Algorithms for Diagnosis of Disorders in Hemostasis
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Introduction

PT (Prothrombin Time) and APTT (Activated Partial Thromboplastin Time) prolongations diagnostic algorithm

Is the patient on anticoagulant therapy?
- YES: Go to flow charts for anticoagulant therapy.
- NO: Is the APTT elevated with a normal PT?
  - YES: Go to Page 6
  - NO: Does the 50:50 mix correct the APTT?
    - YES: Go to Page 6
    - NO: The specimen may be contaminated with heparin, especially if APTT was previously normal in recent days.
      - Is there a need to rule out heparin contamination in specimen in question?
        - NO: Repeat APTT on new sample carefully collected to avoid heparin contamination.
        - YES: Can perform thrombin time ± protamine sulfate, use heparin-absorbing resin and repeat APTT, or do thrombin time with reptilase time to assess presence of heparin in sample.
          - Is heparin responsible for observed result?
            - NO: The patient may have a lupus inhibitor.
            - YES: Subsequent specimens should have much shorter APTT values.

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Go to Page 7
Assays for lupus inhibitor with available tests; the tissue thromboplastin inhibition (TTI) test, platelet neutralization procedure (PNP), and anti-cardiolipin (ACL) antibody assay are commonly used assays for lupus inhibitor.

Is there a lupus inhibitor present by any one of these assays?

Patient has a lupus inhibitor. If PNP fails to correct in the presence of other tests positive for lupus inhibitor, there may be an underlying factor deficiency as well as a lupus inhibitor.

Does the 50:50 mix for the PTT become > 5 seconds longer when the mixture is incubated 60 minutes at 37°C than when the mixture is incubated for 0 minutes?

Inhibitor to Factor VIII: C unlikely. If still suspicious, check Factor VIII: C levels.

Consider the presence of a Factor VIII: C inhibitor. Highest suspicion of an inhibitor lies in patients known to have Hemophilia A, but Factor VIII: C inhibitor also arise spontaneously.

Is Factor VIII: C low?

Inhibitors to Factor IX may be present, particularly in patients with hemophilia B. Can check Factor IX level if suspicious. Factor XI or XII inhibitors may be present, but these are very rare.

For factor VIII: C inhibitors, quantitate inhibitor strength in Bethesda Units.
Patient may have a deficiency of VIII: C, IX, XI (which can result in bleeding) or XII, HMWK, Prekallikrein (which do not result in bleeding).

Perform Factor assays, emphasizing VIII: C, IX and XI.

If Factor VIII: C or IX is selectively decreased, patient may have Hemophilia A (VIII: C) or B (IX) or von Willebrand's disease. The clinical presentations of the Hemophilias and von Willebrand's Disease are usually very different. Is the patient likely to have Hemophilia A or B?

Check for sex-linked inheritance and confirm selective deficiency of Factor VIII: C or IX.

Are vWF: RCo and vWF: Ag decreased?

YES

Deficiency of Factor XI may be a risk factor for bleeding if personal or family history of bleeding exists.

NO

Deficiency of any of these factors does not predispose to bleeding.

Is Factor XI selectively decreased?

YES

von Willebrand's disease is likely diagnosis. Check for non-sex-linked inheritance, autosomal dominant inheritance for most common form of von Willebrand's Disease.

NO

Is Factor XII, HMWK, or Prekallikrein selectively decreased?

YES

Patient may have a mild inhibitor which corrects on 50:50 mix with APTT. Check for presence of inhibitor.

NO
Is the PT elevated with a normal APTT?

**NO**

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**YES**

Does the 50:50 mix correct the PT?

**NO**

Patient may have a very rare Factor VII inhibitor if indicated, can assay for Factor VII.

**YES**

Patient may have mild DIC (Disseminated Intravascular Coagulation).

Any suspicion of DIC?

**YES**

Go to Page 9

**NO**

Patient may have mild Vitamin K deficiency.

Are all Vitamin K-dependent factors selectively decreased?

