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ATYPICAL HEMOLYTIC UREMIC SYNDROME DIAGNOSIS AND TREATMENT

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Atypical hemolytic uremic syndrome (aHUS), more commonly known as complement-related HUS is a kind of thrombotic microangiopathy (TMA) characterized by inherited pathogenic variants in complement genes or acquired autoantibodies against complement factors, predominantly involving kidney [1]. Activation of the alternative complement pathway (AP), which occurs due to dysfunction in complement regulatory proteins or, less commonly, activation of mutations in the complement proteins themselves, constitutes the pathogenesis of aHUS and enables endothelial damage [2]. It may also present as secondary aHUS triggered by COVID-19, Shiga toxin-producing Escherichia coli, or other identifiable conditions [1]. As a triad for the diagnosis of aHUS; thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and acute kidney injury are used, however, there is no universally accepted diagnostic criterion and it is considered inadequate because it is established without even histological findings in the kidney [1]. Complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP, CD46), thrombomodulin, complement factor B (CFB), and complement 3(C3) mutations are the mutations that play a dominant role in the pathogenesis of aHUS [2,3]. In 30% to 40% of patients who respond to complement inhibition, these mutations are not detectable or have genetic variants of unknown significance [2]. In a patient presenting with TMA findings, thrombotic thrombocytopenic purpura (TTP) must be excluded by showing that ADAMTS13 activity is above 10%. Short-acting C5 blockade (eculizumab) should be initiated without delay in those with ADMTS13 levels above 10% and those with severe oliguric acute renal failure [1]. Stool sampling should be done in individuals with diarrhea to detect Shiga toxin and/or microorganisms that produce Shiga toxin. Ravulizumab is a long-acting C5 inhibitor that is considered safe and effective in both treatment-naive adult and pediatric patients and in pediatric patients who have previously received complement inhibition [4]. Ravulizumab's half-life is four times longer than eculizumab (~51.8 days vs. ~11 days) and offers a reduced dosing frequency of up to 4-8 weeks instead of every 2-3 weeks [5]. All patients receiving complement inhibitors should be included in the vaccination program for Neisseria meningitis, Streptococcus pneumonia, and Haemophilus influenza type b, and early signs of infection should be carefully monitored and necessary parenteral antibiotic therapy should be started without delay. Although plasma exchange (PEX) treatment can provide partial benefit, especially in those with CFH, C3, and thrombomodulin gene variants, it has now been replaced by complement inhibitors where available. PEX treatment response is insufficient in CFI variants and does not provide additional benefits to complement inhibitors in MCP (CD46) deficiency [6]. Kidney transplantation treatment is associated with a high risk of recurrence, especially in patients with CFH mutations. However, the post-transplant relapse rate decreased with eculizumab treatment[7]. Iptacopan is an orally available, highly potent proximal complement inhibitor that specifically binds to CFB, the primary driver of the disease, thereby inhibiting AP [8]. Other treatments are being investigated, including alternative pathway-blocking agents and lectin pathway inhibitors.

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INNOVATIONS IN AL AMYLOIDOSIS MANAGEMENT

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Introduction: Immunoglobulin light chain (AL) amyloidosis is the most common type of systemic amyloidosis. AL amyloidosis is considered a plasma cell disorder caused by generally small and slowly proliferating clone of plasma cells in bone marrow that produces nonfunctional immunoglobulins. **Diagnosis:** Considering diagnosis of systemic amyloidosis is to evaluate for the presence of monoclonal paraprotein with electrophoresis and immunofixation of both serum and urine, serum kappa and lambda free light chain (FLC) levels, 24-hour urine protein. If testing confirms presence of a monoclonal immunoglobulin or abnormal FLC ratio, then tissue biopsy necessary for diagnosis should be performed. If amyloid is detected in the biopsy, the type of amyloid must be determined for a complete diagnosis. **Staging:** The most frequently used staging system is the Mayo 2012 model, which assigns a score of 1 for troponin T (≥0.025 μg/L), N-terminal probrain natriuretic peptide (NT-pro BNP; ≥1800ng/L) or BNP ≥400 ng/L, and a difference in serum FLCs (dFLC ≥180 mg/Land is believed to be superior at identifying very high risk individuals (1). An alternative model with high prediction performance is the European 2015 modification of the Mayo 2004 model assigning a score of 1 for troponin T (≥0.035 μg/L), NT-proBNP (≥ 332ng/L) and for stage 3 patients uses the absence or presence of ≥1800 ng/L criteria for IIIA, IIIB designation, respectively (2). Induction Therapy for Newly Diagnosed AL Amyloidosis: Many clinical studies investigated the role of bortezomib-based regimens, which were eventually accepted as the standart of care, the most commonly used regimen is combination of CyBorD. With the completion of the phase III Andromeda trial, the treatment paradigm has started to the addition of daratumumab together with CyBorD in the upfront setting. For patients who are eligible for autologous stem cell transplantation (ASCT), recommended beginning with induction therapy with daratumumab-CyBorD for two to four cycles and then evaluate the response. In patients who achieve a hematological very good partial response (VGPR) or better, forego ASCT and associated treatment-related morbidity and mortality in favor of completion of daratumumab-CyborD induction, followed by daratumumab maintenance for a total of 2 years. **Autologous Stem Cell Transplantation:**

