Webinars

Thrombotic Microangiopathies

Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

STEC-HUS in adults

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Paris – France
22th September 2021

Co-funded by the Health Programme of the European Union

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European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

No conflict of interest

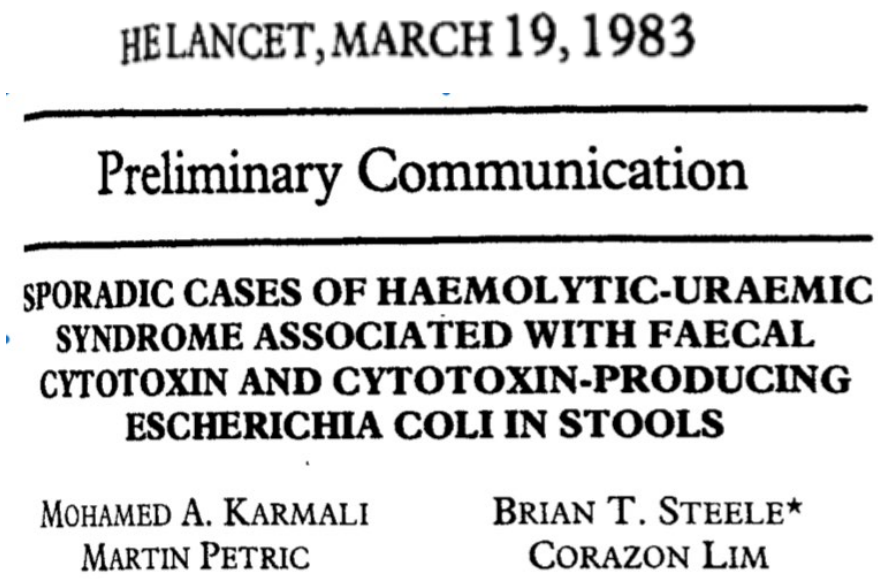
- 30-35min presentation (30 slides max) + 15 min Q&A session
- Microphones will be muted by host to avoid back noise
- Please, stop your video to improve internet connexion
- Send your questions during the presentation through the chat

1. Pathophysiology, epidemiology, clinical course

2. Treatment

3. STEC-HUS in adults, France, 2009-2017

Seminal report



THE LANCET, MARCH 19, 1983

Preliminary Communication

SPORADIC CASES OF HAEMOLYTIC-URAEMIC SYNDROME ASSOCIATED WITH FAECAL CYTOTOXIN AND CYTOTOXIN-PRODUCING ESCHERICHIA COLI IN STOOLS

MOHAMED A. KARMALI MARTIN PETRIC BRIAN T. STEELE* CORAZON LIM

- **15 children**
- Aged 6 months to 10 years
- Sporadic cases
- **15 Diarrhea Anemia AKI**
- 9 RRT
- 10 RBC transfusion
- 4 coma
- **2 deaths**

- Toxin in the stools of 8/15 cases
- Non reversible alterations of « Vero » endothelial cells

« Vero toxine » = Shiga-Toxine

Enterohemorrhagic E Coli (EHEC) 0 157:H7

STEC

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Karmali et al, Lancet, Mars 1983

Tarr et al, Lancet, Avril 2005

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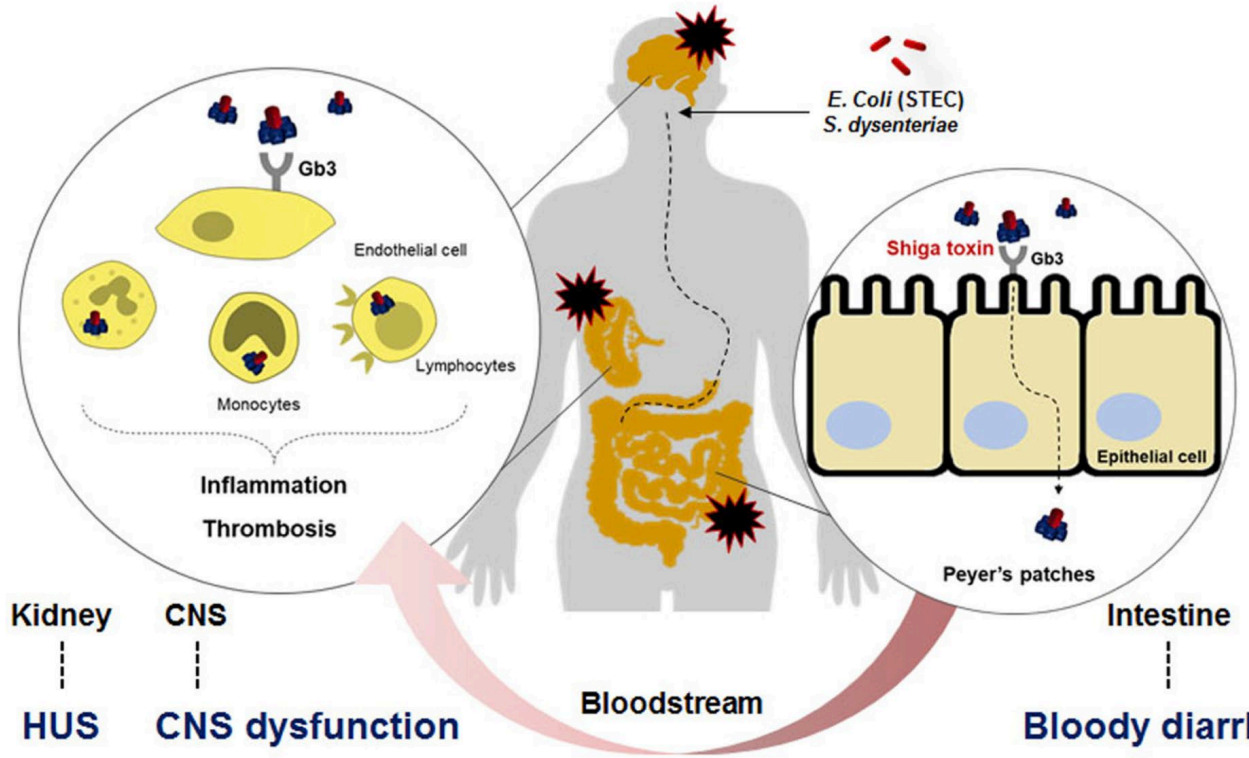
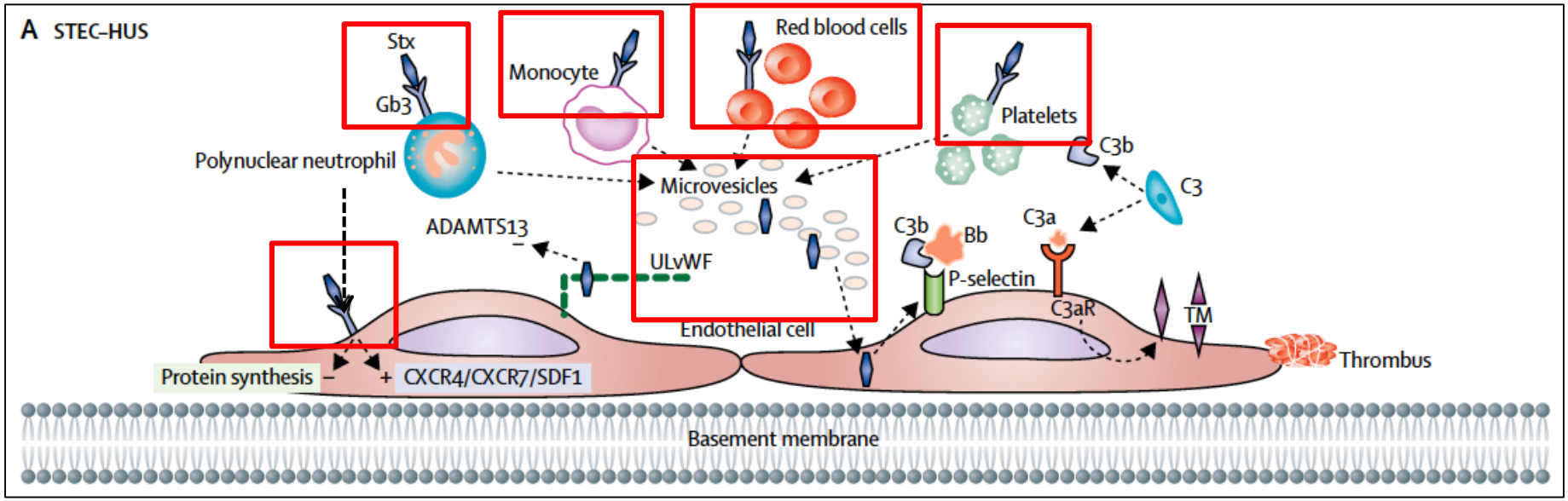
A foodborne disease