**YES**

Vitamin K deficiency likely. Can confirm by correction of factor deficiencies with Vitamin K administration.

**NO**

Patient may have liver disease.

Are liver function tests abnormal?

**NO**

Go to Page 8

**YES**

Presumptive diagnosis of Vitamin K deficiency.

Does PT correct?

**NO**

Administer Vitamin K

**YES**

Liver disease may be a contributory factor in PT prolongation.

Is it important to document Vitamin K deficiency with factor assays?

**YES**

Is the PT elevated with a normal APTT?

**NO**

Go to Page 9

**YES**

Does the 50:50 mix correct the PT?

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Vitamin K deficiency likely. Can confirm by correction of factor deficiencies with Vitamin K administration.

**NO**

Patient may have liver disease.

Are liver function tests abnormal?

**NO**

Go to Page 8

**YES**

Presumptive diagnosis of Vitamin K deficiency.
Patient may have an isolated Factor VII deficiency.

Is Factor VII low?

- NO
  - Patient may have mild deficiencies of Factors II, V or X (common pathway factors), although these deficiencies can affect both the PT and APTT.
  - Are Factors II, V or X low?
    - NO
      - Other, uncharacterized defect responsible for the prolonged PT which corrects on mixing.
    - YES
      - Patient has an apparent Factor II, V or X deficiency. Confirm with repeat testing.
  - YES
    - Patient has an apparent Factor VII deficiency. If congenital deficiency, decreased factor level should be reproducible upon repeat testing.
Both the PT and APTT are elevated.

Do the PT and APTT 50:50 mixes correct?

**YES**
- Patient may have moderate to severe DIC. See Page 10.
- Patient may have moderate to severe Vitamin K deficiency. See Page 7.
- Patient may have a lupus inhibitor with an associated Factor II (Prothrombin) deficiency (PT mix corrects, but APTT mix does not).

**NO**
- Patient may have liver disease. See Page 7.
- Could be heparin contamination with a large amount of heparin. See Page 4.
- Significant elevation of FDP (Fibrin or Fibrinogen Degradation Products) may result in no correction in mixing studies. Check FDP.
- Very rare inhibitors to common pathway Factors I, II, V or X may produce this result.

Is Factor II low and lupus inhibitor test positive? See Page 5.

**YES**
- Diagnosis of lupus inhibitor with Factor II deficiency.

**NO**
- Patient may have an isolated deficiency of a common pathway Factor (I, II, V or X).

Are Factors I, II, V or X low?

**YES**
- Patient has an apparent factor deficiency. Confirm on repeat testing.

**NO**
- Other, uncharacterized defect responsible for observed laboratory results.
There is a suspicion of DIC because
• disorder commonly associated with DIC is present
• unexplained bleeding
• platelet count or fibrinogen level decreased.

Obtain PT, platelet count, fibrinogen level and FDP level.

Is PT prolonged; and Fibrinogen decreased; and Platelets decreased, and FDP increased?

NO

Is PT prolonged; and FDP increased, and Platelets and Fibrinogen normal but decreasing with sequential measurements?

NO

Diagnosis of DIC unlikely, especially if FDP is normal.

NO

Observe patient.

YES

Still suspicious of DIC?

NO

Is there a change in the clinical picture or treatment given which may affect DIC?

YES

A diagnosis of DIC is likely.
O.A.T. (Oral Anticoagulant Therapy) diagnostic and therapeutic algorithm

2. Obtain PT.
3. If INR = 2.0 - 4.5 depending on clinical indication, maintain dose.
4. If INR < 2.0 inadequate anticoagulation, increase dose.
5. If INR exceeds upper limit of therapeutic range for clinical indication, increase dose.
6. If treatment overdose, stop drug, reduce dosage, or remove drugs potentiating treatment effect.
7. If bleeding present?
   - If severity of bleeding major, give Fresh frozen plasma (FFP) to reverse anticoagulation immediately; wait for PT to decrease, monitor closely for further bleeding.
   - If severity of bleeding minor, wait for PT to decrease, monitor closely for further bleeding.
8. If desire to restore appropriate level of anticoagulation as soon as possible following correction of PT?
   - If NO, wait for PT to decrease, do not administer Vitamin K.
   - If YES, administer Vitamin K, wait for PT to decrease, restart treatment at lower dose.
Heparin therapy indicated.

