



## Educational Lectures

### EL1 Von Willebrand Disease

#### EL1-1

##### Mouse models to study von Willebrand Factor structure-function relationships in vivo

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**Objective:** Von Willebrand Factor (VWF) structure-function relationship has been studied only through in vitro approaches. Our aim was to develop a model allowing a subtler analysis of the relative importance of VWF different domains.

**Design and Methods:** We have used the VWF-deficient (VWF<sup>-/-</sup>) mouse model and the hydrodynamic injection technique to obtain mice transiently expressing various VWF mutants. In particular we have introduced point mutations into murine VWF (mVWF) cDNA that inhibit VWF binding to glycoprotein (Gp) Ib (K1362A), to GpIIb/IIIa (D2509G) and to fibrillar collagen (D1742A, S1742A, H1786A). VWF<sup>-/-</sup> mice were injected with wild type (wt) or mutated mVWF plasmid DNA and the effect of these mutations on VWF function in hemostasis and thrombosis was examined.

**Results:** Hydrodynamic gene transfer resulted in high expression of mVWF in plasma. Expression was sustained for 2-3 weeks when a plasmid containing a liver-specific promoter was used. Injection of wt mVWF cDNA in VWF<sup>-/-</sup> mice resulted in correction of bleeding time and restoration of thrombosis after ferric-chloride induced injury. Injection of the GpIb binding mutant resulted in a phenotype very similar to non-injected VWF<sup>-/-</sup> mice. For the GpIIb/IIIa and the collagen binding mutants, although they were able to lead to correction of bleeding time, they did not lead to complete restoration of the thrombotic phenotype.

**Conclusion:** Our model allows the rapid in vivo evaluation of specific mutations on VWF function.

#### EL1-2

##### New guidelines for the diagnosis of von Willebrand Disease

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The classification and diagnosis of von Willebrand Disease (VWD) has traditionally been based on a series of laboratory based phenotypic assays focussed on the quantitative and qualitative assessment of plasma von Willebrand Factor (VWF). These have enabled type 2 VWD (qualitative VWF deficiency) and type 3 VWD (severe VWF deficiency) to be readily diagnosed in many laboratories. The accepted diagnosis of type 1 VWD (reduced plasma levels of normal VWF) has however been recently questioned by the results from large type 1 VWD studies undertaken in Europe and Canada. It is now apparent that type 1 VWD can also include cases where the plasma VWF may contain abnormal subunits when analysed by sensitive multimer profile analysis, but where the ratio of functional activity to antigen level is normal and the proportion of largest multimers are not significantly decreased. The increasing availability of DNA sequencing technology also means that mutation analysis of the VWF gene is allowing for a large number of VWF gene mutations and DNA sequence changes to be detected. The value of mutation analysis in type 2 VWD is accepted. However in type 1 VWD only mutations in the severest forms show high penetrance within affected families. Continuing studies on the nature of mutations and DNA sequence changes in milder forms of type 1 VWD will add to the certainty of VWD diagnosis in these cases.

#### EL1-3

##### Evidence-based treatment of von Willebrand Disease

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The classification and diagnosis of von Willebrand Disease (VWD) has traditionally been based on a series of laboratory based phenotypic assays focussed on the quantitative and qualitative assessment of plasma von Willebrand Factor (VWF). These have enabled type 2 VWD (qualitative VWF deficiency) and type 3 VWD (severe VWF deficiency) to be readily diagnosed in many laboratories. The accepted diagnosis of type 1 VWD (reduced plasma levels of normal VWF) has however been recently questioned by the results from large type 1 VWD studies undertaken in Europe and Canada. It is now apparent that type 1 VWD can also include cases where the plasma VWF may contain abnormal subunits when analysed by sensitive multimer profile analysis, but where the ratio of functional activity to antigen level is normal and the proportion of largest multimers are not significantly decreased. The increasing availability of DNA sequencing technology also means that mutation analysis of the VWF gene is allowing for a large number of VWF gene mutations and DNA sequence changes to be detected. The value of mutation analysis in type 2 VWD is accepted. However in type 1 VWD only mutations in the severest forms show high penetrance within affected families. Continuing studies on the nature of mutations and DNA sequence changes in milder forms of type 1 VWD will add to the certainty of VWD diagnosis in these cases.

