Hematologic Malignancies

H. Joachim Deeg · David T. Bowen
Steven D. Gore · Torsten Haferlach
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Myelodysplastic Syndromes

Second Edition

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Part I

Epidemiology and Clinical Presentation

Clinical Presentation and Differential Diagnosis

1

Bart L. Scott

1.1 Clinical Presentation

The most frequent presenting symptom is fatigue, and the majority of patients have a macrocytic anemia at time of diagnosis (Sekeres et al. 2008). Large retrospective series have indicated that most patients do not have leukopenia or thrombocytopenia at time of presentation (Greenberg et al. 1997). However, there are some patients who do present with recurrent infections and easy bruising and bleeding events. Upon further questioning frequently, a prolonged history of symptomatic anemia can be elicited; however, there are a few patients who present with isolated thrombocytopenia or leukopenia. Few patients have circulating peripheral myeloblasts at time of presentation. Splenomegaly as a presenting sign in MDS is rare and should result in alternative diagnostic considerations such as myeloproliferative neoplasms (MPNs) or MDS/MPN overlap.

1.2 Diagnosis

The diagnosis of MDS is based upon the World Health Organization (WHO) criteria (Table 1.1) (Vardiman et al. 2009). The WHO classification is helpful for determining prognosis (Malcovati et al. 2005) and in selection of therapy (Howe et al. 2004). Despite advancements in classification schemata, there is often discordance among pathologists in diagnosing lesser degrees of dysplasia (Naqvi et al. 2011). In a patient survey, the diagnosis of MDS was delayed on average for 3 years after initial presentation with a hematologic abnormality (Sekeres et al. 2011). The diagnosis of MDS is one exclusion as there are other disorders such as acute myeloid leukemia and myeloproliferative neoplasms which can result in dysplastic changes within the bone marrow. The suggested diagnostic workup is summarized in Table 1.1 (Greenberg et al. 2011).

1.2.1 Differential Diagnosis

Vitamin deficiencies such as folate and vitamin B12 can cause a megaloblastoid anemia with evidence of bone marrow dysplasia; therefore, testing for these vitamin deficiencies is considered a standard part of the evaluation of patients with macrocytic anemia. In addition, copper deficiency

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Table 1.1 Suggested evaluation of MDS

History and physical examination
Complete blood cell count with differential
Reticulocyte count
Bone marrow aspiration with iron stain and biopsy
Cytogenetic testing by karyotype analysis
Serum erythropoietin level
RBC folate, serum B12
Serum ferritin, iron, total iron-binding capacity
Transfusion history
Thyroid-stimulating hormone
Helpful in some clinical situations
Flow cytometry of bone marrow
HLA typing if stem cell transplant candidate
HLA-DR 15 typing if immunosuppressive therapy considered
Jak 2 mutation analysis in patients with thrombocytosis (RARS-T)
Copper level in patients with bone marrow myeloblasts <5 %

Adapted from NCCN Guidelines version 2.2013

has been recently noted to lead to peripheral cytopenias and dysplastic changes within the bone marrow (Gregg et al. 2002; Huff et al. 2007). Excessive alcohol use has also been associated with a macrocytic anemia and dysplastic changes within the marrow. Endocrine abnormalities such as hypothyroidism may result in a macrocytic anemia. There are certain genetic disorders that are associated with the development of MDS such as Fanconi Anemia and dyskeratosis congenita. Therefore, genetic screening may be warranted in certain clinical situations such as a positive family history or young age at diagnosis. Hypoplastic MDS can be difficult to distinguish from aplastic anemia as there are few cells present within the marrow to be analyzed for the presence of dysplasia; cytogenetic testing and measurement of CD34-positive cells by flow cytometry or immunohistochemistry is particularly useful in this situation (Orazi et al. 1997). Testing for paroxysmal nocturnal hemoglobinuria should be considered in patients with early stage MDS as these disorders may coexist (Dunn et al. 1999). Additionally, it is acknowledged that MDS patients with a PNH clone are more likely to respond to immunosuppressive therapy (Wang et al. 2002).

