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Platelets and coagulation

Focus on paediatrics

Thrombocytopenia in pregnancy : ITP or NOT ?

Gestational thrombocytopaenia	Very frequent (65-80 %) Mild decrease in platelet count (10 %) Third trimester Caused by increased blood volume, platelet activation, platelet clearance No adverse outcomes (mother and fetus) Quick resolution after delivery (days-weeks)
Many disorders can be associated with thrombocytopenia during pregnancy Underlying disease should be suspected in case of low platelet count (< 70-80000/µL) during first or early in the second trimester	Look for hypertension, edema, neurologic abnormalities, signs of auto-immune disease Drug history, family history Full blood count, blood smear, schistocytes, Coombs test, clotting tests, liver function, serology BM examination rarely performed Antiplatelet antibodies rarely useful

Haematologic Diseases in Pregnancy – Education ASH 2012
Terry B. Gernsheimer

Causes of thrombocytopenia during pregnancy

Gestational (incidental) thrombocytopenia

- Preeclampsia
- HELLP syndrome
- Acute fatty liver of pregnancy
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Systemic lupus erythematosus
- Antiphospholipid Ab syndrome
- Disseminated intravascular coagulation
- Viral infection
- Nutritional deficiency
- Drug use
- Primary BM disorder

Haematologic Diseases in Pregnancy – Education ASH 2012
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Thrombocytopenia in pregnancy : ITP or NOT ?

Characteristics of ITP during pregnancy	
Frequency	2/1000 pregnant women
Presentation	First trimester
Bleeding symptoms	Mild symptoms and clinical signs
No alternative diagnosis	Medical history
Blood tests	Isolated low platelet count Associated anemia of pregnancy No other abnormality

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Management of ITP during gestation

- In many cases, no treatment is required
- Treatment indicated if bleeding symptoms, low plaletet count (20-30.000/µL), planned invasive procedure
- First-line therapy : Corticosteroids (10-20 mg/day) – IV Igs / Second-Line : Azathioprine
- Little or no experience with vinca alkaloids, cyclophosphamide, cyclosporine, rituximab

Management of ITP during delivery

- ITP is not an indication for Cesarean Section
- The mode of delivery is based on obstetric indications
- Fetal platelet count measurement is not recommended before delivery
- The best predictor of thrombocytopaenia at birth is its occurrence in an older sibling (CS)
- Withold spinal anesthaesia when platelet count < 75.000/µL

Management of the neonate

- Poor correlation between maternal and fetal platelet counts
- History of low platelet count in a previous affected sibling is the best predictor of thrombocytopaenia in the neonate
- Cord blood count should be obtained to determine need for immediate therapy
- Nadir platelet count occurs 2-5 days after birth. If low platelets > IVIg

Proper management of venous thrombo-embolic disease (VTED) in pregnancy.

- Venous thrombo-embolic events (1/1000 pregnancies) can occur at any stage in pregnancy (50 % in the first 20 weeks) but the period of greatest risk is in the weeks after delivery. Most events are ileo-femoral and left sided.

- The clinical diagnosis is unreliable in pregnancy.

- High level of suspicion (unilateral and usually left-sided leg pain and swelling, lower abdominal pain, low-grade pyrexia, dyspnea, chest pain, and hemoptysis)

- The likelihood of VTE is higher when additional risk factors are present (immobility + body mass index of 25 kg/m2).

- Ultrasound venography and ventilation perfusion lung scan remain the diagnostic techniques of choice for deep venous thrombosis and to rule out PE (lower maternal radiation dose / the lower prevalence of coexisting pulmonary problems).

Haematologic Diseases in Pregnancy – Education ASH 2012
Ian A. Greer

Proper management of venous thrombo-embolic disease (VTED) in pregnancy.

- Performing a thrombophilia screen before commencing anticoagulant therapy is not recommended routinely because it will not influence the immediate management of acute VTE

- Low-molecular-weight heparin is the agent of choice for treatment of venous thromboembolism in pregnancy, and treatment should be provided for a minimum of 3 months and for at least 6 weeks after delivery.

- New anticoagulant agents such as dabigatran, rivaroxaban, or apixaban are not recommended in this setting.

Haematologic Diseases in Pregnancy – Education ASH 2012
Ian A. Greer

VTE in the pediatric population : more evidence.

- Technological advances in medicine and imaging techniques have improved awareness of the disease (<1/10.000 to 58/10.000).

- Longer survival of life-threatening or chronic medical conditions all contribute to the increase in VTE rates in this specific population.

- Bimodal distribution : Infants less than 1 one year of age and adolescents on oral contraception are at increase risk for development of VTE.

