

Review Article

Glanzmann's thrombasthenia (defective platelet integrin $\alpha_{IIb}\beta_3$): proposals for management between evidence and open issues

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Summary

Glanzmann's Thrombasthenia (GT) is a rare autosomal recessive bleeding disorder, characterized by a quantitative or qualitative defect of platelet surface $\alpha_{IIb}\beta_3$ integrin. Presently, no specific guideline/algorithm for clinical management for GT is available. Due to the rarity and heterogeneity of inherited platelet abnormalities, recommendations and guidelines are based on reports from opinions and clinical experience of panel of experts, and refer to the general management of platelet disorders. Based on the few evidence in the area and on the strategies in clinical settings of inherited/acquired platelet defects, proposals for management of minor bleeding; moderate/major bleeding unrespon-

sive to conservative management; major surgery; minor surgery and dental procedures for GT patients without, or with platelet isoantibodies are reported. In addition to life-style advices and continuous patient education programs, when and how to employ/combine local measures, antifibrinolytic agents, hormone treatment, platelet transfusions and recombinant activated Factor VII is described. The prospective collection of treatments in GT patients recently established (Glanzmann's Thrombasthenia Registry, GTR), based on a careful definition of clinical settings and outcomes, is likely to provide newer insight for optimizing clinical management in GT.

Keywords

Bleeding, Glanzmann's Thrombasthenia, platelets, platelet isoantibodies, treatment

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Introduction

Glanzmann's Thrombasthenia (GT) is a rare (~600 cases worldwide so far described) autosomal recessive bleeding disorder, characterized by a quantitative or qualitative defect of platelet surface $\alpha_{IIb}\beta_3$ integrin (GpIIb/IIIa, fibrinogen receptor) leading to the failure of platelets to bind fibrinogen, retract a fibrin clot or aggregate after stimulation by agonists such as ADP, thrombin, epinephrine, or collagen alone or in combination (1–3). At variance with its usual incidence (about 1 in a million), higher figures are reported in certain populations where consanguineous marriages are frequent, particular in the Middle East (4–7). Most patients (>2/3) require blood and/or platelet transfusions at least once in their life (7–8). GT is therefore considered a severe haemorrhagic disease. However, bleeding phenotype is dramatically variable, some patients having only minimal bruising, others frequent, severe, potentially fatal haemorrhages.

Presently, no specific guidelines or algorithms for clinical management of GT are available. On the basis of a review of the literature, we briefly discuss clinical features and the available strategies for treatment of GT patients, with the aim of proposals for the management of the different clinical conditions in this setting.

Clinical features

Type/sites of bleeding

Heterozygous subjects, showing about 50% of the surface $\alpha_{IIb}\beta_3$ integrin, are asymptomatic (8, 9). Homozygous (or compound heterozygous) GT patients show a mucocutaneous pattern of bleeding. Epistaxis, menorrhagia, gingival haemorrhage, easy bruising and ecchymoses are very frequent features; gastrointestinal bleeding and haematuria are less common. Haemarthroses and deep haematomas, common in severe haemophilia, seldom

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occur (7, 8). Most GT newborns have no signs of excessive bleeding, however diffuse petechial haemorrhage (4, 8) or umbilical cord bleeding (7) have been reported. This bleeding pattern is similarly reported in the two largest published series (7, 8) of GT patients (Table 1), with some discrepancies in the frequency of symptoms (probably due to the duration of patients' clinical observation).

Among the bleeding symptoms in GT, epistaxis is the most common cause of severe bleeding, often requiring blood transfusions. Epistaxis occurs particularly in children, but usually decreases in frequency and severity in adults. Gingival bleeding, often reflecting poor dental hygiene, is seldom associated with major acute blood loss, but may frequently lead to iron deficiency. Menorrhagia is often a critical challenge in female GT patients. Bleeding at menarche may be severe enough to require transfusions, and in some cases, may be the first bleeding symptom, leading to the diagnosis (8). Only few GT patients experienced intracranial haemorrhage, mostly following trauma. On the whole, spontaneous, unprovoked bleeding, typical of disorders of coagulation and leading to haemarthroses or deep haematomas, is uncommon in GT patients, in which most haemorrhages may be considered an exacerbation of normal bleeding associated with physiologic or pathologic predisposing conditions.

In contrast, bleeding after trauma or invasive procedures, including such minor procedures as circumcision and dental procedures, is common and may be severe (7, 8). Pregnancy itself does not appear to be associated with a serious risk of bleeding, but appropriate interventions may be required at delivery and for at least a week post-partum when high risk of acute or delayed severe vaginal haemorrhage may occur. No excessive bleeding was reported after Caesarean sections when covered by platelet trans-

fusions until complete wound healing (7, 8). An unexpected low number of pregnancies has been reported in GT women (7), suggesting a possible association with placental problems and reduced fertility.

Severity of bleeding

In contrast to the well-defined sites of bleeding, the severity is unpredictable in GT. Some patients never have serious bleeding and are free of bleeding complications once they reach adulthood (8). Such clinical heterogeneity minimally reflects the residual $\alpha_{IIb}\text{-}\beta_3$ integrin detectable on the platelet surface or the type of genetic defect. Therefore the classification of patients according to the $\alpha_{IIb}\text{-}\beta_3$ integrin molecular abnormality (8, 10) into type I (virtually absent, <5%), type II (detectable but significantly reduced, 5–15%) and variant (low-to-normal, dysfunctional) is not useful for predicting bleeding phenotype.

