THROMBOTIC MICROANGIOPATHY

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DISCLOSURES

The following includes a list of current (within the last 24 months) affiliations:

Affiliation / Financial Interest	Organization
Associate Director	Molecular Otolaryngology and Renal Research Laboratory
NIH	2R01DK110023-07
Site Investigator, Advisory Board	Novartis
Site Investigator, Advisory Board	Achillion
Site Investigator, Advisory Board	Apellis
Site Investigator, Advisory Board	Biocryst
Advisory Board	AstraZeneca - Alexion
Advisory Board	Vertex
Agency Review Team	FDA Office of Orphan Product Development
Chair - Data Safety Monitoring Committee	FIT4KID
Data Safety Monitoring Committee	Purespring – C3 siRNA

My conflicts are managed by a University of Iowa mandatory conflict plan.
Both prior and current relationships are on record at the University of Iowa's Conflict in Research Office:
https://coi.research.uiowa.edu/

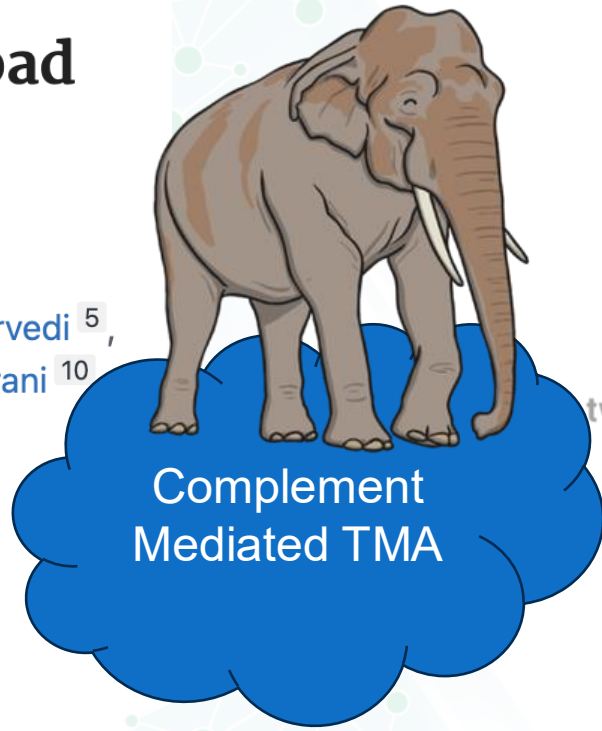
OBJECTIVES

- Brief discussion on the nomenclature of the TMAs.
- Discuss our current understanding of their pathogenesis.
- Give an overview of established and potential treatments of TMAS.
- Discuss unresolved issues in the field.

NOMENCLATURE

An expert discussion on the atypical hemolytic uremic syndrome nomenclature–identifying a road map to precision: a report of a National Kidney Foundation Working Group

Carla M Nester [1], David L Feldman [2], Richard Burwick [3], Spero Cataland [4], Shruti Chaturvedi [5], H Terence Cook [6], Adam Cuker [7], Bradley P Dixon [8], Fadi Fakhouri [9], Sangeeta R Hingorani [10], Anuja Java [11], Nicole C A J van de Kar [12], David Kavanagh [13], Nelson Leung [14], Christoph Licht [15], Marina Noris [16], Michelle M O'Shaughnessy [17], Samir V Parikh [18], Flora Peyandi [19], Giuseppe Remuzzi [16], Richard J H Smith [1], C John Sperati [20], Meryl Waldman [21], Patrick Walker [22], Marina Vivarelli [23]



- Delphi - 24 Experts in different fields but all with experience in TMA
  - 100% of participates felt the “aHUS” nomenclature should be “discarded”
  - 100% felt that a change would allow better categorization of patients
  - 100% felt that the challenge was the [lack of tools to create accurate distinctions]

Kidney Int. 2024 Sep;106(3):326-336

Globally Accepted Definition of Disease

- Thrombotic microangiopathy
  - Microvascular thrombosis
  - Thrombocytopenia
  - Microangiopathic hemolytic anemia

- Vascular endothelial injury
  - Endothelial dysfunction
    - Propagation of a prothrombotic state