**PROPHYLAXIS**

Mini dose-heparin (Subcutaneous).

**THERAPY FOR THROMBOSIS**

Full-dose heparin.

Obtain an APTT.

Present dose inadequate: increase dose.

APTT > 1.5 times mean of normal range.

Significant bleeding?

If severe bleeding, is persistent or life-threatening, give protamine sulfate.

Maintain dose, watch for bleeding.

NO

YES

Stop heparin.

YES

NO

Persistent bleeding?

Re-start heparin at decreased dose.

Significant bleeding?

YES

If severe bleeding, is persistent or life-threatening, give protamine sulfate.

NO

Maintain dose, watch for bleeding.

PROPHYLAXIS

Heparin therapy indicated.

THERAPY FOR THROMBOSIS

Full-dose heparin.

Obtain an APTT.

Present dose inadequate: increase dose.

APTT > 1.5 times mean of normal range.

Significant bleeding?

If severe bleeding, is persistent or life-threatening, give protamine sulfate.

Maintain dose, watch for bleeding.

NO

YES

Stop heparin.

YES

NO

Persistent bleeding?

Re-start heparin at decreased dose.

Significant bleeding?

YES

If severe bleeding, is persistent or life-threatening, give protamine sulfate.

Maintain dose, watch for bleeding.
Algorithm for clinical diagnosis & typing of von Willebrand’s disease

- Personal or Family History of Bleeding
  - Pattern of inheritance not sex-linked
  - Usually mild bleeding associated with trauma, surgery, or dental procedures.

Unlikely to be von Willebrand's Disease
Retest if clinically indicated.

Plasma von Willebrand antigen and Ristocetin cofactor measured.

Plasma Ristocetin cofactor value below normal?

von Willebrand antigen normal?

von Willebrand antigen > 15% higher than plasma Ristocetin cofactor.

Suspect von Willebrand's Disease Type other than (most common) Type I.

Crossed immunoelectrophoresis (CIE) or Western Blot for multimer analysis.

High molecular weight multimers decreased?

Type I von Willebrand's Disease. Test for response to DDAVP.

Suspect von Willebrand's Disease Type I.

Test for Type IIB by platelet Ristocetin aggregation test. Is there hypersensitivity to Ristocetin?

Type IIB von Willebrand's Disease. Avoid DDAVP response testing.

Strong history of bleeding without other identified cause?

May be von Willebrand's Disease. Follow history and laboratory values over time to obtain more definitive diagnosis.

Ristocetin cofactor value < 100%

Cannot completely exclude von Willebrand's Disease since von Willebrand antigen increased above baseline in many mild illnesses and other situations. Retest in 1 - 2 months if clinical suspicion of bleeding.

Is plasma Ristocetin cofactor value below normal range?

von Willebrand antigen > 15% higher than plasma Ristocetin cofactor.

Suspect von Willebrand's Disease Type other than (most common) Type I.

Determine blood type, increased clinical suspicion for von Willebrand's Disease if blood type A, B, or AB rather than type O, since von Willebrand antigen normal levels of type O patients 20-50% less than those of other blood types.

Not type IIB von Willebrand's Disease.
Does the patient have any of the well-established, predisposing factors for thrombosis such as obesity, old age, malignancy, prolonged immobility, or post-operative status?

Clinical evidence of thrombosis.

Suspection exists of primary hypercoagulable state because:
- family history of thrombosis
- recurrent thrombosis without apparent precipitating factor
- thrombosis at an early age
- resistance to conventional anticoagulant therapy.

