not accessible—is emphasized due to high maternal and fetal morbidity and mortality [1]. For iTTP, no major directional changes were made. Therapeutic plasma exchange (TPE) with corticosteroids remains standard of care. The addition of rituximab is conditionally suggested for both initial and relapsed events. Caplacizumab continues to be conditionally recommended, supported by real-world registry and cohort data showing faster platelet recovery, fewer exacerbations, reduced TPE sessions, shorter hospitalization, and mortality consistently below 5% [3,4]. Evidence highlights that early initiation, ideally within three days of diagnosis, maximizes benefit [4]. The update also provides revised good practice statements on antithrombotic therapy. Prophylactic anticoagulation (most often low-molecular-weight heparin) may be considered once platelet counts recover above 50×10^9/L in patients at elevated thromboembolic risk, while antiplatelet agents remain discouraged during the acute phase [1]. Importantly, registry data highlight the long-term morbidity of cTTP, including ischemic stroke, end-stage renal disease, and cardiac dysfunction, as well as pregnancy complications. These findings strengthen the rationale for early and consistent prophylaxis. Regulatory approval of rADAMTS-13 in the United States, Europe, and Japan for both prophylaxis and acute treatment represents a transformative milestone in cTTP management [5]. Conclusion: The ISTH 2025 focused update establishes rADAMTS-13 as the new standard for prophylaxis in cTTP and reaffirms the existing evidence-based triple therapy (TPE, corticosteroids, and caplacizumab ± rituximab) in iTTP. These recommendations, integrating randomized trial results, real-world data, and international consensus, provide globally harmonized, evidence-based guidance to improve outcomes and quality of life for patients with TTP.

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Abstract 006

THE TREATMENT ALGORITHM FOR SICKLE CELL DISEASE

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Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy characterized by the polymerization of Hemoglobin S (HbS), which results from a point mutation in the β-globin gene. The clinical heterogeneity of the disease is dictated by a complex interplay of three core pathophysiological mechanisms: vaso-occlusion (VOC), driven by erythrocyte rigidity secondary to deoxy-HbS polymerization; chronic hemolytic anemia, resulting from a shortened erythrocyte lifespan; and a state of chronic sterile inflammation and ischemia-reperfusion injury, triggered by the scavenging of nitric oxide (NO) by cell-free hemoglobin. While HbSS and HbS/β^0-thalassemia genotypes constitute the most severe phenotypes, therapeutic algorithms are designed to target these fundamental molecular underpinnings. **Foundational Management and Prevention in SCD:** The cornerstone of modern SCD management is rooted in proactive and preventive medicine. Early diagnosis through newborn screening programs facilitates the immediate initiation of penicillin prophylaxis (from 2 months to 5 years of age) and comprehensive vaccinations (against *Pneumococcus*, *Meningococcus*, and *H. influenzae*), which dramatically reduce the risk of invasive pneumococcal disease secondary to functional asplenia. Primary stroke prevention in the pediatric population (ages 2-16) relies on annual Transcranial Doppler (TCD) screening. A time-averaged mean of maximum velocity exceeding 200 cm/sec is an absolute indication for initiating a chronic transfusion program, a measure proven to reduce stroke risk by over 90%. Hydroxyurea remains the cornerstone of this foundational care, recommended for all patients with severe genotypes over the age of 9 months. When titrated to the maximum tolerated dose (MTD), its pleiotropic effects—including the induction of fetal hemoglobin (HbF) and its anti-inflammatory and anti-adhesive properties—significantly modify the disease course. **Management of Acute Complications:** Acute complications warrant standardized and aggressive intervention. The management of vaso-occlusive crises (VOCs) necessitates rapid, multimodal analgesia, featuring the administration of parenteral opioids and non-steroidal anti-inflammatory drugs (NSAIDs) within 30 to 60 minutes of presentation. Acute Chest Syndrome (ACS), a leading cause of mortality, is managed with broad-spectrum antibiotics, supplemental oxygen, and transfusion support. In cases of severe ACS, the 2020 American Society of Hematology (ASH) guidelines recommend exchange transfusion over simple transfusion to rapidly decrease the HbS fraction to less than 30%. Similarly, acute ischemic stroke constitutes a hematologic emergency that mandates immediate exchange transfusion to reduce the HbS level to below 30%. **Chronic Complications and Disease-Modifying Therapies:** For patients with a suboptimal response to or intolerance of hydroxyurea, therapy is personalized with phenotype-specific agents. In the vaso-occlusive-dominant phenotype, options include the P-selectin inhibitor crizanlizumab and the oxidative stress-targeting agent L-glutamine. However, the role of crizanlizumab in the treatment algorithm has become contentious following the failure of its post-approval STAND study to meet its primary endpoint. For the hemolysis-dominant phenotype, voxelotor, a direct inhibitor of HbS polymerization, is effective in increasing hemoglobin levels. Nevertheless, its use has become debatable following the non-renewal of its marketing authorization by the European Medicines Agency (EMA) due to insufficient evidence of clinical benefit and the company's subsequent global withdrawal decision. **Transfusion Support and Associated Management:** Chronic transfusion therapy is a life-saving intervention, particularly for stroke prophylaxis, but inevitably leads to iron overload. Iron chelation therapy should be initiated when serum ferritin levels exceed 1000-1500 ng/mL. The gold standard for monitoring chelation efficacy is the quantitative assessment of hepatic and cardiac iron burden via T2* MRI. To minimize iron accumulation and more precisely achieve target HbS levels, the 2020 ASH guidelines advocate for automated red cell exchange (RCE) over simple transfusions for patients on chronic transfusion regimens. **Conclusion:** The management paradigm for SCD has evolved from reactive care to a multifaceted approach encompassing proactive foundational

therapies, phenotype-specific treatments, and curative strategies. Allogeneic hematopoietic stem cell transplantation and the recently approved gene therapies based on CRISPR-Cas9 (Exa-cel) and lentiviral vectors (Lovo-cel) have ushered in a new era, offering curative potential for eligible patients. The future therapeutic algorithm is anticipated to become even more personalized through the integration of these revolutionary treatments.