Globally Accepted Accepted Causes

- Shiga Toxin Associated HUS
- Thrombotic thrombocytopenic thrombocytopenia
- Complement gene abnormality - mediated TMA
  - Handful of non-complement genes

The plot thickens after that……

Alternative Etiologies with Basic Science Support

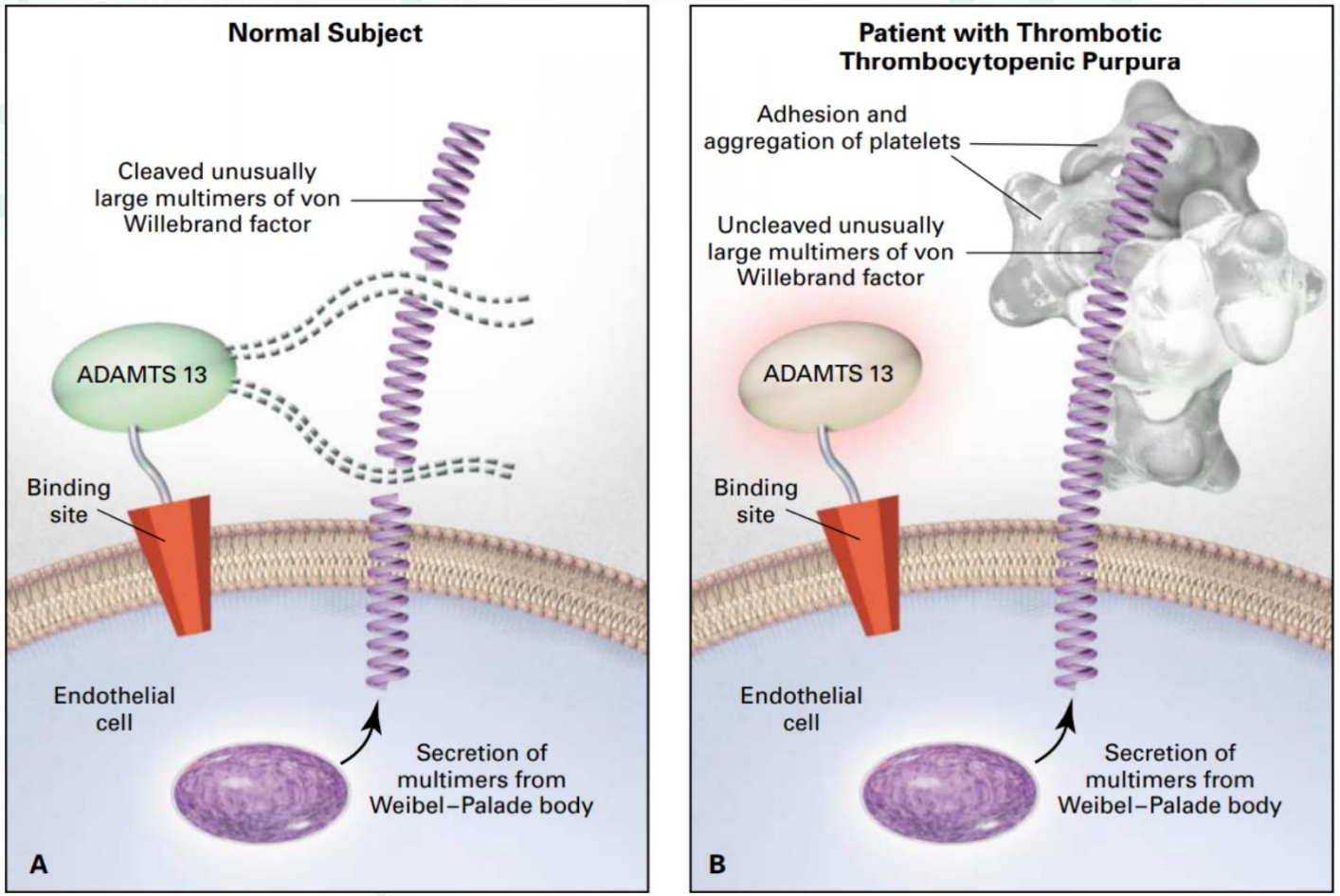
- Cobalamin C deficiency
- Drugs
  - Ie VEGF Inhibitors
- Viruses
- ETC

