Treatment of Anti-Phospholipid Syndrome and Prothrombin Deficiency with Plasma Exchange

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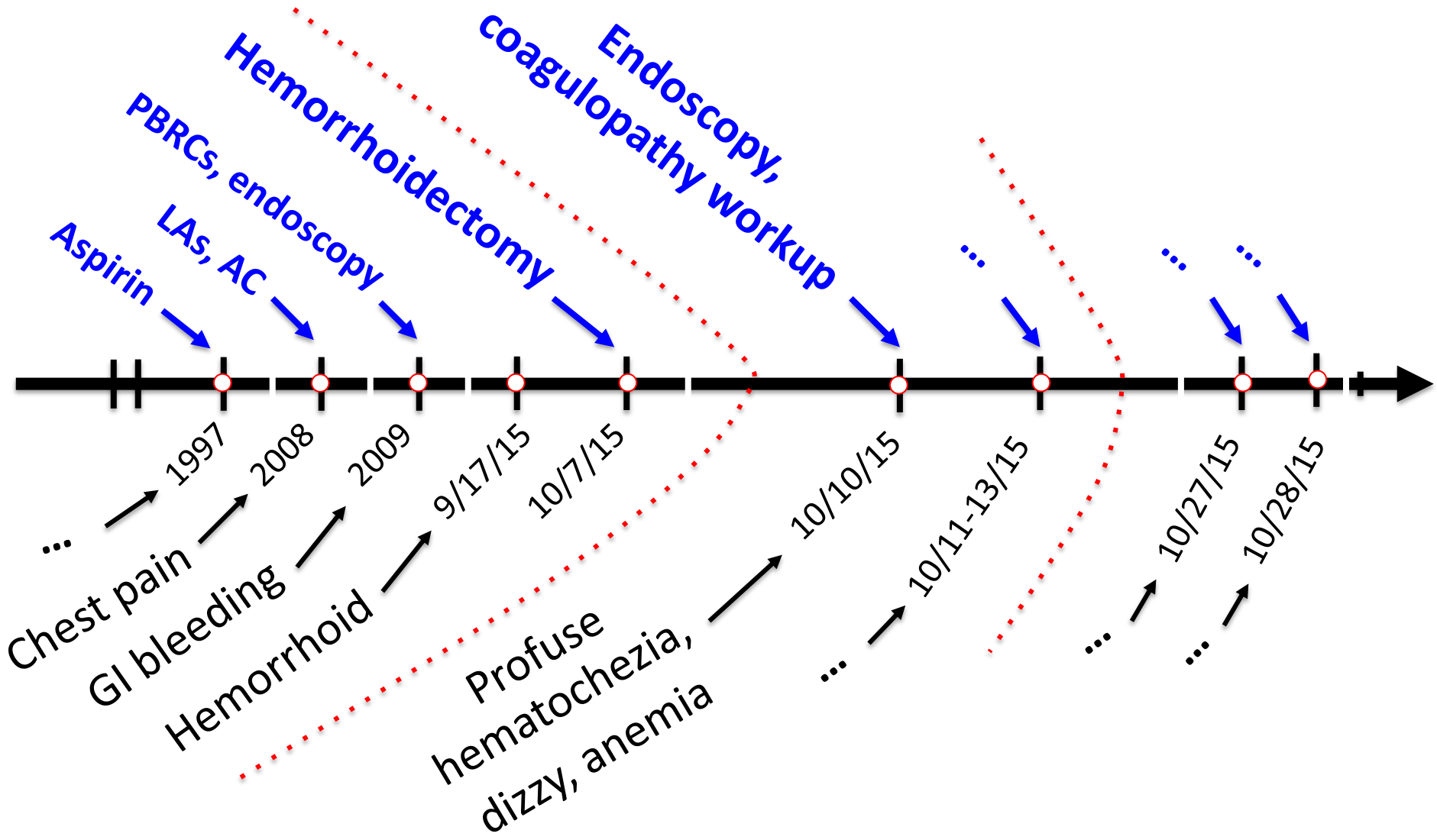
Case