Yu Jin-Jeong et al, JMB 2018

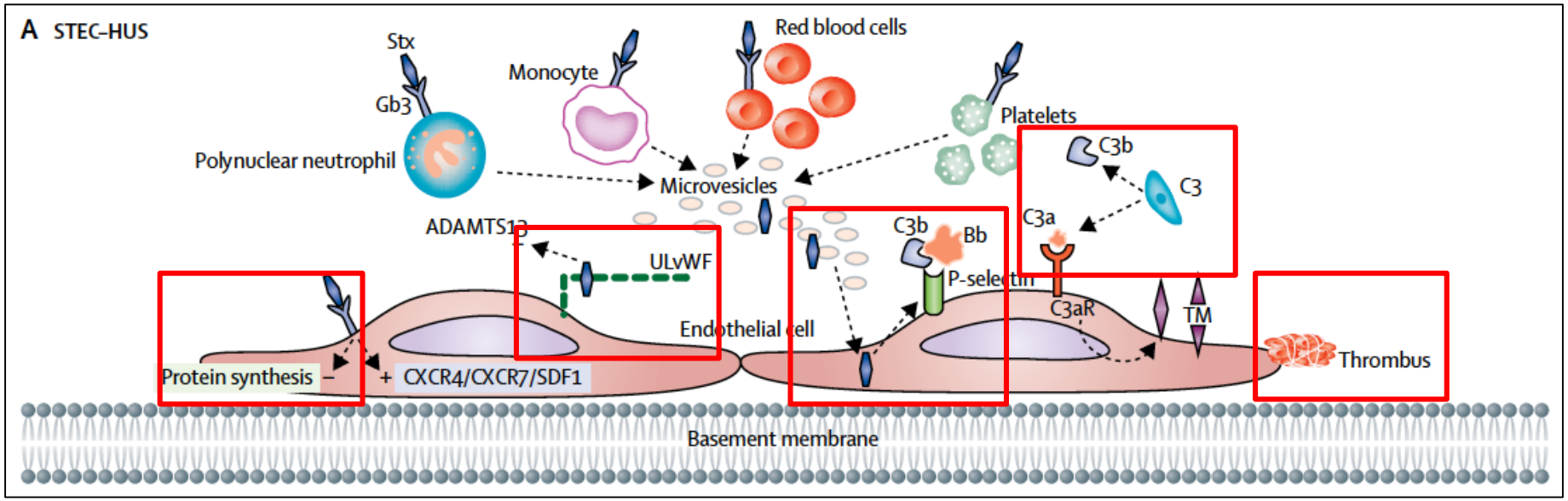
Shiga-Toxin systemic dissemination



- **Stx Receptor: GloboTriaosylceramide (GB3)**
  - **Transport: PNN (TL4?), Monocytes, Platelets, Erythrocytes**
  - **Target tissue: Endothelial cells++, podocytes, neurones,**
- **Microvesicles**

F Fakhouri et al, Lancet 2017

Shiga-Toxin induced vascular injury



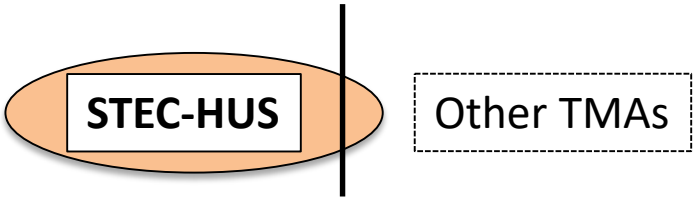
Major endothelial cells alterations

- **Protein synthesis inhibition (mRNA cleavage)**
- **↗ vWF release**
- **Complement pathway activation (Stx2 binds Factor H)**
- **Adhesion molecules expression**
- **Proinflammatory cytokines production**

Platelets activation

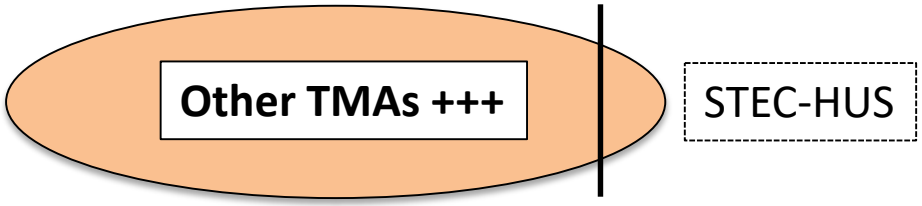
TMAs epidemiology differs between children and adults

Children



- « Typical HUS », 90% of all TMAs.
- 1rst cause of AKI < 3 years
- Death rate 1-2%
- National surveillance network +++
- 100 cases/year France

Adults



- Rare, excepted during outbreaks
- Death rate.. 5 to 88%
- No dedicated surveillance network

Lack of data++

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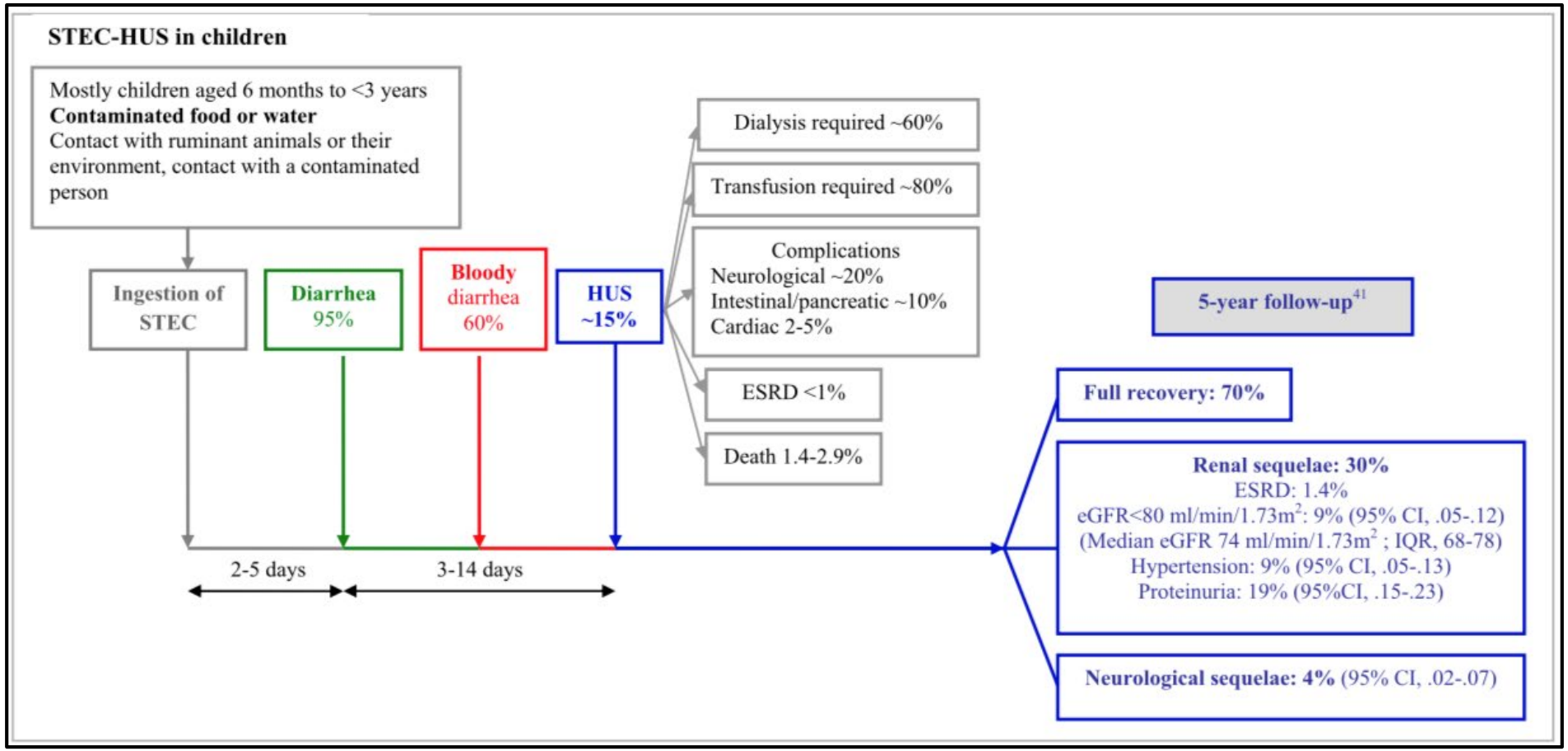
Clinical course in children