Lack of consensus on optimal use of ASCT in patients with AL amyloidosis. A randomized phase II study involving 91 patients comparing high-dose intravenous melphalan (HDM) followed by ASCT with a course of oral melphalan 10 mg/m^2 given once daily and dexamethasone 40 mg given once daily for the first 4 days of a 28 day cycle for up to 18 cycles. At a median follow-up of 3 years, median overal survival (OS) in the HDM arm was significantly worse than those taking high dose melphalan and dexamethasone (22.2 versus 56 months). Clinical studies using modern induction regimens and strict selection criteria emphasize an improved outlook on early survival outcomes in transplantation. . The HOVON104 study evaluated ASCT after four cycles of bortezomib-based induction in 50 patients reported an estimated 3-year OS in the 86% and 72% cardiac response rate in evaluable patients at 2 years.

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CAR-T CELL THERAPY IN LYMPHOMAS: EXPANSİON OF INDICATIONS AND NEW APPROACHES

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CAR-T (chimeric antigen receptor T-cell) therapy represents a revolutionary advance in treating hematologic cancers, offering promising outcomes for lymphoma patients, especially those with relapsed or refractory disease. Initially approved for diffuse large B-cell lymphoma (DLBCL), CAR-T therapy is expanding to address a broader range of lymphomas, including other B-cell and T-cell subtypes. As CAR-T technology evolves, researchers are exploring innovative delivery strategies and engineering methods to enhance efficacy and address the unique challenges of treating different lymphoma types. CAR-T cell therapy works by genetically modifying a patient's T cells to express a receptor targeting specific cancer cell antigens. In B-cell lymphomas, CD19 has proven an effective target, with CAR-T therapies such as axicabtagene ciloleucel and tisagenlecleucel demonstrating remarkable responses. Recent studies reveal high remission rates in DLBCL, mantle cell lymphoma, and follicular lymphoma when using CD19-targeted CAR-T therapy, even in patients who have exhausted other treatment options. The success of these therapies has catalyzed research into additional lymphoma subtypes and new antigen targets, allowing CAR-T cell therapy to benefit an expanding patient population (Denlinger et al., 2022). One notable development is the investigation of CAR-T cell therapy in T-cell lymphomas. T-cell lymphomas pose unique challenges due to their antigen overlap with healthy T cells, leading to risks like T-cell fratricide, where CAR-T cells inadvertently destroy each other. To address this, researchers are designing CAR-T cells targeting less common antigens, such as CD30, which is often overexpressed in Hodgkin lymphoma and some T-cell lymphomas, but not in normal T cells. CD30-directed CAR-T therapies have shown early success in clinical trials, offering hope for relapsed Hodgkin lymphoma patients who lack other viable options (Brudno et al., 2024, Ramos et al., 2020). Localized CAR-T cell therapy is another emerging strategy, particularly for lymphomas affecting the central nervous system (CNS). CNS lymphomas present an additional barrier because CAR-T cells administered intravenously may struggle to cross the blood-brain barrier (BBB) and reach tumor cells. Direct intrathecal CAR-T administration, which bypasses the BBB, has shown promising early results for CNS lymphoma, providing high CAR-T cell concentrations directly within the CNS and improving patient outcomes. This approach may reduce systemic side effects like cytokine release syndrome (CRS) and neurotoxicity, although localized neurotoxicity remains a concern (Sagnella et al., 2022). Engineering advancements are also helping address antigen escape, where cancer cells evade CAR-T cells by losing the targeted antigen. Dual-target CAR-T cells can recognize multiple antigens, reducing the risk of relapse due to antigen loss. For example, dual CD19/CD22 CAR-T therapies are being studied for their ability to sustain long-term remission by targeting two markers common to B-cell lymphomas, thus enhancing durability and reducing escape mutations. Also combining CAR-T with immune checkpoint inhibitors improve CAR-T cell efficacy. (Roddie et al., 2023). In summary, CAR-T cell therapy has transformed the lymphoma treatment landscape, extending beyond DLBCL to address Hodgkin lymphoma, follicular lymphoma, and other challenging subtypes. As new approaches evolve—such as local delivery for CNS lymphoma, dual-target CAR-T constructs, and novel T-cell lymphoma strategies—CAR-T therapy's role continues to expand, offering new hope to patients with previously untreatable lymphomas. Continued innovation will be crucial for refining CAR-T technology, overcoming barriers, and realizing its full potential across diverse lymphoma types.

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PROFESSOR DOCTOR SEREF INCEMAN'S BIOGRAPHY AND LEGACY

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Dr Inceman was born in Istanbul in 1919. He completed his primary education at Galatasaray High School (1940). He graduated from Istanbul University Faculty of Medicine (1940-1946). After graduation, he started his residency at the Internal Medicine Clinic (Capa) of the same faculty. He completed his military service in Erzincan (1949-1950). He worked in the clinic of Professor Jean Bernard, who conducted studies on leukemia and immunohematology at the University of Paris (1950-1951). in 1951, he stayed with Professor Swen Moeschlin at the Internal Medicine Clinic of the University of Zurich, Switzerland for a month. He was promoted to Associate Professor in 1956 and to Professor in 1966. Between 1963 and 1986, he directed the Hematology Department and served as its chairman. He was one of the founding members of THD in 1967 and was its first president. His research interest in the