72 YEARS OLD FEMALE PRESENTED TO KUMC WITH BLEEDING FOLLOWING ROUTINE HEMORRHOIDECTOMY SURGERY

Past Medical History

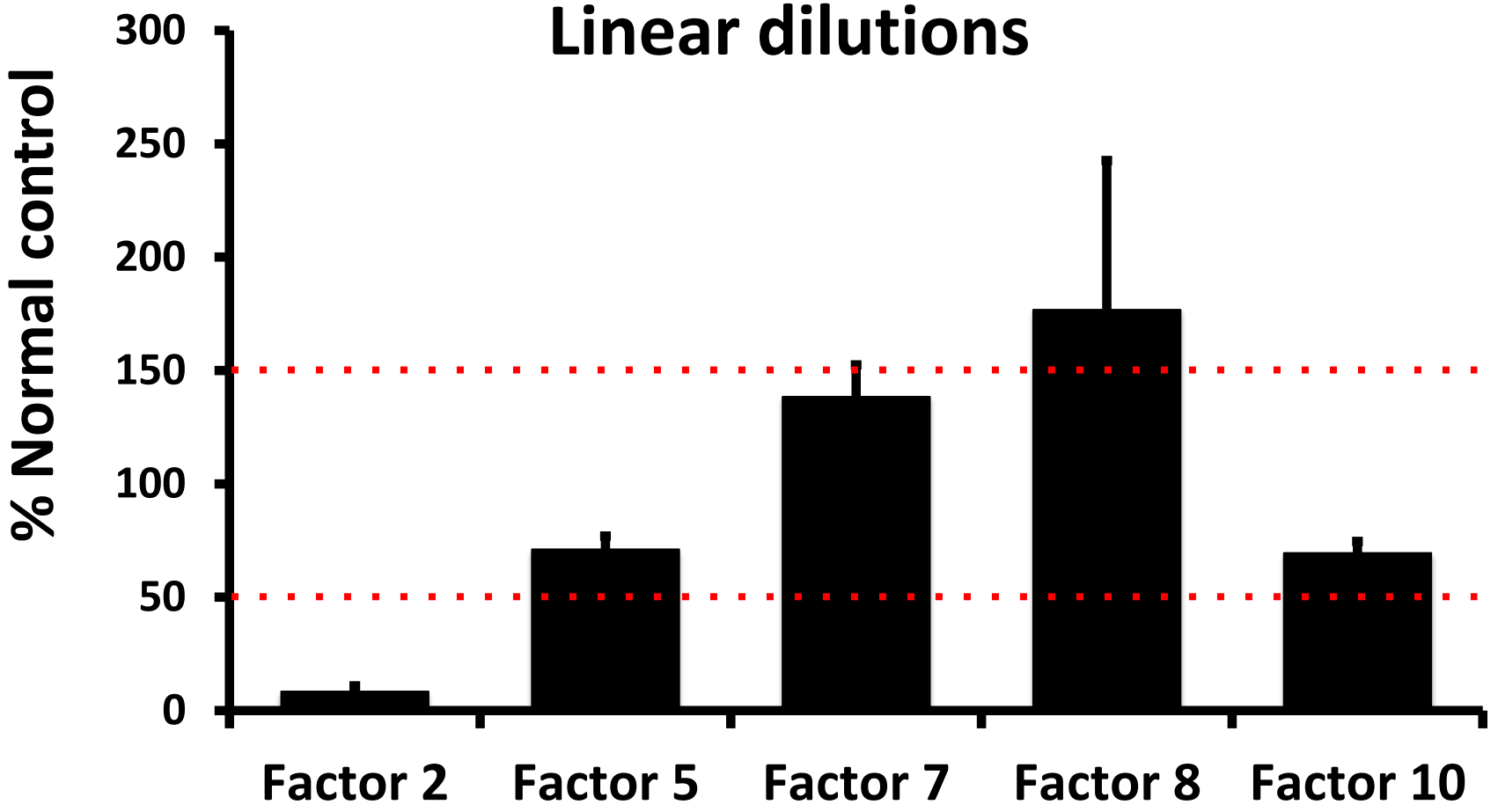
- Surgeries: Bilateral tubal ligation, appendectomy, partial hysterectomy, bilateral bunion surgery
  - No bleeding complications
- 2008: Presented to ER with chest pain
  - Incidentally found prolonged PT and PTT → + Lupus anticoagulant and anticardiolipin antibodies
- 2009: Melanotic stool with severe anemia (Hb 4)
  - Blood transfusion (>10 units)
  - Attributed to long-term use of Aspirin