### EL2 Old and Novel Players in Coagulation

#### EL2-1

##### Factor XII in hemostasis and thrombosis

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The plasma coagulation system reacts quickly to limit blood loss from sites of injury, but also contributes to vascular thrombosis. In current models of hemostatic balance, normal coagulation and thrombosis represent two sides of the same coin, however recent data from gene-deleted mouse models have challenged this dogma. Deficiency of coagulation factor XII (Hageman factor), a serine protease that initiates the intrinsic pathway of coagulation, severely impairs arterial thrombus formation but is not associated with excessive bleeding. These findings suggest that fibrin-generating mechanisms that operate during pathologic thrombus formation involve pathways distinct from those that are active during normal hemostasis. As factor XII selectively contributes to thrombus formation in occlusive disease, but not to normal hemostasis, inhibition of this protease could be ideal targets for drugs to treat or prevent thromboembolic disease with minimal risk of therapy-associated bleeding.

## EL2-2

**Protein disulfide isomerase (PDI) and its effect on tissue factor (TF) activity**Engelmann B<sup>1</sup><sup>1</sup>Ludwig-Maximilians-University, Munich, Germany

The mechanisms mediating the activation of TF, the physiological starter protein of blood coagulation, are largely unknown. We observed that TF activation by cell lysis required the redox-active Cys186/Cys209 pair. Chemical reduction of the cysteines inhibited the coagulation start, while its oxidation triggered TF activity. Stimulation of circulating TF on microparticles was inhibited by suppression of platelet-secreted PDI, a thiol isomerase normally located in the ER that is also present in platelets. Isolated PDI oxidized TF and increased TF activity in monocytes and microparticles. Mass spectrometry indicated that Cys209 is constitutively conjugated with GSH. TF activity was decreased by experimental glutathionylation suggesting that mixed disulfides at Cys209 result in TF encryption. Cleavage of the glutathione linkage of TF by PDI was associated with intrachain disulfide formation which suggests that PDI activates TF by a modified isomerization reaction. Under in vivo conditions, PDI was specifically exposed at the site of vessel injury. Fibrin formation in vivo as measured by intravital videofluorescence microscopy indicated that PDI inhibition by an anti-PDI antibody decreased fibrin deposition by 60%. A similar decrease was seen in platelet-deficient mice indicating that PDI inhibition directly targets fibrin formation. Infusion of PDI enhanced TF-dependent fibrin formation. A PDI variant lacking its redox-active cysteines failed to increase TF activity in vitro and fibrin generation in vivo. Our results suggest that the thiol isomerase PDI represents an injury response signal that stimulates blood coagulation via a new posttranslational mechanism of TF activation.

## EL2-3

**Physiological and pathological role of Factor VII-Activating Protease (FSAP)**Preissner K<sup>1</sup>, Kanse S<sup>1</sup><sup>1</sup>Depart. Biochemistry, Medical School, Justus-Liebig-Universität, Giessen, Germany

Factor VII-activating protease (FSAP) is a novel liver-derived plasma serine protease structurally homologous to plasminogen activators. Based on its properties to activate coagulation factor VII as well as pro-urokinase (pro-uPA), a potential role for FSAP in the regulation of haemostatic proteases is postulated. Moreover, FSAP is a potent inhibitor of vascular smooth muscle cell proliferation and migration in vitro and local application of FSAP in animal models reduces neointima formation. In clinical studies, the G534E single nucleotide polymorphism (Marburg I) of FSAP has been linked to late complications of atherosclerosis and is associated with a low proteolytic activity, particularly towards pro-uPA. In this regard, localization of FSAP to unstable atherosclerotic plaques may contribute to plaque instability. (Auto-)activation of pro-FSAP is provoked by polyanions such as RNA or polyphosphates that are described to promote procoagulant reactions as well. Different protease inhibitors control the activity of FSAP, thereby playing an important role in the balance of FSAP humoral and cellular activities. Together, under various pathophysiological conditions, particularly in the cardio-pulmonary system, FSAP contributes to tissue remodeling and control of cell proliferation based on its specific proteolytic functions.

