
Salut!
Hi!
Hallo!
Hello!
नमस्ते
Bonjour!
Olá!
Ciao!
您好
مرحبا

Pathophysiology of HUS: Role of Infection

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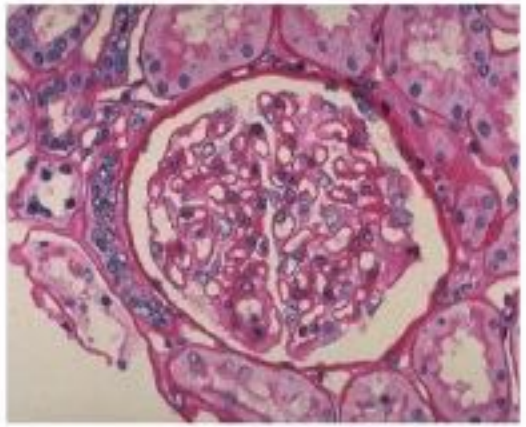
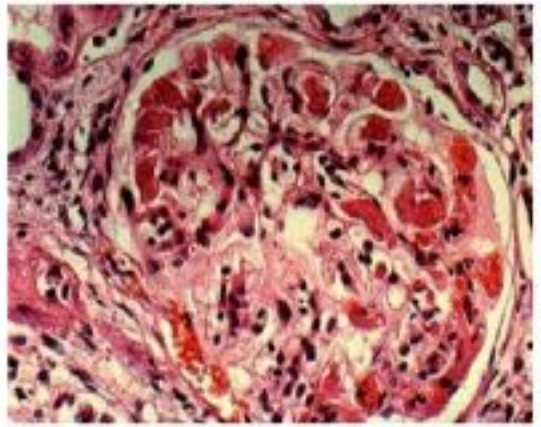
Hemolytic Uremic Syndrome

A thrombotic microangiopathy manifesting with:

- Micro-angiopathic hemolytic anemia
- Thrombocytopenia
- Acute renal failure





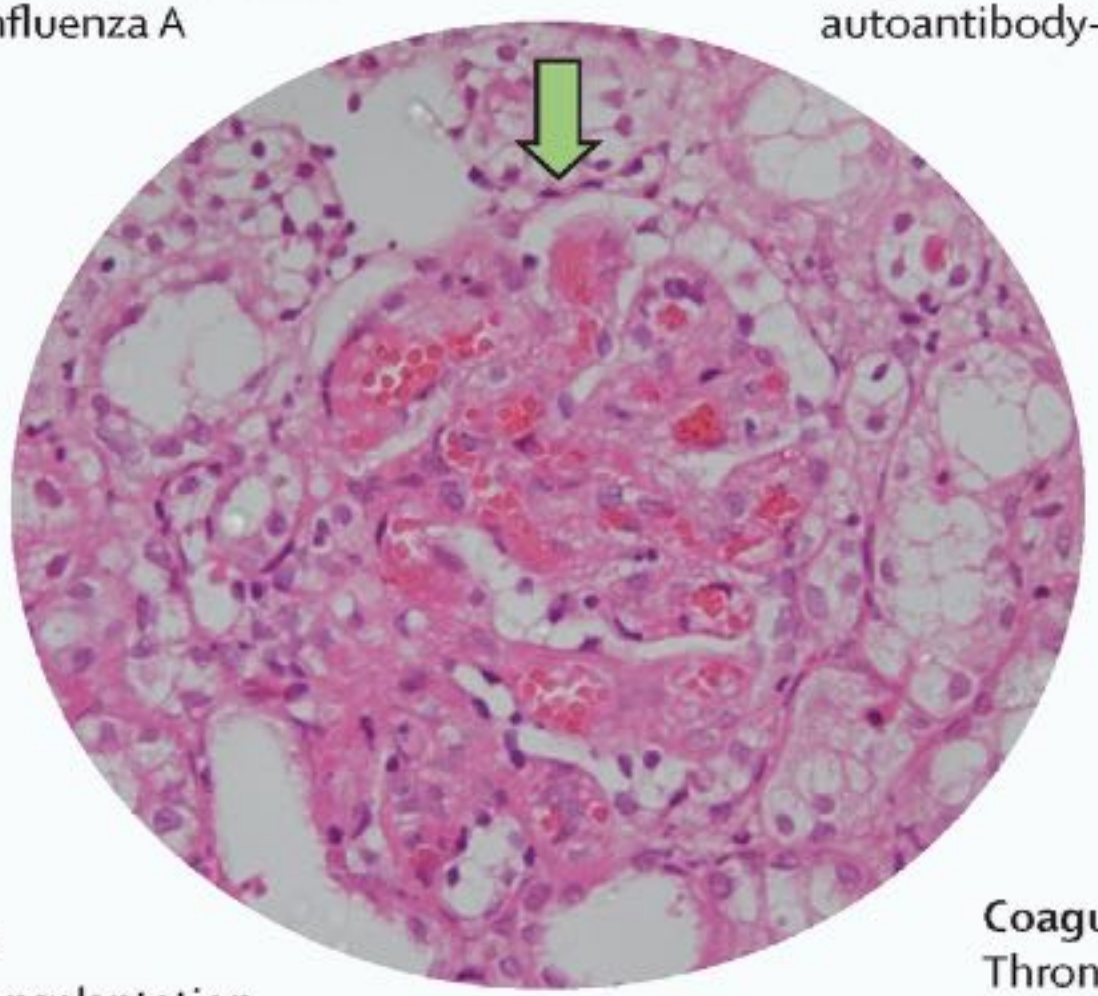
Hemolytic uremic syndrome

Historical perspective

Typical

Infection-associated HUS
Shiga toxin-producing
Escherichia coli HUS
Streptococcus pneumoniae
H1N1/influenza A

Complement-mediated aH
Hereditary: mutations of *CFH*, *CFI*, *C3*, *CFB*, *MCP* and *THBD*
Acquired: factor H autoantibody-associated HUS



Non-complement-mediated aHUS
DGKE
WT1
G6PD

Pregnancy-induced aHUS

Drug-induced aHUS

Metabolism-associated HUS
Cobalamin C disease
Methionine synthase deficiency

ransplant-associated HUS
ematopoietic stem cell transplantation
mbotic microangiopathy
rgan transplantation thrombotic
iopathy

Coagulation-mediated aHUS
Thrombomodulin

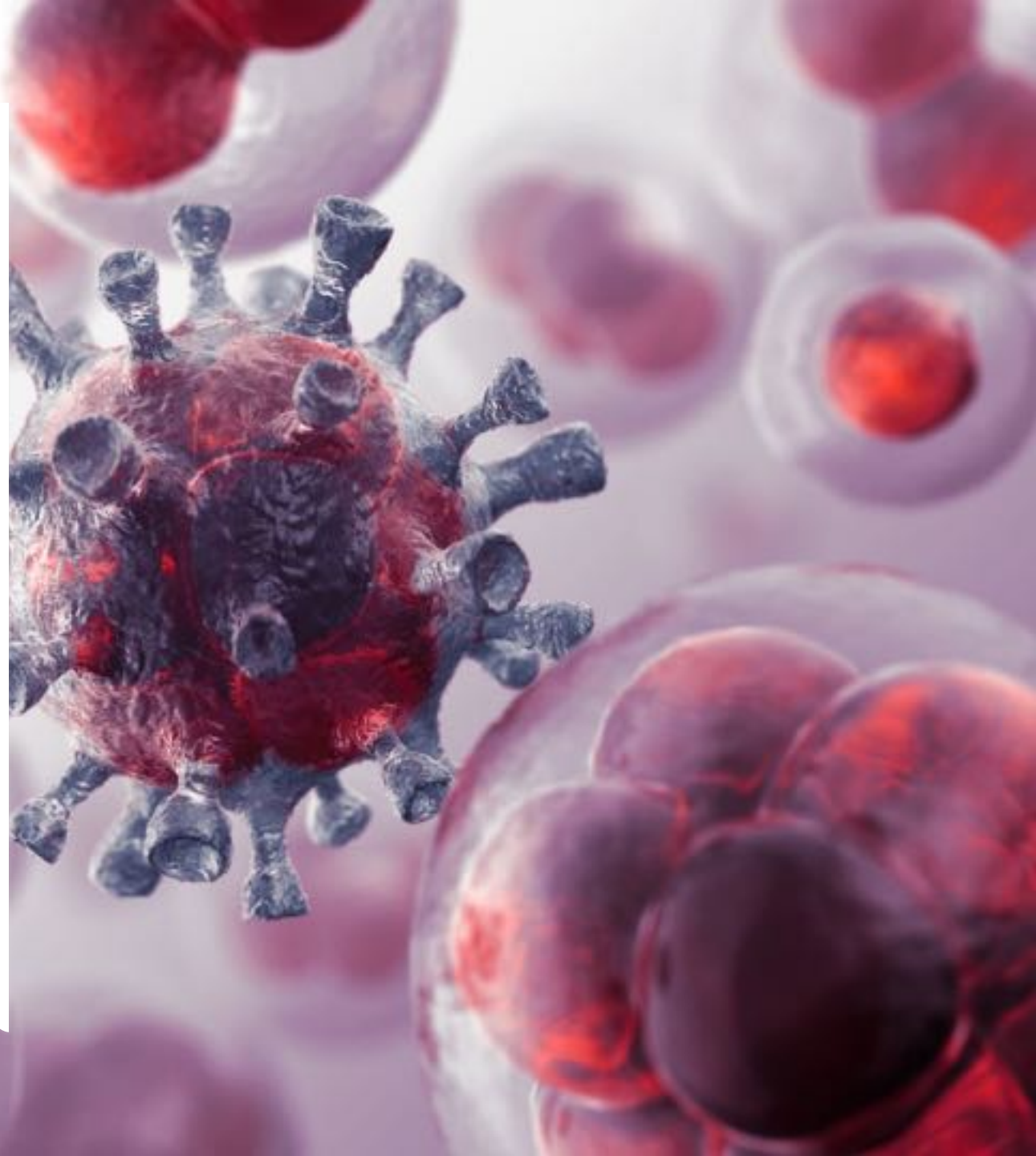
Secondary aHUS
Malignant hypertension
Complement-amplifying conditions

Infection-associated HUS Classification

- **Shiga-toxin producing E-Coli (STEC)**
- **Streptococcal pneumoniae**
- **Others:**