Brief course



Initial Work-up

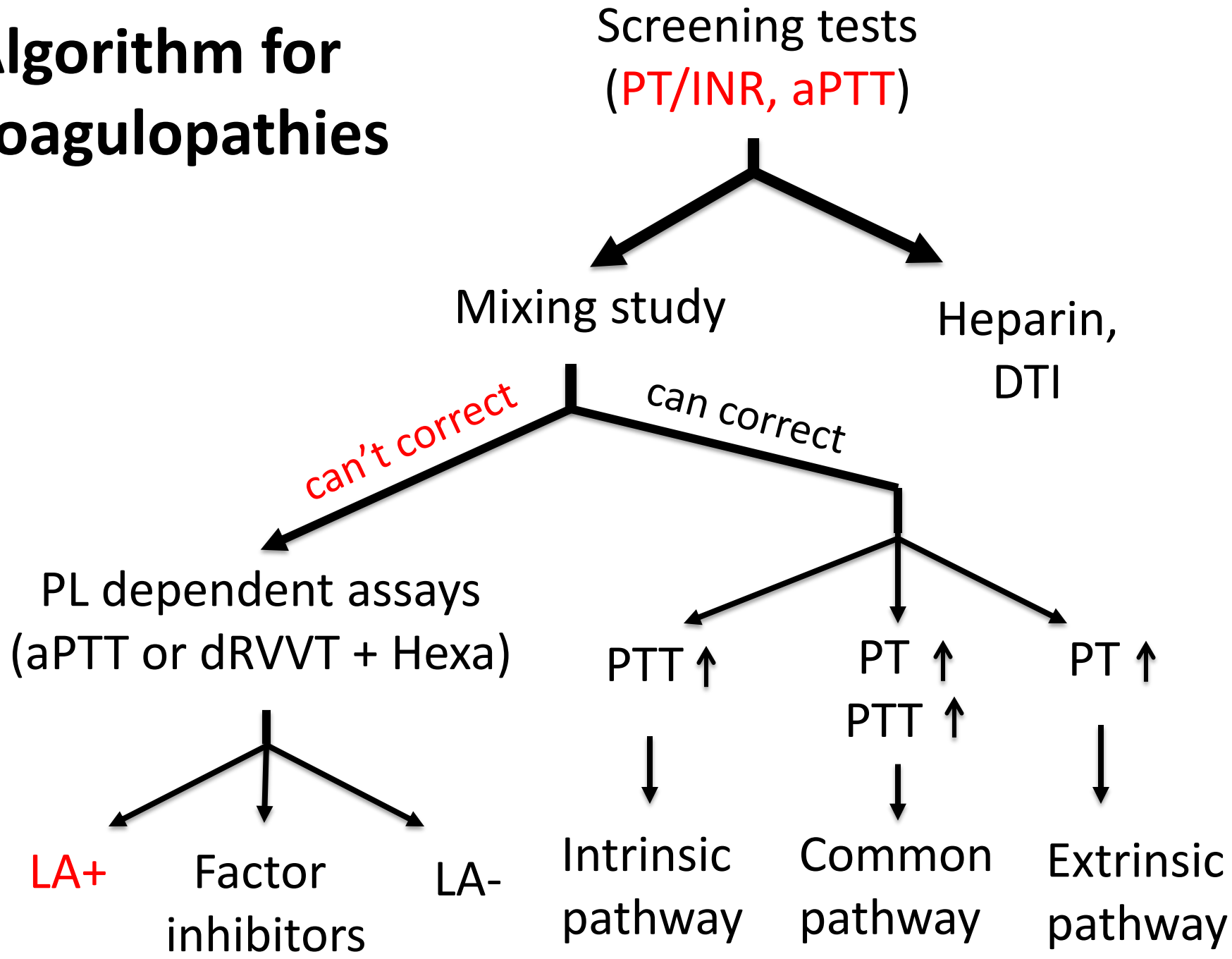
Test	Reported Value	Normal Range
PT/INR	2.2 (HIGH)	0.8-1.2
PTT	87.4 (HIGH)	24.0-40.0
PT mixing study @ 60 mins	1.5 (HIGH)	
PTT mixing study @ 60 mins	82.8 (HIGH)	
Factor 2 assay	10% (LOW)	50-150%
Factor 5 assay	78%	50-150%
Factor 7 assay	153% (HIGH)	50-150%
Factor 8 assay	235% (HIGH)	50-150%
Factor 10 assay	68%	50-150%


Linear dilutions
% Normal control
300
250
200
150
100
50
0
Factor 2
Factor 5
Factor 7
Factor 8
Factor 10

Additional coagulation study

Test	Result	Interpretation
dRVVT	Prolonged	Lupus anticoagulant Abs
Hexagonal Lupus anticoagulant	Positive	Lupus anticoagulant Abs
Anti-β2 GPI IgG	Positive	Support APS diagnosis
Anti-β2 GPI IgM	Positive	
Anti-cardiolipin IgG	Positive	
Anti-cardiolipin IgM	Positive	
Factor 2 inhibitor (activity-based)	<0.4 BU	There is NO Factor 2 inhibitor, therefore previous result of low Factor 2 level was due to lupus anticoagulant Abs against phospholipids in the assay.

Algorithm for coagulopathies



Revised Criteria for Antiphospholipid Syndrome (APS)
(*Sydney Criteria*)

APS: ≥ 1 Laboratory Criteria AND
≥ 1 Clinical Criteria

✓ **Laboratory Criteria**: "≥ 2 occasions 3 months apart"

1. Lupus anticoagulant antibody (LA)
2. Anti-Cardiolipin IgG and/or IgM (αCL)
3. Anti-β_2 Glycoprotein I IgG and/or IgM ($\alpha\beta$2-GPI)

✗ **Clinical Criteria**

1. Vascular **thrombosis** by imaging or pathology
2. **Pregnancy morbidity**
   - b). ≥ 3 consecutive spontaneous abortion of <10wk
   - a). ≥ 1 death of >10wk old fetus with normal morphology
   - c). ≥ 1 premature birth (<34wk) of morphologically normal fetus due to eclampsia or severe preeclampsia or recognized features of placental insufficiency

IS THE PATIENT'S BLEEDING EPISODE RELATED TO LUPUS ANTICOAGULANT OR SURGERY?

