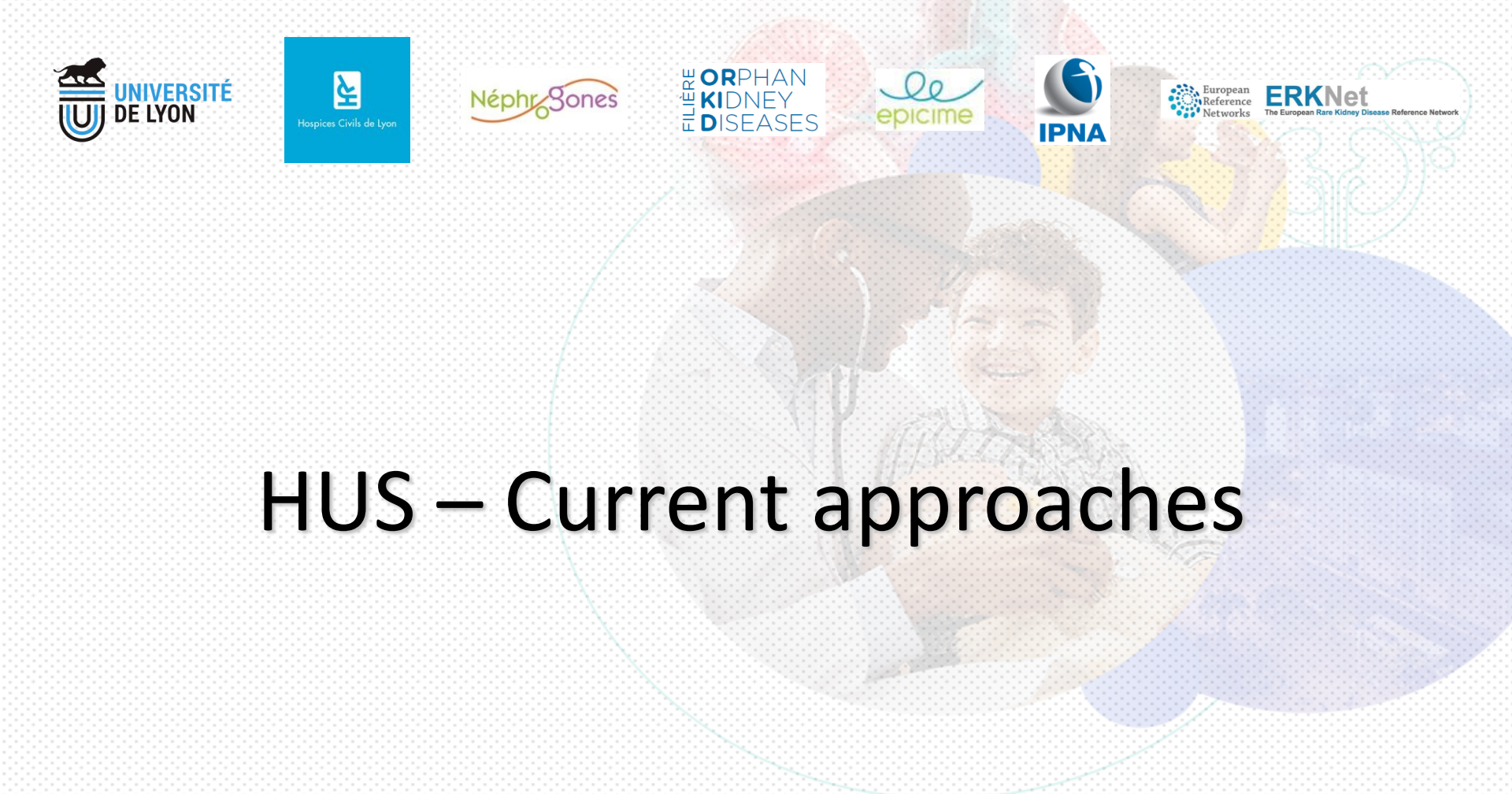

HUS – Current approaches

Pierre Cochat, MD PhD
Professor of Pediatrics
Head, Center for Rare Renal Diseases Néphrogones
Hospices Civils de Lyon & University Claude-Bernard, Lyon, France