1.2.2 Laboratory Features

MDS are disorders of blood; therefore, assessment is focused on hematologic analyses (Table 1.2). A complete blood count with examination of peripheral blood smear and platelet count is standard if MDS is suspected, particularly when looking for enlarged erythrocytes (treating with replacement therapy to rule out folate or vitamin B12 deficiency) or peripheral blasts. Measures for serum iron, total iron-binding capacity, ferritin, and folic acid are also recommended to evaluate for other potential causes of anemia, and lactate dehydrogenase (LDH), haptoglobin, reticulocyte count, and Coombs' tests are needed to rule out an underlying hemolytic process. Serum copper levels should also be tested in any patient with a suspicion of MDS and less than 5 % myeloblasts with a normal karyotype. Copper deficiency has become an increasingly recognized cause of cytopenias with marrow dysplasia (Gregg et al. 2002; Huff et al. 2007). A baseline serum erythropoietin value should be determined prior to the initiation of any growth factor therapy and preferably prior to initiation of red blood cell transfusion support (Hellstrom-Lindberg et al. 2003). Examination of the peripheral blood smear is a central part of the diagnosis of MDS and usually shows a macrocytic or normocytic anemia. Additionally, hypochromic changes, poikilocytosis, and anisocytosis are frequently observed. Abnormalities may be observed within the granulocytic lineage such as the pseudo-Pelger-Huët anomaly and hypogranulation. Thrombocytopenia is present at diagnosis in a minority of patients with MDS (Garcia-Manero et al. 2008). Certain subtypes of MDS are associated with an increased platelet count (del 5q). Morphologic abnormalities observed include enlarged platelets with poor granulation.

1.3 Bone Marrow Examination

Bone marrow evaluation is crucial to establish the diagnosis of MDS. In fact, a final diagnosis must be confirmed based on morphologic criteria available only from marrow examination. Marrow features play a role in treatment planning as well.

Table 1.2 WHO diagnostic classification of Myelodysplastic Syndromes (Vardiman et al. 2009)

Disease	Blood findings	BM findings
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia[a] No or rare blasts (<1 %)[b]	Unilineage dysplasia: ≥10 % of the cells in one myeloid lineage <5 % blasts <15 % of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥15 % of erythroid precursors are ring sideroblasts Erythroid dysplasia only <% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1 %)[b] No Auer rods <1 × 10⁹/L monocytes	Dysplasia in ≥10 % of the cells in ≥2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5 % blasts in marrow No Auer rods ±15 % ring sideroblasts
Refractory anemia with excess blasts-1 (RAED-1)	Cytopenia(s) <5 % blasts[b] No Auer rods <1 × 10⁹/L monocytes	Unilineage or multilineage dysplasia 5–9 % blasts[b] No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5–19 % blasts[c] Auer rods ± [a] <1 × 10⁹/L monocytes	Unilineage or multilineage dysplasia 10–19 % blasts[c] Auer rods ± [a]
Myelodysplastic syndorme—unclassified (MDS-U)	Cytopenias <1 % blasts[b]	Unequivocal dysplasia in <10 % of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS (see Table 1.3) <5 % blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (<1 %)	Normal to increased megakaryocytes with hypolobated nuclei <5 % blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[a]Bicytopenia may occasionally be observe. Cases with pancytopenia should be classified as MDS-U
[b]If the marrow myeloblast percentage is <5 % but there are 2–4 % myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1 % myeloblasts in the blood should be classified as MDS-U
[c]Cases with Auer rods and <5 % myeloblasts in the blood and less than 10 % in the marrow should be classified as RAEB-2. Although the finding of 5–19 % blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have <5 % blasts in the blood if they have Auer rods or 10–19 % blasts in the marrow or both. Similarly, cases of RAEB-2 may have <10 % blasts in the marrow but may be diagnosed by the other two findings, Auer rod + and/or 5–19 % blasts in the blood

For instance, a bone marrow biopsy is the only means to measure cellularity, which can influence the selection of therapy. The majority of patients with MDS have a hypercellular marrow; however, normocellular and hypocellular marrows have been observed (Tuzuner et al. 1995). The presence of marrow fibrosis has a negative impact on prognosis (Buesche et al. 2008), and fibrosis can only be assessed by obtaining a bone marrow biopsy. A marrow aspirate can be examined for evidence of hematopoietic cell maturation abnormalities, excessive marrow blasts (>5 %), and the presence of iron suggestive of ring sideroblasts, and the sample can be used for testing in flow

cytometry, cytogenetics, and fluorescence in situ hybridization testing as well. The presence of at least 10 % of the cells of a specific myeloid lineage (erythroid, granulocytic, or megakaryocytic) should show evidence of dysplasia in order to confirm the diagnosis of MDS. A presumptive diagnosis of MDS may be made by the presence of recurrent cytogenetic abnormalities as discussed below.