Clinical follow-up

Patient discharged home to follow-up in hematology clinic

#1 Recent lower GI bleed without clinical evidence of coagulopathy
#2 Prolonged APTT, secondary to Lupus Anticoagulant
#3 Prolonged PT, likely secondary to in-vitro inhibition of factor II by antiphospholipid antibodies
#4 Antiphospholipid antibodies without evidence of clinical pro-thrombotic syndrome
#5 Possible SLE

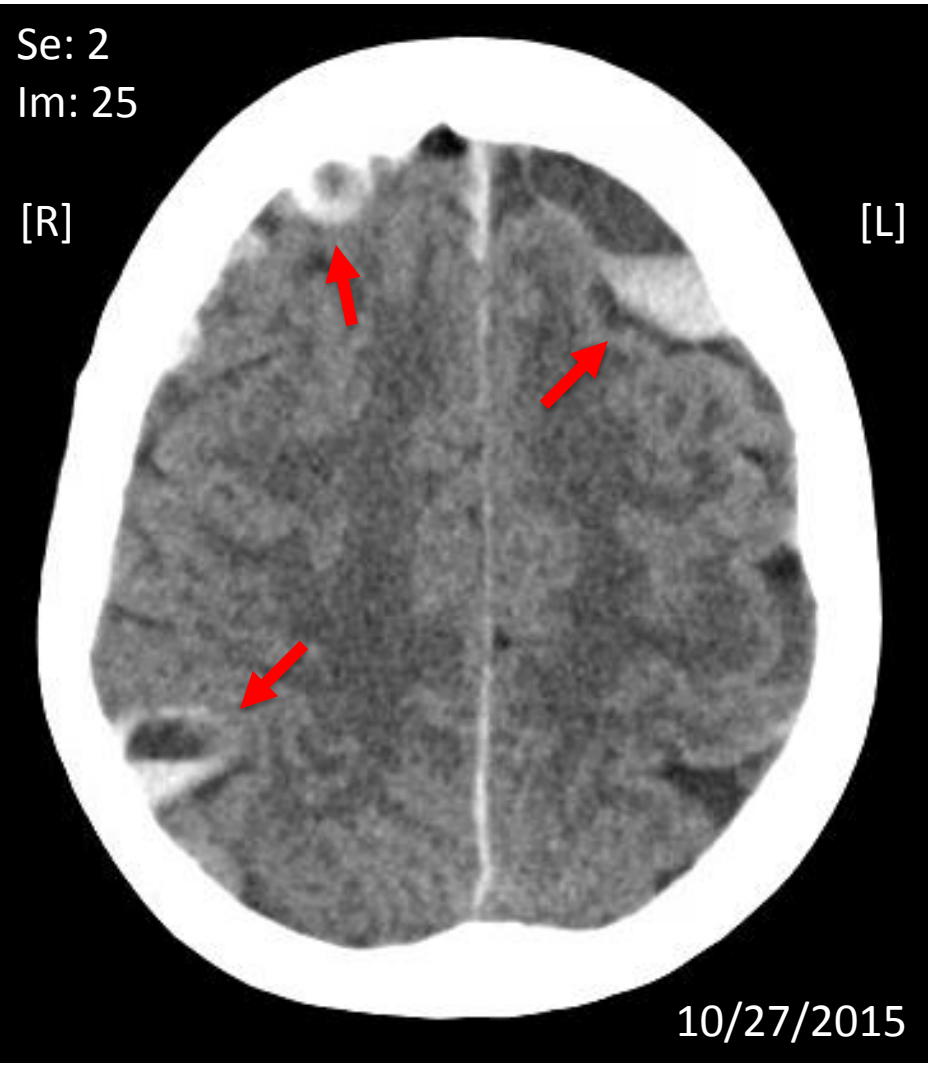
Dr. Yacoub and I had a long discussion with Ms. XXXX and her husband, explaining the constellation of laboratory abnormalities in the context of the patient's bleeding event. Our assessment is as follows:

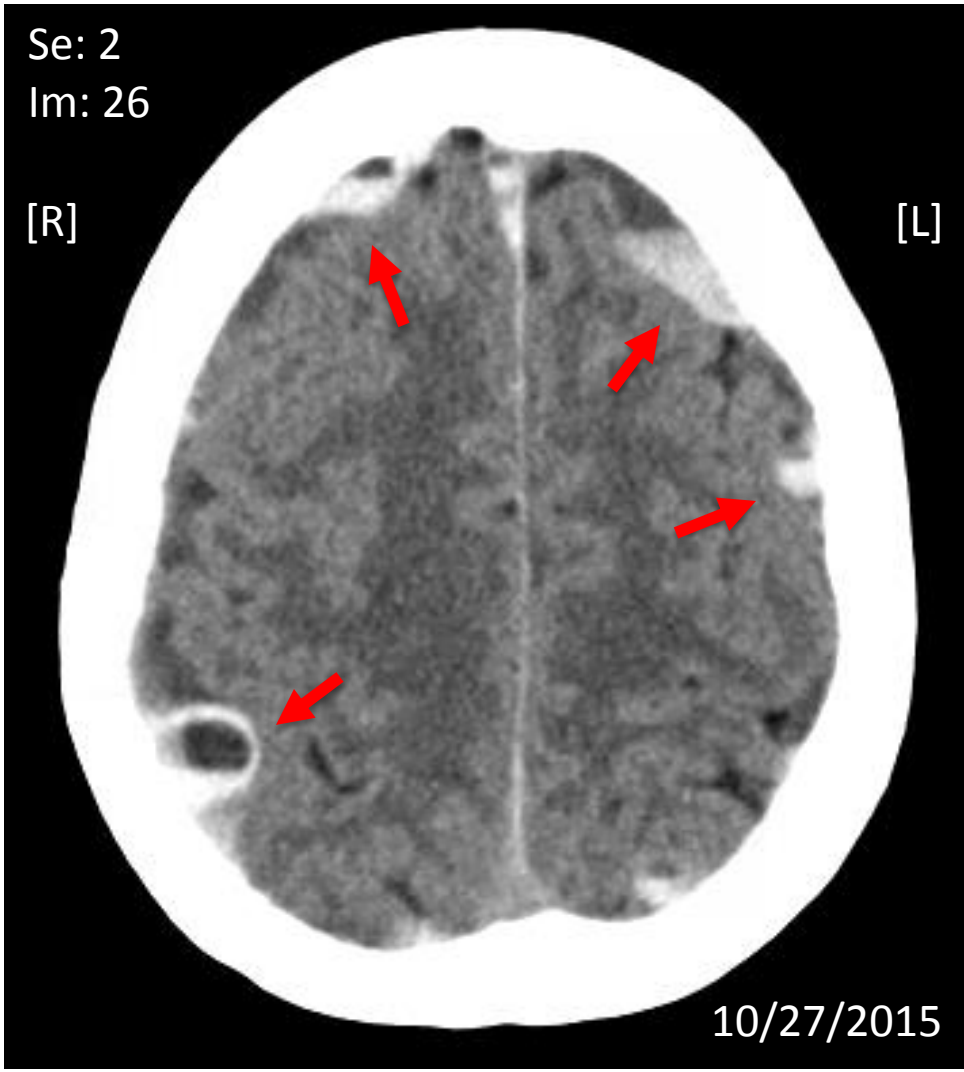
1) The patient does not appear to have a pathologic pre-disposition toward bleeding events. Her previous upper GI bleed was secondary to AVMs, and it was also in the context of copious NSAIDs use. The recent bleeding event, although unfortunate, appears to be due to a not-uncommon complication of her procedure. The patient's history of tolerating multiple surgeries and childbirths argues strongly against a clinical bleeding syndrome.

2) The patient's laboratory abnormalities are complex and quite unique. The prolonged APTT is a known laboratory artifact of antiphospholipid antibodies (Lupus Anticoagulant), and this does not pre-dispose to bleeding events.

3) The prolonged PT is more difficult to explain. Although certainly less common than prolonged APTT, the PT can also be prolonged in some patients with antiphospholipid antibodies, and the reason is not fully understood. However, many patients with antiphospholipid antibodies have antibodies against prothrombin. A subset of these antibodies are actually proteolytic and have "prothrombinase" activity. I am suspicious that this phenomenon best explains the patient's low factor II activity, lack of correction of coagulation studies with mixing, and lack of detectable inhibitor. Furthermore, this proteolytic phenomenon is actually a risk factor for thrombosis, not bleeding (as one might assume), so I think this phenomenon is also consistent with the patient's lack of pathologic bleeding tendency.

7 days later, patient had a headache…and intracranial multifocal hemorrhages





ARE THE PATIENT'S BLEEDING EPISODES AND LUPUS ANTICOAGULANT RELATED?

Further Work-up

Test	Result	Normal Range
Anti-factor 2 Ab ELISA, IgM	165.3 (High)	0.0-19.9
Anti-factor 2 Ab ELISA, IgG	106.8 (High)	0.0-19.9

