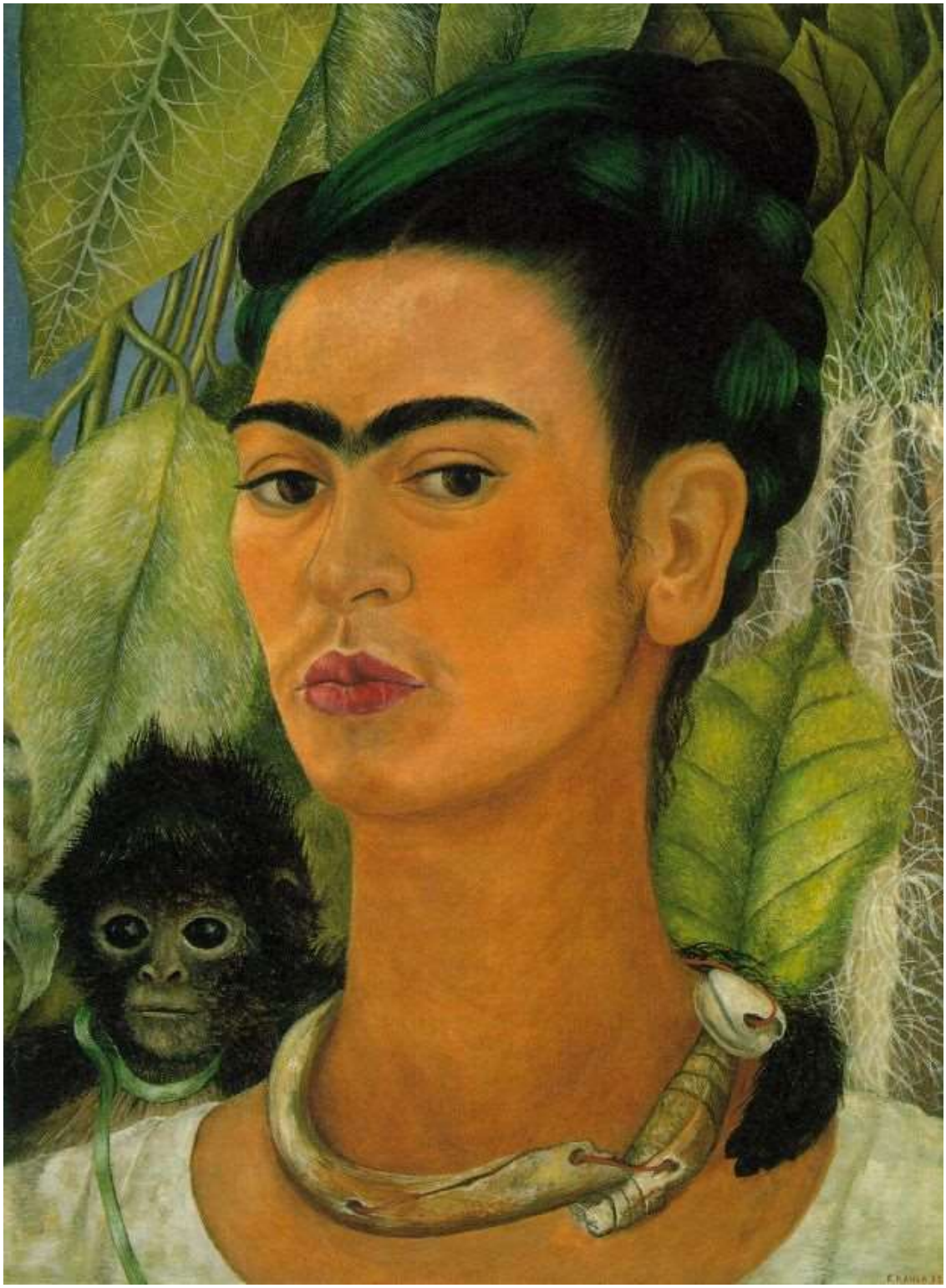
THE NORTHERN HOSPITAL

ANTIPHOSPHOLIPID SYNDROME



"Self Portrait with Monkey", oil on canvas, 1938, Frida Kahlo.