1.4 Cytogenetic Analysis

The WHO diagnostic schema now includes the presence of recurrent cytogenetic abnormalities as presumptive evidence of MDS even in the absence of significant dysplasia (Table 1.3) (Vardiman et al. 2009). Cytogenetic studies are important in determining treatment expectations and can be helpful in determining the most appropriate therapy. For example, patients with deletion 5q are well known to have increased response rates when treated with lenalidomide (List et al. 2006). In addition, specific cytogenetic changes are suggestive of patient prognosis (Schanz et al. 2011). Some mutations have been shown to predict disease progression whereas other genetic derangements may suggest sensitivity to specific medications. The reliability and prognostic significance of cytogenetic analyses have been documented in a multicenter analysis (Haase et al. 2007). The investigators reported that among 2,124 patients in Austria and Germany on whom they carried out cytogenetic testing, 97.6 % were successfully analyzed. They also observed that about half of the subjects had normal genetic profiles, but cytogenetic profiles allowed for the separation of the rest of the subjects into good, intermediate, or poor prognostic categories. The WHO diagnostic system has been revised to include certain cytogenetic changes such as del 5q. The importance of cytogenetic changes in determining prognosis has been emphasized in newer prognostic models (Schanz et al. 2012). It should be noted that t(8;21), inv(16), t(16;16), and t(15;17) would classify a patient as having AML regardless of the myeloblast percentage and occurrence of dysplasia.

Table 1.3 Recurrent chromosomal abnormalities considered sufficient for a presumptive diagnosis of MDS even in the absence of significant dysplasia (Vardiman et al. 2009)

Unbalanced abnormalities	Balanced abnormalities
−7 or del(7q)	t(11;16)(q23;p13.3)
−5 or del(5q)	t(3;21)(q26.2;q22.1)
i(17q) or t(17p)	t(1;3)(p36.3;q21.1)
−13 or del(13q)	t(2;11)(p21;q23)
del(11q)	inv(3)(q21q26.2)
del(12p) or t(12p)	t(6;9)(p23;q34)
del(9q)	
indic(X)(q13)	

Complex karyotype (three or more chromosomal abnormalities) involving one or more of the above abnormalities

1.5 Flow Cytometry

Flow cytometry is emerging as a prominent diagnostic and prognostic test in MDS. Flow cytometry is particularly useful in patients with hypoplastic MDS as it provides an accurate measurement of CD34+ cells and myeloid dyspoiesis which can be helpful to distinguish hypoplastic MDS from aplastic anemia. In addition, flow cytometry of the peripheral blood is the preferred diagnostic tool for PNH. With flow cytometry, multiple myeloid and monocytic antigens can be measured to look for abnormalities in hematopoietic development (Wells et al. 2003). These antigenic aberrancies have been used to develop a flow cytometric scoring system which has been validated in the transplant (Scott et al. 2008) and non-transplant setting (van de Loosdrecht et al. 2008). Additionally, flow cytometry is helpful as a diagnostic tool (Stetler-Stevenson et al. 2001). This is particularly relevant in patients with hypoplastic MDS where there is a low cellularity within the marrow which precludes an accurate assessment of dysplasia by morphology. Another advantage of flow cytometry is the ability to detect small quantities of disease burden known as minimal residual disease (MRD). Patients with MDS who have evidence of MRD pre-transplant are known to be at a higher risk of relapse following stem cell transplantation (Scott et al. 2008). Ultimately, this technology may prove useful in monitoring response to therapy and subsequently

altering treatment choices at earlier time points leading to improved outcomes.

1.6 Summary

MDS is a collection of disorders resulting in low blood counts and a propensity to progress to AML. The most common presentation is fatigue with a macrocytic anemia. The differential diagnosis is broad and requires the collaborative efforts of an experienced hematologist and hematopathologist. A careful history and physical examination is necessary to exclude other potential causes of a macrocytic anemia. Presentations with isolated neutropenia or thrombocytopenia are unusual but have been reported. A comprehensive diagnostic workup includes examination of a peripheral blood smear, bone marrow aspirate, and bone marrow biopsy. Cytogenetic testing is useful from a diagnostic and prognostic perspective and should be performed in all patients who have marrow examinations done to evaluate cytopenias. Newer techniques such as flow cytometry are being incorporated into diagnostic and prognostic schemes. Although our diagnostic tools have improved, a clinical suspicion of MDS in general is necessary to avoid delays in appropriate diagnosis and institution of treatment.

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Epidemiology and Etiology

2

Anneclaire J. De Roos

2.1 Introduction

Epidemiology seeks to describe patterns of disease according to demographic factors and other exposures, thereby elucidating etiologic factors (causes of disease) and predictors of prognosis (such as survival). Epidemiologic research of MDS has been fairly limited in comparison to other hematopoietic cancers (such as acute myeloid leukemia (AML)), no doubt due to difficulty in case-finding from a historical lack of reporting of MDS in cancer registries. The *International Classification of Diseases for Oncology* listed MDS as malignant for the first time in its 3rd edition in 2000 (ICD-O-3) (Fritz et al. 2000), thereby spurring registration of MDS in cancer registries worldwide. As a result, population-based data have been more readily available in the past decade for identifying MDS cases and describing the epidemiology of MDS, and the amount and quality of published studies on MDS have since increased. Nevertheless, the field continues to encounter challenges due to changing case definitions and likely incomplete case identification.