On the other hand, the genetic background in GT is extremely heterogeneous: new mutations have been increasingly reported (11) and well over 100 different putative mutations in either the α_{IIb} (ITGA2B) or β_3 integrin (ITGB3) genes have been collected in the GT database (12). The unpredictability of a severe bleeding phenotype is emphasized by the inconsistency between siblings, who are likely to share the same genetic defect. No evidence is so far available to support the hypothesis that thrombophilic gene polymorphisms, e.g. Factor V Leiden (Arg506Gln) or the prothrombin gene mutation in the 3'-UT region (20210 G>A), provide a protective effect with either less bleeding or an increased survival in individual patients. On the other hand, the rare coexistence of GT with other inherited bleeding disorders (e.g. mild von Willebrand disease) could influence the clinical severity of bleeding. As in other clinical settings, bleeding is likely to be the net result of gene-gene and gene-environment interaction in GT patients. In this respect, the human platelet alloantigen 1 (HPA-1) distribution (13) or a polymorphism in the α_2 -integrin gene coding sequence, affecting $\alpha_2\beta_1$ density on platelets (14), have been correlated to the tendency to bleed in GT patients.

Although prospective data are not available, it has been observed that severity of bleeding decreases with age (1, 8). However, associated conditions predisposing to bleeding, such as angiodysplasia, chronic liver or kidney disease, may result in severe bleeding tendency in elderly patients (15, 16).

Management

There is a general lack of rigorous evidence from randomized or controlled trials concerning treatment of patients with inherited platelet function abnormalities. Therefore, data on clinical management of GT patients can only be derived from case reports or from few, mainly retrospective, case series. In some cases, recommendations are extrapolated from data obtained in other settings (mainly acquired) of platelet disorders. Taking into account the available evidence and current recommendations/guidelines based on expert committee reports (17–20), in the following paragraphs we report the available strategies for treatment in GT patients and proposals for the management of minor bleeding; moderate/major bleeding unresponsive to conservative management; major surgery; minor surgery and dental procedures for

Table 1: Bleeding pattern in the largest published series of GT patients.

| | George et al, Blood, 1990 | Toogeh et al, 2004 |
|--|-----------------------------|--------------------|
| Patients: n, origin | 64, France; 113, literature | 382, South Iran |
| Symptom | | |
| Epistaxis | 55% | 50% |
| Menorrhagia | 98%* | 13%** |
| Bruising/ purpura/ ecchymosis | 86% | 15% |
| Gingival bleeding | 55% | 23% |
| Gastrointestinal bleeding | 12% | 5% |
| Excessive bleeding at surgery ^A | n.r. | 6.4% |
| Haematoma/ haemarthrosis | 3% | 5% |
| Haematuria | 6% | n.r. |
| CNS bleeding | 2% | 0.3% |
| Visceral haematoma | 1% | n.r. |
| Umbilical cord bleeding | n.r. | 0.3% |

Key: n.r., not reported; CNS, central nervous system; *54/55 women; **17/131 women, age 15–45; ^Aincluding circumcision.

Table 2: General principles for management of GT patients.

| Strategy | Principles of management |
|-----------------------|--|
| Conservative measures | Alone only for minor bleeding (when applicable) |
| Adjunctive measures | <ul style="list-style-type: none"> ● Early treatment important for all therapy forms ● Fibrin glue application to active bleeding sites where accessible ● Antifibrinolytic agents (mainly for mucosal bleeding) Tranexamic acid (not licensed in the US): oral 10–25mg/kg q8h; intravenous 10–15 mg/kg q8h ε-aminocaproic acid: oral/intravenous 50–60 mg/kg q4h |
| Platelet transfusions | <ul style="list-style-type: none"> ● For severe bleeding or cases in which other measures fail and for invasive procedures ● One single donor aphaeresis unit (or 6–8 random donor units) represents the standard dose for adult patients; in children 10–15 ml/kg are given. ● HLA-compatible and leukocyte depleted platelets where available and possible. ● Continue until resolution of bleeding and/or wound healing |
| rFVIIa | <ul style="list-style-type: none"> ● Early treatment is important ● Priority of use: <ol style="list-style-type: none"> 1) history of anti-$\alpha_{IIb}\beta_3$ and/or anti-HLA antibodies together with history of platelet refractoriness; 2) prevention of development of iso-antibodies (e.g. women before and during fertile life) ● Bolus injection: dosage: $\geq 80 \mu\text{g/kg}$ at interval of $\leq 2.5\text{h}$, for 3 or more doses for moderate/severe bleeding. After bleeding stops, additional consolidation dose may decrease recurrences. ● Continuous infusion: not effective to stop bleeding, effective to prevent surgical bleeding (but without saving rFVIIa doses or shortening length of treatment). ● Antifibrinolytic agents can be used in conjunction ● If bleeding persists despite rFVIIa: higher dosage patients with platelet antibodies: plasmapheresis or immunoadsorption to remove antibodies, followed by adequate dosage of platelets. |

GT patients without, or with platelet isoantibodies are summarized in the Tables 2–4.

Patient education

Life-style advice and a continuous patient education program are crucial general measures to be implemented. These include the avoidance of trauma and of drugs interfering with platelet function (e.g. acetylsalicylic acid and non-steroidal anti-inflammatory drugs, NSAIDs), emphasis to dental hygiene and regular dental care to prevent gingival bleeding, and vaccination against hepatitis A and B (8, 17, 18).