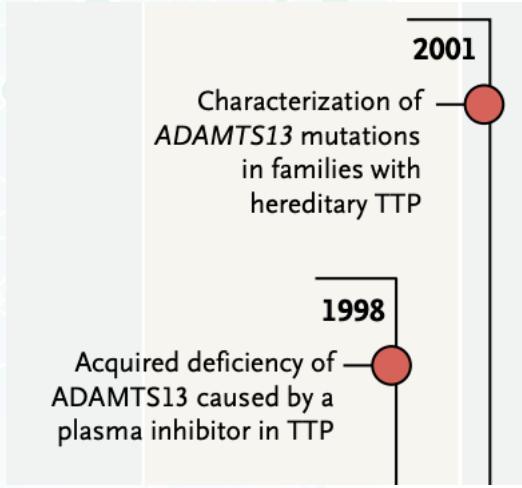
- Regardless of underlying “driver” – what role dose complement play?
  - Which in itself is a question driven by the availability of a therapeutic

WHY IS IT IMPORTANT TO BE PRECISE ABOUT ETIOLOGY?

- The Case of TTP – changes mortality, streamlines approach
  - Survival went from 10% to 78% after PEX was added*
  - Normalization of platelets in 74% of patients**
- The Case of complement mediated TMA
  - TMA event free status went to 80%***

THROMBOTIC THROMBOCYTOPENIC PUPURA?

