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# Acute Myeloid Leukemia in Pediatric Patients: A Review About Current Diagnostic and Treatment Approaches

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## Abstract

Acute leukemia is the most common childhood malignancy, accounting for almost 35% of all childhood cancers. Acute myeloid leukemia (AML) represents 15–20% of pediatric acute leukemia. Majority of AML cases appear *de novo*, however a minority of cases can present as a secondary malignancy. AML is a highly heterogeneous disease and its diagnosis involves a combination of diagnostic analyses including morphology, immunophenotyping, cytochemistry, and leukemic blasts derived from peripheral blood or bone marrow demonstrating cytogenetic and molecular characteristics. Through the identification of recurrent genetic mutations, it has been made possible to refine individual prognosis and guide therapeutic management. The current survival rate of children with AML is approximately 70%. The standard therapeutic regimen is a combination of cytarabine- and anthracycline-based regimens with allogenic stem cell transplantation in appropriate patients. Relapse in pediatric patients suffering from AML occurs in approximately 30% of cases, whereas death occurs in 5–10% of patients as a result of disease complications or chemotherapeutic side effects. In understanding the genetic basis of AML, targeted therapies will have the ability to reduce treatment-related morbidity and mortality. Here, we provide a comprehensive review of AML, its biology, diagnosis and therapeutic management in pediatric patients.

**Keywords:** acute myeloid leukemia, pediatrics, diagnosis, immunophenotype, cytogenetics, classification, treatment, hematopoietic stem cell transplantation

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## 1. Introduction

### 1.1. Epidemiology

Acute leukemia is the most common childhood malignancy, accounting for almost 35% of all childhood cancers. It can be further divided into two main subtypes such as acute lymphoblastic leukemia (ALL), composing 80% of acute leukemia and acute myeloid leukemia (AML) which makes up 15–20% of acute leukemia in pediatric patients [1]. The incidence of AML is greatest in infants at 1.5 per 100,000 individuals per year and decreases to 0.4 per 100,000 individuals aged 5–9 years. After this, the incidence of AML begins to gradually increase reaching its highest point in individuals greater than 65 years of age at 16.2 per 100,000 individuals [1, 2]. A report using data from the surveillance, epidemiology, and end results (SEER) program identified Asian and Pacific Islanders to have the highest rate of childhood AML (0.84 per 100,000) followed by Hispanics (0.81 per 100,000), Caucasians (0.75 per 100,000), and African-Americans (0.66 per 100,000) [3, 4].

### 1.2. Etiology and pathophysiology

The majority of AML cases appear as a *de novo* malignancy in previously healthy individuals, but there have been cases reported in which AML presents as a secondary malignancy. This has been witnessed in individuals with underlying hematological and genetic disorders such as Fanconi Anemia, Bloom Syndrome, Ataxia Telangiectasia, Shwachman-Diamond syndrome, Noonan syndrome, and Dyskeratosis Congenita. The most common genetic factor for the development of AML is trisomy 21 [3]. Children with Down syndrome have a 500-fold increased risk of developing a unique megakaryoblastic subtype of AML. This classically follows a transient myeloproliferative disorder in the neonatal period, which is characterized by somatic mutations in the GATA1 gene [3, 5]. Recently, a familial predisposition to AML has been suggested, as a number of germ-line mutations, such as GATA2, CEBPA, TP53, and RUNX1 have been found in families with an unexplained high risk of AML [3, 6–10]. In addition, exposure to prior therapy involving topoisomerases II, alkylating agents and radiation therapy have also been associated with an increased risk of developing AML as a secondary malignancy [1, 3].

The pathogenesis of AML involves the abnormal proliferation and differentiation of a clonal population of myeloid stem cells [11]. It is thought to arise from at least two classes of cooperating genetic events, known as a two-hit model of leukemogenesis [12–14]. Type I mutations result in increased and uncontrolled activation of pro-proliferative pathways of the leukemic cell and often involve activating genes that are part of signal transduction pathways, such as FLT3 (28% of cases), K/NRAS, TP53, and c-KIT (12, 8, and 4%, respectively) [15]. Type II mutations occur as a result of genetic aberrations in hematopoietic transcription factors leading to the impairment of normal hematopoietic differentiation. The most common type II cytogenetic abnormalities in children, accounting for almost half of all pediatric AML cases are, t(8;21)(q22;q22) in the core-binding factor AML (CBF-AML) and t(15;17)(q22;q21) in acute promyelocytic leukemia (APL) [16–19]. Other translocations are specific only to children and rarely

