathic cytopenias of uncertain significance;
- IDUS, idiopathic dysplasia of unknown significance;
- MDS, myelodysplastic syndromes;
- VAF, variant allele frequency.
- ICC, International Consensus Classification;
- WHO, World Health Organization Classification
- IPSS, International prognostic scoring system
- MDS, Myelodysplastic syndromes;
- RS, Ring sideroblasts;
- RCUD, Refractory cytopenia with unilineage dysplasia;
- RCMD, Refractory cytopenia with multilineage dysplasia;
- MDS-MLD, MDS with multilineage dysplasia;
- MDS-SLD, MDS with single lineage dysplasia;
- MDS-EB, MDS with excess blasts;
- MDS-U, MSD, unclassifiable;
- RCC, Refractory cytopenia of childhood.
- AML, Acute myeloid leukemia.

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