"Surely as in both Western and Mayan tradition, the monkey is a symbol of lust or promiscuity. And in "Escuincle Dog with Me" as in "Remembrance of an Open Wound", something naked and yet absolutely self-contained in the unblinking, undeviating directness of her gaze; like the regard of certain animals and children, it makes the viewer feel naked too. From the evidence of these self-portraits it is perfectly clear that Frida is a woman who has loved and been loved...."

Hayden Herrera, "Frida", 1983.

GREEN:	*Warm and good light.*
REDDISH PURPLE:	*Aztec. Tlapali (Aztec word for "color" used for painting and drawing). Old blood of prickly pear. The most alive and oldest.*
BROWN:	*Colour of mole., of the leaf that goes. Earth.*
YELLOW:	*Madness, sickness, fear. Part of the Sun and of joy.*
COBALT BLUE:	*Electricity and purity. Love*
BLACK:	*Nothing is black, really nothing.*
LEAF GREEN:	*Leaves, sadness, science. The whole of Germany is this colour.*
GREENISH YELLOW:	*More madness and mystery. All the phantoms wear suites of this colour…or at least underclothes.*
DARK GREEN:	*Colour of bad news and good business.*
NAVY BLUE:	*Distance. Also tenderness can be of this blue.*
MAGENTA:	*Blood ? Well, who knows!*

Frida Kahlo, personal diaries, c. 1945.

Frida Kahlo held her first solo exhibition in New York City at the Julien Levy Gallery in November of 1938. Twenty-five of her paintings were exhibited and half of them were sold. It was major triumph for a first time exhibitor. The exhibition catapulted Frida onto the world stage as an Artist in her our right, she was no longer simply the wife of the great Muralist, Diego Rivera. A number of wealthy clients also commissioned Frida to produce new works, amoung them was no less than Anson Conger Goodyear, the President of the Museum of Modern Art, (MOMA) in New York City. Goodyear had desperately wanted to buy "Fulang Chang and I", however Frida had given it as a gift to one of her close American friends, Mary Sklar, the sister of the Art historian, Meyer Schapiro. Frustrated by his loss he immediately commissioned a new self-portrait from her. Frida, agreed to the commission, promptly returned to her hotel room and there over the next few days produced one of her most famous works, "Self-Portrait with Monkey".

Goodyear in the end got one of Frida's most iconic paintings, he need not have mourned missing out on "Fulang Chang and I"!

"Self-Portrait with Monkey" oil on canvas, 1938, was just one of virtually an unbroken line of self-portraits Frida produced over her painting career, that records every stage of her Artistic development. No other Artist in history, save perhaps, Rembrandt van Rijn recorded their life so completely in self-portraits; it was a motif that occupied almost a third (but by some accounts, half) of her known works, especially during the time of her separation and divorce from her husband in 1939, when she painted almost exclusively, her own image. Goodyear's portrait captures an especially lonely period in Frida's life. Unable to have her own children, betrayed by her husband and by her beloved sister who had had an affair with her husband, it was the most desperately lonely period of her life. All this just as her fame as an Artist was beginning to rise. But out of the greatest adversity can be born some of the greatest Art. "Self-Portrait with Monkey" is one of the best examples of her self-portraiture - her face utterly expressionless, the dark eyes uncomfortably gazing back at the viewer, they suggest a deep inner pain, but at the same time they radiate strength, defiance, resilience, there are no tears here. No matter how much the internal hurt, she will survive. "I paint myself, because I am so often alone", Frida once explained, "and because I am the subject I know best".

"Self Portrait with Monkey", shows many hallmark motifs of Frida's. Her elegant long neck, and the elongated hand of her beloved pet monkey, Fulang Chang, one of many pets, surrogates to the children she could never have, recall the style of the late Renaissance, or Mannerism, a period of Art that Frida had studied, knew well and loved. The monkey is both a Western and Mayan symbol of lust or promiscuity; the context here is ambiguous. Is it suggesting love, or barely suppressed lust. A ribbon, a ubiquitous motif of Frida's for the interconnectedness of life, binds her to her pet. She wears a crude ancient Aztec necklace, or rather a choker, that in her anxiety is perhaps constricting her throat. Adding to the sense of suffocation is the dense surrounding jungle, pulsing with the "milk of life" coursing through the leaves, and vines from which new shoots sprout symbolizing the cycle of life. It is a motif seen again in "My Nurse and I", oil on metal, 1937.

