ILLUSTRATED REVIEW

Illustrated State-of-the-Art Capsules of the ISTH 2021 Congress

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Abstract
This year’s Congress of the International Society of Thrombosis and Haemostasis (ISTH) was hosted virtually from Philadelphia July 17–21, 2021. The conference, now held annually, highlighted cutting-edge advances in basic, population and clinical sciences of relevance to the Society. Despite being held virtually, the 2021 congress was of the same scope and quality as an annual meeting held in person. An added feature of the program is that talks streamed at the designated times will then be available online for asynchronous viewing. The program included 77 State of the Art (SOA) talks, thematically grouped in 28 sessions, given by internationally recognized leaders in the field. The SOA speakers were invited to prepare brief illustrated reviews of their talks that were peer reviewed and are included in this article. The topics, across the main scientific themes of the congress, include Arterial Thromboembolism, Coagulation and Natural Anticoagulants, COVID-19 and Coagulation, Diagnostics and Omics, Fibrinogen, Fibrinolysis and Proteolysis, Hemophilia and Rare Bleeding Disorders, Hemostasis in Cancer, Inflammation and Immunity, Pediatrics, Platelet Disorders, von Willebrand Disease and Thrombotic Angiopathies, Platelets and Megakaryocytes, Vascular Biology, Venous Thromboembolism and Women’s Health. These illustrated capsules highlight the major scientific advances with potential to impact clinical practice. Readers are invited to take advantage of the excellent educational resource provided by these illustrated capsules. They are also encouraged to use the image in social media to draw attention to the high quality and impact of the science presented at the congress.
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Anticoagulant Therapy for Splanchnic Vein Thrombosis: Summary of Suggested Treatment Strategies

(Adapted from Di Nisio et al JTH 2020)

Cirrhotic patients

Initial management: Therapeutic dose LMWH
Primary treatment: Switch to VKAs or DOACs (depending on severity of liver dysfunction)
Remarks: Consider early variceal screening and prophylaxis of high-risk varices
Duration: at least 3 to 6 months, consider indefinite if bleeding risk acceptable

Cancer patients

Initial management and primary treatment: LMWH or DOACs.
Remarks: LMWH first choice in patients with endoluminal gastrointestinal cancer or genitourinary cancer at high bleeding risk. Apixaban possible alternative for primary treatment
Duration: at least 3 to 6 months. Consider indefinite if active cancer and low bleeding risk

Other patients

Initial management and primary treatment: DOACs
Remarks: LMWH and VKAs if contraindications to or unavailability of DOACs. DOACs are not specifically approved for splanchnic vein thrombosis
Duration: 3 to 6 months. Consider indefinite if unprovoked or persistent risk factors and low bleeding risk

For references, see Di Nisio et al.¹
Venous thromboprophylaxis in the intensive care unit

Yaseen Arabi MD

Prevention of venous thromboembolism in critically ill patients involves multi-modality approach. A systematic review of randomized controlled trials (RCTs) demonstrated that early mobilization in critically ill patients was associated with a significant reduction in deep vein thrombosis (DVT) (RR 0.16, 95% CI 0.06, 0.47). Avoidance of unnecessary use of central venous catheters, especially in the femoral vein, is an important aspect of DVT preventive strategy. One RCT found that subclavian compared to femoral venous catheterization in critically ill patients was associated with a significant reduction in catheter-related thrombosis documented by ultrasonographic examination (RR 0.09, 95% CI 0.02, 0.36). Pharmacologic thromboprophylaxis with unfractionated or low-molecular-weight heparin, compared to no thromboprophylaxis, also reduces the incidence of DVT (RR 0.51, 95% CI 0.41, 0.63). Data on the effectiveness of pneumatic review that included observational studies demonstrated lower DVT with intermittent pneumatic compression (RR 0.34, 95% CI 0.19, 0.60).
Myeloproliferative neoplasm-associated thrombosis

Tiziano Barbui

For references, see Barbui et al., Tefferi et al., and De Stefano et al.
Venous thrombo-embolism; risk in premenopausal women: Questions still unanswered

