THE DIFFERENTIAL DIAGNOSIS BETWEEN TTP AND ATYPICAL HUS

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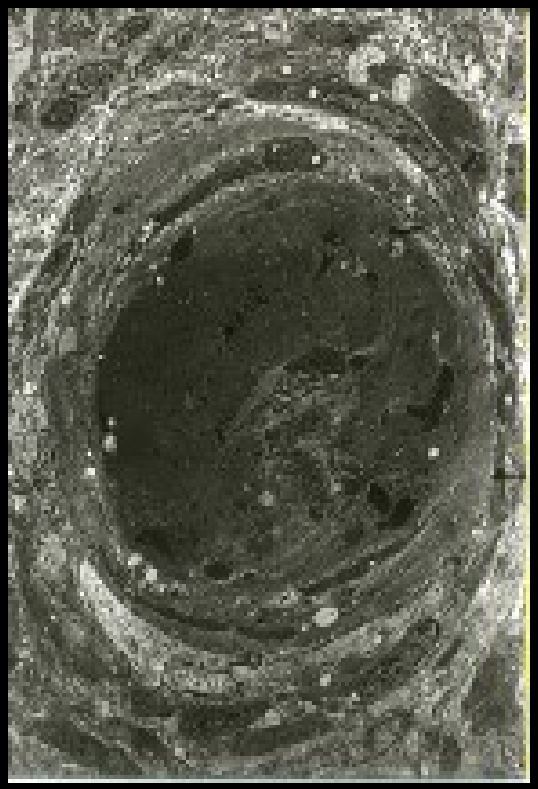
THROMBOTIC MICROANGIOPATHIES (TMAs)

Hemolytic Uremic Syndrome (HUS)/Thrombotic Thrombocytopenic Purpura (TTP)

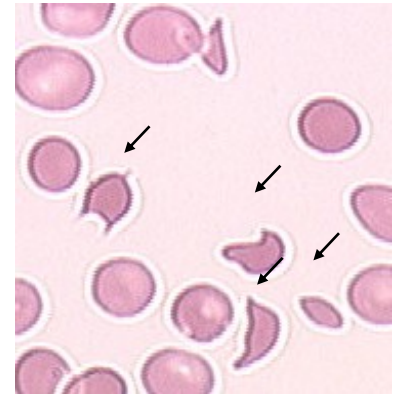


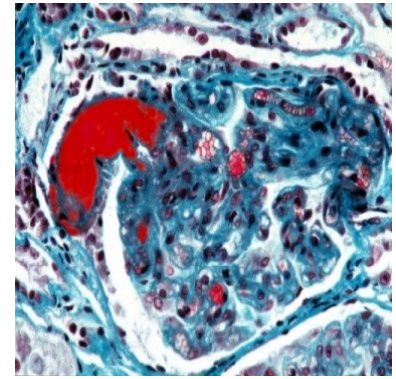
Definition

- Multisystem diseases, with predominant renal involvement in HUS and neurological and cardiac signs in TTP
- Characterized by platelet-rich thrombus formation and microvascular endothelial damage
- Consequent thrombocytopenia, mechanical (microangiopathic) hemolytic anemia and multiorgan dysfunction.

THROMBOTIC MICROANGIOPATHIES (TMAs)

- Microangiopathic hemolytic anemia
- Peripheral thrombocytopenia
- Multiorgan failure of variable severity





TTP

- Acquired
- Congenital

4 cases/million/year

HUS

- Typical (STEC-HUS)
- Atypical (aHUS)

2–4 cases/million/year

Other TMAs

- DIC
- HELLP syndrome
- Catastrophic antiphospholipid syndrome (CAPS)
- Malignant hypertension
- Cancer
- Transplantation
- HIV

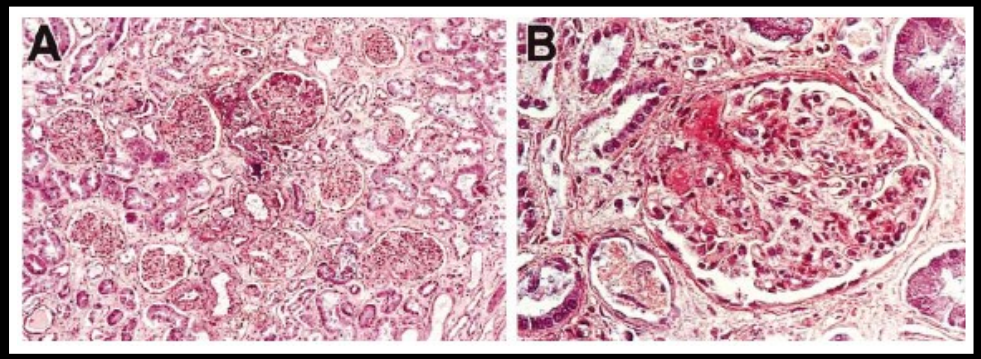
OUTLINE OF THE PRESENTATION

1. Pathophysiology of TTP
2. Pathophysiology of aHUS
3. Differential diagnosis

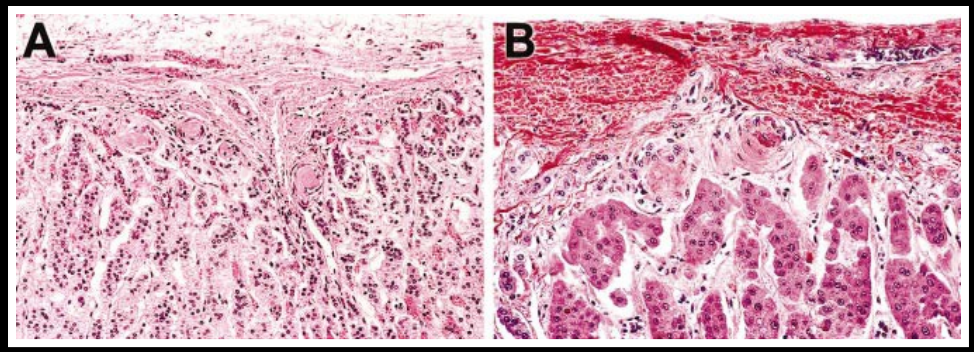
TTP: A MULTI-SYSTEM DISEASE DUE TO INTRAVASCULAR PLATELET AGGREGATION: NOT ONLY IN THE CENTRAL NERVOUS SYSTEM!