found in adults and these include t(1;22)(p13;q13), t(7;12)(q36;p13), and t(11;12)(p15;p13) [20–23]. The NPM1 and CEBPA, type II mutations, are found in approximately 27 and 6% of cases, respectively, and indicate a better prognosis [15]. Moreover, enhanced tyrosine phosphorylation of signal transducer and activator of transcription 3 (STAT3), involved in the stimulation of cellular proliferation and survival, is seen in almost 50% of AML cases and signifies a worse prognosis [24–26]. As stated by the two hit model of leukemogenesis, the pathogenesis of AML is dependent on two classes of cooperating genetic events. A study done by Patel et al. found that the c-KIT mutation has been associated with t(8,21) or inv.(16). Furthermore, they found that NMP1, which is a type II mutation, frequently occurs with FLT3-ITD (a type I mutation) or with mutations in epigenetic genes such as DNMT3A and IDH-1 or IDH-2 [27]. Despite these advancements in the pathogenesis of AML, there still remains much to be discovered on the exact implications that these individual mutations have on the development of AML, particularly in pediatric patients.

## 2. Therapeutic considerations

### 2.1. Classification

The first classification system used to distinguish between the different subtypes of AML was the French-American-British (FAB) classification system established in 1976. It identifies eight subtypes of AML (M0-M7) based on the morphological and cytochemical characteristics of the leukemic cells. The FAB classification was replaced by WHO in 2001 which was then revised in 2008 [28]. The WHO classification of AML was once again revised in 2016, this time integrating genetic information such as, karyotypes and molecular aberrations, with morphology, immunophenotype, and clinical presentation. It defines six major disease entities: AML with recurrent genetic abnormalities; AML with myelodysplasia-related features; therapy-related AML; AML not otherwise specified; myeloid sarcoma; and myeloid proliferation related to Down syndrome (**Table 1**) [29].

In **Table 1**, the subtypes of AML with recurrent genetic abnormalities are listed in accordance to their distinct chromosomal translocation. The newly incorporated provisional category of AML with mutated RUNX1 appears to represent a biologically distinct group with a worse prognosis in comparison to other AML subtypes. The category of AML with myelodysplasia-related changes remains to include a history of MDS as an inclusion criteria, however has been re-structured to better include subtypes with features suggesting a poor prognosis. Lastly, the myeloid proliferations of Down syndrome include transient abnormal myelopoiesis and myeloid leukemia associated with Down syndrome. As mentioned previously, both subtypes involve megakaryoblastic proliferations and are characterized by GATA1 mutations and mutations of the JAK-STAT pathway. Transient abnormal myelopoiesis typically occurs at birth or within the first few days of birth and resolves within 1–2 months. Myeloid leukemia associated with Down syndrome occurs later, but within the first 3 years of life, with or without prior transient abnormal myelopoiesis [29].

Types	Genetic abnormalities
AML with recurrent genetic abnormalities	<p>AML with t(8:21)(q22;q22); RUNX1-RUNX1T1</p> <p>AML with inv.(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFβ-MYH11 APL with PML-RARA</p> <p>AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A</p> <p>ML with t(6;9)(p23;q34.1); DEK-NUP214</p> <p>AML with inv.(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1 AML with BCR-ABL1 (provisional entity)</p> <p>AML with mutated NPM1</p> <p>AML with biallelic mutations of CEBPA</p> <p>AML with mutated RUNX1 (provisional entity)</p>
AML with myelodysplasia-related changes	<p>AML with minimal differentiation</p> <p>AML without maturation</p>
Therapy-related myeloid neoplasms	<p>AML with maturation</p> <p>Acute myelomonocytic leukemia</p> <p>Acute monoblastic/monocytic leukemia acute erythroid leukemia</p> <p>Pure erythroid leukemia</p> <p>Acute megakaryoblastic leukemia acute basophilic leukemia</p> <p>Acute panmyelosis with myelofibrosis</p>
Myeloid sarcoma	Transient abnormal myelopoiesis
Myeloid proliferations related to Down syndrome	ML associated with Down Syndrome

Abbreviations: WHO, World Health Organization; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ML, myeloid leukemia.