Suzanne Cannegieter MD PhD

VTE: Venous thrombo-embolism; PCOS: Polycystic ovary syndrome

For references, see Samuelsson et al, Scheres et al, and Roach et al.
Venous thromboembolism (VTE) is associated with significant morbidity, mortality and healthcare utilization among ambulatory patients with cancer initiating systemic chemotherapy. Direct oral anticoagulants and low molecular weight heparins have been shown to be safe and effective to prevent cancer-associated thrombosis in this patient population. Hence, the use of primary thromboprophylaxis should be considered to decrease the risk of VTE and tailored to minimize the risk of bleeding. Patients should be educated about signs and symptoms of cancer-associated thrombosis and stratified according to their underlying risk of VTE and bleeding for potential consideration of primary thromboprophylaxis. Multidisciplinary approaches (nurses, pharmacists and physicians) are successful models for primary thromboprophylaxis implementation in ambulatory patients with cancer initiating systemic chemotherapy.

DOAC: Direct oral anticoagulants; KS: Khorana Score; LMWH: Low molecular weight heparin; VTE: Venous thromboembolism.
Molecular analysis of vascular gene expression

Audrey C. Cleuren

Vascular heterogeneity, particularly in the endothelial cell (EC) compartment, has long been recognized yet difficult to study given the poor accessibility of these cells. (A) The Ribotag mouse model\textsuperscript{14} enables evaluation of gene expression profiles directly in vivo in a cell-specific manner via translating ribosome affinity purification (TRAP). (B) EC-TRAP combined with high-throughput RNA sequencing provides an accurate in vivo snapshot of organ-specific endothelial gene expression programs. In addition to the extensive EC heterogeneity across organs under physiologic conditions shown here, our data also showed vascular bed-specific EC reactivity after lipopolysaccharide-induced endotoxemia (ref\textsuperscript{15}).
Hemostatic management of postpartum hemorrhage

Peter Collins

Hemostatic management of postpartum hemorrhage
Peter Collins MD

Postpartum hemorrhage (PPH) is caused by obstetric complications but may be exacerbated by impaired hemostasis. Hypofibrinogenemia is the commonest coagulopathy associated with PPH and occurs early in abruptions and amniotic fluid embolism. Depletion of other coagulation factors, thrombin generation and platelets is uncommon until large bleeds have occurred.16

Early hypofibrinogenemia predicts progression to severe hemorrhage, however, laboratory Clauss fibrinogen is usually too slow to be clinically useful during rapid bleeding. Point-of-care viscoelastometric hemostatic assays (VHA) allow surrogate measurement of fibrinogen and predict severe outcomes.17 A double blind RCT showed that fibrinogen >2 g/L is adequate for hemostasis during PPH.18

An all Wales quality improvement programme involving 60,000 deliveries combined accurate measurement of blood loss with VHAs to guide early fibrinogen replacement. It was associated with reduced massive PPH (≥2500 ml) by 23%, decreased red cell and FFP transfusion by 22% and 58%, respectively and reduced severe anemia (Hb <80 g/L) by 33%.
Mechanistic insights from 3-D visualization of thrombus formation in cancer

Laurence Panicot-Dubois

For references, see Carminita et al.¹⁹ and Palacios-Acedo et al.²⁰
Platelets: Influenza and other viral responses

Jane E. Freedman, MD

Growing mechanistic and clinical data demonstrate that platelets perform various immune functions during infection. A platelet can form heterotypic aggregates with various types of immune cells including monocytes, neutrophils, eosinophils, and dendritic cells. Platelets participate in innate and adaptive immunity and act as immune cells during viral infections. Platelets may internalize ssRNA viruses including influenza, HIV, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and encephalomyocarditis. For some viruses, this internalization leads to lysosomal degradation of the viral coat and activation of the pathogen-associated molecular pattern receptor, TLR7 (Toll-like receptor 7). Activation of TLR7 by influenza also results in C3 (complement 3) release from platelets that leads to complement cascade activation and release of neutrophil DNA which can contribute to aggregates.
More than 60 genes have already been discovered as cause of an inherited platelet disorder (IPD). Many of these genes are widely expressed and are associated with broader clinical symptoms than causing solely a bleeding tendency. In this presentation examples will be discussed on how next generation sequencing has proven successful with its implementation in clinical diagnostics and gene discovery. Still at least half of the IPD patients receive no genetic diagnosis. Ideas will be put forward on how to tackle the challenges ahead that include discoveries in the non-coding genome space and setting up improved disease models for IPD that will allow (automated) deep phenotyping.
Functional disulfide bonds in hemostasis and thrombosis

