

Glanzmann Thrombasthenia: Perspectives from Clinical Practice on Accurate Diagnosis and Optimal Treatment Strategies

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Abstract: Glanzmann thrombasthenia (GT) is a rare autosomal recessive disorder of fibrinogen-mediated platelet aggregation due to a quantitative or qualitative deficit of the $\alpha_{IIb}\beta_3$ integrin at the platelet surface membrane resulting from mutation(s) in *ITGA2B* and/or *ITGB3*. Patients tend to present in early childhood with easy bruising and mucocutaneous bleeding. The diagnostic process requires consideration of more common disorders of haemostasis and coagulation prior to confirming the disorder with platelet light transmission aggregation, flow cytometry of CD41 and CD61 expression, and/or exon sequencing of *ITGA2B* and *ITGB3*. Antifibrinolytic therapy, recombinant activated factor VII, and platelet transfusions are the mainstay of therapy, although the latter may trigger formation of anti-platelet antibodies in GT patients and inadvertent platelet-refractory disease. The management of these patients therefore remains complex, particularly in the context of trauma, labour and delivery, and perioperative care. Bone marrow transplantation remains the sole curative option, although the venue of gene therapy is being increasingly explored as a future alternative for definitive treatment of GT.

Keywords: bleeding disorders, inherited platelet defects, platelet aggregation, *ITGA2B*, *ITGB3*, $\alpha_{IIb}\beta_3$

Introduction

Glanzmann Thrombasthenia (GT) is a rare inherited bleeding disorder characterized by dysfunctional fibrinogen-mediated platelet aggregation due to decreased or dysfunctional $\alpha_{IIb}\beta_3$ integrin expression at the platelet surface membrane. This autosomal recessive condition affects approximately 1 in 1,000,000 people,¹ though prevalence reaches up to 1 in 200,000 people² in populations of increased consanguinity, including those coming from Pakistan, Iraqi Jewish groups, nomadic tribes of Jordan, South Indian Hindu communities, Roma camps within France, and the Canadian province of Newfoundland and Labrador.¹⁻⁶

Historical Context

In 1918, Dr. Glanzmann, a Swiss pediatrician, coined the term “thrombasthenia,” or “weak platelets,” when describing a patient exhibiting purpura despite having platelets of normal quantity and appearance on peripheral smear.^{1,7-10} Curiously, he also noted absence of platelet clumping, a prolonged bleeding time, and inferior clot retraction.⁷ Forty-four years later, in 1962, Drs. Caen and Cousin demonstrated

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absence of platelet aggregation in response to ADP, adrenaline, thrombin, and collagen stimulation.^{1,11} In the 1970s, multiple teams^{12–15} studying the platelets of Glanzmann thrombasthenia patients identified a shared underlying deficiency of the membrane glycoprotein IIb/IIIa complex, now known as the $\alpha_{IIb}\beta_3$ integrin.

Role of $\alpha_{IIb}\beta_3$ Integrin

Wild-type platelets express approximately 50,000 copies of $\alpha_{IIb}\beta_3$ integrin at their surface membranes.^{16,17} The α_{IIb} subunit, predominantly expressed within cells of the megakaryocytic lineage,¹⁸ is produced as a pro-peptide comprised of a heavy and light chain linked together by disulfide bridges.^{19–21} In addition to providing intramolecular stability, the integrity of the 674–687 disulfide bridge in particular has also been shown to be necessary for ultimate surface expression of the $\alpha_{IIb}\beta_3$ integrin.²² The α_{IIb} subunit binds its β_3 partner via calcium-dependent bonds prior to undergoing post-translational modifications, including O- and N-glycosylation, within the endoplasmic reticulum and Golgi apparatus.^{20,21} Once integrated into the platelet membrane, each mature subunit within the final receptor complex contains a large globular extracellular domain, a single transmembrane domain, and a small cytoplasmic region that interacts with its neighboring cytoplasmic domain via salt bridge (Figure 1).²⁰ The cytoplasmic domains also interact with other cytoplasmic and

cytoskeletal proteins^{20,23} and facilitate both inside-out and outside-in signaling (Figure 2).^{20,24,25} In its resting state, the $\alpha_{IIb}\beta_3$ integrin receptor exists in a “bent” conformation whose extracellular domains are clasped and have a low affinity for binding ligands.^{1,26,27} A rise in the intracellular concentration of calcium leads to a talin-induced conformational change within the extracellular domains of both subunits, exposing their ligand binding sites.^{26–28} This inside-out activation allows ligand binding sites on each subunit to bind the same fibrinogen molecule, which in turns binds identical ligand binding sites on other platelets to establish a platelet plug.¹ Meanwhile, fibrinogen binding also facilitates unclaspings of the extracellular domains of the α_{IIb} and β_3 subunits^{26,27,29,30} and triggers protein kinase C-mediated cytoskeletal changes and platelet granule secretion, ultimately resulting in platelet spreading and fibrin clot stabilization.¹ Clot formation and stabilization is further enhanced by β_3 's ability to bind von Willebrand factor, fibronectin, and vitronectin.^{1,28,31} Furthermore, β_3 promotes cleavage of Factor Xa, assisting with conversion of prothrombin to thrombin.^{8,32–34} β_3 has also been shown to have a role in fibrin clot retraction that is independent from its ability to bind fibrinogen.^{8,10,35–37} Given the myriad of interactions that must occur for the α_{IIb} and β_3 subunits to reach the platelet membrane and promote platelet aggregation, one can imagine the many opportunities for this process to

