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 rivaroxaban for the treatment of proximal deep vein thrombosis are expected soon. It is likely that these new anticoagulants 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.[1] 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%.[2,3] Management of critical perioperative bleeding includes prompt evaluation, early and (hopefully) correct diagnosis, timely, appropriate and, not infrequently, multimodal approach for the treatment.[1,4,5] 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"*).[6] Generally speaking, perioperative bleeding could be subdivided in "surgical" and "non -surgical or haemostatic bleeding".[1,4,5] 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.[1,7] 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; reoperations in case of previous extensive cardiac, thoracic, or abdominal surgery). The ''*non-surgical or haemostatic bleeding*'', on the contrary, is usually due to a dysfunction/failure in one (or more) of the phases of the haemostatic 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.[1] Main causes of the "non surgical bleeding" are:[1,4,5,6]

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, anaesthesiologists 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).[4,5] MT is commonly defined as the replacement of one blood volume in a period of 24 hr.[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.[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.[5] 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.[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_{INR} and raised fibrin degradation products (FDP) or d-dimers.[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 (PTINR) 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 PTINR 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.[8] According to Hardy[5] 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.[5] Current management of perioperative bleeding should include preventive and proactive measures.[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.[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 a 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.[10,12] This could be the case for the diagnosis of heparin effect or hyperfibrinolysis and the use of protamine sulphate or aprotinin, respectively).[11] Instead of measuring the single "static" conventional coagulation parameters (PT_{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.[9,10] 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[1,8] 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[10] to correct decreased levels of coagulation factors; platelet counts should be kept above 50-100×10^9, 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;[4,5] the role of recombinant activated factor VII to treat bleeding that cannot be controlled by conventional measures remains to be clarified[13] but is more and more considered in rescue protocols.[14] The TEG, taking into account the interaction among fibrinogen, platelets, and the proteins of the coagulation cascade, monitors the viscokinetic changes in the blood during the clotting process as a single dynamic process. The quali-quantitative analysis performed by TEG provides information on the strength and stability of the clot, while the kinetics deter-

mine the adequacy of quantitative factors available for clot formation at the actual core temperature of the patient.[12] Surgery at high risk of bleeding and consequent massive transfusion remains a challenging clinical problem in modern medicine. Anaesthesiologists are more and more involved in the first line treatment of many complex cases of surgical or non surgical bleeding: as recently stated, treatment strategies must be adapted to the clinical context and properly supported by dedicated, dynamic monitoring systems. While the level of evidence supporting specific treatment options is sometimes low, preventive and/or proactive measures could greatly help in rendering the management of perioperative bleeding causative and not only symptomatic.