Philip Hogg PhD

Traditional view of coagulation proteins
- a single disulfide-bonded or covalent form

New view
- multiple disulfide-bonded or covalent forms

Perturbation of the mix of the covalent forms of coagulation proteins could tip the balance between bleeding and clotting in individuals and underlie some hereditary or acquired thrombophilias

For references, see Butera and Hogg,\textsuperscript{24} Hogg\textsuperscript{25}
Disparities in pregnancy outcomes: Differences by condition and community

Andra H. James MD

Maternal mortality per 100,000 live births

<table>
<thead>
<tr>
<th>Region</th>
<th>Maternal Mortality</th>
</tr>
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<tbody>
<tr>
<td>South Asia</td>
<td>200</td>
</tr>
<tr>
<td>East Asia/Pacific</td>
<td>150</td>
</tr>
<tr>
<td>Eastern Europe/Central Asia</td>
<td>100</td>
</tr>
<tr>
<td>Western Europe</td>
<td>50</td>
</tr>
<tr>
<td>North America</td>
<td>10</td>
</tr>
<tr>
<td>Latin American/Caribbean</td>
<td>5</td>
</tr>
<tr>
<td>Middle East/North Africa</td>
<td>2</td>
</tr>
<tr>
<td>Eastern/Southern Africa</td>
<td>1</td>
</tr>
<tr>
<td>West/Central Africa</td>
<td>0</td>
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</tbody>
</table>

Global causes of maternal death

- Hemorrhage: 27%
- Maternal HTN: 14%
- Sepsis: 11%
- Embolism: 3%
- Abortion: 8%
- Other med/surg: 27%
- Other obstetric: 10%

Blood donations per 1000 population by countries’ income: a measure of blood availability

Both the maternal and fetal outcomes of pregnancy vary according to a pregnant woman’s community and her condition. The most devastating outcome is the death of a month. On 2017, there were approximately 295,000 maternal deaths with dramatic differences in maternal mortality based on the region of the world, the country, and women’s underlying conditions. Worldwide, the leading cause of maternal death is hemorrhage. Ninety-nine percent of maternal deaths and 99% of those due to hemorrhage occur in low- or middle-income countries. Whether a hemorrhage originates from inside the uterus (80%), from laceration or incisions (20%), or from an underlying coagulopathy (less than 1%), and acute acquired coagulopathy will evolve unless the hemorrhage is not available, because besides the usual obstetric measures, blood, hemostatic medication and hematologic expertise are necessary to save mothers’ lives.
Specificity of ADAMTS13 and regulation of ADAMTS13 function

Colin A. Kretz
Women are disproportionately impacted by Von Willebrand disease (VWD) due to gynaecological bleeding. Heavy menstrual bleeding (HMB) is the most frequently reported and highest scoring bleeding symptom for women with VWD yet optimal treatment strategies remain uncertain. In pregnancy, there remains controversy regarding the ideal therapeutic plasma Von Willebrand factor (VWF) target at delivery. While thresholds similar to surgery are often utilized, this approach fails to account for the physiological pregnancy-induced increase in plasma Von Willebrand factor (VWF) levels, with median plasma VWF levels >200–250 IU/dl in healthy women at delivery. The limitations of current approaches for women with VWD are reflected in primary postpartum haemorrhage (PPH) rates, which remain increased even when replacement therapy is used.

Postpartum, as plasma VWF levels return, to baseline women with VWD are at a markedly increased risk of secondary PPH following discharge. As women with VWD may be normalized to HMB, recognition of secondary PPH may be delayed or missed.
The impact of aging and inflammation on plasma Von Willebrand factor levels