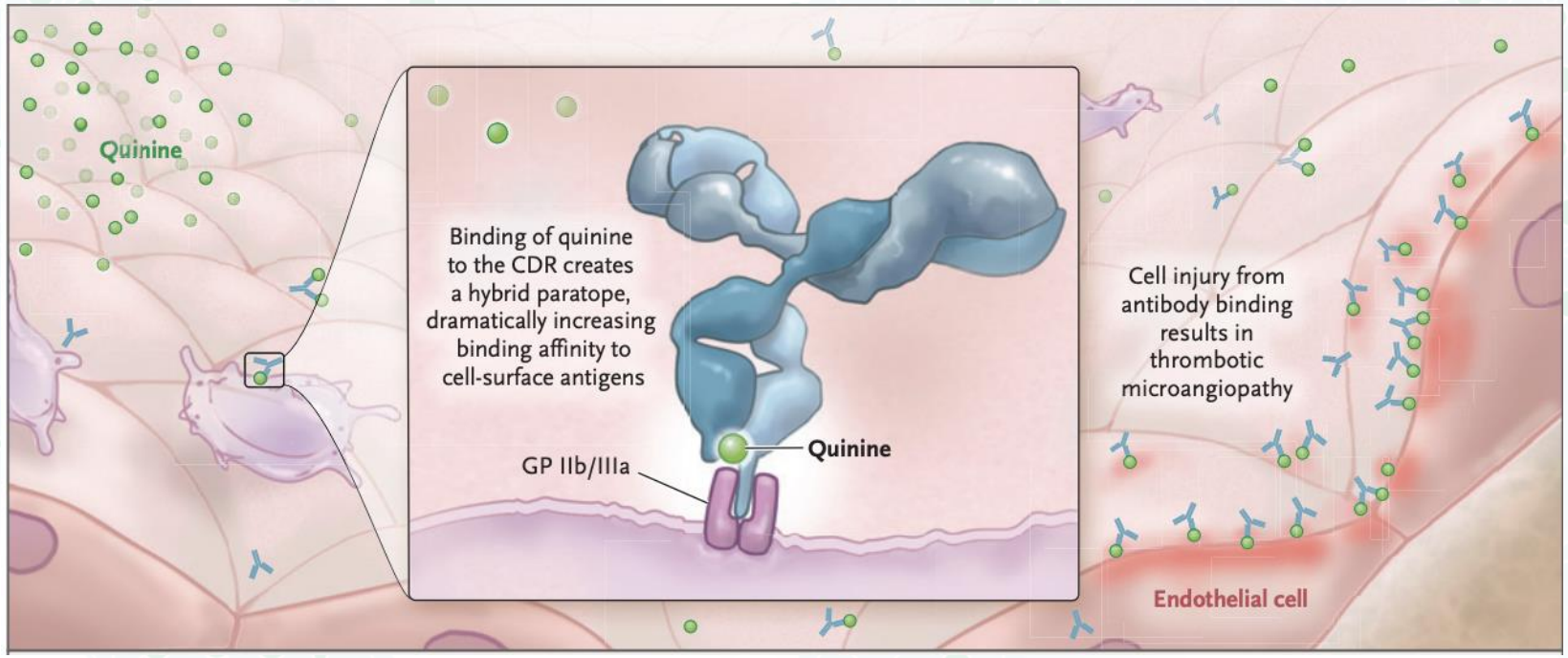




- Patient outcomes remarkably improved once ADAMTS13 was identified.
- Provided for a useful diagnostic set of tools

Belgium J of Hematology Fe,b 2023
N Engl J Med. 2014 Aug 14;371(7):654-66

QUININE



- Classic example of autoantibody mediated TMA
- Unique feature: a drug acts as a “paratope”