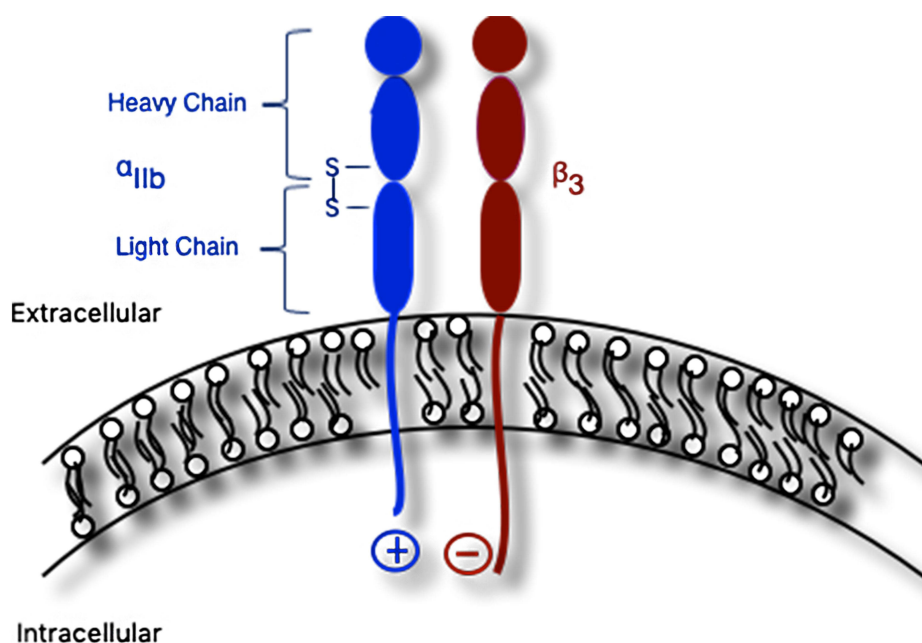


Figure 1 Schematic of $\alpha_{IIb}\beta_3$ integrin composed of α_{IIb} and β_3 subunits. The mature α_{IIb} subunit contains extracellular heavy and light chains linked together via disulfide bridge. Both subunits contain extracellular, transmembrane, and cytoplasmic domains; the latter domains are linked via salt bridge.

