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Review Article

Approach to Paediatric Pancytopenia: When to Suspect Bone Marrow Failure

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Abstract
Pancytopenia in children is an uncommon but potentially life-threatening clinical presentation requiring timely evaluation to distinguish transient, reversible causes from inherited or acquired bone marrow failure (BMF) syndromes. Recent UK cohort studies highlight a substantial proportion of paediatric cases attributable to inherited BMF syndromes. This review presents a structured diagnostic and management approach, focusing on clinical features that raise suspicion for marrow failure and drawing upon recent UK epidemiological data, guidelines, and outcome reports. In UK paediatric series, approximately 23% of children with cytopenia had confirmed pancytopenia, and 37% of these were subsequently diagnosed with Fanconi anaemia via chromosomal breakage assays. Early referral, comprehensive laboratory evaluation, and targeted genetic testing remain central to optimising outcomes, with haematopoietic stem cell transplantation (HSCT) offering survival rates up to 90% in matched sibling donor settings.[1]

Keywords: *Pancytopenia; Bone Marrow Failure; Fanconi Anaemia; Haematopoietic Stem Cell Transplantation; Paediatrics.*

Introduction

Paediatric pancytopenia encompasses a diverse spectrum of disorders, from nutritional deficiencies and viral infections to malignant marrow infiltration. Among these, inherited and acquired bone marrow failure syndromes represent critical diagnoses, as delayed recognition can lead to irreversible marrow aplasia or death[1]. In the United Kingdom, the relative rarity of BMF in children, coupled with the increasing availability of genomic diagnostics, underscores the importance of a methodical approach to investigation and management. This review synthesises recent UK research and clinical guidelines to aid paediatricians in recognising early warning signs for marrow failure and in applying an evidence-based diagnostic pathway.

Pancytopenia represents a complex clinical presentation arising from diverse mechanisms, broadly categorized into reduced marrow

production, marrow infiltration, or peripheral destruction. In pediatric practice, distinguishing benign, reversible causes from inherited or acquired bone marrow failure syndromes (BMF) is paramount. Inherited syndromes such as Fanconi anaemia, Dyskeratosis congenita, and Diamond–Blackfan anaemia account for a significant proportion of pediatric cases and are frequently associated with congenital anomalies and growth impairment, necessitating early genetic evaluation and consideration for haematopoietic stem cell transplantation.

Definition and Epidemiology

Pancytopenia is defined by concurrent anaemia, leukopenia, and thrombocytopenia, adjusted for age-appropriate reference ranges. UK multicentre data from 2020–2024 identified inherited BMF syndromes in nearly 40% of paediatric pancytopenia cases. Fanconi anaemia was the most frequently encountered inherited cause, confirmed through chromosomal breakage assays and subsequent molecular testing. The median age at presentation was approximately six years, with a slight male predominance.

In the majority of the patients, *FANCA* (64%), *FANCC* (12%), and *FANCG* (8%) disease-causing mutations are found. As the products of these genes are important for detecting interstrand crosslinking of the DNA double strands and coordinating their repair through homologous recombination, these mutations can lead to unrepaired DNA double-strand breaks [2]. Therefore, FA has the highest risk for developing cancer, generally from an adolescent age with a reported cumulative risk of 15–20% at the age of 40 and 40% at the age of 50 years.

Acquired aplastic anaemia represented the largest group of non-inherited cases, while myelodysplastic syndromes (MDS) and evolving leukaemia were less common but carried significant prognostic implications.

Aetiological Spectrum

Inherited Bone Marrow Failure Syndromes

Inherited syndromes arise from genetic defects impairing haematopoiesis and often present with characteristic congenital anomalies. Fanconi anaemia, a DNA repair defect, is associated with short stature, café-au-lait macules, and radial ray anomalies[3]. Dyskeratosis congenita, resulting from telomere maintenance defects, typically manifests as nail dystrophy, reticular skin pigmentation, and oral leucoplakia, and may be complicated by pulmonary or hepatic fibrosis. Diamond–Blackfan anaemia presents in infancy with macrocytic anaemia and congenital malformations due to ribosomal protein defects. Shwachman–Diamond syndrome, a disorder of ribosome assembly, is associated with chronic neutropenia, exocrine pancreatic insufficiency, and skeletal anomalies.[4]