## EL3 New Antithrombotics in Acute Coronary Syndrome

## EL3-3

**New Antithrombotics in Acute Coronary Syndrome: Prasugrel**Schrör K<sup>1</sup><sup>1</sup>Institut für Pharmakologie und Klinische Pharmakologie, Universitätsklinikum Düsseldorf, Heinrich-Heine-Universität, Germany

Prasugrel is a new thienopyridine-type antiplatelet agent. Like other thienopyridines prasugrel also blocks irreversibly the P2Y<sub>12</sub> receptor at the platelet membrane. This antagonizes the G<sub>i</sub>-mediated ADP-induced platelet secretion and -aggregation. Prasugrel does not modify the platelet shape change and other G<sub>q</sub>-mediated mechanisms of platelet activation.

Prasugrel is also an inactive prodrug. The active metabolite is generated in vivo by two sequential bioactivation steps: (intestinal) carboxyesterase and the hepatic P450 monooxygenase system. The carboxyesterase step in prasugrel metabolism does not result in a dominating generation of an inactive final metabolite as in case of clopidogrel (SR26334) but generates the precursor thiolactone from which the active metabolite can be formed. Thus, bioactivation of prasugrel involves only one cytochrome-dependent activation step. This possibly explains the more potent and less variable action of prasugrel in comparison to clopidogrel in vivo, because the active metabolites of prasugrel and clopidogrel are equipotent in vitro. The most important cytochromes involved in prasugrel bioactivation are: CYP2C19/9, CYP3A4/5, CYP2B6. There is little evidence for a clinically relevant interaction

of these cytochromes with prasugrel bioactivation, again in contrast to clopidogrel.

Available clinical trials, in particular the TRITON/TRIMI-38 study, confirm a stronger antiplatelet action and efficacy of prasugrel (60 mg/LD/10 mg MD) vs. clopidogrel (300 mg LD/75 mg MD). However, there was a stronger bleeding tendency, in particular in patients at elevated risk (previous cerebrovascular event or TIA, low body weight, older age). Prasugrel was also more effective in diabetics where no increased bleeding was seen. Improved clinical efficacy was also obtained with prasugrel in preventing in-stent-thrombosis. The final clinical position of prasugrel still needs to be defined.

## EL4 Evidence-Based Antithrombotic Therapy in Children

## EL4-2

**Antithrombotic therapy in children with venous thromboembolism**Yang J<sup>1</sup>, Paredes N<sup>1,2</sup>, Chan A<sup>1,2</sup><sup>1</sup>McMaster University, Department of Pediatrics, Hamilton, Canada, <sup>2</sup>Henderson Research Centre, Hamilton, Canada

Antithrombotic therapy has recently become more frequent for the treatment of venous thromboembolism (VTE) in the pediatric population. This can be explained by the increased awareness of morbidities and mortalities of VTE in children, as well as the improved survival rate of children with various kinds of serious illnesses. Considering the large number of years a child is expected to survive, associated morbidities such as post-thrombotic syndrome and risk of recurrence can significantly impact on the quality of life in children. Therefore, timely diagnosis, evidence-based treatment and prophylaxis strategies are critical to avoid such complications. The purpose of this review is to summarize the current available literature about the antithrombotic treatment for VTE in infants and children, and to guide the pediatric medical care provider for making a logical and justifiable decision for their patients.