Myocardial

Pancreas

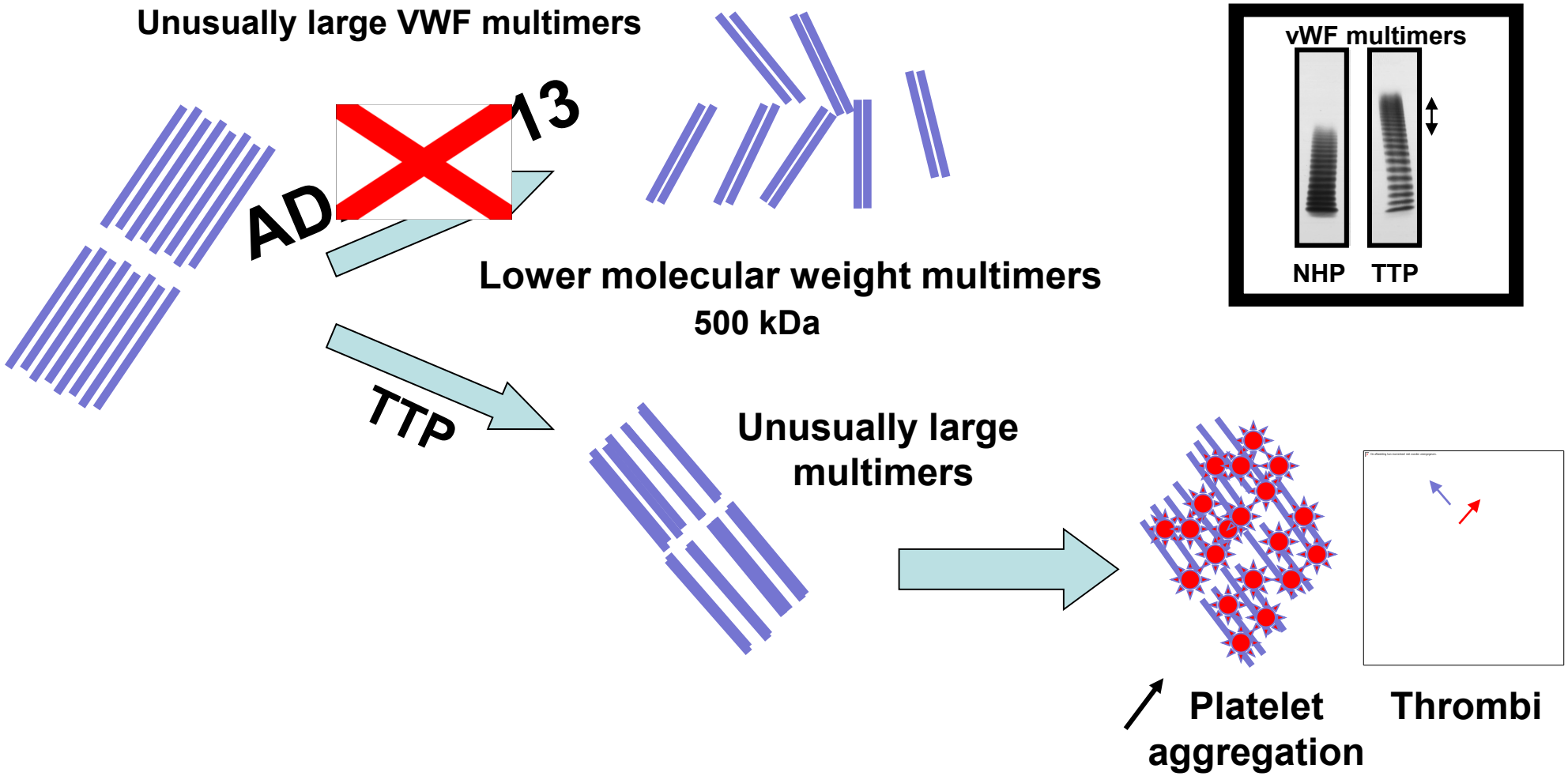


Renal



Adrenal glands

VON WILLEBRAND FACTOR (VWF) AND THE PLASMA VWF-CLEAVING PROTEASE ADAMTS13 IN THE PATHOPHYSIOLOGY OF TTP



Measurement of ADAMTS13 activity

Reference method (FRETS-VWF73)

International standard available

Few laboratories only

Limit for emergency testing: delay in sample transportation and results availability

Commercial kits (VWF73 peptide, fluorimetric / colorimetric)

SELDI-TOF (mass spectrometry)

Interest in simpler laboratory tools to predict severe ADAMTS13 deficiency (activity <5%) and thus to diagnose TTP

