Myelodysplastic syndrome (MDS) and Juvenile Myelomonocytic Leukemia (JMML)

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Classification - The FAB and WHO classifications

The French-American-British (FAB) cooperative group produced the first systematic attempt of a classification dividing myelodysplastic syndrome (MDS) into five subgroups: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML). Distinction among the subtypes was based on the proportion of blasts in the peripheral blood (PB) and bone marrow (BM) and the degree of monocytosis in the blood. The WHO classification of hematological malignancies incorporates clonal cytogenetic abnormalities and lowered the threshold for distinguishing acute myeloid leukemia (AML) from MDS from 30% to 20% of blasts in the BM.

Both the FAB and the WHO proposals were based on review of adult cases although the WHO classification recognizes juvenile myelomonocytic leukemia (JMML) as a separate entity. There are many differences between MDS in children and adults, e.g. RARS is exceedingly rare in children, and constitutional abnormalities are observed in a large fraction of children but very uncommon in adults. The 5q- syndrome is considered a unique entity in adults but has not been reported in children.

Current approach to the classification of childhood MDS

Internationally consensus has been achieved on the classification of MDS in childhood. Myelodysplastic and myeloproliferative disorders in children are separated into three main groups; MDS, JMML, and Down syndrome disease (Table 1).

Table 1: Diagnostic categories of myelodysplastic and myeloproliferative diseases in children

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>I. Myelodysplastic / Myeloproliferative Disease</td>
<td>- Juvenile myelomonocytic leukemia (JMML)</td>
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<tr>
<td>II. Down Syndrome (DS) Disease</td>
<td>- Transient abnormal myelopoiesis (TAM)</td>
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<td>- Myeloid leukemia of DS</td>
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<tr>
<td>III. Myelodysplastic Syndrome (MDS)</td>
<td>- Refractory cytopenia (RC) (PB blasts &lt;2% and BM blasts &lt;5%)</td>
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<td></td>
<td>- Refractory anemia with excess blasts (RAEB) (PB blasts 2-19% or BM blasts 5-19%)</td>
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<td></td>
<td>- RAEB in transformation (RAEB-t) (PB or BM blasts 20-29%)</td>
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MDS is subdivided into refractory cytopenia (RC), RAEB and RAEB-t. The classification is used for both de novo and secondary MDS. The change in nomenclature from RA to RC reflects that anemia is not a prerequisite for the diagnosis but only seen in about 50% and less frequent than neutropenia, thrombocytopenia and macrocytosis. It is suggested to retain the RAEB-t entity but to emphasize that the blast count is insufficient to differentiate AML from MDS.

Myeloid leukemia in children with Down syndrome has unique features and is kept separate as a distinct entity (please see below).

The Toronto group has published a descriptive system designed to assess children with MDS according to category, cytology and cytogenetics (CCC). The CCC system emphasizes the important characteristics of each patient but has an infinite number of possible
subgroups making it difficult to use in clinical practice or research.

The new pediatric modification of the classification emphasizes the clinical relevant subtypes of pediatric MDS and eliminates adult subtypes that are rare or unseen. However, we will still face borderline cases difficult to fit into the classification.

**Primary and secondary MDS**

MDS can arise in a previously healthy child and is conformingly named “de novo” or “primary”. It may also develop in a child with a known predisposing condition and referred to as “secondary”. Secondary MDS is seen in patients a) after chemo- or radiation therapy (therapy-related MDS), b) with inherited BM failure disorders, c) with acquired aplastic anemia and d) with familial MDS. It is to be recognized, however, that children with so-called “primary” MDS may have an underlying yet unknown genetic defect predisposing them to MDS at young age. Therefore, the distinction between primary and secondary disease may become arbitrary.

Myeloid neoplasias in patients with predisposing conditions share the biological characteristics of MDS regardless of the presenting blast count. The prognosis appears to depend primarily on the cytogenetic profile.