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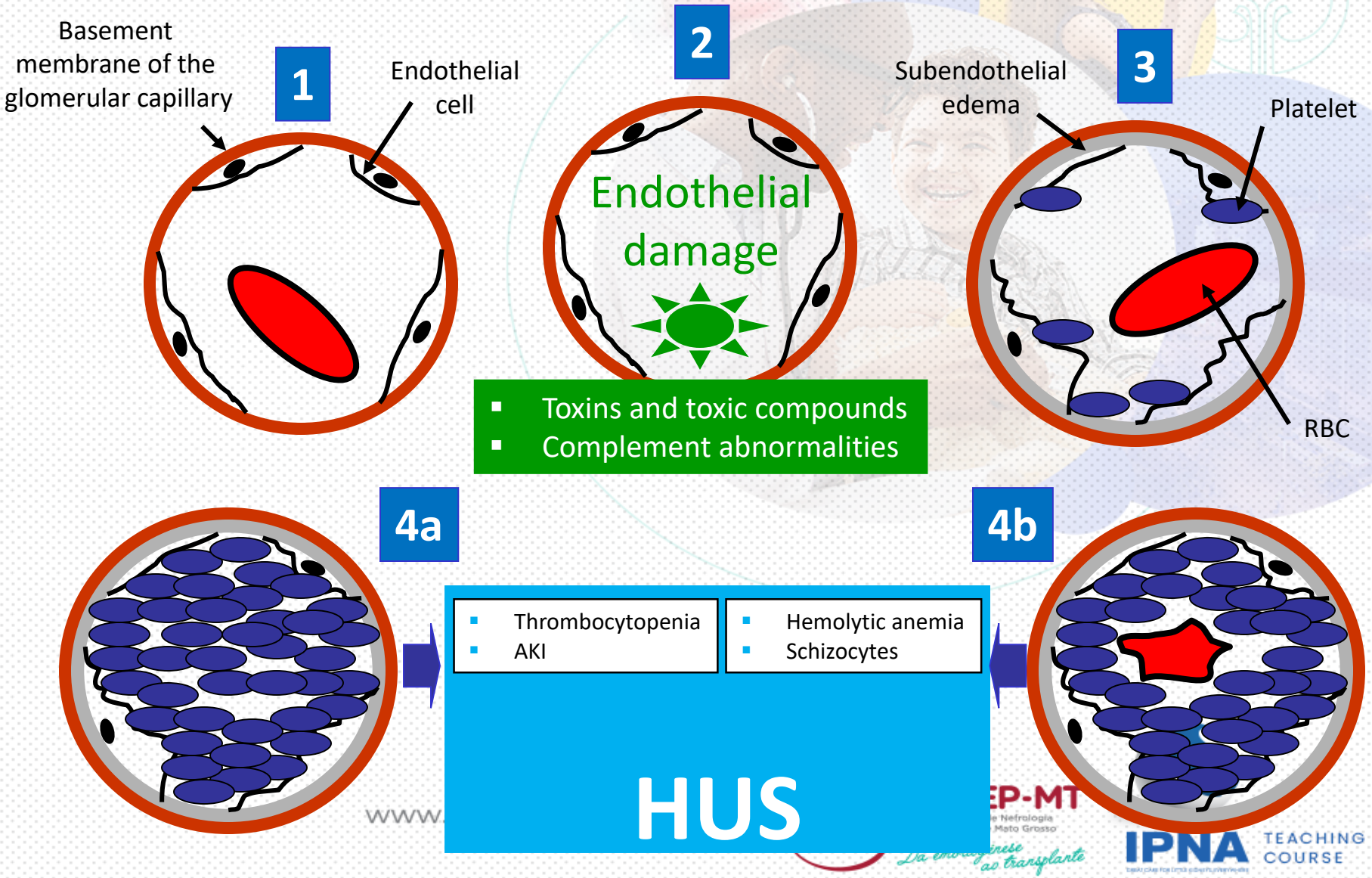
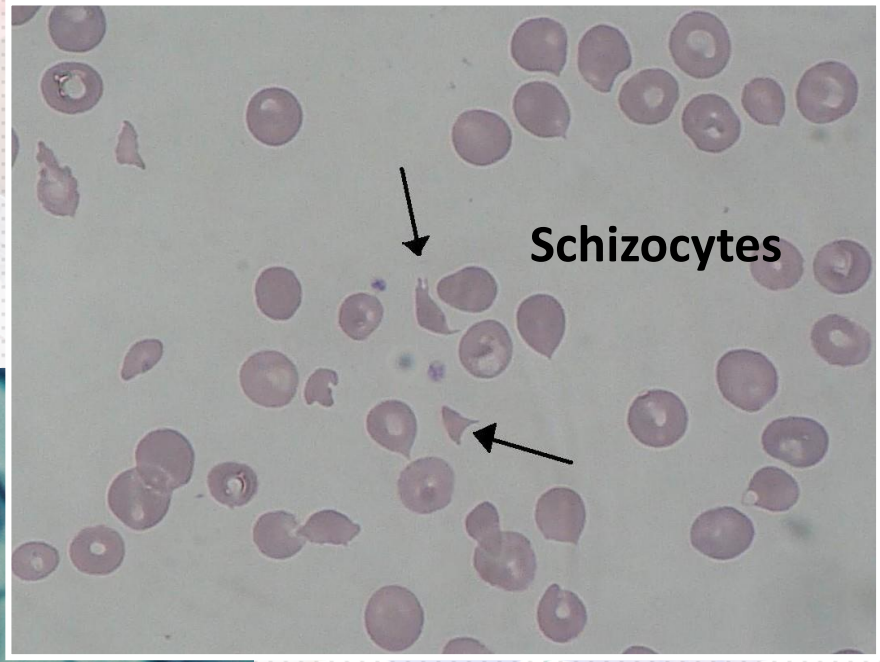