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2.2 Descriptive Epidemiology

2.2.1 Incidence

MDS incidence rates have been described in several reports in the past decade, since the ICD-O-3 classification of MDS as malignant (Fritz et al. 2000), making MDS a reportable cancer in registries worldwide. Prior to that time, incidence rates were described within hospitals or regions that had historically close cancer surveillance. Estimated incidence rates of MDS in the USA from cases registered in the Surveillance, Epidemiology and End Results (SEER) and North American Association of Central Cancer Registries (NAACR) programs are reported as 3.3–3.4 per 100,000 person-years (PY) (Ma et al. 2007; Rollison et al. 2008). These estimates are quite similar to rates reported in Europe and other regions (Table 2.1, all per 100,000 PY) such as the UK (3.8) (McNally et al. 1997), England (3.5) (Phekoo et al. 2006), Germany (2.5) (Neukirchen et al. 2011), Sweden (3.6) (Radlund et al. 1995), New Zealand (3.7) (Rodger and Morison 2011), and Australia (3.2) (Rodger and Morison 2011). Rates are not always perfectly comparable across studies due to differing MDS case definitions (e.g., inclusion of different histologies). The US studies (Ma et al. 2007; Rollison et al. 2008) classified MDS according to the ICD-O-3 (Fritz et al. 2000), which includes refractory anemia (RA, ICD-O-3 9980); refractory anemia with sideroblasts (RARS, ICD-O-3 9982); refractory anemia with excess blasts (RAEB, ICD-O-3

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Table 2.1 Incidence rates of myelodysplastic syndromes (MDS) reported in peer-reviewed published studies

Reference	Region	Period	Population	Case-finding	Classification	Standardization	Incidence (per 100,000/year)
Radlund et al. (1995)	Sweden (Jönköping)	1978–1992	310,000	Local surveillance	FAB	European standard population	3.6
Maynadie et al. (2011)	France (Côte d'Or, Burgundy Region)	1980–2004	467,998–512,272	Specialized local registry of hematologic malignancies, established in 1980	WHO	World standard population	1.3
Williamson et al. (1994)	UK (Bournemouth)	1981–1990	203,000–226,000	Specialized registration of cases diagnosed in a local hospital, with "strenuous efforts to document new cases by adopting a low threshold for performing marrow examination in those with suggestive peripheral blood findings"	FAB	Unstandardized	12.6
McNally et al. (1997)	UK	1984–1993	11–16 million	Specialized registry of the Leukemia Research Fund	FAB	Uniform standard population	3.8
Bauduer et al. (1998)	France (French Basque Country)	1993–1996	290,000	Centralized review of bone marrow slides from one hospital serving the entire region	FAB	Unstandardized	7.7
Neukirchen et al. (2011)	Germany (Düsseldorf)	1996–2005	575,000	Centralized review of bone marrow slides from private physicians and hospitals serving the region	WHO and FAB	European standard population	2.5 (WHO) 3.2 (FAB)
Phekoo et al. (2006)	England (South Thames)	1999–2000	5,499,841	Local registration	FAB	European standard population	3.5
Sant et al. (2010)	Europe (Northern, Central, Southern, Eastern)	2000–2002	89 million	EUROCARE network cancer registries	WHO	Unstandardized	1.8
Ma et al. (2007)	USA	2001–2003	76 million	Surveillance, Epidemiology and End Results (SEER) registry	ICD-O-3	US standard population	3.4
Rollison et al. (2008)	USA	2001–2003	240 million	North American Association of Central Cancer Registries (NAACR)	ICD-O-3	US standard population	3.3

Irwin et al. (2011)	New Zealand (Wellington)	2002–2007	448,956	Review of all bone marrow biopsies performed at Wellington Hospital and a local private pathology laboratory	WHO	Unstandardized	2.7
De Roos et al. (2010a)	USA (Seattle, WA)	2005–2006	350,000	Members of a nonprofit healthcare system with MDS confirmed through SEER registry or chart review	ICD-O-3	US standard population	7.0
Rodger and Morison (2011)	New Zealand	2005–2007	4,200,000	New Zealand Cancer Registry	WHO	World standard population	3.7
Rodger and Morison (2011)	Australia	2005–2007	21 million	Australian Cancer Incidence and Mortality workbooks	WHO	World standard population	3.2

