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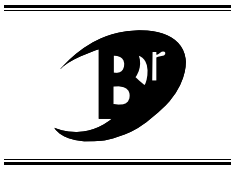

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**REVIEW**

# Myelodysplasic syndromes: A comprehensive review

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**Summary** Myelodysplastic syndromes (MDS) are a set of oligoclonal disorders of hematopoietic stem cells characterized by ineffective hematopoiesis that manifest clinically as anemia, neutropenia, and/or thrombocytopenia of variable severity. The result often is transfusion-dependent anemia, an increased risk of infection or hemorrhage, and a potential to progress to acute myelogenous leukemia (AML). Although progression to acute leukemia can lead to death in patients with MDS, many deaths are consequences of cytopenias and marrow failure in the absence of transformation. Approximately 2/3 of patients succumb to the disease within 3—4 years after presentation, and individuals with high-risk MDS generally survive about 1 year. Given that the disease is more prevalent in the elderly who often have comorbid conditions, the current treatment of MDS consists mainly of supportive care. Curative treatments are restricted to younger, healthy individuals with histocompatible (HLA)-matched donors for allogenic transplant or those able to undergo intensive chemotherapeutic regimens. However, understanding of the pathophysiology of MDS and identification of potential cellular and molecular targets in recent years has led to novel therapeutic approaches. Encouraging results using these heterogeneous therapeutic approaches alone or in combination in Phase I and II trials, have, in turn, called into question previous classification systems and have confirmed the need for an all-encompassing molecular, diagnostic and prognostic staging system.


## Background

### Epidemiology

The incidence of MDS varies from 2.1 to 12.6 cases per 100,000 population per year, but approaches 50

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cases per 100,000 per year in persons over age 70.[1–3] Prevalence is estimated to be 55,000 patients in the United States. The median age of patients is between 60 and 70 years with a male predominance. The increased incidence of MDS has been attributed to an improvement in geriatric medical care and diagnosis as well as to a general aging of the population.[1]

### Etiology

Several risk factors have been implicated in the etiology of MDS, including age, male gender, alcohol, cigarette smoking, ionizing radiation, immunosuppressive therapy, viral infection, benzene and other environmental/occupational exposures.[4–8] These risk factors are seen infrequently and are estimated to account for disease in only 20–30% of patients, who are often described as having secondary MDS.[4] The remainder of idiopathic cases constitute primary MDS. The major subset of secondary MDS is therapy-related MDS (t-MDS) that is increasingly frequent in patients previously treated with chemotherapy and/or radiotherapy.[8,215] In general, t-MDS usually presents as high-risk disease that frequently progresses to AML, and is associated with a poor prognosis regardless of therapy.

## Diagnosis

### Clinical presentation

The disease usually presents as a result of marrow failure in one or more cell lines.[9] Symptoms of fatigue, pallor, exertional dyspnea, infection, bleeding, or bruising are the most common. The diagnosis may be suggested by hematologic abnormalities, commonly macrocytic anemia, found on routine laboratory evaluation. Extramedulary involvement (lymphadenopathy, hepatosplenomegaly) is infrequent and more common in chronic myelomonocytic leukemia (CMML).[10–12] It has been estimated that up to 10% of patients may experience various autoimmune features,[13–16,216] such as vasculitis, and leukemia infiltration to the hypothalamo-neuropophyseal system presenting as diabetes insipidus has been described.[17]

### Marrow and peripheral blood morphological evaluation

Bone marrow aspiration and biopsy are critical to the diagnosis of MDS. In general, the marrow is normo- or hypercellular. However, up to 20% of MDS patients have hypocellularity making it difficult to distinguish from aplastic anemia (AA) or paroxysmal nocturnal hematuria (PNH).[18] Morphologic abnormalities in the blood and bone marrow have been documented in MDS.[9,19,20]

### Differential diagnosis

Other causes of marrow dysplasia including deficiencies of folate and vitamin B12, viral infections (e.g., HIV), antibiotics, cytotoxic chemotherapies, benzene, ethanol, or lead should be ruled out. These are associated with transient findings that resolve upon removing the offending agent or treating the vitamin deficiency.[9,21]

### Other diagnostic tests

Advances in flow cytometry, high-resolution and subtelomeric comparative genomic hybridization array, fluorescence in situ hybridation, polymerase-chain-reaction and chromosome painting have provided means to identify specific genetic abnormalities and help diagnose MDS in certain cases, such as differentiating hypoplastic MDS from AA/PNH.[1,22,217–222] These modalities have also been used to determine the pathogenesis of MDS.

## Pathophysiology

A multistep sequence for the development of MDS has been proposed as a model of pathogenesis.[23–24] The interplay of clonal cytogenetic abnormalities of marrow cells within an abnormal bone marrow microenvironment may allow for a predominant dysplastic clone to be established.[9,23–26,223,224]

### The bone marrow microenvironment

The initial stages of MDS are defined by excessive apoptosis of progenitor cells that leads to ineffective hematopoiesis and is counterbalanced by increased proliferation of hematopoietic elements.[23] The result is a paradoxical finding of peripheral blood cytopenias and normo/hypercellularity in the bone marrow.[27] Proliferative abnormalities may be an intrinsic property of the neoplastic clone or may relate to autocrine and/or paracrine cytokine interaction.[28] Mesenchymal cells in the marrow have been implicated in playing a role.[226,227]

Apoptotic mechanisms control erythropoeisis under normal physiologic conditions.[29] There are