**Table 1.** WHO classification of AML and related neoplasms [29].

In pediatric patients, specifically under the age of 2, it is important to search for translocations that are specific for pediatric AML, as WHO classification does not represent them as new disease categories due to their rarity. These translocations, mentioned above, include t(7;12)(q36;p13) and t(11;12)(p15;p13) [1, 29].

## 2.2. Diagnostic approach

AML is a highly heterogeneous disease in regards to its morphology, immunophenotyping, and its clinical manifestations [1]. The clinical presentation of AML commonly manifests with leukocytosis, anemia, and thrombocytopenia. Fatigue, anorexia, and weight loss are less commonly seen and symptoms such as lymphadenopathy and organomegaly are not usually present. If a patient is left untreated, death will most likely occur secondary to an infection or bleeding [11]. In order to establish a diagnosis of acute leukemia, 20% or more blasts must be

found in the bone marrow or peripheral blood [30]. To further diagnose AML, a combination of analyses is required, including, morphology, immunophenotyping, cytochemistry, and leukemic blasts derived from peripheral blood or bone marrow demonstrating cytogenetic and molecular characteristics [31]. Although there is some overlap between the diagnostic recommendations for AML in children and adults, there are important differences between these two age groups that need to be focused on.

Morphological examination is conducted from blood and bone marrow smears using a May-Grunwald-Giemsa or a Wright-Giemsa stain [30]. The FAB classification is used to define the morphological characteristics of AML, which are based on the lineage of associated phenotypes: undifferentiated, myeloid, monoblastic, erythroblastic, or megakaryoblastic [32]. By looking at the morphology of AML, it is possible to determine the percentage of undifferentiated, atypical, or granulated blasts, intracellular structures such as Auer Rods and the presence of myelodysplasia [31]. Auer Rods are comprised of needle-shaped, azurophilic, cytoplasmic inclusion bodies and are commonly seen in APL, acute myelomonocytic leukemia and in majority of cases of AML with t(8;21) [28]. Once the lineage has been established through morphology, cytochemistry is then used to confirm the affiliation as well as differentiate between myeloid (myeloperoxidase [MPO]-positive) and monoblastic (nonspecific esterase-positive) classification. In certain cases in which the morphology and cytochemistry provide an ambiguous picture, immunophenotyping is required to further support the appropriate diagnosis [31].

Immunophenotyping is necessary to distinguish between AML and ALL. It is also required to classify minimally differentiated AML (FAB M0) and acute megakaryoblastic leukemia (AMKL, FAB M7). In minimally differentiated AML, morphological and cytochemical evaluation do not reveal myeloid differentiation. Although cytochemistry is negative for MPO activity, immunophenotyping is positive for myeloid markers, such as MPO (proenzyme) and/or CD13, CD33, and CD117 [31, 32]. AMKL is a type of leukemia with 20% or more blasts but of this, 50% or more are of megakaryocytic lineage. Immunophenotyping in AMKL is positive for platelet markers, such as CD41 and/or CD61 [30, 31]. The current WHO 2016 classification has not changed significantly from the 2008 classification. Markers required to assign lineages and define otherwise not specified mixed phenotype acute leukemia (MPAL) include MPO, lysozyme, CD11c, CD14, CD64, nonspecific esterase cytochemistry, i(intracellular) CD3, CD19, iCD22, CD79, and CD10 [29]. **Table 2** presents the suggested antigen panel for immunophenotypic analysis required for the diagnosis of AML in pediatric patients. It was modified specifically for pediatric patients by Creutzig et al. from the recommended panel for AML in adults [30, 31].