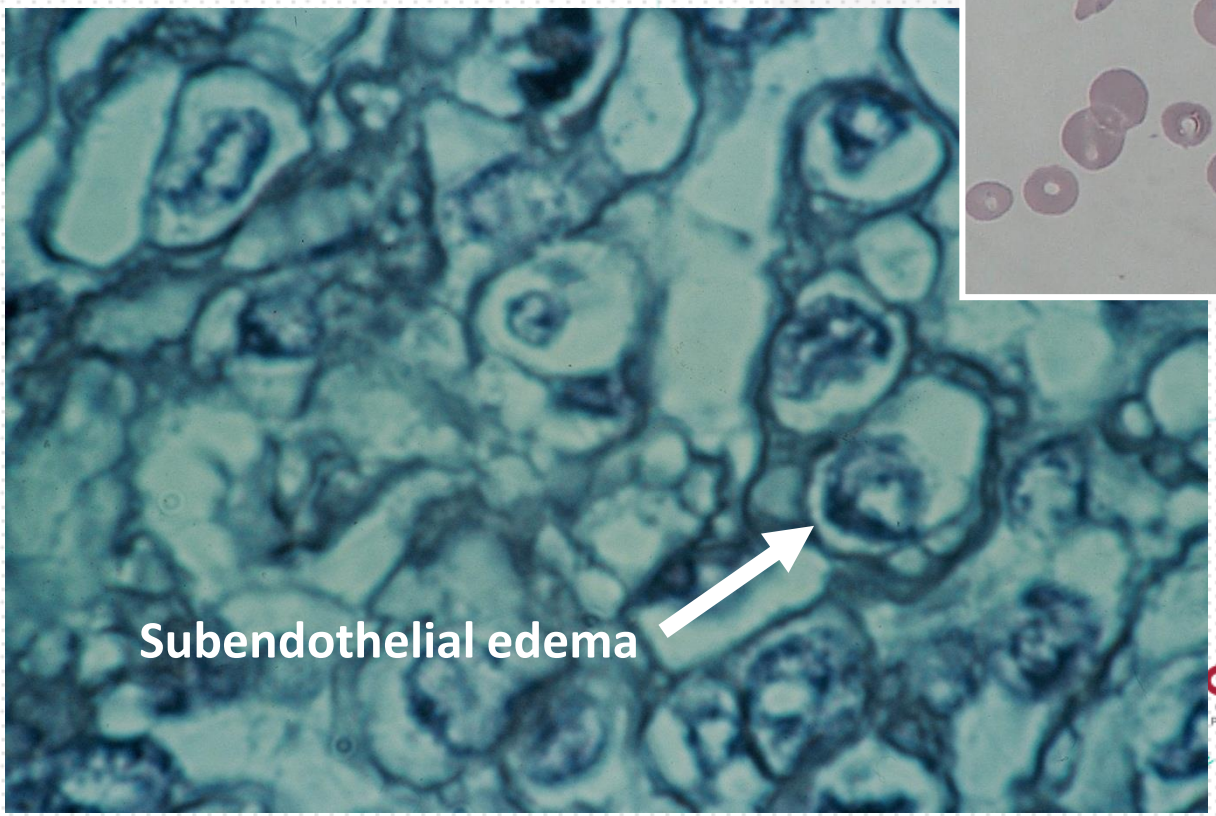
HUS: the most common thrombotic microangiopathy in children