Obtain a battery of tests for hypercoagulable state: Antithrombin III (AT-III), Proteins C & S, Plasminogen, Thrombin Time and Reptilase Time, Lupus Inhibitor Assays.

AT III decreased to < 50% ?

Protein C decreased?

Free Protein S decreased?

Plasminogen decreased?

Is there evidence of dysfibrinogenemia, typically manifested as a prolonged thrombin time and markedly prolonged reptilase time?

Defect responsible for thrombosis remains unidentified.

Does the patient have a lupus inhibitor by any of a variety of lupus inhibitor assays?

An association has been made between thrombosis and the presence of a lupus inhibitor, and this may be an explanation for thrombosis in this patient.
Thrombocytopenia may be due to sequestration of platelets in the spleen.

Does the patient have hepatosplenomegaly with a stable platelet count above 50,000 per mm³?

Differential diagnosis of decreased platelet production includes congenital and acquired disorders of platelet production, most notably marrow infiltration by tumor in leukemia, lymphoma, other malignancies, or marrow fibrosis; drug-induced marrow suppression; aplastic anemia; and maturation or metabolic defects.

Non-immune-mediated, platelet destruction.

Follow infection and follow platelet count.

See DIC algorithm on page 10.

Follow platelet count and other parameters altered in HUS or TTP.
Acquired qualitative platelet disorders diagnostic algorithm

Acquired platelet function disorder suspected:
• history of bleeding not lifelong and no family history of bleeding
• normal tests for coagulation factors.

Is the platelet count low?  NO

Is there evidence of a myeloproliferative disorder?  NO

Yes

Has patient ingested a drug which affects platelet function?

Yes

Remove drug if possible and follow clinical bleeding.

No

Platelet function commonly impaired in uremia and improves with dialysis and/or DDAVP.

No

Increased bleeding time reflects uncharacterized acquired platelet function or vascular disorder.

Is there a renal function defect with increased BUN (Blood Urea Nitrogen)?

Yes

Does the patient have a paraprotein, specifically IgM or IgA paraprotein?

Yes

Treat underlying disorder.
Blood component therapy as indicated for hemostasis.

No

Does the patient have acquired or previously undiagnosed congenital von Willebrand's disease as shown by a low von Willebrand antigen and Ristocetin cofactor or other test for vWD?

No

Increased bleeding time reflects uncharacterized acquired platelet function or vascular disorder.

See evaluation of thrombocytopenia.

Is the patient bleeding or has the patient had a history of bleeding?

No

No further platelet studies.

Same patients with a paraprotein develop a platelet function disorder.

Can follow treatment with von Willebrand antigen and Ristocetin cofactor measurements.
Congenital qualitative platelet disorders diagnostic algorithm

Congenital Platelet Function Defect Suspected
- lifelong bleeding history
- positive family history of bleeding
- normal tests for coagulation factors.

Determine type of vWD by Crossed immunoelectrophoresis (CIE) or multimer analysis.

von Willebrand’s Disease (vWD)?

Confirm absence of vWD with repeat study.

Further evaluation of platelet function not likely to be informative.

Suspicious of additional disorder involving platelets?

Suspicious of congenital platelet disorder as well?

Remove causes of acquired platelet dysfunction.

Can acquired causes of platelet dysfunction be removed?

Perform lab tests for differential diagnosis of congenital platelet disorders.

Acquired platelet function disorder present.

Acquired causes of platelet dysfunction (primarily resulting from drugs, uremia, paraproteins, or underlying myeloproliferative disorder) present?

NO

YES

See Bernard-Soulier Disease.

See Glanzmann's Thromboasthenia.

See Storage Pool Disease.

See Defects in Arachidonate Metabolism.
Bernard-Soulier (BS) disease

From Page 17

Normal platelet aggregations with collagen, ADP, epinephrine, but abnormal response to Ristocetin.

NO

Unlikely to be BS.

YES

Low plasma vWF- and RCo?

YES

vWD previously undiagnosed.