Bruyand M, Med Maladies Infectieuses, nov 2017

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E Coli infection identification is of paramount importance

- **Strain**
  - **Direct techniques**
    - **Stool culture. => serotype (O:H), Antibiogram++. Requires selective culture media, lack of sensitivity, delayed results.**
    - **PCR rectal swab++, but also on any biological sample => serotype (O:H), good sensitivity, fast results (12-24h)++.**
    - **WGS => clusters investigation++**
  - **Indirect techniques**
    - **anti LPS serology (Ag O) => abandonned**
- **Toxin**
  - **PCR => good sensitivity, sub type (Stx1, Stx2a, Stx2b..), associated virulence genes.**
  - **Immunological tests => lack of sensitivity**

Epidemiology: a distorted picture

Limitations

Technique used for detection?
Serotype 0:157 vs others?
Sporadic vs outbreaks?
Surveillance network?

STEC induced illness ≈2,8 M[6]/year
STEC HUS≈ 3890/year

Majowicz et al, FPD 2014
Joseph a et al, Toxin 2020

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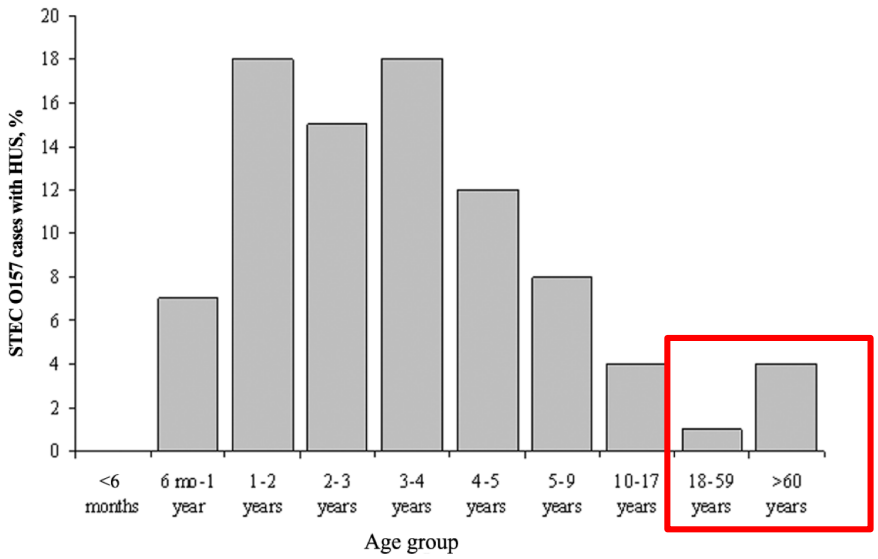
STEC-HUS is indeed a pediatric disease… but not only!

Hemolytic Uremic Syndrome and Death in Persons with *Escherichia coli* O157:H7 Infection, Foodborne Diseases Active Surveillance Network Sites, 2000–2006



Age group	No. of deaths/no. of persons (%)		
	Persons with HUS	Persons without HUS	All
<5 years	4/130 (3.0)	2/678 (0.3)	6/808 (0.7)
5–9 years	1/41 (2.4)	0/450 (0.0)	1/491 (0.2)
10–17 years	0/19 (0.0)	1/525 (0.2)	1/544 (0.2)
18–59 years	0/13 (0.0)	1/1075 (0.1)	1/1088 (0.1)
>60 years	5/15 (33.3)	7/375 (1.9)	12/390 (3.1)
All[a]	10/218 (4.6)	11/3103 (0.4)	21/3321 (0.6)

H Gould and al, CID 2009

The O104:H4 outbreak. Summer 2011

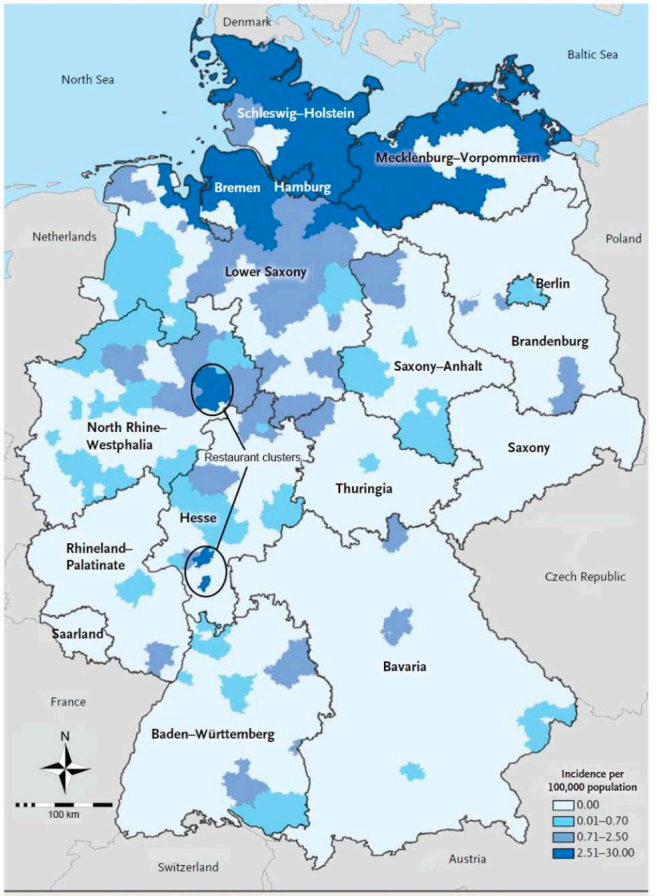


Figure 1. Incidence of the Hemolytic–Uremic Syndrome According to County in Germany.
The incidence shown is per 100,000 population. A total of 845 cases were detected in this outbreak. Cases are attributed to a particular county if that county was the probable site of infection.