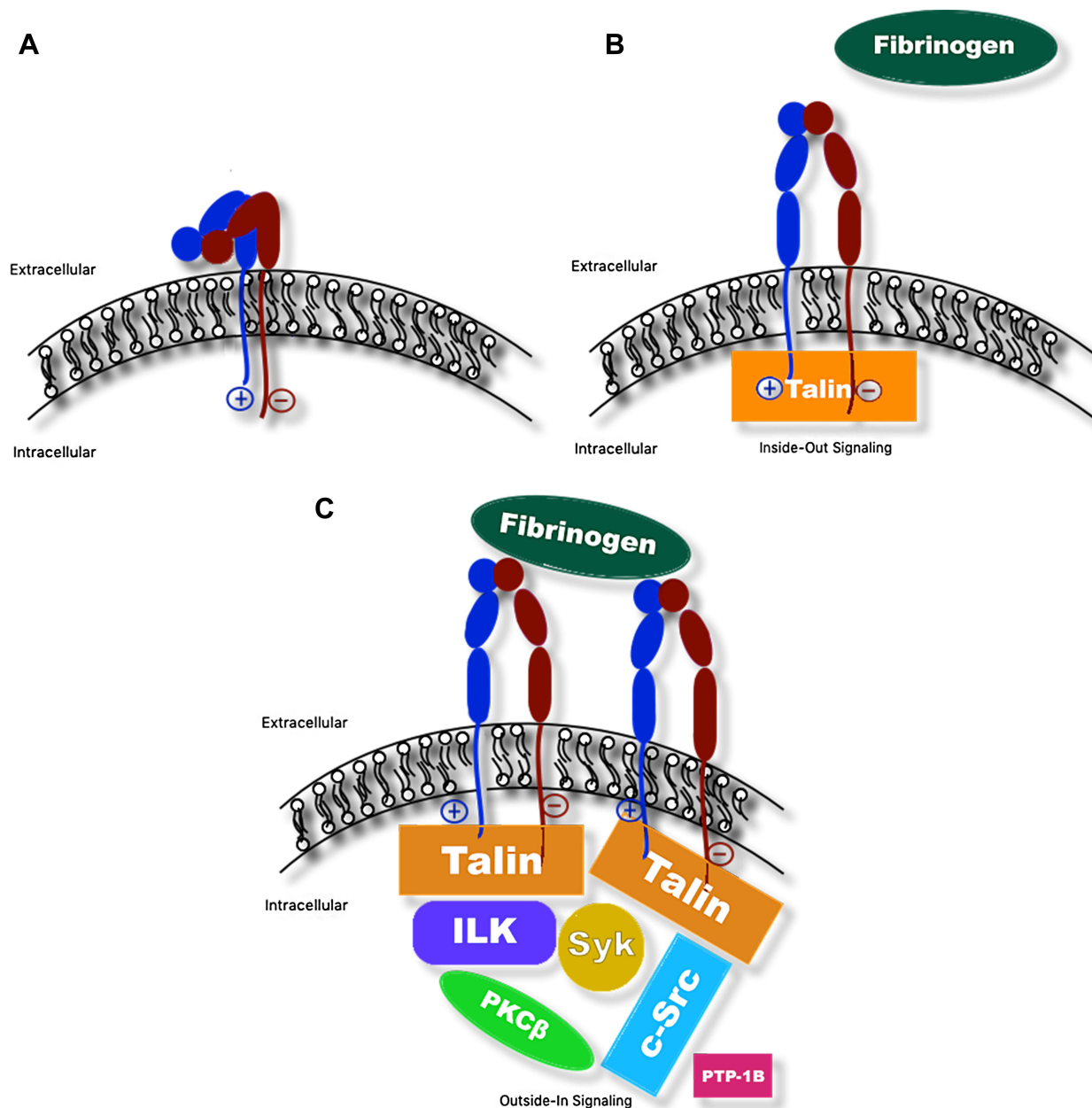


Figure 2 Schematic of $\alpha_{IIb}\beta_3$ integrin undergoing inside-out and outside-in signaling. **(A)** Bent conformation of $\alpha_{IIb}\beta_3$ integrin with intact salt bridge linking cytosolic domains of the subunits (low affinity for binding fibrinogen). **(B)** Binding of intracellular protein talin disrupts salt bridge and triggers separation of the cytosolic region of β_3 from that of α_{IIb} , resulting in a conformational change of the $\alpha_{IIb}\beta_3$ integrin into the upright position. In this position, fibrinogen is able to bind extracellular domains (high affinity for binding fibrinogen; inside-out signaling). **(C)** Fibrinogen, in turn, binds additional $\alpha_{IIb}\beta_3$ integrins to facilitate platelet aggregation, resulting in activation and recruitment of additional intracellular and cytosolic proteins, such as c-Src tyrosine kinase (c-Src), integrin-linked kinase (ILK), spleen tyrosine kinase (Syk), protein kinase C (PKC), and protein tyrosine phosphatase (PTP1B) and others, to facilitate processes including cytoskeletal reorganization for platelet spreading, clot stabilization, and clot retraction (outside-in signaling).

become disrupted. Each of these opportunities for error, in turn, implies the potential for countless theoretical GT-causing genetic variants.

Genetics

The α_{IIb} and β_3 subunits are respectively encoded by *ITGA2B* (65 kbp) and *ITGB3* (17 kbp), which are both

found on chromosome 17 (17q21.31 and 17q21.32, respectively; OMIM # 607759 and OMIM #173470). *ITGA2B* and *ITGB3* expression are not known to be coordinated,^{3,31} however, and mutations in either of these genes can lead to forms of GT that are phenotypically indistinguishable.¹ GT inheritance is typically autosomal recessive and patients may exhibit homozygosity, particularly if

consanguinity is present, or compound heterozygosity.^{8,20,31,38} *ITGB3* mutations are more common, presumably due to its relatively larger coding region of 30 exons in comparison to the 15 exons comprising *ITGA2B*.¹ As of February 2021, 475 *ITGA2B* and *ITBG3* GT-causing mutations have been catalogued in the Glanzmann Thrombasthenia Database (<https://glanzmann.mcw.edu/>) and most commonly include nonsense, missense, and splice site variants.^{1,20} Large deletion and duplication mutations are rare.^{1,20} Mutations leading to a GT phenotype can be manifested by dysfunctional gene expression, protein folding, post-translational processing, trafficking to the platelet membrane, and ligand binding.^{1,8,39–43} In fact, missense mutations impeding such processes have helped researchers to identify functional coding sequences within *ITGA2B* and *ITBG3*.^{20,44–46} For example, *ITGA2B* c.818G>A disrupts the calcium-binding site with the β_3 subunit and has been shown to result in lack of $\alpha_{IIb}\beta_3$ integrin expression at the platelet membrane.^{8,39–41} Alternatively, defects within $\alpha_{IIb}\beta_3$ integrin extracellular ligand binding sites result in a qualitative variant of GT in which quantities of $\alpha_{IIb}\beta_3$ integrin at the platelet membrane are otherwise intact. Such differences in $\alpha_{IIb}\beta_3$ integrin expression at the level of the platelet membrane are the basis for distinguishing clinical types of hereditary GT (Table 1). In Type I GT, platelets' membrane expression of $\alpha_{IIb}\beta_3$ integrin is less than 5% of the wild-type quantity.^{47,48} Type I GT is most common, representing 62–78% of GT cases.^{1,3,4,20} Type II GT, in which 5–25% of normal of $\alpha_{IIb}\beta_3$ integrin expression is maintained,^{4,8,20,47,48} represents about 12–16% of the GT population.^{1,3,4,20} Type III represents a “variant” GT phenotype in which the $\alpha_{IIb}\beta_3$ integrin is present in sufficient quantities at the platelet membrane (ranging from 25% to 100% of reference levels),^{8,20,47,48} but is qualitatively dysfunctional, and represents 8–22% of affected

patients.^{1,3,4,20} Mutations conferring a defective $\alpha_{IIb}\beta_3$ integrin result in varying clinical severities, but tend to involve ligand binding sites, such as *ITGB3* c.719G>A, and inside-out signaling, such as *ITGB3* c.2332T>C.^{8,45,49,50} Interestingly, gain-of-function GT-like cases have also been described involving compound heterozygous *ITGA2B* and *ITBG3* mutations affecting membrane-adjacent residues resulting in auto-activation of $\alpha_{IIb}\beta_3$, reduced $\alpha_{IIb}\beta_3$ expression, and thrombocytopenia.^{1,51–53} In a minority of patients, no mutation may be found, suggesting unidentified causes of GT that could perhaps be attributed to non-sequenced promoter or intron regions, mutated proteins that may help facilitate $\alpha_{IIb}\beta_3$ integrin development and transport, or modulators affecting $\alpha_{IIb}\beta_3$ integrin expression, such as miRNA or epigenetic changes.²⁰

Acquired Glanzmann Thrombasthenia

Acquired GT is a disorder characterized by anti- $\alpha_{IIb}\beta_3$ complex-antibody-mediated platelet destruction.^{57,58} More common than its hereditary counterpart, acquired GT can manifest as primary immune thrombocytopenia (ITP) or occur secondary to autoimmune disorders, malignancies, or organ transplants.^{57–60} Certain medications, including the antimalarial quinine, antiarrhythmic quinidine, and various anticoagulants, including abciximab, have been identified as triggers for acquired GT.^{1,58}

