



Infections induced HUS

a comprehensive diagnostic & therapeutic approach

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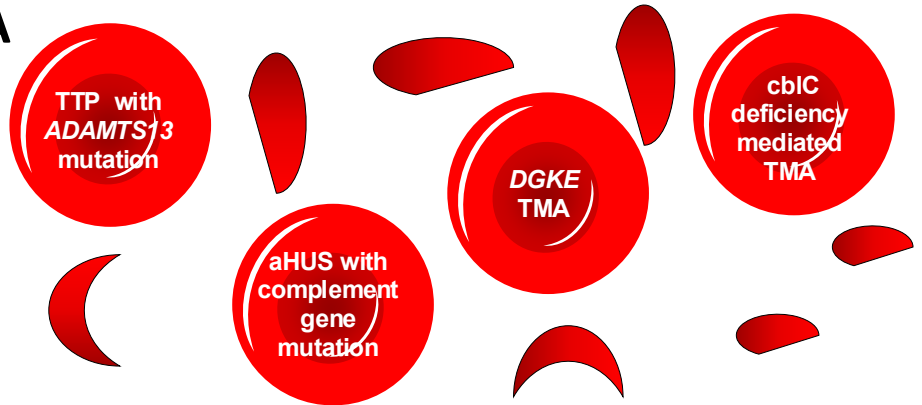
Overview



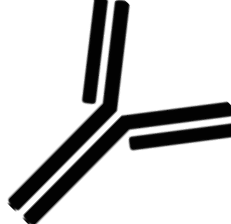
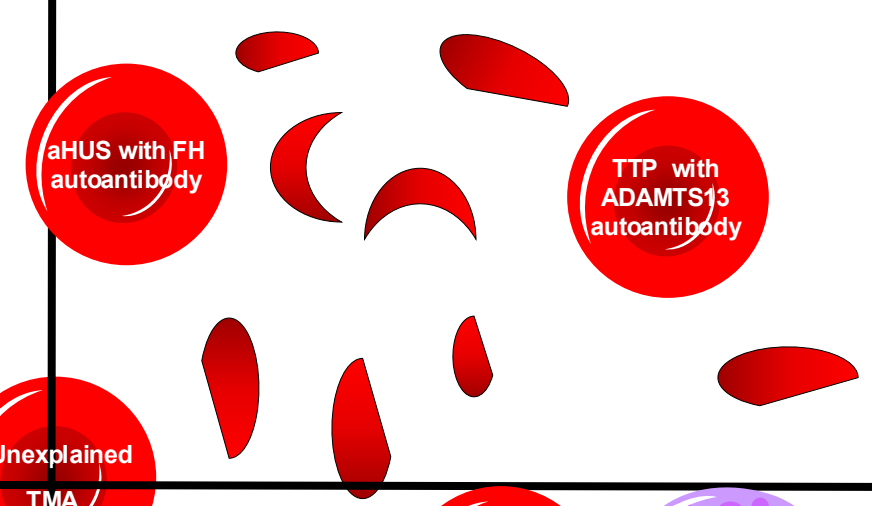
- What is HUS
- HUS history
- **Shigatoxin caused HUS (STEC)**
- Other infections causing HUS
 - Pneumococcal HUS (pHUS)
 - Viral induced