Not all bleeding episodes in GT require systemic therapy, as many minor bleedings can be handled by conservative means. The latter are also often effectively used in association with platelet transfusions and/or haemostatic agents.

Conservative treatment and local measures

Early treatment is important for all forms of therapy in GT (Table 2). Local measures (pressure on bleeding site, tampons for nosebleeds, topical haemostatics, fibrin glue, Yag laser for nasal mucosal bleeds, endoscopic electrocoagulation for gastrointestinal bleeding lesions) may be effective alone for mild bleeding. Epistaxis and gingival bleeding are successfully controlled in most patients by nasal packing or the application of gelfoam soaked in topical thrombin and/or tranexamic acid. Patients with recurrent,

severe nasal haemorrhage may require embolic occlusion of the internal maxillary artery (8). Maintaining adequate humidity of the room, using saline sprays several times a day, and/or application of simple lubricants to nasal mucosa to retain moisture, may help decrease the frequency of epistaxis. For dental extractions, or for haemorrhage accompanying the loss of deciduous teeth, individually prepared plastic splints provide physical support for improving haemostasis. The use of fibrin glue (autologous, if available; otherwise plasmaderived components should be virus-inactivated) is suggested. Similarly, other sealants may be useful for improving local haemostasis during invasive procedures as shown in other patients with coagulation disorders (21).

Antifibrinolytic agents

They act by limiting the endogenous lysis of fibrin clots and have been reported to be effective in controlling mild/moderate mucosal bleeding, including menorrhagia, upper gastrointestinal haemorrhages and bleeding related to thrombocytopenia (22–25). Antifibrinolytic agents have also been used successfully as an adjunct to factor concentrates for dental extraction in haemophilia (26–27). Systemic ε-amino-caproic acid (EACA) or tranexamic acid (not available in the US) should be considered in GT patients, alone or as an adjunct to local measures or to haemostatic agents, including platelet transfusion and recombi-

| Setting | Management |
|---|--|
| Minor bleeding | <ul style="list-style-type: none"> ● Conservative and local measures ● Fibrin glue, antifibrinolytics as needed ● Platelet transfusions if bleeding persists. Single dose usually required, but more if bleeding persists. |
| Moderate and major bleeding unresponsive to conservative management | <ul style="list-style-type: none"> ● Standard treatment: platelet transfusions once to more times daily as clinically indicated, until bleeding stops or wound healing. ● In the event of concealed bleeding, must following haemoglobin level. ● Adjunctive management: fibrin glue, antifibrinolytic agents as indicated. |
| Major surgery* ^o | <ul style="list-style-type: none"> ● Platelet transfusions immediately before procedure ● Platelet transfusions daily or as required post-op for the first 3 days, lower frequency thereafter until resolution of bleeding and wound healing. |
| Minor surgery* | <ul style="list-style-type: none"> ● Conservative – fibrin glue application, antifibrinolytics ● Platelet transfusions: a pre-op dose ± a post-op dose in about 6–8 h if bleeding continues. Continue if persistent severe bleeding |
| Dental procedures* | <ul style="list-style-type: none"> ● Accurate local anaesthetic infiltration technique; fibrin glue application ● General anesthesia – care that endotracheal tubes may cause post-op excessive bleeding. The need for intubation could be circumvented by inhalation anesthetics (e.g. nitrous oxide) ● Oral antifibrinolytics: for 5–10 days <p>General anaesthetics: dose before patient to be on no oral intake the night before; Local anaesthetics: dose the morning before procedure Antifibrinolytic rinse – liberal use during and after procedure</p> <ul style="list-style-type: none"> ● Platelet transfusions: as for minor procedures; single dose generally required. |

[^] In children and women before and during fertile age consider rFVIIa;
^{*} For all invasive procedures, careful surgical technique to minimize trauma/bleeding.
^o Consider indication to thromboprophylaxis in patients with thromboembolic/cardiovascular risk factors, in particular after major surgery and prolonged hemostatic treatment.

Table 3: Management of GT patients without platelet isoantibodies and not refractory to platelet transfusion (to be read in conjunction with “General Principles of Management” in Table 2)[^].

nant activated Factor VII (rFVIIa) (8, 17–20). However, with the exception of the management of dental procedures (Table 3), specific data in GT patients are anecdotal (8, 16, 28), with reported use in association with platelet transfusions or rFVIIa.

Platelet transfusions

They are presently considered the standard treatment for severe haemorrhage in GT, when conservative measures and other agents are unable to control bleeding, and for prophylaxis in surgery (8, 17–19) (Tables 3 and 4). However, also for this therapeutic approach, only few anecdotal cases of management of bleeding or of dental procedures specifically refer to GT patients (28–30) and modality of treatment is still poorly standardized (doses, interval and duration of administration, follow-up).

As the risk of bleeding is poorly predictable by the history in GT patients, platelet transfusions before an invasive procedure should be indicated even in patients with minimal past haemorrhagic symptoms. Sufficient platelet dose should be administered to overcome the interfering effect of dysfunctional thrombasthenic platelets. In the lack of adequate evidence in this setting, clinical experience continues to play a major role. One single donor aphaeresis unit (or 6–8 random donor units) is considered the standard dose for adult patients; in children 10–15 ml/kg are usually given (17, 19, 28–30). For the same reasons, haemostatic efficacy of treatment is often assessed on the basis of general clinical and laboratory data (estimation of blood loss, monitor-

ing haemoglobin levels), more than of any platelet function tests.