Clinical Presentation

Patients with hereditary GT tend to develop easy bruising and mucocutaneous bleeding symptoms (Table 2) early in life, with a mean age of diagnosis of 1 year of age and 15% of GT patients presenting beyond age 14 years.^{2,61} Males with GT may be diagnosed as a result of post-circumcision hemorrhage.^{8,62} Loss of primary teeth is

Table 1 Types of Glanzmann Thrombasthenia and Their Frequencies, with Examples of Genetic Mutations

Type of GT	Relative Expression of $\alpha_{IIb}\beta_3$	Relative Frequency	Example of Functional $\alpha_{IIb}\beta_3$ Defect
Type I	<5% versus Wild-type	62–78%	<i>ITGA2B</i> c.273G>D: $\alpha_{IIb}\beta_3$ unable to transport to the platelet membrane ⁵⁴
Type II	5–25% versus Wild-type	12–16%	<i>ITGA2B</i> c.1772_1773insG: Premature stop codon leading to nonsense-mediated decay of mRNA ⁵⁵
Type III (Variant)	25–100% versus Wild-type (Qualitative Defect)	8–22%	<i>ITGB3</i> c.2259T>C: Defect in outside-in signaling via $\alpha_{IIb}\beta_3$ ⁵⁶

Abbreviation: GT, Glanzmann Thrombasthenia.

Table 2 Clinical Presentations of Glanzmann Thrombasthenia

Clinical Presentation	Note(s)
Easy Bruising	Following minor trauma
Mucocutaneous bleeding	Includes epistaxis; heavy, prolonged, and/or more frequent menstrual bleeding; gingival bleeding; gastrointestinal bleeding (less common)
Excessive bleeding post trauma or surgery	In young boys, may see persistent bleeding following circumcision
Intracranial hemorrhage	Very rare
Hematuria	Very rare
Hemarthrosis	Very rare
Organ bleeding	Very rare

another common source of bleeding during childhood.⁸ In rare cases, abnormal bleeding may not occur until adulthood, when a patient's coagulation system is challenged by childbirth or another severe trauma.^{4,20} Bruising provoked by mild trauma is the most common symptom experienced, followed by mucocutaneous bleeding.⁴ Typically, bleeding symptoms are less severe than those seen in hemophilia patients,^{2,63} although more than two-thirds of patients require one or more platelet and/or red blood cell transfusions over their lifetime.^{20,64} Epistaxis is the most prevalent source of severe bleeding, affecting 60–80% of patients.⁴ This symptom is most prominent during childhood,^{4,65} when the nasal septum is most friable and also most likely to be subjected to the trauma of nose-picking.¹

The majority of females with GT experience heavy, prolonged, and/or more frequent menstrual bleeding.⁴ Gingival bleeding is also a source of concern, affecting up to 60% of patients, and may even result in iron deficiency anemia.⁴ This symptom may be remedied with improved oral hygiene. Gastrointestinal bleeding is more rare, affecting only 10–28% of patients,^{4,20} but may be particularly concerning in the presence of localized angiodysplasia.⁸ Intracranial hemorrhages, hemarthroses, hematuria, and organ bleeds have all been described in GT patients, but are exceedingly rare.^{1,4,8,20}

Diagnosis

As with any patient presenting with easy bruising and/or mucocutaneous bleeding, it is important to take a detailed history of bleeding symptoms. Diagnostic bleeding scores, which quantify a given patient's ongoing bleeding risk based on their historical symptoms and need for interventions, are generally useful for establishing a true bleeding

tendency although no cut-off values have been established for GT.^{1,66} The ISTH/SSC bleeding assessment tool⁶⁷ has, however, demonstrated an ability to identify patients with inherited platelet disorders, once von Willebrand disease has been ruled out. History should also include the presence of any past or present autoimmune or malignant diagnoses, as well as current symptoms that may point to an undetected underlying systemic condition that could trigger acquired GT. Past infections should also be queried, as mutations involving integrin regulatory proteins, including kindlin-3 and calcium and diacylglycerol-regulated guanine nucleotide exchange factor, can affect both platelet and leukocyte integrin function, resulting in a simultaneous immunodeficiency;^{58,68} these patients do not have GT. A medication history should include the use of antiplatelet medications, such as NSAIDs, and other anticoagulants that may suggest an alternative cause. Taking a family history and drawing a pedigree is encouraged, as it could provide critical information to help establish the presence of a familial bleeding disorder spanning multiple generations with a specific pattern of inheritance. When examining the patient, it is important to inspect the skin for signs of bruising as well as the mucocutaneous regions, including the nares, for evidence of bleeding. Additional areas of importance may be guided by history.

Preliminary investigations that are widely available and relatively inexpensive are necessary to help narrow the list of differential diagnoses (Figure 3), given the rarity of GT amongst haemostasis and coagulation disorders; for every one patient diagnosed with inherited GT, there are 1000 people diagnosed with von Willebrand disease,⁶⁹ 95 people diagnosed with immune thrombocytopenia,⁷⁰ and 85 people diagnosed with haemophilia A.⁷¹ In terms of specific inherited platelet defects diagnosed per year, GT

