vention and treatment of venous thromboembolism (VTE) and in some countries for the treatment of acute coronary syndromes. Idraparinux, a subcutaneous, long-acting, indirect Factor Xa inhibitor, is in development. Direct inhibition of thrombin or Factor Xa with synthetic, small molecules is an attractive strategy for the development of novel anticoagulants. After the withdrawal of ximelagatran, dabigatran is now the furthest advanced oral, direct thrombin inhibitor, and an extensive phase III clinical trial programme (the RE VOLUTION trials) has recently determined its efficacy and safety in the prevention of VTE in major orthopaedic surgery. Direct Factor Xa inhibitors in development that show clinical promise in various indications include rivaroxaban, apixaban, betrixaban, LY-517717, YM150, and DX-9065a and its derivative Du-176b. Of these rivaroxaban and apixaban are the furthest advanced. Rivaroxaban has a favourable efficacy and safety profile, relative to enoxaparin, for the prevention of VTE after major orthopaedic surgery as shown in the RECORD trials. The results of trials of riva-roxaban for the treatment of proximal deep vein thrombo-
sis are expected soon. It is likely that these new anticoa-
gulants will revolutionize oral anticoagulant therapy.

BLEEDING DISORDERS

SURGERY AT HIGH RISK OF BLEEDING
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“Some loss of blood is always inevitable”. In spite of sharp and innovative advances in surgical techniques, massive blood loss is still one of the major perioperative complications, able to impact on both morbidity and mortality. Major thoraco-abdominal vascular surgery, major liver surgery including transplantation, neurosurgery, spine surgery, obstetrics complicated by postpartum hemorrhage are among the surgical procedures at risk of critical bleeding (defined as severe, unexpected, and uncontrollable bleeding), a condition able to raise mortality rate from <1% to above 20%. Management of critical perioperative bleeding includes prompt evaluation, early and (hopefully) correct diagnosis, timely, appropriate and, not infrequently, multimodal approach for the treatment. Complex haemostatic derangements and the related bleeding complications have to be managed understanding the specific physiological change(s), thus giving a solid rationale to the treatment, which could not be “simply” or only symptomatic (“give blood and FFP”) but causative (“find the defect and treat it”). Generally speaking, perioperative bleeding could be subdivided in “surgical” and “non-surgical or haemostatic bleeding”. The so called “surgical” blood loss, responsible for up to 70% of the cases is mainly attributable to surgical technical problems and is characterized by uncontrolled bleeding at the operative site, where the problem is usually confined. Proper patient selection and anticipation of technical problems may substantially contribute in reducing surgical bleeding in high-risk patients (eg. patients with portal hypertension or frequent bacterial peritonitis in major liver surgery; reop-
erations in case of previous extensive cardiac, thoracic, or abdominal surgery). The “non-surgical or haemostatic bleeding”, on the contrary, is usually due to a dysfunc-
tion/failure in one (or more) of the phases of the haemo-
static system: it appears as a generalised oozing with spontaneous, multiple sites bleeding (traumatized tissues, puncture sites, surgical wounds etc) without any apparent single bleeding point. Main causes of the “non surgical bleeding” are:

a) pre-existing, previously undetected bleeding disorder;
b) changes induced by drugs (e.g.: aspirin, clopidogrel, NSAIDs, warfarin, LMWH, UFH);
c) coexisting pathologies (eg: liver failure, chronic renal failure);
d) haemostatic derangements induced by:
   - the surgical procedure itself (cardiopulmonary bypass, orthotopic liver transplantation, prostate surgery, fusion spinal surgery, neurosurgery, complicated obstetrics)
   - massive blood loss and massive transfusion in complicated surgery.