## EL4-3

**Pediatric stroke: who should be treated?**DeVeber G<sup>1</sup><sup>1</sup>Hospital for Sick Children, Toronto, Canada

The past decade has seen a dramatic increase in pediatric stroke research. Cohort and case-control studies are clarifying the mechanisms and outcome, however few studies have addressed antithrombotic safety or effectiveness. Three evidence-based guidelines published in the past 5 years have combined accumulating research data with expert consensus to provide recommendations assisting the clinician in selecting therapies for the different sub-types of stroke. The scope, methodology and authorship varies somewhat across these guidelines. Reflecting a paucity of clinical trials, some recommendations disagree. However, for the majority of patients with pediatric ischemic stroke treatment recommendations are consistent. Newborns with arterial ischemic stroke (AIS) without congenital heart disease rarely require antithrombotic treatment given their extremely low (<5%) risk of recurrent stroke. In children with AIS recurrence risk approaches 50% with no antithrombotic treatment. Therefore, antithrombotic treatment is required unless contraindicated. Anticoagulation (heparins, warfarin) is recommended for possible or established dissection and cardiogenic embolism. Antiplatelet treatment (aspirin, 2 - 5 mg/kg/day) is recommended for children with other underlying causes. For neonatal cerebral sinovenous thrombosis (CSVT) most centres provide initial anticoagulation in the absence of hemorrhagic contraindications, and if not, monitor for propagation. Children receive anticoagulation for CSVT more consistently, even in the presence of hemorrhagic venous infarction, modeling the approach in adult CSVT. Access to specialized care further supports decision-making in individual cases. While more studies are necessary, current treatment guidelines offer an interim option to maximize standardized care for pediatric stroke. deVeber G, Kirkham F. *Lancet Neurol*. 2008 Nov;7(11):983-5.

## EL5 Hot Topics in Anticoagulation

## EL5-1

**Thrombosis prophylaxis in patients with ischemic (cardioembolic) stroke – How long is long enough?**Krishnamoorthy S<sup>1</sup>, Lip G<sup>1</sup><sup>1</sup>City Hospital, University Department of Medicine, Birmingham, England, UK

Cardioembolism accounts for approximately 20% of all ischemic strokes, and is associated with high mortality and propensity to recurrences. Approximately 30%



of all ischemic strokes remain 'cryptogenic' despite improved imaging modalities and technological improvements to identify the cause. Of the long list of various cardiac conditions associated with an increased risk of cardioembolic strokes, non-valvular atrial fibrillation is the most common cause. Unsurprisingly, the stroke risk associated with these conditions is highly variable and non-homogenous, with many risk factors additive to the overall risk profile. Treatment with oral anticoagulation substantially reduces the long-term complications associated with cardioembolism in some high-risk patients, for example, in atrial fibrillation. Careful selection of antithrombotic drug regime needs to be carried out in patients individually to minimise the risk of bleeding encountered with such therapy. Apart from atrial fibrillation, there is relatively limited evidence for the role of antithrombotic therapy for other cardiac conditions associated with cardioembolism and how long one should treat.

## EL6 Peripheral Arterial Occlusive Disease (PAOD)

### EL6-1

#### From Doppler to Duplex and MRA: when to use which diagnostic method?

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In developed countries up to a fifth of the population over the age of 60 has lower limb peripheral arterial disease (PAD), as defined by an ankle brachial pressure index (ABI) below 0.9. About a quarter of these people have symptoms, most commonly intermittent claudication (IC). Patients with life-limiting IC or severe limb ischemia (CLI) undergo imaging with a view to open surgical or endovascular intervention. The purpose of imaging is to assess the anatomical location, morphology and extent of disease in order to determine suitability for intervention. Major technical advances have been made in recent years in the development of non-invasive imaging modalities. The imaging test should be carefully chosen, in an evidence based manner, so as to maximise the quality and relevance of information obtained, minimise the risk and inconvenience to the patient, and make the best use of limited resources. Unfortunately there is a paucity of high quality trials on the new and evolving techniques particularly in relation to determining the accuracy of duplex ultrasound (DUS), magnetic resonance angiography (MRA) and computed tomography angiography (CTA) in the investigation of PAD. The available data, supported by everyday clinical experience, suggest that DUS is the only imaging test needed in most patients. If ultrasound is not sufficient, then magnetic resonance angiography rather than computed tomographic angiography represents a suitable diagnostic tool because it is more versatile, more accurate, is not as affected by arterial calcification and does not involve exposing patients to ionising radiation.