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ORIGINAL ARTICLE

Epidemic Profile of Shiga-Toxin–Producing *Escherichia coli* O104:H4 Outbreak in Germany

- May to July 2011, Germany => Europe
- E Coli O104:H4
- 3816 cases
- **845** HUS (22%)
- **88% adults** (2F/1H, aged 42 (median))
- 2% < 5 years old
- 54 deaths

An exceptional strain

- EAEC but not EHEC
- ESBL

=> Extrapolation of these data to all adult cases of STEC-HUS may be hazardous

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Treatments

- **Supportive care (Early saline infusion, BP contrôle, RRT, RBC transfusion)++**
- **Antibiotherapy?**
- **Plasmapheresis?**
- **Eculizumab (anti C5)?**
- **Others (anti toxinic immunotherapy…)?**

Supportive care++

Early Volume Expansion and Outcomes of Hemolytic Uremic Syndrome

Gianluigi Ardissino, MD, PhD,[a] Francesca Tel, MD,[a] Ilaria Possenti, MD,[a] Sara Testa, MD,[a] Dario Consonni, MD,[b] Fabio Paglialonga, MD,[a] Stefania Salardi, BS,[c] Nicolò Borsa-Ghiringhelli, MD,[c] Patrizia Salice, MD,[d] Silvana Tedeschi, MD,[c] Pierangela Castorina, MD,[a] Rosaria Maria Colombo, BS,[e] Milena Arghittu, BS,[e] Laura Daprai, BS,[e] Alice Monzani, MD,[f] Rosangela Tozzoli, MD,[g] Maurizio Brigotti, PhD,[h] Erminio Torresani, BS[e]

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

2016

TABLE 3 Comparison of Short- and Long-Term Outcomes in Patients Addressed to Early FI (Group B) and in Controls (Group A)

	Controls (*N* = 38)	Volume Expansion (*N* = 38)	RR/GMR (95% CI)	*P*
Outcomes during acute phase				
Death, *N* (%)	2 (5.2)	0 (0)	NA	.49
CNS involvement, *N* (%)	9 (23.7)	3 (7.9)	0.33 (0.10–1.14)	.06
Need for RRT, *N* (%)	22 (57.9)	10 (26.3)	0.45 (0.25–0.83)	.01
Days of hospitalization, median (IQR)	12 (7–18)	9 (7–12)	0.75 (0.59–0.96)	.02
Days in PICU, median (IQR)[a]	8.5 (3.5–15.5)	2 (1–4.5)	0.31 (0.12–0.82)	.02
Long-term outcomes				
Extrarenal sequelae, *N* (%)	1 (2.6)	1 (2.6)	NA	.99
Renal sequelae				
Major (CKD II-V), *N* (%)	1 (2.6)	0 (0)	NA	.49
Minor (CKD I), *N* (%)	12 (34.3)	5 (13.2)	0.38 (0.15–0.98)	.03
Total patients with long-term sequelae, *N* (%)[b]	15 (39.5)	5 (13.2)	0.33 (0.13–0.83)	.01

GMR, geometric mean ratio; NA, not applicable.
[a] 8 patients in group A and 8 patients in group B.
[b] Because renal and extrarenal sequelae are not mutually exclusive, the total of long-term sequelae exceeds the number of patients.

Intervention:
Isotonic saline infusion 10 - 15mL/Kg/h

Objective:
+7% over usual weight if alb >30g/L
+10% over usual weight if alb <30g/L

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Plasma exchange

TABLE 2. *Outcome characteristics of plasma exchange in STEC-HUS*

Study	*N*	Start PE after STEC-HUS diagnosis (days)	Nr treatment sessions	Hematological outcome	Renal outcome	Neurological outcome	Death
Adult studies							
Dundas et al. (22,23)	16	Within 24 h	Median 6 (range 1–16)	—	25% needed dialysis after initiation of TPE	—	5 (31%)
Downes et al. (24)	2	—	10–12	Recovery	Full recovery	Full recovery	0
Kanno et al. (25)	1	3	9	Recovery after >2 weeks	Full recovery	Full recovery	0
Kanno et al. (25)	6	—	—	Full recovery	Full recovery	Full recovery, 1 major sequelae	0
Bae et al. (26)	1	—	3 weeks	Recovered within 7d	Full recovery	Full recovery	0
Colic et al. (7)	5	1	Median 5 (range 3–6)	Rapid decline in median LDH levels, raised median platelet counts	Full recovery	Full recovery	0
Menne et al. (8)	251	6.8 (SD 3)	7.3 (4–9)	Rapid ↓ in LDH[†] levels, ↑ platelet counts after start PE (NS)	No difference[†]	No difference[†]	8 (3%). No difference[†]
Kielstein et al. (27)	241	7 (IQR 5–9)	Mean 6.3	-More need for RBC-transfusion (S) -Rapid recovery of platelets No difference[†]	Median endpoint sCreat. was higher	—	14(S)
Soolsma et al. (28)	1	1	—	Recovery	Full recovery	—	0
Metano et al. (28)	3	2–4	2–3	—	—	1 unkown	2
Ko et al. (29)	1	—	—	Initial improvement	No recovery	No recovery	1
Pediatric studies							
Gianviti et al. (31)	11	—	4.5 (3–10)	—	Non-sign. higher GFR/lower sCreat.	—	0
Nakatani et al. (32)	3	Before severe renal failure developed	4.7 (3–7)	Full recovery	Full recovery	Full recovery	0
Valles et al. (33)	12	[‡]	5		1CKD, five patients with proteinuria	2 sequelae,	3
Nathanson et al. (17)	25	3.6[§]	—	—	—	11 full recovery, one minor sequelae, six major sequelae	7
Loos et al. (34)	17	—	—	—	—	—	0

[†]No significant difference in outcome at discharge between patients who received PE and those who did not (only supportive care). [‡]As soon as hemodynamic condition stabilized. [§]After appearance of neurological symptoms. —, unknown or not presented; *N*, number of patients receiving PE; PE, plasma exchange; sCreat., serum creatinine; NS, non-significant; S, significant.

Keenswick et al, Ther Aph Dialysis 2019

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CONCLUSION

Limited and weak current evidence suggests potential efficacy of early plasma exchange in reducing case fatality rates in elderly patients with STEC-HUS and potentially improving outcomes in children with severe involvement. Early institution

Nakatani et al. (32)	3	Before severe renal failure developed	4.7 (3–7)	Full recovery	Full recovery	Full recovery	0
Valles et al. (33)	12	‡	5		1CKD, five patients with proteinuria	2 sequelae,	3
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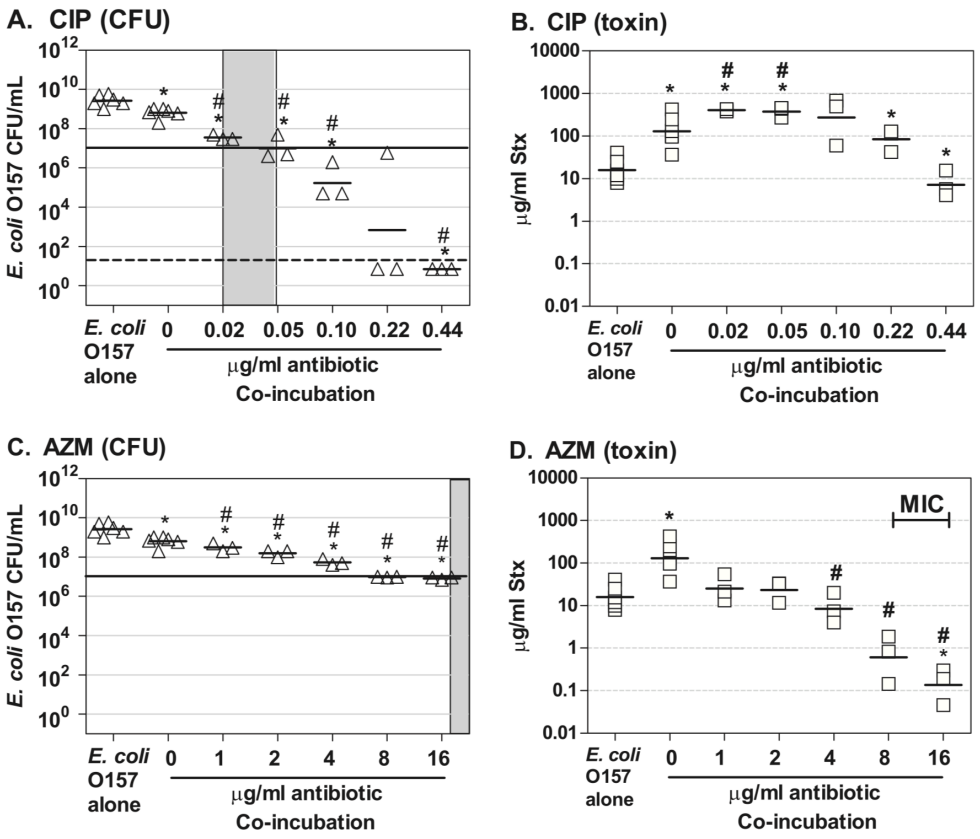
Keenswick et al, Ther Aph Dialysis 2019