Platelet aggregometry is not easily available and time consuming, whereas the evolving thromboelastographic technologies using whole blood analysis are promising approaches in this setting. Because of the ability to measure time of clot formation and its viscoelastic properties, which are sensitive to plasma and platelets, thromboelastography/thromboelastometry is a point-of care device largely used to guide blood component transfusion in trauma patients and during cardiac surgery (31). The specific contribution of platelets during clot formation may be assessed by inhibiting their function (31, 32).

Although studies in larger samples of GT patients and clinical settings are needed, interesting data have been already reported in the management of peripartum (33) or during laparoscopic surgery for endometriosis and bleeding (32). Consumption due to surgery or bleeding and the presence of anti-platelet antibodies may significantly reduce the survival of transfused platelets (32, 34), therefore platelets are transfused daily or generally with higher frequency than according to the theoretical platelet survival. In this respect, checking for the presence of anti-platelet antibodies may be not worthwhile before planning treatment, whereas history of platelet refractoriness should be carefully taken into account. Platelet transfusions should continue until wound healing is complete in cases of surgery (8, 35).

Platelet transfusions carry the residual risk for transfusion-transmitted bacterial and viral infections, along with a risk for

Table 4: Management of GT patients with history of platelet isoantibodies and/or history of refractoriness to platelet transfusion particularly when HLA-matched platelets are ineffective/unavailable (to be read in conjunction with “General Principles of Management” in Table 2).

| Setting | Management |
|---|--|
| Minor bleeding | <ul style="list-style-type: none"> ● Conservative and local measures ● Fibrin glue, antifibrinolytics as needed ● rFVIIa if bleeding persists. Single dose ($\geq 80 \mu\text{g/kg}$) usually required, but more if bleeding persists. |
| Moderate and major bleeding unresponsive to conservative management | <ul style="list-style-type: none"> ● rFVIIa Bolus injection: $\geq 80 \mu\text{g/kg}$ at interval of $\leq 2.5\text{h}$, for 3 or more doses. After bleeding stops, additional 1–2 consolidation doses may decrease recurrences. Adjunctive: Antifibrinolytic agents, particularly in mucosal bleeds. |
| Major surgery* | <ul style="list-style-type: none"> ● rFVIIa regimen not well established: few data available Bolus injection: $\geq 80 \mu\text{g/kg}$ immediately pre-op and intra-op if abnormal bleeding. <ul style="list-style-type: none"> - rFVIIa $\geq 80 \mu\text{g/kg}$ q2h for the first 1–2 days (?) - Q3–4 h for the next 2–5 days as indicated (?) - Q3–6h thereafter as indicated (?) - In any of above, should be increased to every 2–2.5h if persistent bleeding occurs. Continuous infusion: effective, but no saving of rFVIIa or shortening of duration of treatment. Caution for patients with coexisting thromboembolic risk. <ul style="list-style-type: none"> ● Adjunctive therapy: Application of fibrin glue to surgical site Antifibrinolytic agents have been used safely |
| Minor surgery and dental procedures* | <ul style="list-style-type: none"> ● rFVIIa: dosage usually $\geq 80 \mu\text{g/kg}$ immediately pre-op; a second post-op dose 2–2.5h after the first dose; new doses every 2–2.5h until bleeding stops ● Adjunctive therapy Application of fibrin glue to surgical site Antifibrinolytic agents |
| Major/life-threatening bleeding not stopped by rFVIIa | <ul style="list-style-type: none"> ● consider high-dose HLA-matched platelets with or without removal of platelet antibodies by apheresis/immunoadsorption |

** For all invasive procedures, careful surgical technique to minimize trauma/bleeding.
 ° Consider indication to thromboprophylaxis in patients with thromboembolic/cardiovascular risk factors, in particular after major surgery and prolonged haemostatic treatment.

immunologic reactions such as allergy/anaphylaxis, haemolysis due to anti-A or anti-B if transfused across ABO groups and the fearful transfusion-related acute lung injury (TRALI) (36). Additionally, the theoretical risk of transmission of the agent associated with the variant Creutzfeld-Jakob Disease (CJD), should be taken into account, especially in countries with exposure to prions through the food chain. This CJD risk, moreover, is thought to be higher with cellular products and for multiple donor exposures (17, 37).

Therefore, the recommendation in the UK is to give platelet transfusions only if essential, especially in children born after 1996 and otherwise not exposed to prions (17). Patients undergoing repeated platelet transfusion are at risk of developing isoantibodies against $\alpha_{\text{IIb}}\beta_3$ integrin and/or human leukocyte antigens (HLA), with possible refractoriness to future platelet transfusion (8, 38).

The actual incidence, genetic/acquired predisposing factors and clinical impact of anti-platelet isoimmunization in GT are poorly investigated. In this respect, in spite of the lack of rigorous studies, aphaeresed single donor, possibly HLA-matched (and, according to some evidence, also pre-storage leukocyte depleted) platelets should be preferred (if available and possible without delay to compromise clinical situation) to prevent the

formation of multiple HLA-antibodies (8, 17, 19). Successful use of HPA-1-typed platelets from previously screened donors for elective dental surgery has been also reported in this setting (39). Isoantibodies specific to the missing $\alpha_{\text{IIb}}\beta_3$ integrin may also cross placenta to result in harm to the foetus/newborn in pregnant women, causing thrombocytopenia and/or bleeding (8, 17, 40, 41). Although the relationship between the presence/titre of such isoantibodies and the foetal/neonatal outcome is unclear, cases of *in utero* death and intracranial haemorrhage have been reported (41).