Acquired Bone Marrow Failure

Acquired forms, particularly idiopathic aplastic anaemia, which is characterized by the failure of hematopoietic stem cells in the bone marrow, leading to pancytopenia. The pathogenesis involves both immune-mediated and intrinsic mechanisms, as well as genetic and environmental factors[5]. This multifactorial pathophysiology highlights the complexity of aplastic anemia and underscores the importance of a targeted therapeutic approach[6]. Secondary aplastic anaemia may be triggered by drugs such as chloramphenicol, viral infections including Epstein–Barr virus or parvovirus B19, exposure to toxins such as benzene, or therapeutic irradiation. The bone marrow is typically hypocellular without malignant infiltration, and the diagnosis is made after exclusion of inherited syndromes, MDS, and leukaemia.

Pre-Malignant and Malignant Disorders

Although less common, certain clonal disorders may present with pancytopenia. MDS is characterised by ineffective haematopoiesis, cytogenetic abnormalities such as monosomy 7,

and a risk of progression to acute myeloid leukaemia. Juvenile myelomonocytic leukaemia presents with monocytosis, organomegaly, and cytopenia, while acute leukaemia may initially appear as unexplained pancytopenia before the emergence of overt blasts in marrow or blood.[7]

Figure 1: Aetiological categories in pediatric pancytopenia

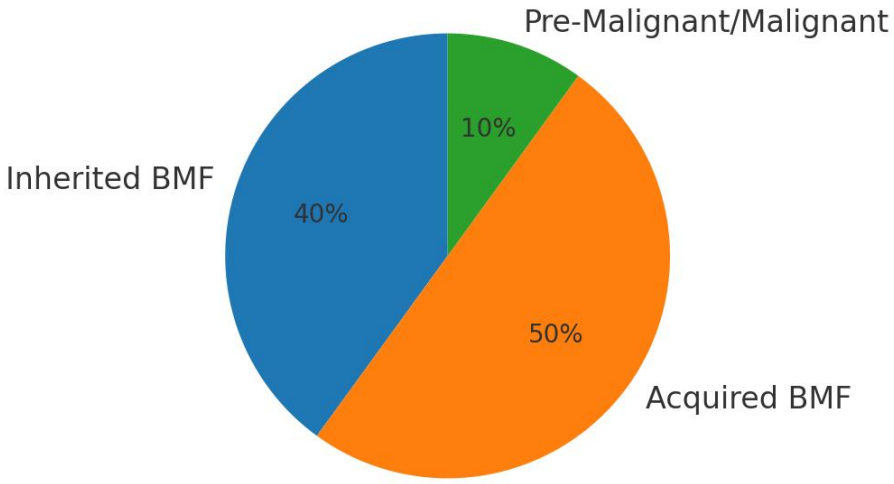

Figure 1: Schematic representation of major aetiological categories in paediatric pancytopenia, with emphasis on inherited bone marrow failure syndromes.

Clinical Red Flags and Diagnostic Approach

Certain features should prompt immediate consideration of bone marrow failure over benign causes. These include short stature, microcephaly, developmental delay, pigmentary skin changes, nail dystrophy, recurrent severe infections, oral ulceration, a family history of unexplained cytopenia, or persistence of cytopenia despite correction of nutritional deficiencies.

The initial evaluation should include a full blood count with differential, reticulocyte count, and examination of the peripheral smear. Viral serologies for Epstein–Barr virus, cytomegalovirus, and parvovirus B19, as well as nutritional markers including serum B12, folate, and ferritin, are important to exclude reversible causes. Bone marrow aspirate and trephine biopsy are mandatory to assess cellularity, exclude malignant infiltration, and obtain material for cytogenetic studies. Chromosomal breakage testing remains the standard for diagnosing Fanconi anaemia, while advanced diagnostics such as flow cytometry for paroxysmal nocturnal haemoglobinuria clones and next-generation sequencing panels are increasingly utilised[8].

