The Fritsma Factor

YOUR INTERACTIVE HEMOSTASIS RESOURCE

Lab Week Case Studies—April 22–28, 2018

George A. Fritsma, MS MLS

Dear Fritsma Factor Cheat Sheet Reader and Blog Participant:

Happy Laboratory Professionals Week! As an added Fritsma Factor benefit, we offer these case studies for your information, gleaned from current and recent Fritsma Factor posts. Please post your answers and discussion to Fritsma Factor via the Contact function or send your comments to George at george@fritsmafactor.com.

An Athletic 59-YO Male with a DVT

I (George) have corresponded with a gentleman since 2009; we've developed an electronic friendship, though we've never met F2F.

"John" first contacted me in 2009, a year after Precision BioLogic and I launched Fritsma Factor. John is a professional man who claims to be overweight but who plays ice hockey for recreation. A puck hit him in the calf in 2009, and when the pain and swelling persisted, he saw his primary care physician who ordered an ultrasound, which indicated deep vein thrombosis. John's doctor started him on a round of Coumadin therapy and monthly PT/INRs. His treatment course was uneventful, and after the Coumadin was discontinued he had a thrombophilia workup that returned normal results except for homocysteinemia. John took over the counter folate, vitamin B6, and vitamin B12 plus a baby aspirin but had discontinued all four sometime along the way. He continues to play hockey.

On February 10, 2018, John experienced new pain in the location of the old clot, this time not related to his physical activities—that is, no identifiable trigger. His primary had retired, so he saw an ER doctor, who ordered a new ultrasound. The radiologist read the old DVT location as having two consolidated clots and one new one. Neither doctor had access to the 2009 image, only a written summary. On the basis of the new finding, John was prescribed Xarelto (rivaroxaban), which he is continuing, and which he reports causes more profuse and prolonged bleeds subsequent to shaving nicks than did the Coumadin. He has been offered no laboratory assay. John is retired, but when he was working he traveled often and never had a travel-associated DVT.

Here are John's questions, which I paraphrase. Please answer and discuss on Fritsma Factor:

- How accurate is his new diagnosis?
- How long will he be required to stay on Xarelto?
- What are the Xarelto bleeding characteristics?
- How is Xarelto best measured, and what is the value of assaying Xarelto?
- Should he have a new set of thrombosis risk tests? Which should be repeated?
- Could the new episode indicate onset of a new risk factor such as lupus anticoagulant or cancer?

A Patient on Xarelto with Elevated D-dimer Results

In 2016, **Dr. Louann Lawrence,** New Orleans, communicated with a patient who had experienced a DVT and PE in 2014 and was being treated with Xarelto (rivaroxaban). The patient's physician routinely ordered a D-dimer to assess the risk of a recurrence after discontinuing the anticoagulant therapy. Following the physician's instructions, the patient discontinues Xarelto for 24 hours before specimen collection, but each time the D-dimer result is around 800 ng/mL D-dimer units, reference limit 240 ng/mL, so therapy is resumed. The patient has since had a D-dimer performed *at* another facility using an alternate technology, yielding a result of 230 ng/mL D-dimer units, within the alternate lab's reference interval. The patient subsequently had a D-dimer performed at a reference laboratory and the results were normal, yet the D-dimer remained elevated to approximately 800 ng/mL DDU when measured *at* the original site. The patient believed the Xarelto was interfering with the DDU.

George discussed this case with **Dean Willett**, Precision BioLogic, who suggested some potential interfering substances such as lipemia, hemolysis, or fibrin degradations products. George also discussed it with **Bob Gosselin**, California, who provided a plausible answer, and with **Jeanine Walenga, PhD**, who offered a slightly different approach to using the D-dimer. But first…

- Do you support the concept of performing a D-dimer before discontinuing anticoagulant therapy?
- Do you support the physician's recommended 24-hour Xarelto discontinuance?
- Could the variation have to do with the formulation of the D-dimer kit?
- Could this be confusion caused by variation in the reporting units?
- Does Xarelto interfere with the D-dimer assay?
- If not, what is causing the elevated D-dimer?
- What is the next step?

A Patient Whose Protein S is Less Than 1%

In March of 2018, George had a phone conversation with a reference lab colleague who generated protein S levels on a patient specimen: free and total protein S concentrations both ≥70%, clot-based protein S activity less than 1%. PT normal, PTT prolonged by about 15 seconds. Dilute Russell viper venom time (DRVVT) primary (screen) test for lupus anticoagulant prolonged, not shortened by platelet phospholipid-rich confirmatory reagent. The colleague reports the same pattern for the tissue thromboplastin inhibition (TTI) screen/confirm test for lupus anticoagulant. The thrombin time was normal. George's colleague reports two other specimens from the same facility with similar findings. No clinical information was available.