- There is a paucity of data on management of VTE based on properly designed clinical trials, but there have been significant advances in the last 2 decades (100 recommendations in the last ACCP Chest Guidelines, most 2C).

- In neonates, higher starting doses of LMWH (Enoxaparin 1.7 to 2 mg/kg/12h) is certainly recommended. All new anticoagulants are in clinical development for the pediatric population.

Not So Genign Hematologic Issues in Children – Education ASH 2012
Anthony KC Chan and Paul Monagle

The neonatal immature coagulation system is functionally balanced.

- Major differences exist in the physiology of coagulation and fibrinolysis in neonates and young children compared with older children and adults.

- These differences, which reflect the immaturity of the neonatal hemostasis system, are however functionally balanced.

- Healthy neonates show no signs of bleeding diathesis and no increased tendency to thrombosis for any given stimulus compared with adults.

Neonatal hemostasis versus older children/adult hemostasis

	Preterm neonates vs term neonates	Neonates vs older children/adults	Approximate age of adult values*
Primary hemostasis			
Platelet count	Decreased (< 32 w)	Same	
Platelet function	Decreased	Decreased†	2-4 wk
% of reticulated platelets	Higher	Higher	NA
VWF level	NA	Higher	3 mo
VWF large multimers	NA	Higher	3 mo
Coagulation factors			
FII, FVII, FIX, FX	Lower	Lower	16 y
FV	Lower	Same or lower	16 y
FVIII	Higher	Same or higher	1 mo‡
FXI	Lower	Lower	1 y
FXII	Lower	Lower	16 y
Fibrinogen level	Same	Same	
Fibrinogen function	NA	Decreased	5 y
Regulation of coagulation			
Antithrombin	Lower	Lower	3 mo
Protein C	Lower	Lower	16 y
Total protein S	Lower	Lower	1 mo
Free protein S	NA	Higher	NA
APCR generation	NA	Reduced	NA
Free TFPI	NA	Lower	Adult
Fibrinolysis			
Plasminogen level	Lower	Lower	6 mo
Plasminogen function	NA	Decreased	NA
tPA	Same§	Higher	5 d
α2 antiplasmin	Lower	Lower	5 d
α2M	Same	Higher	Adult
PAI	Same§	Same or higher	5 d

NA indicates not available; APCR, activated protein C resistance; and TFPI, tissue factor pathway inhibitor.
For reference values of coagulation and regulation of coagulation factors, see Monagle et al, 2006.[14]
*Maximum age reported.
†Decreased response was reported to agonists such as thrombin, collagen, epinephrine, and thrombin activation peptide as tested by flow cytometry.
‡Lower levels compared with adults are reported from 1 mo to 16 y of age.
§Higher levels in extremely preterm neonates on d 10 of life compared with older preterm or term neonates.

Neonatal hemostasis versus older children/adult hemostasis

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% of reticulated platelets	Higher	Higher	NA
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Coagulation factors			
FII, FVII, FIX, FX			
FV			
FVIII			
FXI			
FXII			
Fibrinogen level			
Fibrinogen function			
Regulation of coagulation			
Antithrombin			
Protein C			
Total protein S			
Free protein S			
APCR generation			
Free TFPI			
Fibrinolysis			
Plasminogen level			
Plasminogen function			
tPA			
α2 antiplasmin			
α2M			
PAI			

NA indicates not available; APCR, activat
For reference values of coagulation and re
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Parameter	Neonate vs Children and Adults
Platelet count	Decreased
Platelet function	Decreased
VWF levels and multimers	Increased
FII, VII, IX and X	Decreased
FXI and FXII	Decreased
FV and FVIII	Same
Fg	Same
AT, proteins C and S	Decreased
Fibrinolysis	Increased

The neonatal immature coagulation system is functionally balanced.

- Systemic diseases may affect hemostasis, predisposing ill neonates to increased hemorrhagic or thrombotic complications.

- The immaturity of the hemostasis system in the preterm and very-low-birth-weight neonate may contribute to a higher risk for intraventricular hemorrhage.

- For diagnosis of hemostasis disorders in this population, diagnostic laboratories processing pediatric samples should use age-, analyzer-, and reagent-appropriate reference ranges.