In a note, embedded within her elaborate doodling, from one of her diaries of the mid 1940s Frida records a list of colours to which she ascribes certain emotions and feelings. This seemingly insignificant marginalia, if read as a key, may give some fascinating insight into her emotional state at the time of any given painting. When applying this key to "Self-Portrait with Monkey", we see the faintest stain of reddish - purple; does this suggest her blood, shed as result of some brutal Aztec sacrifice? Black and green-yellow otherwise dominate the image - so, madness, mystery and fear. And the black - is this nothing? - perhaps she is saying, "well make of it all what you will, but really it's nothing - I've just done this purely for the commission of some rich gringo!" - such sentiment would not have been beyond Frida's black sense of humour.

Many of Frida Kahlo's self-portraits appear at first glance to follow the same basic plan, the fixed expressionless gaze, hiding the inner hurt, but at the same time a visage of inner strength, and supreme resilience. This may be true on a superficial level, however each work on deeper inspection is unique in the language of her surrounding symbols and motifs, that give character and life to her feelings, emotions, loves, anxieties at the

moment the work was produced. When we encounter a patient in the ED with a thrombotic disease, we may at first glance see only the same basic picture. But this is to misunderstand profound invisible subtleties. We must always consider the possibility of a very wide range of deeper underlying pathologies, thrombosis of which is simply the final outward and visible manifestation.

Frida Kahlo, c. 1938, silver gelatine print, Julien Levy, Philadelphia Museum of Art.

ANTIPHOSPHOLIPID SYNDROME

Introduction

Antiphospholipid syndrome (APS) is a **systemic autoimmune disease** characterised by **recurrent** episodes of:

- Vascular thrombosis (arterial, venous, microvascular)

And / or

- Pregnancy complications

Associated with:

- Persistent antiphospholipid antibodies.

Testing for **antiphospholipid antibodies** should be considered in patients

- **< 50 years** of age

With

- Unprovoked:
  - ♥ Venous or arterial thromboembolism
  - ♥ Thrombosis at unusual sites
  - ♥ Pregnancy complications.

In general terms treatment is with **antithrombotic therapy** but exact recommendations vary based on **arterial, venous** or **pregnancy** complications.

If associated with systemic lupus erythematosis, **hydroxychloroquine** is recommended both as **primary** and **secondary** prophylaxis.

History

Antiphospholipid syndrome was first described by the British Rheumatologist Graeme R.V. Hughes in 1983. [1]

The syndrome was initially referred to as “Hughes syndrome”.

Epidemiology

The prevalence of APS in the general population is estimated to be 40 - 50 per 100 000.

Although the association with individual antiphospholipid antibodies is controversial, antiphospholipid antibodies are thought to account for around 10 - 15% of **recurrent pregnancy loss**.

APS is frequently associated with systemic lupus erythematosis (SLE) and other autoimmune diseases, but it can occur in the absence of other autoimmune disease in many cases (i.e. primary APS).

In autoimmune disease, especially SLE, the prevalence is as high as 30%.

Classification

Antiphospholipid syndrome can be:

1. A primary disease

Or

2. A disease associated with *another* autoimmune diseases (in particular **systemic lupus erythematosis**).

Pathophysiology

The prothrombotic state in APS is principally due to **3 antiphospholipid antibodies**:

1. Anti-β2- glycoprotein:

   Antibodies to beta2-glycoprotein correlate better with the development of APS than do or anticardiolipin or lupus anticoagulants alone.

2. Anticardiolipin

3. Lupus anticoagulant

The exact pathogenesis of thrombosis and other complications in APS is complex and poorly understood.

In general terms it is it is thought that it results from *multiple interconnected mechanisms* resulting in inflammation, vasculopathy and ultimate thrombosis.