9983); refractory anemia with excess blasts in transformation (RAEB-t, ICD-O-3 9984); refractory cytopenia with multilineage dysplasia (RCMD, ICD-O-3 9985); MDS with 5q deletion (5q− syndrome, ICD-O-3 9986); therapy-related MDS, not otherwise specified (NOS) (t-MDS, ICD-O-3 9987); and MDS, NOS (MDS-U, ICD-O-3 9989). MDS case classification according to the World Health Organization (WHO) revision (adopted in 2001) does not include RAEB-t but rather classifies it as AML (Jaffe 2001). The WHO classification also excludes MDS patients who have had previous chemotherapy. Several of the studies using the WHO classification reported somewhat lower rates, including those from France (1.3 per 100,000 PY) (Neukirchen et al. 2011) and throughout Europe (1.8) (Sant et al. 2010). Several of the European incidence studies, particularly before the year 2000, included chronic myelomonocytic leukemia (CMML) (Bauduer et al. 1998; McNally et al. 1997; Phekoo et al. 2006; Williamson et al. 1994), as defined under the previously used French-American-British (FAB) cooperative group classification system (Bennett et al. 1982); CMML is classified in a myelodysplastic/myeloproliferative neoplasm overlap category by WHO (Jaffe 2001). Rates also differ importantly based on methods of standardization; several rates reported in Table 2.1 are crude (unstandardized) rates (Bauduer et al. 1998; Irwin et al. 2011; Williamson et al. 1994), which do not account for differing age distributions between different regions. Use of the world standard population versus the European or US standard population can also affect results, as the world standard population has a younger age distribution than the European or US alternatives.

Regardless of the methods of rate estimation, MDS incidence increases sharply with age, with a median age at diagnosis in the 70s in the US and European populations (Ma et al. 2007; Neukirchen et al. 2011; Phekoo et al. 2006; Sekeres et al. 2008). Younger median age at diagnosis, typically in the 50s, has been observed in several Eastern countries, such as Japan (Kuendgen et al. 2007), China (Chen et al. 2005), Central Africa (Mukiibi and Paul 1994), and Jordan (Awidi et al. 2009), suggesting different histologies or exposures in these regions compared to Western countries. MDS is more common in men than women, except for the subtype with 5q deletion (Maynadie et al. 2011; Neukirchen et al. 2011). The male excess is most prominent among ages 50 and older. A detailed analysis of the male-to-female MDS incidence ratio in the UK revealed a U-shaped pattern, with a male excess until age 15 (ages at which MDS is extremely rare), a female excess in ages 30–50, and a male excess increasing prominently after age 50 (Cartwright et al. 2002). A similar pattern was observed for most acute myeloid leukemia (AML) and myeloproliferative disease (MPD) subtypes, suggesting a shared etiology. MDS is more common among whites and non-Hispanics than among other racial/ethnic groups in the USA (Ma et al. 2007; Rollison et al. 2008), and American Indians/Alaska Natives have the lowest rates in the USA (Ma et al. 2007). In contrast, higher rates were reported in New Zealand Maoris (4.9 per 100,000) than non-Maori ethnicities (3.7 per 100,000) (Rodger and Morison 2011). A study conducted in Japan suggests lower MDS incidence than in Western countries (Shimizu et al. 1995), and similarly, Asian Americans/Pacific Islanders in the USA have lower rates than US whites (Ma et al. 2007). Any changes in MDS incidence over time have been difficult to establish and when observed have been generally attributed to changes in diagnostic practices and reporting (Germing et al. 2004). In studies that reported MDS incidence by subtype, RA has usually been the most frequently diagnosed type, followed by RARS and RAEB (Bauduer et al. 1998; Ma et al. 2007; McNally et al. 1997). However, reclassification of many previously defined RA as RCMD under the WHO classification has resulted in RCMD as the most common subtype in recent studies (Irwin et al. 2011; Neukirchen et al. 2011). Declarative subtype distributions have been impossible to establish in the US registry-based studies, as approximately half of all cases registered in SEER and NAACR are classified as MDS-U (Rollison et al. 2008). CMML is quite common in the studies that included it under the FAB classification, with frequency ranging from 11 % in the French Basque

region (Bauduer et al. 1998) to 31 % in Bournemouth, UK (Williamson et al. 1994).

It is now recognized that MDS incidence is probably underestimated due to a combination of factors including incomplete case registration and underdiagnosis. There are several lines of evidence suggesting incomplete case registration. Incidence rates vary widely between different regions – between US SEER registries, from 3.0 (per 100,000 PY) in metropolitan Atlanta to 6.6 in the Seattle-Puget Sound region from 2001 to 2008 (2011), and between EUROCARE network European cancer registries, from 0.27 in Eastern Europe to 2.1 in the UK and Ireland from 2000 to 2002 (Sant et al. 2010). Differential reporting practices likely play a role in the geographic discrepancies, although true differences in incidence between regions are also possible. Differential completeness in reporting by registries may occur because of differing case-finding and validation methods (e.g., passive vs. active case-finding). For example, patients who are diagnosed outside of a hospital setting are likely to be missed. This may be illustrated by the fact that only 4 % of cases registered in NAACR (encompassing 82 % of the US population) were reported by physicians' offices, as opposed to hospitals or laboratories (Rollison et al. 2008). A recent US study identified incident MDS patients from Medicare records using an algorithm requiring two claims with an MDS-relevant diagnosis code in addition to ordering of typical diagnostic tests for MDS, specifically blood counts and bone marrow biopsy or aspiration (Cogle et al. 2011). The algorithm had high specificity (99.8 %) and moderate sensitivity (78.1 %) when compared to SEER-identified cases as the gold standard. MDS incidence was much higher using the Medicare algorithm than it was based on SEER-reported cases, with rates among persons 65 years and older of 75 (per 100,000 PY) versus 20, respectively (Cogle et al. 2011). These results suggest that patients diagnosed in the outpatient setting are frequently not reported to SEER.