Frank W.G. Leebeek

In the general population Von Willebrand factor (VWF) levels rise with aging, especially above the age of 40. As is shown in the figure, several mechanisms have been suggested to be responsible for this increase. This may be increased release of VWF from the endothelium, or decreased VWF clearance. Mechanisms contributing to increase of VWF are endothelial dysfunction, comorbidities (hypertension, diabetes), weight gain, atherosclerosis and inflammation. This age-related increase is also observed in patients with type 1 Von Willebrand disease (VWD) and may result in (near) normal levels in elderly VWD patients. It is still disputed whether this rise is associated with attenuation of the bleeding tendency. Results of an observational study on bleeding symptoms over one year have shown that bleeding was not reduced in type 1 VWD patients above the age of 65 compared to those <65 years, however prospective data are still lacking.
The catalytic cycle of vitamin K epoxide reductase (VKOR) and inhibition by vitamin K antagonists are accompanied with redox-state and conformation changes. The hemisphere (pink) and cylinder (grey) illustrate VKOR luminal and transmembrane domain, respectively. VKOR reduces vitamin K epoxide (KO) to quinone (K) and then to hydroquinone (KH2). A catalytic cysteine forms covalent and charge-transfer complex with KO and K, generating mercapto adducts of 3-hydroxyl K (S-KOH) and K (S-KH), respectively. Their binding induces a closed conformation that juxtaposes all cysteines (SH or S-S) for unimpeded electron transfer to reduce the mercapto adduct. VKOR becomes fully oxidized and changes to an open conformation that releases the reaction product. Warfarin competes with the substrates for the partially-oxidized enzyme. Unlike the substrates, warfarin binds also to the fully-oxidized enzyme and removes it from the enzyme pool. The bound warfarin locks HsVKOR in both redox states into a closed conformation.35-37
Pathogenic factor XII mutations: Form determines dysfunction

Coen Maas
Platelet vesicles communicate with the bone marrow during inflammation

Kellie Machlus PhD

During inflammation, platelets are activated and release extracellular vesicles (EVs). These EVs enter the bone marrow (BM), where they bind to resident BM cells including megakaryocytes (MKs). These plasma-originating EVs help communicate changes in the circulation directly into the BM, and may contribute to BM reprogramming during inflammation.
Current and future haemophilia treatment options: Clinician perspective

Michael Makris MD

HEMOPHILIA TREATMENTS

Current

Standard half-life
- FVIII/FIX – Plasma/recombinant

Extended half-life
- FVIII- Fc, PEG
- FIX- Fc, Albumin, PEG

Bypassing agents
- rFVIIa
- Activated PCC

Bispecific antibody

Future

2021

Extended half-life
- Intravenous: FVIII-Fc+XTEN
- Subcutaneous: FVIII, FIX, FVIIa

Bispecific antibodies
- FIX/X mimetics
- Vs other molecules

Rebalancing therapies
- Antithrombin siRNA
- Anti-TFPI
- Anti-APC

Gene therapy
- AAV
- Lentivirus
- Lipid nanoparticles

Shielded spheres
Cerebral venous sinus thrombosis

Ida Martinelli MD, PhD

Clinical suspicion of CVST
- Headache
- Motor deficit
- Seizure
- Visual loss/psychedema
- Mental disorder

Neuro-imaging

Negative
- Unenhanced CT scan

Positive
- Enhanced CT scan and/or MRI

Confirmed CVST

Treatment of the acute phase
- Very severe presentation: Consider Endovascular treatment
- Complications: Consider Concomitant treatments

Anticoagulation
- How long?
  - CVST with transient risk factor: 3-6 months
  - CVST with unmodifiable risk factor: Long term

Evaluation of risk factors

Abbreviations: CVST, cerebral venous sinus thrombosis; CT, computed tomography; MRI, magnetic resonance imaging
Fibrin(ogen)-endothelial cell interactions in inflammation

Leonid Medved, PhD

Transendothelial migration of leukocytes is a key step in their recruitment to sites of inflammation.

Fibrin(ogen) and its degradation products promote leukocyte transmigration and thereby inflammation by interacting with various endothelial cell receptors.

Interaction of fibrin and its degradation product E\(_1\) fragment with the endothelial VLDL receptor (VLDLR) and VE-cadherin occurs through fibrin βN-domains.

Three pathways of fibrin(ogen)-dependent leukocyte transmigration have been proposed: 1. (Mac-1)-Fibrinogen-(ICAM-1)-dependent 2. (CD11c)-E\(_1\) fragment-(VE-cadherin)-dependent 3. Fibrin-VLDL receptor-dependent

