Pediatric Hematopathology

Bone Marrow Disorders, Leukemias, Lymphomas, and Molecular Diagnostics

Birupaksha Biswas

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Pediatric Hematopathology: Bone Marrow Disorders, Leukemias, Lymphomas, and Molecular Diagnostics

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DeepScience

Published, marketed, and distributed by:

Deep Science Publishing, 2025
USA | UK | India | Turkey
Reg. No. MH-33-0523625
www.deepscienceresearch.com
editor@deepscienceresearch.com
WhatsApp: +91 7977171947

ISBN: 978-93-7185-011-7

E-ISBN: 978-93-7185-091-9

https://doi.org/10.70593/978-93-7185-091-9

Citation: Biswas, B. (2025). *Pediatric Hematopathology: Bone Marrow Disorders, Leukemias, Lymphomas, and Molecular Diagnostics*. Deep Science Publishing. https://doi.org/10.70593/978-93-7185-091-9

Preface

Writing a book in pediatric hematopathology is not the simple act of compiling a series of diseases, or the sterile listing of diagnostic algorithms. On a deeper level, it is an effort to write the delicate cross-hatchings of science, childhood and the metaphysics of survival into language. Blood, eternally running through its cycles, has always spoken in contradiction, of life and decay; marrow, buried in the structure of bone, contains the contradiction of buriedness and revealing. To look at the marrow through aspirates, biopsies, flow cytometry, molecular readouts is to join a kind of epistemological pilgrimage, a place where every nucleus, every chromosomal aberration, every cytokine storm is at once a fact and a metaphor.

The child, who is caught up in this clinical and philosophical theatre, is not a diagnostic specimen. Each child is instead a text — a compound of biology and biography — whose illness makes us face the fragility of beginnings. Disease occurs in adults against the backdrop of a long history of exposure and environment and time; when it occurs in children, it appears all the more tragic without enough narrative to hold on to. So it is that pediatric hematopathology, more than any other field, forces us to follow the path toward unity of knowledge and ultimately to harmonize science with ethics, to balance our curative aggression with compassion, and to accept that the smallest patient bears the greatest ontological weight.

The following chapters are not organized as technical stashes, but rather, dialectical waypoints. We will start with the normal child's blood system, the rhythms of the marrow, the dance of precursors, the delicate scaffolding of the forming bone. From that starting point of innocence, the story moves on to perturbations: those of non-neoplastic marrow diseases, congenital failures in the production of hematopoietic machinery, and the mysterious terrains of pediatric myelodysplastic syndromes. Already, in these, likely faster paced chapters, structure and disintegration are playing out, genesis and erosion battling for the upper hand, reminding us that the pathological is merely a perversion of the physiological across a continuum.

Acute leukemias, as the incidents occur with a horrific poignant speed, actually present us with the classic picture of the hematologic catastrophe. Here marrow and blood converge, as blast disseminates, suffocating all but function. Subsequent considerations of lymphomas extend the territory, emphasizing the porousness of diagnostic boundaries, between leukemia and lymphoma, between immune hyperplasia and malignant transformation. Entities such as Burkitt lymphoma or anaplastic large cell

lymphoma serve as a reminder that childhood malignancies are not simply small adults diseases, rather, they are a distinct ontological entity that has been sculpted by developmental immunobiology and characteristic genetic lesions.

Histiocytoses and dendritic cell disease, lying at the cryptic boundaries of hematology and immunology, are a metaphor for the immune system gone mad. In hemophagocytic lymphohistiocytosis or macrophage activation syndrome, the very equipment developed to defend the body against assault becomes the vehicle of its dissipation. You cannot read these diseases without seeing in them a metaphor of self-destruction, of systems overwhelmed with their excess, of life feeding on itself.

The story then evolves toward the ultra-rare but scientifically crucial entities—pediatric plasma cell neoplasms, mastocytosis, myeloid sarcomas, and blastic plasmacytoid dendritic cell neoplasms. Novelty creates a sense of the limits of our knowledge. Their own presence on these pages is however a witness that even the rarest of the diseases should speak up and out, for silence holds them captive in the shadows of the otherwise invisible and invisibility ensnares oblivion.

And finally, the trajectory brings us to the horizon: the expanding borders where morphology intersects molecular cartography, where perception is enhanced by artificial intelligence, where a future is built on immunotherapies and gene editing that was once unimaginable. Stem cell transplants, immune re-weaponization, targeted inhibitors, and computer algorithms fuse together in a new epistemology of pediatric hematopathology—a future that is not linear, but syncretic; not strictly additive, but transformative.

Still, technological brilliance casts ethical shadows. What does it mean to edit a child's genome to lower leukemia risk? Where is the boundary between cure and enhancement? How do we celebrate CAR-T successes in well-resourced systems while facing the reality that many children elsewhere die without diagnosis? These questions run through the book like underground streams, ensuring our excitement is tempered by humility and responsibility.

This preface is a doorway to a manual, yes, but also an invitation to read the book as a meditation on vulnerability, resilience, and the moral work of medicine. "Normal marrow" in Chapter One is more than a schema; it suggests order and rightness. "Acute leukemias" are more than clinical entities; they speak to growth gone wild. "Future directions" are not just forecasts; they are philosophical horizons that ask how we will inhabit science and what kind of world we will build for the children who will inherit it.

If the title hints at a philosophical bent, the goal is not to abstract pediatric hematopathology from marrow and blood, but to engage life where it is most fragile. Blood is more than fluid—it carries ancestry, sacrifice, and hope. Marrow is more than

tissue—it is the workshop where life is cast and recast. Pathology is not only disease; it is a reminder that creation and collapse travel together in every child, every cell, every diagnosis.

My hope is that hematopathologists, oncologists, researchers, and students will come to these chapters for more than technique. The message is simple: medicine is science, but it is also ethics, meaning, and story. To read a marrow aspirate is to interpret; to treat a child with leukemia is to face not only malignancy and prognosis, but mortality and personhood.

This book is both atlas and meditation, manual and elegy. It aims to teach and to unsettle, to illuminate and to provoke. In the end, pediatric hematopathology is not about diseases alone. It is about the children who bear them, the families who stay beside them, and the clinicians who walk the narrow path between science and sorrow.

In every child's marrow there is not just hematopoiesis, but hope. Knowledge demands responsibility. This book is meant as a synthesis and an offering, a vigil kept over the fragile grammar of blood.

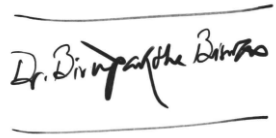

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Table of Contents

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 1: Normal Pediatric Hematopoiesis: Morphology, Physiology, and Bone Marrow Architecture

1 Introduction

Paediatric haematopoiesis is a dynamic and temporally-regulated process that is fundamentally different from that in adults. Neonatal bone marrow is typically hypercellular with abundant proliferating haematopoietic progenitors, as a consequence of high metabolic and developmental requirements in early postnatal life. Such haematologic responses accompany changes in oxygenation thresholds, erythropoietic mass and maturing immunocompetence. This chapter describes the normal morphological and physiological features of pediatric hematopoiesis, including age-specific bone marrow cytological and architectural details, lineage distributions and bone marrow microenvironment.

A. Age-Dependent Marrow Cellularity and Red-to-Yellow Marrow Conversion

Bone marrow cellularity is between 90 and 100% during the neonatal period; there is little fat in the marrow. With age, cellularity decreases, with about 70% of fat found in a 10 year-old and 40–70% in an adult, depending on individual physiological and environmental factors (1,2). The conversion from red to yellow marrow occurs in an orderly centripetal manner, beginning in the peripheral skeleton and advancing toward axial locations, with adult marrow distribution being achieved by approximately 25 years age (3,4). This process is both radiographically discernible and physiologically reversible in stress hematopoiesis, as during chronic anemia or hypoxic conditions (5).

B. Lineage Composition and Differential Cellular Distribution

The cellular constituents of infantile bone marrow change abruptly and widely, reflecting the changing needs for hematopoiesis and immunologic maturation which typify early life. At the time of birth, the marrow is very biased toward erythropoiesis; erythroid precursors make up up to 40% of nucleated marrow cells. Erythroid Predominance The fact that the red pulp exhibits erythroid predominance in the newborn spleen is an adaptation to the hypoxic intrauterine environment found physiologically in the neonate, requiring increased production of red blood cells to supply the tissues of the fetus, which are growing at a very rapid pace (6).The erythroid lineage at this stage is characterized morphologically by abundant early erythroblasts and a high proportion of polychromatic normoblasts, reflecting intense proliferative and maturation activity.

However, it is evanescent at this erythroid preponderance. The erythroid part diminishes abruptly during the first months after birth, as oxygen availability stabilizes and the neonatal hemoglobin gradient changes from fetal hemoglobin to adult hemoglobin. Conversely, the marrow begins to preferentially favor granulopoiesis, which is the predominant lineage five weeks of age, with granulocytic precursors representing >50% of nucleated cells (7). This transition depends on an instinct immune response perfectly developed to quickly react to environmental pathogens after birth. Granulopoiesis at this point is marked by enhanced proliferation and maturation of myeloblasts, promyelocytes, myelocytes, and metamyelocytes with an increased absolute neutrophil count in blood. This maturation correlates with functional need for efficient phagocytic and antimicrobial activity in neonates/young infants.

Concurrently, the lymphoid lineage follows an opposing developmental program. Lymphoid precursors are few as compared to birth due to the relative immaturity of the adaptive immune system in utero. By contrast, in first year of life there is a very vigorous expansion of lymphoid precursors, including B- and T-cell progenitors, that takes place which correlates with the genesis of immunologic memory and development of the peripheral lymphoid organs (6). By 4 to 6 years of age, lymphocyte population reach steady state concentrations similar to adults and the adaptive immune compartment is mature. Lymphoid expansion like that is controlled by complex interactions that include thymic output, peripheral antigen exposure, and the cytokine milieu, most prominently interleukin-7 (IL-7), which supports the survival and differentiation of lymphoid progenitors.

Lastly, plasma cells, womanly either absent or very rare in neonatal marrow, slowly rise in number throughout childhood and adolescence. This rise is representative of the formation of humoral immunity associated with sustained antigenic stimulation and development of secondary lymphoid tissues (8). The peak of plasma cell prevalence

during adolescence correlates with increased immunologic experience and maturation of the bone marrow microenvironment capable of supporting long-lived plasma cells.

Taken together, these changing trends suggest that age-appropriate reference criteria for marrow lineage distribution in the pediatric age group are critical to prevent misinterpretation of normal developmental variation in marrow as an abnormal process. They also demonstrate marrow's ability to adapt to meet the needs of the body during growth and maturation of the immune system.

Table 1: Age-dependent cellular proportions in pediatric bone marrow

Cell Lineage	At Birth (Neonate)	First 2 Months	1 Year	4–6 Years	Adolescence
Erythroid Precursors	~40% of nucleated marrow cells	Rapid decline <20%	Further decline to adult levels	Stable at adult levels (~15–25%)	Stable
Granulocytic Precursors	~30–35% (less dominant than erythroid)	Increase >50%, becoming dominant	Maintain dominance (~50%)	Stable at adult levels (~50–60%)	Stable
Lymphoid Precursors	Minimal (<10%)	Increasing	Approaching adult levels (~20–30%)	Stabilize at adult levels (~20–30%)	Stable
Plasma Cells	Rare or absent	Rare	Increasing	Increasing	Peak prevalence (~2–5%)
Megakaryocytes	Present, small numbers	Present	Present	Present	Present

C. Myeloid-to-Erythroid (M:E) Ratio and Maturation Patterns

In newborns, the myeloid-to-erythroid (M:E) ratio in bone marrow often looks the opposite of adult patterns, reflecting the unique hematopoietic demands of early life. In neonates, the ratio can be as low as 1:3 to 1:4, indicating marked erythroid predominance to support the high oxygen-carrying needs of the perinatal period (9). This skewed balance highlights brisk erythropoiesis as the infant transitions from a relatively hypoxic intrauterine environment to oxygen-rich life outside the womb. The marrow is rich in

erythroid cells across the spectrum—from proerythroblasts to normoblasts—showing vigorous proliferation and maturation of the red cell lineage. As infancy progresses, this erythroid predominance wanes, and the system shifts toward expanding granulopoiesis to build effective innate immunity. Over the first year, the M:E ratio rises and approaches adult values, typically around 2:1 to 5:1, favoring myeloid cells (10). This change reflects the maturation of the granulocytic lineage, with myeloblasts differentiating through promyelocytes, myelocytes, and metamyelocytes to segmented neutrophils, improving postnatal protection against pathogens. These dynamics are mirrored in the marrow's spatial organization, often described as an "inverted pyramid" of maturation (11). Early blasts and precursors cluster near the subcortical regions adjacent to bone trabeculae and the endosteum, within specialized niches rich in stromal cells, osteoblasts, and extracellular matrix that regulate hematopoietic stem cell quiescence and lineage commitment. As cells mature, they migrate toward the vascular sinuses at the apex of this inverted pyramid. There, mature granulocytes, erythrocytes, and megakaryocytes are positioned for release into the circulation. This zonal maturity gradient is essential for steady-state hematopoiesis and provides valuable histologic clues for distinguishing normal maturation from pathological conditions in which this sequence is disrupted.

Together, the age-related shifts in the M:E ratio and these topographically organized maturation patterns underscore the need for age-appropriate interpretation of marrow findings. This perspective is crucial when evaluating pediatric bone marrow aspirates and biopsies, helping differentiate normal developmental physiology from disorders such as erythroid hyperplasia, myelodysplasia, or infiltrative leukemia.D. Hematopoietic Stem Cell Niches and Microenvironmental Dynamics

The pedi-atric hematopoietic microenvironment is a highly specialized, developmentally regulated structure which differs phenotypically and functionally from its adult counterpart. Neonatal MSCs overexpress many of the important hematopoietic-supportive cytokines and niche-derived ligands, such as CXCL12 (stromal cell-derived factor 1) and stem cell factor (SCF), that together provide optimal HSC proliferation, maintenance, and self-renewal support (12). This cytokine-enriched milieu fosters a highly permissive ecosystem conducive to robust HSC expansion, optimizing hematopoietic output during early ontogeny.

Concurrently, the pediatric marrow niche appears to impose intrinsic constraints on the clonal propagation and niche colonization of leukemic stem cells (LSCs), thereby influencing the divergent pathobiology and clinical phenotypes observed between pediatric and adult hematologic malignancies (13). This differential permissivity likely reflects ontogenetic variations in niche cellular constituents, extracellular matrix composition, and paracrine signaling gradients, which modulate leukemogenic potential and therapeutic responsiveness. Understanding these nuanced microenvironmental

distinctions is pivotal for elucidating age-related disparities in leukemia biology and for the rational design of targeted niche-modulating therapeutics.

E. Histological Architecture and Spatial Organization

Histologically, the pediatric bone marrow has a strikingly high cellularity reflective of the high burden of hematopoietic activity necessary to support this phase of rapid growth and maturation of the immune system. The marrow is densely populated with hematopoietic cells exhibiting trilineage maturation—erythroid, myeloid, and megakaryocytic—each occupying distinct yet spatially organized topographic niches that facilitate efficient lineage differentiation and proliferation.

Erythropoiesis is mainly located in well-defined erythroblastic islands, specialized microanatomical structures in which a central macrophage is surrounded by differentiating erythroid precursors from proerythroblasts to orthochromatic normoblasts. The central macrophage serves as a critical regulatory hub, mediating iron transfer, phagocytosing extruded nuclei from late-stage erythroblasts, and secreting cytokines that promote erythroid proliferation and survival. This intimate cellular interaction ensures the tightly regulated production of red blood cells necessary for oxygen transport in the growing child (14).

Granulopoiesis is preferentially concentrated near the endosteal surfaces of bony trabeculae, an anatomical niche rich in osteoblastic cells that modulate hematopoietic stem and progenitor cell fate through direct cell-cell contact and soluble mediators. The proximity to endosteal bone surfaces provides a microenvironment conducive to myeloid lineage commitment and expansion. The granulocytic series—from myeloblasts through segmented neutrophils—demonstrates orderly maturation gradients, with proliferative precursors localized deeper within the marrow and mature granulocytes migrating toward vascular sinusoids for peripheral release (14).

Megakaryocytes, the large, polyploid cells responsible for platelet production, are typically situated within perisinusoidal regions of the marrow. The strategic positioning of these cells next to the sinusoidal endothelium allows the platelet fragments to be released directly into the blood stream. Megakaryocytes are typified by their unique morphological characteristics (abundant cytoplasm and multilobulated nuclei) as their development is highly dependent on thrombopoietin and stromal interactions in this niche (14).

Outside the hematopoietic compartment, the marrow microenvironment consists of a variety of lining osteoblastic cells, sinusoidal endothelial cells, adipocytes, and stromal fibroblasts which structurally, and functionally, contribute to hematopoietic homeostasis. Osteoblasts not only generate the endosteal niche, but also produce and

secrete extracellular matrix (ECM) molecules and cytokines that alter stem cell quiescence, and lineage commitment. Sinusoidal Capillaries Sinusoidal capillaries form a very fenestrated vasculature that is able to let mature blood cells efficiently traffic into the circulation. Adipocytes are less frequent in pediatric marrow than in adult marrow, yet may function to modulate the marrow microenvironment by secreting adipokines, which can also influence hematopoiesis. Stromal fibroblasts also serve as a scaffolding and secrete molecules, such as CXCL12 (SDF-1), that are important in stem cell retention and homing (14).

Immunohistochemistry (IHC), as an adjunct, is indispensable for distinguishing and enumerating the various hematopoietic lineages and degrees of maturation. CD34 and similar markers are used to identify hematopoietic stem and progenitor cells as regions of active blood formation. CD61 (GPIIIa) is limited to megakaryocytes and their precursors, allowing assessment of the megakaryocytic trilineage and stage of maturation. CD68 can be used to demonstrate macrophages, including the central ones in erythroblastic islands, to recognize and to study them in erythropoiesis. Glycophorin-A serves as a sensitive marker for erythroid precursors and permits a detailed characterization of erythropoiesis and maturation in the marrow.

F. Radiologic Correlates and Residual Red Marrow Patterns

Magnetic resonance imaging (MRI) serves as a highly sensitive, non-invasive modality for the evaluation of bone marrow composition and distribution patterns in pediatric patients. It is particularly advantageous due to its ability to differentiate between red (hematopoietic) and yellow (fatty) marrow without ionizing radiation, making it ideal for serial imaging in children. On T1-weighted sequences, red marrow typically exhibits intermediate signal intensity, owing to its higher water and lower fat content, while yellow marrow appears hyperintense due to its abundant fat composition and relatively lower cellularity (16). On T2-weighted and STIR images, red marrow may display slightly elevated signal intensity compared to yellow marrow, although the contrast is less pronounced.

In the normal developmental trajectory, residual red marrow persists in predictable anatomical locations during childhood and adolescence. This red marrow is frequently seen in a symmetric, flame-shaped metaphyseal distribution, especially within long bones such as the femur, tibia, and humerus. The pattern is usually sharply demarcated, homogenous, and bilaterally symmetric, reflecting physiological hematopoietic activity. As such, it is considered a normal variant, particularly in children under the age of 15, where hematopoietic demand remains elevated relative to adults.

However, differentiating residual red marrow from marrow pathology is critical, as infiltrative, neoplastic, or inflammatory processes may exhibit overlapping imaging features. Unlike physiological red marrow, pathologic infiltration—as seen in leukemia, lymphoma, neuroblastoma metastases, or storage disorders—often presents with asymmetric distribution, heterogeneous signal intensity, poorly defined margins, and involvement of atypical skeletal sites (e.g., diaphyses in early reconversion or axial skeleton in metastatic disease) (17). Additionally, pathologic marrow may demonstrate restricted diffusion on diffusion-weighted imaging (DWI), enhancement after contrast administration, or adjacent soft tissue changes, which are not features of normal residual marrow.

Furthermore, systemic factors such as chronic anemia, hypoxia, marrow reconversion, or post-chemotherapy recovery may lead to reappearance or expansion of red marrow in previously fatty areas. These changes, although benign, may mimic pathology and thus require correlation with clinical findings, hematologic parameters, and—when ambiguity persists—biopsy confirmation.

In summary, a nuanced understanding of normal pediatric marrow signal characteristics and distribution patterns on MRI is essential for radiologists and hematopathologists. Misinterpretation can lead to unnecessary invasive procedures or delay in diagnosing genuine marrow disease. Proper integration of clinical context, imaging morphology, and age-specific norms is crucial for accurate interpretation.

G. Clinical and Laboratory Correlates: Peripheral Smear and Aspirate Interpretation

Peripheral blood smears remain a cornerstone for evaluating newborns. They offer a quick, minimally invasive way to assess circulating blood cells. That said, interpreting neonatal smears can be tricky: many normal findings in newborns can look like disease in older children and adults. To avoid misdiagnosis and unnecessary interventions, clinicians need to interpret these smears with a solid understanding of age-specific reference ranges. Polychromasia is a common feature in neonatal blood. It reflects an increased number of reticulocytes and young red cells that still take up stain because of residual RNA. This pattern signals the robust erythropoietic activity typical of the newborn period, driven by the shift from the low-oxygen intrauterine environment to oxygen-rich life outside the womb and the need to quickly expand red cell mass. In fact, reticulocyte counts in neonates are physiologically elevated relative to older children and adults, with values often exceeding 5–7% without indicating pathology (18). This robust erythropoietic response manifests cytologically as basophilic stippling and varying degrees of cytoplasmic polychromasia, features that in older individuals may signal hemolytic processes or marrow stress.

Accompanying polychromasia, neonatal peripheral smears typically display a significant presence of nucleated red blood cells (nRBCs). While the presence of nRBCs in peripheral blood is considered abnormal in adults and older children—often indicative of marrow infiltration, hypoxia, or hemolysis—in neonates it constitutes a normal finding, particularly within the first week of life. The percentage of nRBCs per 100 white blood cells may be as high as 50 or more at birth, progressively declining over the first few weeks postpartum as erythropoiesis stabilizes and extramedullary sites of hematopoiesis regress (18). These nucleated erythroid precursors reflect ongoing marrow activity and the residual fetal hematopoietic program transitioning to the adult pattern. Misinterpretation of physiologic nRBC presence as a marker of marrow stress or hypoxic injury is a common pitfall, emphasizing the need for contextualization with gestational age, perinatal history, and clinical findings.

