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Atypical Haemolytic Ureamic Syndrome in Children

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Haemolytic uraemic syndrome (HUS) is characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia, and organ injury, particularly kidney injury. It is a form of thrombotic microangiopathy (TMA) that affects both adults and children with devastating clinical consequences. The classification and nomenclature of TMA have evolved as the understanding of the underlying pathogenesis has developed over the years. Specifically, atypical HUS (aHUS) refers to complement-mediated TMA, often associated with dysregulation of the alternative complement pathway(AP), resulting in endothelial cell damage. About 50-60% of patients with aHUS inherit variants of complement genes. Alternative complement pathway dysfunction is either related to the loss of function of AP regulators (Factor H, Factor I (CFI), and Membrane Cofactor Protein (MCP) or gain of function of complement pathway components, C3 and Factor B. Anti-factor H antibody-associated aHUS is another important clinical entity in complement mediated aHUS, typically linked to homozygous CFHR1-CFHR3 deletion. Since the advent of C5 inhibitors, the outcomes of patients with aHUS have dramatically improved.

Diagnosing aHUS can be challenging, and a pragmatic approach can assist clinicians in reaching a timely diagnosis and providing appropriate management.
Children with TMA should be evaluated according to their clinical presentation, with priorities depending on the manifestations. The assessment would typically involve investigating thrombotic thrombocytopenic purpura (TTP), Shiga-toxin associated haemolytic uremic syndrome (STEC-HUS), and other secondary causes (such as infection, autoimmune diseases, drugs, malignancy, malignant hypertension, bone marrow transplant-related conditions). Uncommon genetic disorders associated with TMA, such as diacylglycerol kinase epsilon (DGKE) mutation or inborn errors of metabolism resulting in cobalamin deficiency, should also be considered, particularly in young children with TMA.

There is no single definitive biomarker for aHUS; rather, the combined evaluation of clinical and laboratory (hematological, biochemical, and potentially complement function assessment, if available) findings would reflect the progress and response to therapy. The management of HUS depends on the underlying etiology. C5 inhibitors should be used in

children with suspected complement-mediated aHUS, with individualization of the prescription and duration of therapy. However, a challenge remains in resource-limited settings where C5 inhibitors may not be readily available for children in need. A global effort is urgently needed to address these disparities and improve the outcomes of children with HUS worldwide.