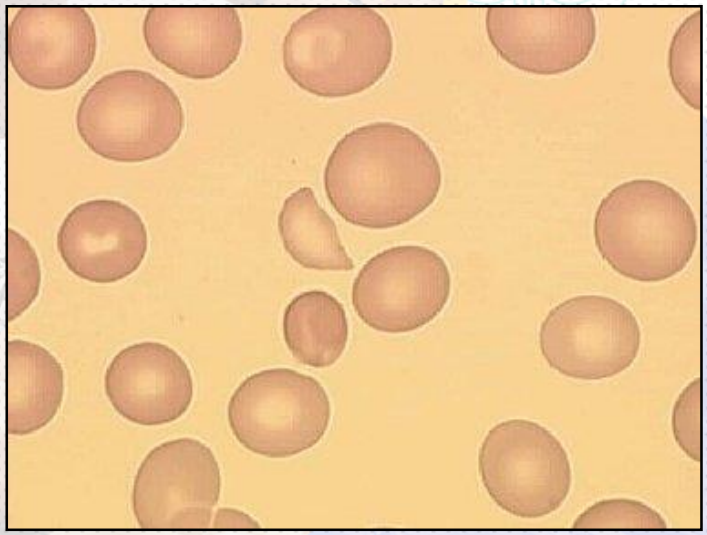


In real life…





Definition

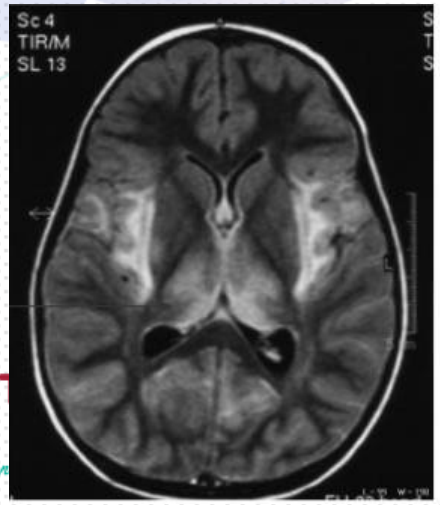


Acute onset: asthenia, pallor, oliguria

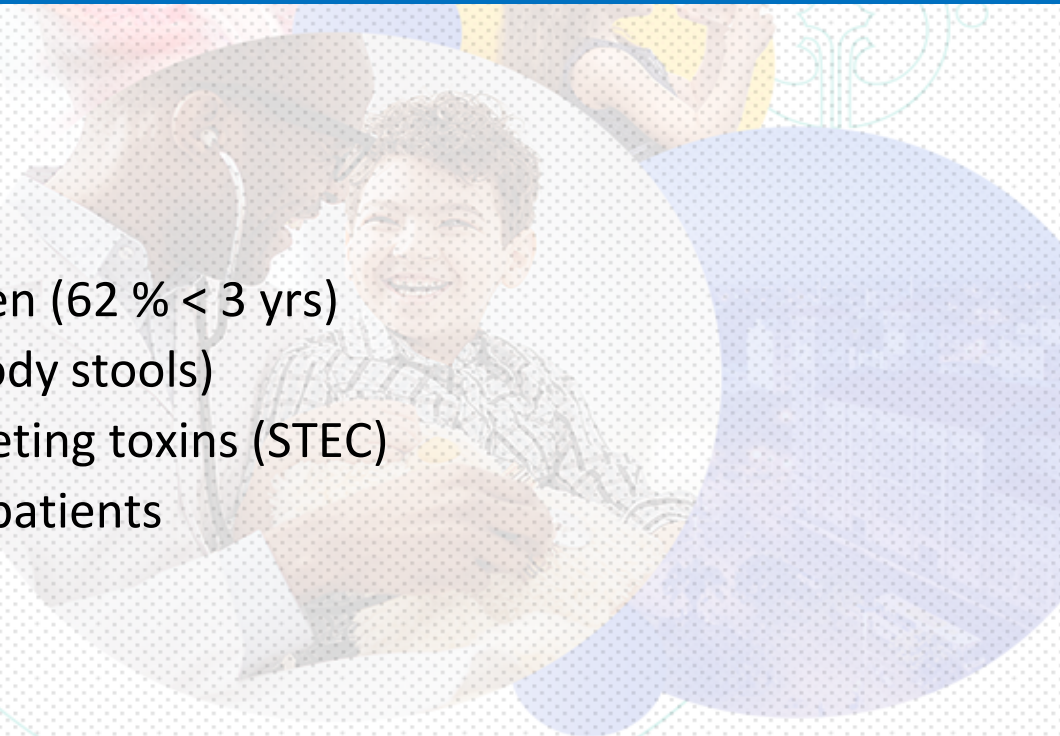
Sometime seizures

- Hemolytic anemia
- Thrombocytopenia
- Acute renal failure

Extrarenal involvement (CNS, heart, pancreas)