Current theory holds that the development of antiphospholipid antibodies occur in **susceptible** individuals following:

- *Incidental exposure* to infectious agents

Or

- Association with rheumatic diseases (in particular systemic lupus erythematosus),

The exact conditions creating such susceptibility however are not understood.

Once antiphospholipid antibodies have been formed, a *precipitant* (or "*second hit*") is then required for the development of the full-blown syndrome.

Precipitants, that have been implicated include:

1. Smoking
2. Prolonged immobilization
3. Pregnancy and the postpartum period
4. Oral contraceptive / hormone replacement therapy
5. Malignancy
6. Nephrotic syndrome
7. Hypertension
8. Hyperlipidemia.

Risk profile:

The risk of thrombosis is increased in the following:

1. Antibodies to beta2-glycoprotein correlate better with the development of APS than do anticardiolipin or lupus anticoagulants alone.

2. High level of antibody titres (particularly IgG)
3. Positivity for multiple antibodies (associated with the highest risk of thrombosis)
4. Additional risk factors for thrombosis at the time of diagnosis:
    - For patients with arterial thrombosis
        - ♥ Hypertension
        - ♥ Smoking
        - ♥ Diabetes mellitus
    - For patients with venous thrombosis
        - ♥ Hyperlipidaemia

Clinical features

The hallmark features of APS are:

1. Recurrent thrombotic events

    - Common types of venous thrombosis include:
        - ♥ Deep vein thrombosis
        - ♥ Pulmonary embolism
    - Common types of arterial thrombosis include:
        - ♥ TIA
        - ♥ Stroke

2. Pregnancy complications:

    These usually manifest as:

    - A fetal death after 10 weeks' gestation
    - *Recurrent* embryonic loss before 10 weeks' duration.
    - Premature birth due to severe pre-eclampsia placental insufficiency

Recurrent thrombotic events are common, with an estimated annual recurrence rate of 5 - 12%, even with anticoagulation.

Other clinical associations:

Other clinical associations include:

1. Haematological abnormalities, including:

    Commonly:

    - A prolonged activated partial thromboplastin time that fails to correct with mixing with normal plasma (owing to the presence of a lupus anticoagulant)
    - Mild to moderate thrombocytopenia.

    Less commonly:

    - Haemolytic anaemia

- Thrombotic microangiopathies e.g. thrombotic thrombocytopenia purpura (TTP).

2. Cognitive dysfunction (even in the absence of strokes)

3. Renal impairment.

4. Cardiac valvular disease

5. Dermatological:

   - Cutaneous manifestations such as severe skin ulceration and necrosis.

Catastrophic APS:

Rarely, patients with APS may present with **simultaneous thromboses affecting multiple organs**, termed "**catastrophic APS**"

Catastrophic APS is fatal in up to 50% of patients if not promptly treated.

Diagnostic criteria:

There are **no current universally accepted diagnostic criteria for APS**, and so caution is needed in extrapolating classification criteria **developed for research purposes** to clinical practice, as they have not been validated for clinical use.

Also less common manifestations of the disease also do not meet current **research criteria**.

One research set of criteria is the "Revised Classification Criteria for Antiphospholipid Syndrome", as follows:

Antiphospholipid syndrome is present if:

1. At least one of the clinical criteria is present.

And

2. One of the laboratory criteria are met.

Clinical criteria are:

1. Vascular thrombosis:

   - One or more clinical episodes of arterial, venous or small vessel thrombosis, in any tissue or organ.

     Thrombosis must be confirmed by objective validated criteria.

For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity:

- One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus.

- One or more premature births of a morphologically normal neonate before the 34th week of gestation *because of*:

  ♥ Eclampsia or severe pre-eclampsia defined according to standard definitions

  Or

  ♥ Recognised features of placental insufficiency.

- Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria are:

1. **Lupus anticoagulant** present in plasma, on two or more occasions at least 12 weeks apart.

2. **Anticardiolipin antibody** of IgG and/or IgM isotype in serum or plasma, present in medium or high titre (i.e > 40 GPL or MPL or > 99th percentile), on two or more occasions, *at least 12 weeks apart*.