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Abstract 007

WALDENSTRÖM MACROGLOBULINEMIA

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Waldenström Macroglobulinemia (WM) is a rare disease. The median age at diagnosis is 70 years and approximately 60 percent of patients are male. The etiology of WM is not fully understood. Approximately 90-95% of WM patients have mutations in the MYD88 L265P gene and 40% have recurrent mutations in the CXCR4 gene. The clonal B cell population leads to abnormal monoclonal IgM production. The pentameric configuration of IgM molecules increases serum viscosity, slowing blood flow through capillaries. In patients with WM, clonal B cells can directly infiltrate hematopoietic tissues, causing cytopenias (e.g., anemia, thrombocytopenia, neutropenia), lymphadenopathy, hepatomegaly, and/or splenomegaly. Rarely, plasmacytoid lymphocytes may infiltrate the central nervous system or meninges. Most patients with WM present with nonspecific constitutional symptoms but up to a quarter of patients may be asymptomatic at diagnosis. Common symptoms include weakness, fatigue, weight loss, and nose and gum bleeding. Bone marrow aspiration and biopsy demonstrating lymphoplasmacytic lymphoma is an important component of the diagnosis of WM. The biopsy specimen is usually hypercellular and densely infiltrated with lymphoid and plasmacytoid cells. Intranuclear vacuoles containing IgM monoclonal protein (Dutcher bodies) are common in the malignant cells of WM. The following criteria must be met for a diagnosis of WM: • IgM monoclonal gammopathy (any level) must be present in the serum. • ≥10% of the bone marrow biopsy specimen must show infiltration by small lymphocytes with plasmacytoid or plasma cell differentiation (lymphoplasmacytic features or lymphoplasmacytic lymphoma) and an intertrabecular pattern. • The infiltrate should express a typical immunophenotype (e.g., surface IgM +, CD5-/+, CD10-, CD11c-, CD19+, CD20+, CD22+, CD23-, CD25 +, FMC7+, CD103-, CD138-). The plasmacytic component will be CD138+, CD38+, and CD45- or less prominent. The differential diagnosis includes chronic lymphocytic leukemia, marginal zone and mantle cell lymphoma. Not every VM patient requires treatment. For asymptomatic patients, follow-up without treatment every 3-6 months is recommended. Treatment is indicated for patients with symptomatic WM if any of the following are attributable to WM: • Systemic symptoms: B symptoms such as recurrent fever, severe night sweats, fatigue and/or unintentional weight loss • Cytopenias: Hemoglobin ≤10 g/dL or platelet count <100,000/microL; cold agglutinin anemia, immune hemolytic anemia, and/or thrombocytopenia • Symptomatic or large (≥5 cm) lymphadenopathy, symptomatic splenomegaly and/or tissue infiltration • End-organ damage: Hyperviscosity, peripheral neuropathy, immunoglobulin light chain (AL) amyloidosis with organ dysfunction, symptomatic cryoglobulinemia, pleural effusions or nephropathy due to WM Symptomatic hyperviscosity in a patient with an indication for treatment requires urgent plasmapheresis. Signs and symptoms associated with hyperviscosity include oronasal hemorrhage, blurred vision, headache, dizziness, paresthesia, retinal vein occlusion, papilledema, stupor, and coma. In patients with treatment indications but without symptoms of hyperviscosity, options include rituximab plus bendamustine or Bruton's tyrosine kinase inhibitors (such as ibrutinib, zanubrutinib, or acalabrutinib). Treatment of relapsed or refractory disease may include Bruton's tyrosine kinase inhibitors, bendamustine plus rituximab, nucleosome analog-based regimens, and venetoclax, if not previously used. High-dose chemotherapy and autologous or allogeneic hematopoietic cell transplantation (HCT) are rarely used in the treatment of WM.

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Abstract 008

REFRACTORY CHRONIC MYELOID LEUKEMIA: A REVIEW OF CURRENT THERAPEUTIC LANDSCAPE AND EMERGING CHALLENGES

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Chronic myeloid leukemia (CML) has become a paradigm of targeted therapy success; however, a proportion of patients develop refractory disease, marked by failure or intolerance to multiple TKIs. Optimal management requires integrating molecular, clinical, and patient-related factors into therapeutic decision-making [1,2]. **Mechanisms of Resistance and Genetic Complexity:** Resistance is commonly mediated by BCR::ABL1 kinase domain mutations. While second-generation TKIs (dasatinib, nilotinib, bosutinib) address many resistant clones, the T315I substitution remains uniquely sensitive to ponatinib [3,4]. Beyond kinase domain changes, clonal evolution with mutations in ASXL1, RUNX1, IKZF1, TP53, and DNMT3A has been increasingly recognized. These lesions, frequently encountered in advanced phases, are associated with poor response to TKIs, higher risk of progression, and inferior survival [5,6]. **Current Therapeutic Approaches:** Ponatinib remains the agent of choice for patients harboring T315I or compound mutations, with careful risk management to mitigate vascular events [4]. Asciminib, a first-in-class STAMP inhibitor targeting the myristoyl pocket of BCR::ABL1, has emerged as a major advance. By restoring kinase autoinhibition, asciminib demonstrated superior efficacy and tolerability over bosutinib in the ASCEMBL trial [3] and has shown promising results in real-world refractory populations. **TKI Selection Considerations:** In clinical practice, TKI selection is