### EL6-2

#### Optimal medical treatment for PAD patients

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Patients with peripheral artery disease frequently suffer from generalized atherosclerosis, and coincident coronary artery and cerebrovascular disease determine patients' prognosis. Therapeutic goals in PAD patients therefore are improvement of symptoms and preservation of the affected extremities as well as effective risk reduction for coronary and cerebrovascular events. Optimal pharmacotherapy - unless contraindicated for other reasons - includes in all PAD patients anti-thrombotic therapy (usually anti-platelet medication like aspirin or clopidogrel) and statins irrespective of patients' cholesterol levels. For hypertension control ACE-inhibitors, angiotensin receptor blockers and beta-blockers are the preferred first-line drugs, mainly considering the high probability of (asymptomatic) coincident coronary artery disease and the pleiotropic side effects of these drugs. Tight glycemic control should be anticipated, as yet however, no drug has been proven superior to others in the PAD population. Targeting walking capacity in patients with intermittent claudication, cilostazol has proven most effective. Unfortunately, the drug is not available all across Europe. Buflomedil, as a less effective alternative, also showed beneficial effects in a recent randomized trial. In patients with critical limb ischemia, intravenous prostanoids are considered beneficial in addition to revascularisation as well as in patients which cannot be revascularized.

### EL6-3

#### Critical limb ischemia

Minar E<sup>1</sup>

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Critical limb ischemia (CLI) is a manifestation of peripheral arterial disease (PAD) that describes patients with chronic ischemic rest pain, or patients with ischemic

skin lesions, either ulcers or gangrene. The clinical diagnosis of CLI should be confirmed by hemodynamic parameters such as the ankle- or toe systolic pressure. The estimated annual incidence of CLI ranges between 500 and 1000 new cases per 1 million, with diabetes being the most important risk factor. The presence of CLI is also a marker for mostly generalized and severe atherosclerosis, and therefore the prognosis of patients is poor concerning overall survival. The primary goals of treatment in patients with CLI are to relieve ischemic pain, heal ulcers, prevent limb loss, improve patient function and quality of life and prolong overall survival. Any kind of revascularization should be done whenever technically possible, and therefore most patients should be referred to a vascular center. Furthermore, in patients with CLI a multidisciplinary approach is recommended to control pain, cardiovascular risk factors and other co-morbid disease. In patients with CLI not eligible for arterial revascularization, prostanoids are the only vasoactive drugs with proven efficacy. The safety and efficacy of the various forms of therapeutic angiogenesis still have to be proven before one can conclude on its role as an additional limb saving strategy.

## EL7 Carriers of Hemophilia

### EL7-1

#### Clinical phenotype of female carriers of the hemophilia gene

Mausier-Bunschoten E<sup>1</sup>

<sup>1</sup>Van Creveldklinik Department of Haematology, University Medical Centre Utrecht, The Netherlands