**Myeloid leukemia of Down syndrome**

Individuals with Down syndrome (DS) have a more than 50-fold increased risk of leukemia during the first five years of life, even after excluding the transient myeloproliferative disorder (TMD) indistinguishable from leukemia occurring in 10 % of newborns with DS. About half the leukemias in children with DS are myeloid often presenting with features of MDS.

Myeloid leukemia in children with DS occurs characteristically at 1-4 years of age with an excess of megakaryoblasts, and almost uniform presence of GATA1 mutation. In contrast to TMD, myeloid leukemia in older children is fatal if untreated but responds to AML treatment with a very favorable prognosis. The myeloid leukemia seen in young children with DS is unique and classified under the unifying term myeloid leukemia of DS (ML-DS). ML-DS is preferred to acute megakaryoblastic leukemia because other phenotypes are observed sharing the same biologic and clinical characteristics. It is no longer appropriate to use the terms MDS and AML in young children with DS.

**Epidemiology**

MDS and JMML are both uncommon in children and adolescents, each constituting less than 5% of all hematological malignancies. Using the pediatric WHO classification the annual incidence per million children 0-14 years of age is 1.8 of MDS, 1.2 of JMML, and 0.9 of myeloid leukemia of Down syndrome. There is an equal sex distribution in MDS and a median age at presentation of 6.8 years. JMML shows in contrast a very low age at onset (1.8 years) and a male predominance. Constitutional abnormalities are relatively frequent in both MDS and JMML. The most common abnormalities are listed in Table 2.

**Table 2: Abnormalities associated with JMML and MDS in children**

<table>
<thead>
<tr>
<th>Associated with JMML</th>
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<tr>
<td>Constitutional conditions</td>
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<tr>
<td>Neurofibromatosis type 1 (NF1)</td>
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<tr>
<td>Noonan syndrome</td>
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<tr>
<td>Trisomy 8 mosaicism</td>
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<table>
<thead>
<tr>
<th>Associated with MDS</th>
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<tr>
<td>Constitutional conditions</td>
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<tr>
<td>Congenital bone marrow failure</td>
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<tr>
<td>Fanconi anemia</td>
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<tr>
<td>Kostmann syndrome</td>
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<tr>
<td>Shwachman-Diamond syndrome</td>
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<tr>
<td>Blackfan-Diamond anemia</td>
</tr>
<tr>
<td>Trisomy 8 mosaicism</td>
</tr>
<tr>
<td>Familial MDS (at least one first degree relative with MDS/AML)</td>
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**Acquired conditions**

Prior chemotherapy/radiation
Aplastic anemia

**Diagnostics - MDS**

The two major diagnostic challenges are to distinguish MDS with a low blast count from aplastic anemia (AA) and other non-clonal BM disorders, and to differentiate MDS with excess
of blasts from AML. The traditional classification has been based on morphology but a number of additional factors need to be considered.

**Refractory cytopenia**

Myelodysplasia may occur in the BM in a variety of disorders of very different etiologies, e.g. infection, drug therapy, and chronic disease. Non-clonal disorders with dysplastic features, e.g. mitochondrial disorders like Pearson syndrome, should not be considered as MDS. It may be difficult to diagnose MDS in children who have a low blast cell count and no clonal marker. The proposed minimal diagnostic criteria may be helpful in this situation (Table 3).

**Table 3: Minimal diagnostic criteria for MDS**

At least 2 of the following:

- Sustained unexplained cytopenia (neutropenia, thrombocytopenia, or anemia)
- At least bilineage morphologic myelodysplasia
- Acquired clonal cytogenetic abnormality in hematopoietic cells
- Increased blasts (>5%)

Since hematopoiesis is often dysplastic in patients with congenital BM failure disorders, it is suggested diagnosing MDS in these patients only if the BM blast count is increased, a persistent clonal chromosomal abnormality is present or hypercellularity in the BM develops in the presence of persistent PB cytopenia.