Since mechanical treatment of this kind of hemorrhage by clipping or vessel ligation is frustrating and useless at
best, anaesthetists are often challenged in the control of the acute bleeding, frequently addressed as "critical bleeding". Volume and rate of blood replacement are used to define "massive blood loss" and "massive transfusion" (MT).\textsuperscript{1-4} MT is commonly defined as the replacement of one blood volume in a period of 24 hr.\textsuperscript{4,5} In the acute setting, dynamic definitions, such as the transfusion of four or more red cell concentrates within one hour or the replacement of 50% of the total blood volume within three hours, could be more appropriate.\textsuperscript{5} Massively transfused patients will show evidence of defective hemostasis in a high percentage of cases. However, hemostatic derangements associated with massive transfusion differ substantially, depending on whether hemorrhage occurs as a result of trauma or during elective complicated surgery.\textsuperscript{6} In case of trauma or trauma surgery, uncontrolled tissue trauma, severe hypoperfusion, acidosis and hypoxia are able to cause damage to the microvasculature and to precipitate disseminated intravascular coagulation (DIC), an acquired syndrome characterized by the chaotic intravascular activation of coagulation and fibrinolysis leading to consumption of platelets, coagulation proteins, fibrinogen and platelets.\textsuperscript{1,4,5} DIC may be provoked by tissue damage due to trauma or by underperfusion, hypothermia, sepsis or obstetric complications. Diagnosis is based on clinical signs of unexpected bleeding or thrombosis, low fibrinogen and/or platelets, prolonged PT\textsubscript{INR} and raised fibrin degradation products (FDP) or d-dimers.\textsuperscript{4,5,8} On the contrary, in elective surgery, tissue trauma is controlled, tissue perfusion should be better maintained by keeping close to normal limits volemia and body temperature (thus avoiding hypoperfusion, hypoxia and acidosis), hemostatic defects should be either anticipated, properly monitored and, hopefully, diagnosed. This should allow a more aggressive and rational treatment of the coagulopathy, often and at least in part dilutional in nature, after aggressive fluid resuscitation based on crystalloids and colloids. Fibrinogen concentration halves after every 0.75 blood volume replaced (fall to <1 g/L after replacement of 12 units of red cells or 1.5 × blood volume). Other clotting factors fall by varying degrees: a prothrombin time ratio (PT\textsubscript{INR}) of >1.5 (clotting factors approximately 50% of normal) will be reached after replacement of 1-1.5× blood volume, or transfusion of 8-12 units of red cells. A PT\textsubscript{INR} of >1.8 (clotting factors approximately 30% of normal) will be reached after replacement of 2× blood volume. Platelet count will halve for every 1× blood volume replaced and, depending on the starting count, will usually fall to 50-100×10^9/L after 2 × blood volume replacement, or transfusion of >15 units of red cells.\textsuperscript{4} According to Hardy\textsuperscript{6} a decrease in fibrinogen concentration is observed initially, while thrombocytopenia is a late occurrence, which makes DIC less common and microvascular bleeding unlikely or as a late event, usually when the situation becomes uncontrolled.\textsuperscript{7} Current management of perioperative bleeding should include preventive and proactive measures.\textsuperscript{1} One of the key points in prevention is the identification of patients who are at increased risk of bleeding, because of haemostatic disorders or drugs. Knowledge of the possible specific haemostatic changes related to the surgical procedure itself is another major point: the complex and phase-specific hemostatic changes induced during liver transplantation are a good example. Apart from the well known coagulation factors defects, hyperfibrinolysis, coagulation factors consumption, thrombocytopenia and heparin or heparin-like substances release from the graft after reperfusion are peculiar derangements in this specific setting able to lead to massive blood loss.\textsuperscript{1,10,11} The pelvic and prostate surgery might be prone to hyperfibrinolysis too, due to liberation of t-PA. Consumption of coagulation factors, platelets and physiological anticoagulants do occur from bleeding and/or hemodilution from crystalloid infusion, but rarely result in a fall significant enough to exacerbate bleeding. Among the proactive measures to be undertaken in case of risk of massive surgical bleeding, monitoring is pivotal, particularly if “near patients testing” is considered (point of care strategy). In case of perioperative hemostatic derangements, pharmacological manipulations and the use of different blood components must be guided by dedicated instrumentation. An ideal device for the intraoperative hemostatic evaluation should give rapid, accurate, reproducible and useful results. An accurate point of care (POC) testing would allow the physician to make real-time decisions regarding the complex interplay of the various hemostatic pathways: real time display of the results of the manipulation (immediate in vitro display of the drug effect and in vivo results early after the intervention) could make the difference.