Thrombotic microangiopathies


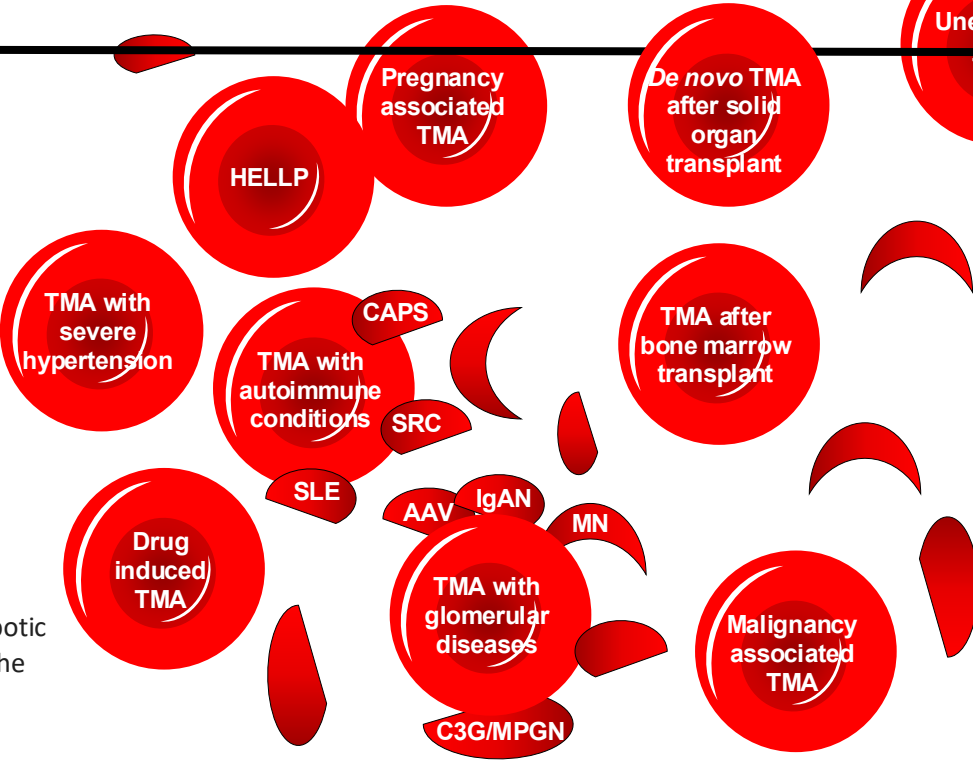
Primary TMA hereditary

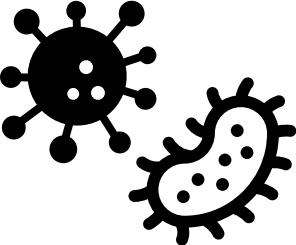
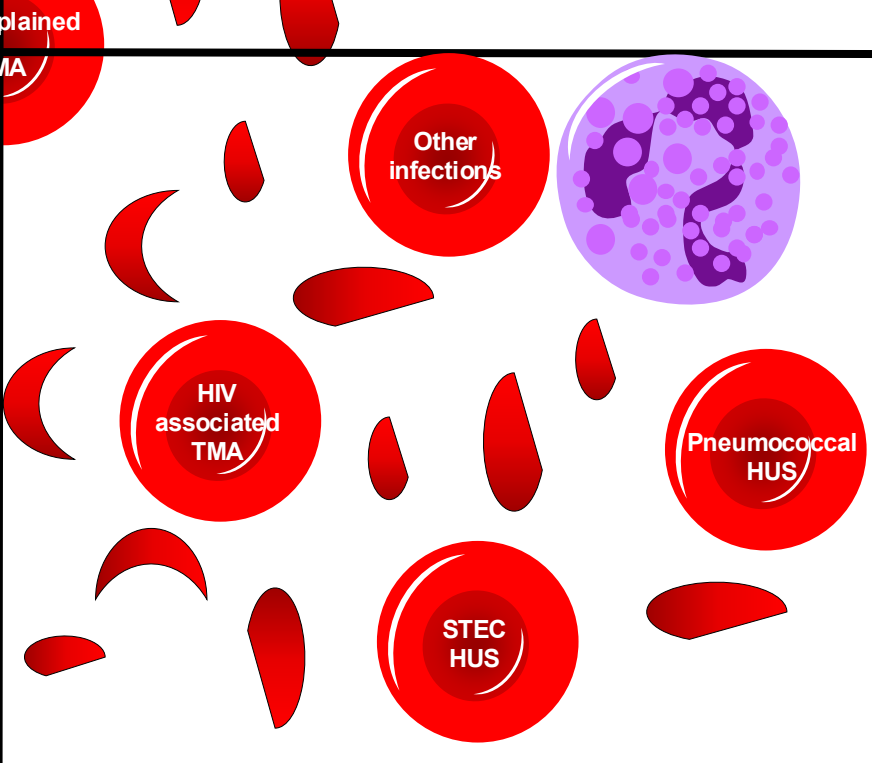
Primary TMA acquired

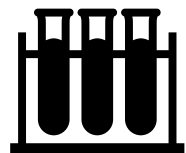
Secondary TMAs

Infection associated TMAs

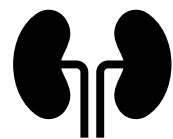
Brocklebank V, Thrombotic Microangiopathy and the Kidney. Clin J Am Soc Nephrol. 2018 - edited