Additionally, neonatal peripheral smears often reveal relative lymphocytosis, a finding that contrasts with the neutrophil predominance characteristic of adult blood. In neonates, lymphocytes may account for up to 50–60% of the white cell differential count, reflecting the developmental immaturity of the myeloid lineage and the prominent role of the adaptive immune system in early life (18). This lymphocytic predominance includes a spectrum of small, mature-appearing lymphocytes alongside larger, more immature lymphoid precursors, which may be misread as abnormal or suggestive of lymphoproliferative disorders if evaluated without age-appropriate reference ranges. The immune system of the neonate is undergoing rapid development at this time and peripheral blood lymphocytes may have reactive features such as cytoplasmic basophilia and prominent nucleoli, making morphology challenging..

In light of these subtleties, pleomorphismazacytoid cells in the peripheral blood smear needs to be correlated with more definitive marrow testing to make the correct diagnosis. Bone marrow aspirates, moreover, offer an incomparable level of information with regard to cellular morphology, maturation and lineage to establish a distinction between physiologic hematopoiesis and any abnormality. Aspiration smears in neonates commonly demonstrate a hypercellular marrow with erythroid hyperplasia and active granulopoiesis that correlate with peripheral findings. Cytologic evaluation of aspirates allows for precise enumeration of blast populations, identification of dysplastic features, and assessment of hematopoietic progenitor cells, all critical for early detection of congenital marrow failure syndromes, inherited anemias, or hematologic malignancies.

Complementing aspirate analysis, bone marrow trephine biopsies afford architectural context and facilitate the evaluation of marrow cellularity, stromal integrity, and spatial relationships among hematopoietic cells, fat, and the vascular niche. In neonates, trephine biopsies typically show markedly increased cellularity, often exceeding 80%, reflecting the marrow’s robust hematopoietic activity (19). The distribution of hematopoietic lineages is generally orderly, with preservation of marrow

microarchitecture, absence of fibrosis, and lack of abnormal infiltrates. However, trephine biopsies are invaluable when aspirate specimens are suboptimal or when bone marrow fibrosis, infiltrative disease, or aplastic processes are suspected, providing additional diagnostic information.

The combined application of bone marrow aspirates and trephine biopsies constitutes the gold standard in marrow evaluation, maximizing diagnostic yield and accuracy. Aspirates provide cellular detail and allow for additional testing including flow cytometry and cytogenetics, whereas trephine biopsies offer gross assessment of marrow composition and the ability to perform immunohistochemical analyses that allow for localization of specific cell populations in the tissue framework. Such a clinically and morphologically integrated approach is especially important for the neonatal population, where hematopoietic indices are rapidly evolving, and where even minor morphologic deviations might represent an early manifestation of significant underlying disease..

It is crucial that the diagnostic workup for neonates is based on clinical correlation and laboratory testing. For example, nRBCs and polychromasia can be seen as normal physiologic entities in a healthy term neonate, but a feature of hypoxic-ischemic injury or hemolytic disease in the setting of perinatal asphyxia or maternal-fetal blood group incompatibility. Similarly, lymphocytosis may be normal in uncomplicated neonates but warrants further evaluation in infants with persistent lymphadenopathy or unexplained cytopenias. Therefore, interpretation of peripheral and marrow findings must be framed within the comprehensive clinical scenario.

In addition, Corollary studies (flow cytometry, cytogenetics, molecular diagnostics) often depend on the quality of marrow aspirate specimens, so it is important to obtain sufficient and optimal specimens at the first evaluation. By flow cytometry, immature, and/or abnormal populations can be identified immunophenotypically, providing a tool that can be used for the detection of congenital immunodeficiencies as well as early leukemic clones. Cytogenetics and molecular studies find evidence of underlying genetic abnormalities associated with marrow failure syndromes or malignancies that may lead to early recognition of the disorder and allow for prognostication and therapeutic planning.

In summary, the neonatal peripheral smear requires an awareness of age-related blood cell values to differentiate normal features such as polychromasia, nucleated red cells, and lymphocytosis from abnormal findings. Bone marrow aspirates and trephine biopsies are complementary procedures that provide cytologic and architectural details, respectively, and the combined approach is essential for optimal diagnostic accuracy. The correlation of morphologic features with clinical and laboratory data, supplemented by advanced ancillary studies, lays the foundation for an appropriate pediatric hematopathologic diagnosis.

H. Integration with Ancillary Modalities

The role of advanced diagnostics in thermal bone marrow scanning The morphological evaluation of pediatric bone marrow must be multimodal in approach, using highly sensitive ancillary techniques, which improve diagnostic accuracy and allow for refined characterization of hematopoietic diseases. Of these, flow cytometry has become an invaluable tool in the pediatric hematopathologist's repertoire. This technique facilitates rapid, multiparametric immunophenotypic profiling of hematopoietic progenitors and mature cells, enabling the identification and quantification of discrete cell populations based on surface and cytoplasmic antigen expression.

Crucially, the interpretation of flow cytometric data in children demands age-specific gating strategies and antibody panels. This is because antigen expression profiles on hematopoietic precursors are developmentally regulated. For example, markers such as CD10, terminal deoxynucleotidyl transferase (TdT), and CD34 exhibit variable expression intensity and distribution patterns throughout different stages of hematopoietic maturation in the pediatric marrow (20). Failure to account for these age-related variations may lead to false-positive interpretations of immature or aberrant populations, thereby complicating the differentiation between normal developmental hematopoiesis and neoplastic processes.

Beyond flow cytometry, molecular diagnostics have transformed the landscape of pediatric hematopathology, providing vital insights into the genetic underpinnings of congenital marrow failure syndromes, clonal hematopoiesis, and leukemogenesis. Conventional cytogenetics (karyotyping) and fluorescence in situ hybridization (FISH) remain foundational for detecting chromosomal abnormalities—such as translocations, deletions, and aneuploidies—that define distinct pediatric leukemia subtypes and prognosticate disease course. The recent introduction of next-generation sequencing (NGS) permits even greater diagnostic power by the ability to probe at high resolution mutations of panels of genes associated with hematopoietic regulation, DNA repair, and oncogenic signaling.

Molecular findings have to be integrated with both morphologic and immunophenotypic data in not only making a diagnosis but in risk classification, therapy decisions, and monitoring of minimal residual disease (MRD). In addition, molecular studies can confirm an inherited disorder of the marrow, such as Fanconi anemia or dyskeratosis congenita, so that intervention can be made early and genetic counseling provided.

Morphology combined with flow cytometry, cytogenetics, and molecular are therefore utilized in a cross sectional manner in the evaluation of pediatric marrow. This chimeric approach raises diagnostic accuracy, allows for the differentiation between reactive and malignant process, and directs individualized patient management

Pediatric hematopoiesis is a distinctively regulated process characterized by age-related morphologic, cellular, and microenvironmental features. Knowledge of the normal evolution of bone marrow is important in differentiating normal variants from disease. A correct interpretation demands a correlation between histology, cytology, flow cytometry, molecular analyses and radiologic imaging, with reference to the child's age and clinical scenario.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 2: Non-neoplastic Marrow Disorders in Children

1 Introduction

On a quiet pediatric ward, six-year-old Aiden was admitted with striking pallor, profound fatigue, and recurrent infections. He was afebrile, but his complete blood count showed pancytopenia—a severe reduction in all blood cell lines. Together, the clinical picture and lab results pointed to a challenging hematologic problem: a hypocellular bone marrow with markedly impaired hematopoiesis. With no clear precipitating cause, the diagnosis was aplastic anemia, a rare but life-threatening marrow failure syndrome. This case underscores the complex, heterogeneous spectrum of non-neoplastic marrow diseases in children and the need for nuanced interpretation and a careful differential diagnosis.

In childhood, non-neoplastic marrow dysfunctions are a diverse group of conditions defined by impaired blood cell production without malignant infiltration. These disorders may be congenital, arising from genetic marrow failure syndromes, or acquired, triggered by external insults, systemic diseases, or idiopathic immune-mediated processes. Despite the range of underlying causes, the presentation often looks similar—cytopenias with a hypocellular marrow or lineage-specific suppression—making both diagnosis and treatment challenging.

Aplastic anemia serves as the model of marrow failure with a very low count of hematopoietic precursors in otherwise structurally normal marrow. The congenital variants, such as Fanconi anemia or Dyskeratosis congenita, are the products of inherited mutations in DNA repair, telomere maintenance, or ribonucleoprotein biogenesis, and result in the progressive marrow aplasia with a multisystemic spectrum. They typically present with phenotypic stigmata—cutaneous abnormalities, skeletal malformations, or pulmonary fibrosis—which can be helpful clinical clues. Acquired aplastic anemia, on the other hand, is usually idiopathic. But may be precipitated by immune-mediated destruction of hematopoietic stem and progenitor cells, exposure to myelotoxic agents,

or viral pathogens such as hepatitis or Epstein-Barr virusMorphologically, the marrow is extremely hypocellular with fat replacement and there is no evidence of dysplasia with residual stromal integrity that helps to differentiate it from neoplasia (1,2).

CEB, however, is a more severe disease than TEC, which is a benign, self-limited disorder of isolated erythroid aplasia. TEC is most common in toddlers and pre-school children and is occasionally preceded by a nonspecific viral prodrome. The signature is a marked reticulocytopenia and anemia in the presence of a normocellular or mildly hypocellular marrow devoid of erythroid precursors. Notably, granulopoiesis and megakaryopoiesis are not impaired, and leukocyte and platelet numbers are spared. Pathogenesis is proposed to be immune-mediated suppression of erythroid progenitors, or direct viral inhibition, but specific aetiologic agents are yet to be identified. Clinical recovery is spontaneous, typically within weeks to months, and the prognosis is excellent without long-term sequelae (3,4).

Pure red cell aplasia (PRCA) encompasses a broader spectrum of disorders characterized by selective erythroid lineage failure. Unlike TEC, PRCA can be congenital, as seen in Diamond-Blackfan anemia (DBA), or acquired, due to autoimmune mechanisms, thymoma, or parvovirus B19 infection. DBA results from ribosomal protein gene mutations causing defective erythropoiesis and often presents with craniofacial anomalies and growth retardation. Bone marrow biopsy in PRCA demonstrates a near-total absence of erythroid precursors with preserved myeloid and megakaryocytic elements, necessitating differentiation from other marrow aplasias and hemolytic anemias (5,6).

The landscape of marrow suppression extends beyond intrinsic marrow disorders, encompassing secondary marrow hypoplasia induced by systemic illnesses such as sepsis, medication toxicity, and viral infections. Sepsis-associated marrow suppression reflects a complex interplay of inflammatory cytokines, marrow microenvironment disruption, and direct pathogen-mediated injury. Drugs such as chemotherapeutics, anticonvulsants, and antibiotics can precipitate marrow aplasia via idiosyncratic or dose-dependent toxicity. Viral infections, particularly parvovirus B19, HIV, and hepatitis viruses, may cause direct cytopathic effects or immune-mediated marrow suppression, often transient but occasionally persistent (7,8).

Morphologically, hypocellular marrow in pediatric patients requires a careful differential diagnosis, as numerous entities can mimic aplasia. Distinguishing congenital marrow failure syndromes from acquired aplastic anemia mandates integration of clinical, morphologic, cytogenetic, and molecular data. Marrow cellularity, fat content, fibrosis, and residual stromal elements must be meticulously assessed, often supplemented by immunohistochemical and flow cytometric analyses. Image-rich differentials highlight

the subtle variations in marrow architecture and cellular composition that guide diagnosis and management (9,10).

The following detailed discussion explores these entities with a focus on pathogenesis, morphologic features, diagnostic criteria, and clinical implications, aiming to equip the clinician and pathologist with an exhaustive understanding of non-neoplastic marrow disorders in children.

A. Aplastic Anemia

Aplastic anemia (AA) constitutes a prototypical marrow failure syndrome, wherein hematopoietic stem and progenitor cells are drastically reduced or functionally incapacitated, leading to pancytopenia. Congenital forms arise from germline mutations affecting DNA repair (Fanconi anemia), telomere maintenance (Dyskeratosis congenita), or ribosomal function (Diamond-Blackfan anemia). Fanconi anemia, for instance, involves defective interstrand crosslink repair resulting in chromosomal instability and progressive marrow failure often manifesting in early childhood. In contrast, acquired aplastic anemia usually stems from an aberrant immune-mediated destruction of hematopoietic stem cells, triggered by an as-yet-unidentified antigen or environmental insult. The marrow in AA is characteristically hypocellular, with residual fatty replacement and absence of malignant infiltrates or fibrosis.

Clinically, AA presents with symptoms attributable to pancytopenia: fatigue, pallor, bleeding diatheses, and recurrent infections. Laboratory evaluation reveals severe anemia, leukopenia, and thrombocytopenia. Bone marrow biopsy is indispensable, demonstrating markedly decreased cellularity (<25%) with diminution across all hematopoietic lineages. Cytogenetic studies are vital to exclude hypoplastic myelodysplastic syndrome or leukemia. Treatment strategies vary depending on etiology, ranging from hematopoietic stem cell transplantation in congenital or severe acquired cases to immunosuppressive therapies such as anti-thymocyte globulin and cyclosporine in idiopathic acquired AA (1,2).

Feature	Description
Etiology	- Idiopathic (70%)- Immune-mediated T-cell destruction of HSCs- Secondary to viral infections (EBV, hepatitis, parvovirus B19)- Drug/toxin induced (chloramphenicol, NSAIDs, benzene)- Radiation exposure- Secondary to inherited marrow failure syndromes (Fanconi anemia, dyskeratosis congenita)
Age at Presentation	Primarily childhood (5–15 years), can present at any age
Clinical Presentation	- Pancytopenia: pallor, fatigue, infections, bleeding/bruising- Absence of organomegaly and lymphadenopathy- No blasts or abnormal cells in peripheral blood
Peripheral Blood Findings	- Normocytic or macrocytic anemia with reticulocytopenia- Severe neutropenia and thrombocytopenia- Absence of circulating blasts or dysplastic cells
Bone Marrow Cellularity	Markedly hypocellular marrow (<25% cellularity), often replaced by fat
Marrow Morphology	- Pancytopenia due to marked depletion of all hematopoietic lineages- No significant fibrosis or infiltrative processes- Absence of dysplasia or malignant cells
Immunohistochemistry	- Marked reduction or absence of CD34+ hematopoietic progenitors- Decreased staining for lineage markers (Glycophorin-A, MPO, CD61)- No clonal proliferation markers
Molecular Diagnostics	- Negative for myelodysplastic syndrome–associated mutations- Telomere length analysis and chromosomal breakage tests for inherited marrow failure syndromes- Paroxysmal nocturnal hemoglobinuria (PNH) clone testing positive in ~50%
Serum Markers	- Elevated erythropoietin (EPO)- Normal vitamin B12, folate, iron studies- Ferritin elevated if multiple transfusions
Treatment Options	- Immunosuppressive therapy (IST): antithymocyte globulin (ATG), cyclosporine, eltrombopag- Hematopoietic stem cell transplantation (HSCT) for eligible patients- Supportive care: transfusions, infection prophylaxis
Prognosis	- Excellent with matched sibling HSCT (5-year survival >90%)- IST response rate ~60–70%; relapses and refractory disease possible- Close monitoring for clonal evolution to MDS or leukemia
Differential Diagnoses	- Hypocellular myelodysplastic syndrome- Inherited marrow failure syndromes (e.g., Fanconi anemia)- Bone marrow infiltration by malignancy- Drug-induced marrow suppression

Key Diagnostic Points	- Diagnosis requires combination of pancytopenia and markedly hypocellular marrow- Exclusion of other marrow failure syndromes by genetic and molecular testing- Serial marrow evaluation may be needed for disease monitoring

B. Transient Erythroblastopenia of Childhood (TEC)

Transient erythroblastopenia of childhood (TEC) is an acquired, self-limiting disorder of erythropoiesis, primarily affecting children between 6 months and 3 years of age. It represents a paradigmatic example of a benign red cell aplasia, marked by a sudden-onset, normocytic anemia with reticulocytopenia, but without abnormalities in leukocyte or platelet counts. Although clinically alarming due to significant pallor and potential hemodynamic compromise, TEC is fundamentally transient in nature and generally resolves spontaneously without the need for therapeutic intervention.

The precise etiopathogenesis of TEC remains incompletely elucidated; however, it is widely postulated to result from immune-mediated transient suppression of erythroid progenitor cells, likely in response to a viral antigenic stimulus. Although parvovirus B19 is the prototypical virus associated with pure red cell aplasia, TEC is considered pathophysiologically distinct. Unlike parvovirus-mediated suppression—which selectively infects erythroid precursors via the P antigen and is often associated with underlying hemolytic conditions—TEC typically affects previously healthy, immunocompetent children and lacks virologic evidence of parvoviral DNA or seroconversion at presentation. The mechanism is more consistent with post-infectious T-cell dysregulation or cytokine-mediated inhibition of erythroid burst-forming units (BFU-E) and colony-forming units-erythroid (CFU-E), though this remains speculative in the absence of consistent immunologic markers (3).

Morphologically, bone marrow aspirates in TEC demonstrate a normocellular to mildly hypocellular marrow, with a pronounced selective erythroid hypoplasia or aplasia. This is characterized by a striking reduction or near-total absence of erythroid precursors, while granulopoiesis and megakaryopoiesis remain quantitatively and qualitatively preserved. The absence of dysplastic features, fibrosis, or clonal abnormalities differentiates TEC from congenital marrow failure syndromes and hypoplastic myelodysplastic syndromes. Importantly, the marrow stroma and vascular niches remain intact, reinforcing the notion that the disorder reflects functional suppression rather than architectural destruction or stem cell exhaustion (4).

Hematologically, the peripheral blood reveals a normocytic, normochromic anemia, typically with hemoglobin concentrations ranging from 6–9 g/dL. The defining feature

is a profound reticulocytopenia, often falling below 1%, indicating an absence of marrow compensation. This laboratory signature is essential for distinguishing TEC from more common causes of pediatric anemia, such as iron deficiency or hemolytic anemias, where reticulocyte counts are either elevated or appropriate for the degree of anemia. Platelet and white blood cell counts remain within normal age-adjusted ranges, and inflammatory markers are usually unremarkable (3).

Clinically, affected children present with progressive pallor and fatigue, often noted by caregivers over days to weeks. Despite the severity of anemia, children are generally non-toxic in appearance, without hepatosplenomegaly, lymphadenopathy, fever, or bleeding manifestations. This well appearance—despite low hemoglobin—is a key distinguishing factor and often helps avoid unnecessary invasive workup when appropriately recognized. However, in cases where symptoms are severe or diagnostic uncertainty exists, bone marrow evaluation may be pursued to exclude conditions such as aplastic anemia, leukemia, or red cell aplasia secondary to other etiologies (3,4).

The clinical course of TEC is characteristically benign, with spontaneous recovery in the majority of cases within 4 to 6 weeks. Reticulocyte counts typically rise before hemoglobin levels normalize, marking the onset of marrow recovery. In rare instances, the erythroid suppression may persist for up to 10–12 weeks, but such cases still usually resolve without long-term sequelae. Transfusion is seldom required unless the child is hemodynamically unstable or demonstrates symptoms of hypoxia or cardiovascular compromise. There is no role for corticosteroids, immunosuppressants, or bone marrow stimulants in TEC, as these do not accelerate recovery and may complicate the clinical picture. Recurrent episodes are extremely rare, and long-term outcomes are uniformly favorable (3,4).

The importance of correctly identifying TEC lies in its potential to be misinterpreted as more ominous conditions, particularly Diamond-Blackfan anemia, early myelodysplastic syndromes, or aplastic anemia, all of which may exhibit erythroid suppression in bone marrow. Unlike TEC, Diamond-Blackfan anemia typically presents earlier in life, is associated with macrocytic indices, congenital anomalies, and has a chronic course requiring ongoing therapy. Aplastic anemia, in contrast, is marked by trilineage cytopenias and global marrow hypocellularity. Recognition of the TEC phenotype thus prevents overtreatment and mitigates parental anxiety related to unnecessary bone marrow procedures or transfusions.

In conclusion, TEC represents a clearly defined clinical entity with characteristic hematologic and morphologic findings, predictable course and very good prognosis. The major diagnostic criteria are pancytopenia with anemia, reticulocytopenia, normal white blood cell and platelet counts, and marrow cellularity with preservation of the architecture except for marked erythroid hypoplasia. Clinicians and hematopathologists

need to be vigilant in recognizing TEC, especially to exclude other red cell aplasias and marrow failure syndromes that have different therapeutic implications. The self-limiting course allows conservative treatment when identified early and avoids unnecessary intervention.

Feature	Transient Erythroblastopenia of Childhood (TEC)
Typical Age at Onset	6 months to 3 years (peak incidence around 18–26 months)
Etiology	Likely post-viral, immune-mediated suppression of erythroid progenitors; exact mechanism remains undefined
Clinical Presentation	Gradual onset of pallor, fatigue, decreased activity; usually afebrile, no bleeding, no lymphadenopathy or hepatosplenomegaly
Peripheral Blood Findings	Isolated normocytic, normochromic anemia with very low reticulocyte count; WBC and platelet counts are normal
Bone Marrow Morphology	Normocellular or mildly hypocellular marrow; marked reduction or absence of erythroid precursors, normal myeloid and megakaryocytic lineages
Serum Markers	Normal to mildly elevated EPO; normal ferritin, iron, and vitamin B12 levels; no hemolysis markers
Immunohistochemistry	Decreased Glycophorin-A staining; CD34+ blasts and other lineage markers within normal limits
Molecular Testing	Negative; no evidence of congenital marrow failure; viral PCR typically not required unless clinical suspicion of B19
Treatment	Supportive only; no transfusions unless symptomatic; spontaneous recovery is expected
Time to Recovery	4–6 weeks in most cases; up to 2 months in some
Prognosis	Excellent; self-limited and non-recurrent in >95% of patients
Key Differentiators	- Older age than congenital PRCA

C. Pure Red Cell Aplasia

Pure Red Cell Aplasia (PRCA) constitutes a rare hematologic disorder characterized by profound, selective suppression of erythroid precursors in the bone marrow, leading to normocytic, normochromic anemia with marked reticulocytopenia. Unlike pan-lineage marrow failure syndromes, PRCA preserves the integrity of granulopoiesis and thrombopoiesis, thus presenting with isolated anemia in the setting of otherwise normal

white cell and platelet counts. PRCA is not a singular disease but a clinicopathologic syndrome encompassing both congenital and acquired etiologies, with distinct pathophysiologic mechanisms and clinical trajectories.