Screening laboratory tests for hemostasis: Neonates versus adults

	Preterm neonates vs term neonates	Neonates vs older children/ adults	Approximate age of adult value*
aPTT	Longer	Longer	16 y
Prothrombin time	Longer	Same or longer	16 y
INR	Higher	Same or higher	16 y
Thrombin time	Longer	Same or longer	5 y
Bleeding time	Longer†	Shorter	1 mo
PFA-100	Longer†	Shorter	1 mo
ROTEM/TEG			
Clotting time	Same	Shorter	3 mo
Clot formation time	Same	Shorter	3 mo
Maximal clot firmness	Stronger	Stronger	3 mo

INR indicates International Normalized Ratio; ROTEM, rotating thromboelastometry; and TEG, thromboelastography.
*Maximum age reported.
†In samples drawn in the first 7-10 d of life.

Bleeding scores should be encouraged.

- There has been an increasing interest in a more precise quantification of bleeding symptoms by the development and validation of bleeding scores.
  - The Vicenza bleeding score
  - Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand disease MCMDM-1 VWD
  - The Pediatric Bleeding Questionnaire.

- These instruments collect data regarding both the presence and severity of a variety of bleeding symptoms and generate a bleeding score by summing the severity of all symptoms reported by a subject.

- They are validated research tools able to discriminate between healthy subjects and those with von Willebrand disease

Condensed version of the bleeding assessment tool.
Bowman et al.

Epistaxis	
0	No or trivial (less than 5)
1	> 5 or more than 10'
2	CONSULTATION ONLY
3	Packing or Cauterization or Antifibrinolytics
4	Blood transfusion or Replacement therapy or Desmopressin

Oral cavity	
0	No
1	Reported at least one
2	CONSULTATION ONLY
3	Surgical hemostasis or Antifibrinolytics
4	Blood transfusion or Replacement therapy or Desmopressin

Surgery	
–1	No bleeding in at least 2 surgeries
0	Not done or no bleeding in 1 surgery
1	Reported in <25% of all surgeries
2	Reported in >25% of all surgeries, no intervention
3	Surgical hemostasis or Antifibrinolytics
4	Blood transfusion or Replacement therapy or Desmopressin

Muscle hematoma	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring Desmopressin or Replacement therapy
4	Spontaneous or traumatic requiring Surgical intervention or Blood transf

Cutaneous	
0	No or trivial (<1 cm)
1	>1 cm and no trauma
2	CONSULTATION ONLY

GI bleeding	
0	No
1	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia
2	Spontaneous
3	Surgical hemostasis or Blood transfusion or Replacement therapy or Desmopressin or Antifibrinolytics

Menorrhagia	
0	No
1	CONSULTATION ONLY
2	Antifibrinolytics or pill use
3	Curettage or Iron therapy
4	Blood transfusion or Replacement ther -apy or Desmopressin or Hysterectomy

Hemarthrosis	
0	Never
1	Post-trauma no therapy
2	Spontaneous no therapy
3	Spontaneous or traumatic requiring desmopressin or Replacement therapy
4	Spontaneous or traumatic requiring surgical intervention or blood transfusion

Bleeding from minor wounds	
0	No or trivial (less than 5)
1	> 5 or more than 5'
2	CONSULTATION ONLY
3	Surgical hemostasis
4	Blood transfusion or Replacement therapy or Desmopressin

Tooth extraction	
–1	No bleeding in at least 2 extractions
0	Not done or no bleeding in 1 extraction
1	Reported in <25% of all procedures
2	Reported in >25% of all procedures, no intervention
3	Resuturing or Packing
4	Blood transfusion or Replacement therapy or Desmopressin

Post-partum hemorrhage	
–1	No bleeding in at least 2 deliveries
0	No deliveries or no bleeding in 1 delivery
1	CONSULTATION ONLY
2	Curettage or Iron therapy or Antifibrinolytics
3	Blood transfusion or Replacement therapy or Desmopressin
4	Hysterectomy

CNS bleeding	
0	Never
1	-
2	-
3	Subdural, any intervention
4	Intracerebral, any intervention

Total assigned score:

Bleeding scores should be encouraged.

- The greatest clinical utility of bleeding scores lies in their high negative predictive value, and perhaps their greatest value is in the identification of patients for whom testing for VWD is not necessary.
- In very young patients the bleeding history may be completely negative due to lack of hemostatic challenges.
- Some laboratory work-up will always be required to exclude a bleeding disorder in a young patient with a positive family history of a bleeding disorder.
- If the bleeding score is elevated and VWF levels are normal, this should be a sign for the hematologist to actively pursue alternate bleeding disorder diagnoses.