Figure 2: Stepwise diagnostic approach

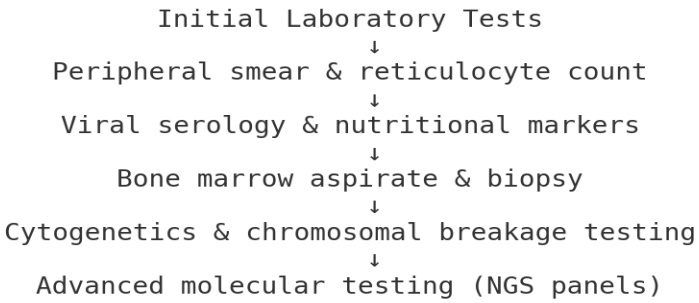

Figure 2: Flowchart outlining a stepwise diagnostic approach to paediatric pancytopenia, from initial laboratory evaluation to advanced molecular testing.

Management Strategies

Management of pancytopenia depends on the underlying diagnosis. Supportive measures include transfusion support for symptomatic anaemia or thrombocytopenia, infection prophylaxis, and judicious use of growth factors. Definitive therapy for severe aplastic anaemia and most inherited syndromes is haematopoietic stem cell transplantation, with matched sibling donor transplants achieving survival rates approaching 90%. Where no suitable donor exists, immunosuppressive therapy with horse antithymocyte globulin, ciclosporin, and eltrombopag remains the mainstay for acquired aplastic anaemia. Gene therapy approaches are under investigation for several inherited BMF syndromes and may alter the treatment paradigm in the coming decade.[9]

Figure 3: Therapeutic strategies and outcomes

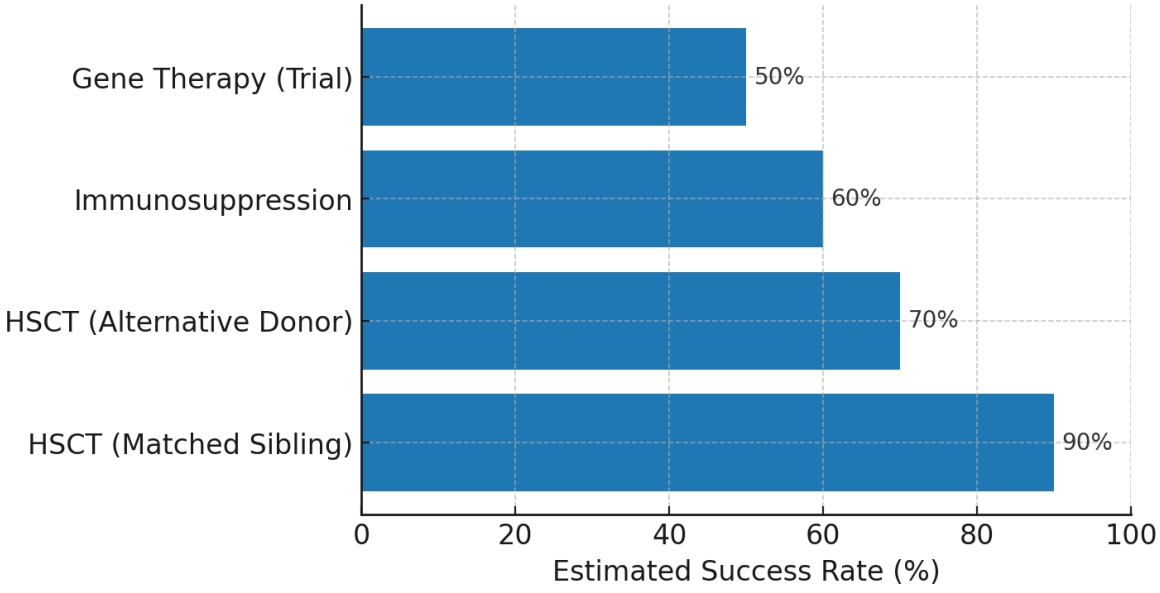

Figure 3: Overview of therapeutic strategies for inherited and acquired bone marrow failure syndromes, including HSCT and immunosuppressive therapy.

Conclusion

The differentiation of bone marrow failure from reversible causes of pancytopenia is a critical task in paediatric practice. Recent UK data reinforce the importance of early genetic testing and prompt referral to specialised haematology services. With ongoing advances in transplant techniques, supportive care, and gene therapy, the prognosis for children with BMF continues to improve. Clinicians should maintain a high index of suspicion in the presence of clinical red flags and adopt an algorithmic, evidence-based approach to investigation and management.[10]

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