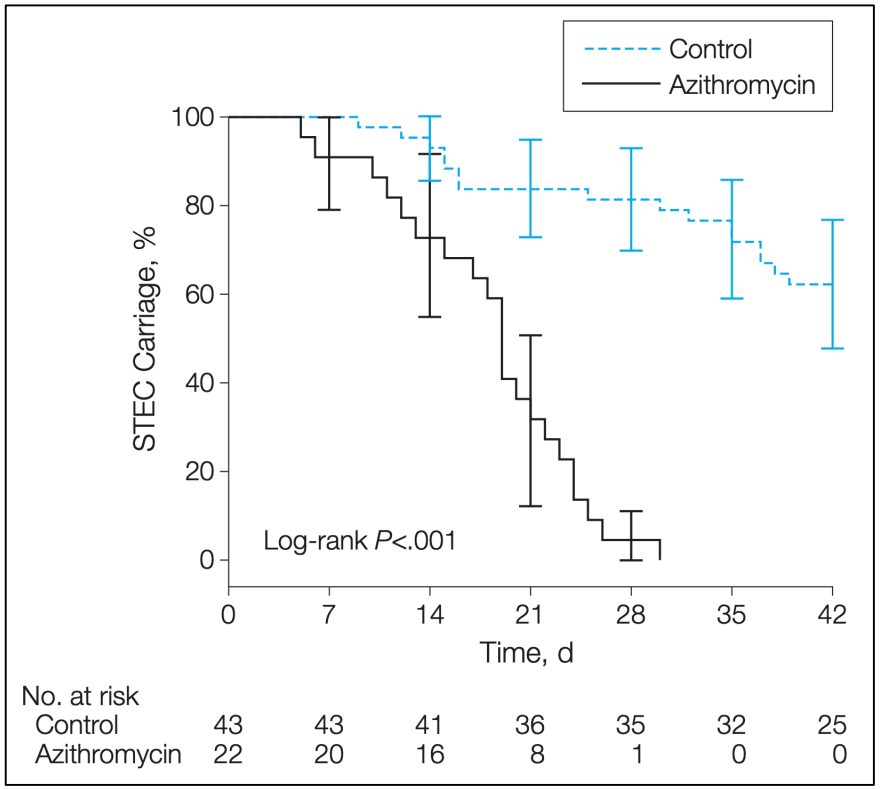
Antibiotherapy?

- **Conflicting evidence++**
- **Difference between bacteriolytic and bacteriostatic antibiotics**



Mc Gannon et al, AAC 2010
Agger et al, JAAC 2015
Bruyand et al, Med Mal Inf 2018

Association Between Azithromycin Therapy and Duration of Bacterial Shedding Among Patients With Shiga Toxin–Producing Enteroaggregative *Escherichia coli* O104:H4



Azithromycin 3 Days

- **Reduces the duration of E. Coli 0104:H4 carriage**
- **No « induced » HUS-case observed**

Nitschke M et al, JAMA 2012

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Background: Complement pathway is activated during STEC HUS

3 children CNS+, PE failure, dramatic improvement with Eculi

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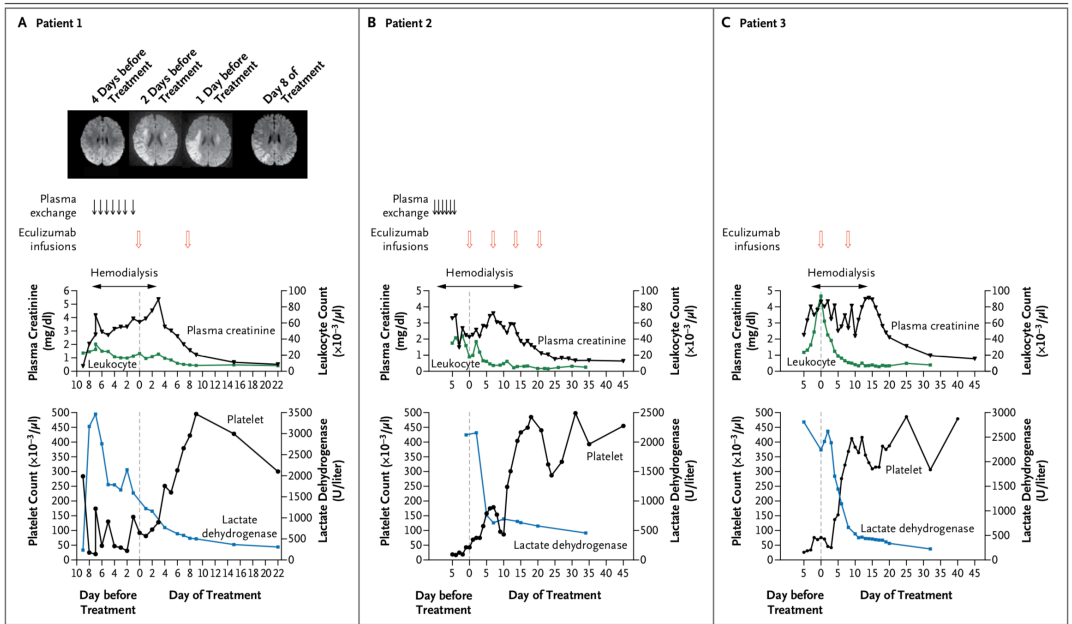


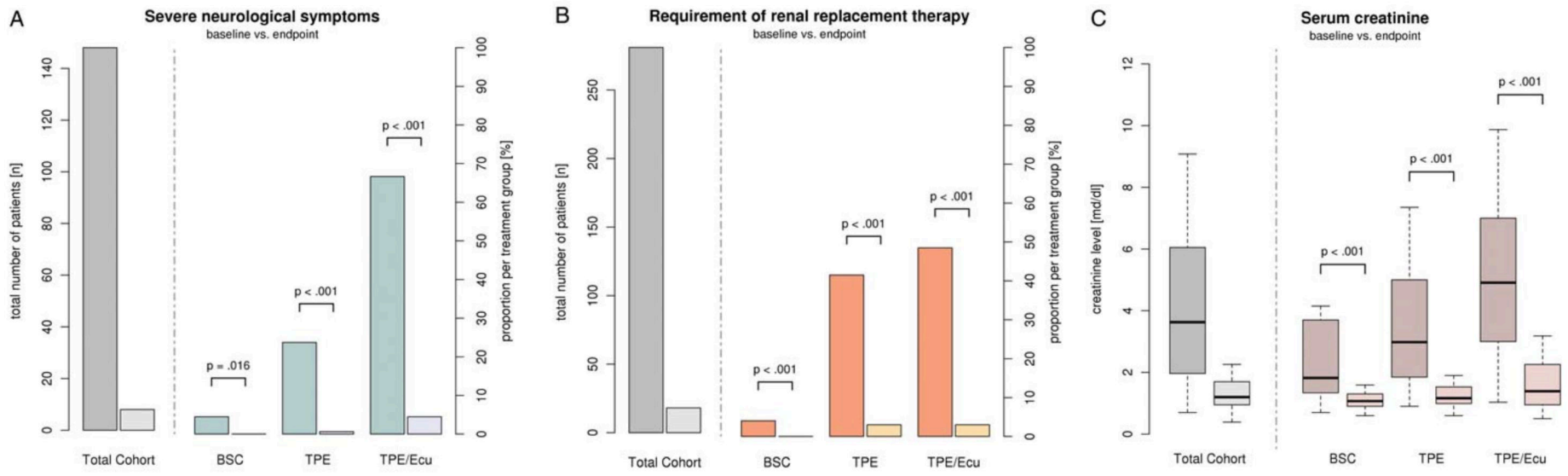
Figure 1. Response to Eculizumab Therapy in Three Children with STEC-HUS and Progressive Central Nervous System Involvement.

