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BERNARD–SOULIER SYNDROME: CURRENT APPROACHES TO DIAGNOSIS AND MANAGEMENT

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Introduction. Bernard–Soulier syndrome (BSS) is a rare inherited platelet disorder characterized by impaired platelet adhesion and defective primary hemostasis. It belongs to the group of inherited platelet function disorders and is associated with a variable bleeding phenotype, ranging from mild mucocutaneous bleeding to severe and potentially life-threatening hemorrhagic complications. BSS is most commonly inherited in an autosomal recessive manner and is caused by pathogenic variants affecting the genes encoding the components of the platelet glycoprotein GPIb-IX-V complex. The most frequently involved genes are GP1BA, GP1BB, and GP9, which encode the GPIbα, GPIbβ, and GPIX subunits, respectively. The GPIb-IX-V complex is an essential receptor on the platelet surface that mediates the interaction between platelets and von Willebrand factor (vWF), particularly under conditions of high shear stress. Under physiological conditions, vascular injury exposes subendothelial structures and promotes the binding of vWF to the damaged vessel wall. The subsequent interaction between vWF and the GPIb-IX-V complex on the platelet surface initiates platelet adhesion and activation. This process represents an essential early step in the formation of the primary platelet plug. In BSS, quantitative deficiency or structural abnormalities of the GPIb-IX-V complex impair platelet adhesion to the site of vascular injury, resulting in defective primary hemostasis and increased bleeding tendency. The clinical manifestations of

BSS are predominantly related to mucocutaneous bleeding. Patients may present with recurrent epistaxis, gingival bleeding, easy bruising, petechiae, prolonged bleeding following dental procedures or surgery, and heavy menstrual bleeding. The severity of bleeding varies considerably between individuals. In severe cases, gastrointestinal, genitourinary, or other major bleeding may occur and can require urgent medical intervention. A characteristic hematological feature of BSS is the combination of thrombocytopenia and abnormally large, often giant, platelets. This morphological finding can provide an important diagnostic clue but may also complicate automated platelet counting because very large platelets can be incorrectly classified by some hematological analyzers.

Diagnosis and Research Methods. The diagnosis of Bernard–Soulier syndrome (BSS) is based on a comprehensive assessment of the clinical manifestations of the disease, complete blood count findings, morphological and functional characteristics of platelets, immunological investigations, and molecular genetic testing. Given the rarity of this disorder and the similarity of its clinical presentation to a number of other inherited and acquired hemostatic disorders, the diagnostic work-up should be systematic and include a thorough differential diagnosis. The initial evaluation includes a complete blood count with determination of the platelet count and assessment of the main erythrocyte and leukocyte parameters. BSS is characterized by thrombocytopenia of varying severity associated with markedly increased platelet size, including macrothrombocytes and giant platelets. Therefore, microscopic examination of a peripheral blood smear is of considerable diagnostic importance. It allows direct assessment of platelet size, shape, and morphological characteristics. The combination of thrombocytopenia with large or giant platelets in a patient presenting with a bleeding phenotype is an indication for specialized evaluation of platelet function and membrane receptors.An important stage of laboratory diagnosis is the assessment of platelet function using platelet aggregation and agglutination tests. One of the most characteristic functional

findings in BSS is markedly reduced or absent platelet agglutination in response to ristocetin. This phenomenon is caused by impaired interaction between von Willebrand factor (vWF) and the GPIb-IX-V receptor complex located on the platelet surface. At the same time, platelet responses to other physiological agonists may remain relatively preserved. This feature is of considerable importance in the differential diagnosis of BSS from other inherited platelet function disorders. Modern diagnostic evaluation of BSS includes assessment of platelet membrane glycoproteins by flow cytometry. This method enables quantitative determination of the expression of individual components of the GPIb-IX-V complex using specific monoclonal antibodies. In Bernard–Soulier syndrome, reduced or complete absence of expression of one or more components of this complex, particularly GPIbα, GPIbβ, and GPIX, may be detected. Flow cytometric findings help confirm a defect of the platelet receptor complex and are important for differentiating BSS from other inherited platelet disorders.To exclude disorders associated with similar abnormalities of primary hemostasis, particularly von Willebrand disease, plasma von Willebrand factor concentration and functional activity may be assessed when clinically indicated. The results should be interpreted in conjunction with platelet function testing. This integrated approach helps distinguish impaired interaction between vWF and the platelet receptor complex from a primary defect of von Willebrand factor itself.Molecular genetic testing plays an important role in confirming the diagnosis. The main genes associated with Bernard–Soulier syndrome are GP1BA, GP1BB, and GP9, which encode subunits of the GPIb-IX-V complex. Identification of a pathogenic variant in one of these genes confirms the inherited nature of the disorder and helps clarify the molecular basis of the defect. In addition, genetic findings may contribute to the investigation of genotype–phenotype correlations. Molecular genetic testing is also of practical importance for the evaluation of family members and genetic counseling.Particular attention should be paid to the accuracy of platelet count determination in patients with suspected

BSS. The presence of large and giant platelets may result in their misidentification by automated hematology analyzers and, consequently, lead to an underestimation of the actual platelet count. Therefore, platelet counts obtained by automated analyzers should be correlated with the findings of microscopic examination of a peripheral blood smear. In uncertain cases, morphological assessment may be critical for the correct interpretation of the severity of thrombocytopenia.