RARS is extremely rare in children. The finding of sideroblastic anemia should prompt investigation for possible mitochondrial cytopathy or disorders of heme synthesis. A trephine biopsy of good quality is mandatory in the evaluation of a child with suspected AA or MDS. A careful search for morphological characteristics at diagnosis will often establish a distinction between the two entities. Hypoplastic MDS tends to show sparsely scattered granulopoietic cells, patchy islands of immature erythropoiesis and in most cases decreased megakaryopoiesis and in some micromegakaryocytes. Overexpression of p53 is suggestive of MDS.

**Refractory anemia with excess of blasts (RAEB) and RAEB in transformation (RAEB-T)**

RAEB is defined by a BM blast count between 5 and 20%. Auer rods are no longer a discriminator for classification. Patients with recurrent cytogenetic abnormalities typically associated with AML, e.g. t(15;17) (PML/RARalpha), t(8;21) (RUNX1/CBFA2T1), inv(16) (CBFB/MYH11), t(9;11) (MLL/MLLT3), should be diagnosed and treated as AML regardless of the blast count.

MDS and true de novo (TDN)-AML display significant differences in pathogenesis and natural course. The cytogenetic differences predicting response to therapy in MDS/AML may reflect the underlying biological nature of the disease. TDN-AML is a chemo-sensitive disease characterized by specific recurring translocations, whereas MDS and secondary AML is characterized by numerical chromosomal abnormalities and are typically resistant to chemotherapy. Patients with adverse cytogenetics have a poor response to therapy irrespective of the proportion of blasts in the BM and have been described as MDS-related AML (MDR-AML).

Monosomy 7 is the most common acquired abnormality in children with MDS. Children with monosomy 7 and MDS have an outcome similar to MDS patients without monosomy 7, whereas patients diagnosed as AML with monosomy 7 have a lower response rate to chemotherapy and a higher relapse rate compared with AML without –7. Monosomy 7 may be regarded as a marker of an MDS-like disease. The WHO classification suggested abolition of the category of RAEB-t including most of these patients as AML with multilineage dysplasia. The cut off point for diagnosis of AML was lowered from the traditional 30% to 20% blast cells. This distinction is clearly an arbitrary one and there must in practice be a continuum between RAEB and AML. There are no data to indicate whether a 20% blast cell cut off is useful in pediatrics. A British study suggested a better outcome following AML therapy in patients with RAEB-t compared with RAEB, however, this was not found in an American study. Until more data are available it is suggested maintaining the RAEB-t category in children.

It is important to recognize that any threshold of blast percentage to separate MDS from AML is
a surrogate marker for the underlying biological behavior of the disease. In patients with ambiguous blast count a more clinical relevant approach may be based upon clinical features, cytogenetics and serial assessment of the BM rather than predicting clinical behavior from a single examination.

**JMML**

JMML is a unique pediatric disorder previously referred to as JCML or CMML. Diagnostic criteria for JMML are listed in Table 4. Blood film appearance is characteristic and often more helpful in diagnostics than BM smear. Mutations in the Ras gene is seen in 20%, in **PTPN11** 35%, **NF1** gene in 15% and clinical NF1 in another 15%, molecular genetics has therefore become very helpful in diagnosing JMML. JMML includes patients with monosomy 7 previously considered to represent a distinct hematological disorder described as the monosomy 7 syndrome. There are no major clinical differences between JMML in children with and without monosomy 7.

Natural course and prognostic factors in MDS

Children with RC or low grade RAEB may show a long and stable clinical course without treatment. Blood transfusions are only required infrequently and severe infections are rarely seen. The condition may smolder with unchanged cytopenia for months or even years but will eventually progress in most patients. In a series of 67 children with primary RC, four died from complications of pancytopenia prior to therapy or progression and 20 progressed to more advanced MDS at a median of 1.7 years from presentation. Although RC with monosomy 7 is associated with a higher risk of progression both RC and RAEB patients with monosomy 7 may show stable disease without treatment for several years. Once progression has occurred the outcome is inferior even after SCT. Spontaneous regression of MDS has occasionally been reported in the literature.