H



Low platelets, haemolytic anaemia, high LDH,
negative DAT, high reticulocytes



U

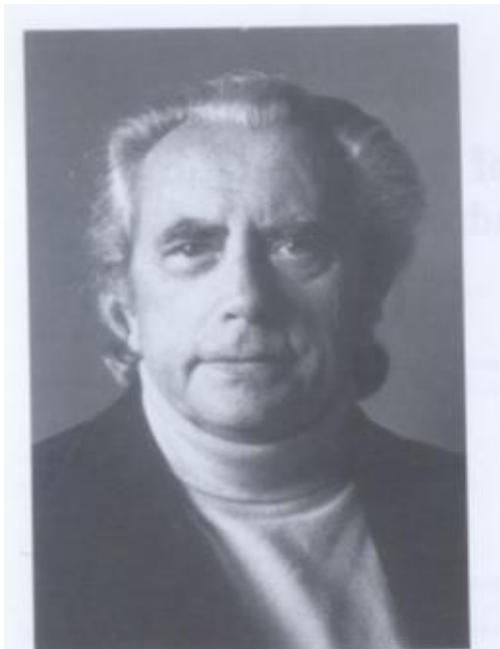


Acute Kidney Injury

S yndrome



1955 - HUS



Hämolytisch-urämische Syndrome: Bilaterale Nierenrindennekrosen bei akuten erworbenen hämolytischen Anämien

*Von C. Gasser, E. Gautier und Annemarie Steck (klinischer Teil) und
R. E. Siebenmann und R. Oechslin (pathologisch-anatomischer Teil)*

Hiezu 4 Abbildungen Seite 929

Aus einer Gruppe von 10 letal verlaufenen Krankheitsbildern, die mit Urämie und hämolytischer Anämie einhergingen, werden 5 akute Fälle beschrieben, die charakterisiert sind durch eine aus unbekannter Ursache plötzlich einsetzende akute intravasale Hämolyse.

1983 – E. coli toxin association



Lancet. 1983 Mar 19;1(8325):619-20.

Sporadic cases of haemolytic-uraemic syndrome associated with faecal cytotoxin and cytotoxin-producing Escherichia coli in stools.

Karmali MA, Steele BT, Petric M, Lim C.

Abstract

A cytotoxin active on Vero cells, less active on hela cells, and inactive on WI38 cells (Vero toxin [VT]) was detected in stool isolates of Escherichia coli from 8 of 15 sporadic cases of haemolytic uraemic syndrome (HUS). Stools from 5 of these 8 patients were examined for faecal VT activity, and all were positive. Of the 7 of 15 patients who did not have VT+ E. coli, 2 were positive for faecal VT, and a third (patient K) had strong serological evidence of VT+ E. coli infection. 2 HUS patients, including patient F, had siblings with uncomplicated diarrhoea who had both VT+ E. coli in the stools and faecal VT activity. Thus 11 of 15 (73%) of the HUS cases had evidence of infection by VT+ E. coli, suggesting that there was an association between these organisms and these cases of HUS. The clustering of 2 HUS patients and their siblings with VT+ E. coli accords with this suggestion, as do the rising titres of VT-neutralising antibody in 2 HUS patients.



Shiga toxin associated HUS

(STEC HUS)