The differential diagnosis of Bernard–Soulier syndrome primarily includes immune thrombocytopenia, von Willebrand disease, Glanzmann thrombasthenia, other inherited platelet function disorders, and various forms of inherited macrothrombocytopenia. The combination of thrombocytopenia, large and giant platelets, markedly impaired ristocetin-induced platelet agglutination, and reduced or absent expression of components of the GPIb-IX-V complex by flow cytometry is particularly diagnostically significant.

Treatment. The treatment of Bernard–Soulier syndrome (BSS) is primarily aimed at preventing and controlling bleeding, as there is currently no standard therapy capable of correcting the underlying genetic defect. The choice of treatment depends on the severity of the bleeding phenotype, platelet count and function, the clinical condition of the patient, and the presence of situations associated with an increased risk of bleeding, such as surgical or dental procedures, trauma, and pregnancy. In patients with mild bleeding manifestations, local hemostatic measures may be sufficient. These include direct pressure, topical hemostatic agents, and appropriate local management of bleeding sites. Antifibrinolytic agents, such as tranexamic acid, may be useful for mucosal bleeding, particularly epistaxis, oral bleeding, and heavy menstrual bleeding. Their use should be individualized according to the clinical situation and contraindications. Platelet transfusion remains an important treatment option for significant or life-threatening bleeding and is frequently considered before major surgical procedures in patients with severe BSS. Transfused platelets provide functional GPIb-IX-V receptors and can temporarily

improve primary hemostasis. However, repeated platelet transfusions should be used cautiously because they may lead to alloimmunization and the development of antibodies against human leukocyte antigens (HLA) or platelet-specific antigens. Such complications may reduce the effectiveness of subsequent platelet transfusions and complicate future management. When platelet transfusion is required repeatedly, the use of leukocyte-reduced and, when appropriate, HLA-matched platelet components may be considered to reduce the risk of alloimmunization. In patients who have developed platelet antibodies, the selection of compatible platelet products becomes particularly important. Management of patients undergoing surgery or invasive procedures requires careful preoperative planning. The bleeding risk should be assessed individually, and a multidisciplinary approach involving a hematologist, surgeon, anesthesiologist, and other relevant specialists may be required. Depending on the type and extent of the procedure, preventive treatment may include antifibrinolytic therapy and platelet transfusion. Local hemostatic measures should also be used whenever possible. Women with BSS may experience significant menstrual bleeding and increased bleeding risk during pregnancy and childbirth. Management should therefore be individualized and coordinated between hematology and obstetric specialists. Antifibrinolytic therapy and, when clinically indicated, platelet transfusion may be considered during periods of increased bleeding risk. Patients should be advised to avoid medications that may further impair platelet function, particularly aspirin and other antiplatelet agents, unless their use is specifically indicated and carefully supervised by a physician. The use of non-steroidal anti-inflammatory drugs should also be carefully evaluated. Patients should receive education regarding recognition of clinically significant bleeding and the need for timely medical attention. In selected severe cases with recurrent, clinically significant bleeding that cannot be adequately controlled with conventional supportive measures, additional therapeutic approaches may be considered in specialized centers. Recombinant activated factor VII (rFVIIa) has

been used in some patients with inherited platelet disorders, particularly when platelet transfusion is ineffective or contraindicated because of alloimmunization. However, its use should be restricted to appropriate clinical situations and performed under specialist supervision. An important component of management is preventive care and patient education. Patients should be informed about the nature of the disease, potential bleeding triggers, the importance of informing healthcare professionals about the diagnosis before invasive procedures, and the need to avoid unnecessary medications that interfere with platelet function. Genetic counseling may also be appropriate because BSS is an inherited disorder.

Thus, Bernard–Soulier syndrome is a rare inherited disorder of primary hemostasis, the diagnosis and management of which require a comprehensive and individualized approach. The diagnostic algorithm should be based on an integrated assessment of clinical manifestations, complete blood count parameters, platelet morphological characteristics, platelet function test results, flow cytometry findings, and molecular genetic testing. Of particular diagnostic significance is the combination of thrombocytopenia with macrothrombocytes and giant platelets, impaired ristocetin-induced platelet agglutination, and reduced or absent expression of components of the GPIb-IX-V complex. Confirmation of the diagnosis using modern laboratory and molecular genetic methods enables timely differential diagnosis with other inherited and acquired disorders of hemostasis, clarification of the molecular basis of the disease, and, when indicated, screening of family members. This is of particular importance for genetic counseling and for determining an appropriate long-term follow-up strategy. Currently, the management of Bernard–Soulier syndrome is primarily aimed at the prevention and control of bleeding manifestations. Depending on the clinical situation, antifibrinolytic agents and transfusion therapy, including platelet transfusions, may be used. Particular attention should be paid to bleeding prevention and careful planning of surgical and invasive procedures. Regular hematological follow-up and

individualized assessment of bleeding risk allow timely adjustment of the therapeutic strategy and reduction of the likelihood of severe complications.

Thus, early recognition of Bernard–Soulier syndrome, laboratory confirmation of the diagnosis, and subsequent individualized patient management are essential for effective disease control and prevention of severe hemorrhagic complications, thereby contributing to the preservation of patients' functional status and quality of life.

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