The use of conventional cytogenetic analysis for the diagnosis of AML is a necessary component of the diagnostic evaluation. It allows for the detection of chromosomal abnormalities in 70–80% of pediatric patients with AML [31]. In the case of which cytogenetic analysis fails, fluorescence *in situ* hybridization (FISH) is an option to detect gene rearrangement. FISH allows for the detection of fusion genes, such as RUNX1-RUNX1T1, CBFβ-MYH11, MLL, and EVI1 as well as the loss of chromosome 5q and 7q material [33, 34]. As previously

Diagnosis of AML	Mandatory Markers to fulfill WHO & EGIL Criteria	Other Markers
Precursor stage	CD34, CD117	CD133, HLA-DR
Myelomonocytic markers	CD11b, CD11c, CD13, CD14, CD15, CD33, CD64, CD65, iMPO, i-lysozyme	CD4, CD36, CD184 (CXCR4)
Megakaryocytic markers	CD41, CD61	CD42
Erythroid marker		CD235a
Leukemia specific antigen		NG2 homolog
Lineage aberrant antigens		CD2, CD7, CD19, CD56
Pan-leukocyte markers		CD11a, CD45

**Table 2.** Immunophenotypic markers in Pediatric Patients for the diagnosis of AML.

mentioned, the two most common cytogenetic abnormalities in children are t(8;21)(q22;q22) in CBF-AML and t(15;17)(q;22;q21) in APL, together making up approximately 50% of pediatric AML [16–19].

Molecular genetics can be performed on bone marrow and/or blood specimens. Both DNA and RNA should be extracted, however if there is a small amount of specimen with a limited number of cells, RNA extraction is preferred. This is because RNA is more suitable for molecular screening for fusion genes and mutations specific to leukemia [30]. The frequency and nonrandom associations of type I and type II mutations (stated previously in Section 1.2) differ between pediatric and adult patients with AML [35]. Mutations in the RAS-RAF-ERK signal transduction pathway (PTPN11, NF-1, N-RAS, K-RAS) occur in 5–21% of pediatric AML cases and even more frequently in cases with CBF-AML and MLL-rearranged AML in young children. C-KIT mutations occur in 4% of all leukemia types, except CBF-AML, in which the incidence raises to approximately 25% in children [15, 30]. Despite the differences between children and adults in the expression of type I and type II mutations routine evaluation as suggested by Creutzig et al. should include FLT2-ITD, WTI, C-KIT, CEBPA, and NPM1 [31].

Gene expression profiling has the ability to contribute to the accurate diagnosis and risk-stratification of pediatric AML patients. However, its use remains limited as large cohorts are required for validation of the true prognostic significance of these genes [36]. Biobanking is strongly recommended for all patients, allowing for confirmation of initial diagnosis, or adding new data in the case of a relapse. Stored material should include AML blasts, DNA, and RNA. Buccal swabs are also recommended to be stored as they allow for discrimination between germ line and somatic genetic aberrations. This material can be used to identify new prognostic markers, monitoring for minimal residual disease (MRD) and contribute to research studies about the biological mechanism, subgroups and leukemogenesis of AML [30, 31].

### 2.3. Prognostic factors

The most relevant prognostic factors for the survival of pediatric AML are genetic and molecular abnormalities and the initial response to treatment. Both of these prognostic factors are

independent and are both usually essential elements of the risk group classification [31, 37]. Presence of a very high blast count at the time of diagnosis is associated with a higher risk of early death and nonresponse [38]. Other favorable prognostic factors include, t(8;21)(q22;q22)/RUNX1-RUNX1T1, t(15;17)(q22;q21)/PML-RARA, NPM1-mutated AML and CEBPA double mutation - amongst a few [31]. A favorable prognostic group is CBF-AML [19, 39, 40]. MLL-translocations have variable outcomes and depend on the associated translocation. In MLL t(1;11)(q21;q23) has a very favorable outcome in pediatric AML. In comparison, those with t(6;11)(q27;q23) and t(10;11)(p12;q23) translocations have been reported to have poor survival rates [31, 41, 42]. Certain prognostic makers vary between children and adults. For example, deletion of 7q in adults is suggestive of an intermediate prognosis; however in pediatric patients it is associated with a poorer outcome. In these pediatric patients, the outcome has been found to be dependent on other cytogenetic abnormalities in the leukemia cell [19, 43]. Other poor prognostic abnormalities that have been described in adult AML, such as abnormalities of chromosomes 3q and 5q and the monosomal karyotypes are very rare in children [44–47].

The type I mutations of WT1 and FLT3-itd are indicative of a poor prognosis. FLT3-itd outcome depends on the allele ratio, whereas both of these mutations are described as events in clonal emulation towards relapse [48].