Underdiagnosis likely also contributes to underestimation of MDS incidence. Definitive diagnosis of MDS requires a bone marrow biopsy, and the fact that potential MDS patients may not undergo detailed work-up likely leads to underdiagnosis of the disease. The third National Health and Nutrition Examination Survey (NHANES) cross-sectional study in the USA identified 11.0 % of men and 10.2 % of women as anemic, with 5.8 % of the anemic population having unexplained anemia and peripheral blood features suggestive of MDS (macrocytosis, thrombocytopenia, or neutropenia) (Guralnik et al. 2004). A similar survey conducted in Italy found unexplained anemia with blood features of MDS in 8.1 % of the anemic elderly (Tettamanti et al. 2010). Underdiagnosis of MDS was also suggested by a study of patients enrolled in a health plan in Western Washington State, which found that half of all patients with new MDS diagnoses (definite/probable or possible cases) were not reported to SEER, and inclusion of all cases led to an overall incidence rate of 10.2 per 100,000 PY (De Roos et al. 2010a). The "possible" cases, identified by diagnosis code and corroborated by chart review, did not receive bone marrow biopsy. There was evidence that definitive diagnosis was less likely to be pursued in less severe cases, as "possible" cases had higher average hemoglobin levels, platelet counts, and white blood cells upon presentation than did SEER cases (De Roos et al. 2010a). A higher than typically reported rate of MDS was also found in a UK study that aimed for complete identification of MDS cases through periodic health examinations followed by pursuit of bone marrow biopsy in patients with suggestive blood findings (Williamson et al. 1994). The estimated (crude) incidence rate in the UK study was 12.6 per 100,000 person-years (including CMML but not including patients with previous chemotherapy or radiotherapy). These studies suggest that underdiagnosis contributes to underestimation of MDS incidence, probably due to less severe cases that typically do not receive diagnostic work-up.

2.2.2 Prevalence and Survival

There are an estimated 12,000 new MDS cases diagnosed per year in the USA and 20,000 in Europe, based on reported incidence rates

(Germing et al. 2008). MDS prevalence, or the number of persons living with the disease, was estimated as 7.2 per 100,000 persons in Germany, using the WHO classification in 2003 (Neukirchen et al. 2011). However, with such a wide range in incidence estimates (Table 2.1), prevalence is uncertain. Based on the NHANES study finding that 5.8 % of the anemic population had "unexplained anemia" with peripheral blood features suggestive of MDS (Guralnik et al. 2004), Sekeres estimated that this finding would translate to 170,000 persons living with MDS in the USA while acknowledging that this figure is likely an overestimate (Sekeres 2011). Nevertheless, current prevalence figures based only on registry-reported incidence rates are probably underestimates due to the issues of incomplete reporting and underdiagnosis described above (Sect. 2.2.1). Furthermore, MDS prevalence is expected to increase as the population in developed countries ages.

The number of prevalent cases is also dependent on survival following MDS diagnosis, which is generally poor. Median survival has been reported as 23–34 months (Irwin et al. 2011; Maynadie et al. 2011; Phekoo et al. 2006). Relative survival, which accounts for competing causes of death by age group, was reported as 47 % 2 years from diagnosis among US cases with MDS as their first primary cancer (Ma et al. 2007). Superior survival has been observed among women compared to men (Ma et al. 2007; Maynadie et al. 2011; Phekoo et al. 2006) and younger versus older patients (Ma et al. 2007; Phekoo et al. 2006). Several studies indicate longer survival among patients in Asian countries than in Western countries (Kuendgen et al. 2007). However, survival can vary widely by MDS subtype (Germing et al. 2008; Ma et al. 2007; Phekoo et al. 2006), in addition to cytogenetic abnormalities, blast counts, number of dysplastic lineages, and blood cell counts (Belli et al. 2002; Bowles et al. 2006; Germing et al. 2008; Greenberg et al. 1997; Haus et al. 2006), and the concept of overall survival has limited utility for individual patients. MDS prevalence will increase as therapies resulting in improved survival are developed and disseminated.