- What could account for these findings?
- What would you do next?

A Hemorrhaging Newborn

Coagulation specialist **David McGlasson** provided this case from several years ago. A pediatric resident was horrified to find a previously healthy newborn hemorrhaging in the nursery. She collected a venous blood sample for a coagulation workup. The PT was 17.2 seconds and the PTT 179 seconds. The resident, who knew the infant was not prescribed an anticoagulant, was skeptical of the results so she collected a fresh sample that yielded similar results. She asked the laboratory scientist for follow-up assistance. The infant suffered acute blood loss but survived to adulthood and remains in good health.

- What follow-up assays would you recommend?
- What results of follow-up assay results would you predict?
- What could have happened to the infant?

A Man Treated for a DVT

A 60 year-old man was treated for deep venous thrombosis with Coumadin. After three weeks' therapy, the physician ordered a thrombosis risk profile. The results are…

Assay	Patient	RI
Protein C activity	35%	>70%
Protein S activity	39%	>65%
Antithrombin activity	57%	78−126%
Factor VIII	125%	50−186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L

- Is he a triple heterozygote?
- What should be done about his therapy?
- What should be done about these results?
- What assays do you include in your thrombophilia profile
- What is the best time to order and perform a thrombophilia profile?

Pre-op Screen

A 49-year old athletic woman who is in otherwise good health is scheduled for arthroscopic knee surgery. Her surgeon orders a routine pre-up screen, which yields the following results.

Assay	Patient	RI
HGB	14.2 g/dL	13.5–15.6 g/dL
PTT	59 s	25–35 s
PT	12.4 s	9.8–12.6 s
TT	18.2 s	<21 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL

The patient reports no bleeding symptoms. The surgeon postpones the procedure and asks the laboratory to "work up" the results.

- What is the laboratory scientist's next step?
- What are the probable outcomes from the reflex test?
- Based on the result of the reflex test, what further assays could be performed?
- Comment on the value of the pre-op screen.

A Middle-aged Man with PE

I (Geo) recently received a message from a fellow medical laboratory scientist in a western US state who was concerned about a friend. The gentleman had experienced a pulmonary embolism and was being treated with Pradaxa (dabigatran) at home. Despite his treatment, he was experiencing increased shortness of breath and was dependent on oxygen. George's colleague asked…

- Can some lab provide an assay for Pradaxa plasma level?
- What assay is available?
- Can the Pradaxa dosage be modified?

George asks further…

- Assuming we learn the Pradaxa is ineffective for this patient, what is the next step?

A Veteran with a Bleeding Disorder

Another historic case from **Dave McGlasson**. "Here is a case I worked up on a man in the early 1980s who VA hospitals were meant for. He was a 50-year-old retiree who had fought in both Korea and three tours of Vietnam. He had enlisted as a private and retired as a full Colonel and was being treated for old knee wounds. I did a full coagulation work-up on him because he experienced severe bleeding every time he was operated on. He did not have any other trauma and had never had any issues with hemorrhaging except in surgery."

"He had a normal CBC, platelet count, PT, and PTT. However his bleeding time (which was still being used back then) was >12 minutes. I performed light transmittance aggregometry and found poor aggregation to ADP, epinephrine and collagen with normal ristocetin aggregation. I also performed a platelet factor 3 (PF3) level and found it normal. His FVIII and VWF by Laurell electrophoresis were normal. The patient was really agitated and apprehensive about the surgery so I started to try to ease him just talking about his military career and his general health. I asked him what he took for pain for the knee problems and he said he couldn't take the stuff they gave him from the VA because it made him feel high."

- What assay has taken the place of the now-discredited bleeding time?
- Does anyone remember how the PF3 was performed and what its results could indicate?
- Can anyone describe Laurell electrophoresis?
- What might account for the prolonged bleeding time and reduced aggregation patterns?
- What could be done to ensure the Colonel doesn't experience bleeding during his next surgical procedure?

A Hemophilic Boy with Frequent Bleeds

An 8-year-old hemophilic boy manages bleeding with very-other-day infusions of Advate, but experiences more and more frequent bleeds.

- What laboratory assay profile may be necessary to learn the reason for his bleeds?
- How are these assay results interpreted?
- What are some alternative therapies that may reduce the number of bleeds?
- What new therapies are currently under investigation?