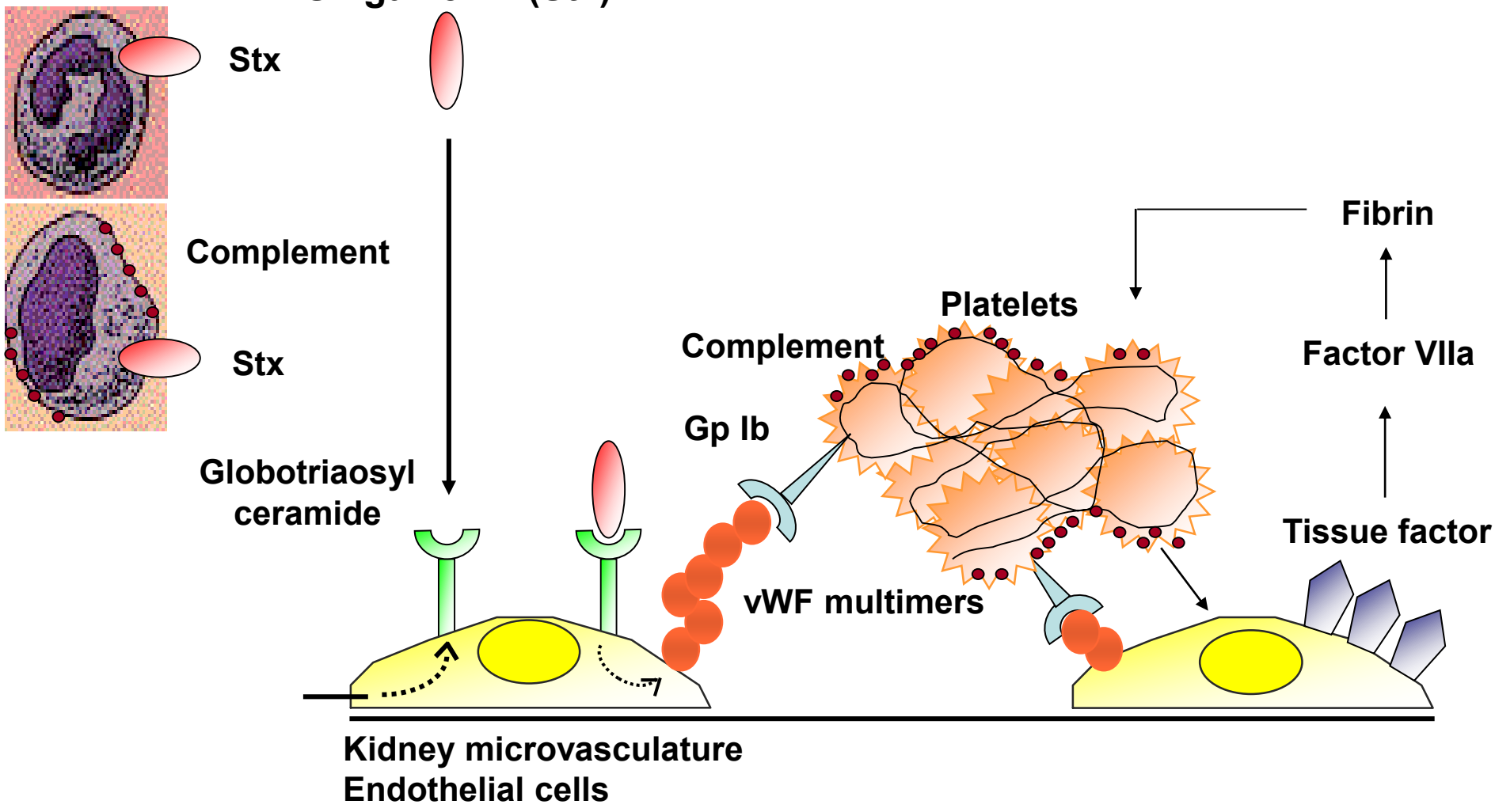
OUTLINE OF THE PRESENTATION

1. Pathophysiology of TTP

Pathophysiology of shiga-toxin E. Coli (STEC) HUS and atypical HUS (aHUS)

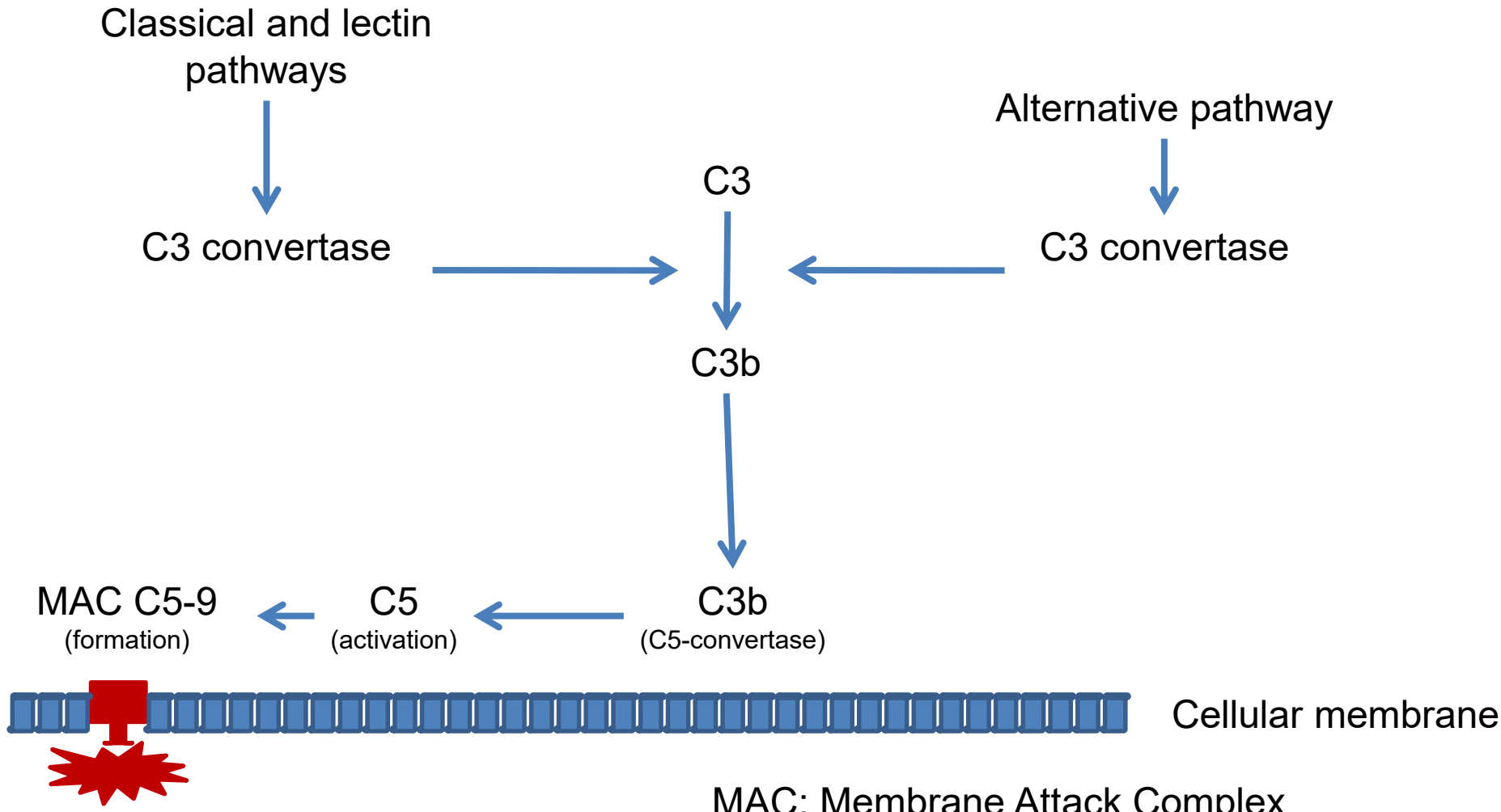
3. Differential diagnosis between TTP and aHUS