❖**Shigella**

❖**Viral Infection: Influenza, HIV, COVID-19…..**



STEC-HUS

STEC-HUS

Historical perspective

Japan

Europe

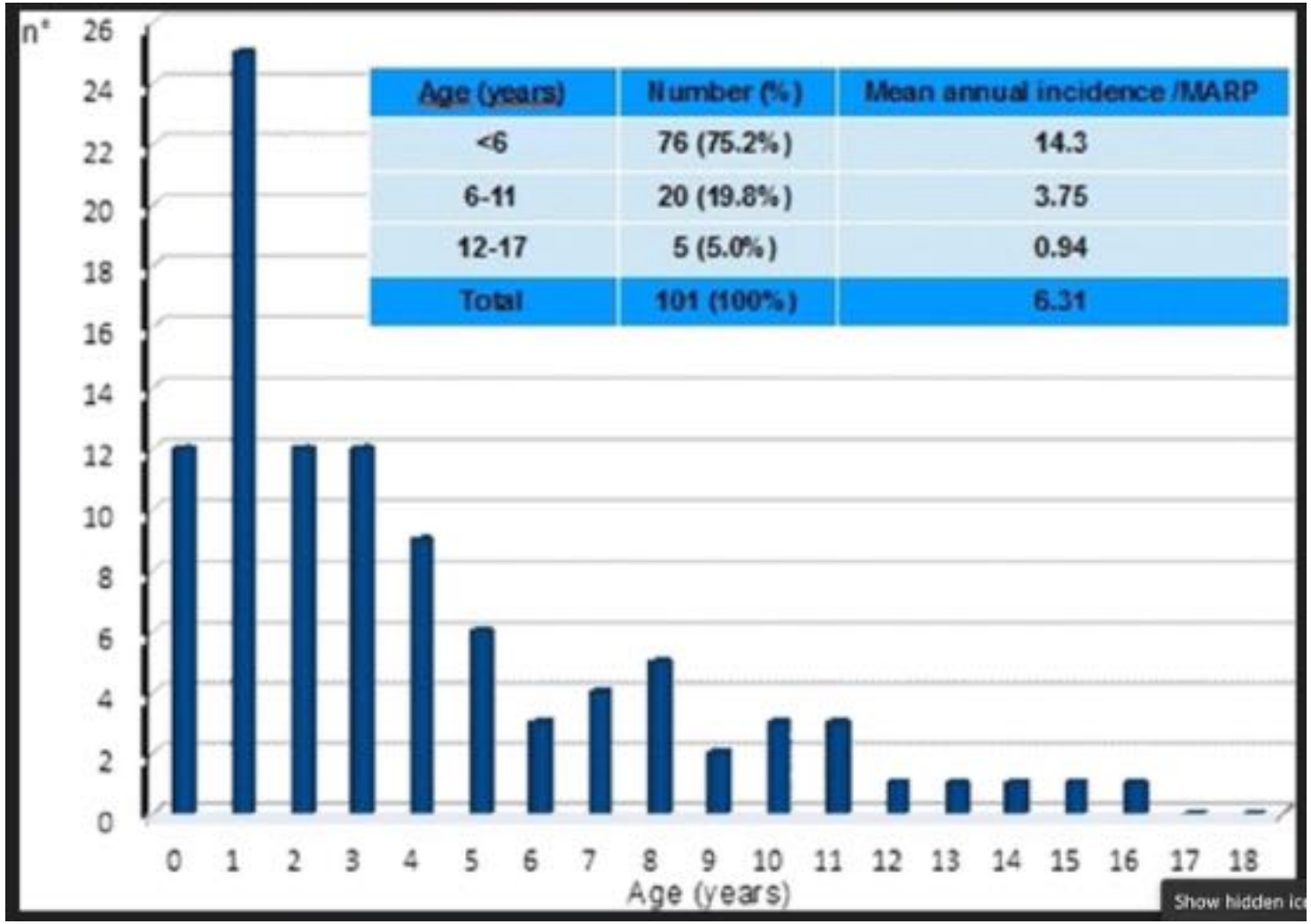
STEC-HUS in children

Bruyand et al.; Médecine et maladies infectieuses 48 (2018) 167–174

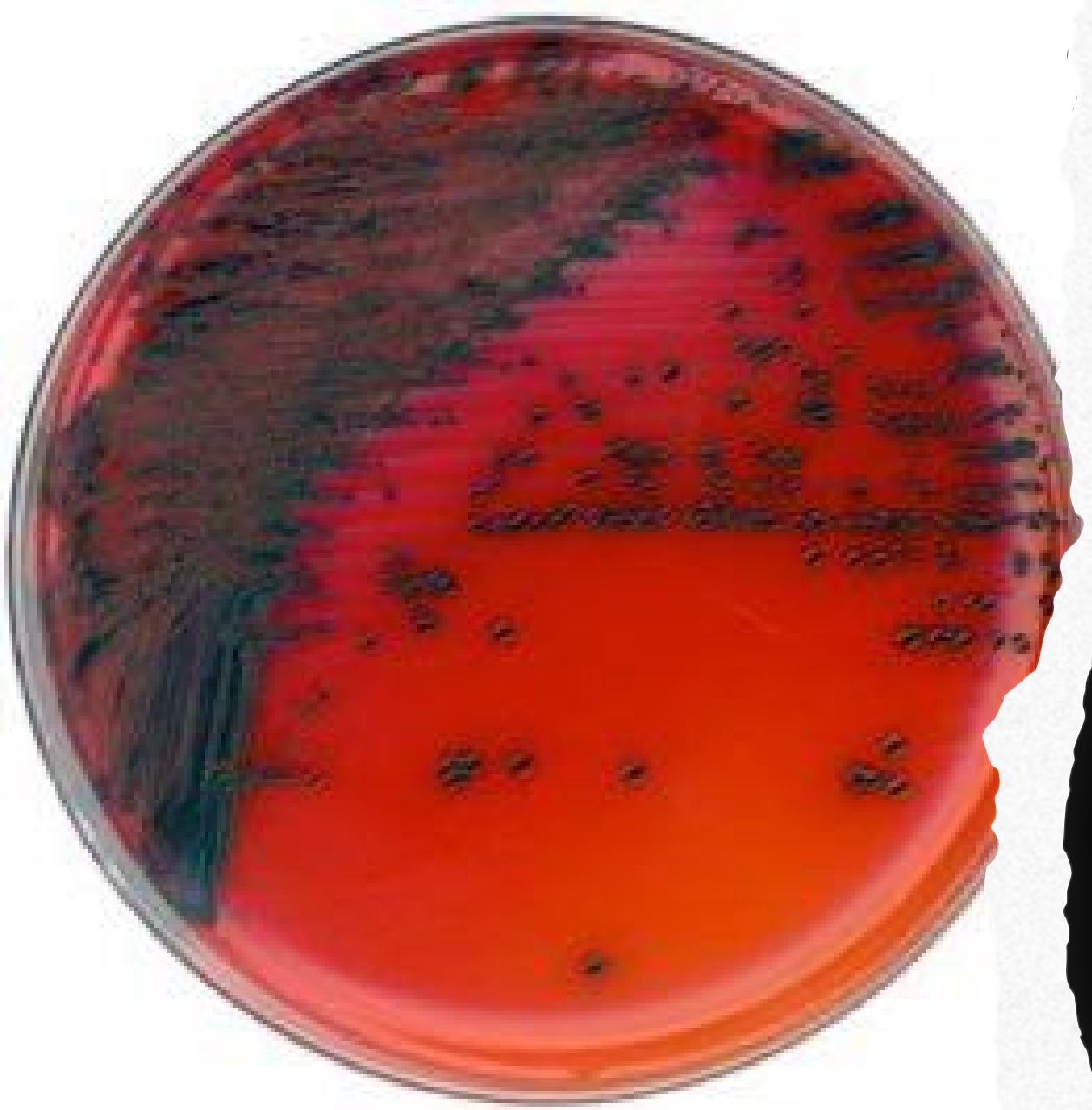
Incidence of HUS in STEC infections

Bruyand et al.; Médecine et maladies infectieuses 48 (2018) 167–174

STEC-HUS by age



Age (years)	Number (%)	Mean annual incidence /MARP
<6	76 (75.2%)	14.3
6-11	20 (19.8%)	3.75
12-17	5 (5.0%)	0.94
Total	101 (100%)	6.31

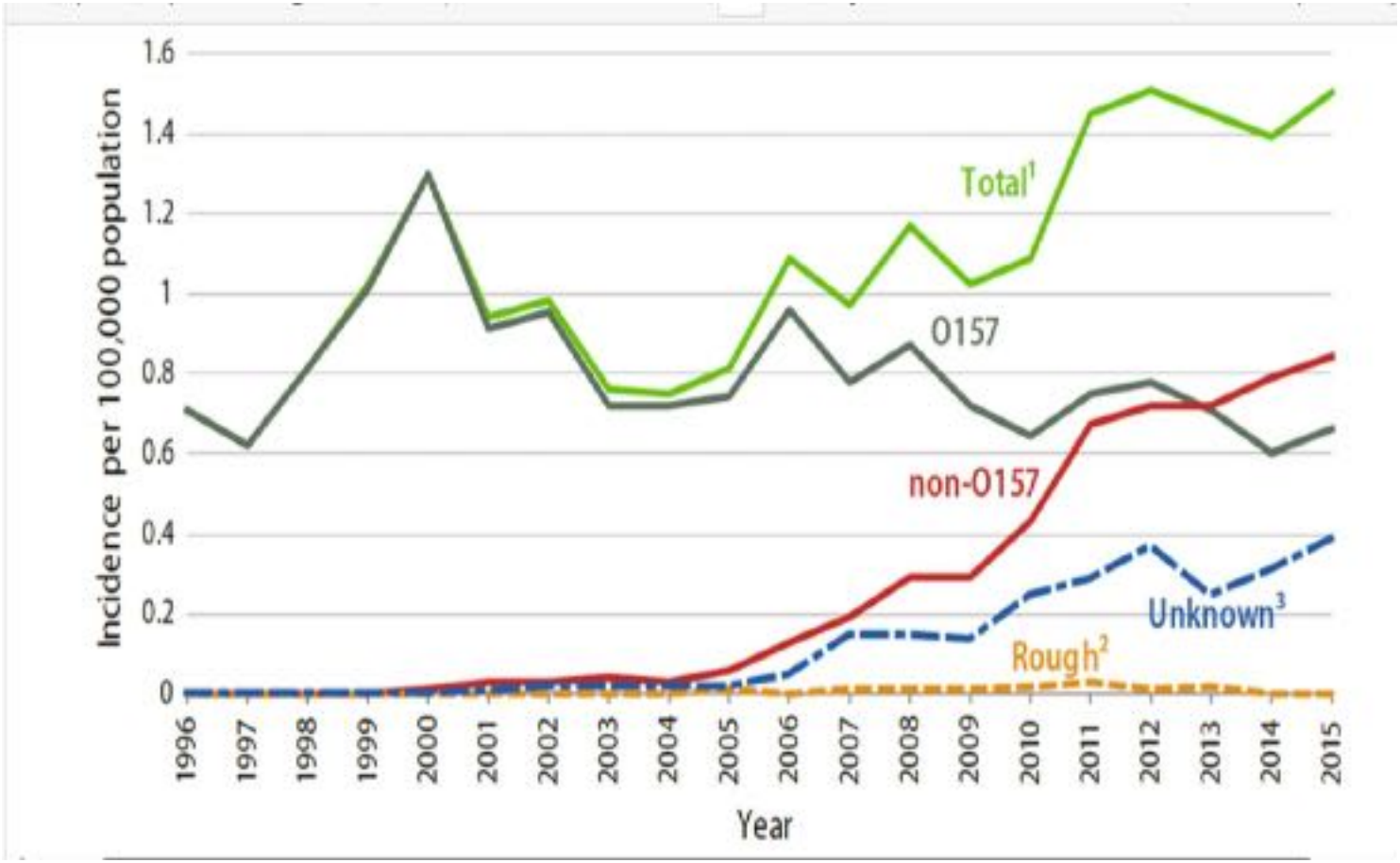


Escherichia coli O157:H7

E-Coli serogroups and HUS

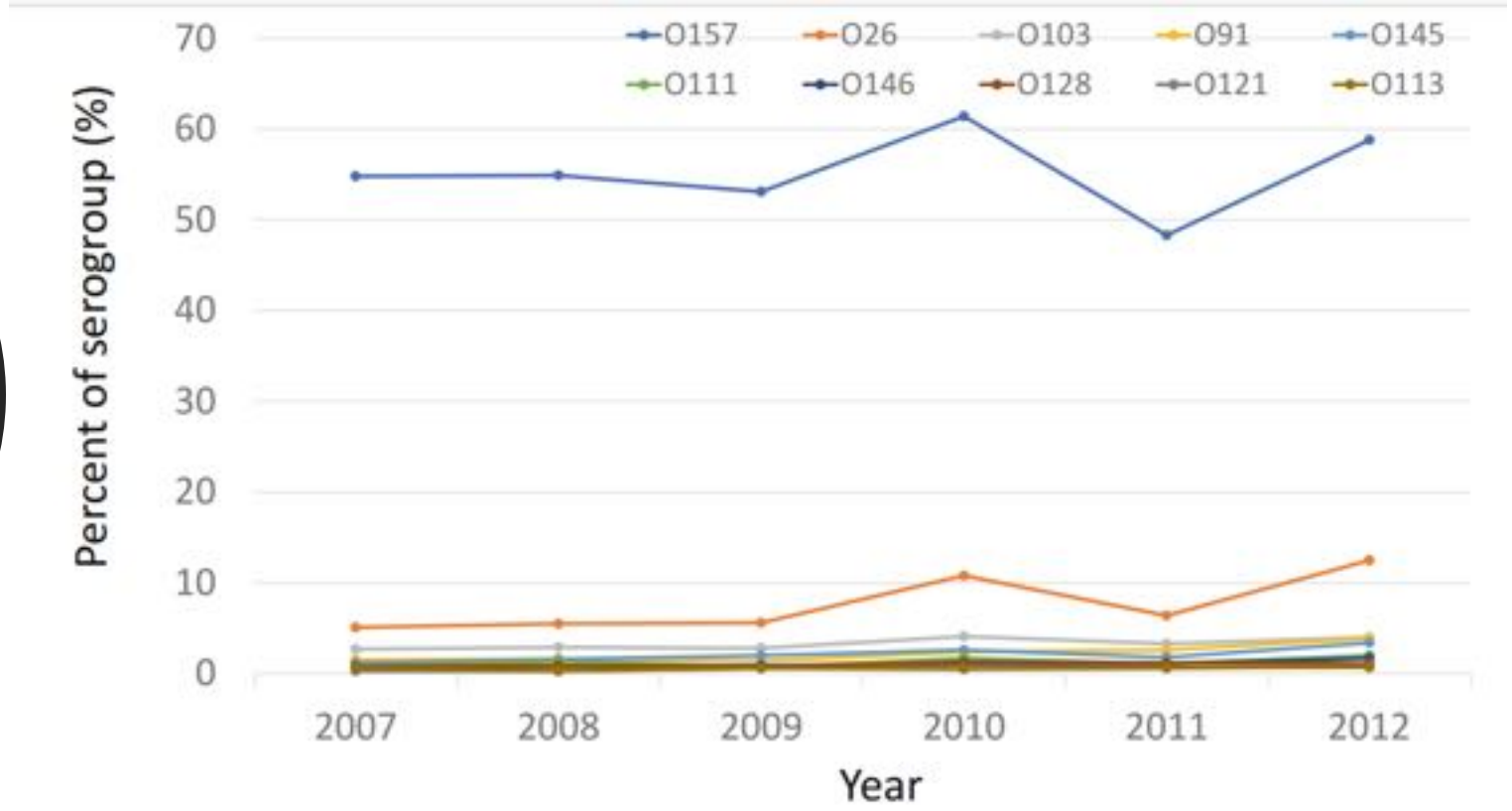
Incidence of STEC Infection by serogroup in USA