- The presence of the drug causes antibody to bind to the GP IIb/IIIa platelet receptor – setting off the thrombotic event
- “Complement has no role”

N Engl J Med 2017;376:74-80

THE CASE FOR VEGFI (IE BEVACIZUMAB)

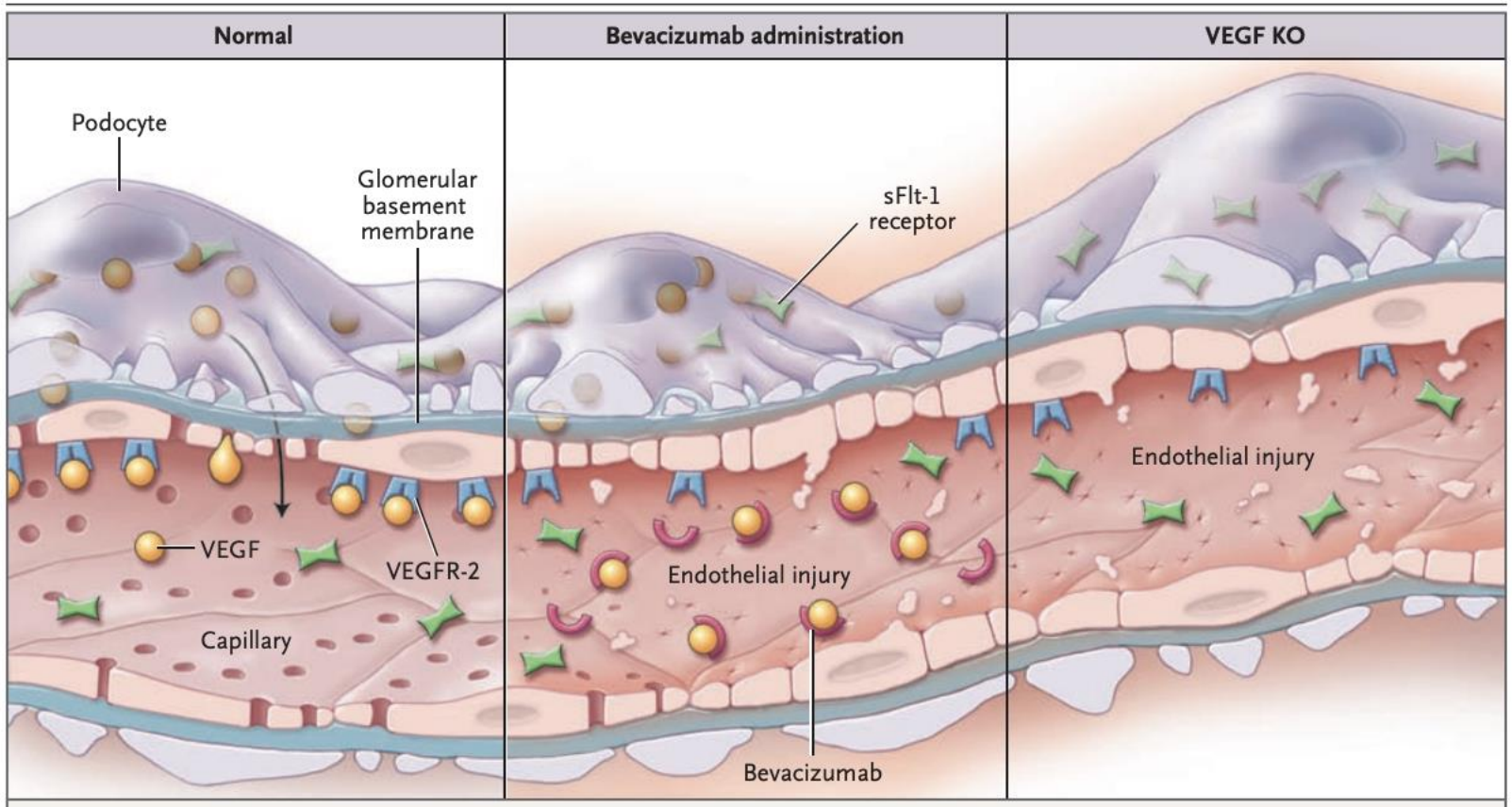
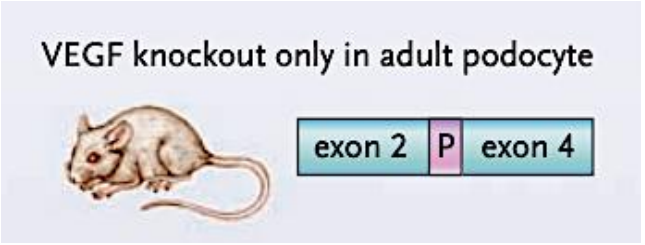