Summary Haemophilia A and B are inherited as X-linked recessive disorders. Since women have two X chromosomes, they are most often heterozygote carriers. Most carriers have adequate levels of clotting FVIII (in haemophilia A) or FIX (in case of haemophilia B). Their mean clotting factor level is 50 % of normal. However, clotting factor levels vary from <1 % to > 150 %, due to lyonization. Carriers with clotting factor levels of less than 60 % of normal may have an increased bleeding tendency. Occurrence of symptoms correlates very closely with plasma concentration of FVIII or FIX. In most cases, clinical symptoms are comparable to those in mild haemophilia, except the carrier may have excessive bleeding during menstruation and after delivery. When FVIII or FIX levels are <20 % of normal, carriers show a 50 % bleeding risk after surgery, tooth extraction or tonsillectomy. In some cases, infusion of clotting factor concentrate or a second operation is required to control bleeding. Recommendations Since 50 % of carriers of haemophilia may have decreased clotting factor levels, and thus are at risk for bleeding tendency, it is important to measure clotting factor levels in all carriers, whether obligatory, proven or possible carriers. As medical interventions and trauma may happen at any age, clotting factor levels should be measured early in life. When a FVIII or FIX level of less than 60 % is found, a carrier should be considered and treated as a (mild) haemophilia patient. Carriers with clotting factor levels of less than 30 % should be regularly seen at a haemophilia treatment centre. Clotting factor replacement is indicated in case of bleeding, trauma and surgery. Carriers with menorrhagia should be treated with tranexamic acid. When this is not sufficient, OC or other hormonal therapy can be prescribed. In persistent menorrhagia, clotting factor correction is indicated.

### EL7-2

#### The impact of genetic alterations on the clinical phenotype

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The understanding of the pathology of haemophilia A and cloning and sequencing of the gene has laid the ground for diagnosis of patients and their female relatives at molecular level. An association between the type of mutations in the factor 8 gene and factor VIII levels could be demonstrated in haemophilia A patients. Such a relation has not been documented in female carriers of haemophilia A. We could show that no statistically significant association between the mutation in the F8 gene and FVIII coagulation activity exists in female carriers. Even females with an inversion in intron 22 can have factor VIII activity in the normal range. Thus, it is reasonable to assume that other factors such as unbalanced inactivation of the X-chromosome, epigenetic modifications of the factor 8 gene, or modifications in other genes influence factor VIII activity in carriers. Previously, skewed X-chromosome inactivation has been demonstrated in single cases of females with low factor VIII activity. Recently, discordant FVIII levels found in monozygotic twins were shown to be due to non-random X-inactivation. Analyses of the human androgen receptor locus in 41 carriers of haemophilia A indicated that non-random X-inactivation is frequent (31 % women exhibited a skewed XCI with X-chromosome ratios of 1 to 3 or higher), and extreme skewing influenced factor VIII concentrations. Interestingly, an association of the genotype of methylenetetrahydrofolate

reductase (MTHFR), an enzyme participating in the methylation process, with factor VIII levels was found. This may indicate that MTHFR is involved in the methylation process of the F8 gene.

### EL7-3

#### Carriers of Hemophilia: Counselling and clinical implications

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In early childhood all potential carriers in haemophilia families should be offered determination of FVIII and FIXC concentrations in order to diagnose those who have a very low concentration and subsequently may manifest a mild to moderate bleeding disorder. When the potential carrier is a teenager the possibility of her being a carrier should be brought to her attention and she should be offered genotype assessment. Her knowledge of haemophilia, ethnic and religious background as well as her own and the family's perception of her being a carrier are factors that may influence her desire to undergo carrier testing at this age. It is important to give the adult woman and her spouse information and counselling before a planned pregnancy. In this situation, the aim is to provide adequate information on the disease and the haemophilic's situation in the country in question, diagnostic procedures, accuracy and limitations of the tests and finally the options in their own situation. Basic analysis of a potential carrier includes calculation of the probability, or odds, for carriership based on pedigree and clotting factor analysis. The genetic diagnosis of haemophilia should be based on the direct identification of the pathogenic mutation in the F8/9 genes. Neutral mutations and the risk of mosaicism in sporadic families may cause misclassification. Potential carriers of haemophilia should be offered qualified assistance in genetic information, testing and counselling to help them to cope with the psychological and ethical problems related to carriership of a genetic disorder.