PATHOPHYSIOLOGY OF SHIGA TOXIN - E. COLI HUS (STEC-HUS)



ATYPICAL HUS
(aHUS,complement-mediated HUS)

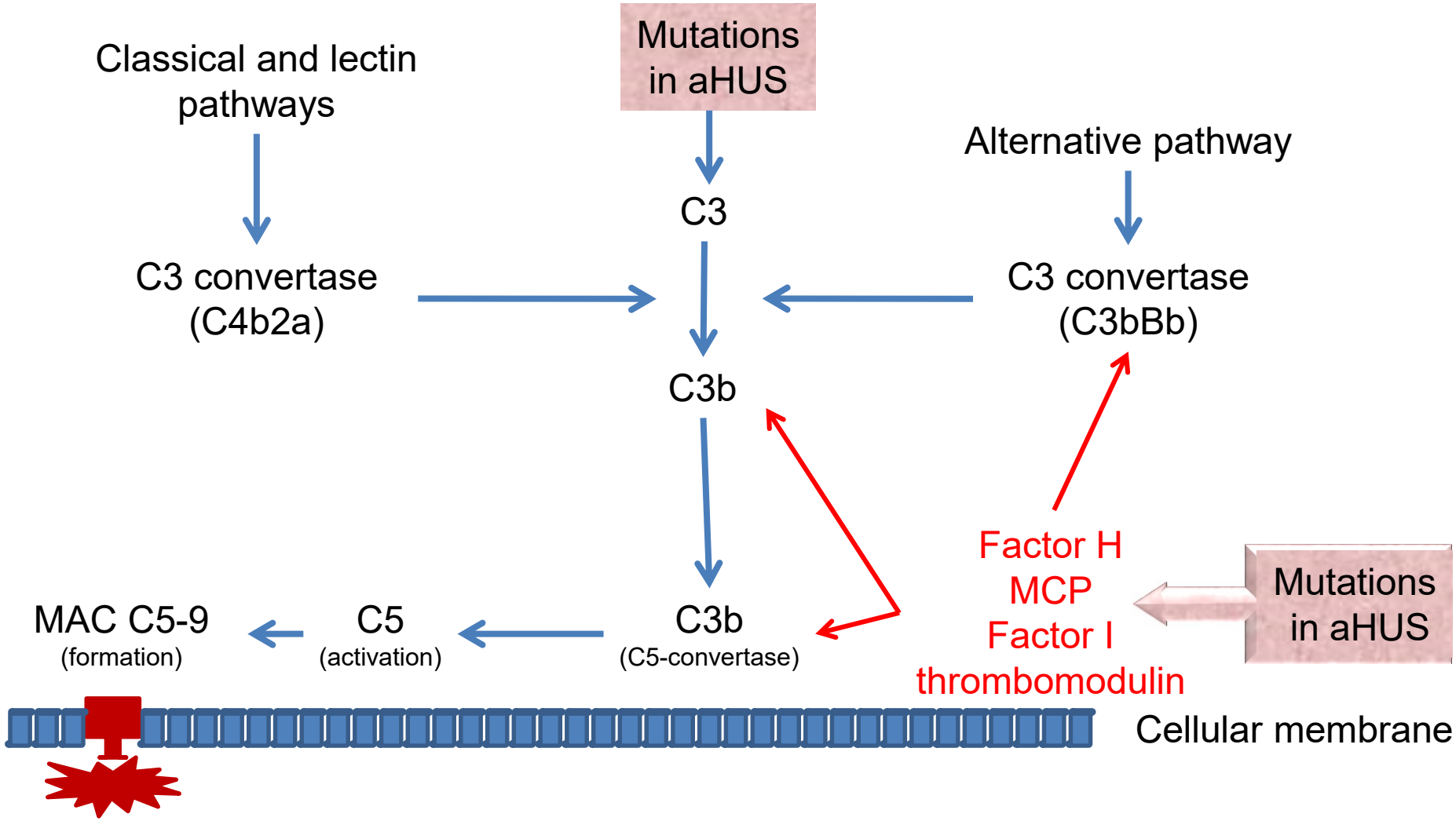
SIMPLIFIED SCHEME OF THE COMPLEMENT SYSTEM



MAC: Membrane Attack Complex
C5a: Anaphylatoxin

Noris M & Remuzzi G. *N Engl J Med* 2009; 361:1676-87.

IN PRESENCE OF COMPLEMENT ACTIVATING CONDITIONS, GENETIC LOSS-OF-FUNCTION OF NATURAL COMPLEMENT INHIBITORS OR GAIN-OF-FUNCTION OF COMPLEMENT FACTORS MAY LEAD TO UNCONTROLLED ACTIVATION OF THE ALTERNATIVE PATHWAY (2 HIT-MODEL)



Noris M & Remuzzi G. *N Engl J Med* 2009; 361:1676-87.

FREQUENCY OF LOSS-OF-FUNCTION AND GAIN-OF-FUNCTION MUTATIONS OF COMPLEMENT GENES

Mutated gene	Frequency reported (%)
Factor H	20-30
Factor I	4-10
C3	5-10
Thrombomodulin	5
Membrane cofacor protein (MCP)	10-15

- No genetic mutation identified in ca. 30-40% of patients with atypical HUS
- Poor diagnostic value of genetic testing

Noris M, *et al. Clin J Am Soc Nephrol* 2010; 5:1844-59;
Fremeaux-Bacchi V, *et al. Clin J Am Soc Nephrol* 2013: 8:554-62.