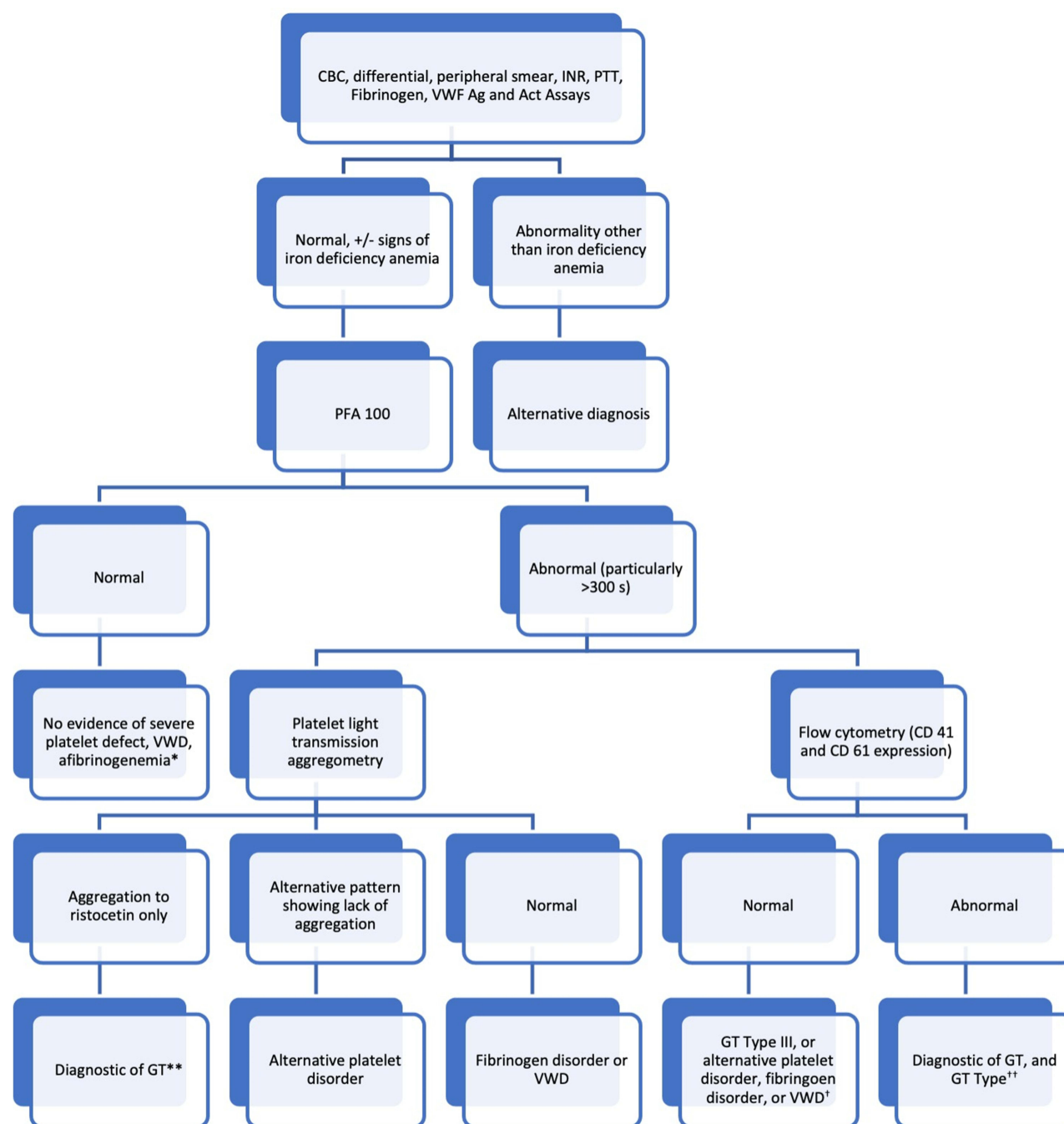


Figure 3 Diagnostic algorithm for GT. *Consider proceeding to platelet light transmission aggregometry if suspicion for platelet defect remains high. **Consider genetic testing to identify specific mutation of *ITGA2B* and *ITGB3* and/or flow cytometry to differentiate GT type. †Consider clot retraction assay (if available) and platelet light transmission aggregometry or genetic testing of *ITGA2B* and *ITGB3* to make the diagnosis of GT Type III. ††Consider genetic testing to identify specific mutation of *ITGA2B* or *ITGB3*.

Abbreviations: CBC, complete blood count; VWF Ag, von Willebrand factor antigen; VWF Act, von Willebrand factor activity; VWD, von Willebrand disease.

represents just 9.8% of this category.⁷² As Dr. Glanzmann discovered,⁷ complete blood count (CBC) and peripheral smear will typically reveal a normal quantity of platelets that are of a normal size and maintain a typical granular pattern, which helps differentiate GT from other platelet disorders, such as Bernard-Soulier and Grey Platelet

Syndromes. In some cases, the CBC might also suggest iron deficiency anemia (IDA), which may be a consequence and/or a cause of abnormal bleeding, as arachidonic acid-induced platelet aggregation has been shown to improve following treatment of IDA.^{73,74} Additional CBC abnormalities would point towards

a diagnosis other than GT. Coagulation studies, including INR, PTT, and fibrinogen, are normal in GT and help rule out coagulation factor deficiencies and fibrinogen disorders that could be alternative, more common causes of bleeding and abnormal platelet aggregation. Additionally, normal von Willebrand factor antigen and von Willebrand factor activity assays are expected and eliminate the possibility of von Willebrand disease.

Additional screening tests may be helpful prior to confirming the diagnosis of GT with platelet light transmission aggregometry, which requires a large volume of blood, 3–4 hours, and a specialized laboratory.⁷⁵ A clot retraction assay can be performed using 1–2 mL of whole blood incubated overnight at 37 degrees Celsius, removing the newly formed clot, and quantifying the relative volume of serum within the remaining plasma sample that was extracted from the clot during the retraction process. The assay can also be performed using platelet rich plasma. Assuming a normal platelet quantity and adequate fibrinogen count and quality, an abnormal clot retraction is consistent with diagnosis of GT, as this assay specifically tests the outside-in signaling of the $\alpha_{IIb}\beta_3$ integrin.^{76,77} Furthermore, a result of no clot retract versus low-to-normal clot retraction can help differentiate between Types I and II GT, respectively.³⁶ It should be noted, however, that this test has fallen out of favour, as it is only available in specialized laboratories and is no longer considered to be a required test in the diagnosis of GT.