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RARE BLEEDING DISORDERS

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Deficiencies of coagulation factors such as afibrinogenemia, FII, FV, FV+FVIII, FVII, FX, FXI, FXIII (RBDs), are autosomal recessive diseases with clinical manifestations ranging from mild to severe and representing 3-5% of all the inherited coagulation deficiencies. Their prevalence in the general population varies between 1 in 500.000 and 1 in 2 million for the homozygous forms, being higher in areas where consanguineous marriages are frequent. Data derived by WFH global survey and the International Registry (www.rbdd.org) report that FXI (37%) and FVII (23%) seem to be the most frequent disorders, followed by Fibrinogen and FV deficiency (10%), FX deficiency (9%), FXIII deficiency (6%) and combined FV+FVIII and FII deficiencies (3% and 2%, respectively). RBDs are generally less severe than hemophilias with FX and FXIII deficiencies as exceptions. These deficiencies are characterized by the early onset of life-threatening symptoms such as umbilical cord and central nervous system bleeding. Central nervous system bleeding is a common symptom also in severe FVII deficiency, where, reported in 15-60% of cases, it presents shortly after birth in association with a high morbidity and mortality. Other severe symptoms such as recurrent hemoperitoneum during ovulation, as well as limb-endangering hemarthroses and soft tissue hematomas, occur with higher frequency in patients with FII, FX, and FXIII deficiency than in other rare coagulation disorders. Common to all rare coagulation disorders, is the occurrence of excessive bleeding at the time of invasive procedures such as circumcision and dental extractions. Bleeding in mucosal tracts (particularly epistaxis and menorrhagia) is also a relative frequent feature. The majority of rare coagulation disorders are expressed phenotypically by a parallel reduction of plasma factors as measured by functional assays and immunoassays (so-called type I deficiencies). Qualitative defects, characterized by normal, slightly reduced or increased levels of factor antigen contrasting with much lower or undetectable functional activity (so-called type II deficiencies), are less frequent. Inherited as recessive traits, rare coagulation disorders are due, in most cases, to mutations in the genes that encode the corresponding coagulation factors. Exceptions are the combined deficiencies of FV+FVIII, and of vitamin-K-dependent proteins (FII, FVII, FIX, and FX), caused respectively by mutations in genes encoding proteins involved in the FV and FVIII intracellular transport, and in genes encoding enzymes involved in post-translational modifications and in vitamin K metabolism. Current treatment of patients affected with RBDs is based on both replacement therapy (cryoprecipitates, PCCs and single factor concentrates) and non-transfusional treatment (antifibrinolytics, fibrin glue, oestrogen-progesterone preparations and desmopressin), remaining replacement therapy the backbone of treatment. Despite the existence of several concentrates, there is no FV concentrate available for the treatment of FV deficiency, yet. Moreover since there are few long-term prospective studies on large cohort of patients, reliable information about clinical management is often scarce, limiting the majority of the existing recommendation to grade C deriving from level of evidence III or IV (case studies or expert committee reports). A recent review of the literature underlined more or less 50 reports containing guidelined for RBDs treatment, most of them confirming previous recommendations. Other studies report the use of rFVIIa in different deficiencies (FV, FVII and FXI) even if rFVIIa is approved only for the treatment

of FVII deficiency. In the latter case, reports describing the prophylactic use of rFVIIa (20-40 μg/kg/week) in children or pointing to the reduction of the rFVIIa doses in surgery, were grade C recommendation. In the two grade B reports, authors conclude that on demand policy can be advocated in patients with severe FXI deficiency during vaginal delivery, circumcision, orthopedic surgery and appendicectomy. Nonetheless the available literature on RBDs and the existence of national databases as well as those of individual Centres, born to collect data on affected patients, the information stored is not sufficient and hardly suitable for any statistical analysis in order to draw any clinical, therapeutical or laboratory guidelines. This lacuna could be made up for by the collection and organization of data and by their accurate statistical analysis. Therefore, a European network involving nine European Treatment Centres (Belgium, Denmark, France, Germany, Greece, Ireland, Slovenia, Turkey, UK) and in association with a group of informatic technicians (Alekos) and the Public Health Executive Agency (PHEA) was to set up in 2007. The aim of this project is to develop a network among these Centres in order to increase the available information on RBDs and to develop a homogenous data collection scheme with the purpose of managing and viewing all inserted data and making them readily available through database queries. In the long run it could be important to realise a network accessible to all Centres in Europe able to communicate on a common platform in terms of protocols, languages and computer systems, and once the on-line database will be well established and correctly operating, spread it worldwide with the final aim to draw up guidelines to assist the physician in clinical practice and patient management.

MOLECULAR GENETICS AND BIOLOGY OF CONGENITAL HEMORRHAGIC DISEASES

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Coagulation deficiences causing bleeding are X-linked or autosomally inherited, the latter being the most rare, with an estimated prevalence in the general population from about 1:500,000 (FVII deficiency) to 1:2,000,000 (prothrombin deficiency). Increased frequency of homozygotes is observed in those countries where consanguineous marriages are relatively common. Gene size and specific mutational mechanisms, as C to T transition in CpG sites and illegitimate recombination, shape the frequency of mutations and deficiencies. The molecular genetic defects have been extensively investigated and characterized for frequent and rare coagulation deficiencies. Analysis of gene mutations highlights their extreme heterogeneity with a majority of causative missense changes. The expression of selected mutants is useful to test residual antigen, function or mRNA of coagulation factors, and to evaluate the contribution of mutation to the clinical phenotype. The comparison of FVII deficiency with haemophilia B provides a valuable model for evaluation of mutation spectra in autosomal or X-linked homologous 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 γ-glutamyl carboxylase and 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 p redictors 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.