(CDC report 2015)



Incidence of STEC infection by serogroup in EU-EEA countries

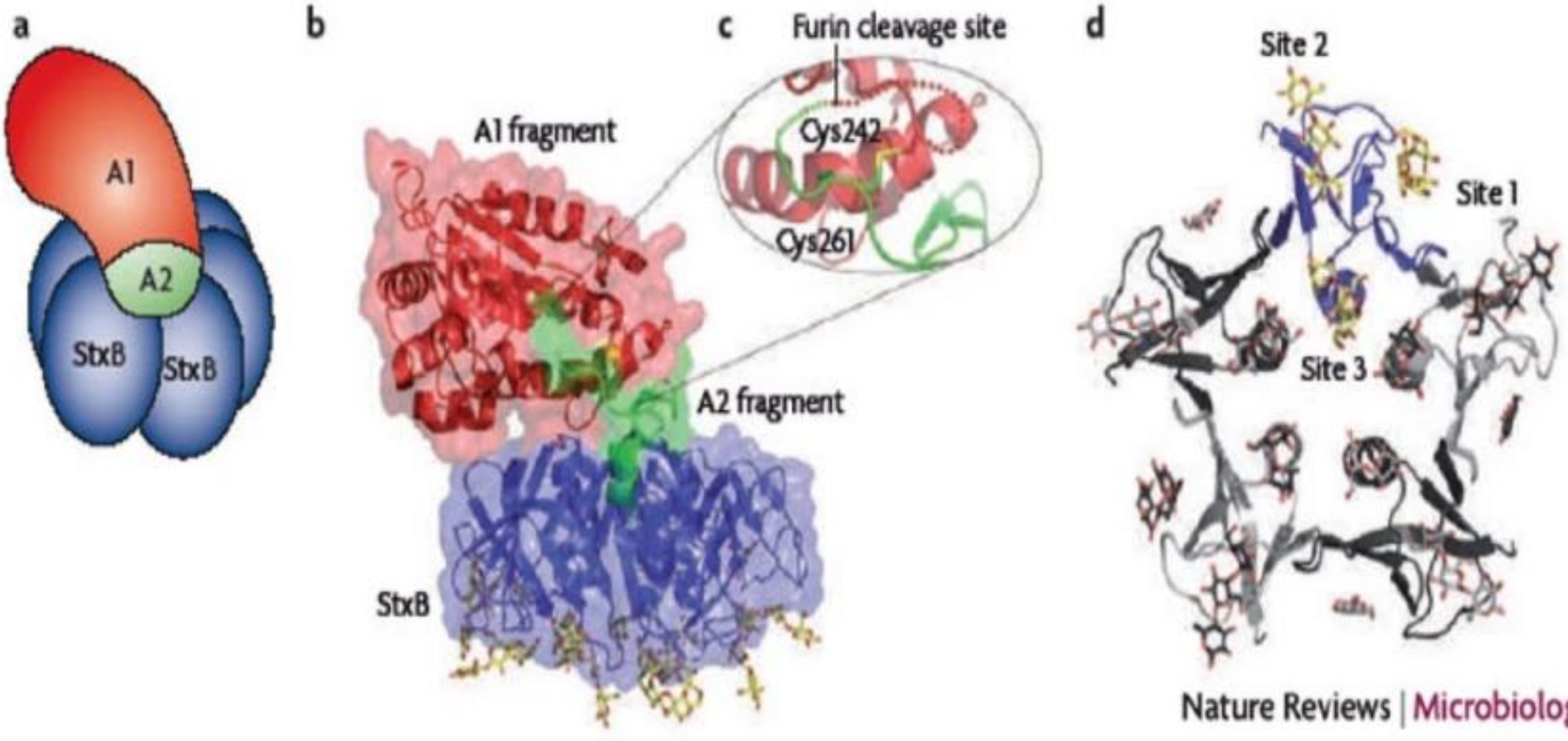
(ECDC report 2015)



Pathophysiology of STEC-HUS

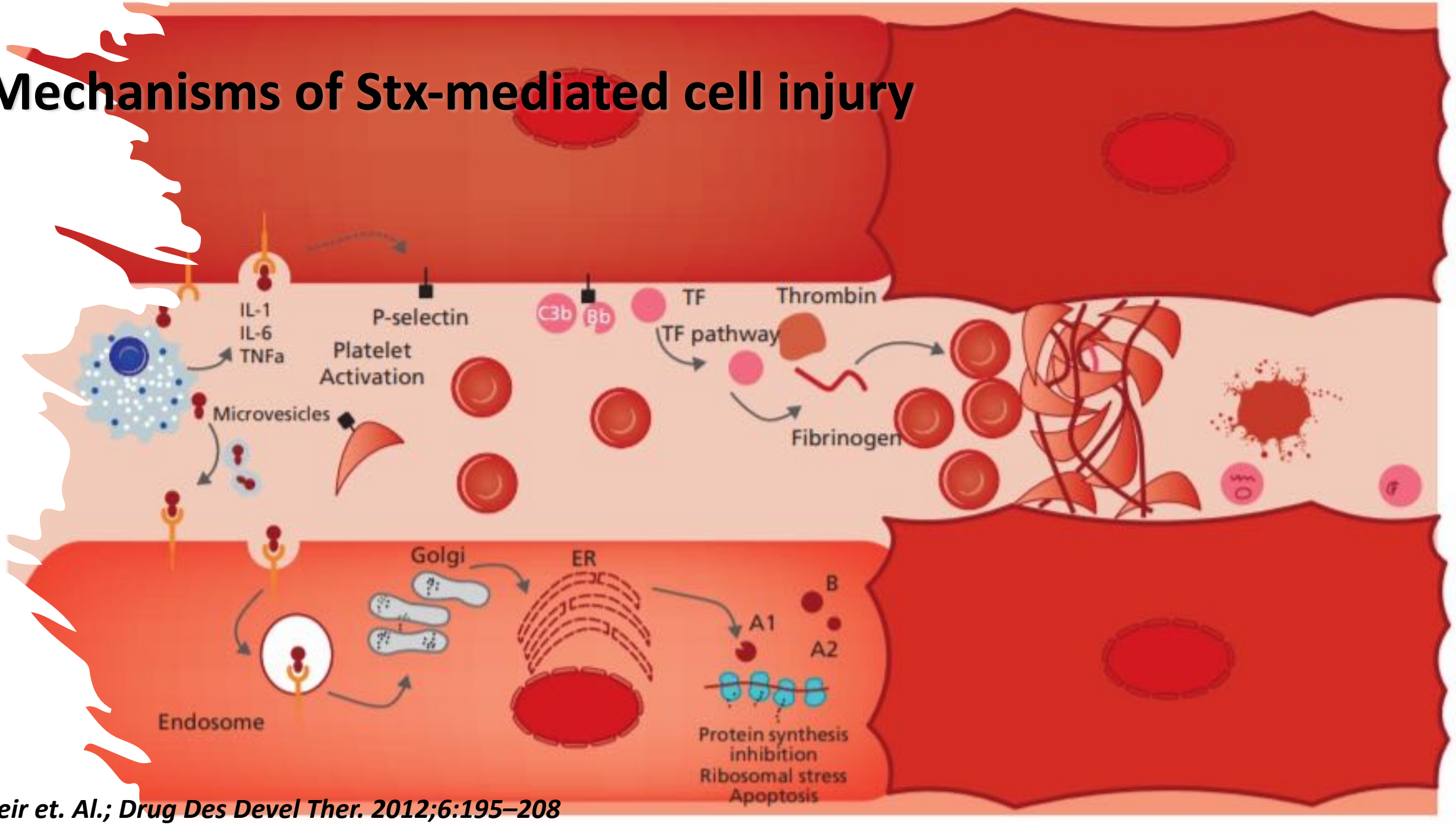
Shiga toxins

Shiga toxin structure



Obrig, Toxins. 2010;2:2769–94

Mechanisms of Stx-mediated cell injury



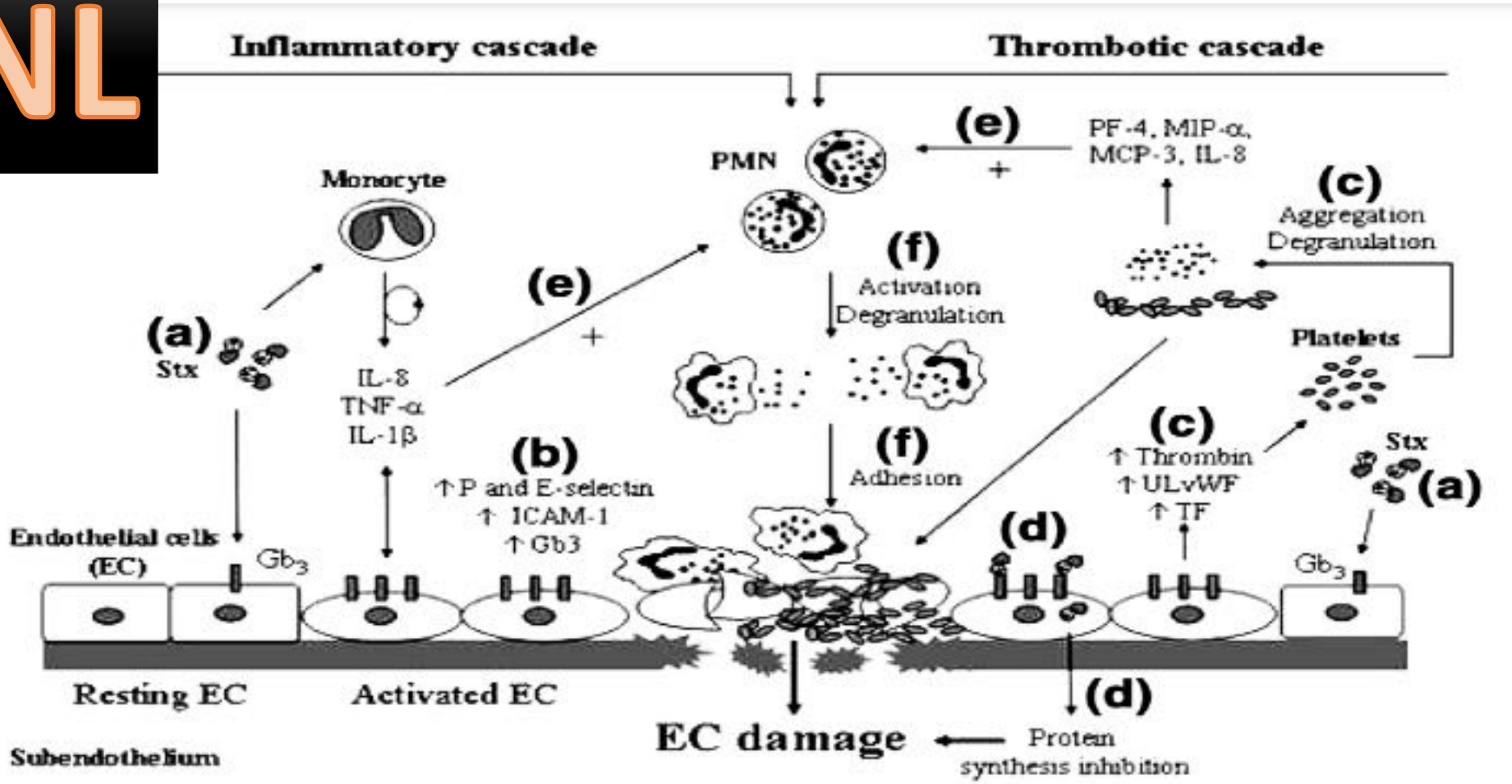
Keir et. Al.; Drug Des Devel Ther. 2012;6:195–208