Platelet function analyzer, or PFA 100, testing requires as little as 2 mL of blood and is a measure of primary hemostasis.^{75,78} By timing platelet plug formation over a membrane in the presence of stimulants (collagen and epinephrine or collagen and ADP) under high shear conditions, samples affected by platelet disorders and von Willebrand disease will be differentiated.⁷⁸ While an abnormal PFA-100 is 100% sensitive for GT,⁷⁵ it does not distinguish GT from severe von Willebrand disease or afibrinogenemia.¹

Platelet light transmission aggregometry is a gold standard for establishing a diagnosis of GT.⁷⁹ This test exposes a blood sample to various agonists to stimulate platelet plug formation and measures the subsequent transmission of light through the platelet suspension.⁸⁰ Platelet aggregation in the presence of ristocetin, but not in the presence of ADP, collagen, thrombin, or adrenaline (<10% of reference values) is pathognomonic for the disorder.^{36,47,77} It may be necessary to repeat testing once to confirm the results or compare with a control sample in parallel, given

the multiple pre-analytical and analytical variables that may affect the outcome of this investigation.^{1,80–83}

Once Glanzmann thrombasthenia has been diagnosed, there are additional tests that are helpful for further characterization of the disorder. Flow cytometry with monoclonal antibody panels against CD41 and CD61 can quantify deficiencies in α_{IIb} and β_3 expression at the platelet membranes, respectively, and allow for identification of Type I (<5% expression) and Type II (5–25% expression) GT.⁸⁴ Flow cytometry typically reveals at least 50% α_{IIb} and β_3 expression in Type III GT.^{36,84} Differentiating GT type is particularly helpful for risk stratifying patients who may develop alloimmunization following platelet transfusion (see Platelet Refractoriness and Alloimmunization). Furthermore, flow cytometry can also be used to identify specific antibodies against $\alpha_{IIb}\beta_3$ in cases of acquired GT.^{84,85} Genetic sequencing of *ITGA2B* and *ITGB3* may also be performed to confirm the specific mutations involved. Multiple groups^{86–89} have recently developed high-throughput molecular diagnostic assays for patients with GT and other inherited bleeding disorders. It should be noted though that at this time, there does not seem to be a correlation between specific mutation and phenotype severity⁸ and even family members sharing similar mutations have been shown to have significant variability amongst their clinical outcomes.²⁰

Management

Routine Follow-Up and Anticipatory Guidance

Any patient diagnosed with GT should be referred to a tertiary care centre with a haematologist experienced in treating patients with inherited bleeding disorders. This centre must be able to manage patients outside of regular clinic hours should severe bleeding occur. During regular clinic hours, the patient should have access to a multidisciplinary team, including a nursing coordinator, physiotherapist, social worker, and psychologist as necessary.^{2,90} Good oral hygiene and routine dental follow-up are also of the utmost importance.⁹¹ Patients with GT can and should receive routine vaccinations with the additional step of providing 15 minutes of applied pressure to the site to encourage proper hemostasis.⁹⁰ Additional immunization against hepatitis A and B is encouraged, given heightened risk for exposure to blood products.⁹⁰ Patients should receive adequate teaching about GT, including education on preventing bleeds, such as avoiding

certain medications, including aspirin and NSAIDs, and high-impact physical activities. Patients should be counseled regarding recognition of bleeds and necessity of urgent medical intervention for prolonged or worrisome bleeding, as delay in treatment has been implicated in both hospital length of stay and overall treatment response.^{92,93} Any patient with a diagnosis of GT, or any clinically significant bleeding disorder, should wear a MedicAlert bracelet or similar piece of identification to flag their condition to emergency medical personnel in the event of incapacitation.

Pregnant women who have been diagnosed with GT, or whose partners have been diagnosed with GT, should be considered for prenatal testing if the parents of the fetus are consanguineous. Prenatal diagnosis is routinely confirmed by genetic testing,¹ although flow cytometry has also been used.⁹⁴ Pregnant women who are known to have GT should also be screened for anti- $\alpha_{IIb}\beta_3$ antibodies via monoclonal antibody-specific immobilization of platelet antigen (MAIPA) assay regularly throughout gestation,⁹⁵ as these antibodies can cross the placenta and cause dangerously low platelet levels in the fetus.^{31,96,97} Mothers must be counseled about this risk and for this reason, it is important to test the newborn's platelet count within the first few hours life⁸ if maternal antibodies have been detected. While mothers with GT are not expected to experience increased bleeding during the pregnancy itself, specific planning surrounding labour and delivery is indicated in order to prevent excessive bleeding in the intra- and post-partum periods (see Site-Specific considerations below).

General Approach to Bleeding

Minor bleeding episodes may be initially managed at home using manual compression and/or antifibrinolytic therapy. Depending on the bleeding site, manual compression may be achieved by applying pressure with gauze or, in the cases of epistaxis, pinching the soft cartilages of the nares closed using the index finger and thumb. Cold compresses are not recommended, as they have been shown to impair haemostasis and coagulation in patients with and without bleeding disorders.^{98,99} The use of oral antifibrinolytic therapy,^{31,47} including tranexamic acid (TXA) and aminocaproic acid, can be easily administered in the home setting and may be critical for stopping a bleed in its early stages. Antifibrinolytics should not be administered to patients experiencing gross hematuria, however.^{100,101}

GT patients with bleeding that is refractory to these methods should seek emergency medical attention.

Patients with GT experiencing severe bleeding require some combination of three main treatment options to achieve haemostasis: antifibrinolytics, recombinant activated factor VII (rF7a), and platelet transfusion. DDAVP has also been used,^{47,102} although study results have been inconsistent¹ and further investigation is needed in this area. In addition to providing haemostasis, the need for red blood cell transfusion must always be considered. These transfusions should be sourced from washed or frozen red blood cells in order to remove any residual platelets that could trigger alloimmunization.³¹ Unfortunately, the urgency of the situation may preclude the ability to wait for these products to become available and the risks and benefits of transfusing fresh non-washed pRBCs must be carefully weighed.