\textsuperscript{0,11} This could be the case for the diagnosis of heparin effect or hyperfibrinolysis and the use of protamine sulphate or aprotinin, respectively.\textsuperscript{11} Instead of measuring the single “static” conventional coagulation parameters (PT\textsubscript{INR}, aPTT, platelet count), a comprehensive way to “dynamically” assess the hemostatic profile (from clot formation to clot lysis or retraction) could be provided by thromboelastography, able to consider core temperature too.\textsuperscript{10,12} Pharmacological manipulation when and if appropriate and/or blood derivatives are the mainstays of the treatment of the bleeding surgical patient, after an appropriate diagnosis has been made. The mainstays of blood based interventions remain fresh frozen plasma, platelets and cryoprecipitate. According to the UK Blood Transfusion Services guidelines\textsuperscript{1,5} prolongation of the PT INR /APTT not due to heparin should be maintained below 1.5 by using fresh frozen plasma at a dose of 15 ml/kg; very recent data suggest a 1:1 ratio of PRC: FFP\textsuperscript{9,10} to correct decreased levels of coagulation factors; platelet counts should be kept above 50-100×10^9/L, by the use of platelet transfusions; and if the fibrinogen is particularly low it should be kept above 0.8-1.0 g/dL by using cryoprecipitate. Pharmacological drugs able to reduce or modulate blood loss during surgery include DDAVP, antifibrinolytics, protamine sulphate: the role of recombinant activated factor VII to treat bleeding that cannot be controlled by conventional measures remains to be clarified but is more and more considered in rescue protocols.\textsuperscript{11} The TEG, taking into account the interaction among fibrinogen, platelets, and the proteins of the coagulation cascade, monitors the visco-kinetic changes in the blood during the clotting process as a single dynamic process. The qualitative analysis performed by TEG provides information on the strength and stability of the clot, while the kinetics deter-
Surgery at high risk of bleeding and consequent autosomal recessive diseases with clinical manifestations.
genes. FVII and FX deficiencies show extensive similarity in their mutational patterns, with potentially null mutations less represented in FVII than FIX gene. A few coagulation factors circulate as multisubunit proteins (FXIII, fibrinogen, FXI and von Willebrand factor). This implies that heterozygous mutations can cause severe quantitative deficiencies (dominant negative effect) through formation of mutant and wild-type polypeptide heterodimers. This mechanism has been suggested for von Willebrand disease and also for factor XI deficiency. Several studies indicate the presence of genetic and acquired factors modulating the clinical expression of deficiencies. Genetic factors have been found to have a major effect on plasma concentrations of haemostatic proteins. In particular for FVII, they account for 57-63% of level variations. Intragenic polymorphisms strongly contribute to FVII levels in normal subjects and up to 5-fold differences in FVIIa values are associated to different genotypes. Combination of polymorphisms and gene mutations could contribute to clinical variability. Several studies have highlighted the biosynthetic pathways of coagulation factors, which include several post-translational modifications required for factor secretion and function. Alterations in genes, which participate in the protein maturation process, are candidate to produce or modulate coagulation deficiencies, and might contribute to explain their large variability in the clinical expression. A good example is offered by combined deficiency of coagulation factors V and VIII, in which most of the patients have mutations in genes involved in the intracellular transport of both factors. Other candidates are suggested by combined deficiency of all vitamin K-dependent coagulation factors, a rare bleeding disorder caused by mutations in the genes coding for the enzymes involved in the recycling of the reduced form of vitamin K. Further complexity in the understanding of genotype-phenotype relationships is represented by the delicate balance between coagulation/anticoagulation that ultimately produces the haemostatic phenotype. Key coagulation factors, like thrombin and FV, have procoagulant as well as anticoagulant functions. Coinheritance of FV Leiden leads to enhanced thrombin generation and can mitigate clinical course in patients with severe FVII deficiency due to homozygosity for a splicing mutation, indicating that abnormalities could counterbalance each other. The knowledge of mechanisms underlying the phenotypic diversity of the coagulation deficiencies could improve genetic counselling and provide elements for individually oriented prophylaxis/therapy approaches.