Pathophysiology of STEC-HUS

Inflammatory components

Pathophysiology of STEC-HUS

PMNL

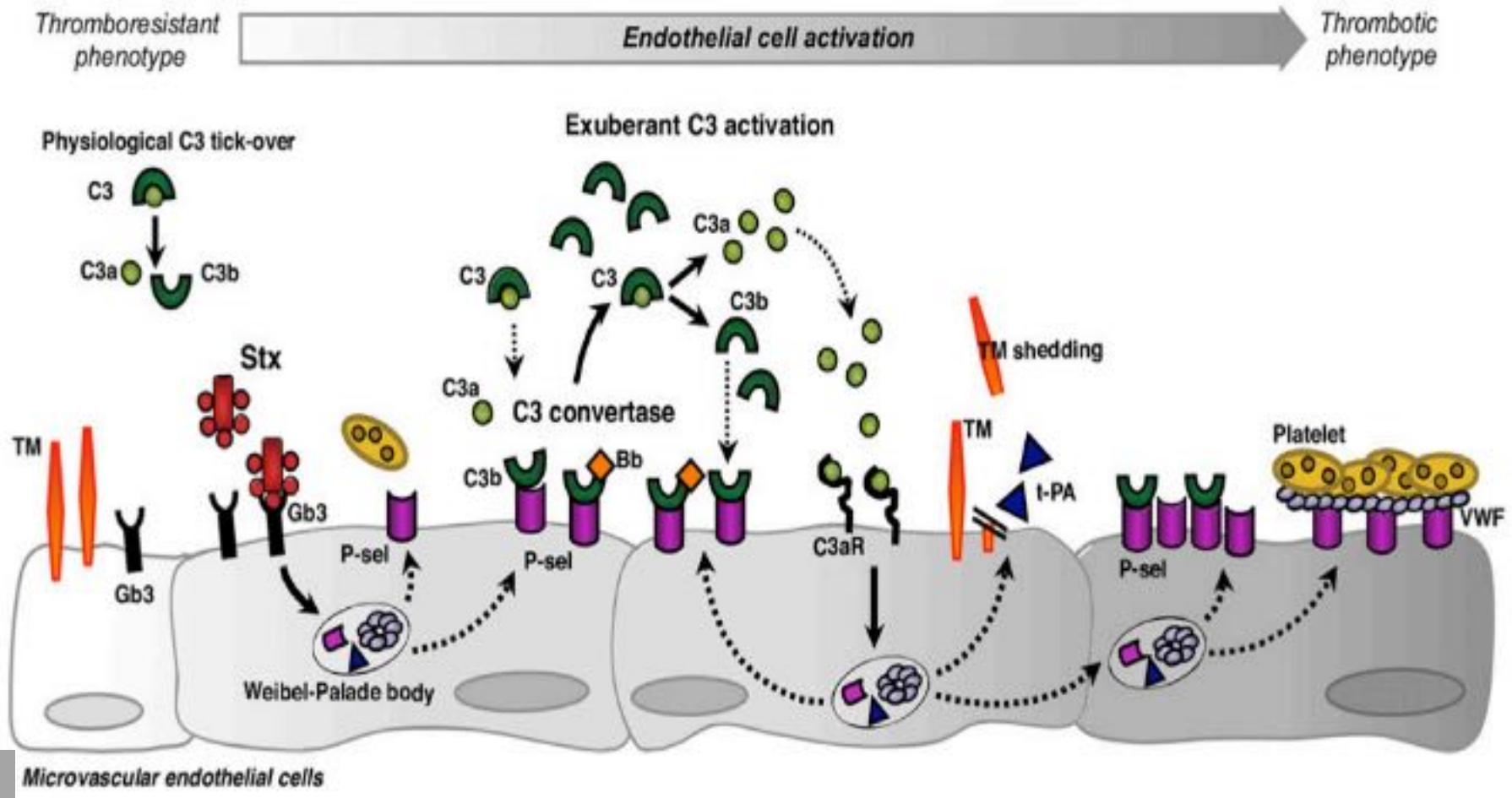


- Increased serum anti LPS Abs
- Low superoxide dismutase activity

Quoted from Exeni et.al.; Pediatr Nephrol. 2018;33:2057–71.

Pathophysiology of STEC-HUS

CAP



- Low serum C3 levels
- Increased factor Bb
- Increased soluble membrane attack complex (SC5b-9)

Quoted from Exeni et.a.l; Pediatr Nephrol. 2018;33:2057–71.

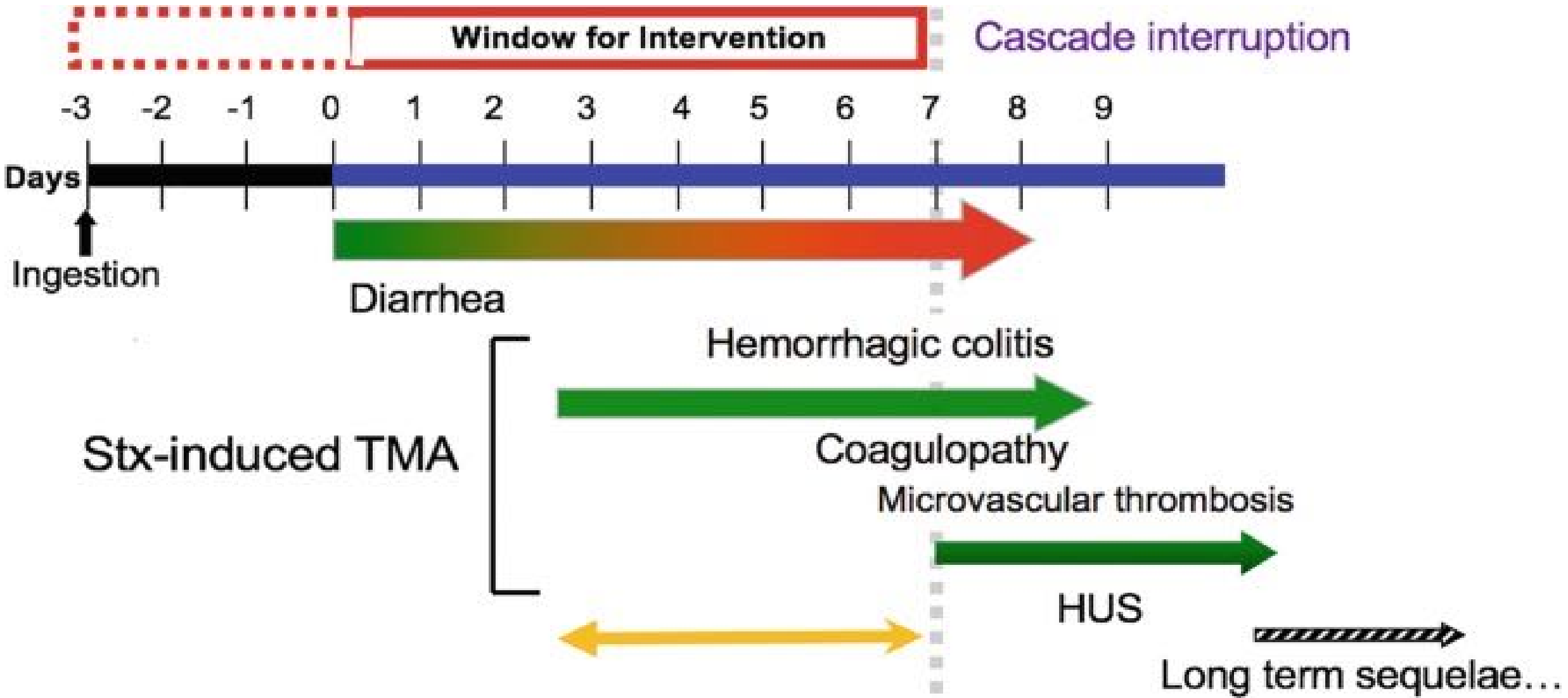
Pathophysiology of STEC-HUS

CAP

Shiga toxins

PMNL

Clinical course of STEC-HUS



The diagnosis of STEC-HUS

1.

History-taking

Physical examination

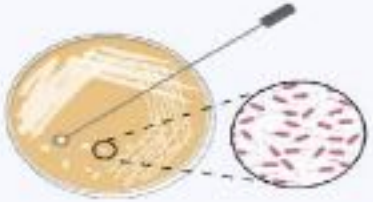
Blood

Urine

Feces

Sample collection

2.



STEC culture and isolation

Antibiotic sensitivity test

EIA test

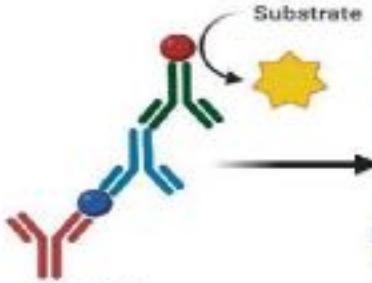
Or

Real-time PCR

Or

MALDI-TOF-MS

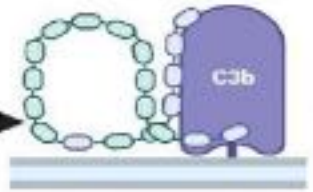
3.



ELISA

anemia
thrombocytopenia
abnormal renal function
hypocomplementemia

proteinuria
hematuria
cylindruria



Complement activation monitoring

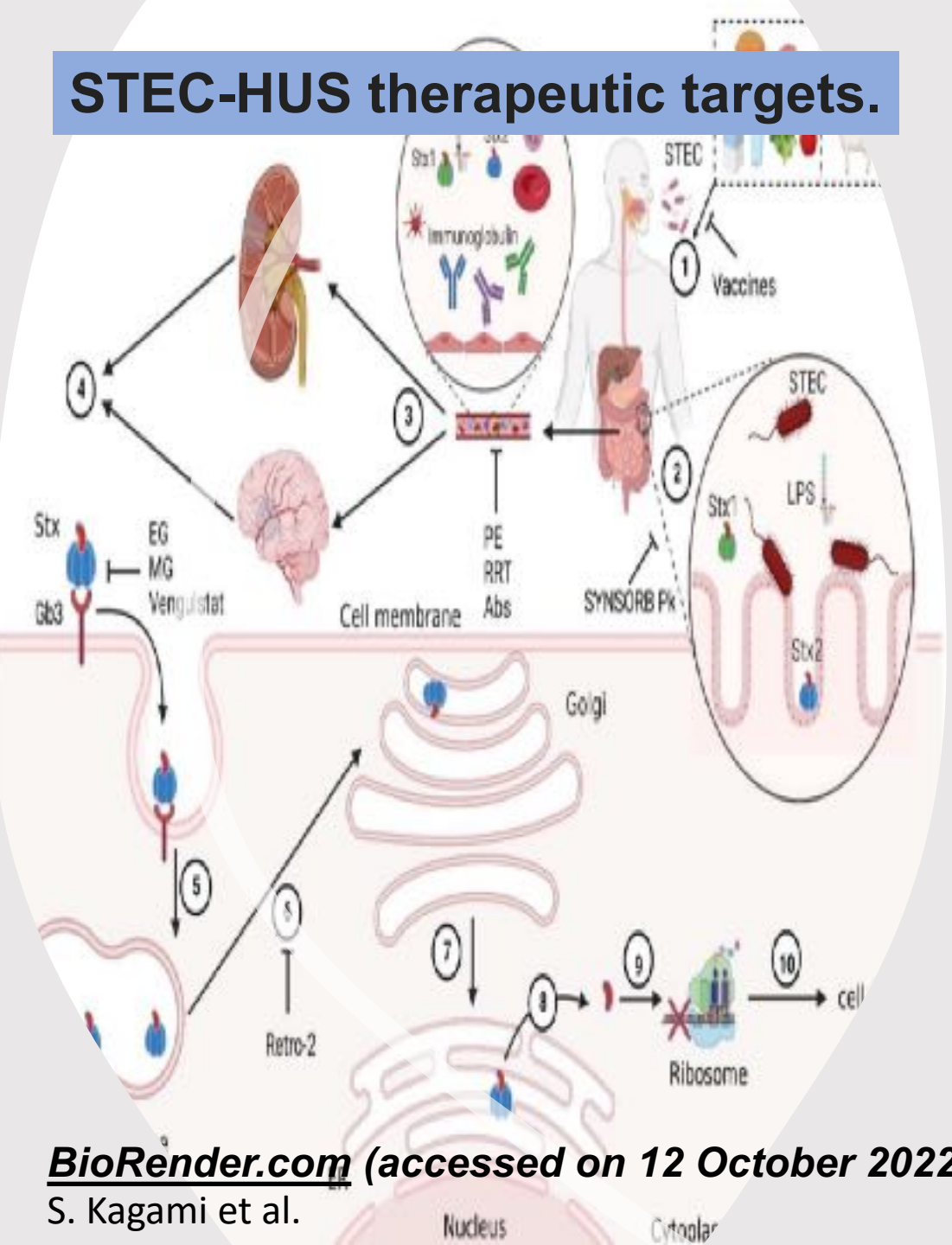
If necessary

Genetic mutations

Next-generation sequencing

Liu et. Al., Toxins 2023, 15(1)

STEC-HUS therapeutic targets.