The congenital form of PRCA is typified by Diamond-Blackfan Anemia (DBA), a ribosomopathy resulting from mutations in ribosomal protein (RP) genes, most commonly RPS19, although more than 20 ribosomal protein genes have been implicated to date. These mutations result in defective ribosome assembly, causing nucleolar stress and p53-mediated apoptosis of erythroid progenitors. This selective vulnerability of erythropoiesis is not fully understood, but evidence suggests a high metabolic demand and protein synthesis dependency in erythroid precursors, rendering them uniquely susceptible to ribosomal dysfunction (5).

Children with DBA typically present within the first year of life—often in the neonatal period—with severe macrocytic anemia and low reticulocyte counts. Approximately 50% of patients exhibit congenital anomalies, including craniofacial dysmorphisms (e.g., micrognathia, hypertelorism), thumb or radial defects, cardiac malformations, and growth retardation. Short stature and developmental delay may also be present. Unlike TEC, which is transient and typically self-resolving, DBA is chronic and frequently requires long-term transfusion support or pharmacologic intervention. Elevated erythrocyte adenosine deaminase (eADA) levels and fetal hemoglobin are common laboratory findings, assisting in the diagnostic workup (5).

In contrast, acquired PRCA occurs later in life and encompasses a broad spectrum of causes. Autoimmune PRCA—in which cytotoxic T-lymphocytes or autoantibodies selectively target erythroid precursors—is the most common form. It may arise idiopathically or in association with thymomas, systemic lupus erythematosus (SLE), large granular lymphocytic (LGL) leukemia, or lymphoproliferative disorders. In thymoma-associated PRCA, removal of the tumor does not always lead to hematologic recovery, underscoring a complex immune dysregulation. Acquired PRCA may also be secondary to infections, most notably parvovirus B19, which exhibits tropism for erythroid progenitors via the P antigen. In immunocompetent hosts, this typically results in transient aplastic crises, whereas in immunocompromised patients (e.g., transplant recipients, HIV-infected individuals), the aplasia can become persistent and life-threatening (6).

Additional infectious triggers of PRCA include Epstein-Barr virus, hepatitis viruses, and HIV, though the evidence linking these agents to isolated red cell aplasia remains circumstantial in many cases. Drug-induced PRCA—though rare—has been reported with agents such as isoniazid, phenytoin, chloramphenicol, and recombinant erythropoietin, particularly in patients who develop anti-erythropoietin antibodies.

From a morphologic standpoint, PRCA is defined by a striking paucity or near-total absence of erythroid precursors in the bone marrow, with preservation of the myeloid and megakaryocytic series. In severe cases, proerythroblasts and basophilic erythroblasts may be entirely absent, while the remainder of the marrow cellularity remains age-appropriate and topographically intact. No dysplasia or blast excess is typically observed. Bone marrow biopsy reveals normal architecture, and in autoimmune PRCA, an increased population of CD8+ cytotoxic T-cells may be evident. Immunohistochemical stains and flow cytometry may help in identifying subtle lymphoproliferative processes or underlying cytotoxic populations (6).

Hematologic features in PRCA include normocytic, normochromic anemia, frequently with hemoglobin levels between 5 and 9 g/dL and reticulocytopenia below 1%. Iron stores are often elevated due to ineffective erythropoiesis and transfusion history, and erythropoietin levels are typically elevated in an appropriate compensatory response. Serum LDH and bilirubin remain normal in contrast to hemolytic anemias, and the absence of leukopenia or thrombocytopenia differentiates PRCA from aplastic anemia or MDS.

The diagnostic approach to PRCA mandates a structured evaluation to exclude mimickers such as hemolysis, nutritional deficiencies (e.g., folate, B12), marrow infiltration, and other causes of anemia with low reticulocyte response. In congenital cases, genetic testing for ribosomal protein gene mutations confirms the diagnosis of DBA, while elevated eADA and macrocytosis provide supporting evidence. In acquired cases, a comprehensive workup should include viral PCRs, autoimmune serologies, flow cytometry, T-cell clonality assays, and imaging studies for thymoma if clinically indicated.

Management of PRCA is dictated by etiology. In DBA, treatment options include chronic corticosteroid therapy, red cell transfusions, and hematopoietic stem cell transplantation (HSCT) for refractory cases or those developing iron overload. Newer therapies targeting p53 regulation and ribosome rescue (e.g., leucine, L-leucine supplementation, lenalidomide) are under investigation. In acquired autoimmune PRCA, immunosuppressive therapy—with agents such as prednisone, cyclosporine, rituximab, or antithymocyte globulin—is the mainstay. For parvovirus-induced PRCA, particularly in immunodeficient hosts, intravenous immunoglobulin (IVIG) is the treatment of choice and often leads to rapid erythroid recovery. In thymoma-associated PRCA, thymectomy may offer hematologic remission in a subset of cases but frequently requires adjuvant immunosuppression.

The prognosis of PRCA varies significantly. DBA, while chronic, may remit spontaneously in some patients during adolescence. However, others remain transfusion-dependent and at risk for iron overload, endocrine dysfunction, and secondary

malignancies. Acquired PRCA, particularly autoimmune variants, often respond well to immunosuppressive therapy, though relapses can occur. Parvovirus-related PRCA, in contrast, has an excellent prognosis in immunocompetent individuals but may become life-threatening in immunodeficient patients if not treated promptly.

In conclusion, pure red cell aplasia represents a heterogeneous group of disorders unified by the pathologic hallmark of selective erythroid suppression. Its causes span from inherited ribosomal disorders to immune dysregulation and viral infections, necessitating a thorough clinical and diagnostic workup. Histopathologic evaluation remains essential, particularly in distinguishing PRCA from other causes of anemia with reticulocytopenia. Accurate identification of the underlying etiology is critical, as management strategies differ markedly across the spectrum, and prompt, etiology-directed therapy can lead to durable remission in many cases.

Feature	**Congenital PRCA (Diamond-Blackfan Anemia)**	**Acquired PRCA (Idiopathic or Secondary)**
Typical Age at Onset	Neonatal period to first year of life	Variable; often after 1 year of age
Etiology	Germline mutations in ribosomal protein genes (e.g., RPS19, RPL5, RPL11)	Immune-mediated (idiopathic), viral (e.g., parvovirus B19), thymoma, autoimmune disease, hematologic malignancy
Inheritance Pattern	Mostly autosomal dominant, sometimes de novo	Not inherited; acquired
Associated Anomalies	Present in ~50%: craniofacial dysmorphisms, thumb/radial anomalies, cardiac defects, short stature	Typically absent; if present, point to underlying systemic disease (e.g., lupus, thymoma)
Clinical Presentation	Pallor, fatigue, failure to thrive; usually no hepatosplenomegaly	Sudden anemia, reticulocytopenia; may follow viral illness or drug exposure
Peripheral Blood Findings	Severe macrocytic anemia, very low reticulocyte count, normal WBC/platelets	Normocytic or macrocytic anemia, isolated low Hb, severe reticulocytopenia, normal WBC/platelets
Bone Marrow Morphology	Normocellular with selective erythroid aplasia, normal myeloid/megakaryocytic lineages	Normocellular or mildly hypocellular marrow, marked erythroid hypoplasia or

		absence, preserved other lineages
Serum Markers	↑ eADA, ↑ fetal hemoglobin, normal iron/ferritin	Often elevated EPO, ↑ ferritin (especially in chronic cases), viral serologies may be positive
Molecular Testing	Ribosomal gene mutations (e.g., RPS19, RPL11); telomere studies if dyskeratosis suspected	Negative for congenital mutations; parvovirus B19 PCR, autoantibodies, thymoma imaging may assist
Immunohistochemistry	Decreased glycophorin-A, reduced erythroid markers; CD34 preserved	Same as congenital; if viral, may show parvovirus capsid antigen or NS1 positivity
Treatment	Corticosteroids, transfusions, HSCT in severe cases; gene therapy under investigation	Underlying cause-directed: IVIG for parvovirus, immunosuppressive therapy (steroids, cyclosporine, ATG) for autoimmune forms
Prognosis	Variable; many require chronic transfusions; spontaneous remissions rare	Usually good if reversible cause identified; may relapse if immune-mediated
Key Differentiators	Congenital onset, anomalies, macrocytosis, ribosomal mutations	Acquired onset, post-infectious or autoimmune, normal growth and development

D. Marrow Suppression in Systemic Illness

Bone marrow hypoplasia secondary to systemic illness embodies a complex and often reversible disruption of hematopoiesis, resulting from a multifactorial convergence of inflammatory cytokine cascades, direct cytotoxic insult, stromal microenvironmental perturbations, and immune-mediated suppression. In contrast to primary marrow failure syndromes, the hypocellularity observed in these conditions is typically secondary to external pathophysiologic stressors and is often transient if the underlying etiology is addressed in a timely manner.

One of the most prominent systemic causes of marrow suppression is sepsis, particularly in the setting of disseminated bacterial infections, where an overwhelming cytokine storm exerts profound effects on hematopoietic stem and progenitor cells (HSPCs). Pro-

inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, and interferon-gamma (IFN-γ) play critical roles in mediating this suppression. These cytokines inhibit progenitor proliferation, induce apoptosis of HSPCs, and disrupt stromal support functions, thereby impeding lineage commitment and maturation. Additionally, endotoxemia and microbial products such as lipopolysaccharides (LPS) directly impair the marrow vascular niche, further compounding hematopoietic suppression. The clinical consequence is often a transient pancytopenia, most notable during the acute phase of systemic infection, particularly in neonates and immunocompromised children, where hematopoietic reserve may already be limited (7).

Drug-induced marrow suppression represents a major iatrogenic cause of cytopenias in pediatric populations, especially in hospitalized or chronically ill children. Numerous pharmacologic agents are implicated, including chemotherapeutic drugs (e.g., methotrexate, cytarabine), antimicrobials (e.g., chloramphenicol, sulfonamides), anticonvulsants (e.g., phenytoin, carbamazepine), and immunosuppressants (e.g., azathioprine, mycophenolate). The mechanisms by which these agents induce marrow suppression vary and may include dose-dependent cytotoxicity, idiosyncratic hypersensitivity reactions, or immune-mediated destruction of progenitor cells. Certain drugs, such as chloramphenicol, exhibit mitochondrial toxicity, impairing nucleated cell metabolism and replication. In cases of reversible drug-induced aplasia, cessation of the offending agent usually results in gradual hematopoietic recovery. However, continued exposure may lead to irreversible marrow injury, mimicking aplastic anemia in its clinical and histologic presentation (8).

Among infectious causes, viral-induced marrow suppression occupies a central role. Parvovirus B19, perhaps the most well-characterized virus in this regard, has a unique tropism for erythroid progenitors—specifically the BFU-E and CFU-E compartments—due to the expression of the P antigen on their surface. The virus induces direct cytopathic effects, leading to a marked drop in reticulocyte production and profound anemia. While healthy individuals typically recover within 7–10 days, those with underlying hemolytic disorders (e.g., sickle cell disease, hereditary spherocytosis) may develop transient aplastic crises, necessitating transfusion support. In immunocompromised children, persistent infection may lead to chronic pure red cell aplasia, as viral clearance is dependent on intact humoral immunity (7).

Other viral pathogens, including hepatitis B and C viruses, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV), have been implicated in marrow suppression through more indirect mechanisms. These may involve immune dysregulation, interference with marrow stromal integrity, or chronic antigenic stimulation resulting in T-cell–mediated suppression of progenitor cells. In HIV-infected children, marrow suppression may also reflect the cumulative effects of opportunistic infections, nutritional deficiencies, and long-term antiretroviral therapy.

The resultant cytopenias—particularly anemia and neutropenia—can significantly complicate disease management and therapeutic decision-making (8).

Histologically, marrow specimens from patients with systemic illness–associated marrow suppression exhibit a variable spectrum of findings. The marrow cellularity may range from hypocellular to normocellular, depending on the timing of biopsy in relation to the inciting event. Maturation arrest, particularly in the erythroid lineage, is frequently observed. In some cases, the marrow may show a shift toward early progenitors without maturation into terminal stages, mimicking myelodysplastic processes. However, unlike clonal disorders, dysplasia is absent, and no blast excess is evident. Infectious agents, if directly involved (e.g., parvovirus B19), may be identified via immunohistochemistry or in situ hybridization. Stromal cells may appear reactive or activated, particularly in inflammatory states such as sepsis or autoimmune conditions. Iron stores are usually preserved or elevated, especially in chronic illness or in transfused patients.

Crucially, differentiating secondary marrow suppression from primary bone marrow failure syndromes (e.g., aplastic anemia, myelodysplastic syndromes) necessitates a careful synthesis of clinical history, laboratory data, and ancillary studies. The temporal relationship between symptom onset and exposure to infectious or pharmacologic agents is vital. Rapid resolution of cytopenias following withdrawal of a drug or resolution of infection strongly favors a secondary etiology. Flow cytometry may assist in ruling out hematologic malignancies, while viral PCR panels, autoimmune markers, and drug level assays can clarify underlying causes.

Moreover, in pediatric practice, nutritional deficiencies (e.g., copper, folate, vitamin B12, and zinc) must also be excluded, particularly in chronically ill or malnourished children, as these can exacerbate marrow suppression and confound diagnostic interpretation.

Management of secondary marrow suppression is primarily supportive and etiology-directed. In infectious cases, appropriate antimicrobial or antiviral therapy may reverse cytopenias. For drug-induced cases, prompt discontinuation of the offending agent is paramount. In cases of profound or prolonged pancytopenia, hematopoietic growth factors (e.g., G-CSF, erythropoietin) may be used cautiously, though their efficacy in transient suppression remains variable. Transfusion support may be required for symptomatic anemia or thrombocytopenia. Bone marrow biopsy is warranted in cases where cytopenias are severe, prolonged, or unexplained, particularly if there is concern for evolving primary marrow pathology.

Category	Etiology	Pathophysiology	Clinical Features	Bone Marrow Findings	Diagnostic Markers /Tests	Management
Sepsis	Bacterial, fungal, viral infections causing systemic inflammatory response	Cytokine storm (TNF-α, IL-6, IFN-γ) induces marrow stromal dysfunction; myelosuppressive microenvironment; transient stem/progenitor cell arrest	Fever, organ dysfunction, cytopenias (often neutropenia and thrombocytopenia), shock in severe cases	Hypocellular or normocellular marrow with maturation arrest, decreased granulopoiesis	Blood cultures, inflammatory markers (CRP, procalcitonin), marrow biopsy if indicated	Treat infection aggressively, supportive care, growth factors in some cases
Drug-induced	Chemotherapeutics, antibiotics (chloramphenicol), anticonvulsants, NSAIDs, immunosuppressants	Direct cytotoxicity to hematopoietic stem cells or progenitors; immune-mediated destruction	Variable cytopenias depending on drug; often pancytopenia; bleeding, infections	Hypocellular marrow with reduction of all hematopoietic lines; sometimes dysplastic changes	Medication history, drug levels, marrow biopsy	Discontinue offending drug, supportive care, hematopoietic growth factors
Viral Infections	Parvovirus B19, EBV, CMV, HIV, Hepatitis viruses	Direct infection and cytopathic effect on erythroid or other	Anemia (especially with parvovirus B19), constitutional	Parvovirus: erythroid aplasia with preserved other	PCR for viruses, serology, marrow biopsy	Supportive care, antiviral therapy if available, immunogl

		progenitors; immune dysregulation	symptoms, lymphadenopathy in EBV	lineages; EBV: reactive lymphocytosis; HIV: variable suppression		obulins for B19
Nutritional Deficiencies	Vitamin B12, Folate, Copper deficiency	Impaired DNA synthesis; ineffective hematopoiesis	Anemia, glossitis, neurologic symptoms (B12), neutropenia, thrombocytopenia	Marrow: megaloblastic changes, nuclear-cytoplasmic asynchrony	Serum B12, folate, copper levels	Nutritional supplementation
Systemic Autoimmune Disorders	SLE, Juvenile idiopathic arthritis	Autoimmune-mediated marrow suppre				

E. Image-Rich Differentials of Hypocellular Marrow

Hypocellular bone marrow in pediatric patients poses a formidable diagnostic challenge due to its wide-ranging etiologic possibilities, spanning genetic marrow failure syndromes, acquired hematopoietic aplasia, secondary suppression, and marrow infiltration. In children, age-specific baseline marrow cellularity complicates the interpretation further, with younger age groups typically demonstrating hypercellular marrow relative to adults. Therefore, determining “hypocellularity” must always be contextualized to age-adjusted norms.

The initial morphologic assessment of bone marrow biopsy specimens involves a detailed analysis of overall cellularity, evaluated against the expected percentage (approximated by 100% minus the patient’s age), along with lineage-specific representation, topographic organization, and presence of maturation arrest, stromal disruption, or fibrotic or neoplastic infiltrates. Particular attention must be paid to the trilineage hematopoiesis pattern—whether suppression is pan-lineage (as in aplastic

anemia), lineage-selective (as in PRCA), or disorganized (as seen in early myelodysplastic syndromes or marrow infiltration).

Immunohistochemistry (IHC) provides indispensable lineage-specific markers, including CD34 (hematopoietic precursors), CD61 (megakaryocytes), CD68 (histiocytes/macrophages), Glycophorin-A (erythroid elements), and MPO (myeloid cells), which are used to confirm or quantify residual progenitor populations. Also, fibrosis assessment (using reticulin or trichrome stains) and detection of clonal infiltrates (e.g., Langerhans cells, leukemic blasts, and metastatic tumor) help provide morphologic clarity of the diagnosis.

Molecular diagnostics, such as NGS panels, measurement of telomere length and gene mutation analyses (e.g., RPS19, TERC, GATA2) are becoming increasingly crucial to the recognition of congenital marrow failure syndromes and occult clonal hematopoiesis. Cytogenic studies (karyotype, FISH) can identify cryptic chromosomal abnormalities of myelodysplastic evolution or inherited syndromes, such as Fanconi anemia (e.g., chromosomal breakage). Flow cytometry can also identify abnormal immunophenotypes that can suggest either leukemic (or lymphoproliferative) disease.

Radiological correlation with MRI of PET-CT can be useful, especially if the marrow signal does not reflect the expected age-related red-to-yellow conversion. Diffuse low T1 signal on MRI can be indicative of infiltrative disease, marrow edema, or early aplasia. Focal lesions, however, suggest possible localized infiltration or neoplastic deposits.

In the end, a complete work-up of hypocellular marrow in children should include:

1. Clinical context (past infections, pharmacologic exposure, syndromic features);

2. Laboratory test results (pattern of cytopenia, reticulocyte count, serum ferritin, vitamin levels);

3.Histologic morphology; and

4. Ancillary testing results.

Failure to synthesize these data points may result in misclassification of reversible conditions as irreversible marrow failure or, conversely, under-recognition of a progressive clonal disorder masquerading as transient suppression (9,10).

Table 1: Differentials Hypocellular Marrow in Children

Etiology	Age of Onset	Clinical Clues	Peripheral Blood Findings	Bone Marrow Histology	IHC/Molecular Features	Ancillary Tests
Fanconi Anemia (Congenital Marrow Failure)	Infancy to early childhood	Short stature, café-au-lait spots, thumb anomalies, renal malformations	Pancytopenia, macrocytosis, high fetal Hb	Hypocellular; trilineage suppression; early fibrosis	Negative CD34; increased apoptosis; chromosomal breakage positive	DEB test; NGS for FANCA/FANCC mutations
Dyskeratosis Congenita	Childhood to adolescence	Skin hyperpigmentation, nail dystrophy, oral leukoplakia	Anemia, neutropenia, thrombocytopenia	Progressive hypocellularity; telomere shortening features	Reduced CD34; positive p53 in some cases	Telomere length testing; DKC1, TERT mutation analysis
Acquired Aplastic Anemia	Any age	Recent viral illness, drug exposure, hepatitis	Pancytopenia, normal MCV, low retic count	Severely hypocellular; empty fat-rich spaces	Decreased CD34/CD61/Gly-A; no fibrosis	Viral PCR; PNH clone analysis; T-cell receptor rearrangement
Transient Marrow Suppression (e.g., Sepsis, Viral)	Any age, often acute onset	Recent infection or systemic illness	Mild-to-moderate pancytopenia; reticulocytopenia	Normo- to mildly hypocellular; preserved stroma	Normal IHC; absence of clonal markers	Viral serology (e.g., B19, EBV); inflammatory markers

Drug-Induced Marrow Suppression	Variable; after medication exposure	Recent drug start (e.g., antibiotics, anticonvulsants)	Pancytopenia or selective cytopenia	Hypocellular; possible dysmaturation	No clonal markers; CD34 variably decreased	Drug history review; rechallenge not recommended
Parvovirus B19-Associated Red Cell Aplasia	Common in ages 1–10 yrs	Sudden anemia in known hemolytic disease or immunosuppressed	Severe anemia, very low reticulocytes; WBC and platelets normal	Normocellular marrow; absent erythroid precursors	Decreased Glycophorin-A; positive B19 IHC	Parvovirus PCR or IgM; viral load monitoring
Myelodysplastic Syndrome (Hypocellular Variant)	Rare in children	Refractory cytopenia; occasional dysplasia in smear	One or more cytopenias; possible macrocytosis	Hypocellular; dysplasia; abnormal localization of precursors	Abnormal CD34/CD117 coexpression; cytogenetics abnormal	Karyotyping; NGS panels (RUNX1, GATA2, TP53)
Leukemic Marrow with Hypocellularity (Early Phase)	Variable	Constitutional symptoms; lymphadenopathy	Cytopenias; blasts may be absent in PB	Hypocellular; focal lymphoid clusters or subtle blasts	Aberrant flow cytometry phenotype (e.g., CD10+/CD34+/TdT+)	Flow cytometry; bone marrow repeat in 1–2 wks if equivocal
Metastatic Tumor Infiltration (e.g., Neuroblastoma)	<5 years	Abdominal mass, weight loss, bone pain	Cytopenias; leukoerythroblastic smear	Hypocellular with focal infiltrates; pseudo-rosettes	Synaptophysin+/NSE+ tumor cells	MRI; urinary catecholamines; PET-CT
Nutritional Marrow Suppression (e.g., B12,	Any age, often gradual	Malnutrition, GI disorders, restrictive diets	Anemia ± neutropenia; macrocytosis common	Hypocellular or normocellular; dyserythropoiesis	Megaloblastic changes; increased apoptosis	Serum B12, folate, copper, ceruloplasmin

Copper Deficiency)

Conclusion

Non-neoplastic marrow disorders in children comprise a complex and heterogeneous group of pathologies characterized by impaired hematopoiesis without malignant infiltration. Accurate diagnosis requires an integrative approach, combining clinical assessment, laboratory data, morphologic evaluation, and advanced ancillary techniques. Understanding the pathophysiologic mechanisms underlying congenital and acquired marrow failure syndromes, transient erythroid aplasia, and marrow suppression secondary to systemic illness is essential for optimal patient management and prognostication.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 3: Congenital Bone Marrow Failure Syndromes

1 Introduction

The The human bone marrow is like a hidden factory, working silently inside our bones to create the blood cells we need to survive—red cells to carry oxygen, white cells to fight infections, and platelets to stop bleeding. In healthy children, this system works smoothly from birth, adjusting and growing with the child. But in some rare children, this factory is faulty from the very beginning.