### EL8 Coagulation Testing Prior to and During Surgery

#### EL8-1

##### Hemostatic testing prior to elective surgery – yes

Albert F<sup>1</sup>, Eichler H<sup>2</sup>, Haubelt H<sup>3</sup>, Loreth R<sup>1</sup>, Matzdorff A<sup>4</sup>, Peetz D<sup>5</sup>, Pindur G<sup>2</sup>, Schinzel H<sup>5</sup>, Seyfer U<sup>6</sup>, Hellstern P<sup>3</sup>

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Hemorrhagic disorders must be excluded prior to any operation or other invasive procedure that has the potential to involve serious bleeding. When assessing the individual risk of bleeding, screening tests of hemostasis must be combined with the patient's clinical history and symptoms, and any history of bleeding must be explored under direct medical supervision using a standardized questionnaire. However, this bleeding history is neither very specific, nor is it particularly sensitive. Screening tests that have been found to be useful include platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT) and clottable fibrinogen. No reliable, sensitive and specific screening test is however available today to screen for platelet dysfunction or von Willebrand disease. A specialized coagulation laboratory should be involved when the bleeding history or laboratory screening indicate a potential hemorrhagic disorder.

#### EL8-2

##### Hemostatic testing prior to elective surgery – NO

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In Germany preoperative coagulation tests are commonly used, based on the belief that these tests should identify patients with an increased bleeding risk. But published evidence does not longer support this approach for both traditional screening tests and novel techniques for global assessment of hemostasis. Unselected screening yields many false positive results and detects irrelevant disorders. It leads to postponement of surgery, anxiety in parents and patients, and is not cost effective. Even worse, it does not reliably detect relevant bleeding disorders such as the most common coagulopathy, von Willebrand disease. The history of a patient and his/her relatives is a more important tool to detect patients at risk. According to international guidelines and a joint statement of different German medical societies, a standardized questionnaire should be mandatory in preoperative screening. A diagnostic pathway should be employed to identify patients in which specific

laboratory tests are necessary. Because neither laboratory tests nor questionnaires can infallibly predict or exclude bleeding, instructions for the postoperative period and the management of unexpected or excessive bleeding have to be established.

### EL8-3

#### Point of care testing during surgery – YES

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Clinicians should aim to minimize empiric hemostatic intervention and indiscriminate transfusion (blood-sparing medicine). Appropriate use of procoagulant agents depends on the clinical judgment and the results of timely coagulation data. Especially rotational thrombelastometry (ROTEM) with a battery of test kits (EXTEM, INTEM, APTEM, FIBTEM, HEPTEM) permit rapid and accurate differential diagnosis of coagulopathy as a point-of-care (POC) monitoring (1). Means of intraoperative POC-platelet function testing have also become available (e.g. multiple electrode aggregometry). Because of the multifactorial nature of bleeding in major surgery and trauma, POC-guided algorithms should support the clinician's discretion, and have repeatedly and uniformly been found to reduce transfusion requirements in both routine and high-risk major surgery (evidence-based medicine). If POC methods help to minimize direct costs of blood products, avoid costly adverse effects of transfusion, shorten surgical procedures, frequency of re-openings, and intensive care stay, they have a massive potential for significant cost savings. Limitations of POC tests such as handling mistakes by anesthesiologists may be overcome by ongoing quality control, training, and user meetings. Routine coagulation tests performed at the central laboratory have a long turn-around time, lack relevant pathophysiological information in massive bleeding and cannot guide intraoperative coagulation therapy adequately, are costly and have several methodological limitations. However, routine coagulation tests are the basis for perioperative evaluation of static coagulation disorders. In summary, POC-testing should be regarded as the gold standard of individualized coagulation diagnosis for tailored therapy in the intraoperative setting. 1) *Minerva Anestesiol* 2007;73:401-15

