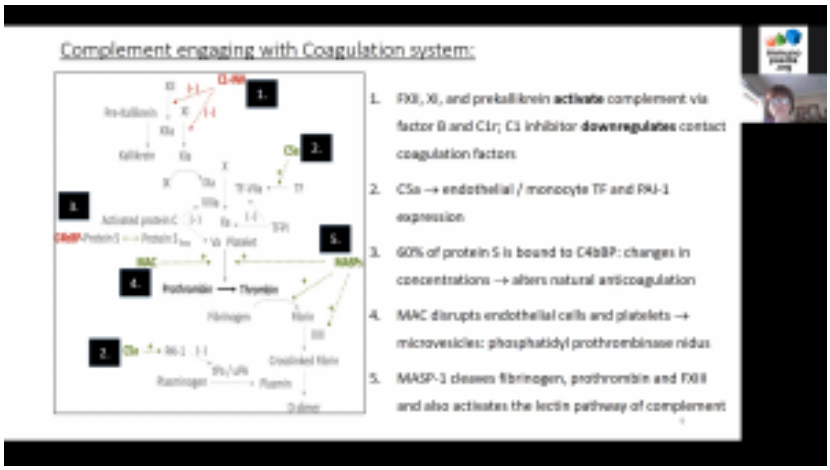
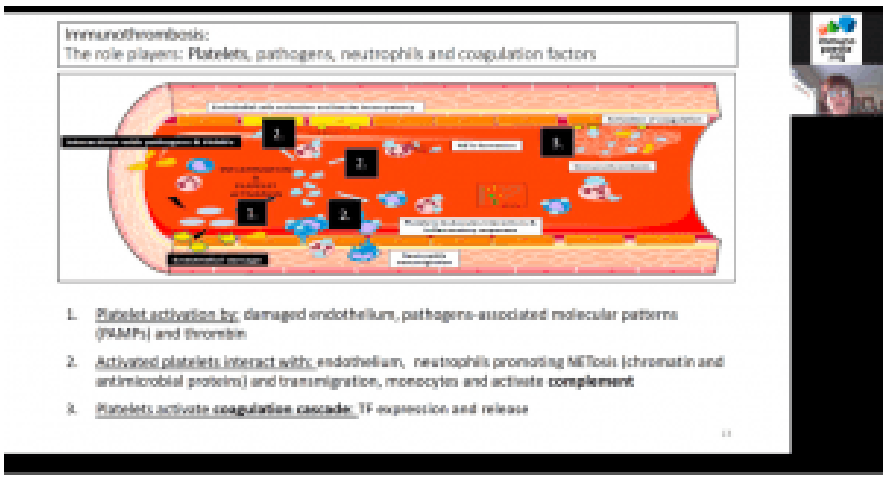
Immunothrombosis & COVID-19

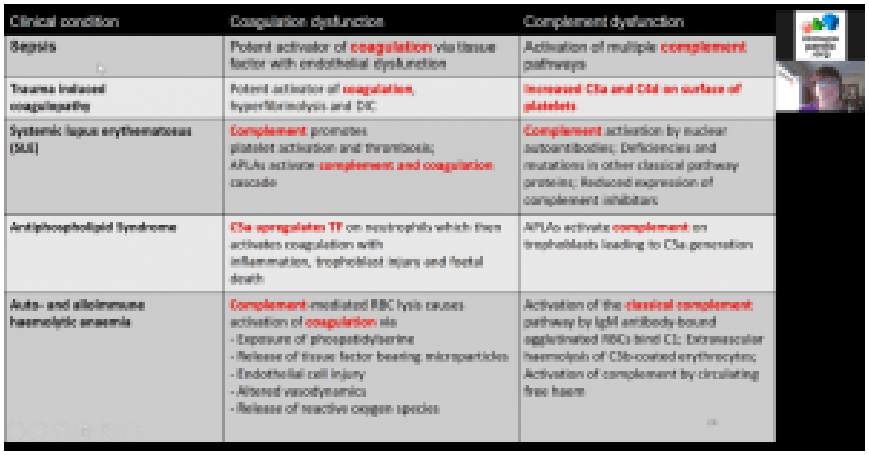
This week we highlight SAIS/Immunopaedia COVID-19 Webinar featuring talks by haematopathologists Dr Susan Louw and A/Prof Jessica Olpie on immunothrombosis & COVID-19. Immunothrombosis is the direct interaction of activated leukocytes with platelets and coagulation function, this interaction usually involves dysregulation of neutrophil extracellular trap formation.