Congenital bone marrow failure syndromes are hereditary genetic disorders in which the bone marrow is unable to produce adequate amount of healthy blood cells. They are not the result of infections, toxins, or external pathogens that enter the child's genome — rather, they are "baked into" the child's DNA.

These disorders are rare, often misunderstood, and deeply life-altering for affected children and their families.

Picture a baby born free of any sign of illness, only to become noticeably pale, or covered in unexplained bruises, or constantly getting sick by the time he or she is six months old. Or a toddler whose blood counts are shockingly low, even though there's no evidence of infection or illness on the surface. For parents, the path to diagnosis is often frustrating and confusing. For doctors, spotting the patterns early can make the difference between life and death.

Unlike acquired bone marrow failure, which may result from medications, toxins, or autoimmune diseases, congenital bone marrow failure syndromes are rooted in defective genes. Each of these syndromes affects the body in unique ways—some damage only red blood cell production, while others impair all three cell lines. Some also involve other organs, causing abnormalities in the skin, bones, or even the digestive system.

In this chapter, we will explore four major congenital bone marrow failure syndromes seen in children:

1. Fanconi Anemia, a condition involving chromosome instability and physical anomalies.
2. Diamond-Blackfan Anemia, a disorder with selective red cell failure and characteristic facial features.
3. Shwachman-Diamond Syndrome, which affects both bone marrow and the pancreas.
4. Dyskeratosis Congenita, a telomere disorder that causes premature aging of cells.

To make these complex syndromes easier to understand, we will introduce each one with a brief, real-life-inspired story of a child living with that condition. These stories reflect the emotional and clinical challenges faced by families and physicians. Following each story, you will find a detailed explanation of the disease, and an easy-to-use summary table for quick reference.

Understanding these rare conditions isn't just about memorizing facts—it's about learning to recognize silent signals, thinking broadly, and caring deeply. These children depend on our ability to detect the invisible early, to act quickly, and to treat gently.

A. Fanconi Anemia

Meena was only six years old when her parents noticed she bruised very easily. Her gums bled after brushing, and she was always tired. Blood tests showed that her hemoglobin, white cells, and platelets were all very low. She was later found to have short stature and dark patches on her skin. A special chromosome breakage test confirmed Fanconi anemia. Her parents were devastated to learn that Meena had a high risk of developing leukemia if untreated.

What is Fanconi Anemia?

Fanconi anemia (FA) is a rare, inherited disorder characterized by mutations in genes involved in the DNA damage response and repair pathway, particularly those responsible for fixing DNA interstrand crosslinks. These genetic defects lead to genomic instability, making cells highly susceptible to chromosomal breakage. As a result, FA manifests with progressive bone marrow failure, typically presenting in early childhood with pancytopenia. In addition to hematologic abnormalities, affected individuals often have congenital malformations, including short stature, radial ray defects (such as absent or hypoplastic thumbs), skin pigmentation abnormalities like café-au-lait spots, and structural anomalies involving the kidneys, heart, or eyes. FA also confers a markedly increased risk of hematologic malignancies, especially acute myeloid leukemia (AML), as well as solid tumors, particularly of the head, neck, and gynecologic tract. Diagnosis

is confirmed by chromosomal breakage testing using agents such as diepoxybutane (DEB) or mitomycin C (MMC). Management includes supportive care, androgen therapy, and hematopoietic stem cell transplantation (HSCT), which is currently the only curative treatment for the marrow failure component.

Feature	Details
Genetics	Autosomal recessive (most common), X-linked rare
Key Clinical Features	- Pancytopenia - Short stature - Café-au-lait spots - Thumb/radial anomalies
Age of Presentation	5–10 years (variable)
Blood Picture	Low Hb, WBCs, and platelets
Marrow Findings	Hypocellular marrow with reduced all lineages
Special Tests	Chromosomal breakage test (DEB or MMC)
Complications	High risk of AML and solid tumors
Treatment	Supportive care, androgens, HSCT (curative)

B. Diamond-Blackfan Anemia

Aarav was just three months old when his mother noticed he was unusually pale and sleepy. Doctors discovered he had a dangerously low hemoglobin, but his white cells and platelets were normal. Further testing revealed almost no red cell precursors in his bone marrow. Genetic testing confirmed Diamond-Blackfan anemia. His parents were heartbroken, realizing their infant would likely need chronic transfusions or a transplant in the future.

What is Diamond-Blackfan Anemia?

Diamond-Blackfan anemia (DBA) is a rare congenital red cell aplasia caused by mutations in genes encoding ribosomal proteins, which are essential for normal ribosome biogenesis and function. These mutations impair the production of red blood cells by disrupting the proliferation and differentiation of erythroid progenitor cells in the bone marrow. As a result, affected individuals typically present in infancy—often within the first few months of life—with severe macrocytic anemia, while white blood cells and platelets remain relatively preserved. In addition to hematologic abnormalities, many

children with DBA exhibit congenital anomalies, such as craniofacial dysmorphism, thumb malformations, and short stature. There is also an increased lifetime risk of malignancies, including acute myeloid leukemia and solid tumors. Despite its selective impact on erythropoiesis, DBA is a systemic disorder with variable expression, and long-term management often involves corticosteroids, red blood cell transfusions, iron chelation, and potentially hematopoietic stem cell transplantation.

Feature	Details
Genetics	Mostly autosomal dominant; ribosomal protein gene mutations
Key Clinical Features	- Severe anemia - Craniofacial anomalies - Thumb defects - Short stature
Age of Presentation	First year of life (often <6 months)
Blood Picture	Macrocytic anemia with low reticulocytes
Marrow Findings	Markedly reduced or absent erythroid precursors; other lineages normal
Special Tests	Elevated eADA (erythrocyte adenosine deaminase), genetic testing
Complications	Iron overload from transfusions; malignancy risk
Treatment	Steroids, blood transfusions, HSCT

C. Shwachman-Diamond Syndrome

Zaid was a four-year-old boy who visited the hospital often due to infections. He was thin, had chronic diarrhea, and poor growth. Blood tests often showed neutropenia. After many months, doctors diagnosed him with Shwachman-Diamond syndrome. It explained both his pancreas issues and bone marrow problems. His family was overwhelmed by how one condition could affect so many organs.

What is Shwachman-Diamond Syndrome?

Shwachman-Diamond syndrome (SDS) is a rare, inherited genetic disorder primarily affecting the bone marrow and exocrine pancreas, though it can involve multiple organ systems. It is caused most commonly by mutations in the SBDS gene, which is involved in ribosome assembly and cellular stress responses. Children with SDS typically present with exocrine pancreatic insufficiency, leading to malabsorption, steatorrhea (fatty

stools), and poor weight gain or growth. Hematologically, neutropenia is the most consistent finding, predisposing affected children to recurrent and sometimes severe bacterial infectionsCytopenias can progress with time, and the risk of MDS and AML is elevated. Skeletal malformations are also frequent, including metaphyseal dysostosis and chest wall deformities and, in more severe cases, leading to short stature and orthopedic problems. Early detection and supportive therapy, and possibly enzyme replacement and hematologic monitoring, are essential for the treatment of this complicated syndrome.

Feature	Details
Genetics	Autosomal recessive; SBDS gene mutation
Key Clinical Features	- Neutropenia - Exocrine pancreatic insufficiency - Skeletal abnormalities
Age of Presentation	Infancy to early childhood
Blood Picture	Neutropenia; variable anemia or thrombocytopenia
Marrow Findings	Hypocellular marrow, sometimes dysplastic features
Special Tests	Fecal elastase (pancreatic insufficiency), SBDS gene analysis
Complications	Risk of myelodysplastic syndrome (MDS) and leukemia
Treatment	Pancreatic enzyme replacement, antibiotics, G-CSF, HSCT

D. Dyskeratosis Congenita

Sana, who was nine years old and had long eyelashes and unusually colored skin. She had nail dystrophy and white patches in the mouth. Blood tests revealed low platelets and anemia. Further work-up led to a diagnosis of dyskeratosis congenita. Doctors told her that her telomeres were too short — they were, essentially, a ticking clock — and that her bone marrow was wearing out too soon. Her parents were devastated.

What is Dyskeratosis Congenita?

Dyskeratosis congenita (DC) is a rare inherited disorder caused by defective telomere maintenance leading to cellular senescence and progressive multi-organ failure. Telomeres shorten faster in DC patients than would be expected for age because they have mutations in genes encoding components of the telomerase complex. This shortened rate of proliferation will eventually result in premature aging of stem cells, most severely affecting sites where tissue maintenance is rapid. Clinically, DC is

characterized by a classic triad of skin hyperpigmentation, nail dystrophy, and oral leukoplakia; however, the manifestations may be more widespread. Over time, it can cause progressive bone marrow failure, pulmonary fibrosis, liver cirrhosis, and an increased risk of malignancies. The severity and onset of symptoms vary depending on the specific gene mutation involved and its inheritance pattern.

Feature	Details
Genetics	X-linked, autosomal dominant or recessive; defects in telomerase genes
Key Clinical Features	- Skin hyperpigmentation - Nail dystrophy - Oral leukoplakia
Age of Presentation	Childhood to adolescence
Blood Picture	Progressive pancytopenia
Marrow Findings	Hypocellular marrow with progressive failure
Special Tests	Telomere length assay (flow-FISH), genetic testing for telomerase complex
Complications	Pulmonary fibrosis, liver disease, high cancer risk
Treatment	Supportive, HSCT (only curative but high risk), androgens in some cases

E. Morphologic Red Flags & Confirmatory Tests

When treating a child with possible bone marrow failure, there are some red flags of morphology and clinical presentation which can direct a diagnosis, if only before molecular results become available.

Red Flag	Suggestive of
Thumb/radial defects	Fanconi anemia, Diamond-Blackfan anemia
Macrocytic anemia with low retics	Diamond-Blackfan anemia, Aplastic anemia
Pancreatic insufficiency	Shwachman-Diamond syndrome
Nail/skin/oral lesions	Dyskeratosis congenita
Hypocellular marrow	All congenital BMF syndromes
Early-onset pancytopenia	Fanconi anemia, Dyskeratosis congenita
Neutropenia with infections	Shwachman-Diamond syndrome

Test	Use
Chromosome breakage (DEB/MMC)	Fanconi anemia
eADA level / genetic panel	Diamond-Blackfan anemia
SBDS gene sequencing	Shwachman-Diamond syndrome
Telomere length (flow-FISH)	Dyskeratosis congenita
Bone marrow biopsy	Evaluates cellularity and lineage status
Whole exome sequencing	Helpful in unclear

HSCT (Hematopoietic Stem Cell Transplantation), AML (Acute Myeloid Leukemia), DEB (Diepoxybutane), MMC (Mitomycin C), eADA (Erythrocyte Adenosine Deaminase), G-CSF (Granulocyte Colony-Stimulating Factor), MDS (Myelodysplastic Syndrome), DC (Dyskeratosis Congenita), FA (Fanconi Anemia), DBA (Diamond-Blackfan Anemia), SDS (Shwachman-Diamond Syndrome), BMF (Bone Marrow Failure), FISH (Fluorescence In Situ Hybridization).

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 4: Pediatric Myelodysplastic Syndromes (MDS) and Germline Predispositions

1 Introduction

Pediatric myelodysplastic syndromes (MDS) represent a diverse set of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, peripheral cytopenias, and an increased risk of transformation to leukemia. In contrast to adult MDS, pediatric MDS has distinctive biologic and clinical characteristics, different genetic landscapes, and developmental consequences. These neoplasms are frequently associated with germline predispositions that underscore the genetic susceptibility inherent in early-onset marrow failure syndromes and myeloid malignancies. The World Health Organization (WHO) and the International Consensus Classification of Childhood Cancer (ICCC) have iteratively refined the classification criteria, incorporating cytogenetic, morphologic, and molecular parameters tailored for the pediatric context [1,2].

The new WHO 5th edition establishes pediatric MDS as a separate category from their counterparts in adults, and it highlights entities such as refractory cytopenia of childhood (RCC), which is a provisional diagnosis that encompasses marrow hypocellularity and dysplasia involving predominantly the erythroid and/or megakaryocytic lineages, with consistent blasts of less than 5% [3]. This event generally have a relatively indolent clinical behaviour however be well known to represent a precursor to frank acute myeloid leukemia (AML) in some patients. Morphologically, RCC demonstrates a paucity of blasts, dyserythropoiesis manifesting as nuclear irregularities, multinuclearity, and cytoplasmic vacuolization, alongside hypolobated or micromegakaryocytes [4,5]. The granulocytic dysplasia, less marked, may be seen as hypogranularity and nuclear hyposegmentation.

Pediatric MDS frequently has clinical and morphological overlap with inherited bone marrow failure syndromes (IBMFS) and requires extensive germline genetic testing. Germline mutations in pivotal hematopoietic regulatory genes such as GATA2, SAMD9/SAMD9L, RUNX1, and DDX41 have emerged as fundamental drivers of

predisposition syndromes, conferring variable penetrance and phenotypic expressivity [6-9]. GATA2 deficiency, a paradigmatic example, results from monoallelic loss-of-function mutations affecting a zinc finger transcription factor crucial for hematopoietic stem cell maintenance and lymphatic development. Clinically, GATA2 mutation carriers present with monocytopenia, NK cell deficiency, and a predisposition to MDS/AML often characterized by monosomy 7 or del(7q), portending a poor prognosis [10,11]. Morphologically, marrow aspirates reveal trilineage dysplasia with frequent hypolobated megakaryocytes, myeloid hypogranularity, and often hypocellularity due to stem cell exhaustion [12].

SAMD9 and SAMD9L mutations constitute a distinct germline predisposition characterized by gain-of-function alterations leading to cytokine-independent growth inhibition and bone marrow hypocellularity. These genes are located on chromosome 7q21, a region frequently deleted in pediatric MDS, implicating a pathogenic interplay between germline mutation and somatic genetic loss. The resultant phenotype includes marrow failure, monosomy 7-associated MDS, and immune dysregulation, with a subset of patients developing AML [13,14]. Morphologic evaluation often reveals marked erythroid and megakaryocytic dysplasia, with reticulin fibrosis in advanced stages [15].

RUNX1 germline mutations, associated with familial platelet disorder with propensity to myeloid malignancy (FPD/AML), represent a well-characterized syndrome conferring a significant lifetime risk of MDS and AML. RUNX1 encodes a transcription factor integral to hematopoietic differentiation. Germline heterozygous mutations disrupt normal myeloid maturation, resulting in thrombocytopenia and qualitative platelet defects preceding malignant transformation. Marrow morphology may show variable dysplasia, increased blasts in progressive disease, and frequent acquisition of secondary somatic mutations such as ASXL1 and NRAS [16,17].

DDX41 mutations have recently been implicated in familial myeloid neoplasms, typically manifesting in adulthood but occasionally presenting in adolescence or childhood. These mutations affect RNA helicase function critical for pre-mRNA splicing and genomic stability. The marrow morphology is consistent with MDS with multilineage dysplasia, and genetic analyses often reveal concurrent somatic mutations in TET2 and TP53, correlating with adverse outcomes [18,19].

The diagnostic approach to pediatric MDS necessitates an integrative evaluation combining morphological assessment, cytogenetics, flow cytometry, and increasingly, comprehensive next-generation sequencing (NGS) panels capable of detecting somatic and germline variants. Morphology remains pivotal, especially the assessment of dysplasia across erythroid,

granulocytic, and megakaryocytic lineages. The presence of excess blasts, defined variably depending on classification schema but generally ≥5% in pediatric cases, elevates the risk of progression to AML [20].

Cytogenetic abnormalities profoundly influence prognosis and therapeutic decision-making. Monosomy 7, del(7q), and trisomy 8 are the most prevalent chromosomal aberrations in pediatric MDS, often associated with germline predispositions and higher leukemic transformation rates [21,22]. The International Prognostic Scoring System (IPSS) adapted for pediatric patients incorporates blast percentage, cytogenetics, and degree of cytopenias to stratify risk and guide hematopoietic stem cell transplantation (HSCT) timing [23].

The molecular landscape of pediatric MDS is distinct from adult cases, with a lower frequency of mutations in epigenetic regulators such as DNMT3A and TET2, and a higher prevalence of germline predisposition mutations. Recent large-scale genomic studies have highlighted the recurrent involvement of spliceosome components (e.g., SF3B1), cohesin complex genes (e.g., STAG2), and signal transduction molecules (e.g., NRAS) in pediatric cohorts [24-26]. Functional studies elucidate how these mutations disrupt hematopoietic differentiation and promote clonal evolution.

Growing evidence shows that families with known germline mutations should receive genetic counseling and appropriate screening. Because these mutations can produce very different symptoms—or sometimes none at all—management is complex and is best handled by a multidisciplinary team that includes haematology, clinical genetics, and psychosocial support [27]. At the same time, studies are exploring therapies that act on the underlying pathways, including agents targeting DNA repair, epigenetic regulators, and the immune system [28–30].

Pediatric MDS reflects a complex interplay among clonal haematopoiesis, inherited genetic susceptibility, and environmental influences. Accurate classification and risk assessment require integrating morphologic, cytogenetic, and molecular data. As germline predisposition is increasingly recognized, pediatric MDS is being reframed as a model for inherited childhood marrow failure syndromes that can progress to myeloid neoplasia, underscoring the need for careful clinical and genetic evaluation. Morphologic assessment describes abnormalities in the bone marrow and peripheral blood; genetic testing identifies germline and somatic mutations; clinical features capture the patient's symptoms and signs; and prognostic markers help estimate outcomes and the risk of progression.

Entity	Key Morphologic Features	Common Genetic Abnormalities	Clinical Features	Prognostic Implications
Refractory Cytopenia of Childhood (RCC)	Hypocellular marrow, erythroid and megakaryocytic dysplasia, <5% blasts	Often normal karyotype; occasional monosomy 7	Persistent cytopenias; mild to moderate symptoms	Generally indolent; risk of progression to AML
GATA2 Deficiency-associated MDS	Trilineage dysplasia, hypolobated megakaryocytes, hypocellular marrow	Germline GATA2 mutations; frequent monosomy 7	Monocytopenia, NK cell deficiency, recurrent infections	High risk of progression; poor prognosis if monosomy 7 present
SAMD9/SAMD9L Mutation-associated MDS	Marked erythroid and megakaryocytic dysplasia, marrow fibrosis	Germline SAMD9/SAMD9L gain-of-function; del(7q)	Bone marrow failure, immune dysregulation	Risk of clonal evolution; variable progression
RUNX1 Germline Mutation (FPD/AML)	Variable dysplasia; thrombocytopenia with abnormal platelet morphology	Germline RUNX1 mutation; secondary mutations in ASXL1, NRAS	Familial thrombocytopenia; increased AML risk	High risk of leukemic transformation
DDX41 Germline Mutation-associated MDS	Multilineage dysplasia, increased blasts in advanced disease	Germline DDX41 mutation; somatic TET2, TP53 mutations	Usually adult onset; rare pediatric cases	Poor prognosis in presence of secondary mutations
Monosomy 7 and del(7q) MDS	Dysplastic changes in all lineages, increased blasts	Chromosomal losses involving chromosome 7	Severe cytopenias, often in germline predisposed cases	Associated with poor prognosis and AML progression
Spliceosome and Cohesin Complex Mutations	Variable dysplasia, often multilineage,	Somatic mutations in SF3B1, STAG2, SRSF2	Cytopenias, variable clinical severity	Prognostic impact depends on

	sometimes ring sideroblasts	mutation burden

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 5: Chapter: Acute Leukemias in Children

1 Introduction

Imagine four-year-old Anya—bright-eyed and full of energy—who suddenly turns pale, becomes unusually tired, and develops bruises with no clear cause. She starts having repeated fevers and swollen lymph nodes, alarming her parents. A blood test shows a very high white blood cell count, but many of those cells are immature "blasts." A bone marrow biopsy confirms the diagnosis: acute lymphoblastic leukemia (ALL), the most common leukemia in children. Stories like Anya's are sadly familiar, yet the biology, natural history, and treatment of acute leukemias are complex and fascinating.