Diagnosis

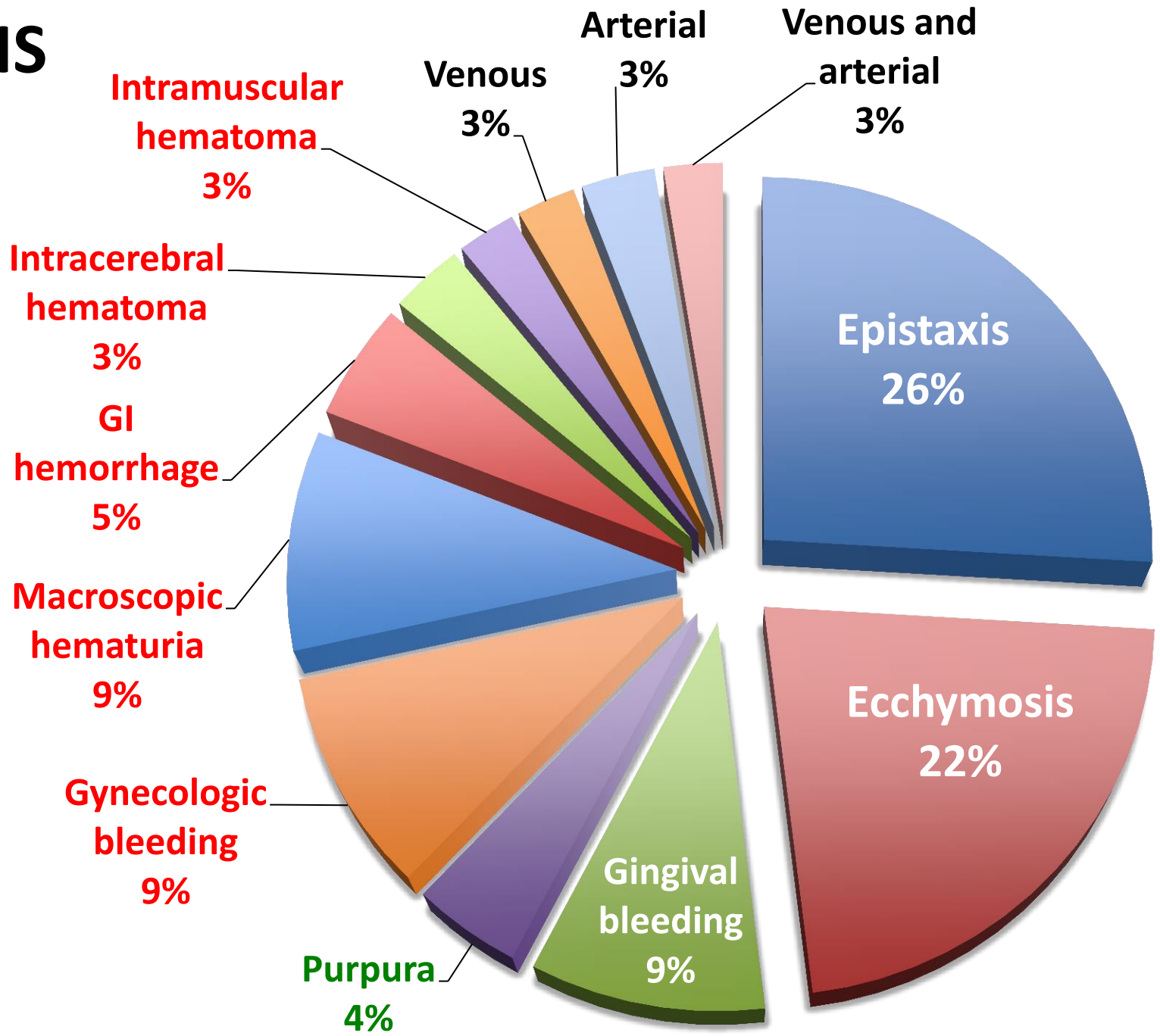
LUPUS ANTICOAGULANT HYPOPROTHROMBINEMIA SYNDROME

Lupus Anticoagulant Hypoprothrombinemia Syndrome (LAHS)

- Definition:
    - Lupus anticoagulant activity AND
    - Acquired Factor 2 deficiency
- Most common clinical presentation: bleeding

• **Common causes of bleeding in antiphospholipid Ab$^+$ patients**
Lupus anticoagulant hypoprothrombinemia syndrome (LAHS)
Thrombocytopenia *(Note: This patient had a normal platelet count.)*
Catastrophic APS or other thrombotic microangiopathies
Other situations (eg, excessive anticoagulation, surgery, etc.)

LAHS


Intramuscular hematoma 3%
Venous 3%
Arterial 3%
Venous and arterial 3%
Intracerebral hematoma 3%
GI hemorrhage 5%
Macroscopic hematuria 9%
Gynecologic bleeding 9%
Purpura 4%
Gingival bleeding 9%
Ecchymosis 22%
Epistaxis 26%

APS VS LAHS

Features	APS	LAHS
Most common clinical features	Thrombosis, Pregnancy morbidity	Bleeding
Laboratory tests	LA, αCL, αβ2-GPI, others	LA, Factor 2 <60%
Management	Immunosuppressants, Anticoagulation	Immuosuppressants, Factor 2 concentrate
Prognosis	5% mortality rate, but 50% for Catastrophic APS	4% mortality rate; 11% recurrent rate
Most common cause of death	Thrombosis	Bleeding
Challenge	Proper time to stop or start anticoagulation	

Medicine (Baltimore). 2012 Sep;91(5):251-60.