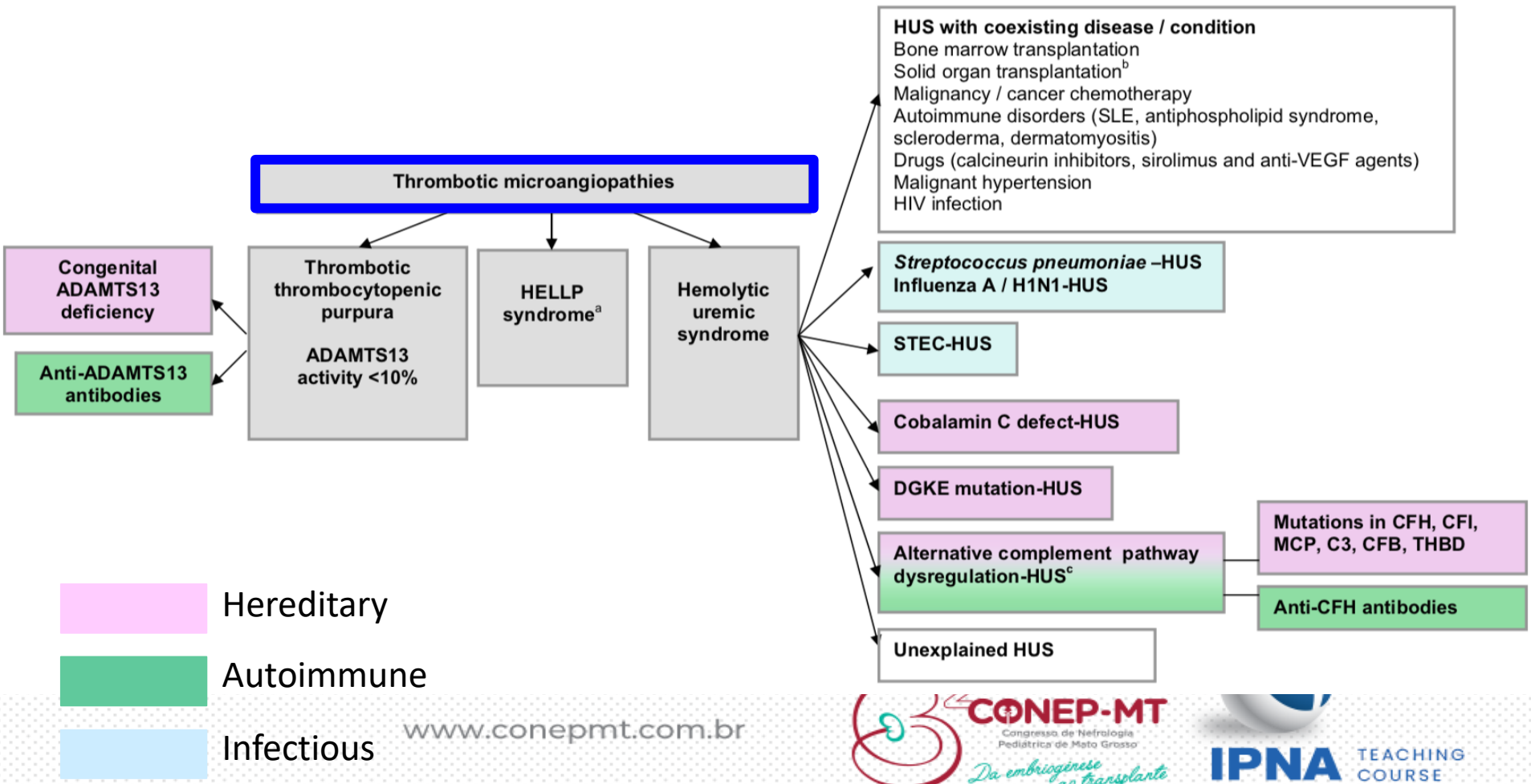


Typical/atypical HUS



- 90 % Typical HUS (D+)
  - Infants and young children (62 % < 3 yrs)
  - Prodromic diarrhea (bloody stools)
  - Infection with *E coli* secreting toxins (STEC)
  - Good prognosis in most patients
- 10% Atypical HUS (D-)
  - No prodromic sign
  - Heterogenous group of diseases
    - Complement abnormalities (inherited, immunization)
    - Systemic disease: SLE, cancer, allograft nephropathy
    - Toxic exposure: anticalcineurins, radiotherapy
  - Poor prognosis (extrarenal damage)

Thrombotic microangiopathy: a wide spectrum



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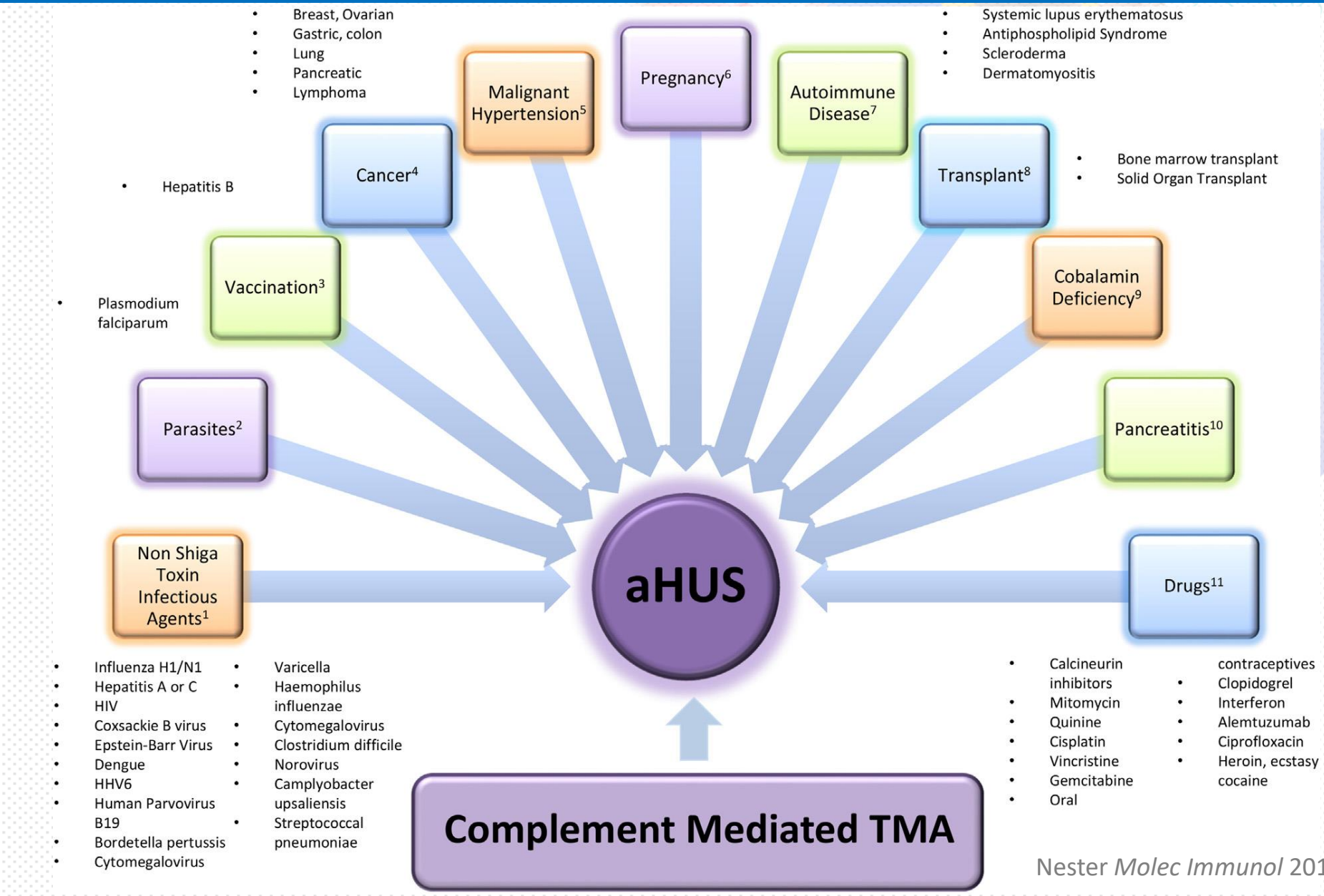
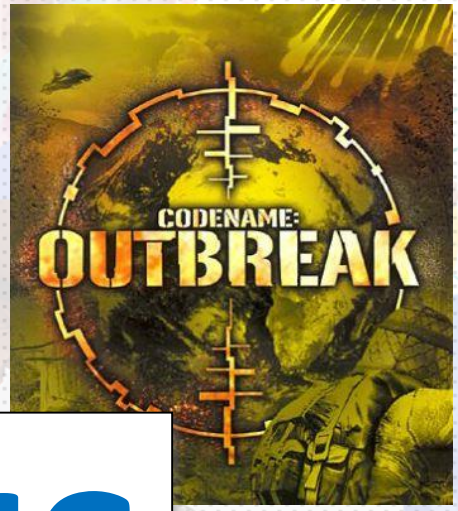
Loirat *Pediatr Nephrol* 2016