Two of the proposed fibrin(ogen)-dependent pathways of leukocyte transmigration are based on the bridging mechanism. The first one suggests that fibrinogen bridges leukocytes to the endothelium through the interaction with endothelial receptor ICAM-1 and leukocyte integrin Mac-1 to promote leukocyte transmigration\(^{41}\) (left panel). The second one suggests that fibrin degradation product E\(_1\) fragment promotes leukocyte transmigration by bridging leukocytes to the endothelium through the interaction with endothelial VE-cadherin and leukocyte integrin CD11c (left panel), and the β15-42 fragment inhibits this interaction and thereby inflammation.\(^{42}\) Our studies revealed that interaction of fibrin with the endothelial VLDL receptor promotes transendothelial migration of leukocytes through the fibrin-VLDL receptor-dependent pathway (left panel), identified two monoclonal antibodies inhibiting this interaction, and clarified the molecular mechanism underlying this pathway and the inhibitory role of β15-42 in this pathway\(^{43}\) (right panel). These antibodies exhibited significant anti-inflammatory properties and may represent potential therapeutics for treatment of fibrin-dependent inflammation.
# Fibrin(ogen) in human disease

Marguerite Neerman-Arbez PhD

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<th>Fibrin(ogen)</th>
<th>Mechanism</th>
<th>Consequence</th>
<th>Outcome</th>
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<td>Mutations</td>
<td>Quantitative defects: low or absent fibrinogen</td>
<td></td>
<td>Bleeding, Thrombosis</td>
</tr>
<tr>
<td></td>
<td>Qualitative defects: abnormal clot structure</td>
<td></td>
<td>Bleeding, Thrombosis</td>
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<tr>
<td></td>
<td>Amyloidosis</td>
<td></td>
<td>Renal disease, hypertension, CVD</td>
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<tr>
<td>Inappropriate post-translational</td>
<td>Abnormal clot structure</td>
<td></td>
<td>Bleeding, Thrombosis</td>
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<td>modifications</td>
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<tr>
<td>High levels (e.g. inflammation)</td>
<td>Hypercoagulability, metabolic dysfunction</td>
<td></td>
<td>CVD, Cancer: worse outcome</td>
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<tr>
<td>Abnormal localisation</td>
<td>Inflammation, demyelination</td>
<td></td>
<td>Neurological disease, Renal disease</td>
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<tr>
<td>- in CNS</td>
<td>Amyloidosis</td>
<td></td>
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<tr>
<td>- in kidney</td>
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<tr>
<td>Interaction with</td>
<td>Limits antimicrobial role of fibrinogen</td>
<td></td>
<td>Microbial infections</td>
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<td>virulence factors</td>
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<tr>
<td>Extra-hepatic expression (carcinoma)</td>
<td>Increases cancer growth and Invasive potential</td>
<td></td>
<td>Cancer: worse outcome</td>
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With fibrin, produced by thrombin-mediated cleavage, fibrinogen plays important roles in many physiological processes.\(^{44,45}\) Formation of a stable blood clot, containing polymerised and cross-linked fibrin, is crucial to prevent blood loss and drive wound healing upon injury. Balance between clotting and fibrinolysis is essential. Several diseases are the consequence of altered levels of fibrinogen, others are related to structural properties of the molecule. Inflammation leads to elevated circulating levels of fibrinogen and hypercoagulability, a risk factor for cardiovascular disease (CVD). The source and localisation of fibrin(ogen) also has clinical implications. Fibrin(ogen) has been associated with cancer development and progression. While fibrin(ogen) is implicated in defense against pathogens, in other settings it enhances bacterial virulence.
Markedly elevated plasma VWF:Ag levels and VWF propeptide levels are present in children with severe *Plasmodium falciparum* malaria, consistent with acute endothelial cell (EC) activation and Weibel Palade body (WPB) secretion. Higher VWF levels correlate with worse clinical outcomes. Pathological ultra-large (UL-) VWF multimers are also a feature of cerebral malaria. In vitro studies have demonstrated that UL-VWF strings on the surface of activated EC can recruit platelets. Subsequently, the platelet-decorated UL-VWF strings can then tether malaria-infected red blood cells (IRBC) under physiological shear stress. In particular, *P. falciparum* erythrocyte membrane protein 1 (PfEMP-1) on the IRBC interacts with platelet CD36. Collectively, these findings support the hypothesis that VWF plays role in regulating microvascular sequestration of IRBC in children with cerebral malaria.