Recombinant activated factor VII (rFVIIa)

Because of its ability at high doses to improve the impaired thrombin generation of GT patients through the direct activation of FX on platelet surface and to partially restore platelet aggregation possibly through the involvement of other membrane receptor pathways (42–43), recombinant activated factor VII (rFVIIa) provides an alternative haemostatic strategy in this setting.

After the first successful use in 1996 in a GT child with severe recurrent epistaxis (44), many case reports and some case series of rFVIIa for prophylaxis and treatment of bleeding in GT patients have been published over the last decade (44–47). In

2004 the results of an international survey evaluating the use of rFVIIa in 59 GT patients (1–72 yrs, median 22, of whom 42% had anti-HLA or anti- $\alpha_{\text{IIb}}\beta_3$ alloantibodies) for 108 bleeding episodes (76 severe, 32 moderate; 45 nose, 29 oropharyngeal, 17 gastrointestinal), and 34 invasive procedures (9 major, 12 minor surgery, 13 dental procedures) were published (16). With the obvious limitations of its retrospective design, this survey represents the largest collection of treatments in GT patients and provided broad suggestions for clinical use of rFVIIa in this setting:

- 1) success rates with rFVIIa bolus injections are highest with 'optimal' regimens, defined as treatments with dosage ≥ 80 $\mu\text{g}/\text{kg}$ at intervals of ≤ 2.5 hrs, for at least 3 doses;
- 2) success rates are lower in gastrointestinal bleedings, where local causes of bleeding often co-exist;
- 3) continuous infusion is successful for surgical procedures;
- 4) as previously reported in the series published by Almeida et al (46), regardless of dosing and/or scheduling, rFVIIa treatment, if used, should be started early (83% success within 6 hrs);
- 5) the use of rFVIIa is safe, being associated with severe adverse events in 2 cases (1.4%) in the international survey, both occurring in subjects with risk factors for clotting, in addition to receiving rFVIIa by prolonged continuous infusion at high dose (25–30 $\mu\text{g}/\text{kg}/\text{h}$) and on simultaneous treatment with antifibrinolytic agents. Cancer, age and prolonged bed rest were the risk factors in a subject that developed bilateral deep vein thrombosis and pulmonary embolism; gynaecological surgery had been recently carried out in a patient that developed a clot in the renal pelvis and ureter. Presently, rFVIIa is licensed in the EU for GT patients with platelet alloimmunization and history (past or present) of platelet refractoriness (Table 4).

In patients with circulating isoantibodies and severe/life-threatening bleeding, the combined use of rFVIIa with high-dose HLA-matched platelets and/or removal of isoantibodies by apheresis/immunoabsorption have been reported (40, 48, 49).

Hormonal treatment

High-dose progesterone is common practice to control severe menorrhagia in female GT patients with oestrogen dominance leading to an excessively proliferative endometrium. Bleeding usually stops within 24 hours, and then the progesterone dose can be decreased and continued for several weeks. Menstrual bleeding will occur on withdrawal and is usually not severe. Maintenance treatment with oral contraceptive pills should then begin (8, 50). More than one dose daily may be required to prevent breakthrough bleeding (8). Similar to von Willebrand disease, oestrogen-progesterone combinations have been reported for the management of bleeding angiodysplasia of the gut in some GT patients (15).

Desmopressin

1-deamino-8-D-arginine vasopressin, DDAVP has been shown to be effective in a series of acquired and inherited platelet function abnormalities (51, 52). In practice, clinical efficacy of DDAVP in GT patients have not always been observed; in spite of the lack of clear relationships between correction of bleeding

time and clinical efficacy, a reduction/correction of bleeding time after DDAVP administration has been seldom reported in GT (52). Therefore, DDAVP is usually not recommended for GT patients.

Open issues and research areas

Despite significant advances in the understanding of pathophysiology and the molecular and genetic background of GT, a series of challenges and open issues remains regarding the treatment and prophylaxis of bleeding. If the relationships between genetic/molecular defects and bleeding phenotype are poorly understood, possible implications of the molecular basis of the disease on clinical management, including platelet antigen isoimmunization and responsiveness to the different therapeutic approaches, are unknown.

Platelet transfusions remain the first-choice treatment for persistent or severe bleeding and for haemostatic cover of major invasive procedures. However, optimal modalities of platelet transfusions are not well standardized and treatment with HLA/HPA-1-selected platelets seem promising but few data are presently available (17, 19, 39). The possible anti- $\alpha_{\text{IIb}}\beta_3$ or anti-HLA isoimmunization (and consequent platelet transfusion refractoriness), together with the residual risks of blood-borne pathogens related to blood products, are of concern, especially for younger patients. Among reasons for giving rFVIIa in the international registry, beyond present or past history of platelet immunization, the prevention of platelet antigen immunization or of transfusion-transmitted infections was reported in 80% of cases (16). These objectives are more important in clinical choices for children (17) and women in fertile age (40, 41, 48). Therefore, in each case and for each patient, a careful risk- and cost-benefit evaluation, taking into account the ready availability of the different treatment options, is needed for choosing the best therapeutic approach.