Shown are data indicating rapid clinical improvement after the administration of monoclonal C5 antibody eculizumab in three children with the hemolytic–uremic syndrome associated with infection with Shiga-toxin–producing *Escherichia coli* (STEC-HUS), resulting in central nervous system involvement (as shown in Patient 1 in Panel A). In all three children, there was a rapid normalization in plasma creatinine levels and leukocyte counts, as well as in platelet counts and lactate dehydrogenase levels.

Lapeyraque et al, NEJM 2011

Best supportive care and therapeutic plasma exchange with or without eculizumab in Shiga-toxin-producing *E. coli* O104:H4 induced haemolytic–uraemic syndrome: an analysis of the German STEC-HUS registry

377 patients, BSC n=57, PE n= 241, PE / Ecu n=193



No benefit of Eculi + EP vs EP (propensity score matching)

Kielstein et al, NDT 2012

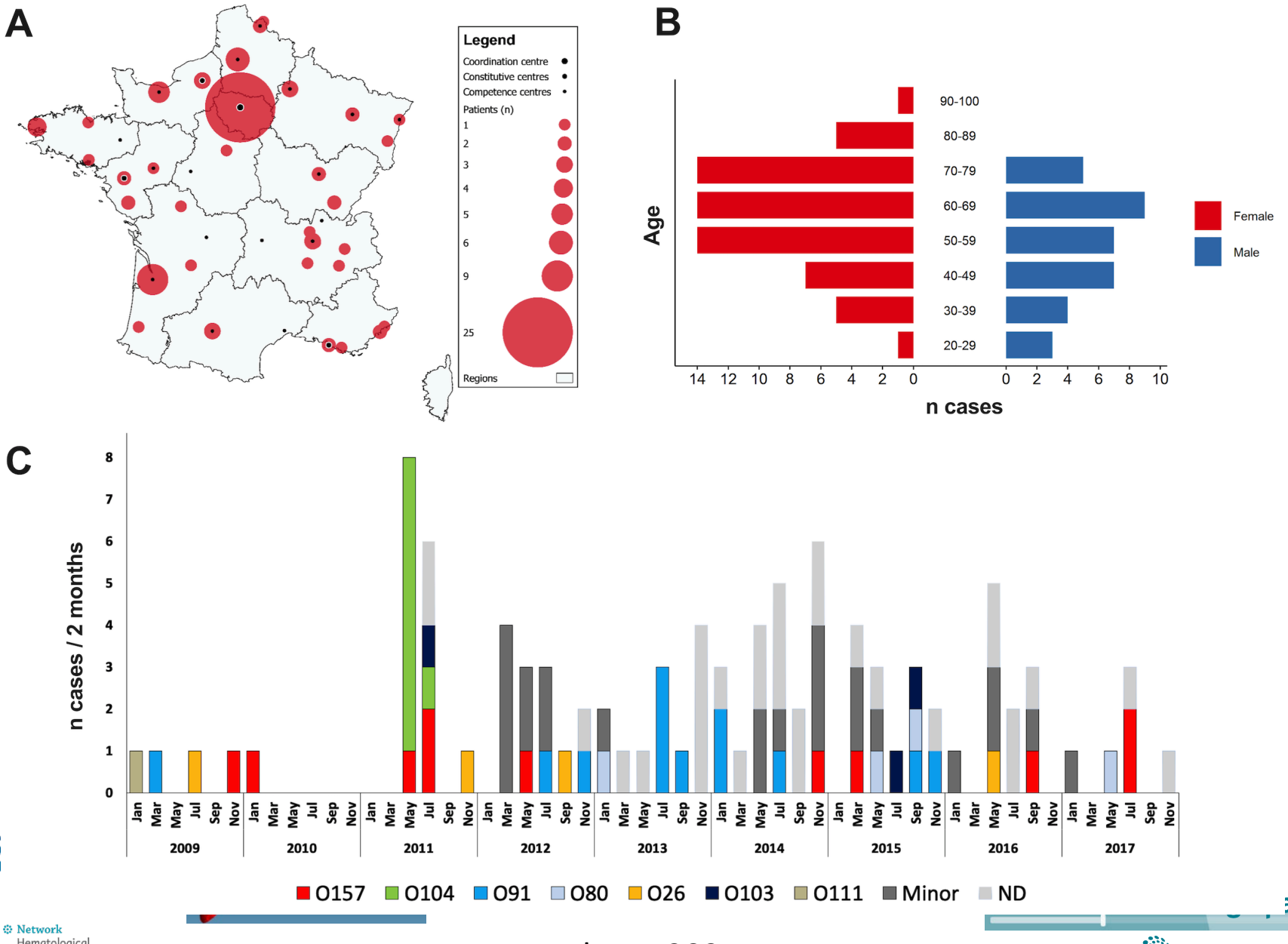
Ongoing studies

- **Eculi SHU (France, Children) => Negative (Oral Com)**
  - **Early treatment with Eculi (1 month) vs Placebo**
  - **Severe forms excluded (CNS and heart)**
- **ECUSTEC (UK, Children): => Interrupted (Sponsor)**
  - **Early treatment with Eculi (D1, D8) vs Placebo**
  - **All severity**
- **ZithroSHU (France, Children): => Inclusions completed**
  - **Azithromycine (3j) vs Placebo**
  - **Severe forms excluded (CNS and heart)**

- **Limited data in adults otherwise (case reports or little series)**

- **French experience 2009-2017 (retrospective)**
  - **Adult patients with TMA and Stx identification in any sample**
  - **CNR-MAT cohort**
  - **NRC-*Escherichia Coli, Salmonella, Shigella* (Institut Pasteur)**
- **=> 96 Patients with available data identified**

Epidemiology in France 2009-2017



B Travert et al, EID 2021

Patients

Table 1. Characteristics of adults with Shiga toxin–associated hemolytic uremic syndrome, France, 2009–2017*

Characteristic	Value
Median age, y (IQR)	60.5 (47.00–71.00)
Sex	
M	35 (36.5)
F	61 (63.5)
Median age-weighted Charlson Comorbidity Index (IQR)	2.00 (1.00–4.25)
Tobacco use within previous 3 y	12 (12.5)
>1 underlying condition	69 (71.9)
Cardiovascular disease	48 (50.0)
Arterial hypertension	38 (39.6)
Stage 4 CKD	3 (3.1)
Digestive disorder§	29 (30.2)
Gastrointestinal disorder	18 (18.8)
Biliopancreatic disorder	9 (9.4)
Hepatic disorder	4 (4.2)
Autoimmune or inflammatory disease¶	11 (11.5)
Immunodeficiency	27 (28.1)
History of bone marrow or solid organ transplant#	8 (8.3)
Hematologic disease**	8 (8.3)
Active cancer††	8 (8.3)
HIV‡‡	3 (3.1)
Primary immunodeficiency§§	2 (2.1)
Neuropsychiatric disorder¶¶	18 (18.8)
Treatment	
Immunosuppressive treatment	12 (12.5)
Corticosteroids	11 (11.5)
Calcineurin inhibitors	7 (7.3)
Azathioprine or mycophenolate mofetil	7 (7.3)