The new oral anticoagulants

	Apixaban ELIQUIS	Rivaroxaban XARELTO	Dabigatran PRADAXA
Mechanism of action	direct FXa inhibitor	direct FXa inhibitor	direct FIIa inhibitor
Oral availability	~50 %	80 %	6.5 %
Route of administration	oral	oral	oral
Dosing	2x/day in all indications	1x/day (AF, DVT and PE)	1x/day (DVT prevention) 2x/day (VTE, AF)
Pro-drug	No	No	Yes
Food effect	No	No	No
Renal Clearance	~27 %	36 %	85 %
Mean Half-Life (T1/2)	~12h	7–11 h	14–17 h
Tmax	3 h	2–4 h	0.5–2 h
Drug interactions	CYP 3A4 and P-gp inhibitors CYP 3A4 inducers	CYP 3A4 and P-gp inhibitors CYP 3A4 inducers	P-gp inhibitors P-gp inducers

Eikelboom et al. *Circulation* 2010;121:1523

New oral anticoagulants: which one should my patient use?

- Dabigatran and rivaroxaban are licensed as alternatives to warfarin for stroke prevention in patients with atrial fibrillation and apixaban is likely to soon follow.

- Differences in study design, characteristics of the patients enrolled, and quality of warfarin management render cross study comparisons problematic.

- In the absence of head-to-head trials, it is impossible to say that one drug is better than another.

- Until such trials are done, therefore, it is likely that the unique pharmacologic properties and the differences among the agents that have arisen from the clinical trials will drive the decision as to which of the new agents to choose.

The New Era in Antithrombotic Therapy – Education ASH 2012
Jeffrey I. Weitz and Peter L. Gross

Is there a role for warfarin anymore ?

- Rivaroxaban, Dabigatran and Apixaban have demonstrated effectiveness, safety, and adherence that are comparable or superior to warfarin in the clinical trial setting.
- None of the novel agents requires routine laboratory testing. These new agents present potential advantages, such as fixed dosing and dramatically reduced intracranial hemorrhaging.
- They also have limitations such as the dependency of the renal function and the absence of antidote.

- Clinical practice is however very different from the clinical trial setting.

- *“In the randomized trials, all of the patients received the same amount of education. But how much education will be provided to patients prescribed these agents in clinical practice if they are not followed in an anticoagulation clinic?”*

The New Era in Antithrombotic Therapy – Education ASH 2012
Jeffrey I. Weitz and Peter L. Gross

Is there a role for warfarin anymore ?

- New oral anticoagulants require the same patient education on the risk of stroke in nonvalvular atrial fibrillation and the benefits of anticoagulation

- New oral anticoagulants have significant rates of bleeding:
  - patients need to be aware of signs and symptoms, how to respond, precautionary measures to minimize trauma and risk of bleeding

- New agents have no INR monitoring concerns and fewer drug-drug and food-drug interactions, but still have unique considerations for each agent, including how to manage missed doses.