Image created with BioRender.com.
Von Willebrand Factor structure-function in the regulation of cancer metastasis

Jamie O'Sullivan

For reference, see Patmore et al\textsuperscript{59}
Pulmonary embolism in children

Madhvi Rajpurkar MD

Pulmonary Embolism in Children
Current knowledge and future perspectives
Madhvi Rajpurkar, MD

Epidemiology
- Increasing rate but infrequent at individual centers
- Two distinct patterns: In-situ pulmonary artery thrombosis and classic thrombo-embolic PE
- Highest risk in adolescent females
- African American 2.38 X higher rate

Clinical Prediction Rules
- Significant delay in time to diagnosis
- D-dimer often positive, but not discriminative
- Adult criteria (Wells, PERC etc.) have poor predictive values

Risk Stratification and prognosis
- Adult risk prediction models do not correlate well with outcomes
- High rate of thrombolysis
- Non-validated measures used for thrombolytic therapy

Duration of Therapy and Outcomes
- Pooled mortality reported is 26%
- Recurrent VTE rate is 5.5-19%
- Optimal duration unknown: KIDSDOTT trial results pending
- Post-PE syndrome not defined

Future perspectives
- BEEPERS (Bedside Exclusion of Pulmonary Embolism in children without Radiation) study: PERC-Peds criteria to exclude PE
- FUVID study: Evaluate post-PE functional outcomes
- Setting up institutional pediatric PERTs

For references, see Biss et al, Carpenter et al, Rajpurkar et al
Intermolecular interactions that stabilize multimeric FXIII

Verena Schroeder PhD

**Intermolecular Interactions that Stabilize Multimeric FXIII**

**What holds the A subunits together?**

The activation peptide, and in particular the sequence 8FGGR12R, stabilizes the FXIII A₂ dimer [1]

Four intersubunit interactions located at the dimer interface stabilize the A₂ dimer [2]:
- Arg11 - Asp343
- Lys113 - Asp367
- Lys257 - Glu401
- Arg260 - Asp404

Domains of the A subunits: Activation peptide (AP), β-sandwich, core domain, β-barrel 1, β-barrel 2

**What holds the A and B subunits together?**

In the B subunits, the N-terminal Sushi domains 1 and 2 are responsible for binding to the A subunits, stabilizing the FXIII A₂B₂ tetramer

In the A subunits, β-barrel 1 and β-barrel 2 domains bind to the B subunits

Figures modified from [3] where also further references can be found

For references, see Handrkova et al., 53 Li et al., 54 Schroeder et al55
Hemophilia A is an X-linked bleeding disorder that affects 1 in 5,000 males worldwide due to a deficiency in blood coagulation factor VIII (fVIII), an essential protein for the proteolytic activation of factor X to Xa. Through the past 20 years, the structure and function of fVIII have come into focus. New atomic-level structural findings illustrate a detailed domain organization of fVIII structure, 56 novel localized and domain-scale conformational changes, the molecular nature of the fVIII/Von Willebrand factor complex, and pathogenic antibody epitopes. 57,58 Further structural characterization of fVIII circulatory complexes will uncover the fundamental basis for its procoagulant cofactor function and may aid in next-generation bioengineering efforts to improve fVIII stability and circulatory half-life while minimizing its immunogenicity. These efforts may prove vital for both fVIII replacement and gene therapy approaches.
Do platelet transfusions work?

S.J. Stanworth and Laura Green

A number of randomised trials have evaluated the risk-benefit ratio for platelet transfusion for prophylaxis and treatment of major bleeding. Trials in some settings have indicated evidence of harm with more 'liberal' use of platelets, although a benefit to improve outcomes has also been found in major bleeding. Our understanding of donor, storage and processing characteristics on outcomes following platelet transfusion have been inadequately investigated. We need a better understanding of how platelet transfusions affect both haemostasis and inflammation in patients, to indicate which patients really require platelet transfusions.
Prothrombotic fibrin clot properties and vascular diseases

Anetta Undas MD, PhD

Clinical conditions associated with prothrombotic fibrin clot phenotype

Anetta Undas MD, PhD

Fibrin clot structure characterized by fiber diameter and pore size differs between healthy persons and patients with thromboembolic diseases. Prothrombotic fibrin clot phenotype is associated with faster formation of denser fibrin mesh, relatively resistant to lysis, as reflected by prolonged clot lysis time (CLT). Increased plasma fibrin clot density has been reported in patients with prior or acute thromboembolic events.
RELATIONSHIP DISCLOSURE

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