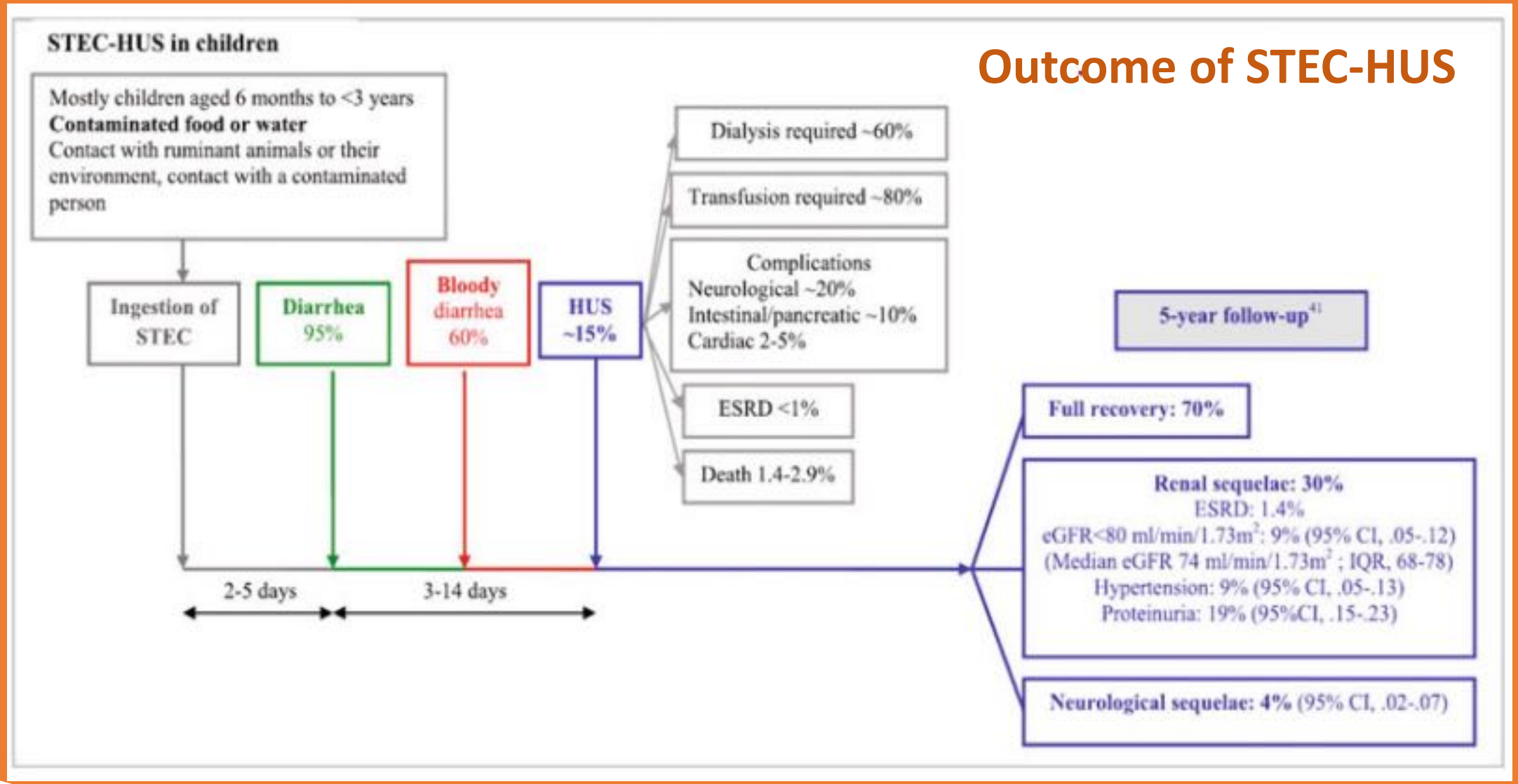
***BioRender.com* (accessed on 12 October 2022)**

S. Kagami et al.

Table 3 Summary of developed interventions based on mechanisms (first line of table) for HUS treatment. Summarized from review Muhlen et al. 2020

Shiga toxin binding	Scavenging Shiga toxin mimicking GB3 receptor	Intracellular interference with Stx	Inhibitors	Natural products	Inflammation/ immunomudualtion	Antibiotics
Oral bovine colostrum[a]	Synsorb Pk[b]	Chloroquine[c]	Pyocins[c]	White carob tree[a]	Eculizumab[a,b]	
Recombinant antibodies in plants for cattle feed (elimination from reservoir)[c]	Starfish/Daisy carbohydrate ligands, Super Twig (carbosilan)[c]	Retro1,2 Ac-PPP-tet, TVP[c]	Phages[c]	Ziziphus mistol extract[c]	Steroids[a]	
Humanized Stx targeting antibodies like Urtoxazumab[c], 13C4,11E10 Stx targeting camelid antibodies[c]	Neutralizing peptides binding to GB3[c]			Elagitannin[c]	IVIG[a]	
	Oral administered bacteria expressing GB3[c]					
	Nanoparticles displaying Stx ligands[c]					
	GB3 expression inhibitors[c]					

Outcome of STEC-HUS



Quoted from Kagami et al, in Pediatric Nephrology, 2021 F. Emma et al. (eds.), © Springer-Verlag GmbH Germany, part of Springer Nature https://doi.org/10.1007/978-3-642-27843-3_99-1

SD1-HUS

SD1-HUS

500 cases

Review > Trans R Soc Trop Med Hyg. 2012 Jul;106(7):395-9. doi: 10.1016/j.trstmh.2012.04.001. Epub 2012 May 10.

Haemolytic uraemic syndrome during shigellosis

Thomas Butler [1]

Affiliations + expand

PMID: 22579556 DOI: 10.1016/j.trstmh.2012.04.001

Abstract

Haemolytic uraemic syndrome (HUS), which is comprised of the triad of haemolytic anemia, thrombocytopenia and renal insufficiency, occurs in about 13% of dysenteric patients with shigellosis due to Shigella dysenteriae type 1 (SD1) infections, who are mostly children less than five years old in Africa and Asia. With a case-fatality rate of about 36%, it is the leading cause of death in SD1 outbreaks. Research suggests that Shiga toxin and lipopolysaccharide from the causative bacteria play roles in pathogenesis. The risk of HUS is increased when inappropriate antimicrobial drugs, against which infecting bacteria are resistant, are used or when any antimicrobial drug is given more than four days after the start of diarrhoea. To prevent HUS, it is advised to initiate an appropriate drug early and to consider withholding antimicrobial therapy in patients presenting more than four days after the onset of diarrhoea.

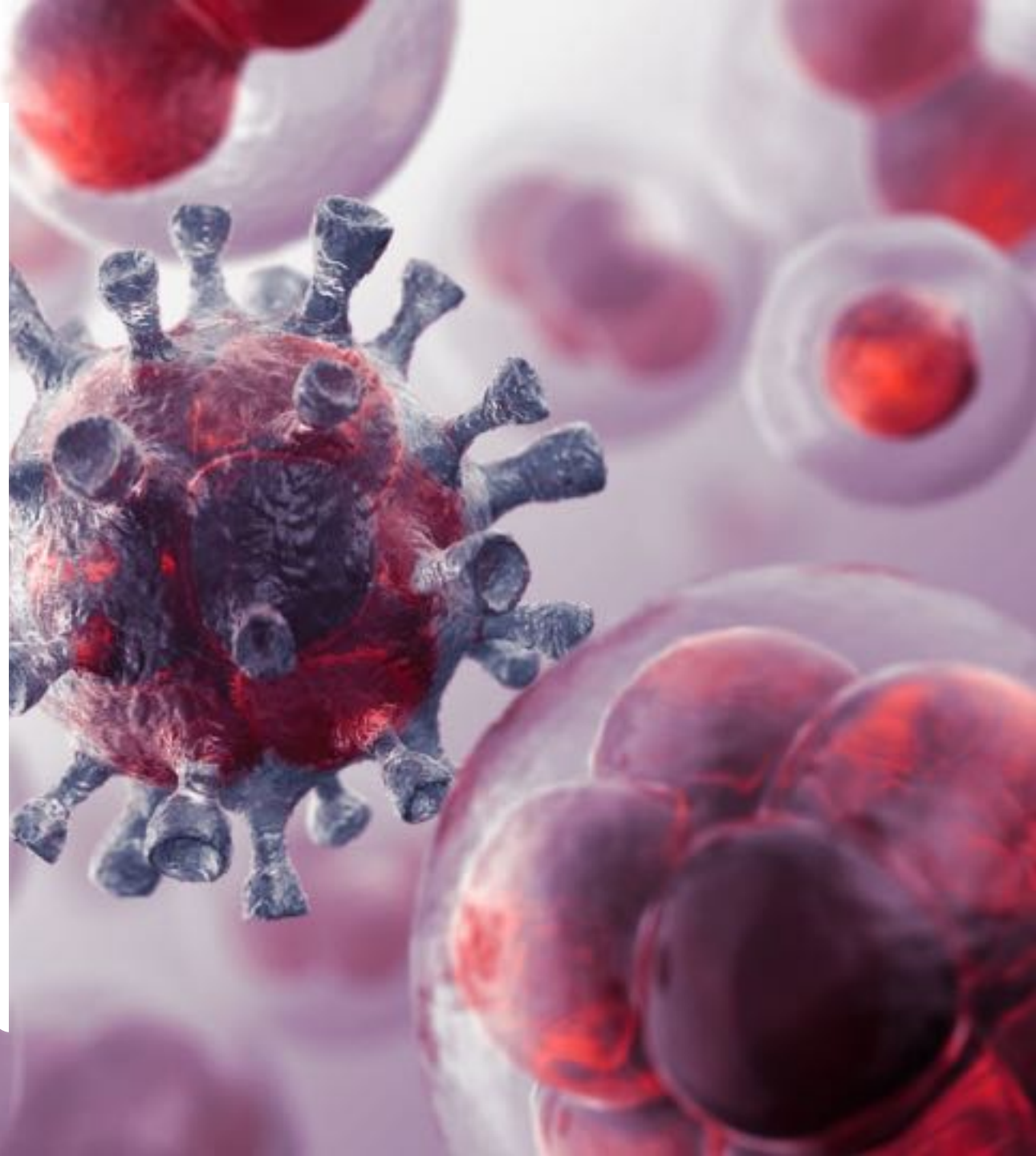
- **13% of dysenteric patients with shigellosis due to Shigella dysenteriae type 1 (SD1) infections develop HUS.**
- **Mostly children less than five years old.**
- **HUS develops 4-17 days after the onset of bloody diarrhea.**
- **The risk of HUS is increased with delay in the start of appropriate antimicrobial drugs.**
- **Shiga toxin and lipopolysaccharide play roles in pathogenesis.**
- **Mortality rate is 36%.**

Infection - Associated HUS Classification

- **Shiga-toxin producing E-Coli (STEC)**
- **Streptococcal pneumoniae**
- **Others:**

❖**Shigella**

❖**Viral Infection: Influenza, HIV, COVID-19…..**



Sp-HUS

Monatsschr Kinderheilkd (1902). 1971 Jan;119(1):2-8.

[Severe pneumonia with hemolysis caused by neuraminidase. Detection of cryptantigens by indirect immunofluorescent technic]

[Article in German]

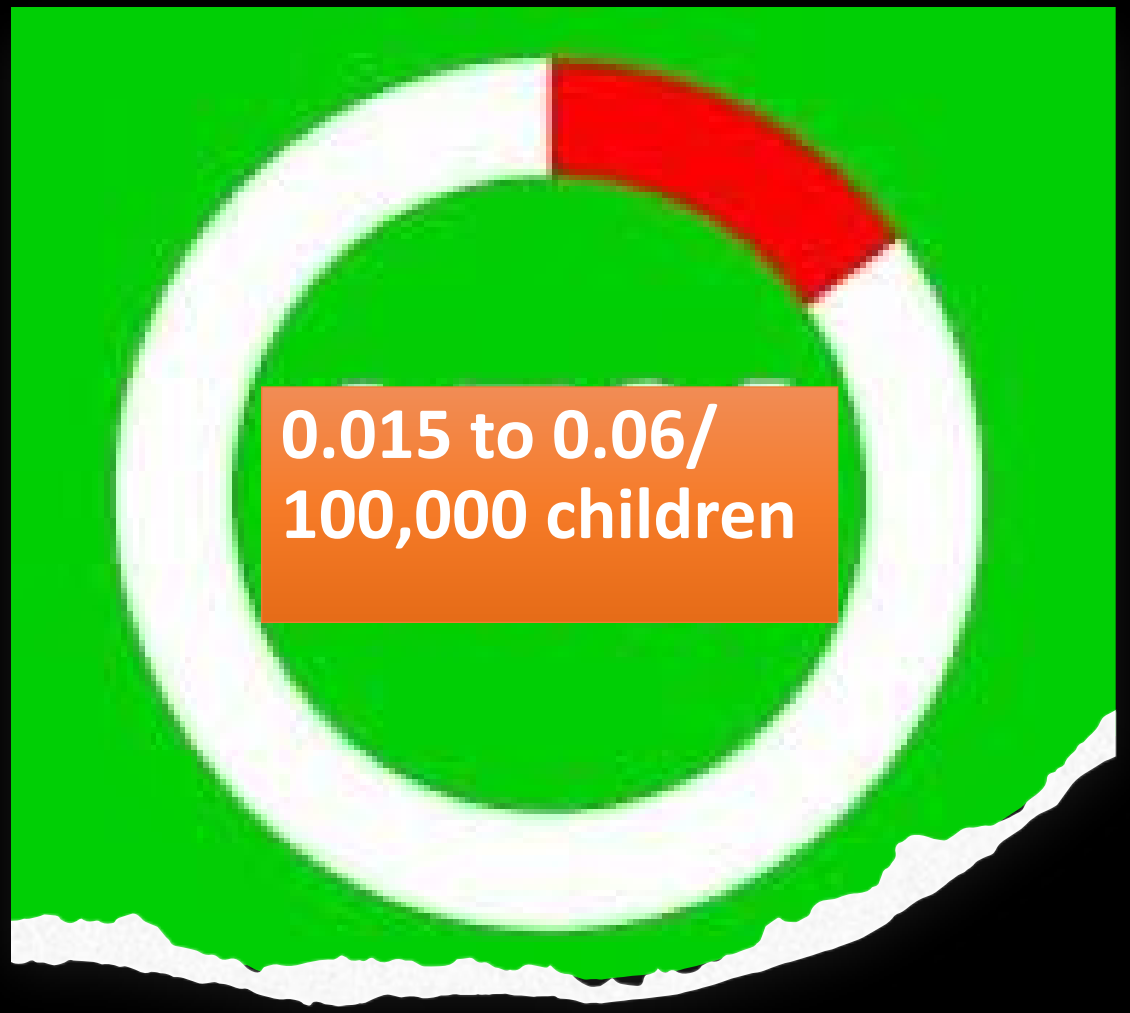
K Fischer, A Poschmann, H Oster

PMID: 4926219

Sp-HUS in children

Bruyand M et al,. Médecine et maladies infectieuses 48 (2018) 167–174

Incidence of HUS in Streptococcal pneumoniae infections.