#### **2.4. Pediatric AML treatment**

The current survival rate of children with AML has increased to approximately 70%. This increase has been achieved by better risk stratification and intensification of chemotherapeutic regimens. The treatment of childhood AML should be risk adapted according to various biological factors in order to avoid over treatment in patients with a favorable prognosis and provide adequate chemotherapy to improve outcome in those with a less favorable prognosis [31]. This allows for the destruction of leukemia cells with the hope of avoiding side effects or as little late side effects as possible. With regards to infant AML, the most powerful prognostic factor for the outcome has been found to be favorable cytogenetics and a blast count of less than 5% after induction therapy [49].

The standard chemotherapeutic regimen consists of a combination of 4–5 cycles of cytarabine and anthracycline-based regimens with allogeneic stem cell transplantation in appropriate patients [1]. Induction therapy typically includes 1 or 2 cycles of chemotherapy in both children and adults. Standard induction therapy involves 3 days of an anthracycline and 7–10 days of cytarabine (“3 + 7” or “3 + 10”). This induction regimen achieves complete remission in greater than 85% of children and adolescence. A third drug, such as etoposide or 6-thioguanine, can be included in induction, but their benefits have not yet been proven [50]. There are a number of various anthracyclines that have been evaluated through randomized controlled pediatric trials. Daunorubicin and mitoxantrone resulted in similar overall survival; however treatments with a mitoxantrone base resulted in lower relapse rates [51]. In comparison, idarubicin and liposomal daunorubicin had similar survival rates, but liposomal daunorubicin was more effective in cases with a RUNX1/RUNX1T1 translocation and caused less treatment-related mortality [52]. Studies have shown that higher doses of anthracyclines improve the outcome in children and adults [53, 54]. However, at higher doses there is an increased risk



for toxicity, especially acute and late cardiotoxicity. A cumulative dose of  $>300$  mg/m<sup>2</sup> has been associated with significant later cardiac toxicity and should take into consideration factors such as the patients age and sex [55, 56]. To avoid reaching peak serum concentrations, suggestions of splitting the dose, or using prolonged drug infusions have been proposed, however there have been conflicting benefits of dose scheduling and no conclusion on the best regimen has yet been reached [57, 58]. Dexrazozane is another option to reduce cardiotoxicity during anthracycline exposure and has been proven to be beneficial [59]. Failure of induction therapy is seen in 10–15% of pediatric patients. The subsequent outcomes for a patient with induction failure are similar to the patient with AML who relapsed early ( $<12$  months after remission) [60, 61]. These patients, similar to patients that have relapsed, have been shown to have the highest end free survival after stem cell transplantation in comparison to after chemotherapy (31.2 vs. 5%,  $p < 0.0001$ ) [62].

A considerable challenge in the treatment of children with AML is to prolong the initial remission. This is done with additional chemotherapy, similar to that in induction, but with the addition of non-cross-resistant drugs and high dose (HD) cytarabine [63, 64]. The ideal number of post remission cycles of therapy remains unclear, but appears to require at least two courses of intensive therapy, with the addition of the induction course. A study done by the United Kingdom Medical Research Council randomly assigned adult and pediatric patients to four or five courses of intensive therapy. There was no advantage seen in relapse free and overall survival in patients treated with five courses [51, 65].

The benefits of the intensification of cytarabine have been studied by a number of trials. In most studies, intensification of cytarabine from 12 to 36 g/m<sup>2</sup> did not improve survival in adult AML patients [66]. However, a study by the Cancer and Leukemia Group B (CALGB) in adults showed that four courses of HD cytarabine (3 g/m<sup>2</sup> per every 12 h on days 1, 3, and 5) were superior to four courses of lower dose cytarabine (100 mg/m<sup>2</sup> continuous intravenously on days 1–5) but only in patients with CBF-AML and CN-AML [63, 67]. Several pediatric trials (NOPHO AML 93, AML-BFM 2004, AML 10, and AML99 of the JPLSG) showed that the use of intensive chemotherapy courses that include HD cytarabine reduced relapse rates [67–72].