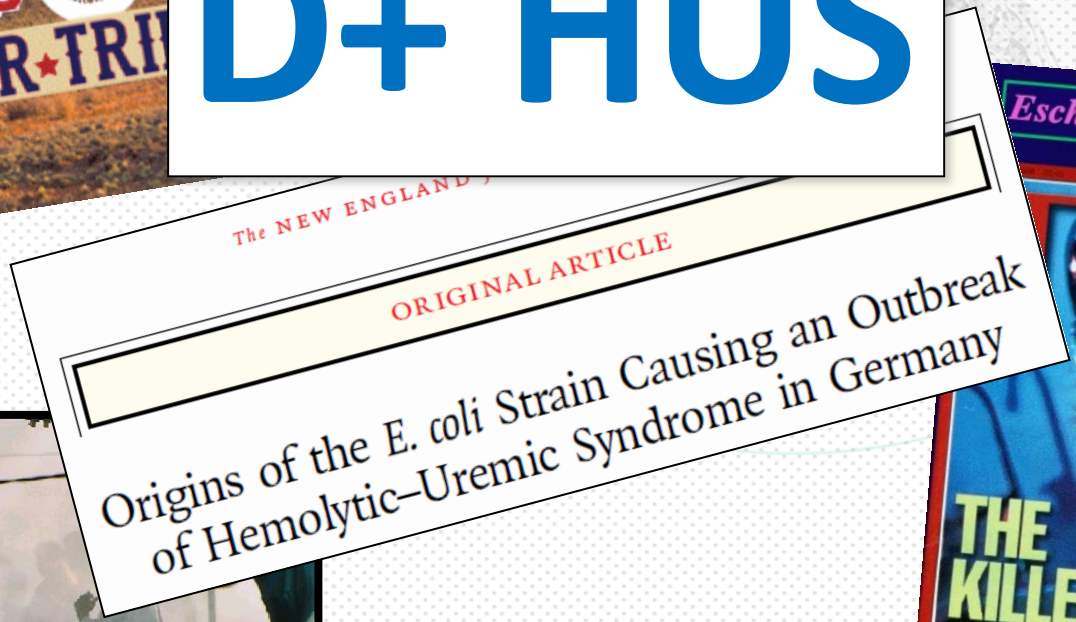
aHUS in details



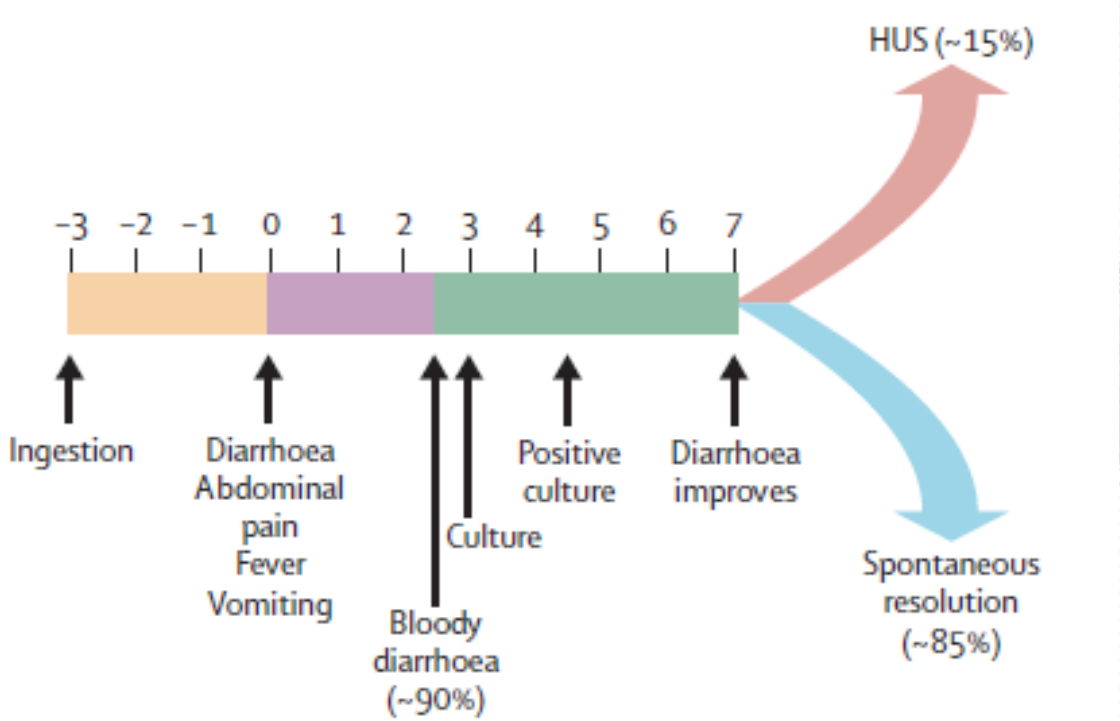
Nester *Molec Immunol* 2015



D+ HUS



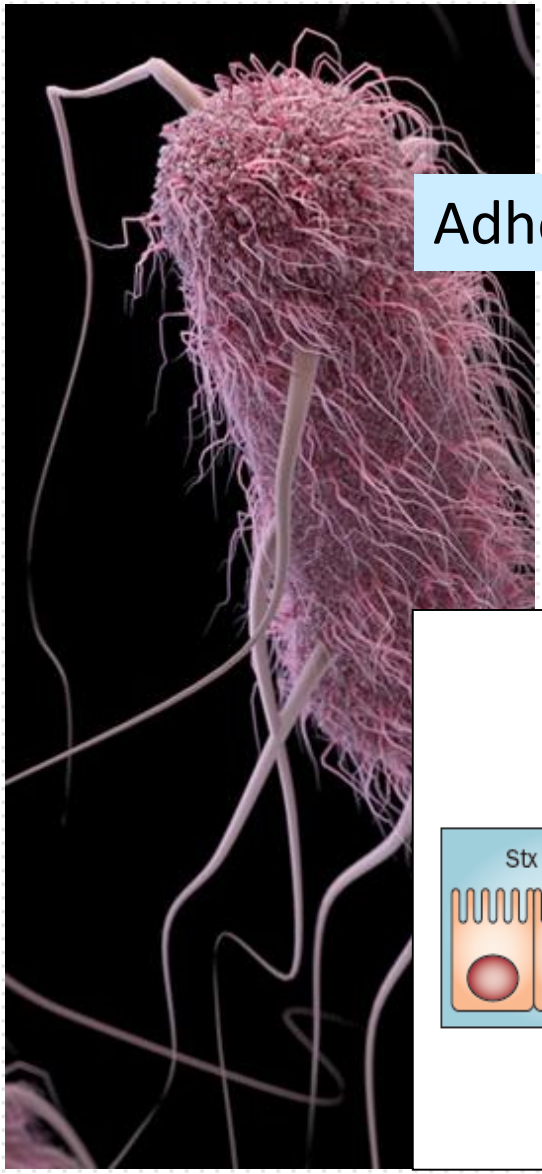