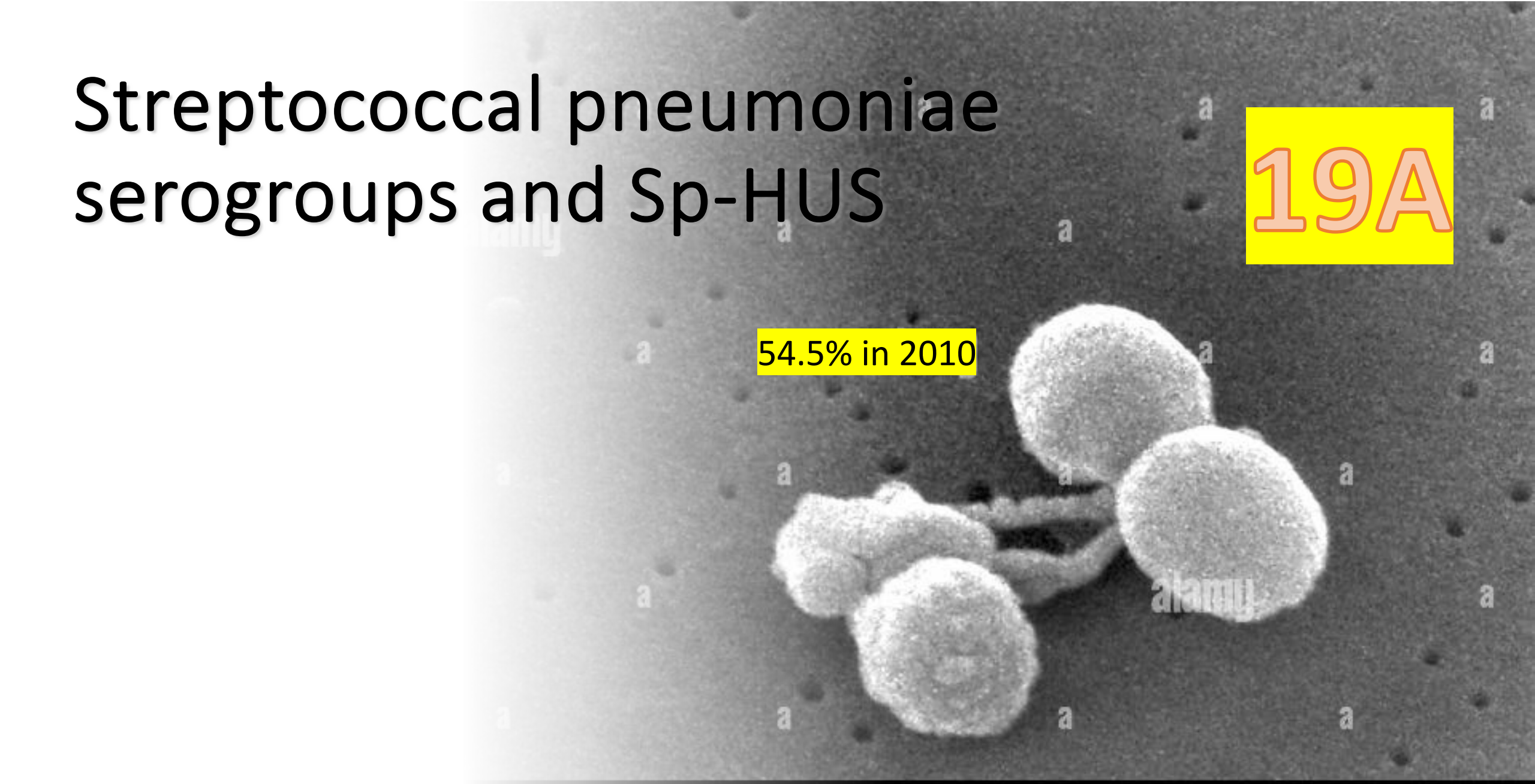


Copelovitch & Kaplan, Pediatr. Nephrol. 2008, 23, 1951–1956.

Streptococcal pneumoniae serogroups and Sp-HUS

19A

54.5% in 2010

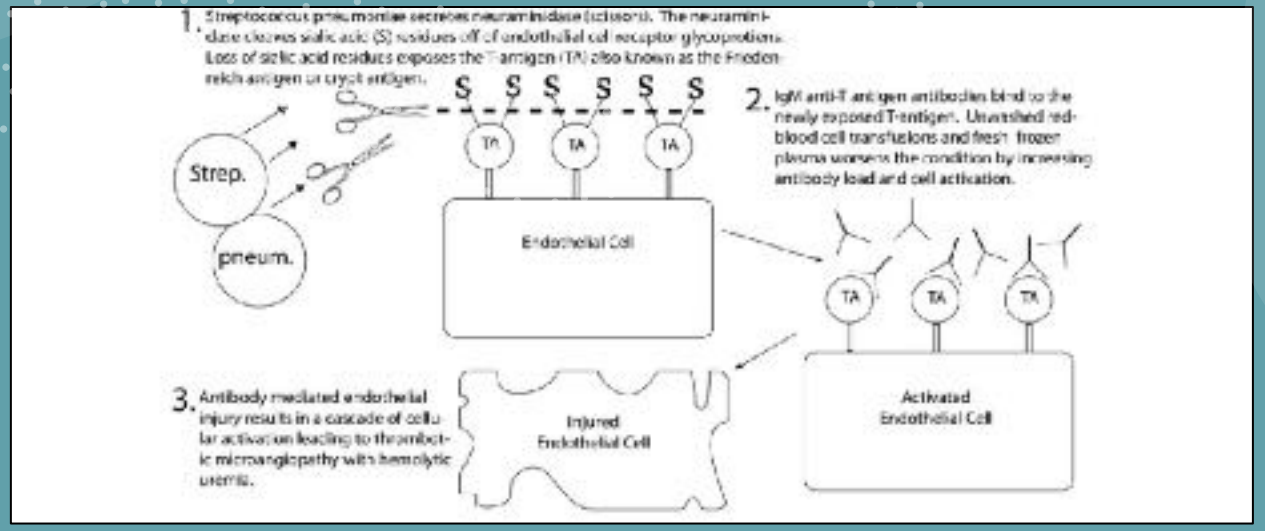


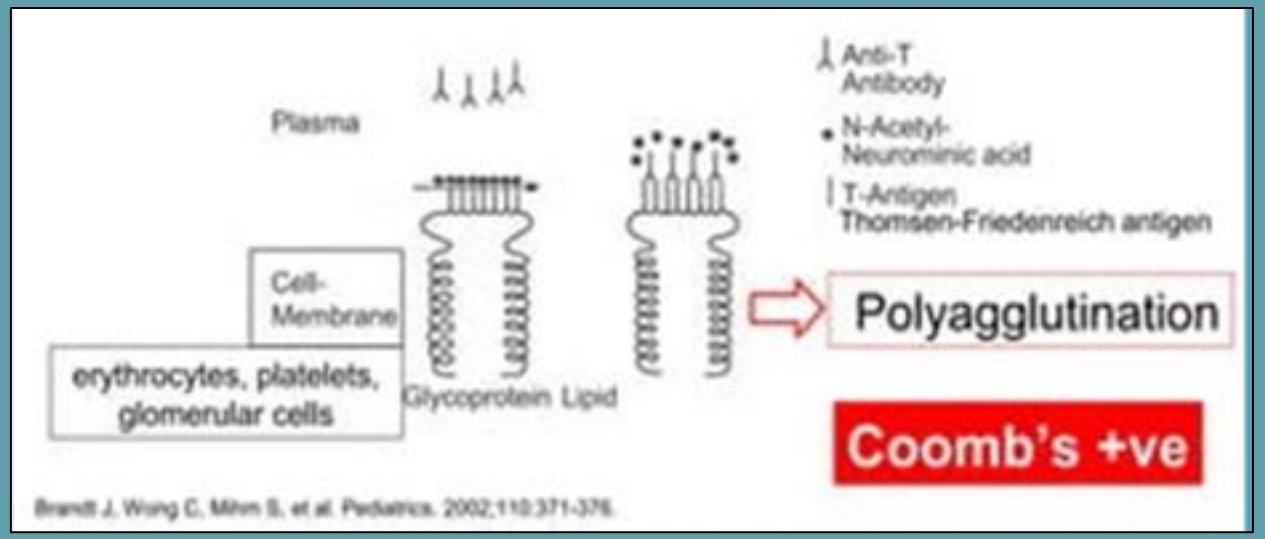
Copelovitch & Kaplan;. Pediatrics. 2010;125(1):e174–82.