31% of patients presented one or more TMA favoring condition

B Travert et al, EID 2021

Clinical features

Fever: 16%

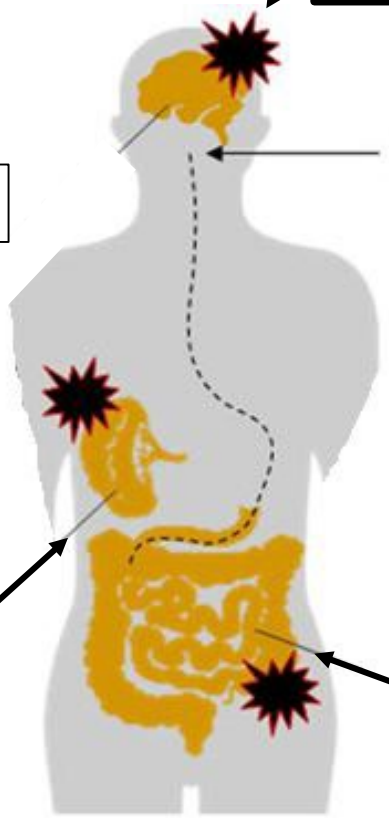
High Blood Pressure: 43%

Platelets (med-IQR): 56 G/L (35-114)

CNS Involvement: 76%
Focal deficiency / coma / seizure 52%

Mechanical Ventilation 35,4%

Cardiac manifestations 43%



AKI 100%
Creatininemia (med) 221 µmol/L
Oligoanuria 67%
KDIGO 1 2%
KDIGO 2 17%
KDIGO 3 74%
RRT 64%

Diarrhea 83%
Bloody 49%
Severe colitis 12%

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Laboratory features

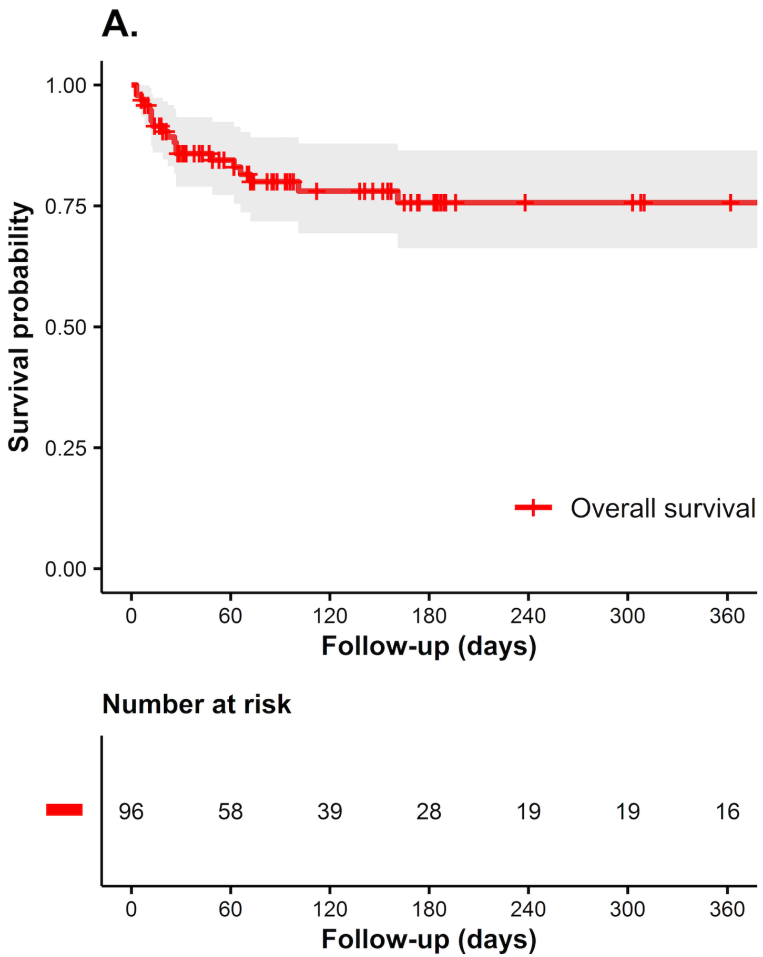
Sample source	
Stools	**89/96**
Urines	7/96
Blood cultures	4/96
Multi site	5/96
Toxine subtype	
Stx1	**20/84**
Stx2	**72/84**
Stx1 et 2	9/84
ND	12/96

Low C3 in 5/69
No significant CAP abnormality (69/96)