Progression of E coli O157:H7 infection in children



Tarr *Lancet* 2005

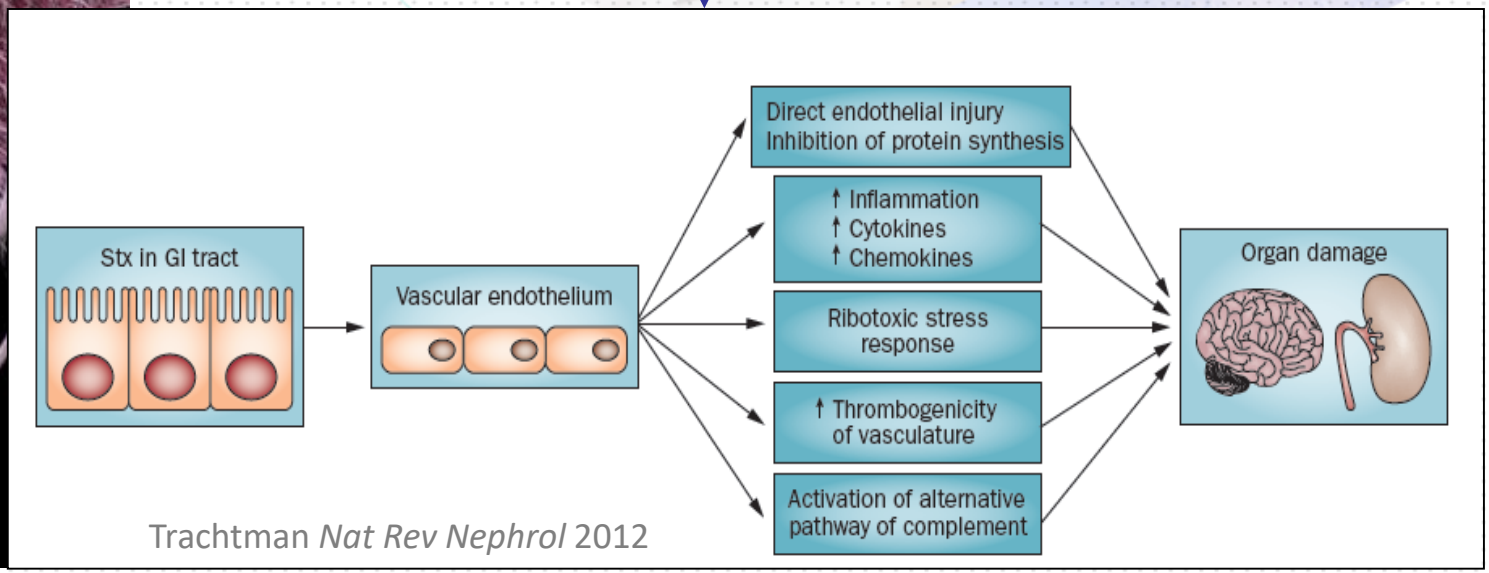
Typical HUS: consequences of STEC infection