Unsolved questions concern the definition of failure of treatment and strategies for patients unresponsive to first-line therapies, especially when alloantibodies are detectable. Higher rFVIIa doses (180–200 $\mu\text{g}/\text{kg}$) have been successfully and safely used in some patients (16, 53); as shown in haemophilia with inhibitors (54), it is conceivable that these or also higher rFVIIa doses may be even more effective than standard doses and that such regimens can be tried in patients with severe bleeding or failure after standard treatment, but presently no data support this notion. Moreover, combined approaches with platelet transfusion and rFVIIa may be hypothesized for patients in which, in spite of a history of alloimmunization, full refractoriness to platelet transfusions is not shown or with non-optimal responsiveness to rFVIIa (16). In spite of continuous improvements of platelet function assays (55), these issues reflect the lack of validated laboratory tests or techniques for monitoring the efficacy of the different treatment approaches in this setting (32–34, 56, 57). In this respect, as previously mentioned, the recently proposed assays, thromboelastogram and the evolving techniques using whole blood/platelet rich plasma analysis, including thrombin generation (32, 33, 56–58), need to be further investigated in GT patients.

Defining optimal regimens of rFVIIa treatment (doses, duration, bolus injections or continuous infusion, and associated measures), in particular for haemostatic cover of major surgery in which data are quite limited (16, 59), and the appropriate parameters for monitoring its efficacy and safety remain the main open issues. Also in this case, the encouraging thromboelastographic data (56, 57) should be validated in this and other settings of rFVIIa treatment.

As in other congenital bleeding disorders, an emerging issue is represented by indications for thromboprophylaxis in patients with cardiovascular/thromboembolic risk factors and/or undergoing major surgery. GT patients have been shown to be not protected from development of atherosclerosis (60) and cases of venous thromboembolism have been reported in patients with congenital (61) or acquired risk factors (62, 63), as spontaneous events (61–64) or as a complication of haemostatic treatment (16). Fewer data are available concerning the management of these thrombotic events (62, 64) and their long-term follow-up.

Due to the rarity and the heterogeneity of inherited platelet function disorders, the conduct of large and methodologically rigorous studies in this setting, from which adequate strength data for evidence-based recommendations for clinical manage-

ment should be drawn, remains an improbable task (17, 19). The proposals for management reported here are based on the few available evidence in the area, utilizing also recommendations employed in other clinical settings of congenital or acquired platelet defects as appropriate. According to the current methodology for clinical guidelines (65), these suggestions are necessarily classifiable as the lowest level of evidence (IV) and in the weakest grade of recommendation (C). Nevertheless, a prospective registry of treatments in GT patients has been recently established (<http://www.glanzmann-reg.org>) to assess the efficacy and safety of rFVIIa and the other systemic haemostatic agents (66). Employing agreed suggestions for management and a careful definition of clinical settings and outcomes, the prospective collection of a larger number of treatments and patients is likely to be the most practical strategy for optimizing clinical approaches to treatment and defining future guidelines for inherited platelet function disorders such as GT.