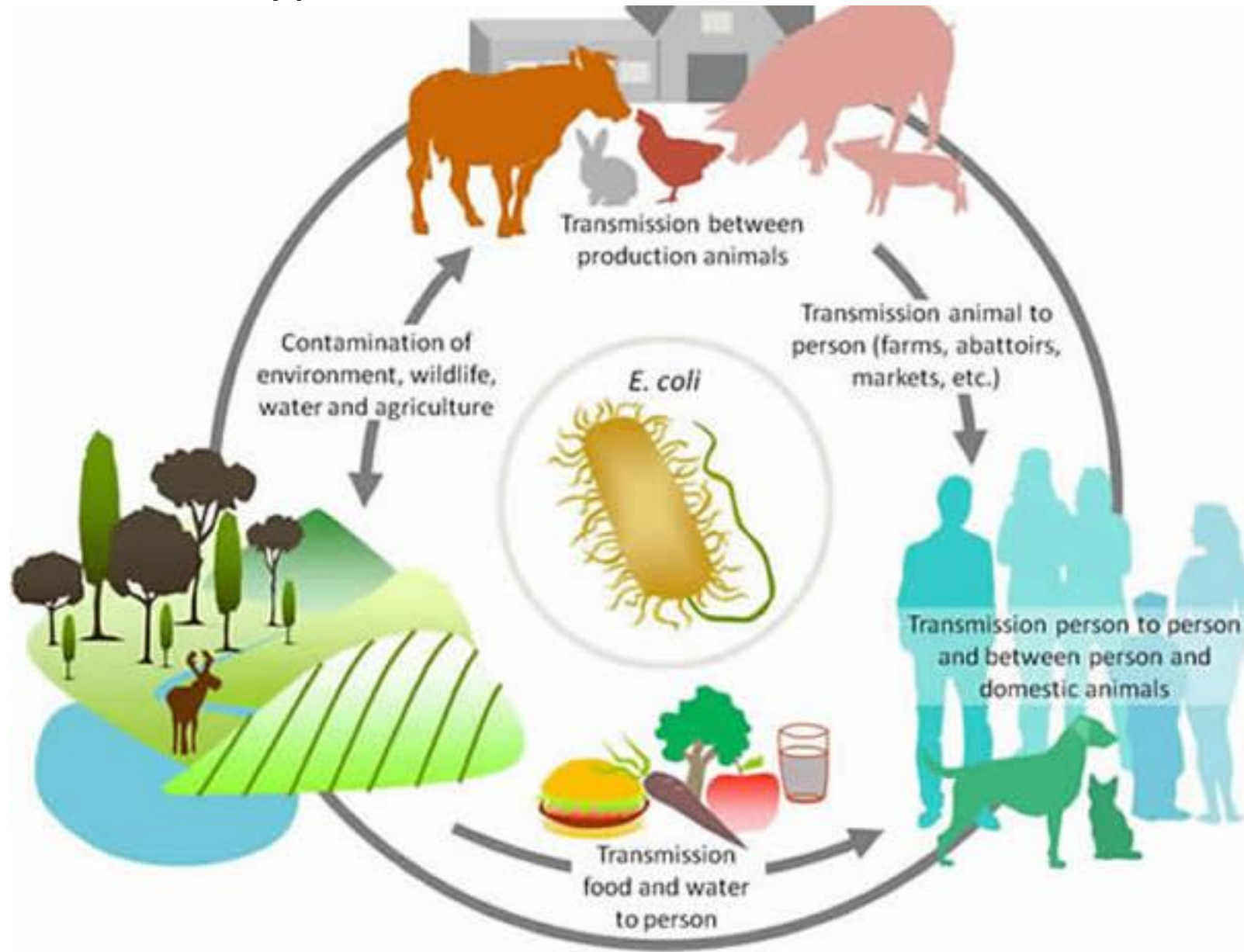
Incidence and Epidemiology



- 1.7 cases/100,000 person year (EU)
- ages 1 to 4 years incidence of 6.0 cases / 100,000 person year
- Highest incidence in Argentina with 7.25-17 / 100,000 person year
- Seasonal peak in summer in Europe

ECDC ECDC surveillance report. Surveillance of seven priorities food-and waterborne diseases in the EU/EEA

- STEC (formerly VTEC) are a sub-group of E.coli that can secrete shiga toxin
- Commonest serotype associated with human disease is O157