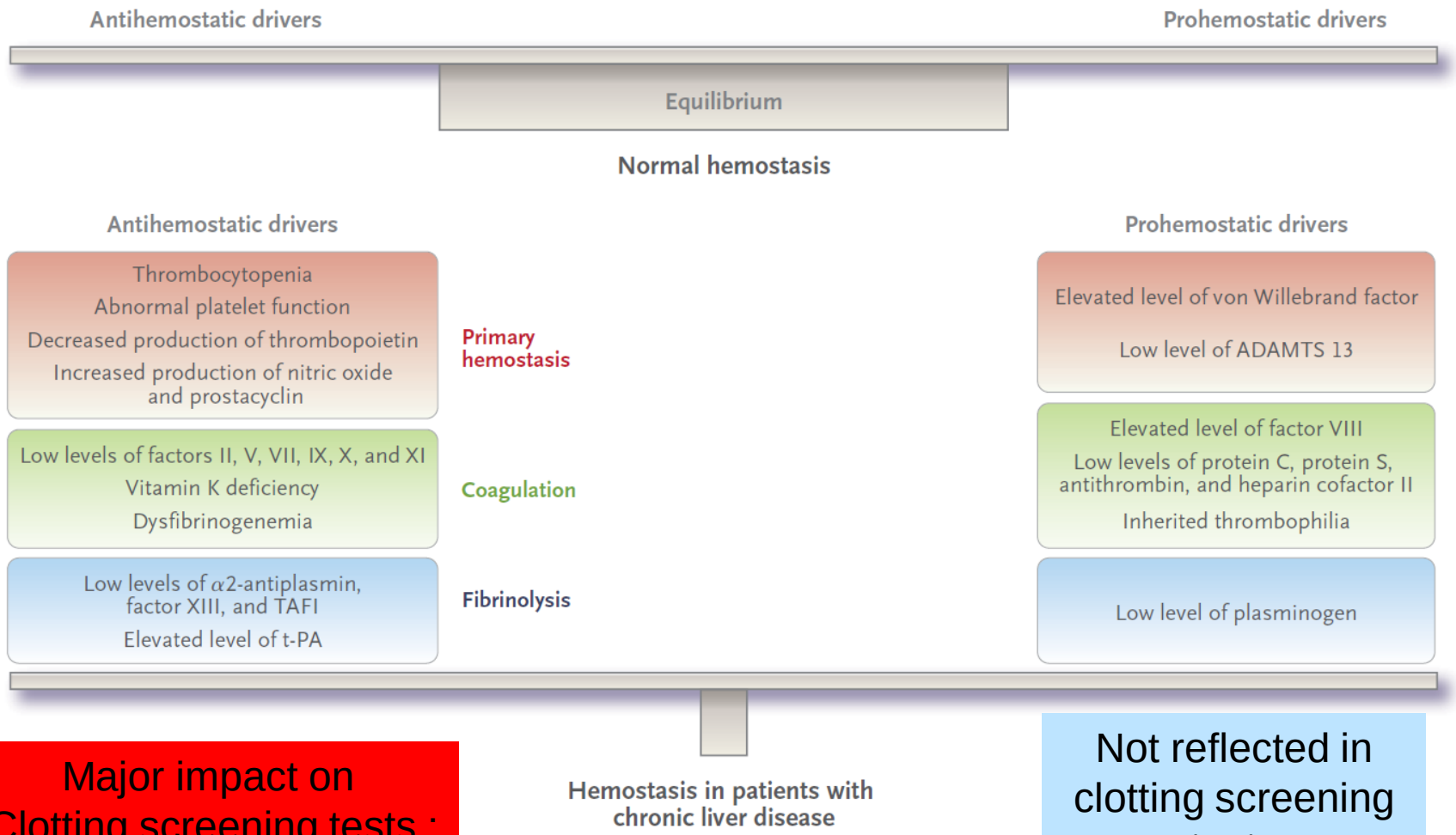
- **CAREFUL SELECTION, EDUCATION AND APPROPRIATE FOLLOW-UP OF PATIENTS ON NOACs IS CRITICAL**

The New Era in Antithrombotic Therapy – Education ASH 2012
Jeffrey I. Weitz and Peter L. Gross

Hemostatic defects in liver and renal dysfunction are overestimated.

Everyday bleeding disorder – Education ASH 2012
P. MANNUCCIO MANNUCCI and A. TRIPODI

Haemostasis in liver disease



Major impact on Clotting screening tests : Prolonged APTT, PT

Not reflected in clotting screening tests

Hemostatic defects in renal dysfunction are overestimated.

- In patients with uremia, the bleeding tendency (mainly expressed by gastrointestinal bleeding and hematoma formation at kidney biopsy) is reduced dramatically by the improvement of anemia obtained with the regular use of erythropoietin.

Hemostatic defects in liver and renal dysfunction are overestimated.

- In cirrhosis, the most severe and frequent hemorrhagic symptoms (acute bleeding from esophageal varices) are not explained by blood clotting abnormalities.

- In patients with cirrhosis, low endogenous anticoagulant factors (antithrombin, protein c) in plasma compensate for the concomitant decrease of procoagulants.

- Rebalance also occurs for hyperfibrinolysis and platelet abnormalities.

- The commonly measured tests (APTT, PT) in patients with cirrhosis do not reflect the decrease of coagulation inhibitors.

- Transfusional and nontransfusional hemostatic medications are of little value as adjuvants to control bleeding in advanced liver disease.

- Particularly in uremia, but also in cirrhosis, thrombosis is becoming a cogent problem.

After DVT, Compression Stockings Do not Prevent Post-Thrombotic Syndrome (SOX Trial)

- 398 patients were randomized to Active-ECS (elastic compression stockings) and 408 to Placebo-ECS. Baseline features were similar in both groups. Sixty percent were male, the mean age was 55 years, and the most proximal extent of DVT was the iliac or femoral vein in 70% of patients and the popliteal vein in 30% of patients.

- The intervention group wore knee length, 30-40 mm Hg, Class II graduated ECS. The placebo stockings appeared identical to A-ECS but lacked therapeutic compression.

- Approximately 70% of patients in both groups continued wearing the stockings throughout study follow-up, and over 80% of these patients in both groups reported wearing them for at least three days per week.

- The cumulative incidence of PTS at 750 days was 14.8% in A-ECS vs. 12.3% in P-ECS (p=0.49).

- **While stockings do not actually prevent the development of the post-thrombotic syndrome, they may still have a role in the management of venous symptoms after DVT.**

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Thank you for your attention