POOR DIAGNOSTIC VALUE OF CIRCULATING COMPLEMENT MARKERS IN aHUS PATIENTS

Complement markers	Disease phase	% abnormal
Reduced C3 serum levels	Acute	18%
Increased C5a levels*	Acute	19%
Increased C5b-9 levels **	Acute	19%

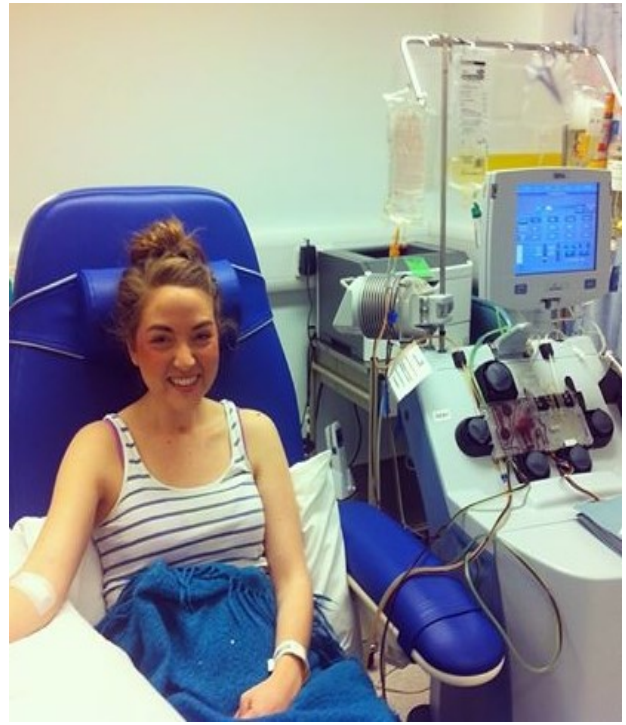
* Anaphylatoxin
** Membrane attack complex

Noris M et al. Blood 2014; 124:1715-26

Why is it important to diagnose aHUS and differentiate it form TTP

PLASMA THERAPY

Plasma infusion



Plasma exchange

Circulating ‘disease-causing factors’ can be removed by exchange and missing plasma factors can be replaced by the infusion of normal plasma.

Plasma therapy is still the only therapy with near complete global availability and therefore it remains an important treatment, definitely for TTP but also for aHUS, despite poor long-term renal outcome.

ATYPICAL HEMOLYTIC UREMIC SYNDROME: MAIN OUTCOMES

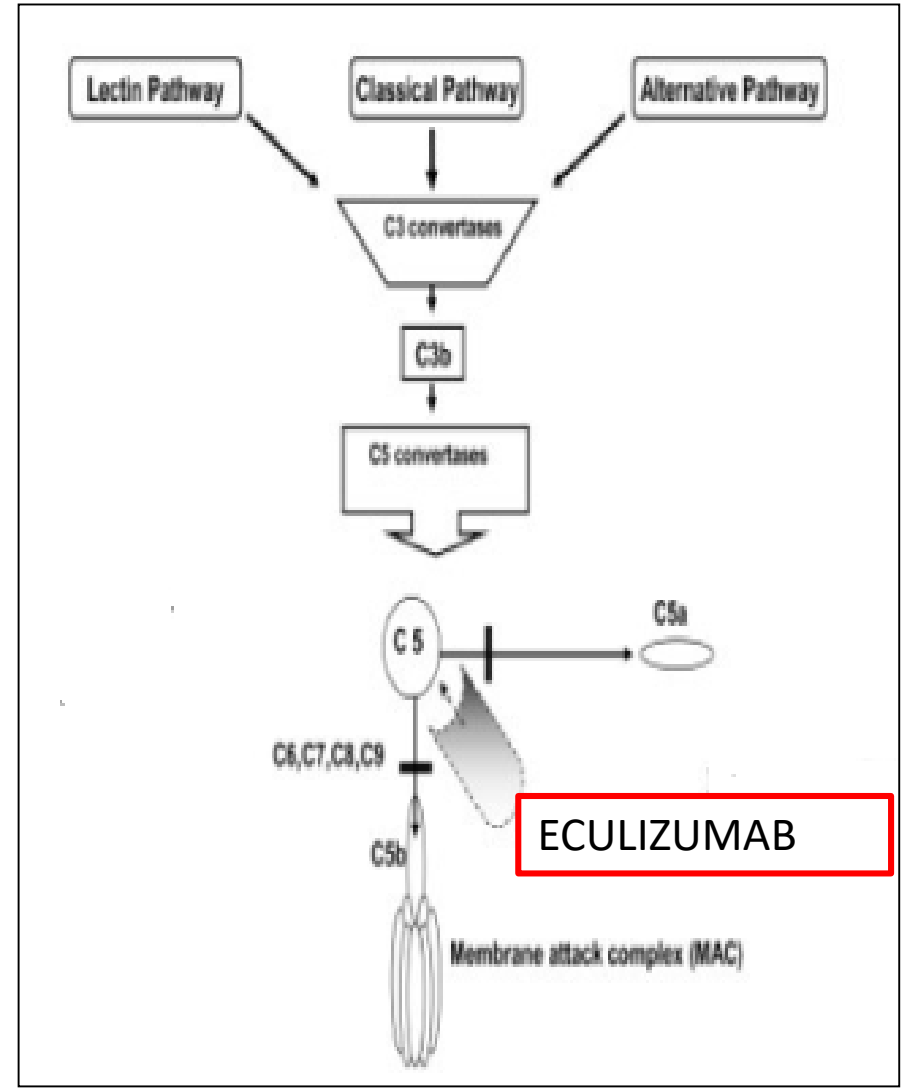
- Case-fatality rate: 25%
- Rate of progression to end-stage renal disease: 50%

COMPLEMENT ACTIVATION AND aHUS

- Eculizumab
  - A humanized monoclonal anti-C5 antibody that impedes the formation of the anaphylatoxin C5a and the membrane attack complex C5b-9
  - Dramatic clinical responses to its infusion in aHUS patients

- The key of its therapeutic adoption is the differentiation of aHUS from TTP

ECULIZUMAB: MECHANISM OF ACTION



THE DILEMMA IN TMA MANAGEMENT

TMA (TTP or atypical HUS): life-threatening diseases that require early intervention

Targeted, pathophysiology-based therapies are now available

Severe acquired (autoAb-mediated) ADAMTS13 deficiency (<5% activity)

Plasma exchange. Immunomodulating therapy (rituximab)

Detectable ADAMTS13 activity (≥5% activity)

Complement blockers (eculizumab)

So far however, diagnostic tools aimed at differentiating one disease from the other are not available as routine assays in an emergency…