Antifibrinolytics, in addition to being available enterally, can be administered intravenously or topically using antifibrinolytic-soaked gauze or gel foam. Fibrin glue and topical thrombin are additional topical alternatives/complements to antifibrinolytics.

Platelet transfusion has been a mainstay of GT therapy for years. However, the benefit of providing functional platelets must be weighed against the risk of causing alloimmunization and rendering a patient refractory to subsequent platelet transfusions. GT Type I patients are at particular risk of alloimmunization against α_{IIb} and β_3 due to their inherent lack of self-expression of these antigens.^{20,31} Given the possibly fatal implications of platelet refractoriness, platelet transfusions should be reserved for life-threatening hemorrhages in the GT population.³¹ The use of platelet transfusions in girls and pre-menopausal women should be particularly avoided whenever possible given the added risk of transplacental antibody transfer causing future neonatal alloimmune thrombocytopenia.^{1,96} If and when choosing to transfuse platelets, they should be HLA-matched, leukocyte-reduced whenever possible to avoid HLA-alloimmunization.³¹ ABO compatibility offers an additional layer of protection³¹ and patients who have received any blood products, including only red blood cells, should be regularly screened for antibodies. Furthermore, there have even been some reports of antibody presence in non-transfused patients,^{20,31,103} which may have been infection-induced.

rF7a is an expensive^{47,104,105} but efficacious treatment for patients with GT experiencing moderate to severe bleeding. rF7a has a long shelf life at room

temperature^{106,107} and is approved in several countries for use in patients with hemophilia, congenital factor VII deficiency, and GT. In particular, it is approved in the United States for use in GT patients who are refractory to platelets as well as in Europe for patients with GT who cannot receive platelets. Various studies have reported partial or better responses to rF7a for 67–93%^{104–106,108} of nonsurgical hemorrhages in GT patients, with or without the help of antifibrinolytics. Its efficacy has been found to be irrelevant to antibody presence.¹⁰⁵ rF7a's mechanism of action for GT patients is not entirely understood.¹⁰⁴ However, it is thought that through activation of factor X, rF7a facilitates generation of thrombin, which can then bind and activate GT platelets via intact GP1b receptors.^{31,106,109,110}

It is important to note that dosing of rF7a varies based on indication, and patients with GT typically require fewer total doses than hemophilia patients with inhibitors do.¹¹¹ Patients with GT typically require 80–140 µg/kg intravenous every 2.5 hours or less until hemostasis is achieved.^{61,104} Continuous infusions of rF7a have only been rarely used and are not well studied.¹⁰⁴

Site-Specific Considerations

As epistaxis is a major source of bleeding in children with GT, efforts should be made to prevent over-drying of the nasal mucosa in affected patients. These methods include use of humidifiers, saline nasal sprays and Vaseline gel. Some patients may find it helpful to sleep in a seated position when experiencing mild nasal or oral bleeding. Major epistaxis requires the expertise of an otolaryngologist. A 2010 retrospective study⁶⁵ of 5 children with GT presenting on 63 occasions with epistaxis reported a hospitalization rate of 72%. Forty-two percent of these admissions required intensive care. While anterior nasal packing with or without topic hemostatic treatments were successful about one-third of the time, the administration of a bovine collagen matrix was deemed successful in just one-half of cases.

Oral cavity bleeding can commonly present in the setting of gingivitis. Daily flossing is therefore highly encouraged. Those with gingival bleeding may benefit from using antifibrinolytic therapy as a mouthwash.^{2,5,6} Children are also at risk of oral bleeding with the routine loss of primary teeth. Loose teeth can be treated with fibrin glue to help mitigate blood loss.^{3,112,113} Plastic splints can also be used to physically support hemostasis.¹¹⁴

Heavy uterine bleeding affects most women with GT. Efforts should be made to quantify this symptom using standardized scales, such as the Pictorial Blood Loss Assessment Chart.^{115,116} GT patients with heavy menses should be treated first line with antifibrinolytics. Patients who have refractory bleeding should be reviewed by a gynecologist and considered for oral contraceptive therapy or hormonal intrauterine devices, with or without adjunctive antifibrinolytics. Intravenous high-dose estrogen therapy over 1–2 days is an effective measure for these patients and should be administered in consultation with a gynecologist.^{35,117} It should be considered prior to administration of rF7a or platelet transfusion if bleeding is not life-threatening.

Bleeding associated with childbirth is a major concern in women with GT. Surprisingly, up to 50% of women with GT may not be diagnosed until facing the haemostatic challenges of labour and delivery.^{1,96} Epidural anesthesia is contraindicated in this population due to additional bleeding risks and an alternative pain management plan should be arranged beforehand.^{1,77} Women in labour for vaginal delivery or preoperative for caesarean section should be started on rF7a and antifibrinolytics in the presence of evidence of abnormal bleeding and may benefit from platelets as well. Platelets may continue to be required up to 7 days after delivery.^{8,118,119} Women experiencing postpartum hemorrhage should be managed with packed red blood cells and uterotonics.¹²⁰