The International Prognostic Scoring System (IPSS) for MDS weighted data on BM blasts count, cytopenia and cytogenetics and separated patients into four prognostic groups. The IPSS has been very useful in adults but is less informative in children.

**Treatment of MDS**

MDS is a clonal early stem cell disorder with very limited residual non-clonal stem cells. Myeloablative therapy is therefore the only treatment option with a realistic curative potential. A diversity of therapy strategies like hematopoietic growth factors, differentiating agents, hormones, amifostine, low dose cytotoxic drugs, or experimental agents have been investigated in adults and in the elderly not candidates for SCT. None of these approaches have been documented to prolong survival and

**Table 4: Diagnostic guidelines for JMML adopted from 27**

<table>
<thead>
<tr>
<th>Suggestive clinical features</th>
<th>Hepatosplenomegaly</th>
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<tr>
<td></td>
<td>Lymphadenopathy</td>
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<td></td>
<td>Pallor</td>
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<tr>
<td></td>
<td>Skin rash</td>
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<tr>
<td>Laboratorial criteria</td>
<td>No Ph chromosome, no bcr-abl rearrangement</td>
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<tr>
<td>Minimal criteria (all 3 must be fulfilled)</td>
<td>PB monocyte count &gt; 1 x 10⁹/L</td>
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<td></td>
<td>Bone marrow blast count &lt; 20%</td>
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<tr>
<td>Criteria for definite diagnosis</td>
<td>Hemoglobin F increased for age</td>
</tr>
<tr>
<td>(at least 2 must be fulfilled)</td>
<td>Myeloid precursors in blood smear</td>
</tr>
<tr>
<td></td>
<td>White cell count &gt; 10 x 10⁹/L</td>
</tr>
<tr>
<td></td>
<td>Clonal abnormality</td>
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<td></td>
<td>GM-CSF hypersensitivity of myeloid progenitors</td>
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they are generally not indicated in children and adolescents. Given the lack of recurrent molecular abnormalities in MDS rational drug development aiming at molecular targeted therapy is problematic.

Immunosuppressive therapy has been successful in some adults with MDS and low blast count, especially in patients with BM hypoplasia and HLA-DR15 (DR2)34. Other studies have been less optimistic reporting a significant burden of side effects 35. Preliminary data have shown a few long lasting responses in children with RC treated with anti-thymocyte globulin36. Whether immunosuppressive therapy can result in sustained responses in childhood RC is not known. Children with MDS are at high-risk of cytopenia related complications and optimal supportive care should be the primary focus during all phases of the disease course.

Conventional intensive chemotherapy without SCT is unlikely to eradicate the primitive pluripotent cells involved in MDS rendering the therapy non-curative in most patients. Most studies found a significant morbidity and mortality of induction chemotherapy with a complete remission rate of less than 60%, many relapses, and overall survival less than 30%13;25. The treatment related mortality has been between 10 and 30%25;26. A few studies have reported an outcome in MDS patients not significantly different from that in AML26;37. Some studies suggested that those with RAEB-T or AML following MDS have a superior outcome compared with RAEB 25;26 indicating that RAEB-T consists of a heterogeneous group of patients and that a purely morphologically based classification is insufficient for a treatment relevant stratification4.