Differential diagnosis

GENERAL ASPECTS OF aHUS DIFFERENTIAL DIAGNOSIS

Clinical evaluation	**No reliance on prevalent organ symptoms (CNS-TTP vs kidney-aHUS/bloody diarrhea, not only in STEC-HUS)**
Shiga-toxin tests	PCR Coli positivity on stool samples distinguishes STEC-HUS from aHUS (and from TTP and other TMAs)
ADAMTS13 plasma	**Levels below 5% differentiate TTP from aHUS**
Complement tests	Normal, in many patients with aHUS
Genetic tests	**Results are not available in real time and are not diagnostic**
Two simple laboratory tests :	may help to predict severe ADAMTS13 deficiency

SIMPLE PREDICTION OF SEVERE A13 DEFICIENCY

Patient characteristics	Adjusted OR	95% CI
Creatinine <200 µmol/L (<2.26 mg/L)	23.4	8.8, 62.5
Platelets <30 x 10^9/L	9.1	3.4, 24.8

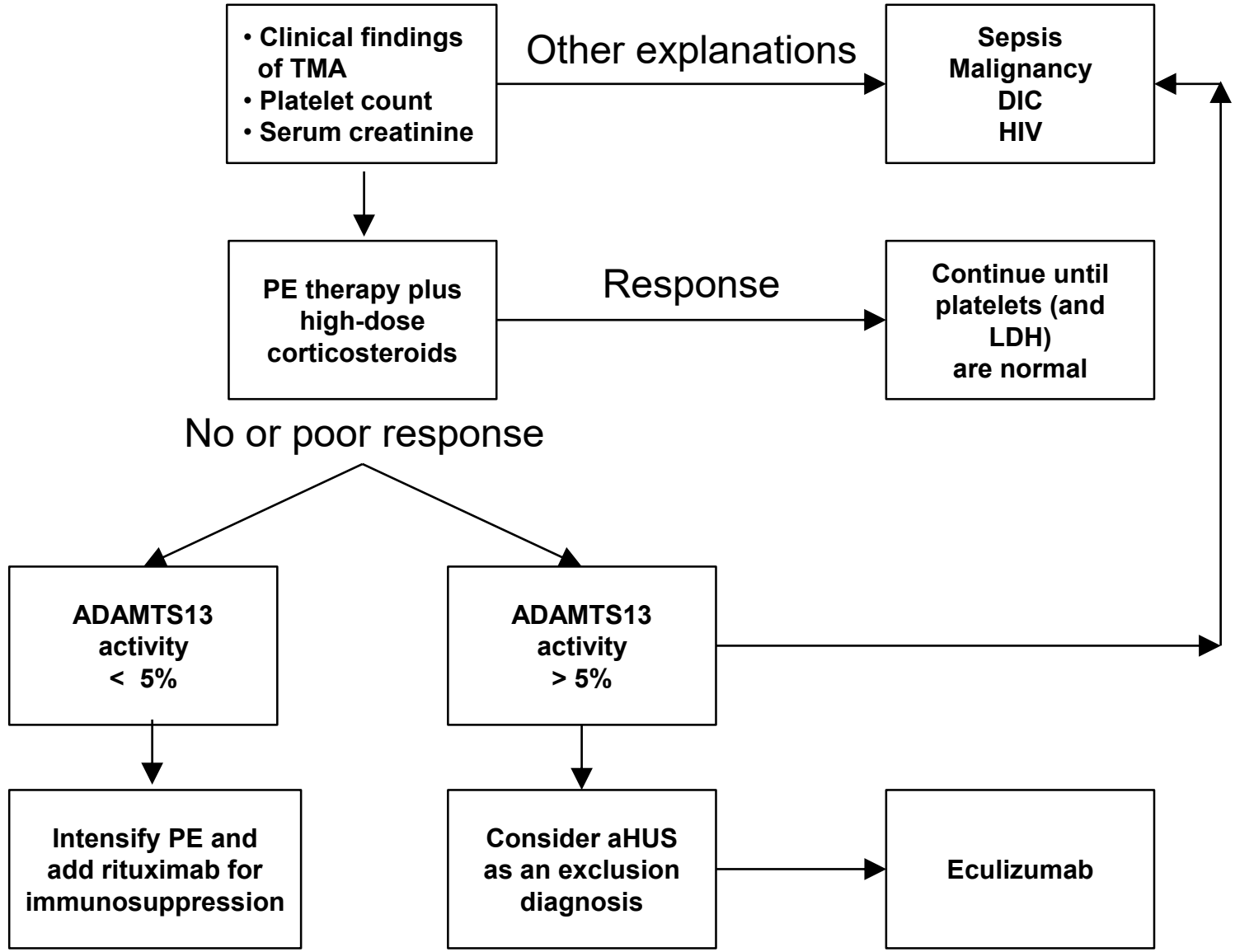
Prediction of severe ADAMTS13 deficiency

Sensitivity: 98.1%
Specificity: 48.1%

Positive predictive value: 85%
Negative predictive value: 93.3%

Coppo P *et al. Medicine (Baltimore)* 2004;83:233-44
Coppo P *et al. PLoS One* 2010;5:e10208

MANAGEMENT OF PATIENTS WITH A SUSPECTED THROMBOTIC MICROANGIOPATHY



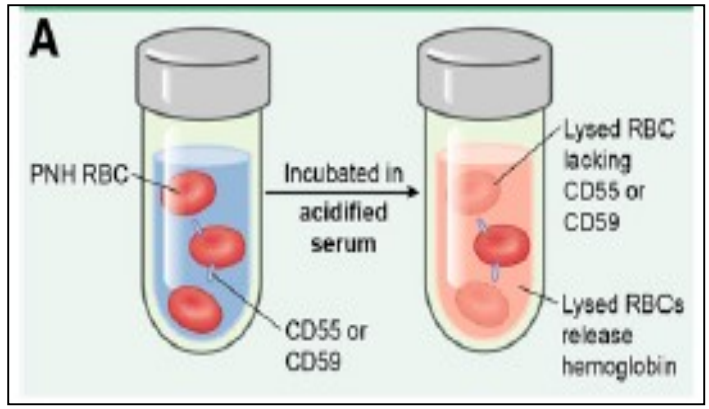
TMA: thrombotic microangiopathy; **PE:** plasma exchange; **LDH** lactate dehydrogenase