Hematopoietic stem cell transplantation (HSCT) is used as post remission consolidation therapy. Allogenic HSCT (allo-HSCT) has been found to have a greater benefit than autologous HSCT (auto-HSCT). Several trials have found no benefit of auto-HSCT compared with nonmyeloablative chemotherapy during the first complete remission [69, 73–76]. In addition, the degree of toxicity associated with the conditioning regimen greatly out ways the benefits/use of auto-HSCT [77]. In comparison, prospective trials of transplantation in children with AML suggest that 60–70% of children with HLA-matched donors will experience long-term remissions when treat with an allo-HSCT during their first remission [69, 74]. Although there is a significantly lower relapse risk associated with allo-HSCT as compared with post-remission chemotherapy, the improvement in overall survival is controversial [78–80]. The current utilization of allo-HSCT involves incorporation of risk classification to determine whether transplantation should occur during the first remission. There is consensus that favorable-risk patients should not be transplanted in first complete remission but only after the first relapse and achievement of a second complete

remission [73, 78, 79, 81]. Some benefit has been shown in allo-HSCT during first complete remission in intermediate- and high-risk patients. A meta-analysis combining the results of the POG-8821, CCG-2891, COG-2961, and MRC-Leuk-AML-10 showed benefit for allo-HSCT in intermediate-risk patients only [78]. Weakness in this analysis was due to a large percentage of patients not assigned to a risk group resulting in potential selection bias. If transplantation is chosen in pediatric AML, myeloablative chemotherapy is preferred over total body irradiation as the latter is associated with an increased risk of secondary malignancies and more late effects [82–84]. A large prospective CIBMTR cohort study of children and adults with AML, MDS, and CML, showed superior survival of patients in the early stages of the disease and less toxicity with busulfan-based regimens as compared to total body irradiation [85]. Despite these results, the optimal preparative regimen remains undetermined [86–88]. In summary, the role of HSCT in pediatric patients with AML in the first complete remission should continue to be assessed, particularly within specific risk groups. However, there is a consensus that HSCT should be offered to all children with relapsed AML once second remission has been achieved and that favorable-risk patients should not be offered HSCT [79].

The presence of CNS involvement at diagnosis and at relapse is seen in 5–10% of childhood AML cases. An increased risk of CNS involvement is seen in patients with hyperleukocytosis, monocytic leukemia (FAB M4 and M5, especially those with *inv(16)* or 11q23 chromosomal abnormalities), MLL gene rearrangement, and younger age [89]. All pediatric patients receive CNS treatment, even if no CNS involvement is detected. This is done with the presumption that systemic chemotherapy has little efficacy in penetrating the blood–brain–barrier to eradicate any potential AML blasts in the CNS. The most common regimen used for CNS treatment involves intrathecal chemotherapy—single agent cytarabine or methotrexate, or triple cytarabine, methotrexate and hydrocortisone. Other treatments such as cranial irradiation have also proven to be effective in the treatment of CNS involvement in pediatric AML. According to European protocols, prophylactic cranial radiotherapy is used in pediatric patients with AML. This is based on German pediatric AML studies, BFM-78 and BFM-83 where the use of cranial irradiation suggested to prevent both CNS and systemic relapse [89, 90]. However, due to its high side effect profile (including late toxicities and secondary malignancies), prophylactic cranial irradiation still remains controversial and is used less frequently in other countries [90].

As a result of AML being a highly heterogeneous disease and its ability to present in different ways, management may vary based on age group or the type of AML. One special group is children with DS, as they have a 14–20-fold risk of developing leukemia. In addition to the increased risk of AML during the first 3 years of life, about 10% of neonates with DS also develop a TMD, which usually disappears spontaneously [91]. Despite TMD self-resolving within 4–10 weeks, it can cause severe and life threatening complications such as hydrops fetalis, pleural effusions, liver cirrhosis with hyperbilirubinemia, organomegaly, or hyperleukocytosis [92]. Approximately, 10–20% of these patients will develop myeloid leukemia with megakaryoblastic features (ML-DS) within the first 3 years. Treatment of ML-DS involves intensity reduced chemotherapy and no HSCT in the first complete remission. As children with DS are susceptible to chemotherapy, the event free survival and survival rates are >85% [92–95].