Perioperative Bleeding

The rate of perioperative bleeding in patients with inherited functional defects has been reported at 24.8%, with cardiovascular and urological surgeries bearing a particularly significant risk.¹²¹ The principles for preventing and managing surgical bleeds are similar to those for nonsurgical hemorrhages: patients tend to be managed with a combination of antifibrinolytics and rF7a, with or without platelets. One international retrospective review sponsored by Novo Nordisk Health Care AG involving 96 GT patients¹²² who underwent 101 surgeries in which rF7a and platelets were used, with or without antifibrinolytics, reported 100% efficacy in achieving hemostasis, regardless of alloimmunization status. This success rate was maintained for minor procedures when only rF7a and antifibrinolytics were given to patients with a history of antibodies and refractoriness. The same study found that this success rate decreased to 88.9% when rF7a was used without antifibrinolytics. The group that received platelets with or without antifibrinolytics had a success

rate of just 67%. Another international survey in which ties to Novo Nordisk Health Care AG were disclosed reported 67% success in preventing surgical bleeding in 9 GT patients undergoing major operations and 92% of 25 GT patients undergoing minor procedures, with or without antifibrinolytics.¹⁰⁵ rF7a dosing in surgical patients is 80–90 ug/kg intravenously immediately prior to surgery, with at least 2 repeated doses every 2–6 hours;¹²³ some sources^{61,106,122} recommend dosing as high as 140 u/kg. Patients undergoing major operations are expected to require additional doses, with one review¹⁰⁴ on rF7a use in surgical patients reporting median durations of treatment of 7 hours and 2 days for minor and major operations, respectively. In the post-operative period, haemostasis can be monitored clinically along with trending of hemoglobin.⁴⁷

Platelet Refractoriness and Alloimmunization

Any GT patient presenting with refractoriness to platelet transfusion likely requires rF7a and should be considered for packed red blood cell transfusion. Anti-platelet antibodies, should always be suspected in the case of platelet refractoriness.⁸ The prevalence of alloimmunization, due either to anti- $\alpha_{IIb}\beta_3$ or anti-HLA antibodies, is as high at 30% in the general GT population.⁶¹ Patients who have developed HLA antibodies should be treated with HLA-compatible platelets. Alloimmunization against $\alpha_{IIb}\beta_3$ resulting in lack of response to all platelet transfusions, however, is a life-threatening complication for GT patients. Patients whose mutations prevent any $\alpha_{IIb}\beta_3$ expression at the platelet membrane are theoretically at the highest risk for developing anti- $\alpha_{IIb}\beta_3$ antibodies.³¹ Women seem to be more affected than men, although this risk may be due to the prevalence of transfusions for uterine bleeding.^{20,31} A relationship between number of past platelet transfusions and presence of platelet refractoriness in the GT population has not been established, however, and even residual platelets within red blood cell transfusions can trigger alloimmunization.^{31,124,125} When anti- $\alpha_{IIb}\beta_3$ antibodies are present, platelet transfusions in conjunction with antifibrinolytics have still been successful 71% of the time for non-surgical hemorrhages.¹⁰⁶ However, rF7a has been shown to be effective in 91% of non-surgical bleeds, regardless of antibody status.¹⁰⁶ rF7a has similarly been shown to be successful in treating 88% of surgical bleeds in antibody patients.¹²² Patients with antibodies have been shown to require more doses of rF7a than those without.^{106,122}

Alloimmunization has been reported in up to 70% of pregnant women with GT.^{1,61} Pregnant mothers with GT who are immunized by fetal platelet antigens will produce antibodies that can later cross the placenta and induce life-threatening thrombocytopenia and hemorrhage in the fetus.^{31,96,97} Methods to lower antibody titre prenatally include plasma exchange, steroids, and intravenous immunoglobulin (IVIG),^{8,95,126,127} with IVIG dosing of 0.5–1g/kg per week associated with 97.3% success.^{95,128}

Thrombosis Secondary to Recombinant Activated Factor VII

The rate of thromboses secondary to rF7a use in GT patients fortunately remains low. One literature review of rF7a use in GT patients found a thromboembolic event rate of 1.4% amongst 221 bleeding episodes.¹⁰⁴ A review including data from the Glanzmann Thrombasthenia Registry found 5 cases of thromboembolism amongst 490 instances of rF7a use for nonsurgical bleeding and perioperative prophylaxis.¹²⁹ Two of these cases occurred in patients over the age of 65 years, with one featuring additional risk factors of immobilization, surgery, and continuous rF7a infusion. Thromboembolic diagnoses reported in GT patients receiving rF7a within the literature include deep vein thrombosis, pulmonary embolism, ureteric obstruction, and intracardiac thrombi.^{105,130–132}

Curative Therapy

Bone marrow transplantation has proven to be a curative option in several GT patients, including those with anti-platelet antibodies.^{31,133–139} In many cases, conditioning therapy has helped alleviate antibodies, which can otherwise threaten engraftment.^{50,117} Transplant has typically been performed in the pediatric population, with chronic graft versus host disease being a major morbidity.

Though still in the experimental stages, gene therapy has been explored as an option for treating GT. In 2011, Fang et al¹⁴⁰ demonstrated increased $\alpha_{IIb}\beta_3$ expression in GT dog models who had been transfected with peripheral blood stem cells engineered to express human *ITGA2B*. Three years later, Sullivan et al¹⁴¹ generated induced pluripotent stem (iPS) cells from peripheral monocytes of 2 GT patients and transfected the iPS cells with α_{IIb} cDNA at the AAVS1 locus, accompanied by a megakaryocyte-specific promoter. Thereafter, these patients exhibited $\alpha_{IIb}\beta_3$ platelet expression surpassing 50% and 70%.

Future Steps

The diagnosis and management of patients with GT continues to have many associated challenges. Diagnosis requires testing in specialized laboratories and further genetic testing, at least at this point, does little to help predict severity. However, by continuing to grow the Glanzmann Thrombasthenia Registry, our understanding of GT's various mutations will become more developed. Currently, the mainstay of treatment remains supportive. However, as recognition of anti-platelet antibodies becomes more prevalent, the demand for curative options will certainly increase. To meet this demand, bone marrow transplant regimens will need to become more standardized for this population and recognized as a treatment option early in life. Moreover, the further development of gene therapy technology for GT patients will offer an alternative option to cure this otherwise lifelong disease.

Disclosure

The authors reported no conflicts of interest for this work.

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