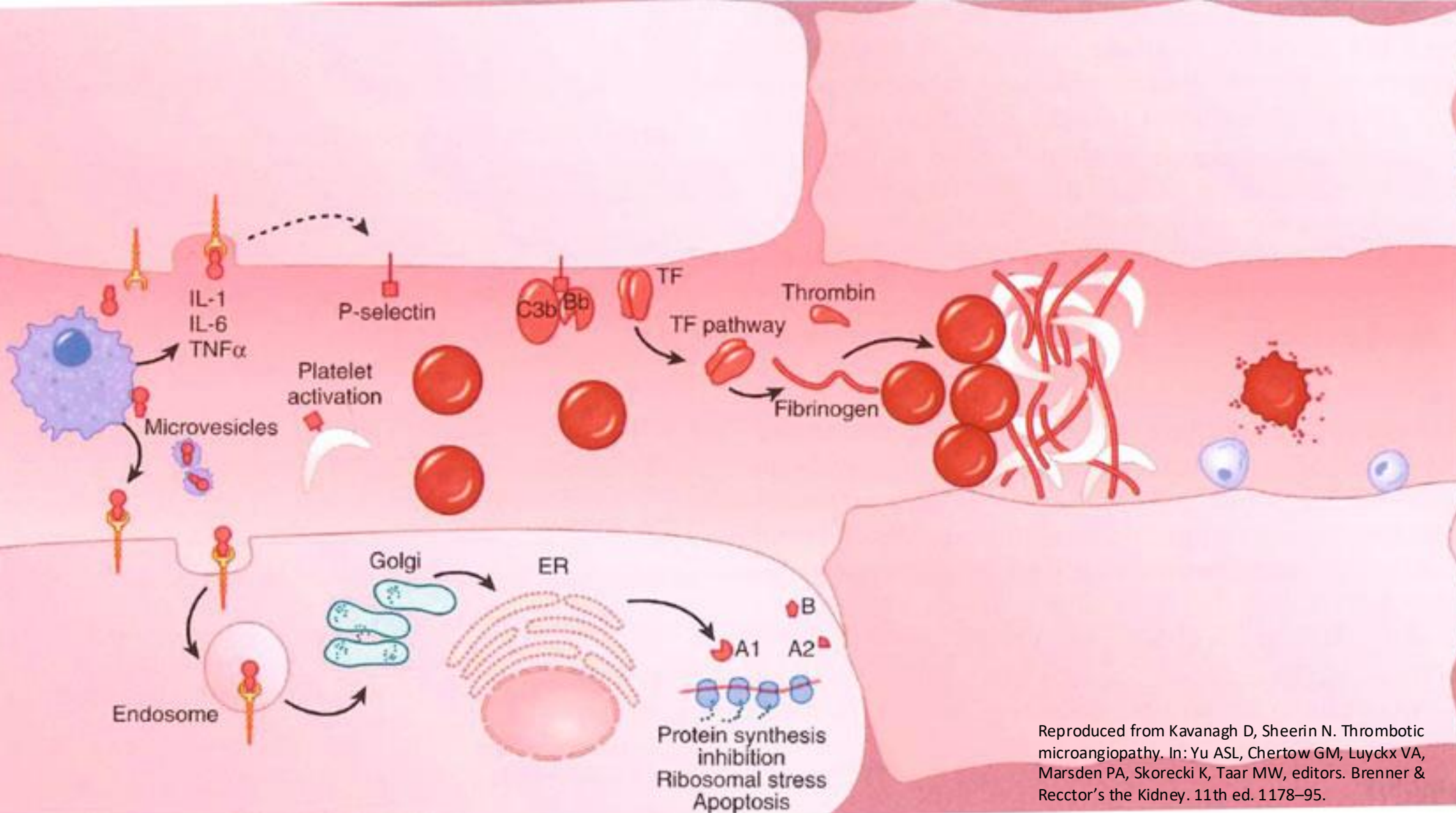


Prevalence of STEC O157:H7 in UK cattle

- Herd-level prevalence rate (mean, 95% CI)
 - 0.236 (0.166–0.325) Scotland
 - 0.213 (0.156–0.283) England and Wales
- Pat-level prevalence rate (mean, 95% CI)
 - 0.106 (0.067–0.163) Scotland
 - 0.069 (0.044–0.107) England and Wales
- Seasonal variation in infection
- Contaminated food, water, direct contact with infected animals and humans