2.3 Disease Etiology

2.3.1 Therapy-Related MDS

Among the few known risk factors for development of MDS is prior cytotoxic therapy. MDS is sometimes termed "secondary" (vs. "primary" or de novo) if its diagnosis follows treatment with chemotherapy or radiation for any of a variety of diseases (but most frequently for cancer) or if following accidental exposure to ionizing radiation or benzene (discussed in Sect. 2.3.2.3). We will use the terms "therapy-related" and "de novo" MDS (instead of "secondary" and "primary," respectively), as use of the word "secondary" differs in the context of cancer registration (2000). Therapy-related myeloid neoplasms (t-MN) are defined by the WHO classification as one, heterogeneous entity that contains a composite of MDS, AML, and MDS/MPN (Vardiman et al. 2009). Sekeres et al. reported from a survey of 101 US physicians that 10 % of recently diagnosed MDS patients were considered to be therapy related based on recent chemotherapy, radiation therapy, or other chemical exposure (Sekeres et al. 2008). However, based on the fact that 26 % of newly diagnosed MDS patients reported in SEER from 2001 to 2006 had previous cancers (De Roos et al. 2007), previous cancer treatments may contribute to a greater proportion of newly diagnosed MDS than clinically recognized. The risk of developing t-MN differs greatly according to the type of the initial cancer. For example, up to 10 % of patients treated for lymphoproliferative neoplasm developed t-MN within 10 years, whereas approximately 0.55 % of breast cancer patients developed t-AML within 8 years (Leone et al. 2010). These differing risks are certainly due to varying cytotoxicities of treatment regimens as well as the underlying susceptibility for myeloid neoplasm of the patient group with the initial cancer (i.e., the same genetic profile may increase susceptibility to both lymphoproliferative and myeloid neoplasms).

Clinical observations suggest a worse prognosis for therapy-related MDS than for de novo MDS (Finch 2004; Levine and Bloomfield 1992;

Singh et al. 2007). Therapy-related MDS cases have been observed to be less responsive to treatment and evolve more frequently into AML (Finch 2004; Levine and Bloomfield 1992). Comparisons of histopathologic features of therapy-related and de novo MDS indicate biologic differences that may account for differences in clinical outcomes. Clonal chromosomal abnormalities are found in 40–50 % of patients with de novo MDS compared to up to 95 % of therapy-related MDS (Catenacci and Schiller 2005) (although it is notable that newer, more sensitive technologies detect such abnormalities in a larger proportion of de novo MDS (Tiu et al. 2011)). Additionally, the proportion of "high-risk" cytogenetics (e.g., deletions of chromosome 7 or complex karyotypes) is higher in therapy-related than de novo MDS (Bloomfield 1986; Rubin et al. 1990). Monosomy of chromosome 5 or deletion of 5q (−5/5q−) and/or monosomy of chromosome 7 or deletion of 7q (−7/7q−) is frequently associated with prior chemotherapy, in particular with alkylating agents (Leone et al. 2010). In contrast, no prototypical chromosomal patterns have been found for radiation-related myeloid neoplasms (Leone et al. 2010). Similar to clinical observations, an analysis of SEER data observed shorter survival for MDS patients who had a previous cancer diagnosis than for de novo cases and found that the increased risk was fairly constant throughout a 47-month period of follow-up after MDS diagnosis (De Roos et al. 2007). Shortened survival associated with previous cancer was most pronounced for MDS cases diagnosed within 5 years of the previous cancer diagnosis, although previous lymphoproliferative neoplasm was associated with shorter MDS survival even when MDS was diagnosed up to 20 years after the lymphoproliferative neoplasm diagnosis. Previous radiation treatment for cancer was an independent predictor of death in MDS patients, significantly so for MDS cases diagnosed between 5 and 10 years after irradiation (De Roos et al. 2007). These results suggest that previous cancer therapies may contribute to MDS etiology up to a decade or longer after treatment.

2.3.2 Lifestyle and Environmental Risk Factors for MDS

Few risk factors are known for MDS, aside from therapies for previous cancers and other conditions. Epidemiologic research to date has largely focused on smoking, alcohol consumption, and occupational exposures to solvents and alcohol. Epidemiologic studies of "lifestyle" (e.g., smoking, alcohol, obesity) and "environmental" (e.g., occupation, hobbies) risk factors for MDS are summarized in Table 2.2. Most studies have relied on convenience samples of MDS cases and controls, such as hospital patients. Because approximately one-third of MDS patients develop AML (Steensma and Bennett 2006), MDS was sometimes considered in the past as "preleukemia" or "aleukemia" in epidemiologic studies or was grouped with AML. Indeed, MDS may share risk factors with AML, as demonstrated by similar magnitude risks observed in the cohort of atomic bomb survivors in Hiroshima and Nagasaki, Japan, with significant excess risks of AML and MDS of 4.3 and 5.3 per 1 Gy dose of ionizing radiation, respectively (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation NRC 2006; Preston et al. 1994; Richardson et al. 2009). Nevertheless, aside from direct genotoxicity to the bone marrow, potential mechanisms of development of these myeloid cell neoplasms are not well understood, and there are also likely to be risk factors that are not shared between AML and MDS.