Pathophysiology of Sp-HUS

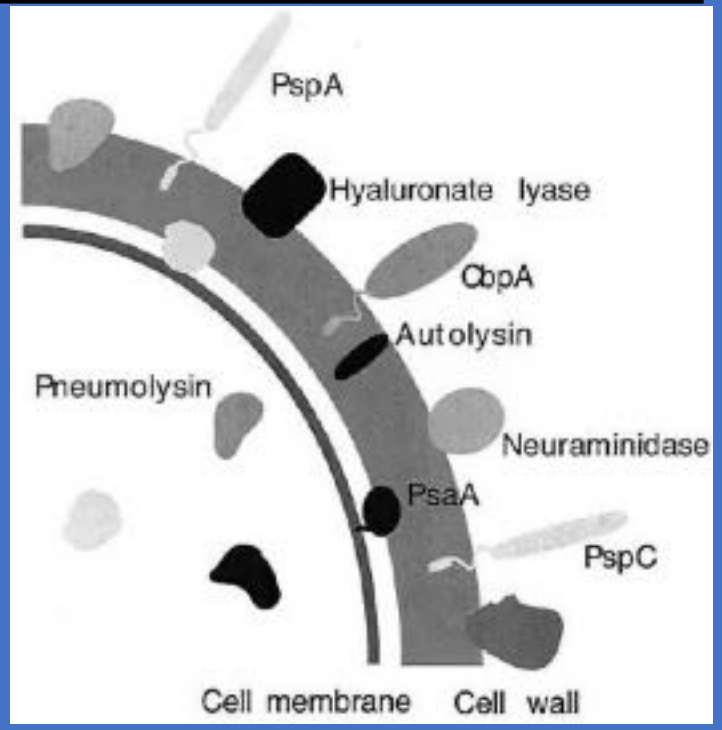
Neuraminidase

Mechanisms of neuraminidase -mediated cell injury

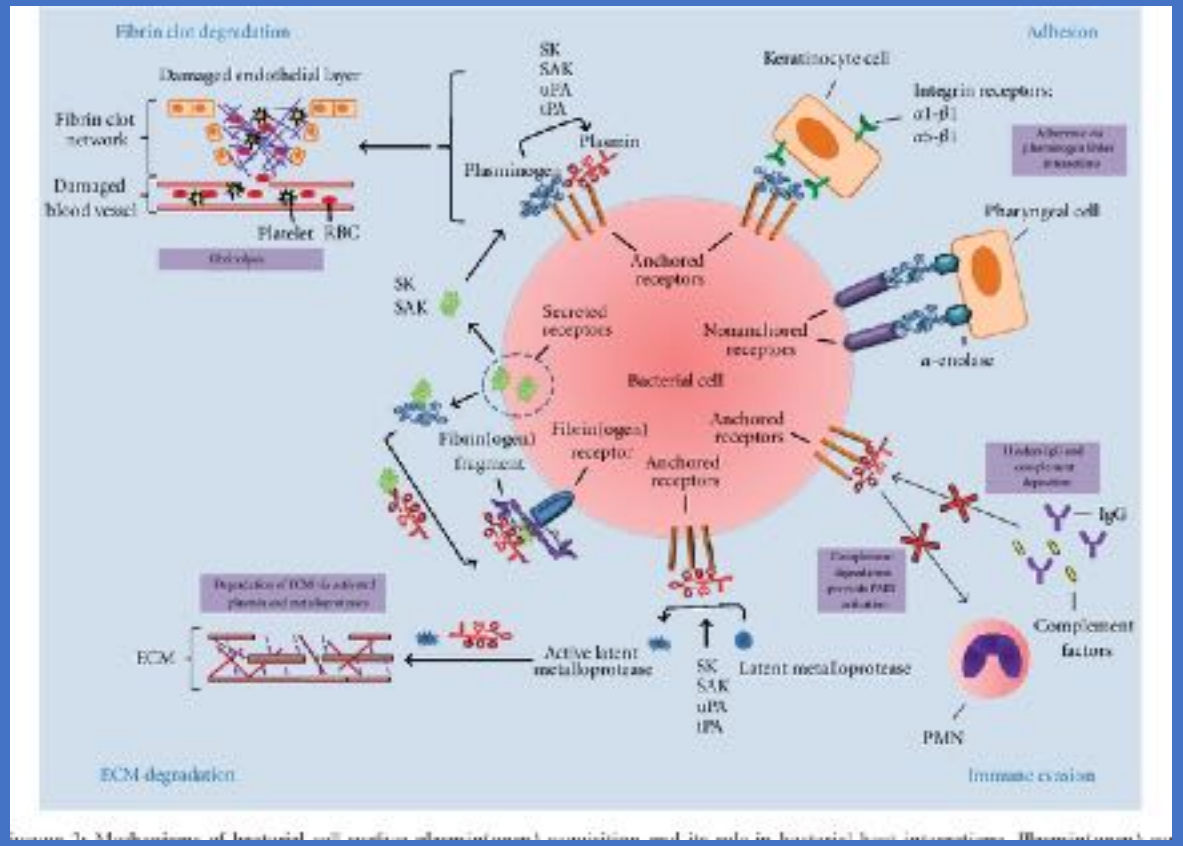




PspC

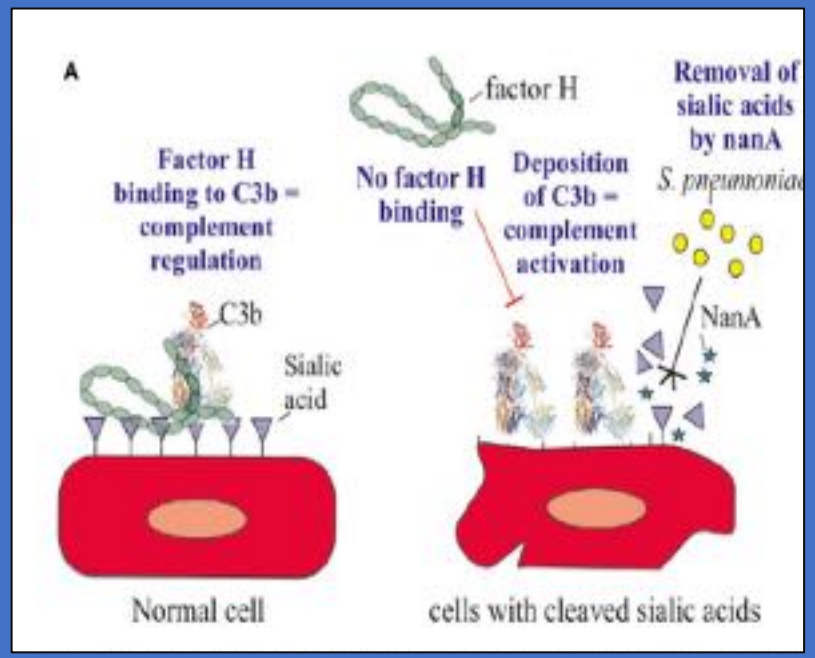


Pathophysiology of Sp-HUS

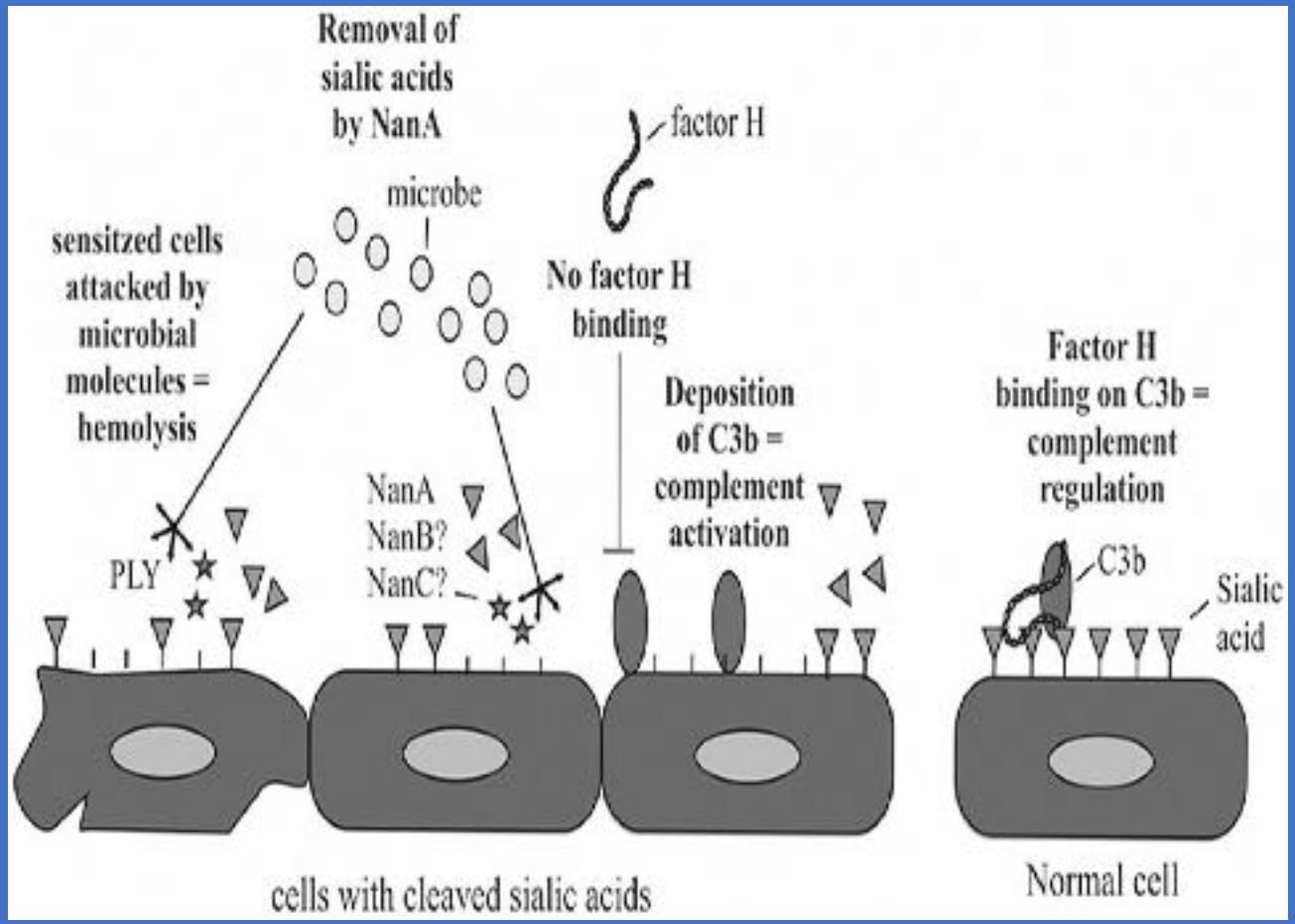


Meinel et al., J. Infect. Dis. 2018, 217, 358–370

Factor H



Pathophysiology of Sp-HUS



Spinale et al.; Curr. Opin. Pediatr. 2013, 25, 203–208

Complement dysregulation

Case Reports > Med Hypotheses. 2013 Sep;81(3):400-3. doi: 10.1016/j.mehy.2013.05.030. Epub 2013 Jun 17.

Does dysregulated complement activation contribute to haemolytic uraemic syndrome secondary to Streptococcus pneumoniae?

Rodney D Gilbert [1], Arvind Nagra, Mushfequr R Hac

- 3/5 patients had mutations and/or risk haplotypes in the complement genes.

Pathophysiology of Sp-HUS

Case Reports > Int J Med Microbiol. 2018 Dec;308(8):1096-1104. doi: 10.1016/j.ijmm.2018.08.007. Epub 2018 Aug 29.

Complement depletion and Coombs positivity in pneumococcal hemolytic uremic syndrome (pnHUS). Case series and plea to revisit an old pathogenetic concept

Martin Bitzan [1], Omar AlKandari [2], Blair Whittemore [3], Xiao-Ling Yin [4]

- Activation of the classic pathway secondary to exposing T-antigens on different cells.
- Activation of the alternative pathway secondary to decreased factor H binding to endothelial cells.

Pathophysiology of Sp-HUS

PspC

Factor H

Neuraminidase

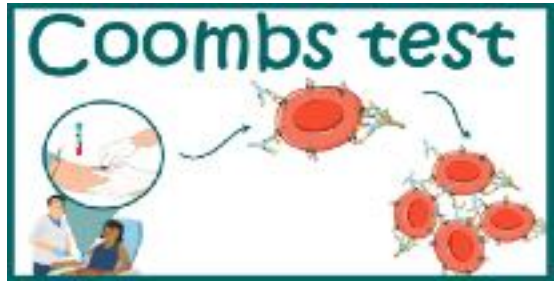
Complement dysregulation

HUS

- Fluorescein-labelled peanut lectin (Arachis hypogaea) agglutination test.

Sensitivity: 100%

Specificity: 48%



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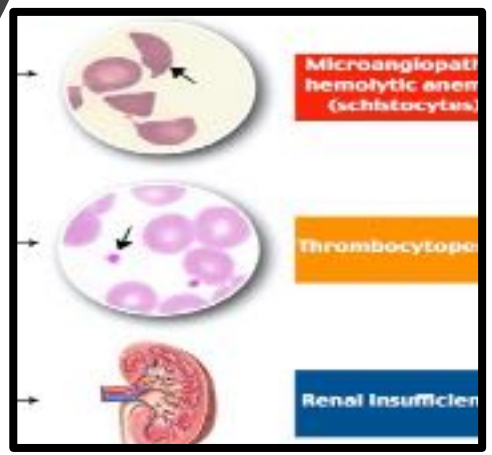
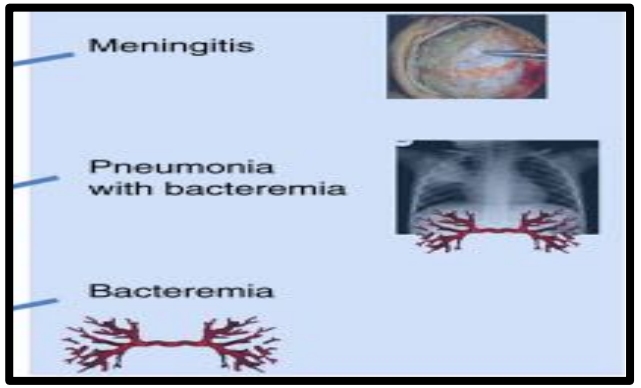




Invasive Streptococcus pneumoniae infection

- The presence of pneumococcal growth.
- Antigen detection.
- Positive PCR from blood or physiologically sterile biological fluid.

Quoted from Agarwal & Latifthoge; Pathogens. (2021), 10, 727

Diagnosis of Sp-HUS

Definite case

- Presence of HUS.
- Presence of invasive Streptococcal pneumoniae infection.
- Absence of DIC.

Probable case

- Presence of HUS.
- Presence of invasive Streptococcal pneumoniae infection.
- Presence of DIC.
- Presence of T-Antigen activation.