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References

- Caen JP, Castaldi PA, Leclerc JC, et al. Congenital bleeding disorders with long bleeding time and normal platelet count. 1. Glanzmann's thrombasthenia. *Am J Med* 1966; 41: 4–18.
- Nurden AT, Caen JP. An abnormal platelet glycoprotein pattern in three cases of Glanzmann's thrombasthenia. *Br J Haematol* 1974; 28: 253–260.
- Di Minno G, Thiagarajan P, Perussia B, et al. Exposure of platelet fibrinogen binding sites by collagen, arachidonic acid and ADP: inhibition by a monoclonal antibody to the α IIb- β 3 IIb-IIIa complex. *Blood* 1983; 61: 140–148.
- Reichert N, Seligsohn U, Ramot B. Clinical and genetic studies of Glanzmann's thrombasthenia in Israel. *Thromb Diath Haemorrh* 1975; 34: 806–820.
- Khanduri U, Pulimood R, Sudarsanam A, et al. Glanzmann's thrombasthenia. A review and report of 42 cases from South India. *Thromb Haemost* 1981; 46: 217–221.
- Awidi AS. Congenital hemorrhagic disorders in Jordan. *Thromb Haemost* 1984; 51: 331–333.
- Toogeh G, Sharifian R, Lak M, et al. Presentation and pattern of symptoms in 382 patients with Glanzmann thrombasthenia in Iran. *Am J Hematol* 2004; 77: 198–199.
- George JN, Caen JP, Nurden AT. Glanzmann's thrombasthenia: the spectrum of clinical disease. *Blood* 1990; 75: 1383–1395.
- Stormorken H, Gostrad GO, Solum NO, Pande H. Diagnosis of heterozygotes in Glanzmann's thrombasthenia. *Thromb Haemost* 1982; 48: 217–221.
- Caen JP. Glanzmann's Thrombasthenia. *Baillieres Clin Haematol* 1989; 2: 609–625.
- D'Andrea G, Colaizzo D, Vecchione G, et al. on behalf of the Glanzmann's Thrombasthenia Italian Team (GLATIT). Glanzmann's Thrombasthenia: identification of 19 new mutations in 30 patients. *Thromb Haemost* 2002; 87: 1034–1042.
- Glanzmann Thrombasthenia Database, last update February 12, 2009, available at <http://sinaicentral.mssm.edu/intranet/research/glanzmann/menu>, last accessed on March, 31, 2009.
- Ghosh K, Kulkarni B, Nair S, Mohanty B. Human platelet alloantigen polymorphism in Glanzmann's thrombasthenia and its impact on the severity of the disease. *Br J Haematol* 2002; 119: 348–353.
- D'Andrea G, Margaglione M for the Glanzmann's Thrombasthenia Italian Team (GLATIT). Glanzmann's thrombasthenia: modulation of clinical phenotype by alpha2C807T gene polymorphism. *Haematologica* 2003; 88: 1378–1382.
- Coppola A, De Stefano V, Tufano A, et al. Long-lasting severe intestinal bleeding in an old patient with multiple mucosal vascular abnormalities and Glanzmann's thrombasthenia. Three-yr pharmacological management. *J Int Med* 2002; 252: 271–275.
- Poon M-C, d'Oiron R, Von Depka M, et al. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. *J Thromb Haemost* 2004; 2: 1096–1103.
- Bolton-Maggs PHB, Chalmers EA, Collins PW, et al. A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. *Br J Haematol* 2006; 135: 603–633.
- Hayward CPM, Rao AK, Cattaneo M. Congenital platelet disorders: overview of their mechanisms, diagnostic evaluation and treatment. *Haemophilia*. 2006; 12 (suppl. 3): 128–136.
- Società Italiana per lo Studio dell'Emostasi e della Trombosi. *Trattamento delle emorragie e preparazione alle manovre invasive nel paziente con piastrinopenia e/o piastrinopenia ereditaria od acquisita*. Last update 4 June 2007 [Article in Italian]. Available at www.siset.org/lineeguida/LG4.pdf last accessed on March 31, 2009.
- Nurden P, Nurden A. Congenital disorders associated with platelet dysfunctions. *Thromb Haemost* 2008; 99: 353–363.
- Lefebvre JM, Qanadli SD, Kacher S, et al. A new vascular sealant (Sealgel) to achieve rapid hemostasis after percutaneous angioplasty in anticoagulated patients: clinical feasibility and preliminary results. *Eur Radiol* 2001; 11: 454–459.
- Stael von Holstein CCS, Eriksson SBS, Kallen R. Tranexamic acid as an aid to reducing transfusion requirements in gastric and duodenal bleeding. *Br Med J* 1987; 294: 7–10.
- Bartholomew JR, Salgia R, Bell WR. Control of bleeding in patients with amegakaryocytic thrombocytopenia. *Arch Intern Med* 1989; 149: 1959–1961.
- Shpilberg O, Blumenthal R, Sofer O, et al. A controlled trial of tranexamic acid therapy for the reduction of bleeding during treatment of acute myeloid leukaemia. *Leuk Lymphoma* 1995; 19: 141–144.
- Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomized controlled trial of ethamsylate, mefenamic acid and tranexamic acid. *Br Med J* 1996; 313: 579–582.
- Walsh PN, Rizza CR, Matthews JM, et al. Epsilon-Aminocaproic acid therapy for dental extractions in haemophilia and Christmas disease: a double blind controlled trial. *Br J Haematol* 1971; 20: 463–475.
- Sindet-Pedersen S, Stenbjerg S. Effect of local antifibrinolytic treatment with tranexamic acid in hemophiliacs undergoing oral surgery. *J Oral Maxillofac Surg* 1986; 44: 703–707.
- Kantarci A, Cebeci I, Firatli E, et al. Periodontal management of Glanzmann's thrombasthenia: report of 3 cases. *J Periodontol* 1996; 67: 816–820.
- Sundqvist SB, Nilsson IM, Svanberg L, Cronberg S. Pregnancy and parturition in a patient with severe Glanzmann's thrombasthenia. *Scand J Haematol* 1981; 27: 159–164.
- Bisch FC, Bowen KJ, Hanson BS, et al. Dental considerations for a Glanzmann's thrombasthenia patient: case report. *J Periodontol* 1996; 67: 536–540.
- Kettner SC, Panzer OP, Kozek SA, et al. Use of abiciximab-modified thrombelastography in patients undergoing cardiac surgery. *Anesth Analg* 1999; 89: 580–584.
- Male C, Koren D, Eichelberger B, et al. Monitoring survival and function of transfused platelets in Glanzmann thrombasthenia by flow cytometry and thrombelastography. *Vox Sang* 2006; 91: 174–177.
- Monte S, Lyons G. Peripartum management of a