STX cell injury mechanism

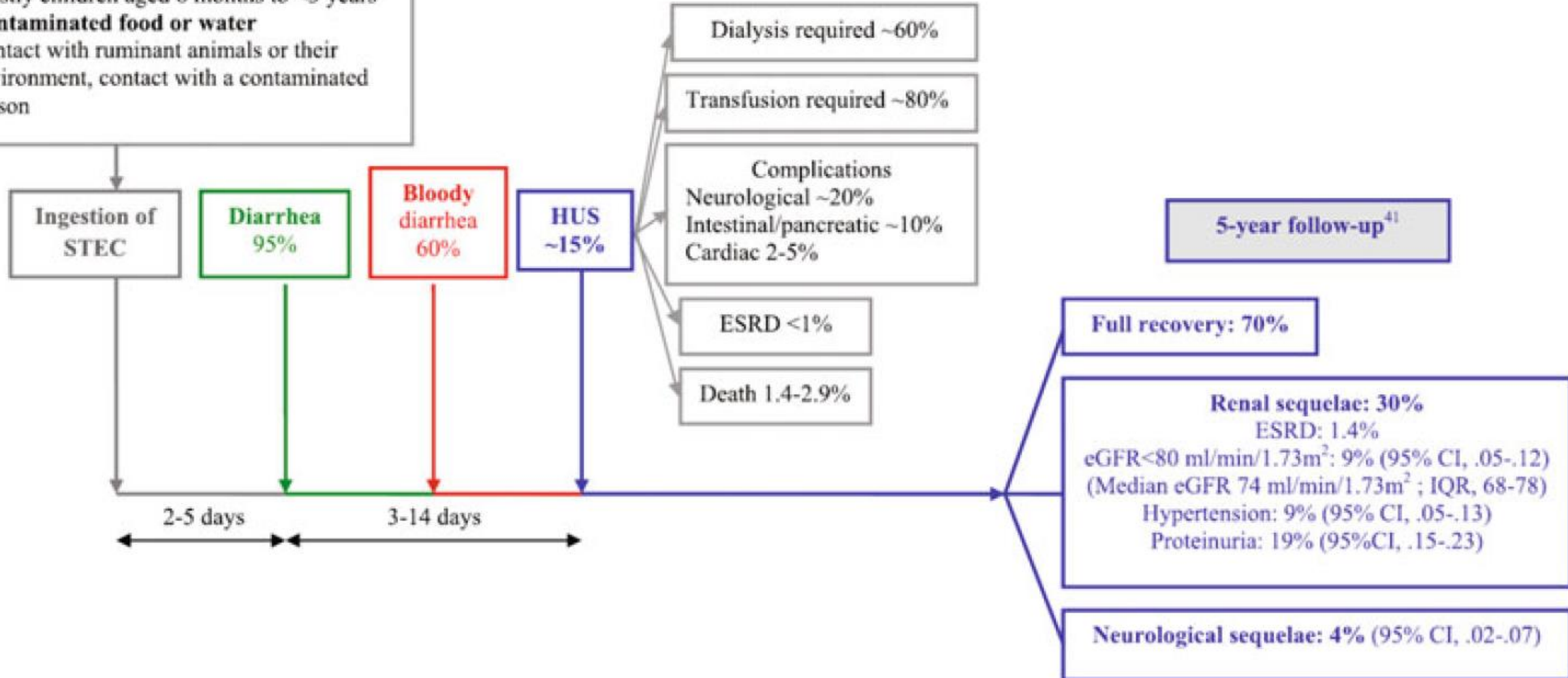


Reproduced from Kavanagh D, Sheerin N. Thrombotic microangiopathy. In: Yu ASL, Chertow GM, Luyckx VA, Marsden PA, Skorecki K, Taar MW, editors. Brenner & Rector's the Kidney. 11th ed. 1178–95.

Clinical course

STEC-HUS in children

Mostly children aged 6 months to <3 years
Contaminated food or water
Contact with ruminant animals or their environment, contact with a contaminated person

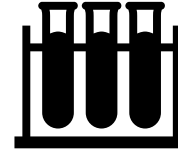
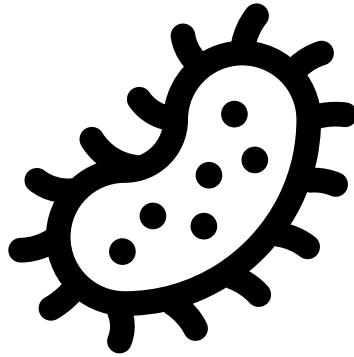


HUS

Low platelets,
haemolytic anaemia
high LDH
negative DAT
high reticulocytes

Acute Kidney Injury

STEC infection

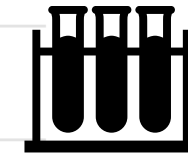
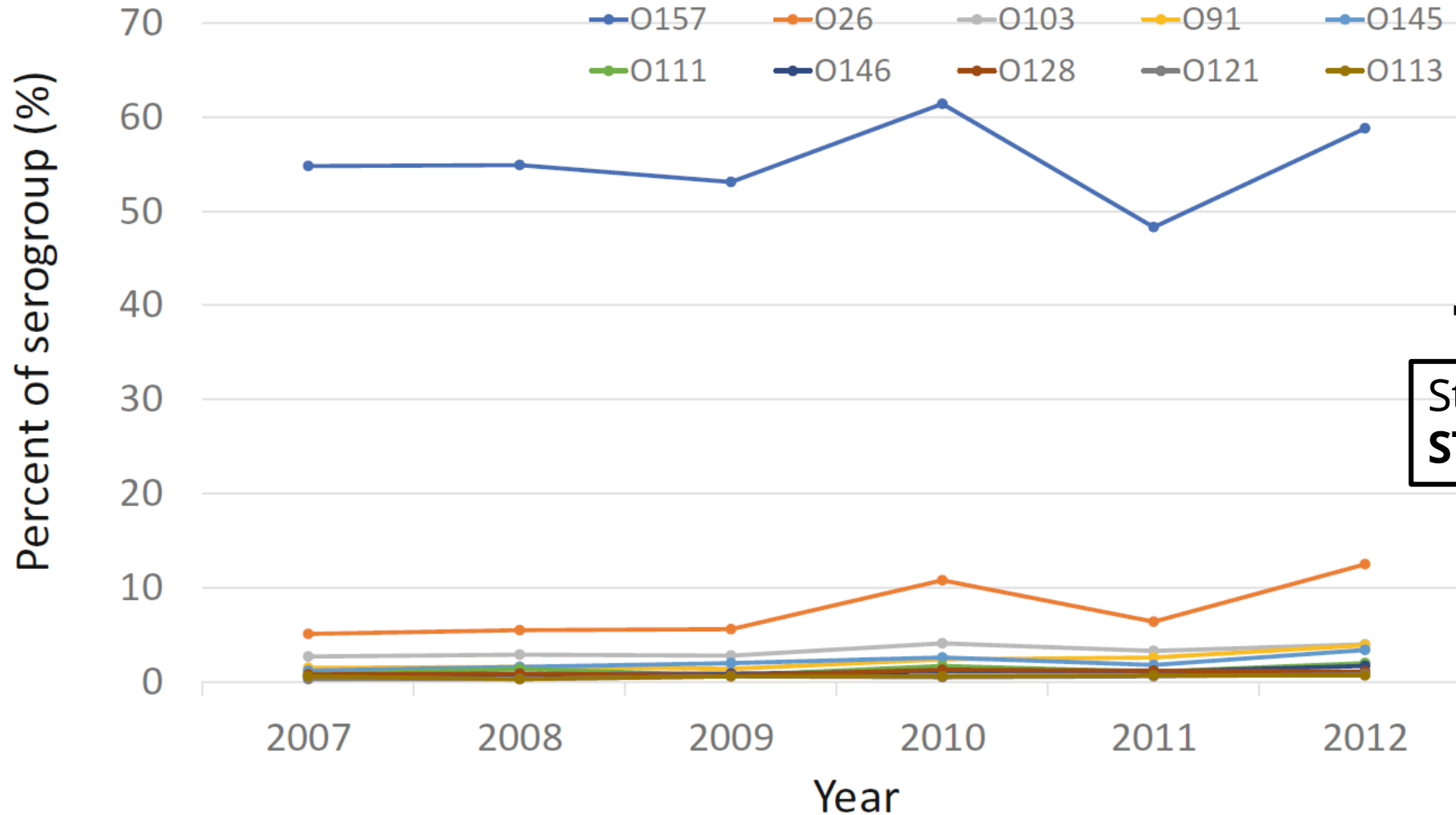