Lupus anticoagulant-hypoprothrombinemia syndrome: report of 8 cases and review of the literature.

Mazodier K, et al

Abstract

The lupus anticoagulant-hypoprothrombinemia syndrome (LAHS)--the association of acquired factor II deficiency and lupus anticoagulant--is a rare disease drastically different from antiphospholipid syndrome in that it may cause predisposition not only to thrombosis but also to severe bleeding. …between 1960 and April 2011, LAHS has been reported in 74 cases. …Corticosteroids should be considered the first-line treatment, but the thrombotic risk strongly increases during treatment … the disease is persistent and severe hemorrhagic complications are common.

WHY WAS THE FACTOR 2 INHIBITOR ASSAY NEGATIVE?

Non-neutralizing inhibitors

- Bind factors and rapidly clear them from circulation.
- Laboratory investigations appear to have factor deficiency. However, mixing study appears non-correcting because there's LA antibodies present.
- Mechanism frequently cited in LAHS.

Our Patient's Hospital Course vs Factor 2 Levels

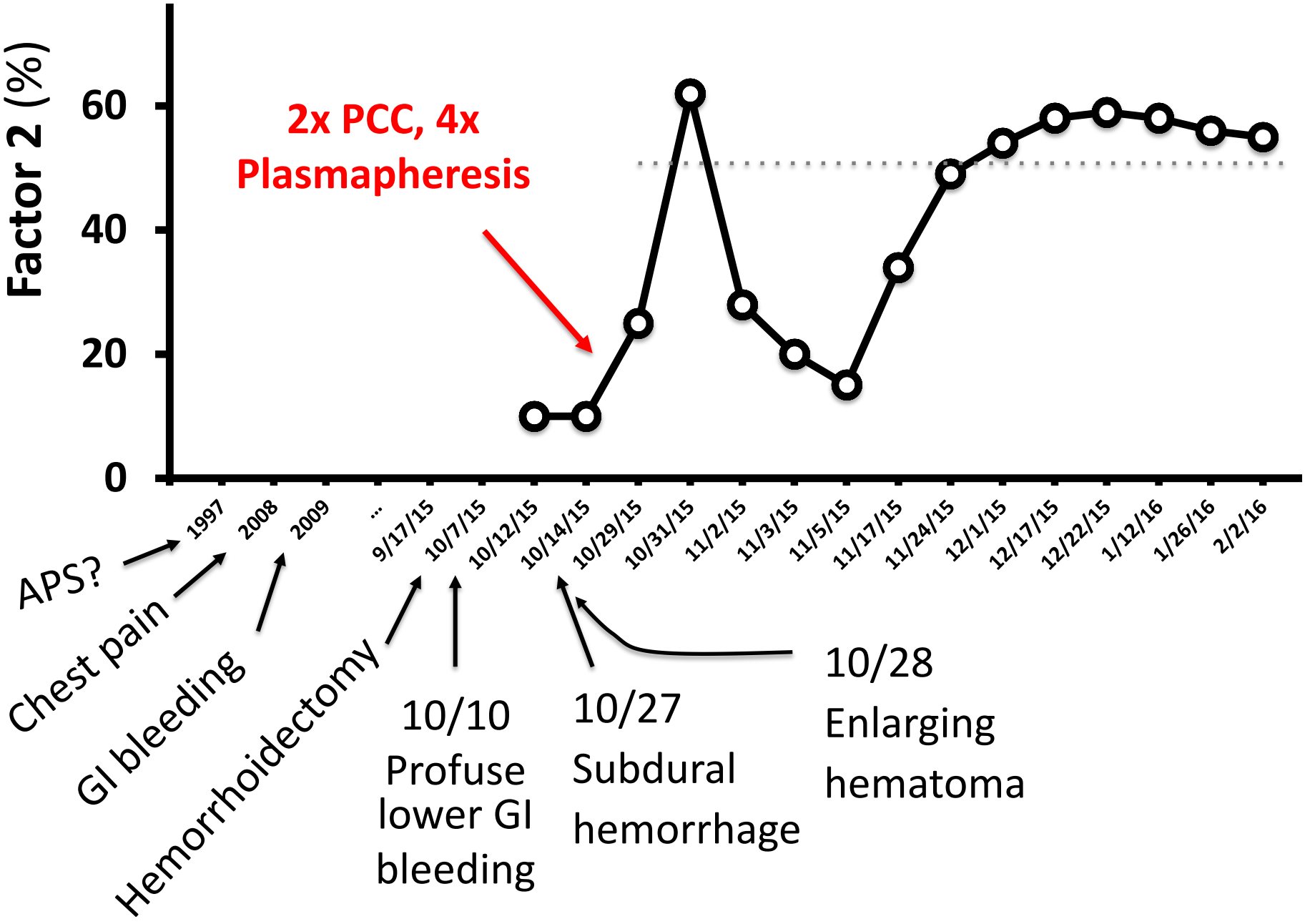


Chart Review (Last refresh: 11:01:10 PM)