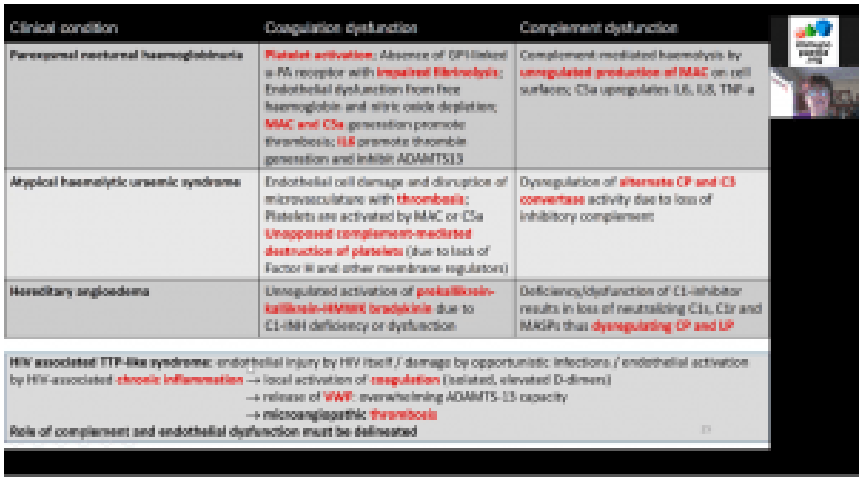
Dr Susan Louw began her talk titled "Immunothrombosis: lessons from other conditions" with a brief background on Thrombosis and how physiological process if left unchecked can lead to pathology. She discussed how cross-talk between the immune system (macrophages, complement proteins, neutrophils) and coagulation cascade (platelets and tissue factors) can cause to immunothrombosis. She then gave an in-depth yet brief overview of how coagulation proteins engage with the complement cascade (see image below) and the role of innate cells (macrophages and neutrophils) and cytokines in



immunothrombosis. Further, she then highlighted that platelets, well known for their role in blood-clotting, have immunomodulatory properties. Dr Louw concluded her talk describing clinical conditions associated with immunothrombosis (see below).

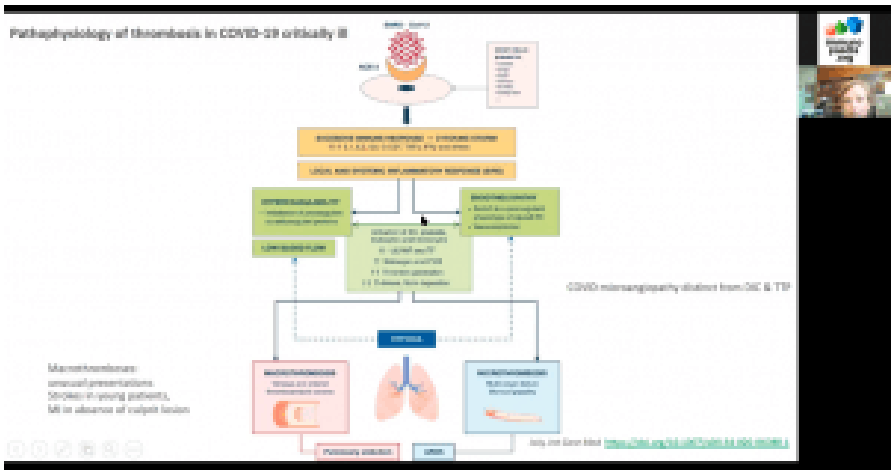


Clinical condition	Coagulation dysfunction	Complement dysfunction
Sepsis	Potent activator of **coagulation** via tissue factor with endothelial dysfunction	Activation of multiple **complement** pathways
Trauma induced coagulopathy	Potent activator of **coagulation**, hyperfibrinolysis and DIC	**Increased C3a and C4d on surface of platelets**
Systemic lupus erythematosus (SLE)	**Complement** promotes platelet activation and thrombosis; APLAs activate **complement and coagulation** cascade	**Complement** activation by nuclear autoantibodies; Deficiencies and mutations in other classical pathway proteins; Reduced expression of complement inhibitors
Antiphospholipid Syndrome	**C5a upregulates TF** on neutrophils which then activates coagulation with inflammation, trophoblast injury and foetal death	APLAs activate **complement** on trophoblasts leading to C5a generation
Auto- and alloimmune haemolytic anaemia	**Complement**-mediated RBC lysis causes activation of **coagulation** via - Exposure of phosphatidylserine - Release of tissue factor bearing microparticles - Endothelial cell injury - Altered vasodynamics - Release of reactive oxygen species	Activation of the **classical complement** pathway by IgM antibody-bound agglutinated RBCs bind C1; Extravascular haemolysis of C3b-coated erythrocytes; Activation of complement by circulating free haem