Leukemia (from the Greek leuk-, "white," and haima, "blood") is one of the best-studied cancers of the blood-forming system. Since Rudolf Virchow first noted the unusually thick, viscous blood seen in some patients, our understanding has shifted dramatically—from a mysterious wasting illness marked by pallor, bleeding, and fatigue to a model disease for molecular oncology. At its core, leukemia is a clonal disorder of hematopoietic stem and progenitor cells driven by genetic changes that promote unchecked growth, block normal maturation, and resist programmed cell death. The result is a buildup of blasts or dysfunctional mature white cells in the bone marrow, blood, and sometimes other organs. This crowding disrupts normal blood production, leading to anemia, infections from immune deficiency, and an increased tendency to bleed; leukemic cells can also infiltrate sites outside the marrow. Leukemia isn't a single disease but a family of biologically distinct conditions. Modern classification separates it into acute versus chronic forms and into myeloid versus lymphoid lineages—distinctions that directly guide therapy and influence prognosis. Advances such as cytogenetics, flow cytometry, and next-generation sequencing have greatly improved diagnostic precision, and emerging spatial transcriptomic tools are beginning to reveal the hidden ecosystem of leukemic niches.Despite the revolution of genomics, the earliest hints of leukemia still reside within the whispers of the blood count and the patient's symptomatology. The triad of anemia, recurrent infections, and bleeding manifestations continues to herald the presence of marrow infiltration. Patients may present with

progressive fatigue, pallor of the mucous membranes, and tachycardia due to insufficient erythrocyte mass. Neutropenia predisposes to recurrent bacterial or fungal infections, while thrombocytopenia manifests with petechiae, ecchymoses, gingival bleeding, or more ominously intracranial hemorrhage. In acute leukemias, the onset is often abrupt, with weeks to months of rapidly worsening cytopenias. Children with acute lymphoblastic leukemia may present with bone pain, lymphadenopathy, or hepatosplenomegaly. Adults with acute myeloid leukemia frequently display gum hypertrophy, cutaneous nodules, or systemic signs of marrow failure. Chronic leukemias, in contrast, often emerge insidiously. A middle-aged or elderly individual may discover lymphocytosis incidentally on routine testing, leading to the diagnosis of chronic lymphocytic leukemia. A patient with chronic myeloid leukemia may be asymptomatic except for splenomegaly, or they may complain of early satiety and weight loss. Peripheral smear examination, though old-fashioned, remains revealing: blasts with high nuclear-cytoplasmic ratios and open chromatin in acute leukemias, smudge cells in CLL, or myelocyte–metamyelocyte bulges in CML. Thus, even before the advent of molecular analysis, the blood continues to whisper its secrets to the trained eye.

Leukemia classification rests upon two orthogonal axes: the tempo of disease, acute versus chronic, and the lineage of the malignant clone, lymphoid versus myeloid. Acute leukemias are defined by proliferation of immature blasts exceeding 20% in bone marrow or blood, with consequent marrow failure, and they are medical emergencies due to their fulminant course. Chronic leukemias involve more mature cell populations, with slower progression but insidious complications such as splenic sequestration or immune dysregulation. Within the lymphoid lineage, acute lymphoblastic leukemia predominates in children, while chronic lymphocytic leukemia is the most common adult leukemia in the Western world. The myeloid axis features acute myeloid leukemia, the archetypal adult acute leukemia, and chronic myeloid leukemia, the prototype of a genetically defined malignancy driven by the BCR-ABL1 fusion. The older French–American–British system emphasized morphology and cytochemistry, dividing AML into subtypes M0 through M7. The contemporary WHO classification integrates cytogenetics and molecular aberrations, recognizing that leukemia biology is written in its genome, and the 2022 update further consolidates disease entities based on driver mutations and chromosomal rearrangements.

Table:1. FAB Classification of Acute Myeloid Leukemia (Older WHO Reference)

FAB Subtype	Name	Key Morphological / Clinical Features
M0	Minimally differentiated AML	Blasts lack clear myeloid differentiation by morphology/cytochemistry; immunophenotyping required.
M1	AML without maturation	Predominantly myeloblasts; minimal evidence of maturation.
M2	AML with maturation	Myeloblasts with maturation beyond promyelocyte stage; often associated with t(8;21).
M3	Acute Promyelocytic Leukemia (APL)	Abnormal promyelocytes with multiple Auer rods; strong association with t(15;17); high risk of DIC.
M4	Acute Myelomonocytic Leukemia	Both granulocytic and monocytic differentiation present.
M4Eo	AML with eosinophilia (M4Eo)	Myelomonocytic with abnormal eosinophils; often linked to inv(16) or t(16;16).
M5	Acute Monocytic / Monoblastic Leukemia	M5a: monoblasts predominate; M5b: promonocytes predominate; gum hypertrophy and tissue infiltration common.
M6	Acute Erythroid Leukemia	Erythroid precursors dominate with dysplasia; blasts >30% of non-erythroid cells.
M7	Acute Megakaryoblastic Leukemia	Blasts express megakaryocytic markers (CD41, CD61); marrow fibrosis frequent; seen in Down syndrome.

Table: 2. WHO 2022 Classification of Acute Myeloid Leukemia

Category	Subtype / Entity	Key Genetic or Clinical Features
AML with defining genetic abnormalities	AML with RUNX1-RUNX1T1	t(8;21)(q22;q22.1); favorable prognosis
	AML with CBFB::MYH11	inv(16)(p13.1q22) or t(16;16); favorable prognosis
	Acute Promyelocytic Leukemia (APL)	PML::RARA fusion, t(15;17); high risk of DIC

	AML with KMT2A rearrangement	Various partners (e.g., AF9, ENL); poor prognosis
	AML with DEK::NUP214	t(6;9)(p23;q34); often with basophilia
	AML with BCR::ABL1	Rare; aggressive course
	AML with MECOM rearrangement	inv(3)(q21q26.2) or t(3;3); poor prognosis
	AML with NUP98 rearrangement	Frequently pediatric; adverse prognosis
	AML with other rare fusions	e.g., FUS::ERG, ETV6::RUNX1-like fusions
AML with mutated genes	AML with NPM1 mutation	Common in adults; generally favorable unless FLT3-ITD present
	AML with CEBPA mutation (biallelic)	Associated with better prognosis
	AML with TP53 mutation	Usually with complex karyotype; poor outcome
AML, myelodysplasia-related	AML with MDS-related gene mutations	e.g., ASXL1, SRSF2, RUNX1, EZH2, BCOR, STAG2
	AML with MDS-related cytogenetic abnormalities	e.g., −7, del(7q), del(5q), complex karyotype
AML, not otherwise specified (NOS)	AML with minimal differentiation	Lacks lineage-specific markers
	AML without maturation	Predominantly blasts, limited maturation
	AML with maturation	Blasts with evidence of maturation
	Acute myelomonocytic leukemia	Granulocytic and monocytic differentiation
	Acute monocytic/monoblastic leukemia	M5a (monoblasts) or M5b (promonocytes)
	Pure erythroid leukemia	Predominant erythroid lineage

	Acute megakaryoblastic leukemia	Megakaryocytic markers (CD41, CD61); often with fibrosis
	Acute basophilic leukemia	Rare; basophil precursors dominate
	Myeloid sarcoma	Extramedullary tumor mass of myeloid blasts
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis	Neonates with trisomy 21; spontaneous regression possible
	Myeloid leukemia associated with Down syndrome	Occurs in young children; linked to GATA1 mutations

Acute lymphoblastic leukemia exemplifies malignant transformation of lymphoid progenitors, either of B-cell or T-cell lineage. It is the commonest childhood cancer, with a peak incidence between ages two and five, though adults also suffer more aggressive forms. Children frequently present with fever, pallor, easy bruising, and lymphadenopathy. Hepatosplenomegaly is common, and bone pain due to marrow expansion is often reported. Central nervous system involvement may manifest as headaches, cranial nerve palsies, or seizures. In adults, constitutional symptoms and cytopenias dominate, with generally poorer prognosis compared to pediatric disease. Lymphoblasts are small to medium cells with high nuclear-cytoplasmic ratios, fine chromatin, and inconspicuous nucleoli. Flow cytometry delineates B-ALL, typically CD19+, CD79a+, CD10+, and T-ALL, expressing cytoplasmic CD3, CD7, and variable CD2 or CD5. The genomic landscape of ALL is heterogeneous. In pediatric ALL, the ETV6-RUNX1 fusion defines a favorable subgroup, whereas IKZF1 deletions or JAK mutations confer adverse risk. Adult ALL commonly presents the BCR-ABL1 fusion, similar to CML in lymphoid blast crisis, the treatment approach consists of chemotherapy and tyrosine kinase inhibitors. ALL seldom presents in the form of an extramedullary tumor, known as lymphoblastic lymphoma. A dramatic example of this is B lymphoblastic lymphoma in tongue, in which sheets of pleomorphic lymphoblasts are interspersed with tingible-body macrophages, which appear to simulate aggressive non-Hodgkin lymphoma. These cases illustrate the varied presentations of this disease.

Acute myeloid leukemia is the most common acute leukemia of adults (median age at diagnosis is approximately 65–70). Its signature is the rapid division of myeloblasts, which clog the medulla and spill into the blood. Patients present with fatigue, infections and mucocutaneous bleeding. Subtype-specific presentations help weave the clinical tapestry: gingival hypertrophy in monocytic AML, skin nodules or chloromas of myeloid

sarcoma, and catastrophic disseminated intravascular coagulation in acute promyelocytic leukemia. The prototypical morphologic clue is the Auer rod, a linear aggregate of reddish material in the cytoplasm/cytoplasmic remnants of blasts that is pathognomonic for myeloid differentiation. Blasts are usually big, with ample cytoplasm, crescent shaped nuclei, and large nucleoli. M0, minimally differentiated, to M7, megakaryoblastic, were recognized by the FAB classification. WHO (now) favors genetic lesions: favorable risk is t(8;21), inv(16), t(15;17); intermediate risk is NPM1 or CEBPA mutations without FLT3-ITD; adverse risk is TP53 mutations or complex karyotype. NGS has uncovered recurrent mutations in FLT3, NPM1, DNMT3A, RUNX1, IDH1, IDH2, and others These provide prognostic implications, and are increasingly used for targeted therapy, such as FLT3 inhibitors or IDH inhibitors. Spatial transcriptomics is now providing a map of leukemic stem cell niches that are treatment resistant, shedding light on the microecology of relapse. AML therefore is emblematic of the intersection of traditional morphology with the accuracy of genomic medicine.

Acute myeloid leukemia, classical considered a disease of the 'elderly' is a disease with aplastic anemia although it's biological spectrum is not only stratified by age.Certain molecularly defined subtypes, particularly those associated with translocations involving KMT2A (MLL) or NUP98 fusions, straddle the boundary between adult and pediatric leukemogenesis. These aberrations, while uncommon in adults, are disproportionately represented in children and confer highly aggressive behavior. In rare circumstances, AML diagnosed in adulthood may evolve or relapse with molecular features characteristic of pediatric-type leukemias, blurring conventional age demarcations. This phenomenon underscores the concept that leukemia is not merely an age-linked disease but a continuum of stem-cell derangements, where clonal evolution can remodel an ostensibly adult AML into a phenotype that mirrors the genetic and clinical landscape of childhood leukemia.

CML remains the quintessential model of targeted therapy. It accounts for about 15 to 20% of adult leukemias and arises from the t(9;22)(q34;q11) translocation, producing the BCR-ABL1 fusion kinase. Median age at diagnosis is 55 to 60 years. Many patients are asymptomatic, with leukocytosis discovered incidentally. Others present with splenomegaly, early satiety, night sweats, or weight loss. The disease evolves through three phases: chronic, accelerated, and blast crisis. CBC reveals extreme leukocytosis with left-shifted myeloid precursors and basophilia. Bone marrow shows marked myeloid hyperplasia. Cytogenetics demonstrates the Philadelphia chromosome, while PCR confirms BCR-ABL1 transcripts. Although imatinib revolutionized therapy, resistance emerges via secondary mutations such as the notorious T315I substitution. Second- and third-generation TKIs have extended survival dramatically. Spatial genomic analyses now reveal resistant stem cell niches that persist despite systemic suppression, accounting for minimal residual disease. CML thus stands as a triumph of

molecular oncology while reminding us of the resilience of malignant stem cell reservoirs.

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in Western countries, with a strong predilection for older men. It arises from a clonal expansion of small, mature B cells. Many people are diagnosed incidentally and feel well at first; others present with lymph node enlargement, hepatosplenomegaly, or complications such as autoimmune hemolytic anemia or recurrent infections due to hypogammaglobulinemia. Smudge cells on a peripheral smear are characteristic in CLL and can support the diagnosis, though they are not specific on their own.

Staging systems help frame risk at presentation. The Rai system ranges from stage 0 (isolated lymphocytosis) to stage IV (thrombocytopenia). The Binet system categorizes patients as A, B, or C based on the number of involved lymphoid areas and the presence of anemia or thrombocytopenia. Beyond clinical staging, molecular risk is critical: TP53 alterations, unmutated IGHV, and NOTCH1 mutations are linked to more aggressive disease, whereas mutated IGHV generally predicts a more indolent course. Richter transformation—the evolution of CLL into diffuse large B-cell lymphoma—signals a shift to an aggressive clinical phenotype. CLL sits at the crossroads of immune dysregulation and malignancy, and often requires nuanced, individualized treatment strategies.

Although chronic myeloid leukemia (CML) and CLL are classically adult diseases, both can evolve in ways that resemble pediatric hematologic malignancies. In CML, clonal instability or therapy-driven selective pressure can culminate in lymphoid blast crisis, mimicking acute lymphoblastic leukemia, a cancer typically seen in children. Far less commonly, CLL can undergo Richter transformation into high-grade lymphoid neoplasms with features analogous to aggressive pediatric lymphomas or lymphoblastic leukemias. These phenomena highlight how leukemic clones can rewire lineage programs and remind us that the boundaries between adult and pediatric leukemias are more permeable than simple age cut-offs suggest; they reflect the underlying mutational trajectory and microenvironmental cues that steer clonal evolution.

Even in an era of advanced genomics, basic red cell indices still offer useful clues. Acute leukemias often present with normocytic or macrocytic anemia and an elevated RDW. CML typically shows a normocytic anemia with basophilia. In CLL, autoimmune hemolysis can lead to anemia with reticulocytosis. While nonspecific, these patterns can raise early suspicion and prompt definitive testing.

Bone marrow examination remains the backbone of leukemia diagnosis. Aspirates provide cytologic detail for blast counting, while core biopsies reveal architecture—fibrosis, necrosis, nodular involvement. Classic cytochemical stains add context: myeloperoxidase supports myeloid lineage; periodic acid–Schiff is often positive in

lymphoblasts; nonspecific esterase marks monocytic differentiation. Immunophenotyping and immunohistochemistry (for markers such as CD34, CD117, CD20, and CD3) refine lineage assignment, and reticulin staining grades fibrosis. Despite the power of sequencing, marrow evaluation remains the gold standard that ties morphology to molecular findings.

Next-generation sequencing (NGS) has transformed hematologic diagnostics. It enables mutation profiling—such as FLT3, NPM1, and CEBPA in AML; JAK/IKZF1 lesions in ALL; and TP53 or SF3B1 in CLL—guiding prognosis and therapy. NGS-based minimal residual disease assays can reach deep sensitivity, informing treatment duration and transplant decisions. It can detect cryptic fusions missed by conventional karyotyping, particularly with RNA-based methods. Still, there are limits: very small subclones may fall below detection thresholds, and clonal evolution between diagnosis and relapse means each test is a snapshot in time. Even so, NGS has become integral to modern leukemia care.

Spatial genomics and transcriptomics add another layer by mapping gene expression back onto tissue architecture. In ALL, they illuminate routes of CNS infiltration. In AML and CML, they help identify therapy-resistant stem cell niches. In CLL, they reveal dynamic interactions among tumor cells, stroma, and immune infiltrates. These insights can forecast resistance, pinpoint sanctuary sites, and inspire niche-directed immunotherapies—shifting the focus from targeting cells alone to reprogramming the ecosystems that protect them.

The trajectory of leukemia diagnostics captures the spirit of precision medicine. Morphology and cytochemistry were joined by immunophenotyping and cytogenetics; now NGS, single-cell multi-omics, and spatial platforms are expanding the view. Emerging approaches—integrating DNA, RNA, and epigenetics at single-cell resolution, coupled with AI to unify complex datasets—are poised to refine prediction and personalize therapy. Microenvironment-directed strategies that disrupt protective niches may further tip the balance in favor of durable remissions.

Leukemia, once inscrutable and uniformly fatal, is now dissected through complementary lenses: the story told by blood smears, the architecture of bone marrow, the signatures of chromosomal alterations, and the detailed maps of mutational and spatial profiling. Integrating these layers doesn’t just define a diagnosis; it reveals the biology that drives prognosis and therapeutic response. The field is moving steadily from description to mechanism, from broad empiricism to tailored intervention—and with it, from resignation to well-founded hope.

Table: 3. A Comprehensive Overview of Leukemias

Category	Subtype / Entity	Key Features	Typical Age Group	Genetic / Molecular Associations
Acute Lymphoid Leukemia (ALL)	B-cell ALL	Most common pediatric cancer; bone pain, lymphadenopathy, CNS infiltration	Children (2–5 yrs peak); also adults (poorer prognosis)	ETV6-RUNX1 fusion (favorable), BCR-ABL1 (adults, high-risk), IKZF1 deletions
	T-cell ALL	Mediastinal mass, high WBC count, CNS involvement	Adolescents & young adults	NOTCH1 mutations, TAL1 rearrangements
	Lymphoblastic Lymphoma	Extramedullary mass (often mediastinal, rare sites like tongue)	Children & adolescents	Similar to ALL; T-cell origin common
Acute Myeloid Leukemia (AML)	AML with RUNX1-RUNX1T1	Morphology with maturation; favorable risk	Adults & older children	t(8;21)
	AML with CBFB-MYH11	Myelomonocytic with eosinophilia; good prognosis	Children & adults	inv(16) or t(16;16)
	Acute Promyelocytic Leukemia (APL)	Abnormal promyelocytes; DIC risk	Young to middle-aged adults (rare in children)	PML-RARA fusion (t(15;17))
	AML with NPM1 mutation	Common in adults; variable prognosis	Primarily adults	NPM1, ± FLT3-ITD
	AML with CEBPA mutation	Better prognosis (biallelic mutations)	Adolescents & adults	CEBPA
	AML with KMT2A rearrangements	Aggressive; overlaps pediatric & adult AML	Infants and young	KMT2A fusions (MLL gene)

			children; also adults	
	AML with TP53 mutation / complex karyotype	Therapy-related, poor prognosis	Older adults	TP53, complex cytogenetics
	Pure Erythroid Leukemia	Rare, aggressive	Adults > children	TP53, complex karyotype
	Acute Megakaryoblastic Leukemia	Associated with marrow fibrosis; in Down syndrome	Children <4 yrs (esp. with trisomy 21)	GATA1 mutations
	Myeloid Sarcoma	Extramedullary tumor mass (skin, lymph node, bone)	Both adults & children	Often associated with AML fusions
Chronic Myeloid Leukemia (CML)	Chronic Phase	Often incidental leukocytosis, splenomegaly	Middle-aged adults; rare in children (<5%)	BCR-ABL1 fusion (t(9;22))
	Accelerated / Blast Phase	Cytopenias, basophilia, progression to acute leukemia (often lymphoid, mimicking pediatric ALL)	Adults; occasionally children in blast crisis	Secondary BCR-ABL1 mutations (e.g., T315I)
Chronic Lymphocytic Leukemia (CLL)	Typical CLL	Most common adult leukemia; lymphocytosis, AIHA, infections	Elderly adults (~70 yrs); extremely rare in children	TP53, SF3B1, NOTCH1 mutations; IGHV status prognostic
	Richter Transformation	Transformation into aggressive lymphoma / ALL-like disease	Adults	TP53 loss, MYC abnormalities
Myeloid Proliferations of Childhood	Transient Abnormal	Neonates with Down syndrome;	Newborns with trisomy 21	GATA1 mutations

	Myelopoiesis (TAM)	spontaneous regression possible		
	Myeloid Leukemia of Down Syndrome	Children <5 yrs; increased sensitivity to cytarabine	Infants and young children with trisomy 21	GATA1, cohesin mutations
Other Rare Pediatric Leukemias	Mixed-Phenotype Acute Leukemia (MPAL)	Blasts show both myeloid and lymphoid markers	Children & young adults	BCR-ABL1, KMT2A rearrangements
	Juvenile Myelomonocytic Leukemia (JMML)	Aggressive myeloproliferative disorder	Young children (<4 yrs)	RAS pathway mutations (PTPN11, NRAS, KRAS, NF1)

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

DeepScience
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Chapter 6: Pediatric Lymphomas and Related Hematologic Neoplasms

1 Introduction

It often starts in silence: a 7-year-old previously happy, untroubled child is taken to a health facility because of a swelling on the side of the neck that has been slowly enlarging, over weeks, despite antibiotics. The mass has been also gradually enlarging, hardening, and becoming immobile, accompanied by mediastinal nodes compressing the airway and causing nocturnal cough and dyspnea. The nights are the restless ones with sweating and intermittent fevers and the parents racked with frustration, watching their child wasted by the cruelty of uncertainty. It is in the pediatric ward that physicians witness the Janus face of pediatric lymphomas as both a safe haven and a struggle, since they are forced to face the biological paradox constituting pediatric lymphomas: malignancies, which are aggressive to the extreme in growth kinetics, but paradoxically among the most curable of human cancers when placed in the sights of timely and precision-guided therapy [1]. This "paradox" has characterized pediatric hematopathology, placing CNS Ls as a formidable clinical opponent and a research opportunity of cure.

Pediatric lymphomas are the third most frequent type of pediatric malignancy following leukemias and central nervous system tumors, accounting for about 10–15% of childhood cancer worldwide [2]. While indolent, low grade lymphomas predominate in older patients, the range in children contains markedly aggressive, rapidly proliferating diseases. These tumors, encompassing Hodgkin lymphoma, Burkitt lymphoma, anaplastic large cell lymphoma, diffuse large B-cell lymphoma, and lymphoblastic lymphoma, are characterized by high-grade histology, brisk mitotic indices, and rapid doubling times [3]. However, these same characteristics impart exquisite sensitivity to combination chemotherapy and with a prompt diagnosis and treatment, long-term survival is possible in most cases [4].