APL is a distinct subtype of AML and is characterized by t(15;17). This translocation involves a breakpoint that includes the retinoic acid receptor and leads to production of the promyelocytic leukemia (PML)-retinoic acid receptor alpha (RARA) fusion protein [96]. Treatment is usually begun immediately with all-trans retinoid acid (ATRA) as APL is associated with an increased risk of a life threatening hemorrhage. In children, a dose of 25 mg/m<sup>2</sup> per day of ATRA should be started and has shown to produce equivalent outcomes to the higher dose of 45 mg/m<sup>2</sup> per day that is commonly used in adults [97–99]. Arsenic trioxide has proven to be an effective agent in combination with ATRA in the treatment of newly diagnosed, refractory, or relapsed APL [77]. In patients with hyperleukocytosis treated with ATRA or arsenic trioxide, approximately 10% of children can develop APL differentiation syndrome. This syndrome is characterized by fever, weight gain, respiratory distress, pleural, and pericardial effusions. The incidence of APL differentiation syndrome can be reduced by combining ATRA with chemotherapy. Pseudotumor cerebri occurs in 11% of children during initial ATRA administration and can be treated with steroids [97, 100].

Although there have been major improvements in treatment outcomes, AML remains a life-threatening malignancy. Approximately, 30% of pediatric patients relapse, with only 30–40% of these relapsed patients surviving, indicating a poor outcome [101, 102]. AML is a highly heterogeneous disease and through gaining knowledge on its molecular and genetic background it will allow new targeted and patient-specific therapies to become available to children.

## 2.5. Supportive treatment

The estimated incidence in children with high-risk AML of severe bacterial infections is 50–60% and the estimated incidence of invasive fungal infections is 7.0–12.5% [103–105]. The improved outcome in children with AML over the last 10 years may be associated to better supportive care strategies.

Hyperleukocytosis (WBC greater than 100,000/ $\mu$ L) at initial diagnosis is associated with an increased risk of CNS hemorrhage and leukostasis. Patients with monocytic or myelomonocytic (FAB M4 and M5) as well as APL and hyperleukocytosis are at an increased risk of early death [106, 107]. Treatment involves emergency care with intensive monitoring and careful hydration with the addition of rasburicase [108]. In more severe cases involving symptomatic coagulopathy, exchange transfusion or leukapheresis may be required. Controlled and effective reduction in cells with enforced diuresis or hemodialysis, may prevent the occurrence of tumor lysis syndrome [106–108].

Hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF) during AML induction therapy are not recommended in the pediatric population. Although a randomized study in children with AML evaluated G-CSF administered after induction chemotherapy showed a reduction in duration of neutropenia there was no difference in infectious complications or mortality [109]. In addition, a higher relapse rate has been recently demonstrated

for children who over express the differentiation defective G-CSF receptor isoform IV [110]. Therefore, the routine prophylactic use of G-CSF or GM-CSF is not recommended for children with AML but remains an option in shortening neutropenia in critically ill patients.

Bacterial infections occur in up to 70% of children during AML therapy [111]. A retrospective study from St. Jude Children's Research Hospital (SJCRH) in patients with AML found that the use of intravenous cefepime or vancomycin in conjunction with oral ciprofloxacin or a cephalosporin significantly reduced the incidence of bacterial infection and sepsis compared with patients receiving only oral or no antibiotic prophylaxis [112]. Another retrospective study reported a significant reduction in Gram positive, sterile-site infections with antibiotic prophylaxis [113]. While it is suggested that antibiotic prophylaxis is beneficial, prospective randomized trials are required in pediatric patients with AML.

The incidence of invasive fungal infections is up to 15% in children with AML, which is similar to that in adults. They are most commonly caused by *Candida* and *Aspergillus* species [114]. Prophylaxis should be administered to all children with agents such as voriconazole, itraconazole, micafungin, or caspofungin. Due to drug interactions (e.g., itraconazole and voriconazole) and variable pharmacokinetics, voriconazole should be held during courses of chemotherapy and levels should be monitored periodically. Prophylaxis for *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole should also be administered [114, 115].

### 3. Conclusion

The diagnosis and treatment of AML has significantly improved over the past decades. Risk stratification has allowed for more targeted and specific therapy while avoiding, over treatment in low-risk patients and allowing for more intensive therapy in others. AML is a highly heterogeneous disease and through gaining knowledge on its molecular and genetic background as well as international collaboration, it will allow new targeted and patient-specific therapies to become available, particularly in pediatric patients.

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