Low ADAMTS13 activity (<10%) 2/72

10 patients had STEC-positive urine or blood samples

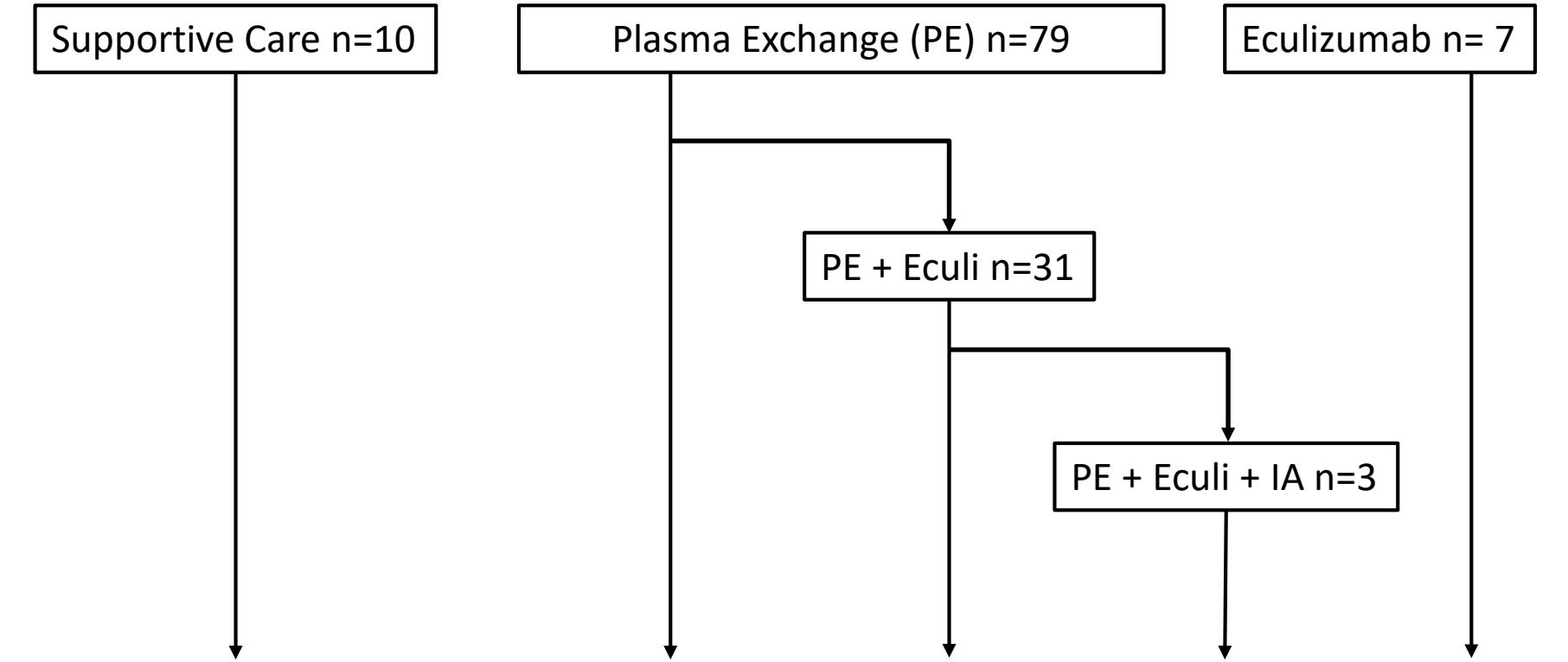
Overall Survival



In hospital death 19,8%

B Travert et al, EID 2021

Treatment



Deceased (D3-D152) n= 19/96

Alive n= 77/96

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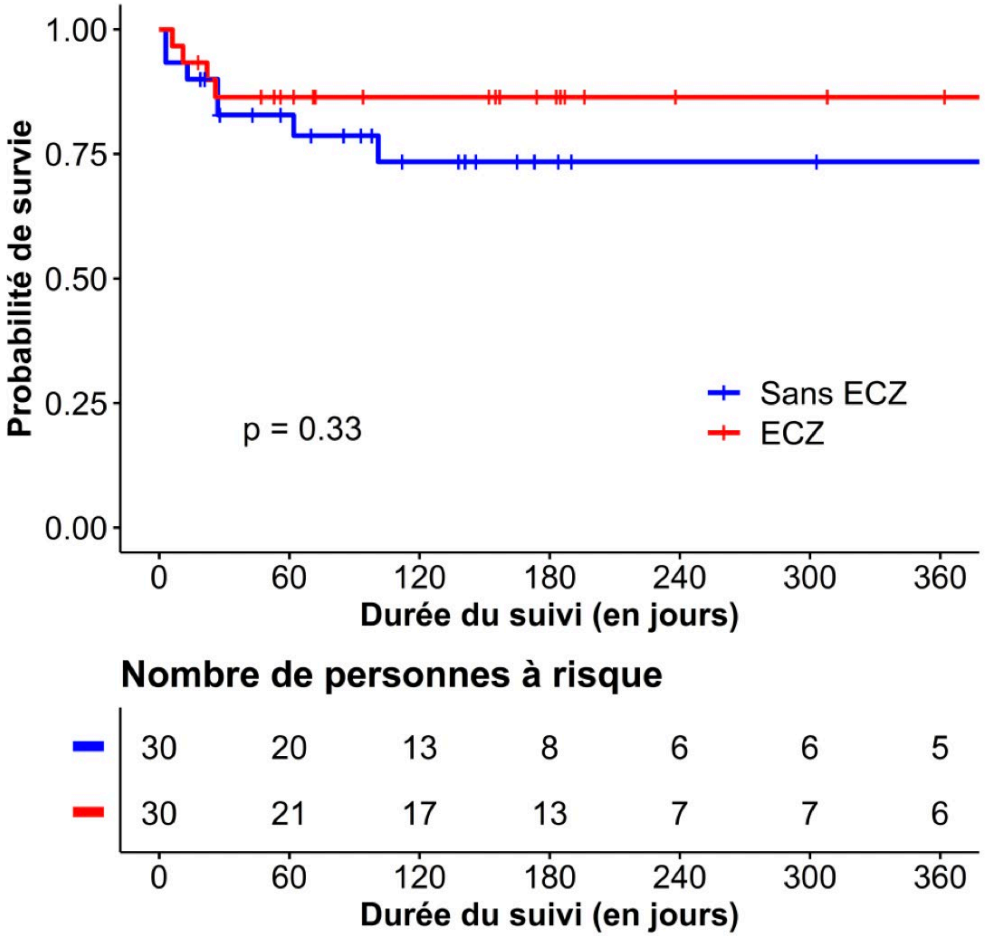
Predictive factors of survival

	Univariate			Multivariate		
	HR	***p***	**[95% CI]**	**HR**	***p***	**[95% CI]**
Age	1,04	0,01	[1·01-1·07]	1,03	0,09	[1·00-1·06]
CCS	1,15	0,02	[1·03-1·28]			
Immunodeficiency	4,36	0,002	[1·7-11·07]	**3,54**	**0,02**	**[1·24-10·14]**
Digestive disease	4,07	0,003	[1·6-10·14]	2,04	0,19	[0·70-5·90]
Major Neurological Event	2,9	0,04	[1·04-8·06]	**3,40**	**0,04**	**[1·05-11·04]**
Mechanical ventilation	2,71	0,03	[1·09-6·74]			
Hemodyalisis	5,57	0,02	[1·3-24·16]	3,49	0,1	[0·77-15·79]

B Travert et al, EID 2021

Survival according to Eculizumab use (Propensity score matching)



Survival analysis (Log rank test) *p*=0,33

Conclusions

- **STEC-HUS is a severe systemic disease.**
- **Specific treatments remain an unmet need.**
- **Adult cases have a worse prognosis than children.**
- **The severity of adult cases is partly explained by the high frequency of underlying conditions, especially immunodeficiency.**
- **CNS involvement is more frequent, whereas diarrhea may be absent. This encourages systematic testing for Stx in cases of TMA.**
- **STEC-HUS may be induced by extradigestive infections.**
- **Sporadic cases occur all over the year, with a great diversity of serotypes. Considering the epidemic potential, an active surveillance of all cases, including adult cases, seems warranted.**

CNR-MAT
Paul Coppo
Benoit Travert
Eric Rondeau
Adrien Joseph
Cedric Rafat
Yahsou Delmas
Lionel Galicier
Veronique Fremeaux-Bacchi
Agnes Veyradier
Elie Azoulay
Lila Bouadma
…

Thank you!

NRC-*Escherichia Coli*
Patricia Mariani Kurkdjian
Stephane Buonacorsi
Aurélie Cointe
François-Xavier Weill

Pediatricians
Julien Hogan
Theresa Kwon

Do they resemble TTP?

French Score 2 points if

- Creatinine < 200 µmol/L
- Platelets < 30 G/L

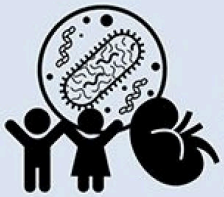
French Score 2 Admission	**5/96**
French Score 2 H48	**2/96**

Including 1 ADAMTS 13 < 10%

Does STEC-HUS unveil preexisting CAP abnomalities?

Complement gene variants and Shiga toxin producing *E. coli* associated hemolytic uremic syndrome

CJASN
Clinical Journal of American Society of Nephrology



Post-diarrheal HUS
n = 108

French Controls
n = 80

1000 Genomes Controls
n = 503

- ❑ Complement Factor H
- ❑ Membrane Cofactor Protein
- ❑ Complement Factor I
- ❑ C3
- ❑ Complement Factor B
- ❑ Thrombomodulin

	Shiga toxin positive HUS n = 75	1000 Genomes Controls n= 503
Pathogenic variants with minor allele frequency < 0.1%	4% (3/ 75)	0.8% (4/ 503)
	OR: 5.2; 95% CI: 1.1-24; p=0.03	
Variants with minor allele frequency < 1%	16% (12/ 75)	12% (60/ 503)
	OR: 1.4; 95% CI: 0.7-2.0; p=0.34	

In Shiga toxin positive -HUS patients, the frequency of increased sC5b9 or of rare variants was not different in those requiring dialysis or not, and in patients ± CNS manifestations during the acute phase

Conclusions Rare variants and complement activation biomarkers were not associated with severity of Shiga toxin associated-HUS. Only pathogenic variants with minor allele frequency <0.1 % are more frequent in Shiga toxin positive-HUS patients than in controls.

Véronique Frémeaux-Bacchi, Anne-Laure Sellier-Leclerc, Paula Vieira-Martins, Sophie Limou, et al. ***Complement Gene Variants and Shiga Toxin Producing E. Coli Associated Hemolytic Uremic Syndrome.*** CJASN doi: 10.2215/CJN.05830518.
Visual Abstract by Edgar Lerma, MD, FACP, FASN

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

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Webinars
Thrombotic Microangiopathies
EuroBloodNet Topic on Focus