3. **Anti-β2-glycoprotein 1 antibody** of IgG and/or IgM isotype in serum or plasma (in titre > 99th percentile), present on two or more occasions, *at least 12 weeks apart.*

Less common manifestations of APL syndrome that **do not appear** in the above criteria include:

1. Haematological:

- Thrombocytopenia (usually mild and asymptomatic)

- Haemolytic anaemia

2. Neurological:

- Cognitive dysfunction (unrelated to stroke)

- White matter lesions (on imaging)

3. Cardiac:
   - Valvular lesions (e.g. valve thickening and nodules)
   - Coronary artery disease and myocardial infarction
4. Renal:
   - Glomerular disease
   - Thrombotic microangiopathy
5. Cutaneous:
   - Livedo reticularis/racemosa
   - Splinter haemorrhages
   - Cutaneous necrosis and ulceration

Investigations

Testing for **antiphospholipid antibodies** should be considered in patients

- **< 50 years** of age

With

- Unprovoked:
  - ♥ Venous or arterial thromboembolism
  - ♥ Thrombosis at unusual sites
  - ♥ Pregnancy complications.

Antiphospholipid antibodies

The diagnosis of APS is established by the presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2- glycoprotein 1) **and** the appropriate clinical presentation.

Antibodies should be present on **repeat testing** at **least 12 weeks apart** given they can appear *transiently* in other conditions (e.g. infection).

Testing for other antiphospholipid antibodies directed at other antigens (e.g. antiphosphatidylserine/prothrombin antibodies) remains controversial, and their routine use is not recommended.

False positive results may occur. Antiphospholipid antibodies may be seen in up to 12% of the general population, with the prevalence increasing with age.

In the **absence** of **APS**, antiphospholipid antibodies may be seen with:

- Infections
- Medications
- Malignancy.

Although the antiphospholipid antibodies are thought to be the key to the development of thrombosis in APS, the majority of otherwise healthy individuals with antiphospholipid antibodies will not develop APS, particularly when the antibodies are seen in **isolation** or in **low titres**, or are **absent on repeat testing**.

Management

The management of APS involves 4 domains:

1. Primary prophylaxis for first thrombotic events and obstetric events
2. Secondary prophylaxis for venous and arterial thrombotic events
3. Management of recurrent thromboses
4. Management of obstetric complications.

APS must be managed by a Haematologist / Rheumatologist/ Obstetrician on a case by case basis.

In **general terms**:

Primary prophylaxis

Aspirin:

The use of aspirin to prevent a first thrombotic event in the presence of antiphospholipid antibodies remains **controversial**.

However, it may be *considered* in patients with:

- High risk antiphospholipid antibodies (i.e. triple or multiple positivity, lupus anticoagulant, persistent medium to high titre antibodies)

And if

- Other thrombotic risk factors are present, (e.g. hypertension, smoking, diabetes, hyperlipidaemia, or recent surgery).

Hydroxychloroquine:

For patients with APS associated with **SLE**, **hydroxychloroquine** has been shown to be of benefit as primary prophylaxis leading to a reduction in thromboembolic events and is thus recommended.

However, the use of hydroxychloroquine in *primary* APS is currently **not** recommended.

Prevention of venous thrombosis

In patients with APS who develop unprovoked **venous thrombosis**, anticoagulation with **unfractionated heparin** or **low molecular weight heparin** followed by a **vitamin K antagonist (warfarin)** is recommended.

An international normalised ratio (INR) of 2 - 3 is recommended.

Higher intensity warfarin (INR, 3 - 4) has not been shown to reduce the risk of recurrent venous thrombotic events and is associated with a higher rates of bleeding.

Anticoagulation should continue **long term** as the risk of recurrent thrombosis is high if treatment is stopped.

Patients undergoing long distance air travel may consider adopting other general measures for venous thromboembolism prevention (e.g. compression stockings).

Prevention of arterial thrombosis

There is no consensus due to lack of high quality evidence for the optimal management of APS with **arterial** thrombosis.