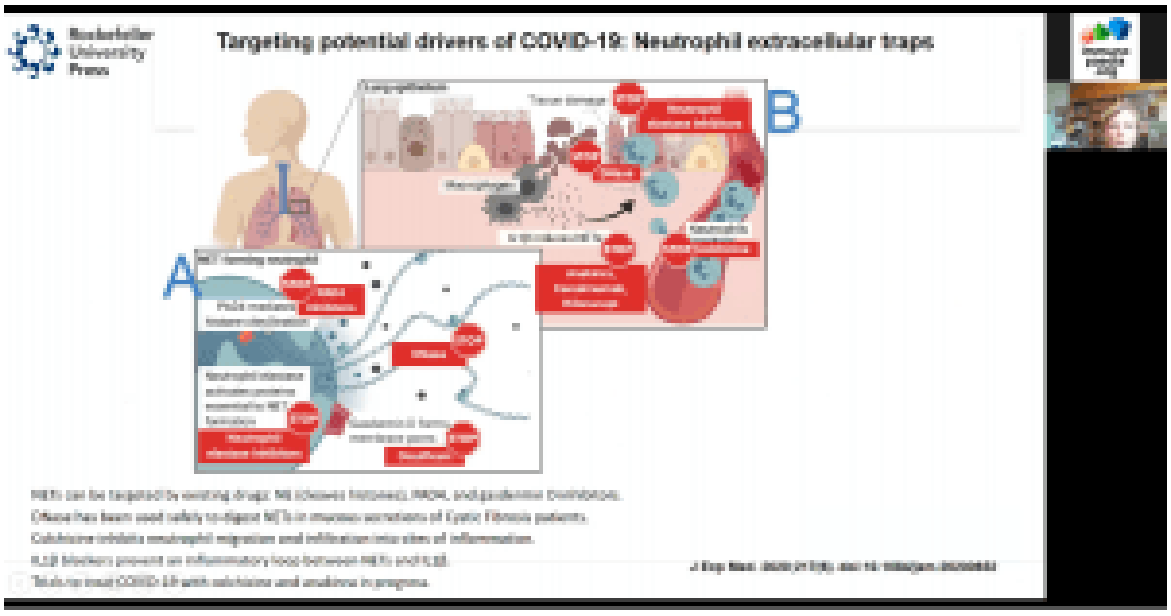


Clinical condition	Coagulation dysfunction	Complement dysfunction
Paroxysmal nocturnal haemoglobinuria	**Platelet activation**; Absence of GPI linked u-PA receptor with **impaired fibrinolysis**; Endothelial dysfunction from free haemoglobin and nitric oxide depletion; **MAC and C5a** generation promote thrombosis; **IL6** promote thrombin generation and inhibit ADAMTS13	Complement-mediated haemolysis by **unregulated production of MAC** on cell surfaces; C5a upregulates IL6, IL8, TNF-a
Atypical haemolytic uraemic syndrome	Endothelial cell damage and disruption of microvasculature with **thrombosis**; Platelets are activated by MAC or C5a **Unopposed complement-mediated destruction of platelets** (due to lack of Factor H and other membrane regulators)	Dysregulation of **alternate CP and C3 convertase** activity due to loss of inhibitory complement
Hereditary angioedema	Unregulated activation of **prekallikrein-kallikrein-HMWK bradykinin** due to C1-INH deficiency or dysfunction	Deficiency/dysfunction of C1-inhibitor results in loss of neutralizing C1s, C1r and MASPs thus **dysregulating CP and LP**

HIV associated TTP-like syndrome: endothelial injury by HIV itself / damage by opportunistic infections / endothelial activation by HIV-associated **chronic inflammation** → local activation of **coagulation** (isolated, elevated D-dimers)
→ release of **VWF**, overwhelming ADAMTS-13 capacity
→ **microangiopathic thrombosis**
Role of complement and endothelial dysfunction must be delineated



Jessica Opie's talk focused on "Thrombosis in COVID-19". A/Prof Opie gave an overview of homeostatic properties [coagulation factors (clot formation), coagulation inhibitors (clot controlling) and fibrinolysis (clot-dissolving)] associated with blood vessel injury. She then provided evidence which demonstrated that severe COVID-19 pathology is associated with dysregulation of tissue repair and blood vessel formation of the lung endothelial membrane. She also discussed how cytokine storm and dysregulation of the complement pathway contributes to excessive NETosis and is associated with severe COVID-19 pathologies (such as hypercoagulability, endotheliopathy, macrothromboisis and microthromobisis). She ended her talk describing how targeting either NETosis (using NET inhibitors) and the complement cascade could be potential therapies for severe COVID-19.



Summary by Cheleka Mpande