Adapted from Cataland and Wu (Blood.2014;123:2478),

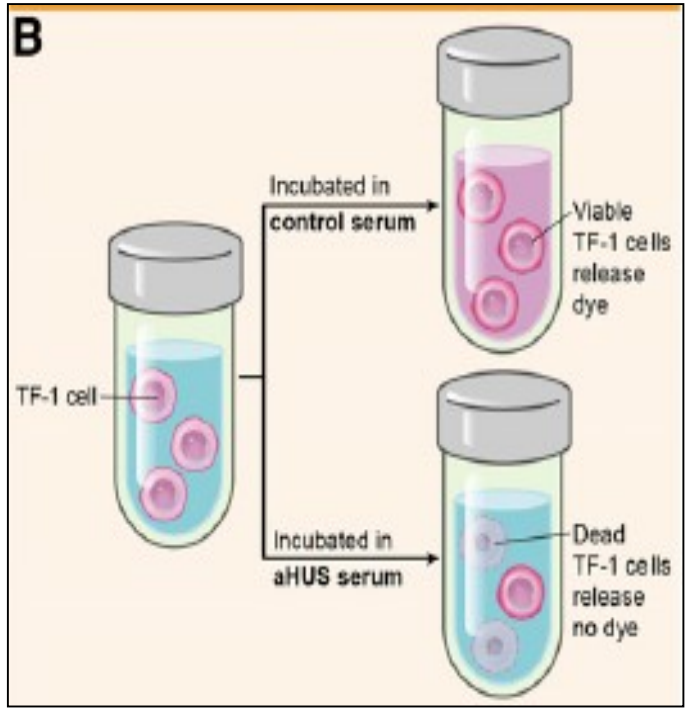
Atypical HUS:
not only a diagnosis of exclusion?

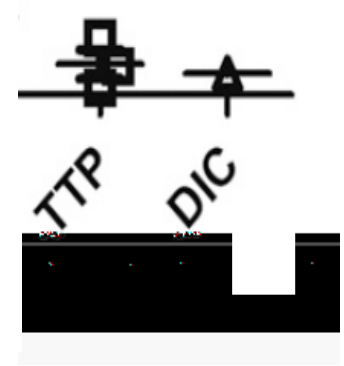
ATYPICAL HUS MAY BECOME A DIAGNOSIS OF INCLUSION

Ham test for PNH



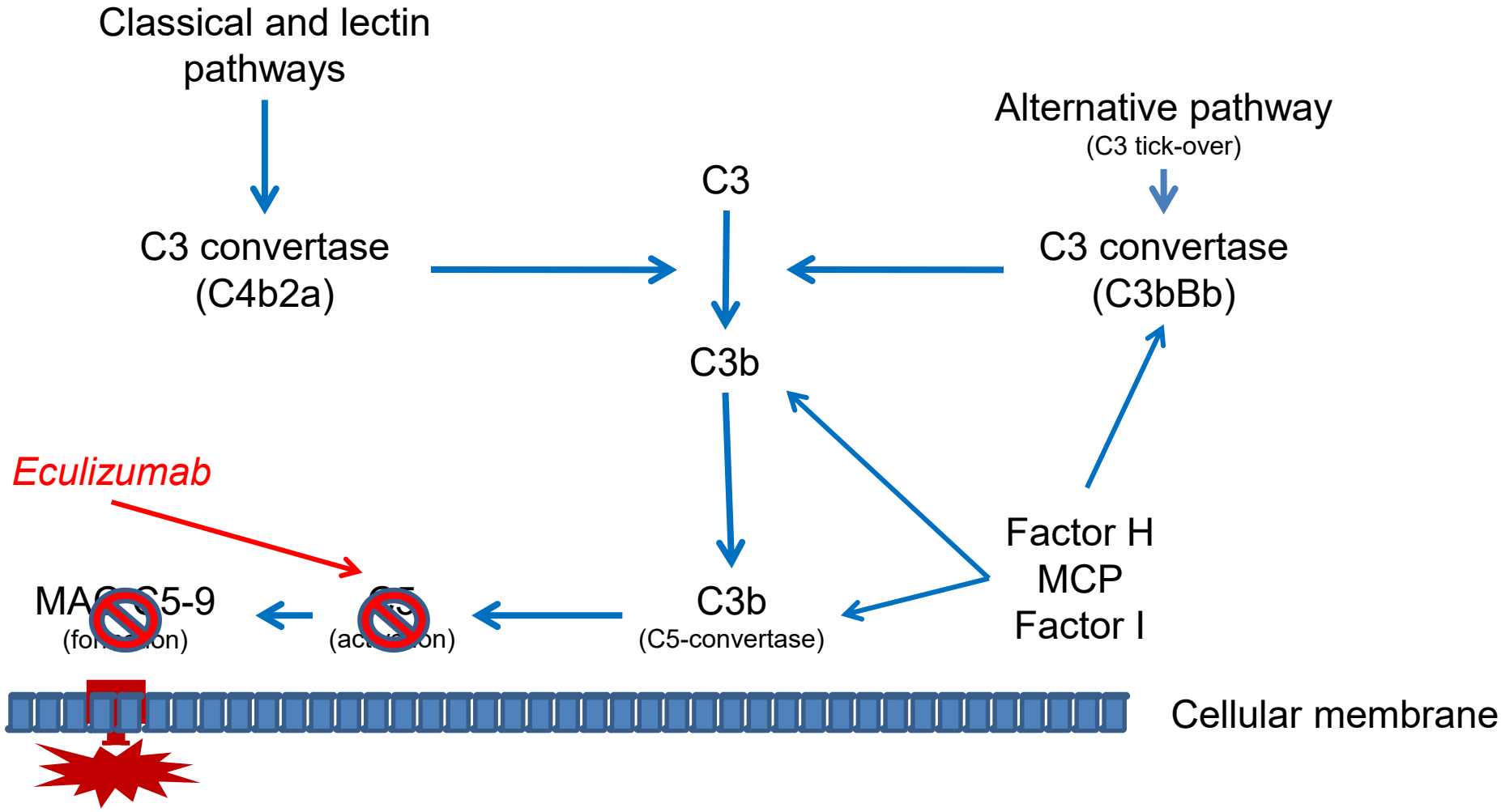
Indirect Ham test for aHUS





Gavriilaki et al. Blood 2015;125:3637-3646

ECULIZUMAB: HOW TO MONITOR AND TAILOR SUCH AN EXPENSIVE THERAPY



Noris M & Remuzzi G. *N Engl J Med* 2009; 361:1676-87.