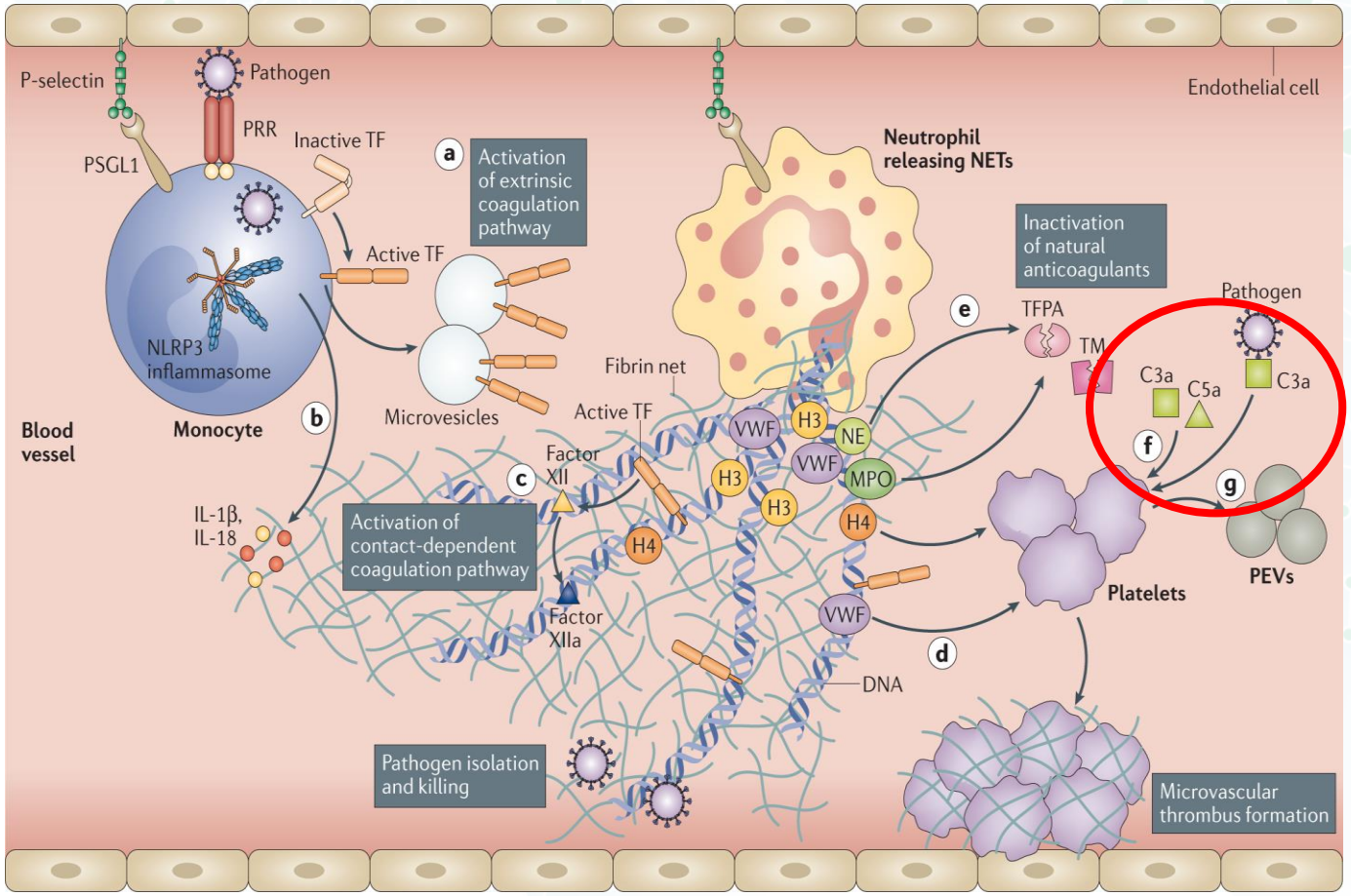
Figure 3. Hypothetical Model of Disruption of VEGF Signaling in Renal Thrombotic Microangiopathy.
The loss of function of vascular endothelial growth factor (VEGF) through genetic deletion (VEGF KO), pharmacologic inhibition, or an elevated level of circulating soluble fms-like tyrosine kinase 1 (sFlt-1) that binds VEGF is associated with damage to the glomerular endothelium characterized by swelling and thrombotic microangiopathy. VEGFR-2 denotes kinase insert domain receptor.