HL in childhood, especially in older children and adolescents is taken as a model disease. The classic Hodgkin lymphoma characterized by the presence of Reed–Sternberg cells,

large, dysmorphic, binucleate cells, are found in a background that is rich in inflammatory response at the histological level and is responsible for approximately 40% of pediatric lymphomas in developed countries [5]. Nodular sclerosis and mixed cellularity types are more common in the pediatric population [6]. Pathogenetically, HL represents a disease of immune evasion: Reed–Sternberg cells initiate constitutive activation of the transcription factor NF-κB in a cell-autonomous fashion, secrete immunosuppressive cytokines and up-regulate the PD-L1/PD-L2 ligands as a result of genetic alterations of chromosome 9p24. 1 [7]. Epstein–Barr virus (EBV) is not responsible in all cases, but it is a critical etiologic cofactor in a significant subset of pediatric cases, particularly in resource-limited areas [8]. Clinically, pediatric Hodgkin lymphoma often manifests with painless cervical or supraclavicular lymphadenopathy, mediastinal widening, and systemic B symptoms—fever, night sweats, and weight loss [9]. Historically (Ann Arbor stage) and, more recently (COG-modified criteria) staging systems determine intensity of therapy [10]. Pediatric schedules aim at curing the disease while minimizing long-term toxicity, and therefore utilize reduced chemotherapy with or without involved-field radiotherapy [11]. Modern cure rates exceed 90%, but at a cost that is often temporal rather than immediate in the form of cardiotoxicity, pulmonary fibrosis, infertility, and second malignancies [12]. Therefore, the story of pediatric HL is not just a tale of oncologic victory but also of survivorship burden [13].

Paediatric non-Hodgkin lymphomas are a relatively diverse group of neoplasms, which are uniformly aggressive and which include nearly all high-grade histologies [14]. This contrasts significantly with adult NHL, where the indolent types predominate. Pediatric NHL often presents as an extranodal disease: abdominal masses in Burkitt lymphoma, mediastinal compression in lymphoblastic lymphoma, or systemic involvement in anaplastic large cell lymphoma [15]. The urgency of diagnosis is crucial, as delayed recognition can lead to devastating complications including tumor lysis syndrome, bowel perforation, or airway obstruction [16]. Diagnostic work-up is based on histopathology, immunophenotyping by flow cytometry or immunohistochemistry and cytogenetic/molecular studies that determine the classification [17].

Burkitt lymphoma is without a doubt the most classic pediatric lymphoma, characterized by abnormally high proliferative activity and a pathognomonic MYC oncogene translocation to immunoglobulin (Ig) loci, most often t(8;14)(q24;q32) [18]. The histology features are characteristic: sheets of intermediate-sized lymphoid cells with basophilic cytoplasm, interspersed by histiocytes, creating the characteristic “starry sky” appearance [19].Burkitt lymphoma manifests in three epidemiologic forms: endemic, sporadic, and immunodeficiency-associated [20]. Endemic Burkitt lymphoma, prevalent in equatorial Africa, is tightly associated with Epstein–Barr virus infection and frequently involves the jaw or orbital bones [21]. Sporadic Burkitt lymphoma, more common in Western countries, usually arises in the abdomen, often presenting as an

ileocecal mass [22]. Immunodeficiency-associated Burkitt lymphoma, seen in HIV-infected children or post-transplant settings, underscores the centrality of immune surveillance in restraining MYC-driven oncogenesis [23]. From a therapeutic standpoint, Burkitt lymphoma is one of the triumphs of pediatric oncology: despite frightening kinetics, short but high intensity, multiagent chemotherapy regimens cure almost 90% of patients when you have good resources [24]. Nonetheless, the prognosis is less certain in low-income areas where delayed diagnosis, lack of supportive care, and abandonment of treatment interfere and detriment the results [25].

Anaplastic large cell lymphoma (ALCL) is the archetypical T-cell lymphoma in childhood, and makes up 10–15% of childhood NHL [26]. Morphologically, it consists of large pleomorphic cells with oval to horse-shoe shaped nuclei located eccentrically (so-called “hallmark cells”) [27]. Immunophenotypically, ALCL is consistently CD30-positive and in 60–80% of cases it has a rearrangement in the ALK gene on 2p23 (NPM1-ALK involving t(2;5)(p23;q35)) [28].ALK-driven constitutive tyrosine kinase activity underpins the disease, while additional lesions in the JAK-STAT pathway contribute to oncogenesis [29]. Clinically, ALCL often presents with advanced-stage disease, extranodal involvement of skin, bone, or lung, and systemic B symptoms [30]. Despite this, ALK-positive status paradoxically confers a relatively favorable prognosis compared to ALK-negative variants [31]. Targeted therapies, such as ALK inhibitors, are emerging as promising adjuncts, particularly in relapsed or refractory disease [32].

Diffuse large B-cell lymphoma (DLBCL), though far more common in adults, does occur in pediatric populations, where it typically presents as extranodal disease involving the gastrointestinal tract, mediastinum, or bone [33]. Pediatric DLBCL tends to exhibit germinal center B-cell immunophenotype and carries a better prognosis than its adult counterpart [34]. Intensive chemotherapy regimens, such as LMB or B-NHL protocols, yield long-term survival exceeding 80% [35]. Unique pediatric subtypes include primary mediastinal large B-cell lymphoma, which shares molecular affinities with Hodgkin lymphoma, notably 9p24.1 alterations leading to PD-L1/PD-L2 overexpression [36]. Immunotherapy with checkpoint blockade, already transformative in relapsed adult HL, is being explored in this context [37].

The borderland between lymphoma and leukemia is exemplified by lymphoblastic lymphoma (LBL), a neoplasm of immature lymphoid precursors that is pathobiologically indistinguishable from acute lymphoblastic leukemia, save for the degree of marrow involvement [38]. The arbitrary diagnostic threshold—25% blasts in the marrow—determines whether a child is labeled with lymphoma or leukemia [39]. T-lymphoblastic lymphoma commonly presents as a bulky mediastinal mass in adolescent males, often with pleural or pericardial effusions [40]. B-lymphoblastic lymphoma, rarer, manifests with nodal or extranodal masses and shares genomic alterations with B-ALL, such as PAX5 deletions or ETV6 rearrangements [41]. Therapy parallels ALL

regimens, with prolonged multi-phase chemotherapy including CNS prophylaxis [42]. The distinction between LBL and ALL, while clinically useful, underscores the continuum of lymphoid neoplasia [43].

In addition to these canonical entities, rare pediatric lymphomas demand attention. Post-transplant lymphoproliferative disorders (PTLD) represent a unique intersection of iatrogenic immunosuppression and viral oncogenesis, driven primarily by EBV [44]. Pediatric PTLD can manifest as polymorphic proliferations or overt monomorphic lymphomas, including Burkitt-like or diffuse large B-cell forms [45]. Primary effusion lymphoma, though exceedingly rare in children, has been described in immunodeficient states, typically associated with HHV-8 co-infection [46]. Pediatric follicular lymphoma, a distinct variant from adult follicular lymphoma, often presents with localized disease in the head and neck region and carries a favorable prognosis [47]. Similarly, pediatric marginal zone lymphoma, rare and often extranodal, tends to behave indolently compared to adult counterparts [48].

Molecular and genomic advances have redefined the taxonomy of pediatric lymphomas. High-throughput sequencing has uncovered recurrent mutations in ID3, TCF3, and CCND3 in Burkitt lymphoma [49]; recurrent ALK fusions and JAK-STAT pathway alterations in ALCL [50]; and frequent PD-L1/PD-L2 copy number gains in Hodgkin lymphoma [51]. Epigenetic modifications, microRNA dysregulation, and aberrant immune checkpoint pathways have emerged as additional layers of pathogenic insight [52]. These discoveries are not merely academic—they inform targeted therapy development. Anti-CD30 antibody-drug conjugates, such as brentuximab vedotin, are now incorporated into pediatric ALCL trials [53]. Checkpoint inhibitors, such as nivolumab and pembrolizumab, are being evaluated in relapsed HL and PMBCL [54]. CAR-T cell therapy, initially transformative in ALL, is under early investigation for relapsed pediatric lymphomas [55]. The therapeutic landscape, once defined solely by cytotoxic chemotherapy, is entering an era of immunologic and molecular precision [56].

The survivorship burden in pediatric lymphoma is profound. As cure rates approach or exceed 80–90%, attention must shift to long-term toxicities: anthracycline-induced cardiomyopathy, alkylator-induced infertility, radiation-induced secondary malignancies, and psychosocial sequelae [57]. The pediatric hematopathologist plays a critical role not only in initial diagnosis but in guiding risk-adapted therapy to balance cure against late effects [58]. Furthermore, global inequities persist: while survival exceeds 80% in high-income countries, it plummets to below 30% in many low-income regions [59]. Late diagnosis, lack of supportive care, and therapeutic abandonment contribute to this disparity [60]. Thus, pediatric lymphomas are not only biological diseases but also diseases of systems, infrastructure, and inequities [61].

Ultimately, the story of pediatric lymphomas is that of a battlefield where biology, therapy, and humanity intersect. Hardveloping The affected children carry not only the burden of aggressive disease in the short term but a lifetime's worth of survivorship. Pathologists, oncologists, and scientists lead a precarious journey between cure and complication, between rapid growth and therapeutic response. This paradox of malignancies that are simultaneously horrific in their swiftness and hopeful in their curability is, in many ways, the purview of the pediatric hematopathologist. In the very act of narrating and naming these afflictions, however, one does more than just define disease: one also looks unflinchingly at the lost childhood, the postponed futures, and the possibility of redemption through science [62].

Integrated Summary Table:1. Pediatric Lymphomas and Related Hematologic Neoplasms

Entity	**Typical Age/Presentation**	**Key Morphology**	**Genetic/Molecular Features**	**Therapeutic Notes**
Hodgkin Lymphoma (Nodular sclerosis, Mixed cellularity)	Adolescents; cervical/mediastinal nodes, B symptoms	Reed–Sternberg cells in inflammatory milieu	NF-κB activation; PD-L1/PD-L2 gains; EBV association	ABVD/BEACOPP; >90% survival; long-term toxicity monitoring
Burkitt Lymphoma	Children; endemic (jaw), sporadic (abdomen), immunodeficiency-associated	"Starry sky" pattern	MYC translocations (t(8;14)); EBV in endemic cases	Intensive, short-course chemotherapy; high cure in HICs
Anaplastic Large Cell Lymphoma (ALCL)	Children/adolescents; systemic, skin, soft tissue	Hallmark cells with horseshoe nuclei; CD30+	ALK fusions (t(2;5)); JAK-STAT lesions	ALK-positive: better prognosis; ALK inhibitors, anti-CD30 therapy
Diffuse Large B-Cell Lymphoma (DLBCL, incl. PMBCL)	Children/adolescents; extranodal abdominal/mediastinal disease	Large pleomorphic B-cells	BCL6, MYC, PD-L1/PD-L2 alterations	LMB/B-NHL protocols; >80% survival; immunotherapy emerging
Lymphoblastic Lymphoma (T- or B-LBL)	Adolescents; mediastinal mass (T-LBL),	Small blasts, high N:C ratio	NOTCH1 (T-LBL); PAX5, ETV6 (B-LBL)	ALL-like therapy with CNS prophylaxis

	extranodal (B-LBL)			
Post-Transplant Lymphoproliferative Disorder (PTLD)	Children post-transplant; systemic or nodal	Polymorphic or monomorphic B-cell lesions	EBV-driven proliferation	Reduction of immunosuppression; rituximab; chemo
Pediatric Follicular / Marginal Zone Lymphomas	Children; localized, head/neck or extranodal	Follicular or marginal zone architecture	Distinct from adults; often lacks BCL2 rearrangement	Excellent prognosis; localized therapy

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 7: Histiocytic and Dendritic Cell Disorders of Childhood

1 Introduction

This is not about lymphadenopathy or bone-marrow infiltration, but about fever, about a 3 year-old boy who had been dry as an overbaked pork pie from the detriment of time, and his mother remembered only the constant warmth, until eventually it became as if he were always in fires for clothing. His abdomen puffs out with each passing week, his spleen is so big that his belly officially measures more than a pregnant woman's at term, and his skin, once healthy with a radiant glow, is scabbed over with subtle waxy lesions on the scalp and trunk.

Are physicians arguing this is occult infection vs. rheumatologic storm, but with ferritin in the thousands and BM aspirations showing engulfed erythrocytes in activated macrophages, the diagnosis of HLH becomes clear with foreboding certainty [1]. Among the entities encountered in the field of pediatric hematopathology, few are both the subject of more urgency and despair than the histiocytic and dendritic cell disorders, a group of diseases that traverses the line between neoplasia, immune dysregulation, and inflammatory Disaster.

In the past 2 decades the classification of histiocytic and dendritic cell disorders has significantly evolved, largely though the World Health Organization (WHO) classification and the Histiocyte Society classification [2]. This heterogeneous group of formerly overlapping and confusing syndromes is now further classified into 5 major categories: (1) Langerhans-related, (2) cutaneous and mucocutaneous, (3) malignant histiocytoses, (4) Rosai–Dorfman disease, (5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome [3]. Despite being originated from mononuclear phagocyte system or dendritic derivatives, their clinical courses range from benign self-limited proliferations to rapidly fatal cytokine storms. It is a group that can be

particularly difficult to the pediatric hematopathologist who needs to be purely morphologically alert and molecularly sensitive.

A. Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is likely the most familiar and prototypical of the histiocytic disorders. Initially referred to as 'histiocytosis X' before the clonal nature of the proliferating cells was recognised, LCH is a disease characterized by the development of CD1a-positive Langerhans cells with their characteristic Birbeck granules visible on electron microscopy [4]. Its incidence is quoted as being 2–5 new cases per million children a year [5]. Clinical presentations range from solitary eosinophilic granuloma of bone to life-threatening multisystem disease involving liver, spleen, bone marrow, and central nervous system [6]. The BRAF V600E mutation, found in ~50% of cases, revolutionized our understanding of LCH as a neoplastic process with MAPK pathway activation [7]. Other MAPK pathway mutations, including MAP2K1 and ARAF, extend this paradigm [8]. Histologically, lesions demonstrate histiocytes with grooved nuclei, admixed with eosinophils, lymphocytes, and plasma cells [9]. Therapeutically, stratification is based on risk organ involvement; vinblastine-prednisone remains frontline, with cladribine, cytarabine, and BRAF/MEK inhibitors now incorporated into relapsed settings [10]. Long-term survivors are not exempt from sequelae—endocrinopathies, neurodegeneration, and growth impairment remain enduring scars [11].

B. Juvenile Xanthogranuloma and Related Cutaneous Disorders

Juvenile xanthogranuloma (JXG) epitomizes the cutaneous and mucocutaneous histiocytoses, manifesting as solitary or multiple yellow-red papules in infants and young children [12]. Although usually benign and self-resolving, systemic forms can involve ocular structures, risking blindness, or visceral organs with potentially fatal outcome [13]. Histologically, JXG lesions contain foamy histiocytes and Touton giant cells within a xanthomatous background [14]. Immunophenotypically, they express CD68 and Factor XIIIa but lack CD1a and langerin, distinguishing them from LCH [15]. The molecular pathogenesis remains less clearly delineated, though recent sequencing has identified MAPK pathway alterations in a subset [16]. Other cutaneous histiocytoses of childhood include benign cephalic histiocytosis and generalized eruptive histiocytosis, both usually self-limiting [17].

C.Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is not a neoplasm but a fulminant immune dysregulation syndrome characterized by uncontrolled activation of cytotoxic T cells and macrophages, leading to cytokine storm, multi-organ failure, and high mortality [18]. Primary (familial) HLH is driven by biallelic mutations in genes governing cytotoxic granule exocytosis, including PRF1, UNC13D, STX11, and STXBP2 [19]. Secondary HLH arises in the context of infections (notably EBV), malignancies, or rheumatologic disorders [20]. Diagnostic criteria include fever, splenomegaly, cytopenias, hyperferritinemia, hypofibrinogenemia, and hemophagocytosis in marrow or tissue [21]. The Histiocyte Society's HLH-2004 protocol, combining dexamethasone, etoposide, and cyclosporine, remains the standard of care, while hematopoietic stem cell transplantation is curative for genetic forms [22]. Despite therapeutic advances, outcomes remain grim, particularly for EBV-driven HLH in children [23].

D.Rosai–Dorfman Disease

Rosai–Dorfman disease (RDD), or sinus histiocytosis with massive lymphadenopathy, presents classically with painless cervical lymphadenopathy in children and adolescents [24]. Extranodal involvement—skin, nasal cavity, bone, CNS—occurs in 40% of pediatric cases [25]. Histologically, large S100-positive histiocytes with emperipolesis (engulfment of intact lymphocytes) are diagnostic [26]. RDD was historically considered reactive, but recent studies reveal KRAS and MAPK pathway mutations in subsets, redefining it as clonal [27]. Most cases follow a benign course with spontaneous remission, though systemic disease may require corticosteroids, chemotherapy, or targeted inhibitors [28].

E.Malignant Histiocytoses and Dendritic Cell Sarcomas

True malignant histiocytic proliferations are rare but devastating in childhood. Histiocytic sarcoma, characterized by sheets of atypical, CD68-positive, CD163-positive cells with aggressive behavior, may arise de novo or in association with prior hematologic malignancies [29]. Dendritic cell neoplasms—interdigitating dendritic cell sarcoma, follicular dendritic cell sarcoma, fibroblastic reticular cell tumors—are exceptionally rare in pediatrics but underscore the malignant potential of antigen-presenting cell lineages [30]. Their recognition requires immunohistochemistry (S100, CD21, CD35, fascin) and exclusion of mimickers [31]. Prognosis is poor, and no standardized therapy exists [32].

F.Molecular Landscape and Pathogenetic Insights

Genomic profiling has redefined the taxonomy of these disorders. MAPK pathway activation is the unifying signature of Langerhans-related histiocytoses, encompassing BRAF V600E, MAP2K1, and ARAF mutations [33]. JXG and RDD similarly demonstrate MAPK alterations in subsets, suggesting a molecular continuum [34]. In HLH, defects in perforin/granule exocytosis genes define familial forms, while EBV-driven lymphoproliferation illustrates viral subversion of cytotoxic immunity [35]. Malignant histiocytoses often harbor TP53, CDKN2A, and RAS pathway mutations [36]. This convergence of pathways suggests potential roles for MEK inhibitors, JAK inhibitors, and immunotherapy in refractory disease [37].

G.Clinical Challenges and Global Disparities

Despite molecular clarity, diagnostic and therapeutic challenges persist. In low-resource settings, delayed recognition of HLH or misdiagnosis of LCH as infection can prove fatal [38]. Supportive care infrastructure, including access to stem cell transplantation, is often lacking [39]. Survivors may suffer neurocognitive sequelae, endocrinopathies, or secondary malignancies [40]. Thus, pediatric histiocytic and dendritic cell disorders are not merely biological curiosities—they are global health challenges demanding multidisciplinary vigilance.

Table:1. Pediatric Histiocytic and Dendritic Cell Disorders

Entity	Typical Age/Presentation	Histopathology	Immunophenotype	Molecular Features	Therapeutic Notes
Langerhans Cell Histiocytosis (LCH)	Infants/children; bone lesions, skin rash, multisystem disease	Grooved nuclei, eosinophilic infiltrate	CD1a+, Langerin+, S100+	BRAF V600E, MAP2K1, ARAF	Vinblastine + steroids; BRAF/MEK inhibitors in refractory disease
Juvenile Xanthogranuloma (JXG)	Infants; cutaneous papules, rare ocular/visceral disease	Foamy histiocytes, Touton giant cells	CD68+, FXIIIa+; CD1a–, Langerin–	MAPK mutations (subset)	Self-limited; steroids/chemo for systemic disease

Hemophagocytic Lymphohistiocytosis (HLH)	Infants/children; fever, hepatosplenomegaly, cytopenias	Activated macrophages with hemophagocytosis	CD68+, CD163+	PRF1, UNC13D, STX11, STXBP2 mutations; EBV association	HLH-2004 protocol; HSCT for familial forms
Rosai–Dorfman Disease (RDD)	Children/adolescents; massive cervical lymphadenopathy, extranodal sites	Large histiocytes with emperipolesis	S100+, CD68+, CD163+	KRAS, MAPK mutations	Often self-limited; steroids/targeted therapy if systemic
Histiocytic Sarcoma	Rare, any age; aggressive systemic disease	Atypical large histiocytes	CD68+, CD163+, lysozyme+	TP53, RAS mutations	Aggressive chemotherapy; poor prognosis
Dendritic Cell Sarcomas (IDCS, FDCS, FRC tumors)	Extremely rare; nodal or extranodal masses	Spindled dendritic cells	IDCS: S100+, Fascin+; FDCS: CD21+, CD35+	Various, not well defined	Surgical excision ± chemo; poor outcome

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 8: Pediatric Plasma Cell and Rare Hematologic Neoplasms

1 Introduction

The story opens with a twelve-year-old whose easy smile once lit up her family's small home. Then came the unshakable fatigue, the unexplained bruises, and the bone pain that doctors initially chalked up to growing pains or mild anemia. Within months, imaging showed lytic lesions in her bones, her blood was heavy with paraprotein, and her marrow was crowded by cells that didn't belong. Serum electrophoresis revealed a monoclonal spike, and the bone marrow biopsy showed sheets of abnormal plasma cells. That is how her family faced a diagnosis almost never seen in children: pediatric multiple myeloma (PMM), a disease usually linked to old age that, on rare occasions, intrudes on childhood [1]. The grief on her parents' faces wasn't naïveté—it was the harsh reality that some "diseases of age" can steal youth first.

A. Pediatric Multiple Myeloma: Epidemiology and Clinical Spectrum

Multiple myeloma (MM) is largely a disease of older adults, with a median age at diagnosis of about 69 years [2]. Pediatric multiple myeloma (PMM) is extraordinarily rare—fewer than 1% of MM cases—and only a few hundred have been reported worldwide [3]. When it appears in children, it often presents more aggressively: diffuse osteolytic bone disease is common, and hypercalcemia and renal failure occur proportionally more often; the slower, indolent courses sometimes seen in adults are uncommon in pediatric cases [4]. Historically, median survival in PMM has been 18–30 months—worse than in adults—though modern therapies have modestly improved outcomes [5].