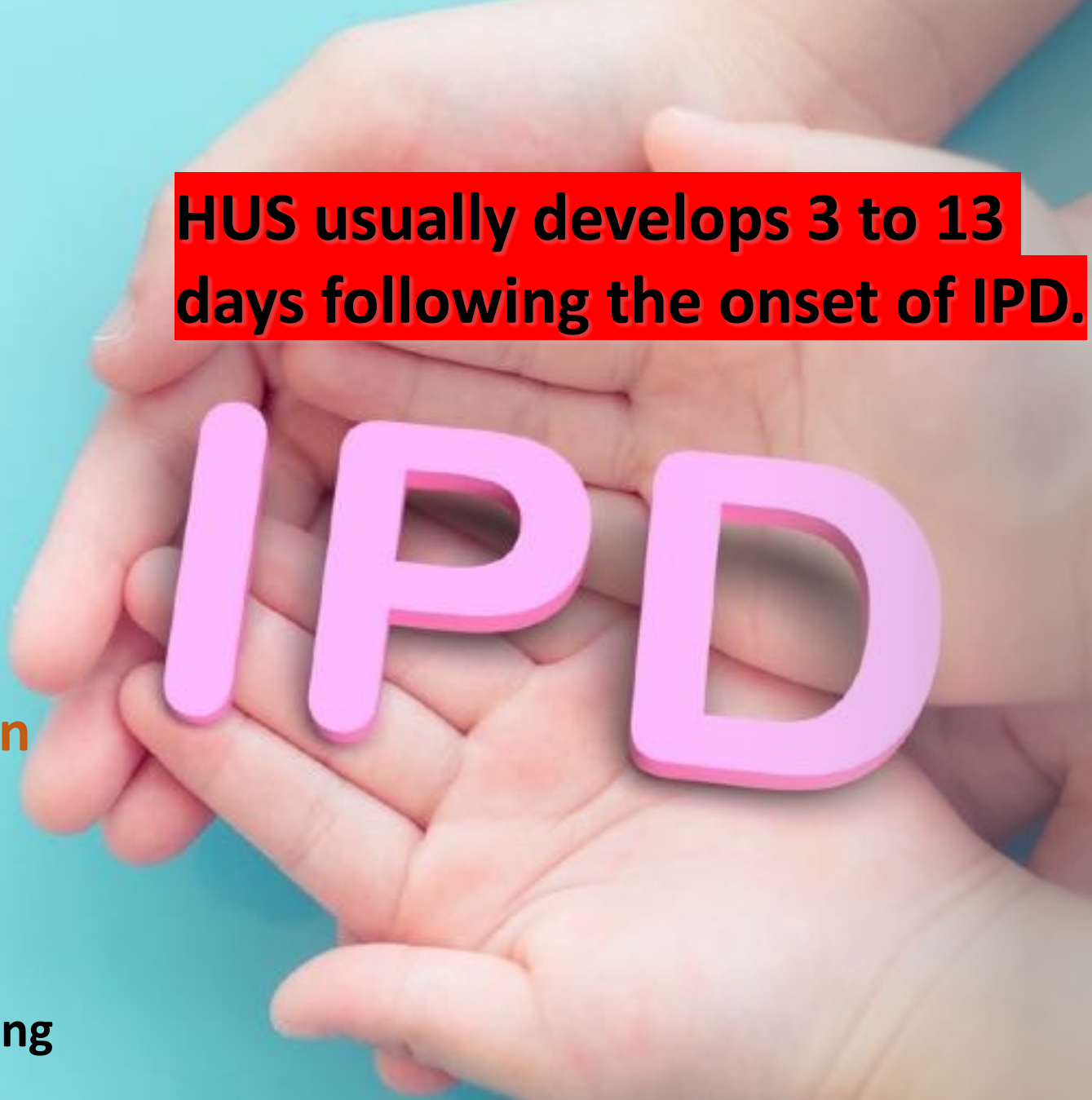
Possible case

- Presence of HUS.
- Presence of pneumonia, meningitis or other evidence of invasive infection without identification of specific organism.
- Presence or absence of DIC.
- Presence of T-Antigen activation.

Copelovitch et.al.; Pediatrics 2010, 125, e174–e181.
Cody & Dixon; Pediatr. Clin. N. Am. 2019, 66, 235–246.

Clinical course of Sp-HUS

HUS usually develops 3 to 13 days following the onset of IPD.



- **90%** have complicated pneumonia (50% need ventilation).
- **60%** have meningitis.
- **30%** have bacteremia **(Overlap with some of the symptoms of multi-organ failure seen with pneumococcal sepsis).**
- **25%** develop extra-renal complications (Hepatitis, cholecystitis, pancreatitis, hearing deficit, and limb ischemia).

Quoted from Agarwal & Latifthoge; Pathogens. (2021), 10, 727

Management of Sp-HUS

- Eradication of Streptococcus pneumoniae infection
  Vancomycin and an extended-spectrum cephalosporin.
- Management of renal injuries
  RRT (HD or PD) must be initiated early in patients with severe kidney injury.
- Management of hematologic injuries
  Washed red blood cells or platelets must be used.
- Plasma exchange
  ASFA reports insufficient evidence to establish the efficacy or the risk/benefit ratio.
- Eculizumab
  There may be a role for use in severe cases especially those with reduced C3.

Quoted from Agarwal & Latifthoge; Pathogens.(2021), 10, 727

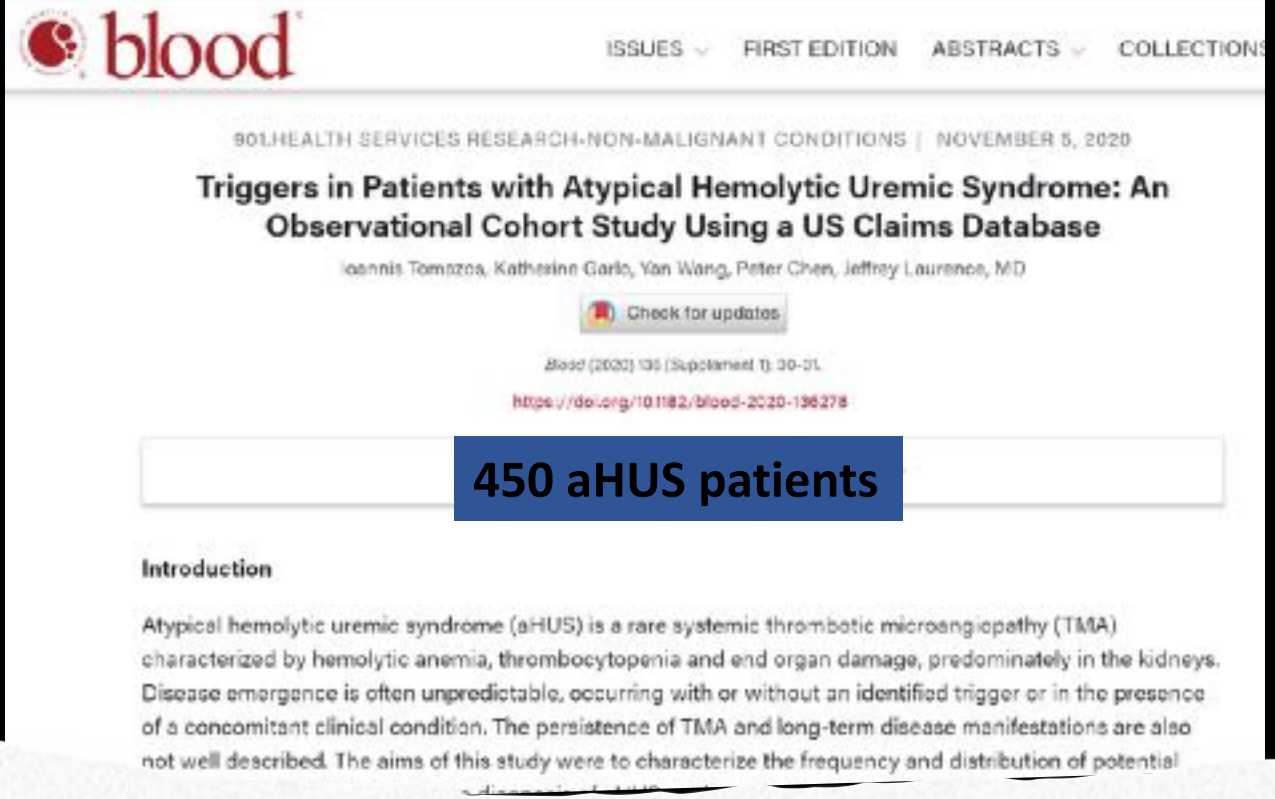
Outcome of Sp-HUS

Sp-HUS patients have, compared to STEC-HUS patients, more complicated clinical course, longer periods of oliguria and more days of intensive care.

- **Proteinuria: 20-28%**
- **Hypertension: 19-30%**
- **ESRD: 10%**
- **Death: 11-16%**

Quoted from Agarwal & Latifthoge; Pathogens.(2021), 10-727

Infection and aHUS



blood

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS

901HEALTH SERVICES RESEARCH-NON-MALIGNANT CONDITIONS | NOVEMBER 5, 2020

Triggers in Patients with Atypical Hemolytic Uremic Syndrome: An Observational Cohort Study Using a US Claims Database

Ioannis Tomazos, Katherine Garlo, Yan Wang, Peter Chen, Jeffrey Laurence, MD

Check for updates

Blood (2020) 136 (Supplement 1): 30-31

https://doi.org/10.1182/blood-2020-136278

450 aHUS patients

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare systemic thrombotic microangiopathy (TMA) characterized by hemolytic anemia, thrombocytopenia and end organ damage, predominately in the kidneys. Disease emergence is often unpredictable, occurring with or without an identified trigger or in the presence of a concomitant clinical condition. The persistence of TMA and long-term disease manifestations are also not well described. The aims of this study were to characterize the frequency and distribution of potential

Potential triggering condition reported at 0–3 months prior to the date of first aHUS/TMA diagnosis	Number of patients, n (%) (N = 147)
Infections	92 (63)
Upper respiratory infection	49 (33)
Bacterial infection	26 (18)
HIV	3 (2)
Viral infection	8 (5)
Gastroenteritis	27 (18)
Chemotherapy	28 (19)
Systemic lupus erythematosus (all)	26 (18)
Lupus nephritis	1 (1)
Excluding lupus nephritis	25 (17)
Pregnancy-related triggers (all)	10 (7)
Postpartum	5 (3)
Pre-eclampsia	3 (2)
Pregnancy	10 (7)
	1 (1)

Triggers in atypical HUS

Tomazos, et al.; Blood 2020, 136, 30–31

Pediatr Nephrol (2018) 33:2009–2025
DOI 10.1007/s00467-017-3783-4

REVIEW

25 cases

Influenza-associated thrombotic microangiopathies

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83%: Influenza A (55%: H1N1).

40%: RRT.

Median age: 15years.

83.3%: Complete.

Neuraminidase productivity.

Activation of vascular endothelial cells and/or platelets.

Direct injury.

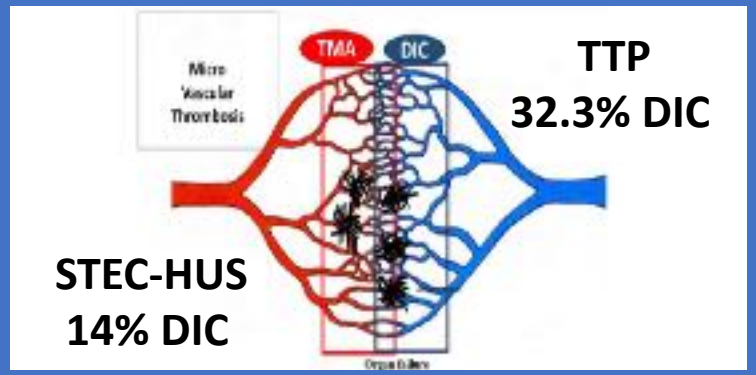
?

87.3%: Complement gene mutations

Influenza infection is a trigger for the development of HUS in patients with CAP regulator protein haploinsufficiency.

Sepsis/DIC/HUS

Sepsis/DIC/HUS



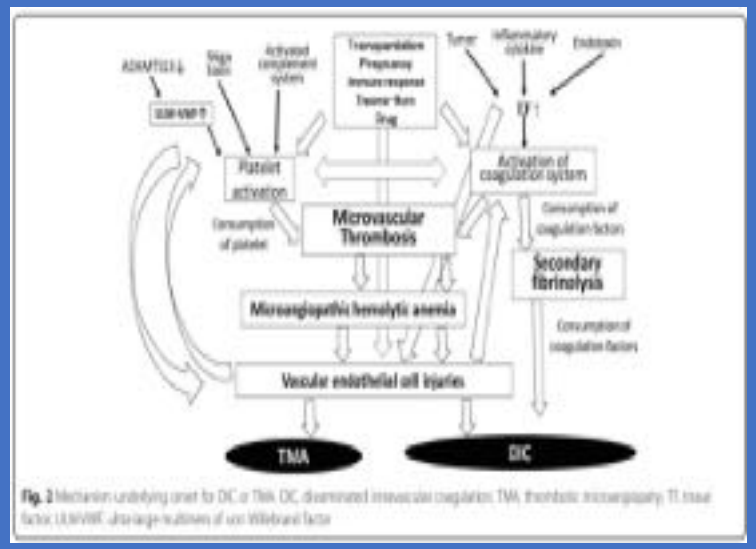


Table 3 Differences and similarities between TMA and DIC

		Severe DIC	Severe TMA
Symptoms	Organ failure	Often (Lung, Kidney, Shock)	Usually (Kidney, CNS)
	Bleeding and bleeding tendency	Frequent	Frequent
	Blood pressure	Low	High
	Hematuria	Sometimes	Frequent
	Anemia	Often	Usually
Laboratory data	Platelet count	Low	Low
	Hemoglobin	Often low	Low
	Fibrin related markers	Markedly high	Slightly high
	Prothrombin time	Often prolong	Normal
	Antithrombin	Often low	Normal
	Albumin	Often low	Normal
	Creatinine	Often high	High
	Total bilirubin, LDH	Often high	High
Treatments	Supportive therapy	Recommended	Recommended
	Blood transfusion (RBC, FFP)	Recommended	Recommended,
	Blood transfusion (PC)	Recommended	Not recommended
	Anticoagulant	Recommended (Japan)	Not mentioned
	PE/FFP	Not mentioned	Recommended
	Special treatment	AT, rhTM (Japan)	Hemodialysis (HUS), Eculizumab (aHUS), Rituximab (TTP)

Quoted from Wada et al. Thrombosis Journal (2018) 16:14

- Infections are involved in more than 90% of HUS cases.
- The Shiga toxin producing Escherichia coli (STEC) is the most common.
- The Streptococcus pneumoniae-associated HUS is reported in 4–5% of total HUS.
- Direct endothelial cell injury by products of the infectious agents play a central role in the pathophysiology of infection-related HUS.
- Acquired complement dysregulation secondary to infection may be involved in infection-related HUS.
- Infections may trigger the disease in aHUS patients with heterozygous gene mutations.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