- Podocytes VEGF production critical to glomerular endothelial health
- Conditional knockout
- Classic features of TMA 4 weeks after induction
- IHC – negative for complement components

N Engl J Med 2008;358:1129-36

COVID-19

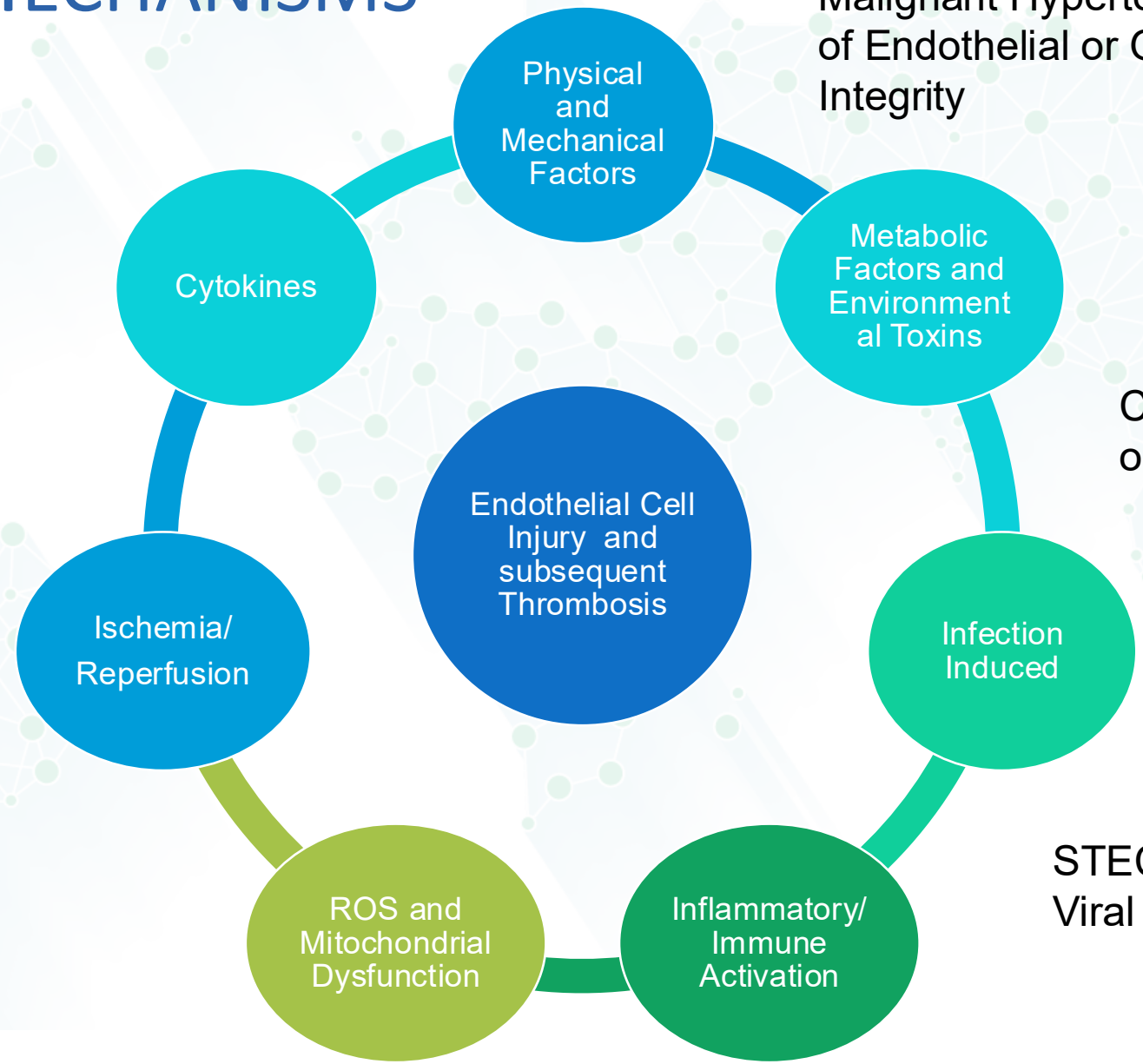


- Direct injury of endothelial cells by the virus
- Activation of the coagulation cascade
- Neutrophil Infiltration leading to NET formation
- Induction of hypoxemia causing upregulation of TF expression by hypoxia-inducible transcription factors
- Formation of thrombosis
- Activation of complement
  - Recruitment and activation of platelets, monocytes and neutrophils
- Increase in pro-inflammatory cytokines causing direct cell damage

Nature Reviews Immunology volume 21, pages319–329 (2021)

Molecular Mechanisms

- The Point: there are lots of things that injure the endothelium – setting the stage for TMA
- They will not all involve complement



Malignant Hypertension, Loss of Endothelial or Glycocalyx Integrity

Cobalamin Pathway Abn or Drug Toxicity

STEC HUS or Viral Infection

GOAL

- The gold standard: how do we define PRECISELY the underlying driver of a given TMA
  - Then consider how short of that are we willing to be as practitioners?
  - Are secondary pathways a reasonabl target (ie complement or cytokines)

OBJECTIVES

1. What are the preferred nomenclature and classification of TMAs?
2. Should the primary versus secondary classification of TMA be dropped and replaced by a new schema?
3. How should the NKF roadmap be incorporated/implemented in the preferred nomenclature?
4. In the NKF roadmap nomenclature, which etiologies of TMA are dependent on the terminal complement pathway?
   A. Because this is the available therapeutic (which I would argue is short-sighted)
5. Is the distinction between complement-mediated and complement-amplified helpful?
   A. Can we think about TMAs like we do renal failure (ie AKI and CKD)

OBJECTIVES

6. In etiologies of TMA not dependent on complement, what are their underlying mechanisms?
7. What are the knowledge gaps in the mechanisms of TMA that limit implementation of a comprehensive diagnostic schema?
8. What should a workup look like
9. How do patients feel about a potential change in nomenclature?