- patient with Glanzmann's thrombasthenia using Thrombelastograph®. *Br J Anaesth* 2002; 88: 734–738.
34. Nurden A, Combrié R, Nurden P. Detection of transfused platelets in a patient with Glanzmann thrombasthenia. *Thromb Haemost* 2002; 87: 543–544.
 35. Bell JA, Savidge GF. Glanzmann's thrombasthenia proposed optimal management during surgery and delivery. *Clin Appl Thromb Haemost* 2003; 9: 167–170.
 36. MacLennan S, Williamson LM. Risks of fresh frozen plasma and platelets. *J Trauma* 2006; 60 (Suppl. 6): S46–S50.
 37. Seghatchian J. Universal leucodepletion: an overview of some unresolved issue and highlights of lesson learned. *Transf Apher Sci* 2003; 29: 105–117.
 38. Makris M, Conlon CP, Watson HG. Immunization of people with bleeding disorders. *Haemophilia* 2003; 9: 541–546.
 39. Conte R, Cirillo D, Ricci F, et al. Platelet transfusion in a patient affected by Glanzmann's thrombasthenia with antibodies against GPIIb-IIIa. *Haematologica* 1997; 82: 73–74.
 40. Vivier M, Treisser A, Naett M, et al. Glanzmann thrombasthenia and pregnancy. Contribution of plasma exchange before scheduled cesarean section. *J Gynecol Obstetr Biol Reprod. (Paris)* 1989; 18: 507–513.
 41. Léticée N, Kaplan C, Lémery D. Pregnancy in mother with Glanzmann's thrombasthenia and isoantibody against GPIIb-IIIa: is there a foetal risk? *Eur J Obst Gynecol Reprod Biol* 2005; 121: 139–142.
 42. Lisman T, Adelmeijer J, Heijnen F, et al. Recombinant factor VIIa restores aggregation of alpha_{IIb}beta₃ deficient platelets via tissue factor-independent fibrin generation. *Blood* 2004; 103: 1720–1727.
 43. Hedner U. Factor VIIa and its potential therapeutic use in bleeding-associated pathologies. *Thromb Haemost* 2008; 100: 557–562.
 44. Tengborn L, Peturson B. A patient with Glanzmann's thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. *Thromb Haemost* 1996; 75: 981–982.
 45. Poon M-C, Demers C, Jobin F, Wu JW. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. *Blood* 1999; 94: 3951–3953.
 46. Almeida AM, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. *Br J Haematol* 2003; 121: 477–481.
 47. Kaleelrahman M, Minford A, Parapia LA. Use of recombinant factor VIIa in inherited platelet disorders. *Br J Haematol* 2004; 125: 95–96.
 48. Ito K, Yoshida H, Hatoyama H, et al. Antibody removal therapy used successfully at delivery of a pregnant patient with Glanzmann's thrombasthenia and multiple anti-platelet antibodies. *Vox Sang* 1991; 61: 40–46.
 49. Martin I, Kriaa F, Proulle V, et al. Protein A Sepharose immunoabsorption can restore the efficacy of platelet concentrates in patients with Glanzmann's thrombasthenia and anti-glycoprotein IIb-IIIa antibodies. *Br J Haematol* 2002; 119: 991–997.
 50. Vijapurkar M, Mota L, Shetty S, Ghosh K. Menorrhagia and reproductive health in rare bleeding disorders: a study from the Indian subcontinent. *Haemophilia* 2009; 15: 199–202.
 51. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; 90: 2515–2521.
 52. Coppola A, Di Minno G. Desmopressin (DDAVP) in inherited disorders of platelet function. *Haemophilia* 2008; 14 (Suppl. 1): 31–39.
 53. Chuansumrit A, Suwannuraks M, Sri-Udomporn N, Po et al. Recombinant activated factor VII combined with local measures in preventing bleeding from invasive dental procedures in patients with Glanzmann thrombasthenia. *Blood Coagul Fibrinolysis* 2003; 14: 187–190.
 54. Kenet G, Lubetsky A, Luboshitz J, et al. A new approach to treatment of bleeding episodes in young haemophilia patients: a single bolus megadose of recombinant activated factor VII (NovoSeven). *J Thromb Haemost* 2003; 1: 450–455.
 55. Gremmel T, Steiner S, Seidinger D, et al. Comparison of methods to evaluate clopidogrel-mediated platelet inhibition after percutaneous intervention with stent implantation. *Thromb Haemost* 2009; 101: 333–339.
 56. Lak M, Scharling B, Blemings A, et al. Evaluation of rFVIIa (NovoSeven) in Glanzmann patients with thromboelastogram. *Haemophilia* 2008; 14: 103–110.
 57. Dargaud Y, Bordet JC, Trzeciak MC, et al. A case of Glanzmann's thrombasthenia successfully treated with recombinant factor VIIa during a surgical procedure: observations on the monitoring and the mechanism of action of this drug. *Haematologica* 2006; 91: ECR20.
 58. Spronk HMH, Dielis AWJH, De Smedt E, et al. Assessment of thrombin generation II: Validation of the Calibrated Automated Thrombogram in platelet-poor plasma in a clinical laboratory. *Thromb Haemost* 2008; 100: 362–364.
 59. Coppola A, Tufano A, Agangi A, et al. Recombinant Factor VIIa in a patient with Glanzmann's thrombasthenia undergoing gynecological surgery: open issues in the light of a successful treatment. *Thromb Haemost* 2004; 92: 1450–1452.
 60. Shpilberg O, Rabi I, Schiller K, et al. Patients with Glanzmann Thrombasthenia lacking platelet glycoprotein αIIbβ3 (GPIIb/IIIa) and αvβ3 receptors are not protected from atherosclerosis. *Circulation* 2002; 105: 1044–1048.
 61. Ten Cate H, Brandjes DP, Smits PH, et al. The role of platelets in venous thrombosis: a patient with Glanzmann's thrombasthenia and a factor V Leiden mutation suffering from deep venous thrombosis. *J Thromb Haemost* 2003; 1: 394–395.
 62. Gruel Y, Pacouret G, Bellucci S, Caen J. Severe proximal deep vein thrombosis in a Glanzmann thrombasthenia variant successfully treated with a low molecular weight heparin. *Blood* 1997; 90: 888–890.
 63. Philips R, Richards M. Venous thrombosis in Glanzmann's thrombasthenia. *Haemophilia* 2007; 13: 758–759.
 64. Seretny M, Senadheera N, Miller E, Keeling D. Pulmonary embolus in Glanzmann's thrombasthenia treated with warfarin. *Haemophilia* 2008; 14: 1138–1139.
 65. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *Br Med J* 1999; 318: 593–596.
 66. Poon MC, Zotz R, Di Minno G, Abrams ZS, et al. Glanzmann's thrombasthenia treatment: a prospective registry on the use of recombinant human activated Factor VII and other hemostatic agents. *Semin Hematol* ((Author: ■■■■■■ please complete reference))