Immunophenotypically, the malignant plasma cells in PMM are similar to those in adults and are positive for CD38, CD138, MUM1/IRF4, have aberrant loss of CD19 and CD45,

and exhibit occasional CD56 expression [6]. However, subtle distinctions are becoming apparent: a predilection for higher proliferative indices (as measured by Ki-67 labeling) and possibly for IgA or IgG heavy chains is exhibited by pediatric cases, while there is a much lower frequency of light-chain-only disease, which is so characteristic of older-age myeloma [7].

The matrix of PMM is equally as complex as that of myeloma, with something of a ‘maze-like’ molecular framework. Recurrent IgH translocations involving t(11;14)(q13;q32)/CCND1-IGH, t(4;14)/FGFR3-IGH, and t(14;16)/MAF have also been observed via high-throughput sequencing, even in children, thus indicating that similar pathogenetic paradigms can operate across different settings [8]. However, hyperdiploid karyotypes are overrepresented in pediatric cases of CLL, and may represent a biologic subset of this disease independent from adult clones [9]. Chromosomal 13q deletion, 17p/TP53 deletion, and 1q gains are negative prognostic factors that were not dependent on age, and they are found also in pediatric series [10]. Somatic mutations in RAS/RAF pathways, NF-κB modulators and chromatin modifiers mirror this adult arsenal [11] albeit with a lower total mutational load, giving rise to the conundrum of how fewer insults might result in equally aggressive biology [12].

PMM seldom limits to marrow. EMD is seen in 30% of pediatric presentations, in contrast to older individuals with CLL [13]. Sites include liver, spleen, skin, and soft tissue masses. Neurologic complications—leptomeningeal spread, spinal cord compression—are not uncommon, complicating already fragile therapeutic trajectories [14]. Hyperviscosity syndrome, renal failure secondary to light chain cast nephropathy, and fulminant infections are particularly devastating in children, who lack the physiologic reserve of adults [15]. Moreover, paraneoplastic syndromes such as amyloidosis are rare but reported, underscoring the protean manifestations of this malignancy [16].

Treatment regimens for PMM have historically been extrapolated wholesale from adult protocols, as prospective pediatric trials are virtually non-existent. Combinations of proteasome inhibitors (bortezomib), immunomodulatory agents (lenalidomide, thalidomide), and corticosteroids form the backbone [17]. High-dose melphalan followed by autologous stem cell transplantation (ASCT) is considered feasible in older children and adolescents, with encouraging responses reported in case series [18]. However, overall outcomes remain inferior to adult cohorts, possibly due to biologic aggressiveness and diagnostic delays [19]. The role of novel therapies—monoclonal antibodies (daratumumab, elotuzumab), CAR-T cells targeting BCMA, bispecific T-cell engagers—remains largely speculative in pediatrics, though anecdotal responses hint at future promise [20].

B. Extramedullary Plasmacytomas in Children

Distinct from disseminated PMM are **solitary plasmacytomas**, either osseous or extramedullary. In children, extramedullary plasmacytomas (EMP) are vanishingly rare, with fewer than 50 cases reported in the literature [21]. Common sites include upper aerodigestive tract, paranasal sinuses, and nasopharynx [22]. Pediatric EMPs tend to present as localized masses without systemic features, although long-term risk of progression to MM, well documented in adults, is uncertain in children due to sparse longitudinal data [23]. Histology reveals monoclonal plasma cell infiltrates with immunohistochemical light chain restriction [24]. Radiotherapy remains curative for localized lesions, with complete remission rates >80% [25]. Chemotherapy is generally reserved for unresectable or relapsed disease [26]. The question at issue is, the EMP in children is a strictly local clonal disorder or simply the most embryonic hint of systemic myeloma [27].

C. Pediatric Plasma Cell Disorders in the Context of Other Marrow Neoplasms

This is no mere academic exercise, as the combination of pediatric plasma cell tumors with myeloid and lymphoid neoplasms has been reported, either as hybrid appearances or as composite lesions. Myeloma associated with acute lymphoblastic leukemia (ALL) or histiocytic sarcomas indicate the combined origin of marrow...[28]. In children, these are particularly puzzling and it is not completely clear whether these are de novo events or if they are therapy related secondary transformations [29]. The genomic patchwork of translocations and copy number changes frequently traverses classificatory taxonomy, reminding the haematopathologist that the creation of rigid nosological boundaries is artifice [30].

If pediatric multiple myeloma is another anachronism of age, pediatric mastocytosis is another reminder of the protean flexibility of the hematopoietic lineages. Take the nine-month-old who became an unpredictable skin of urticated papules, those raised "wheals" his parents' touch, caress would conjure up wheals, flushing, and inconsolable crying. For months, physicians attributed the lesions to allergic dermatitis until a skin biopsy revealed a dense dermal infiltrate of spindle-shaped mast cells, tryptase-positive, KIT (CD117)–driven, forming the bedrock of cutaneous mastocytosis [21]. The tragic irony is that even benign forms, like urticaria pigmentosa of infancy, can confound parental bonding, as the mere act of holding one’s child can precipitate wheals, flushing, and systemic degranulation events.

E. Pediatric Mastocytosis

Mastocytosis in childhood bifurcates into cutaneous and systemic forms. Cutaneous mastocytosis predominates, manifesting as urticaria pigmentosa, diffuse cutaneous mastocytosis, or solitary mastocytomas [22]. The disease typically presents in infancy or early childhood, with spontaneous regression in adolescence for many. However, systemic mastocytosis, although rare, carries significant morbidity, with infiltration of marrow, liver, spleen, or gastrointestinal tract [23]. WHO classification recognizes mastocytosis as a clonal KIT-driven stem cell disease, but in pediatrics, the natural history is distinct—cutaneous dominance, low progression to systemic disease, and a high prevalence of self-resolving cases [24].

Pathology and markers: In children, skin lesions are made up of tight clusters of mast cells in the dermis. These cells can look round or spindle-shaped, and they contain granules that stain with toluidine blue or Giemsa [25]. On immunostaining, mast cells are positive for CD117 and tryptase, and often CD25; in systemic disease they may also show abnormal expression of CD2 or CD30 [26]. Blood tryptase levels generally track with how extensive the disease is, but in kids they are less reliable for predicting outcomes than in adults [27].

Genetics: The key driver in mastocytosis is the KIT gene, which encodes a receptor tyrosine kinase needed for mast cell growth and survival. In adults, the KIT D816V mutation is found in over 80% of cases and is almost diagnostic by itself [28]. Pediatric cases are more genetically diverse: many have non-D816V mutations in exons 8, 9, or 11, some of which are linked to milder courses and disease limited to the skin [29, 30]. Even so, a subset of children do carry D816V, reminding us that pediatric disease can occasionally mirror adult-type systemic mastocytosis with more serious implications [31].

Clinical course and care: Children can have very different experiences with this condition. Skin spots and plaques can worsen with heat, friction, or certain drugs that trigger mast cell release, including NSAIDs, opioids, and radiocontrast agents. Severe systemic issues—like anaphylaxis, poor nutrient absorption, enlarged liver/spleen, or bone involvement—are less common but can be severe when they occur [32]. Management centers on avoiding triggers and using H1 and H2 antihistamines; leukotriene receptor blockers help some patients, and corticosteroids or phototherapy are considered in select cases [33]. More aggressive treatments—such as cladribine or tyrosine kinase inhibitors like imatinib or midostaurin—are rarely used in children and are reserved for stubborn systemic disease with targetable KIT mutations [34]. The outlook is generally good: more than 80% of pediatric cases improve or resolve on their own, though careful follow-up is important because a small number progress to systemic mastocytosis or even mast cell leukemia [35].

F. Myeloid Sarcoma in Childhood

What it is: Myeloid sarcoma (MS) is a tumor made of immature myeloid cells that forms outside the bone marrow. It was once called "chloroma" because it can look green from myeloperoxidase. In kids, MS can show up in bone, skin, soft tissues, the central nervous system, the orbits, or lymph nodes [36]. It often appears at the same time as acute myeloid leukemia (AML), but it can also come first, sometimes months before leukemia is detectable in the marrow [37].

How common and why it happens: MS is seen in about 3–9% of pediatric AML cases and tends to involve the orbits and CNS more often in children [38]. Its biology isn't fully understood, but theories include abnormal expression of adhesion and homing molecules (like CD56, CXCR4, and integrins) that draw blasts to tissues, and supportive local stromal environments that help them grow [39].

Diagnosis: Under the microscope, MS shows sheets of blasts that replace normal tissue and can look like other tumors, including lymphoma, rhabdomyosarcoma, or Ewing sarcoma, which makes it easy to misdiagnose based on appearance alone [40]. Immunohistochemistry is crucial: blasts typically express myeloperoxidase, CD117, CD33, CD13, and CD68, and some cases also express CD56 or even atypical lymphoid markers [41].

Genetics and risk: The genetic changes in MS usually mirror those seen in accompanying or later AML, including t(8;21)(q22;q22)/RUNX1-RUNX1T1, inv(16)/CBFB-MYH11, and 11q23/KMT2A rearrangements [42]. In children, t(8;21) is particularly common and often goes with orbital disease, while KMT2A rearrangements are linked to worse outcomes [43]. Importantly, an isolated MS almost always progresses to AML if not treated systemically, underscoring that it is fundamentally a manifestation of a systemic disease [44].

Presentation, prognosis, and treatment: Children may present with proptosis from an orbital mass, spinal cord compression, or gum overgrowth. Solitary lesions are often mistaken for other conditions, leading to delays and inadequate local therapy until AML is recognized [45]. Prognosis largely depends on the AML genetics: core-binding factor (CBF) abnormalities generally predict better outcomes, whereas KMT2A rearrangements signal higher risk [46]. Surgery or radiation alone is not enough; treatment must follow AML-type systemic chemotherapy, even for isolated MS [47]. Hematopoietic stem cell transplantation is considered for high-risk or relapsed cases, though pediatric data are limited [48]. Newer targeted agents (FLT3 inhibitors, IDH1/2 inhibitors) and venetoclax have not been studied systematically in pediatric MS, but given parallels with AML, they may hold promise [49].

Although they look very different, pediatric mastocytosis and myeloid sarcoma both arise from the myeloid family and represent opposite ends of its behavior: one is an overgrowth of mature effector cells, the other a buildup of immature blasts that spread outside the marrow. Both can masquerade as more common skin or soft tissue problems, so accurate, integrated diagnosis is critical to avoid delays that can impact outcomes [50].

One sobering example is a seven-year-old boy who first noticed an ordinary-looking bruise on his thigh. Within four days it turned into a purple plaque and then into multiple skin nodules. His parents thought they were insect bites, and pediatricians initially suspected a fungal infection. A few weeks later, his bone marrow was found to be packed with blasts of dendritic lineage—blastic plasmacytoid dendritic cell neoplasm (BPDCN) [41]. Cases like his capture a core paradox in pediatric hematopathology: rare, often hidden lineages that barely draw notice in health can, when they turn malignant, present with dramatic, confusing, and rapidly evolving disease that demands swift, precise diagnosis.

G. Blastic Plasmacytoid Dendritic Cell Neoplasm in Childhood

BPDCN is a very rare hematologic malignancy, accounting for 80% of pediatric patients [44]. Systemic spread develops rapidly, with marrow, lymph nodes, spleen, and CNS infiltration [45].

Diagnosis is further dependent on the identification of a signature immunophenotypic constellation: CD4+, CD56+, CD123high, and TCL1+, while lacking expression of cell-lineagedefining markers for B, T, and myeloid cells [46]. They frequently have coexpression of BDCA-2 (CD303), CD304 (neuropilin), and CD2AP, confirming their plasmacytoid dendritic origin [47]. Misdiagnosis is common, and early forms are often diagnosed as “NK/T-cell lymphoma,” as AML, or undifferentiated sarcoma [48].

Molecular lesions involve recurrent TET2, ASXL1, NRAS, and IKZF1 inactivation, directing epigenetic deregulation as a disease pathogenic machinery [49]. This is the genetic architecture of pediatric BPDCN although the latest data indicate a higher incidence of KMT2A rearrangements associates with particularly aggressive course [50]. It is relatively refractory to conventional AML- or ALL-like treatments, with median survival <2 years, even in children [51].

Standard chemotherapy produces remissions, but relapse is the norm. Allogeneic SCT is still the only potential cure in good physical condition of pediatric patients [52]. In adults, the treatment landscape has changed significantly with the development of targeted therapy using tagraxofusp (a CD123-targeted Diphtheria Toxin fusion protein) [53]. Only limited pediatric data exist, but early publications indicate its tolerability and

efficacy in achieving long-lasting remissions [54]. Clinical trials of venetoclax and hypomethylating agents and novel CD123-directed CAR-T therapies are currently in progress [55].

H. Rare Marrow-Based Tumors in Children

In addition to BPDCN and plasma cell disorders, pediatric bone marrow may also be the source of tumors so rare as to be little more than academic footnotes, but whose identification is important.

1. Myeloid Sarcoma (an expanded reflection)
   As already covered, MS also bridges a gap between systemic AML and localized tumor biology, emphasizing marrow neoplasms do not value anatomic limits [56].

2. Histiocytic Sarcoma and Interdigitating Dendritic Cell Sarcoma
   Histiocytic and dendritic cell sarcomas resembling lymphomas are sometimes found in the pediatric marrow. These are frequently linked with clonal evolution from a pre-existing lymphoid neoplasm, similar to cases of transdifferentiation [57].

3. Mixed-Phenotype Acute Leukemias (MPAL) with extramedullary masses
   Children could present sarcoma-like masses, but were later discovered to have MPAL with a mixture of lymphoid and myeloid involvement. Such cases highlight the spectrum between the classical leukemias and uncommon sarcomatoid tumors of marrow origin [58].

4. Other Ultra-Rare Entities
   Plasmacytoid sarcomas [57], myelolipomas with atypia [58], hybrid stromal–hematopoietic tumors (anecdotal) make the pathologist scratch the head trying to put them in a nosological box [59]. Every case adds not to the frequency but to the depth of our appreciation of the hematopoietic continuum.

The overarching therapeutic dilemma in pediatric rare marrow neoplasms is the absence of prospective clinical trials. Management is extrapolated from adult data, case series, or institutional experience. Pediatric oncologists face the dual challenge of therapeutic aggression versus long-term toxicity. Radiation, alkylators, and transplantation save lives but at the cost of growth disturbances, infertility, cardiopulmonary late effects, and secondary neoplasms [60]. Thus, the pursuit of biologically targeted therapies—KIT inhibitors in mastocytosis, CD123-directed therapy in BPDCN, BCMA-directed therapy in pediatric myeloma—represents not merely a therapeutic luxury but an ethical imperative.

Table.1: Summary of Pediatric Plasma Cell and Rare Hematologic Neoplasm

Entity	Typical Age/Presentation	Key Sites of Involvement	Immunophenotype	Genetic/Molecular Features	Prognosis in Pediatrics
Pediatric Multiple Myeloma (PMM)	Adolescents; bone pain, anemia, renal failure	Marrow, bone, occasional extramedullary	CD38+, CD138+, MUM1+, CD19−, CD56 variable	t(11;14), t(4;14), t(14;16), hyperdiploidy, RAS mutations	Aggressive; median survival <3 yrs, improved with ASCT
Extramedullary Plasmacytoma (EMP)	Children/adolescents; localized mass	Upper aerodigestive tract, sinuses, soft tissue	Plasma cell phenotype with light chain restriction	Rare cytogenetics; uncertain systemic risk	Usually favorable with local therapy; uncertain long-term progression
Pediatric Mastocytosis	Infants/early childhood; cutaneous wheals, urticaria pigmentosa	Skin ± marrow/systemic organs	CD117+, tryptase+, CD25+, CD2/CD30 (systemic)	KIT mutations (often non-D816V in children)	Cutaneous forms regress; systemic rare, variable prognosis
Myeloid Sarcoma (MS)	Any pediatric age; proptosis, CNS/soft tissue masses	Orbit, bone, skin, lymph nodes, CNS	MPO+, CD117+, CD33+, CD68+, CD56 variable	t(8;21), inv(16), KMT2A rearrangements	Mirrors AML biology; prognosis depends on cytogenetics
Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)	Older children; skin nodules, marrow/CNS spread	Skin, marrow, lymph nodes, CNS	CD4+, CD56+, CD123+, TCL1+, CD303/CD304+	TET2, ASXL1, NRAS, IKZF1; KMT2A in children	Extremely poor; <2 yrs median survival; HSCT/tagraxofusp emerging

Histiocytic/Dendritic Cell Sarcoma	Rare; lymphadenopathy, marrow involvement	Lymph nodes, marrow, extranodal sites	CD68+, CD163+, S100+, CD1a− (histiocytic); S100+, CD45−, fascin+ (dendritic)	Sporadic; often transdifferentiation from lymphoid tumors	Aggressive, often refractory
Other Rare Entities (BPDCN variants, hybrid stromal-hematopoietic neoplasms)	Isolated case reports	Variable	Mixed	Heterogeneous	Prognosis poorly defined, often dismal

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 9: Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndromes in Childhood

1 Introduction

The tale begins with a four-year-old girl in a remote village hospital, her body consumed by relentless fevers that defied every antibiotic known to her physicians. Her abdomen was swollen, the contour of her spleen visibly pushing against her frail skin, while her parents whispered prayers into the night. Initially misdiagnosed as typhoid fever, then malaria, then sepsis, the true specter lurking behind her deteriorating state was a storm more insidious: hemophagocytic lymphohistiocytosis (HLH). By the time bone marrow aspiration revealed macrophages ravenously devouring hematopoietic precursors, the child had already succumbed to disseminated coagulopathy and multiorgan failure. Her story, like countless others scattered across medical records and unpublished anecdotes, represents the devastating diagnostic elusiveness of HLH in pediatrics [1].

A. Pediatric hemophagocytic lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH) represents not a single disorder but a clinicopathological syndrome of immune dysregulation, in which the innate and adaptive arms of immunity become locked in a cycle of unchecked activation. It manifests as hyperinflammation orchestrated by excessive cytokine release, impaired cytotoxic lymphocyte function, and macrophage-driven hemophagocytosis [2]. Pediatric HLH, though rare, carries a catastrophic potential: untreated, it is almost universally fatal within weeks to months [3].

The incidence of HLH is estimated at 1–2 per 100,000 children annually, though underdiagnosis and misclassification mean the true burden may be higher [4]. Distinctions between primary (familial, genetic) and secondary (acquired, reactive) forms are increasingly blurred, with discoveries of germline mutations even in cases

once considered “secondary.” Nonetheless, for pedagogical clarity, HLH in children is traditionally subdivided into familial HLH (FHL), syndrome-associated HLH (inherited immunodeficiencies with HLH phenotype), and secondary HLH (triggered by infections, autoimmune disease, or malignancy) [5].

HLH was first delineated in 1952 by Farquhar and Claireaux, who described two infants with a fatal “familial hemophagocytic reticulosis” characterized by fever, hepatosplenomegaly, cytopenias, and histiocytic proliferation with hemophagocytosis [6]. Since then, successive decades have transformed HLH from an obscure familial disease to a paradigmatic model of hyperinflammatory syndromes, now encompassing secondary HLH, macrophage activation syndrome (MAS), and cytokine storm syndromes observed in infections such as Epstein–Barr virus (EBV), H1N1 influenza, and more recently, SARS-CoV-2 [7].

The HLH-2004 diagnostic criteria remain the most widely applied clinical framework: diagnosis requires either a molecular confirmation of HLH-related mutations or fulfillment of five of eight clinical and laboratory criteria: persistent fever, splenomegaly, cytopenias in ≥2 lineages, hypertriglyceridemia/hypofibrinogenemia, hemophagocytosis, low/absent NK-cell activity, hyperferritinemia, and elevated soluble IL-2 receptor (sCD25) [8].

Familial HLH represents the archetypal inborn error of immunity, wherein genetic mutations cripple cytotoxic lymphocyte function. To date, at least five genetic subtypes (FHL1–FHL5) have been characterized [9].

1. FHL2 is caused by PRF1 mutations encoding perforin, a pore-forming protein essential for granzyme delivery during NK and CD8+ T-cell cytotoxicity [10]. Children with FHL2 often present in early infancy with fulminant HLH, reflecting the absolute necessity of perforin in immune homeostasis.

2. FHL3 results from mutations in UNC13D, encoding Munc13-4, a protein crucial for priming cytotoxic granules for exocytosis [11].

3. FHL4, linked to STX11 mutations, impairs syntaxin-11, disrupting membrane fusion in cytotoxic vesicle trafficking [12].

4. FHL5 is caused by mutations in STXBP2 (Munc18-2), a chaperone for syntaxin, with presentations often including severe colitis and early-onset HLH [13].

5. FHL1, historically described in consanguineous families, remains genetically undefined, though linkage to chromosome 9q21 has been suggested [14].

The common thread across all FHL subtypes is defective NK and CD8+ T-cell cytotoxicity, culminating in inability to terminate immune activation once triggered. In the absence of cytotoxic resolution, antigen-presenting cells and T cells engage in a vicious cycle of reciprocal activation, releasing torrents of IFN-γ, TNF-α, IL-6, and IL-18, driving macrophage hyperactivation and hemophagocytosis [15].

Beyond FHL, HLH arises in the context of other inherited immunodeficiencies, where impaired cytotoxic pathways are secondary to broader syndromic defects.

1. Chediak–Higashi syndrome (CHS), due to LYST mutations, is characterized by giant lysosomal granules, oculocutaneous albinism, and recurrent infections. The "accelerated phase" of CHS is indistinguishable from HLH, with uncontrolled lymphohistiocytic activation [16].
2. Griscelli syndrome type 2 (GS2), caused by RAB27A mutations, manifests with partial albinism and HLH. Rab27a is critical for docking of lytic granules; its deficiency disrupts NK/T cytotoxicity [17].
3. X-linked lymphoproliferative disease (XLP1 and XLP2), due to SH2D1A (SAP) or XIAP mutations, respectively, predisposes to EBV-triggered HLH. Children with XLP may remain clinically silent until EBV infection unleashes fulminant HLH or lymphoma [18].