### EL9 Treatment of ITP

#### EL9-1

##### Natural course of immunthrombocytopenia

Imbach P<sup>1</sup>

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Few population based or patient-based registries and no controlled studies are available on the natural course of immunthrombocytopenia ITP. The incidence of newly diagnosed ITP is 5,6-6,6:100'000 adults and 4,8-7,3:100'000 children. The follow-up with or without treatment in the Intercontinental Cooperative ITP Registry I (n=2031) recognized 32% persistence of ITP at 6 months, from which (n=308) 25,8% recovered within 6-12 months, and 11% continued to have platelet counts below 20K at 12 months. In adults a population based analysis of patients 2 years after diagnosis of ITP showed 59% recovery, 21% moderate, 8% severe ITP, 8% secondary ITP and 4 patients died. From a pooled analysis of 17 clinical case series (n=1817 adults) 49 patients had fatal hemorrhage with an age adjusted risk of 0,004, 0,012 and 0,13 per year for age groups younger than 40, 40-60 and over 60 years, respectively. The predicted 5 years lethality rates ranged from 2,2% to 47,8% in the three age groups. These numbers may document the need of evidence based data concerning patients' management, health related quality of life, morbidity, risk of severe bleeding or of postsplenectomy infection and economic aspects. As a first step registries with longterm observation of children and adults are needed (eg. PARC ITP, see [www.unibas.ch/itpbasel](http://www.unibas.ch/itpbasel)). The unknown etiology of ITP should be further studied, such as by genetic analyses.

#### EL9-2

##### Acute ITP – to treat or not to treat

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Paediatric ITP is usually self-limiting, with 70-80% complete remission within 8 weeks. In adults ITP is usually chronic, and may be complicated by other pathology predisposing to bleeding. Despite low counts serious bleeding is rare (in children 3-5% in several studies). More than 80% of children have mild clinical manifestations (cutaneous signs and minor mucosal bleeding alone). Intracranial haemorrhage is rare at all ages, is unpredictable and can occur at any time during the illness usually when the count is very low. 'Wet purpura' is not predictive of more serious bleeding. Pharmacological therapies at all ages are associated with significant side



effects and occasional deaths. Treatment may interfere with quality of life more than the illness itself. Drug therapy can be withheld in the majority of children with appropriate education of the child and family. Pharmacological intervention should be individualised, taking into account the person's needs and lifestyle as well as bleeding. Antifibrinolytic agents benefit mucosal bleeding. Similarly, in chronic ITP, many need no active pharmacotherapy. Adults are more complex but those with a platelet count above  $20 \times 10^9/l$  often need no treatment since bleeding is rare, and those adults with refractory ITP live with very low counts for years with no significant bleeding suggesting the need to re-evaluate the balance of risks of treatment vs bleeding. It is notable that more adults with ITP die from infection, probably related to therapy, than from bleeding.

#### EL9-3

##### Chronic ITP – new agents

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First generation thrombopoietic growth factors (rhTPO and PEG-rHuMGDF), investigated in late '90s, proved effective in increasing platelet count in normals, in thrombocytopenia due to chemotherapy and also in a few cases of immune thrombocytopenic purpura (ITP). Clinical development was stopped since one of them induced antibodies in the recipients that cross reacted with endogenous thrombopoietin (eTPO). New generation of thrombopoietic growth factors with no sequence homology with eTPO were constructed with ingenious techniques. Of them, romiplostim, a peptibody, was recently approved for clinical use in USA and eltrombopag, a non-peptide, orally active small molecule is expected to be approved shortly. Both agents were able to predictably increase platelet count in normal volunteers and in patients with ITP. With appropriate dosages (1–10 µg/kg /kg weekly subcutaneously for romiplostim; 50–75 mg/die per os for eltrombopag) platelets increase significantly after 7–10 days. By discontinuing treatment, platelet count returns to baseline level in 10–15 days. The response rate is above 70–80 %, also in patients that had undergone several lines of treatment, including or not splenectomy. Due to the lack of a curative potential and to the incomplete knowledge of long-term side effects, the place of these new drugs in the management of ITP is still unsettled and their use is best restricted to refractory patients or in preparation of splenectomy.