TREATMENT OF HAEMOPHILIACS WITH INHIBITORS

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Inhibitor development represents the main complication of haemophilia treatment because it makes replacement therapy ineffective and prophylaxis unfeasible. The management of patients with inhibitors includes two
main issues: treatment of bleeding episodes and inhibitor eradication. The therapeutic choice in case of bleeding is strictly related to current inhibitor titre, anamnestic response and bleeding severity. High-dose factor replacement represents the first choice in all patients with low-responding inhibitors (i.e. historical inhibitor titres always < 5 BU/mL), or in patients with high-responding inhibitors (i.e. historical inhibitor peak >5 BU/mL) and current low titre in case of life-threatening bleeding. On the other hand, by-passing agents (i.e. rFVIIa and/or aPCC) represent the first line therapy in the presence of high-titre inhibitors. In particular, rFVIIa should be preferred to avoid anamnesis and to allow the decrease of inhibitor titres in candidates to immune tolerance induction (ITI). The attempt at eradicating inhibitors by ITI regimens is mandatory, especially in children. ITI regimens are based on regular administration of factor VIII concentrates both at high (up to 200 U/kg/day) or low doses (50 U/kg/thrice weekly) and, usually, the product chosen corresponds to that used prior to inhibitor development. ITI outcome is defined on the basis of inhibitor titre and factor VIII pharmacokinetics (namely in vivo recovery and half-life), being the success defined as persistently undetectable inhibitors, in vivo recovery >66% of the expected value and half-life ≥6 hours. ITI is a demanding therapeutic approach, nevertheless when success is achieved (60-80%), patients can take advantage of optimal factor replacement therapy and prophylaxis.

**IMMUNE TOLERANCE INDUCTION IN HAEMOPHILIA A WITH INHIBITORS: THE ITALIAN RETROSPECTIVE-PROSPECTIVE REGISTRY (PROGNOSTIC FACTORS IN IMMUNE TOLERANCE, THE PROFIT STUDY)**

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**Introduction.** Induction of immune tolerance (ITI) is presently the only therapeutic approach able to eradicate or reduce the inhibitor production in haemophiliacs. The optimal dose regimen and type of FVIII product for ITI, however, are still unknown and the cost-benefit ratios of such treatment are unclear, since treated patients show heterogeneous clinical features. National registries are useful to monitor the practice of ITI treatment and to identify predictors of response helpful to optimise the selection of ITI candidates. **Methods.** Thanks to a grant from the National Ministry of Health, with the external co-funding by CSL Behring, the Italian Association of Haemophilia Centres (AICE) established in 2005 a retrospective-prospective registry (the PROFIT Study) to collect clinical, laboratory and genetic data on ITI treatment in haemophilia A. ITI outcome was centrally reviewed according to the current definitions of success (undetectable inhibitor and normalised FVIII pharmacokinetic parameters, PK), partial response (inhibitor titer <5 BU/mL and/or abnormal PK) and failure. **Results.** At February 2008, data on 102 ITI courses (1996-2007) in 94 haemophiliacs (90 severe, 91 high-responders) were provided by 24 Centres. Patients underwent the first ITI at a median age of 4.8 yrs (0.3-52.5; 55% <7yrs) with a median pre-ITI titer of 4.1 BU/mL (<0.5-200; 71% <10) and a median of 21 mo. (0-332; 59% <24) from the diagnosis. Median historical peak was 64 BU/mL (1.5-800; 78% <200). FVIII/VWF products were used in 28% of courses and recombinant FVIII in the remaining at doses ≥100IU/Kg/d in 35% and 75%, respectively (range: 25 IU/Kg/qod-220 IU/Kg/d). The outcome of first courses completed in 85 patients was success in 43 (51%), partial response in 14 (16%) and failure in 28 (33%). Median time to achieve success was 6 mo. (1.5-40). The median success follow-up was 3.3 yrs (0.3-10.4); a relapse occurred after 7 yrs in one patient. Median pre-ITI titer, historical peak, ITI-peak and daily FVIII dose in patients who achieved the success compared to those who failed were: 2.4 vs. 7.2, 42 vs. 128, 20 vs. 400 BU/mL and 100 vs. 170 IU/Kg/d, respectively. **Conclusions.** The PROFIT Registry is collecting a detailed picture of ITI practice in Italy over the last decade. Despite the presence of ≥1 known negative predictors of response in about 2/3 of patients, 68% achieved complete or partial response, allowing bleeding control with FVIII treatment or prophylaxis. Regimens with intermediate-high FVIII doses and recombinant products are more frequently prescribed. Inhibitor-related variables (historical peak, titer at ITI start, peak on ITI) are likely to be the most important predictors of outcome.