These syndromic HLH variants highlight the genetic heterogeneity underpinning pediatric HLH and underscore the need for early genetic testing in any child presenting with hyperinflammatory syndromes.

Primary HLH often presents in infancy or early childhood with unremitting fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathy, and transaminitis [19]. Neurological involvement—seizures, irritability, ataxia, CSF pleocytosis—is common and portends poor prognosis. The median age of onset is <1 year in FHL2 and FHL3, though later-onset presentations into adolescence have been documented, often associated with hypomorphic mutations or environmental triggers [20].

Without treatment, familial HLH is uniformly fatal. Historical series before the advent of etoposide-based therapy reported median survival of <2 months from diagnosis. Today, with standardized protocols (HLH-94, HLH-2004) and the availability of hematopoietic stem cell transplantation (HSCT), long-term survival in genetically confirmed FHL approaches 50–60%, though relapses remain common in the pre-HSCT interval [9].

While primary HLH arises from **germline defects of cytotoxic lymphocyte function**, the majority of pediatric HLH cases encountered in tertiary hospitals fall under the rubric of **secondary HLH**, a designation historically intended to describe reactive hyperinflammatory syndromes triggered by infections, autoimmune conditions, or malignancies in otherwise immunocompetent hosts [21]. Yet the genetic revolution has blurred this dichotomy: hypomorphic or heterozygous mutations in canonical FHL genes may predispose children to exaggerated immune activation following environmental triggers, effectively collapsing the distinction between "primary" and "secondary" HLH [22]. Infections remain the most common precipitants of pediatric secondary HLH. **Epstein–Barr virus (EBV)** is the prototypical and most extensively studied infectious trigger, responsible for a high proportion of pediatric HLH in East Asia [23]. EBV-driven HLH is often fulminant: infected B cells serve as reservoirs of viral latency, stimulating relentless cytotoxic T-cell and NK-cell activation. In genetically susceptible children, the inability to eliminate EBV-infected cells precipitates catastrophic immune activation.Other viral agents include **cytomegalovirus, adenovirus, parvovirus B19, H1N1 influenza, and SARS-CoV-2**, the latter demonstrating striking overlap between HLH and severe COVID-19–associated cytokine storm in children [24]. Bacterial and parasitic pathogens such as **Leishmania donovani** also induce HLH, with visceral leishmaniasis representing an endemic driver of HLH in the Indian subcontinent [25].Speaking of **Malignancy-associated HLH (M-HLH)** , which wpuld account for approximately 10–15% of pediatric HLH cases, frequently in the context of T-cell or NK-cell lymphomas and leukemias [26]. These children often present with rapidly progressive disease, and HLH may obscure the underlying malignancy. In rare cases, HLH itself may represent a paraneoplastic hyperinflammatory response, with cytokine cascades driven by malignant lymphoid cells.

B. Pediatric Macrophage Activation Syndrome (MAS)

A seven-year-old girl, long known to the pediatric rheumatology clinic for her systemic juvenile idiopathic arthritis, returned with persistent fevers, lethargy, and a quiet pallor that unsettled even her exhausted mother. The joints that once dictated her pain were strangely silent, yet her skin carried a waxy hue, her eyes sunk with fatigue, and bruises dotted her arms where no trauma was recalled. Within days, her hemoglobin dropped precipitously, her platelets vanished, and the laboratory whispered a cruel secret: ferritin levels climbing into the tens of thousands, fibrinogen plummeting to a whisper, and a storm of inflammation unraveling her small frame. What had once been thought an ordinary disease flare was unmasked as macrophage activation syndrome—an invisible tempest where her own immune system consumed her from within. Despite the swift interventions of corticosteroids and biologics, her family watched helplessly as intensive

care became her world, a reminder of how swiftly a familiar chronic illness in childhood could spiral into a life-threatening storm.

Macrophage activation syndrome (MAS) represents a secondary HLH variant triggered by underlying autoimmune or autoinflammatory diseases, most notably systemic juvenile idiopathic arthritis (sJIA), but also systemic lupus erythematosus and Kawasaki disease [27]. MAS often masquerades as a flare of the underlying rheumatologic condition, delaying recognition. Hyperferritinemia, cytopenias, and hypofibrinogenemia are crucial diagnostic red flags in this context [28].

The immunopathology of HLH is characterized by the triad of impaired cytotoxicity, sustained antigenic stimulation, and hypercytokinemia.

1. Impaired cytotoxic lymphocyte function: In both primary and secondary HLH, NK cells and CD8+ T cells fail to clear infected or malignant targets, allowing persistent immune synapse stimulation [29].
2. Continuous T cell and macrophage activation: Continuous immune synapse carries the ongoing unrestrained T cell proliferation as well as excessive IFN-γ production, which activates macrophages to produce IL-6, IL-18 and TNF-α [30].
3. Cytokine storm: High levels of IFN-γ, II-1β, IL-6, IL-18, and sCD25 drive the systemic inflammation and hemophagocytosis and are associated with multi-organ dysfunction [31].

This process is not specific to HLH. It reflects what is observed pathophysiologically in CRs induced by CAR-T and in severe viral infections, however in HLH, it has self-perpetuating cytotoxic abnormalities [32].

And finally, with clinics, secondary HLH can present in many guises. Key features include:

1. High grade fever- may be the sentinel signal.
2. Hepatosplenomegaly: seen in >90% of pediatric HLH [33].
3. Cytopenias: pancytopenia is common, from both marrow haemophagocytosis and cytokine inhibition.
4. Hyperferritinemia: levels >10,000 ng/mL are strongly predictive of HLH in children [34].
5. Coagulopathy: hypofibrinogenemia, hypertriglyceridemia, and disseminated intravascular coagulation.

6. Neurological involvement: irritability, seizures, encephalopathy, often associated with CSF pleocytosis.
7. In MAS, arthritis flares are paradoxically muted, while cytopenias and liver dysfunction dominate, misleading clinicians unless high suspicion is maintained [35].

C. HLH-2004 Criteria and Their Limitations

While widely used, the HLH-2004 criteria were designed for clinical trials and may not capture all pediatric cases. For example, hemophagocytosis on marrow aspirate is neither sensitive nor specific, and NK-cell activity assays are not widely available in low-resource settings [8].

HLH-2004 Diagnostic Criterion	Details	Key Limitations in Pediatrics
Persistent fever	Unremitting high-grade fever ≥38.5°C	Non-specific; overlaps with sepsis, autoimmune flares, and malignancy.
Splenomegaly	Enlargement of spleen, often progressive	Common in infections (malaria, EBV, leishmaniasis) → poor specificity.
Cytopenias (≥2 lineages)	Hb <9 g/dL, platelets <100×10⁹/L, neutrophils <1.0×10⁹/L	Mimicked by sepsis, marrow suppression, chemotherapy, aplastic anemia.
Hypertriglyceridemia and/or hypofibrinogenemia	TG ≥265 mg/dL; fibrinogen ≤150 mg/dL	Affected by nutritional status, liver disease, and systemic infections.
Hemophagocytosis	Demonstrated in bone marrow, spleen, or lymph nodes	Not pathognomonic; may be absent early or appear in severe infections, sepsis, malignancy.
Low/absent NK-cell activity	Functional cytotoxicity assay	Not universally available; results delayed; influenced by acute illness, sample transport.
Hyperferritinemia	Ferritin ≥500 µg/L (often >10,000 in HLH)	Non-specific; elevated in sepsis, liver failure, systemic inflammatory syndromes.

Elevated soluble IL-2 receptor (sCD25)	Reflects T-cell activation	Specialized assay; poor accessibility in low-resource settings; high cost.

Diagnosis requires ≥5 of 8 criteria, but many pediatric patients with fulminant HLH may not meet all early; conversely, overlap with sepsis, malignancy, and MAS complicates specificity. Genetic confirmation may not be rapidly available, delaying therapy.

Therefore, to overcome this challenge let us, simplify it as -

Criterion	**Reliability in Pediatric HLH**	**Comment**
Fever	★★★☆☆ (Moderate)	Nearly universal, but non-specific; overlaps with infections and malignancies.
Splenomegaly	★★☆☆☆ (Low–Moderate)	Common but not specific; seen in malaria, EBV, leishmaniasis.
Cytopenias (≥2 lineages)	★★★★☆ (High)	Strong indicator, but differential includes marrow suppression, aplasia, chemotherapy.
Hypertriglyceridemia / Hypofibrinogenemia	★★★★☆ (High)	Often present in true HLH; better discriminative value than splenomegaly.
Hemophagocytosis in marrow/spleen/lymph nodes	★★☆☆☆ (Low)	May be absent early; not specific (also in sepsis, malignancy, severe infections).
Low/absent NK-cell activity	★★★☆☆ (Moderate)	Specific but not always accessible; assay availability limits pediatric use.
Hyperferritinemia	★★★★★ (Very High)	Ferritin >10,000 µg/L is strongly predictive in children; most useful laboratory marker.
Elevated sCD25 (soluble IL-2 receptor)	★★★★☆ (High)	Reliable if available, but assay costly and not rapid.

Most reliable markers: hyperferritinemia, cytopenias, hypofibrinogenemia; Least reliable: splenomegaly, hemophagocytosis alone.

Novel markers such as CXCL9 (reflecting IFN-γ activity), soluble CD163, and serum IL-18 may refine pediatric HLH diagnosis. Gene panel sequencing is increasingly employed to identify hypomorphic variants in HLH-related genes among patients initially labeled as "secondary" [29].

The management of HLH is among the most formidable challenges in pediatric hematopathology. The therapeutic paradox lies in the need to dampen an overactivated immune system while simultaneously safeguarding the host from overwhelming infection or underlying malignancy [36]. Untreated HLH used to be universally fatal; nowadays regimens, although not curative in themselves, have greatly improved survival, so a diagnosis of HLH is not a death sentence any longer if detected early.

C. The HLH-94 Protocol: A Landmark

The HLH-94 protocol, developed by the Histiocyte Society, is still an integral part in the treatment of HLH [37]. This regimen combines:

1. An anti-topoisomerase II agent etoposide killing activated T cells.
2. A corticosteroid with systemic anti-inflammatory and immunosuppressive effects dexamethasone.Suppresses the immune system by reducing activity and volume of the lymphatic system, producing lymphocytopenia.
3. Cyclosporine A, in order to suppress T cells (later modifications).
4. Intrathecal MTX in those with CNS involvement.
5. The HLH-94 study established that early etoposide initiation was a life-saving treatment, especially in EBV-associated HLH, where it supports reduction of hyperactivated CD8+ T cells, which cause the cytokine storm [38].

D. HLH-2004: Refinements and Controversies

Modifications in the HLH-2004 protocol include early cyclosporine administration and a new schedule for intrathecal therapy in patients with CNS disease [39]. Yet debates persist: while survival improved, cyclosporine-related nephrotoxicity and hypertension are notable concerns, and the timing of CNS-directed therapy remains contested.

E. Hematopoietic Stem Cell Transplantation (HSCT)

For primary/familial HLH and refractory secondary HLH, allogeneic HSCT is the only curative intervention [40]. Survival rates with reduced-intensity conditioning (RIC) regimens have markedly improved, minimizing regimen-related toxicity while preserving engraftment [41].

Donor availability, however, continues to constrain outcomes, particularly in resource-limited settings. Haploidentical transplantation with post-transplant cyclophosphamide has emerged as a viable option where matched donors are scarce [42].

Long-term sequelae of HSCT in HLH survivors include graft-versus-host disease, endocrinopathies, and neurocognitive impairment due to both disease and treatment-related factors [43].

The therapeutic landscape of pediatric HLH has evolved from broad immunochemotherapy to a more nuanced paradigm incorporating targeted biologics, small-molecule inhibitors, and experimental genetic strategies, reflecting its identity as a prototypical cytokine-driven storm. Among anti-cytokine therapies, emapalumab, an anti–IFN-γ monoclonal antibody, has gained FDA approval for refractory primary HLH, where trials demonstrated both biomarker reduction and clinical benefit in children unresponsive to conventional regimens [44]; tocilizumab, an anti–IL-6 receptor antibody, though primarily employed in cytokine release syndromes, has shown anecdotal utility in secondary HLH and MAS [45], while anakinra, an IL-1 receptor antagonist, is particularly effective in MAS complicating systemic juvenile idiopathic arthritis, often serving as a corticosteroid-sparing intervention [46]. Parallel to these, ruxolitinib, a JAK1/2 inhibitor, has emerged as a potent suppressor of IFN-γ, IL-6, and related cytokine signaling pathways, with pediatric series documenting rapid ferritin decline and clinical stabilization, marking it as a bridge to transplantation [47]. At the experimental frontier, gene therapy holds theoretical curative promise, as CRISPR/Cas9-mediated correction of *PRF1* and *UNC13D* defects in preclinical systems hints at a future where HSCT may no longer be indispensable [48]. Nonetheless, outcome continues to be dismal: untreated HLH is universally fatal [49], and even under therapies according to HLH-94/2004, long-term survival still ranges at 50–60% (except for those with a familial form) and improves only when infection-associated secondary HLH is detected early and managed effectively [49]. The factors determining outcome include early administration of etoposide for EBV-HLH, availability of timely HSCT for genetically confirmed disease and CNS involvement associated with irreversible disease and poor survival; in contrast, MAS has a relatively more favorable course if diagnosed early and treated with corticosteroids/biologics, although relapses and chronic morbidities are common in pediatric survivors [50].

Without therapy, pediatric HLH is universally fatal. With HLH-94/2004 regimens, overall survival at 5 years is 50–60% for familial HLH, and higher for infection-triggered secondary HLH when treated promptly [49]. Prognosis depends heavily on:

1. Etoposide at an early stage in EBV-HLH.
2. Expeditious HSCT in genetically proven patients.
3. CNS invasion, a worse prognostic factor because of irreversible neurological sequela.
4. The prognosis for MAS is generally good when it is recognised and treated promptly with corticosteroids and biologics, although it can relapse [50].

In high-income countries, molecular diagnostics, NK-cell functional assays, and access to HSCT are available, whereas in low- and middle-income countries, carcinogenesis is frequently based on clinical suspicion and basic labs. This discrepancy accounts for the grossly elevated mortality in resource-limited environments, since children will die before any definitive therapy can be launched [42]. Filling these gaps mandates an international partnership, a telemedicine approach to diagnostic networks and cost-adjusted regimens.

Table.3: Pediatric Hemophagocytic Lymphohistiocytosis (HLH) and Macrophage Activation Syndromes (MAS): Clinical, Pathological, and Therapeutic Integration

Domain	**Primary HLH**	**Secondary HLH (Infection/ Malignancy)**	**MAS (Autoimmune-Associated)**
Etiology	Germline mutations (PRF1, UNC13D, STX11, STXBP2, etc.)	EBV, CMV, Leishmania, T/NK lymphoma, leukemia	Systemic JIA, SLE, Kawasaki disease
Age of Onset	Infancy to early childhood (median <1 year)	Any pediatric age, often school-age/adolescence	School-age children with rheumatologic disease
Pathogenesis	Defective NK/T-cell cytotoxicity → uncontrolled activation	Infection/malignancy triggers immune hyperactivation (± genetic predisposition)	Autoimmune flare triggers cytokine storm, defective downregulation
Clinical Hallmarks	Fever, hepatosplenomegaly,	Severe sepsis-like syndrome,	Arthritis flare overshadowed by cytopenias,

	pancytopenia, CNS involvement	hepatosplenomegaly, cytopenias	coagulopathy, hepatopathy
Key Biomarkers	Ferritin >10,000 µg/L, sCD25, CXCL9	Ferritin >10,000, elevated IL-18, hypertriglyceridemia	Ferritin >5,000, IL-18, falling ESR despite inflammation
Diagnostic Challenges	Overlaps with severe infections; genetic confirmation required	Masked by infection/malignancy; biopsy may be misleading	Mimics autoimmune flare; needs high suspicion
Therapy	HLH-94/HLH-2004, HSCT (curative)	HLH protocols + infection/malignancy treatment	Corticosteroids, cyclosporine, biologics (IL-1, IL-6 blockade)
Novel/Adjunctive Therapy	Emapalumab, ruxolitinib, gene therapy (experimental)	Tocilizumab, JAK inhibitors, virus-specific T-cell therapy	Anakinra, canakinumab, tocilizumab
Prognosis	Poor without HSCT; ~50–60% survival post-transplant	Better if infection treated + HLH controlled	Generally favorable with early biologic use
Global Considerations	Requires advanced molecular labs and HSCT access	High mortality in low-resource settings	Dependent on pediatric rheumatology expertise

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-091-9

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Chapter 10: Artificial intelligence and machine learning

1 Introduction

The domain of pediatric hematopathology is perched precariously on the cusp of a dialectical precipice where the ancient certitudes of classical morphology are being increasingly supplanted, not so much superseded as over-traced, by digital technologies, molecular diagnostics, and immunogenetic cartographies which themselves insinuate as veritable epistemological scaffolds. In this liminal frontier, the future of hematopathology cannot be conceived as a stagnant continuum of current wisdom, but as a perpetual pendulum swing between morphological memory and genomic futurity.

A. Artificial Intelligence and Computational Morphology

The incorporation of artificial intelligence (AI) in the assessment of the hemic system signifies a profound epistemological break and a challenge to our very foundation. Algorithms, including deep learning convolutional neural networks, have recently shown ability not only to automatically recognize leukemic blasts but also to probabilistically stratify the leukemic subtypes with accuracy close to, sometimes surpassing, level of seasoned morphologists.. Yet, AI in this terrain does not merely mimic human diagnostic acuity; it engenders a new paradigm wherein pattern recognition is no longer limited by anthropocentric thresholds of visual perception. Instead, imperceptible pixel-level subtleties, hitherto occluded to the human retina, become diagnostic variables of weighty significance.

Nevertheless, AI cannot be simplistically construed as a panacea; it embodies the ambivalence of any emergent technology. The opacity of algorithmic decision-making (the so-called “black box problem”) raises epistemic anxieties, for what utility lies in a diagnostic pronouncement devoid of hermeneutic transparency? Thus, the trajectory of AI in pediatric hematopathology must inevitably navigate the interstice between efficiency and explicability, between computational omniscience and clinical accountability. The ultimate telos may not be the replacement of the human

hematopathologist but the genesis of an augmented diagnostician, wherein the machine's inexhaustible analytic stamina is counterbalanced by human interpretative wisdom.

B. Targeted therapy and the molecular rethinking of treatment

Cancer care is moving from broad, non-specific chemotherapy toward precisely targeted drugs. By mapping the genetics of leukemia, we've identified actionable mutations, abnormal kinase signaling, and failures in cell-death pathways. Therapies like FLT3 inhibitors, BCL2 blockers, and tyrosine kinase inhibitors now let us match treatment to the tumor's specific biology. What used to be a one-size-fits-all approach is becoming a tailored set of options. In children, effectiveness isn't the only goal; we also have to protect growth, hormones, and brain development. The ethical challenge is clear: eradicate malignant cells without leaving lasting harm on a developing body. Pediatric targeted therapy can't simply copy adult successes. It needs its own careful path—one that pairs molecular precision with developmental safety.

C. Stem cell transplantation and the push for lasting cures

Allogeneic stem cell transplant remains one of the most powerful curative tools in pediatric blood disorders, malignant and non-malignant alike. The approach itself is evolving. Traditional myeloablative conditioning can cure but at a high cost of toxicity. Reduced-intensity conditioning (RIC) aims to maintain efficacy while being more tolerable. At the same time, wider use of haploidentical transplants—supported by post-transplant cyclophosphamide—has eased donor shortages and expanded access to curative therapy. Looking ahead, induced pluripotent stem cell–derived blood progenitors, edited ex vivo to correct disease-causing mutations, suggest a future where a child's own "cleaned" cells could replace donor grafts. That would not only advance transplant medicine, it would fundamentally change what transplantation means.

D. Immunotherapy and harnessing the immune system

The immune system has moved from backdrop to centerpiece in treatment. CAR T-cell therapy—reprogramming a child's own T cells to attack B-cell malignancies—has transformed care for pediatric ALL and demonstrated what immune-based therapies can do. These advances come with risks. Cytokine release syndrome, neurotoxicity, and antigen escape show how powerful therapies can create new vulnerabilities. Next-generation CAR designs—armored CARs, dual-target approaches, and self-regulating synthetic circuits—aim to boost efficacy while improving safety and control. Beyond CAR T cells, natural killer (NK) cell therapies, bispecific T-cell engagers, and

checkpoint inhibitors are expanding the immunotherapy toolbox and reshaping pediatric oncology.

E. Ethical, societal, and philosophical horizons

Progress isn't just technical—it's ethical. Gene editing, especially CRISPR/Cas9, brings immense promise and hard questions. Should we correct harmful blood disorders at the embryo stage? Where is the line between therapy and enhancement, and who gets to draw it? Access is another urgent issue. Many of the most advanced therapies—targeted biologics, CAR T cells, modern transplant strategies—remain out of reach in low-resource settings, reinforcing global survival gaps. A just future demands that innovation be paired with equitable access. The field's trajectory is not linear. It's a convergence of AI, targeted therapy, transplantation, and immunotherapy—disciplines that collide and recombine. The hematopathologist of tomorrow won't just read slides or analyze molecular data; they'll connect morphology, genomics, and machine learning to guide care with both precision and perspective. These emerging tools aren't just gadgets. They push us to rethink childhood illness, treatment, and recovery.

Pediatric hematopathology is about more than marrow and blood counts; it is about growth, vulnerability, and the responsibility to use science for children whose lives are most at risk. Ultimately, behind every genome and cytokine panel is a child. Each bone marrow sample represents both fragility and strength. When we braid together morphology, genetics, AI, transplant, and immunotherapy, we renew a collective promise: no child should be left behind. Humility must anchor that promise. Blood carries identity and history; to repair it is both healing and a step into mystery. The hematopathologist's work is technical and ethical—reading cells and reading the stakes. The future will demand bold reinvention and steady compassion, because beneath every dataset and slide is a child waiting—for relief, dignity, and a tomorrow. In that light, pediatric hematopathology is not just a science or an art, but a vigilant commitment to protect the most fragile lives.