2.3.2.1 Lifestyle

Several lifestyle-related factors including smoking and alcohol consumption have been investigated as potential causes of MDS in multiple studies. However, the risks associated with these factors are as yet not well described in terms of etiologically relevant timing of exposure and histologic subtype-specific effects. Smoking has been significantly or nonsignificantly associated with increased risk in multiple studies (Bjork et al. 2009; Dalamaga et al. 2002; Ido et al. 1996; Ma et al. 2009; Mele et al. 1994; Nisse et al.

Table 2.2 Epidemiologic studies of lifestyle and environmental factors in relation to myelodysplastic syndromes (MDS)

Reference	Study design, region, and time period of case diagnosis	Study population	Data collection	Results[a]
Goldberg et al. (1990)	Hospital-based case–control study	52 de novo MDS cases recruited from hospital over undefined time period	Questionnaire with items about smoking, lifetime occupational history, and exposure to solvents, insecticides, and other chemicals through occupation and hobbies	*Solvents*
	USA (Philadelphia, PA)	52 controls from the same hospital (primary care and cardiology) and one of its affiliates, excluding those with previous cancer or blood dyscrasia, matched by age, sex, and socioeconomic group	"Significant" exposure defined as five or more contacts with these agents per lifetime	"Significantly" exposed: 20 % cases vs. 42 % controls ($p=0.9$); note that cases with prior benzene exposure were excluded from the study
	1976–not specified			*Pesticides* "Significantly" exposed: 71 % cases vs. 29 % controls ($p=0.002$)
Albin et al. (2003)	Population-based case–control study	330 MDS cases cytogenetically analyzed at the Department of Clinical Genetics, Lund	Telephone interview conducted in 1995–1997 with the study subject or next of kin (next-of-kin interviews were conducted for 88 % of cases and 26 % of controls), containing questions on smoking, lifelong occupation, specific job tasks, hobbies, and hair dye	*Solvents*
	Southern Sweden 1976–1993	337 population controls, matched by age, gender, and county of residence	Assessment of occupational and hobby exposures by an occupational hygienist	Exposed: OR = 1.4 (95 % CI = 0.9–2.2) Moderate or high exposure: OR = 0.8 (95 % CI = 0.3–1.9) Duration 15–20 years: OR = 1.2 (95 % CI = 0.7–2.0) Benzene: OR = 1.0 (95 % CI = 0.5–1.7) Chlorinated organic solvents: OR = 0.8 (95 % CI = 0.3–1.9) *Pesticides* Exposed: OR = 0.8 (95 % CI = 0.5–1.4) *Other significant associations* EMF occupational exposure, high: OR = 2.6 (95 % CI = 1.0–6.2)

Brown et al. (1990)	Population-based case–control study	63 cases of "myelodysplasia" from IA registry and from a special surveillance network of MN hospitals and pathology laboratories	In-person interview with questions on smoking, alcohol consumption, residential history, lifetime occupational history, and farming history	*Alcohol consumption*
Brown et al. (1992)	USA (IA and MN)	818 controls from random-digit dialing (ages <65) and Medicare (ages ≥65)	Assignment of occupational exposures by a job-exposure matrix	Any: OR = 1.6 (95 % CI = 0.9–2.7)
Blair et al. (2001)	1981–1984			Consumption >23 drinks/week: OR = 2.1 (95 % CI = 1.0–4.6) Beer or wine only: OR = 1.2 (95 % CI = 0.5–2.5) Liquor only: OR = 0.9 (95 % CI = 0.3–2.4) Other combinations: OR = 2.4 (95 % CI = 1.3–4.6) *Solvents* Benzene, high exposure: OR = 2.6 (95 % CI = 0.7–9.7) *Pesticides* Ever farmed: OR = 0.8 (95 % CI = 0.5–1.4) Farmed ≥45 years: OR = 0.5 (95 % CI = 0.2–1.4) Insecticides: OR = 0.6 (95 % CI = 0.3–1.1) Herbicides: OR = 0.7 (95 % CI = 0.3–1.5) Fungicides: OR = 0.7 (95 % CI = 0.2–3.2) *Other significant associations* Industrial groups Nonmetallic minerals, except fuels: OR = 5.9 (95 % CI = 1.2–30) Plumbing, heating, and air conditioning: OR = 4.0 (95 % CI = 1.1–15) Miscellaneous nondurable goods: OR = 4.7 (95 % CI = 1.1–20)

(continued)