Future Directions

- In the absence of a trial, we have to stop saying something worked without strict criteria
- We should encourage mechanistic investigations
- We need to solve the nomenclature issue.
  - Chronic complement driven disease
  - Acute complement exacerbated disease

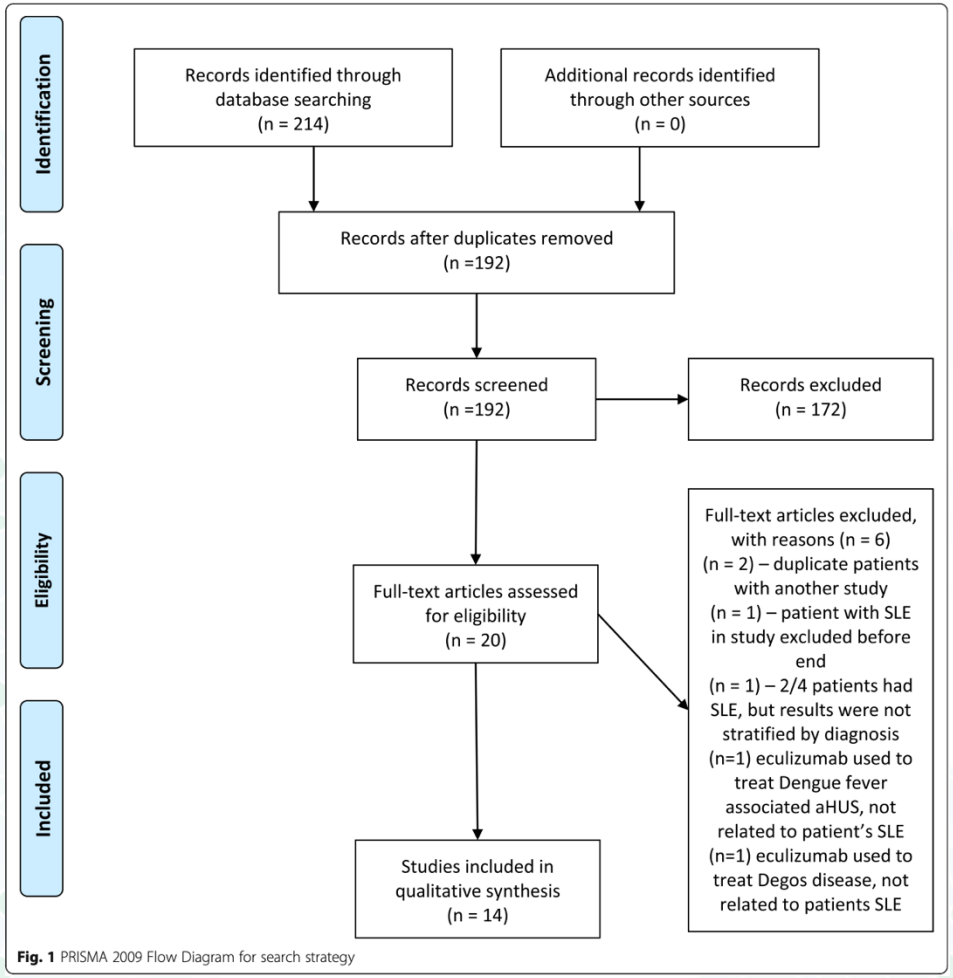


Fig. 1 PRISMA 2009 Flow Diagram for search strategy

Lupus and TMA and TCB - 14 Reports

- Authors reported 93% efficacy (28/30 cases)
- 12/30 had Cytoxan exposure before
- 8/30 with no data at all on exposures

BMC Nephrology (2020) 21:245

CONCEPTUALIZATION (IF YOU NEED A MONIKER TO TEACH IT BETTER)

- Non complement mediated TMAs ie TTP, STEC HUS, etc (call them by their proven name)
- Acute complement acTivation (ACT1 and ACT2)
  - Relieves you of the responsibility to figure out why
  - Allow the temporary use of TCB
  - ACT1 – no clear association related data
  - ACT2 – repeated cases associated – gives a start for next round of research
    - Ie IBD related, Influenza related, drug related
  - May require fewer safety measures
- Chronic complement AcTivity (CAT)
  - This is the classic “aHUS” pt – either genetic abnormality or autoantibody driven
  - Presumed to have higher safety requirements

THANK YOU

I want to quote a mom/advocate:

https://www.ahusallianceaction.org/since-you-asked-ahus-nomenclature/

"The evolution from one umbrella term to a more precise, subtype-specific language reflects exactly what good medicine looks like as it matures: the more carefully we look, the better we can treat each person as an individual rather than a category. "

Linda Burke