Notes/Trans | Encounters | Surgeries | Anesth | Labs | Imaging | Meds | Procedures | Cons/Ref | Th

Filters | Refresh | Route | Review Selected | Apply Default Sorting

18 records match filters, all records loaded — Current Meds Only

Filters: Current Meds Only

Date	AMB...	Medication	Order Detail	Provider	End Date
1/15/2016	AMB	alendronate (FOSA...	Take 1 Tab ...	Pim Jetanalin, MD	
	AMB	ascorbic acid(+) (V...	Take 1 Eac...	HISTORICAL PROVID...	
1/15/2016	AMB	atovaquone (MEPR...	Take 10 m...	Pim Jetanalin, MD	
	AMB	calcium carb and c...	Take 1 Tab ...	HISTORICAL PROVID...	
	AMB	cyanocobalamin (V...	Take 1,000...	HISTORICAL PROVID...	
11/10/2015	AMB	cyclophosphamide...	Take 5 Cap...	Abdulraheem Yacoub,...	5/8/2016
11/3/2015	AMB	docusate (COLAC...	Take 1 Cap...	Mohammad Taha, MD	
	AMB	ferrous sulfate 325 ...	Take 325 ...	HISTORICAL PROVID...	
10/16/2015	AMB	flecainide (TAMBO...	Take 1 tabl...	Matthew Jones, DO	
	AMB	folic acid 400 mcg ...	Take 800 ...	HISTORICAL PROVID...	
11/16/2015	AMB	hydroxychloroquin...	Take 1 Tab ...	Julian Magadan, MD	
	AMB	lactobacillus rham...	Take 1 Cap...	HISTORICAL PROVID	
11/3/2015	AMB	levothyroxine (SYN...	Take 1 Tab ...	Mohammad Taha, MD	
11/3/2015	AMB	melatonin 3 mg tab	Take 1 Tab ...	Mohammad Taha, MD	
11/3/2015	AMB	metoprolol XL (TOP...	Take 1 Tab ...	Mohammad Taha, MD	
1/15/2016	AMB	omeprazole DR(+) ...	Take 1 Cap...	Pim Jetanalin, MD	
11/16/2015	AMB	predniSONE (DELT...	Take with 2...	Julian Magadan, MD	
11/16/2015	AMB	predniSONE (DELT...	Start 50 m...	Julian Magadan, MD	

CTX till 5/8/2016

Hydrochloroquine

Prednisone

Update on 2/9/2016

Assessment and Plan:

Ms. Xxxx is a 72-year-old lady with SLE who presents to KUMC Hematology/Oncology Fellows Clinic to follow-up on acquired Factor II deficiency secondary to antiphospholipid antibodies.

#1 Acquired Factor II Deficiency, secondary to antiphospholipid antibodies
#2 Pancytopenia, likely secondary to cyclophosphamide toxicity
#3 Pulmonary emboli

1) We have obtained a CTA of the chest, and this has confirmed the presence of small pulmonary emboli. We'll initiate anticoagulation with lovenox.

2) We will discontinue cyclophosphamide, given that Ms. xxxx's Factor II assay has been stable in the normal range and that she appears to be having significant toxicity.

3) Continue prednisone and plaquenil. Decrease prednisone to 10 mg daily.

Update on 2/13/2016

W. J. P.
Admission Date: 2/13/2016

Reason for Consult:
Known pt with antiphospholipid and bleeding hx, here with shock, e/o sepsis. On lovenox as of 2/9 for PE, now with hemoptysis reported on transport. Please assist with med management.

Assessment/Plan:

…

#Recent history of PE

- Evidenced by CTA on 2/9/2016. She was started on Lovenox 60mg BID and she has been taking this medication with good compliance until yesterday.
- Anticoagulation on hold for now

Death Pronouncement by Jessica Chia, MD at 02/14/16 0449

Author: Jessica Chia, MD
Filed: 02/14/16 0451
Status: Signed
Service: Pulmonary
Note Time: 02/14/16 0449
Editor: Jessica Chia, MD (Physician)
Author Type: Physician
Note Type: Death Pronouncement

Physician Death Pronouncement

[redacted]

Physician Pronouncing Death: Jessica Chia, MD: Pager 2068

Date Death Pronounced: 2/14/06

Time Death Pronounced: 0442 am

Service Attending Physician: Kyle Brownback, MD

Service Resident Physician: N/A

After identification of patient confirmed, death was pronounced on the basis of:
Patient unresponsive to verbal or tactile stimuli, No heart sounds heard or pulses palpated, Pupils fixed and dilated, no pupillary light or corneal reflex and ventilator still delivering breaths though no spontaneous respiratory effort nor any cardiac circulation

The following family or contacts were notified of patient's death: Family at bedside- husband, daughter, sister, and extended family members

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Acknowledgment

I appreciate Dr. Xiuxu Chen work on this case, as well as critical comment on the presentation.

Thank you for your attention.