SCT is the therapy of choice for virtually all forms of MDS in childhood. Studies specifically addressing the question of SCT in children have indicated a probability of disease-free survival (DFS) following transplant with an HLA-matched family donor (MFD) of about 50%38;39. Children receiving a graft from an HLA-matched unrelated donor (MUD) have previously suffered a higher transplant-related mortality (TRM) and lower DFS but more recent studies have shown survival following MUD-SCT comparable to MFD-SCT40;41. A preparative regimen consisting of busulfan, cyclophosphamide and melphalan42 has shown a high anti-leukemia effect. For patients with advanced MDS the potential benefit of AML-type induction chemotherapy prior to SCT to reduce relapse and improve DFS remains a controversial issue. Prior chemotherapy may increase TRM43. Considering the significant morbidity and mortality of induction chemotherapy and the high rate of TRM following SCT most children with MDS may benefit from SCT as first line therapy sparing the toxicity related to induction chemotherapy. Children without a matched donor and progressive disease should be considered for haploidentical SCT44.

Relapse following SCT is associated with a very grave outcome. Especially early relapse detected by increasing mixed chimerism may benefit from withdrawal of immunosuppressive therapy and donor leukocyte infusion45.

Children with MDS secondary to chemo- or radiation therapy generally have a very poor survival. AML-type therapy may induce remission but very few patients remain in remission and even SCT has been reported to offer cure to only 20 - 30% of patients36;47.

The few published cases of SCT in MDS arising from congenital BM failure disorders or acquired aplastic anemia indicate a poor outcome for this heterogeneous group of patients. Early SCT before neoplastic transformation or during less advanced MDS may be associated with improved survival48;49.

Natural course and prognostic factors of JMML

JMML is a rapidly fatal disorder if left untreated. Low platelet count, age above 2 years, high Hemoglobin F and high bone marrow blast count at diagnosis are the main factors predicting a short survival29. Non-transplanted children presenting with a low platelet count (< 33 x 10^9/ L) died within a year from diagnosis29. Blastic transformation is infrequent with JMML and most untreated patients die from organ failure due to infiltration of the leukemic cells.

Treatment of JMML

Clinical and hematological responses in JMML have most consistently been described for 6-mercaptopurine administered as single-agent60. There are, however, no data indicating that
therapy with 6-mercaptopurine influences the length of survival.

Intensive chemotherapy is mostly unsuccessful in JMML because of an increased risk of treatment related death, a low rate of true remissions and long-term survival less than 10% \(^{29;50;51}\). Allogeneic SCT is the only curative approach for JMML resulting in long-term survival in more than half the patients \(^{52;54}\). If no family donor is available a matched unrelated donor SCT is recommended. Generally, SCT shortly after diagnosis is advocated, and younger age at SCT may predict for improved survival. A conditioning regimen of total body irradiation (TBI) and cyclophosphamide has often been used\(^{55}\). Radiation-induced late effects like endocrine dysfunction including severe growth retardation and neuropsychologic sequelae may be especially deleterious for this group of very young children. Therefore, avoiding TBI is particularly attractive in JMML. Several investigators have reported similar outcome for patients conditioned with TBI compared to non-TBI regimens\(^{52;53}\). In a retrospective analysis of the European Working Group on MDS in Childhood (EWOG-MDS) busulfan-based myeloablative therapy offered a greater anti-leukemic efficacy than TBI\(^{54}\). The current study of EWOG-MDS uses a preparative regimen with busulfan, cyclophosphamide and melphalan has produced event-free survival around 50% with no difference between related and unrelated donor\(^{54}\). Disease recurrence remains the major cause of treatment failure. Too intensive GvHD prophylaxis increases the risk of relapse\(^{54}\) whereas acute or chronic GvHD is associated with a lower risk of relapse\(^{52;54}\). Relapse occurs early at a median of 2-4 months from transplantation\(^{53;54}\) and generally within the first year. Re-emerging donor cells and frank relapse have been successfully eradicated by reduction of ongoing immunosuppressive therapy\(^{56}\). Reducing intensity and duration of GvHD prophylaxis may significantly contribute to successful leukemia control. Donor lymphocyte infusion (DLI) in JMML relapse is largely unsuccessful\(^{57}\).

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