Owing to the higher rates of recurrent arterial thrombosis in APS, experts recommend anticoagulation with warfarin, aiming for an INR > 3.0, or combination aspirin and warfarin with an INR target of 2 - 3.

Although cohort studies suggest a lower rate of recurrent thrombosis with warfarin at INR > 3, RCTs did not show a difference in recurrence rate with warfarin with a higher INR target.

A small RCT and retrospective review suggested a lower rate of recurrent arterial thrombosis on combination aspirin and warfarin.

Data from a prospective cohort study, the Antiphospholipid Antibody and Stroke Study, suggested that warfarin or aspirin monotherapy were equally effective in preventing ischaemic stroke in patients with a prior history of stroke and a single positive

antiphospholipid antibody test result. Therefore, some experts have suggested that such patients could be managed with aspirin alone, provided there are no other indications for anticoagulation.

Recurrent thrombosis on anticoagulation

A **recurrent thrombotic event** *despite* therapeutic anticoagulation is a well recognised but relatively uncommon scenario.

There is no high quality evidence to support a particular management strategy in this scenario.

Potential options include:

1. Intensifying warfarin therapy to INR 3 - 4.

2. Adding aspirin (although this is associated with a higher risk of bleeding)

3. Adding hydroxychloroquine

4. Adding a statin:

    - Statins have pleiotropic immunomodulatory, anti-inflammatory and antithrombotic properties however clinical trials are lacking.

5. Using a different anticoagulant such as low molecular weight heparin

6. Using a combination of the above.

Obstetric APS

The current recommended treatment is:

- Low dose aspirin

And

- Prophylactic dose low molecular weight heparin.

For patients with obstetric and thrombotic complications, treatment should include low dose aspirin and therapeutic dose low molecular weight heparin.

However, up to 20% of pregnancies are unsuccessful despite this treatment.

Risk factors for an unsuccessful pregnancy include:

- Triple antiphospholipid antibody positivity

- Associated autoimmune disease

- Thrombotic manifestations.

Treatments for *refractory* obstetric APS include:

- Hydroxychloroquine
- Low dose prednisolone until 14 weeks' gestation
- Immunoglobulin
- Plasma exchange and immunoadsorption.

Asymptomatic antiphospholipid antibody carriers should be considered for **post-partum** thromboprophylaxis given the increased risk of thrombosis in this period.

Low dose aspirin has been used as primary prophylaxis in patients with antiphospholipid antibodies, but there are no clear data showing a benefit and further studies are needed.

Catastrophic APS

Catastrophic APS is characterised by multiple thrombi with a systemic inflammatory response and has a **high mortality rate**.

Due to the rarity of this condition and the high mortality rate, there are no controlled trials evaluating optimal treatment.

A retrospective review from the international registry of patients with catastrophic APS found that **anticoagulation, high dose steroids, plasma exchange and/or immunoglobulin (triple therapy)** had the highest rate of survival and is recommended, albeit with low certainty, as the treatment for catastrophic APS.

Newer therapies:

Direct oral anticoagulants (DOACs):

There is currently insufficient evidence to make recommendations on the use of **DOACs** (i.e. direct oral anticoagulants) in APS.

Immunomodulatory therapy:

Immunomodulatory therapy are being increasingly investigated on account of the immune-based mechanisms involved in APS.