NO

Aggregation to Ristocetin normalized when patient's platelets mixed with normal plasma?

NO

Tentative BS

NO

Not BS.

YES

Giant platelets on smear?

NO

BS confirmed.

YES

Very likely BS.

Surface membrane, protein analysis performed (research lab). Is the amount of glycoprotein lb decreased?

NO

Not BS.

YES

BS confirmed.
Glanzmann’s thrombasthenia (GT)

From Page 17

- Flat or nearly flat platelet aggregation tracings to all agonists.
  - NO
  - YES

- Clot retraction normal.
  - NO
  - HIGHLY LIKELY TO BE GT UNLESS PLATELETS WERE INADVERTE NTLY MADE NONFUNCTIONAL WHILE PROCESSING SAMPLE.
  - YES

- Platelet measurement of glycoprotein IIb: IIIa (research lab).
  - YES
  - STILL SUSPICIOUS OF GT FROM BLEEDING HISTORY OR OTHER WORK-UP?
  - NO

- NOT LIKELY TO BE GT.

- NO

- NOT GT.
From Page 17

Abnormal Platelet Aggregations, typically limited to first wave response only.

Platelet ATP and ADP assays.

\[
\text{ATP} / \text{ADP} > 3.0
\]

\[\text{YES}\]

Dense granule deficiency. Therefore, patient has either \(\alpha\) or \(\alpha\delta\) SPD.

Radio Immuno Assay (RIA) for \(\beta\) - thromboglobulin (BTG) or platelet factor 4 (PF4) an \(\alpha\) granule marker.

\[\beta\text{TG decreased?}\]

\[\text{YES}\]

\(\alpha\) SPD

\[\text{NO}\]

No SPD

\[\beta\text{TG or PF4 decreased?}\]

\[\text{YES}\]

\(\alpha\delta\) SPD

\[\text{NO}\]

\(\alpha\) SPD
From Page 17

Abnormal platelet aggregations, typically limited to first wave response only.

Most of the following tests are performed in a research lab

Assay for \( ^{14} \text{C} \) - AA conversion to metabolites.

Since aspirin inhibits cyclooxygenase (CO) irreversibly, and generates lab results identical to that found in CO deficiency, repeat drug history - be complete.

Medication with ASA (Acetyl Salicylic Acid) identified?

\( ^{14} \text{C} \) - TXB\(_2\) formed?

Drug - induced platelet defect.

Assay for \( ^{14} \text{C} \) - PGH\(_2\) conversion to metabolites.

No defect in AA/TX pathway.

TXA\(_2\) receptor deficiency likely. Confirm with additional research lab tests.

\( ^{14} \text{C} \) - TXB\(_2\) formed?

CO deficiency likely.

RIA for CO antigen if possible since low immunologic CO value confirms deficiency.

Corroborate absence of aspirin and look for family and personal history of bleeding to substantiate congenital CO deficiency.

Low CO antigen?

CO deficiency diagnosed.
1. Monitoring of the Anticoagulant Therapy with Vitamin K Antagonists
   Practical and technical-scientific aspects
   F. D’Agostino, G. Cambié, D. Fugazza, M. Nardella, L. Bevilacqua, A. Lombardi, L. Preda

2. Multicentre Assessment of a New High-Sensitivity Thromboplastin for Analysis of Patients Receiving Oral Anticoagulant Therapy
   A. Buggiani, N. Erba, B. Morelli, M. Spagnotto

3. Protein C Activity Measurement. Evaluation of a New Snake Venom-Activated Method (ProClot) in Comparison with a Thrombin-Activated Method
   A. Tripodi, F. Franchi, P.M. Mannucci

4. A New Thromboplastin Based Method (IL Test™ Protein S) for the Determination of Functional Protein S
   R.G. Malia, P.C. Cooper

5. The Anticoagulants: Protein C and Protein S
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6. Coagulation Glossary
   E. Finotto, A. Lombardi, L. Preda, G. Semprini