Stool culture
STEC (stx1, stx2) PCR



Symptomatic

Diagnostic



Stool culture
STEC (stx1, stx2) PCR



Fluid management

- volume expansion using isotonic solution reduces severe HUS symptoms
- clinically dehydrated patients had an OR of death of 3.71 (95% CI, 1.25–11.03) and that intravenous fluid administration up to the day of HUS diagnosis was associated with a decreased risk of renal replacement therapy (OR 0.26 [95% CI, 0.11–0.60])

Treatment of STEC HUS



Antibiotics

In vitro lead to increase of STX production and release
beta-lactams and trimethoprim/sulfamethoxazole **negative**
fosfomicin and fluoroquinolones **some benefit**
weighed on individual risk and benefit for the patient

Platelets transfusion

- platelet infusion should be weighted based on individual patient risks of bleeding.

Anaemia management

hemoglobin of 70 g/L, based on severity symptoms of anaemia

Blood pressure control

Infection-Related Hemolytic Uremic,
Syndrome (HUS), Shoji Kagami, Muller
Dominik, Michal Malina, and Akira Ashida

Possibilities for future therapies



- Shiga toxin binding
Urtoxazumab
- GB3 receptor saturation
Synsorb Pkb
Carbohydrate ligands, nanoparticles
- Inflammation and immunomodulation
 - **Eculizumab**
 - ~~Steroid treatment, IVIG, and anticoagulation~~
 - ~~Plasma infusion, plasma exchange, and immunoadsorption~~
- Intracellular interference

Eculizumab and STEC

ECUSTEC

	Eculizumab, N = 17 (%)	Placebo, N = 19 (%)	difference ^a (95% CI)	p- value
CSS (excluding any participants who have died)^b				
Mean (SD, N)	11.5 (8.4, 15)	14.6 (7.7, 19)	-2.5 (-7.8 to 2.8)	0.3
Minimum-maximum	1-28	2-29		

No conclusions can be drawn about the efficacy of eculizumab in STEC HUS from the ECUSTEC trial, and so unfortunately, the data are unable to inform clinical practice.

ECULISHU

RRT <48h, n (%)	Total (n=86)	Eculizumab (n=44)	Placebo (n=42)	P value
Success	43 (50%)	19 (43.2%)	24 (57.1%)	0.196 ¹

The rate of RRT <48 hours did not differ similar hematologic evolution and extrarenal manifestations

Eculizumab treatment does not appear to be associated with improved renal outcome during acute phase of the disease but may reduce long-term kidney sequelae.

Future therapies ?