Disposition

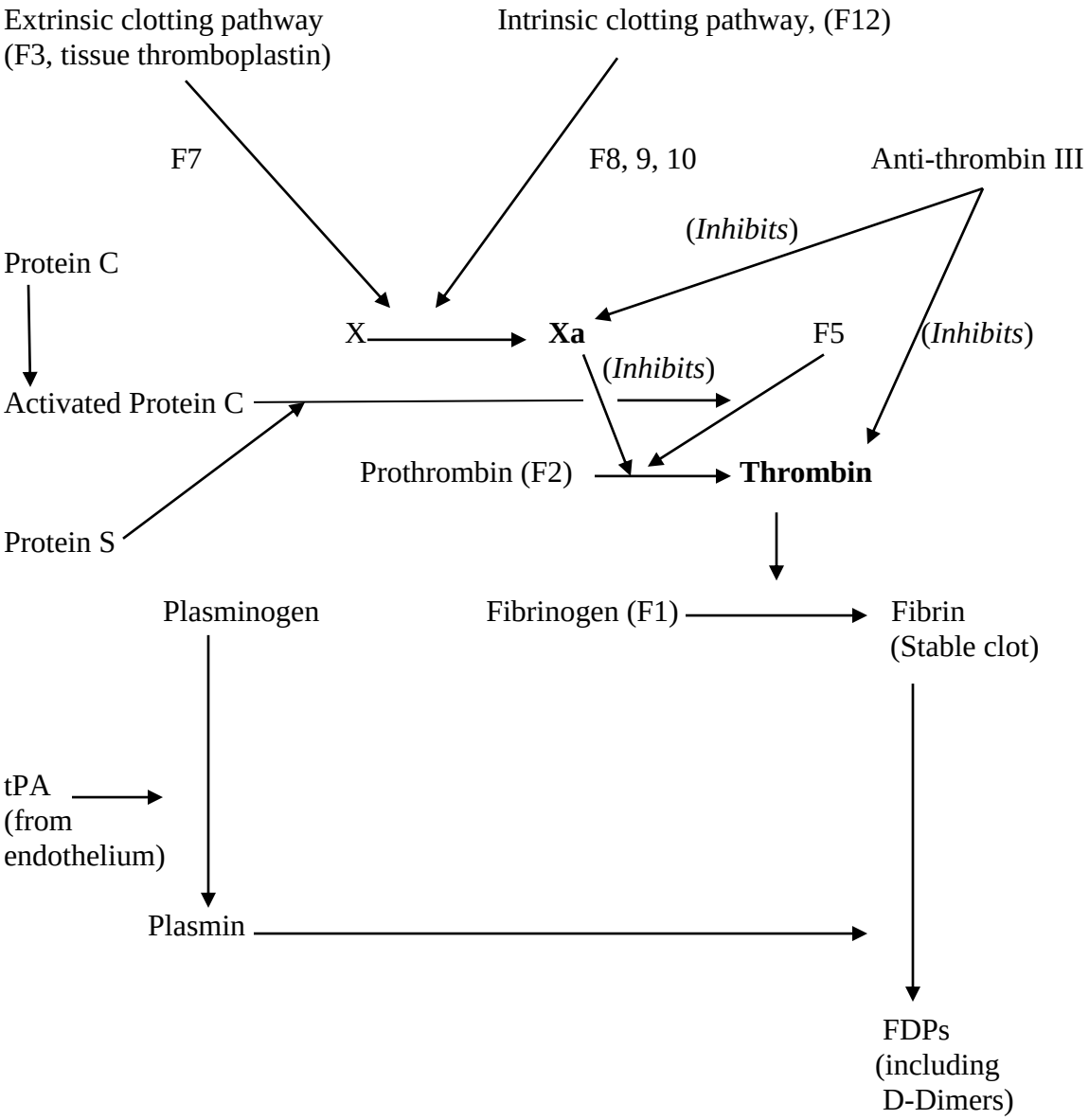
APS is generally managed by Haematologists.

If associated with an autoimmune disease (such as SLE), it may also be managed by a Rheumatologist.

Obstetricians are also involved in the management of pregnancy-related complications of APS.

Appendix 1

The coagulation cascade and fibrinolytic system:



"Frida Kahlo sitting on her bed", gelatin silver print, c. 1945, (Lola Alvarez Bravo).

.....something naked and yet absolutely self-contained in the unblinking, undeviating directness of her gaze; like the regard of certain animals and children, it makes the viewer feel naked too....(Hayden Herrera).

References

1. Hughes GRV. Thrombosis, abortion, cerebral disease and lupus anticoagulant. Br Med J 1983; 187: 1088 - 1089.

2. Veronica Mezhov, Julian D Segan, Huyen Tran, Flavia M Cicuttini. Antiphospholipid syndrome: a clinical review. MJA 211 (4) 19 August 2019.

    - doi: 10.5694/mja2.50262

Dr. J. Hayes
October 2019.