The evaluation of lower C5b-9 deposition on microvascular endothelial cells (HMEC-1) by Eculizumab requires cell cultures and confocal microscopy, so that it is hardly feasible in the average laboratory

Noris et al. Blood 2012; 124:1715

Journal of Thrombosis and Haemostasis, **12**: 1440–1448 DOI: 10.1111/jth.12615

IN FOCUS

Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome

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See also Wehling C, Kirschfink M. Tailored eculizumab regimen for patients with atypical hemolytic uremic syndrome: requirement for comprehensive complement analysis. This issue, pp 1437–9.

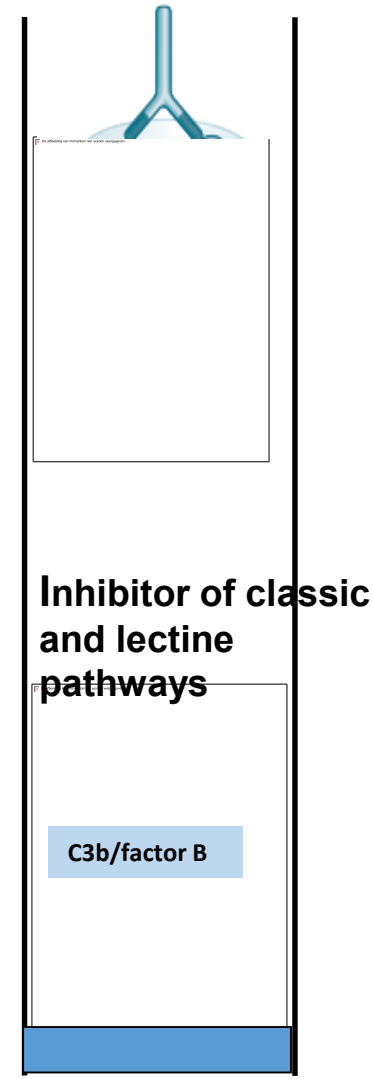
COMPLEMENT FUNCTIONAL TESTS

Labelled anti-C5b9

Serum dilution

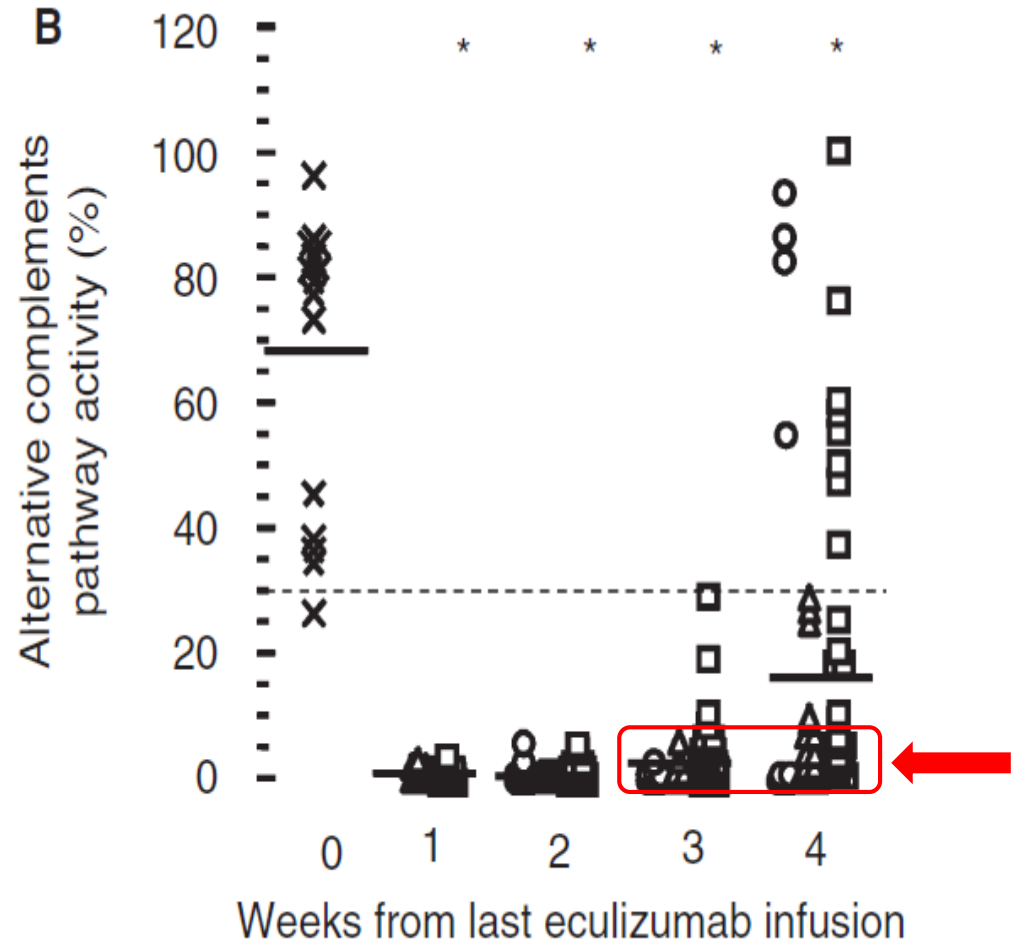
Specific inhibitor

Specific activator



Alternative Pathway

COMPLEMENT FUNCTIONAL TESTS TO TAILOR ECULIZUMAB DOSING



CONCLUSIONS: KEY HOME MESSAGES

1. TMAs, either HUS or TTP, are life-threatening diseases but their prognosis may be favorable provided early diagnosis and optimal treatment

2. To distinguish aHUS from TTP remains mandatory in the era of targeted therapies, i.e. complement blockade, rituximab, ADAMTS13 replacement products (plasma-derived, recombinant), inhibitors of VWF reactions with platetels (aptamers, nanobody)

3. ADAMTS13 activity remains the most reliable tool to distinguish TTP from HUS

4. If ADAMTS13 activity is not available in an emergency, platelet count and creatinine levels can be used to predict (to some degree) ADAMTS13 activity (undetectable vs. detectable)

5. New emerging laboratory tests may help to diagnose aHUS more specifically and to tailor eculizumab dosing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Thank you for listening