- Shiga toxin binding
Urtoxazumab
- GB3 receptor saturation
Synsorb Pkb
Carbohydrate ligands, nanoparticles
- Inflammation and immunomodulation
 - **Eculizumab**
 - ~~Steroid treatment, IVIG, and anticoagulation~~
 - ~~Plasma infusion, plasma exchange, and immunoadsorption~~
- Intracellular interference

Pneumococcal HUS



- The *Streptococcus pneumoniae*-associated HUS (pHUS)
- 4–5% of total HUS
- annual incidence is estimated to be 0.015 to 0.06 per 100,000 children
- Invasive pneumococcal disease (IPD)
 septicemia, meningitis and complicated pneumonia.
- Incidence of IPD has **decreased** with vaccine programmes but incidence of pHUS has **increased**

Pneumococcal HUS



Pathophysiology

Invasive pneumococcal infection

Bacterial neuraminidase cleave sialic acid from glycoproteins

Exposure of the normally hidden Thomsen-Friedenreich Antigen (T-Antigen, Gal β 1-3GalNac)

Downstream immune mechanisms then damage or destroy T antigen-expressing cells (RBC, endothelial cells), leading finally to TMA and MAHA.

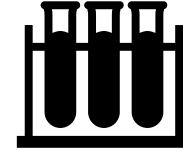


HUS

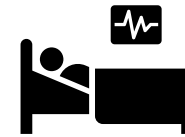
Low platelets,
haemolytic anaemia
high LDH
~~negative DAT~~
high reticulocytes

Acute Kidney Injury

Pneumococci
infection related



Pneumococci microbiology
DAT +
T antigen



Treatment of primary
condition (antibiotics)

Other pathogens

Shigella

- 500 cases of HUS in shigellosis
 - Manifestations of HUS develop late
 - Incidence of HUS in 13%
 - post-HUS mortality of 36%
- **Appropriate antimicrobial treatment**

Viral infections

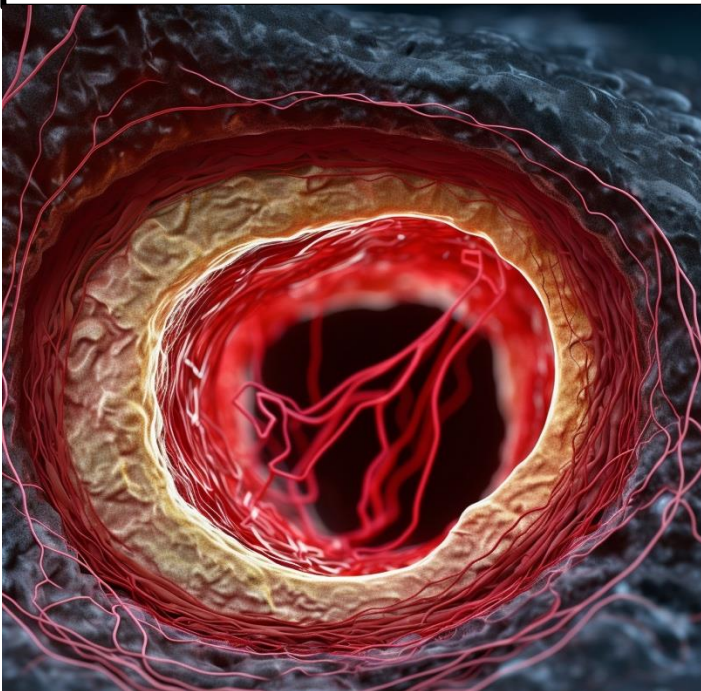
Cases of HUS with influenza A and B (neuraminidase?)

Adenovirus

HIV, cytomegalovirus, HHV6, parvovirus B19

Microangiopathies

Intravascular RBC fragmentation that produces schistocytes on the peripheral blood

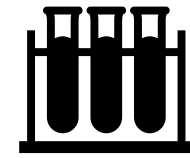


DIC

Activation of the coagulation system

Sepsis
Trauma
Malignancy
Pregnancy

hemolysis is **not** a major feature of the disorder.



A score of **5** or higher is compatible with **DIC**

Presence of an underlying disorder known to be associated with DIC (no=0, yes=2)

Coagulation results
Platelet count (> 100k = 0
< 100k = 1, < 50k = 2)

Fibrin degradation products such as D-Dimer (no increase = 0, moderate increase = 2, strong increase = 3)

Prolonged prothrombin time (< 3 sec = 0, > 3 sec = 1, > 6 sec = 2)

Fibrinogen level (> 1.0g/L = 0; < 1.0g/L = 1)

National Renal Complement Therapeutics Service