(*Shiga-like toxin Escherichia coli* or verotoxin)



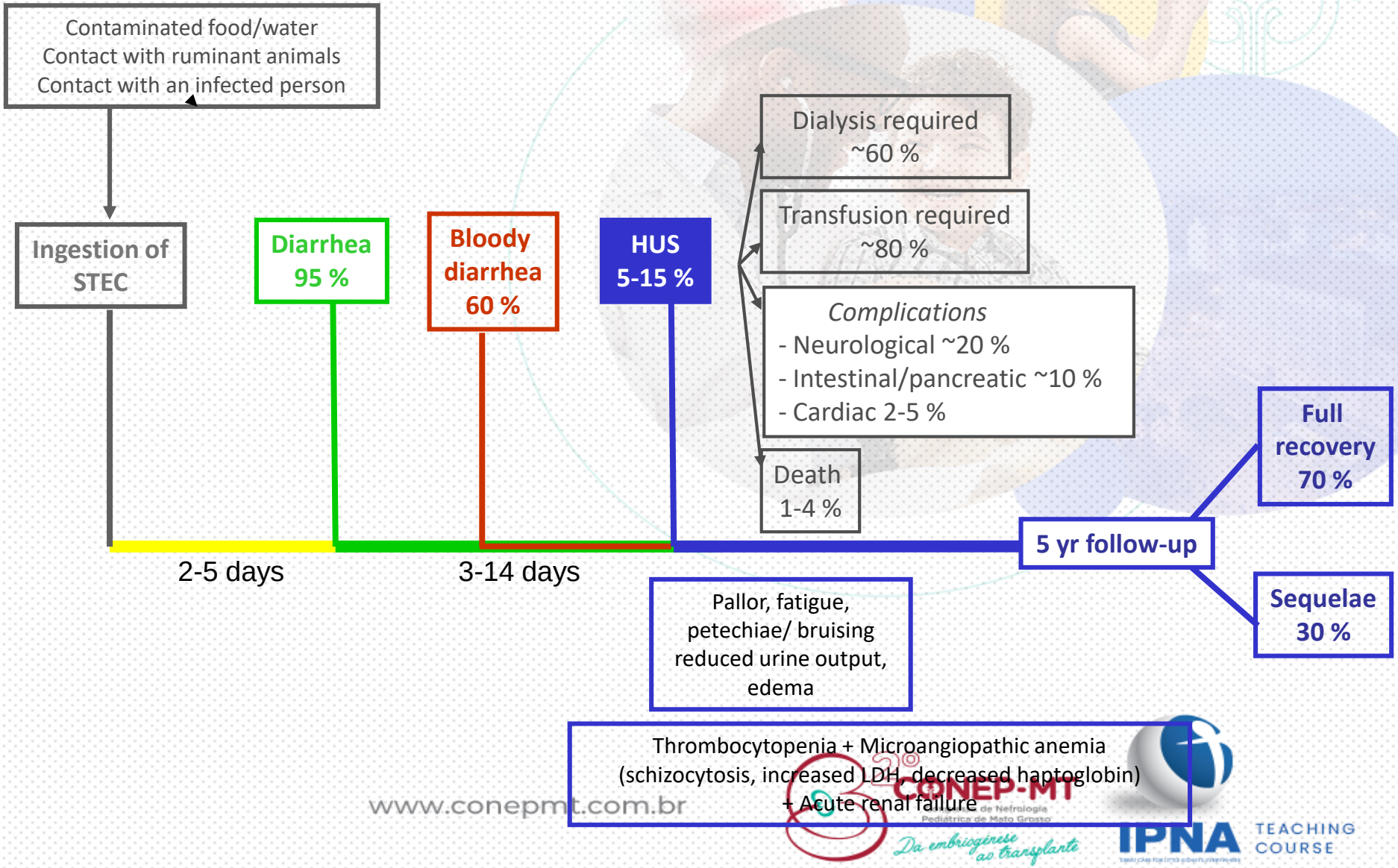
Adhesion of *E coli* to enterocytes

Production of shigatoxines



Trachtman *Nat Rev Nephrol* 2012

STEC-HUS: an unalterable scenario in children



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Rosales *Clin Infect Dis J* 2012 – Mody *J Pediatr* 2015 – Keir *Hematol Oncol Clin N Am* 2015

D+ HUS in France

Online epidemiological survey in children < 15 yrs

- ~100 cases per year
- Annual incidence
  - 0.7 per 100,000 children < 15 yrs
  - Comparable
    - To others occidental Europe countries
    - To USA and Canada
  - High incidence in Argentina
    - 22 per 100,000 children < 5 yrs

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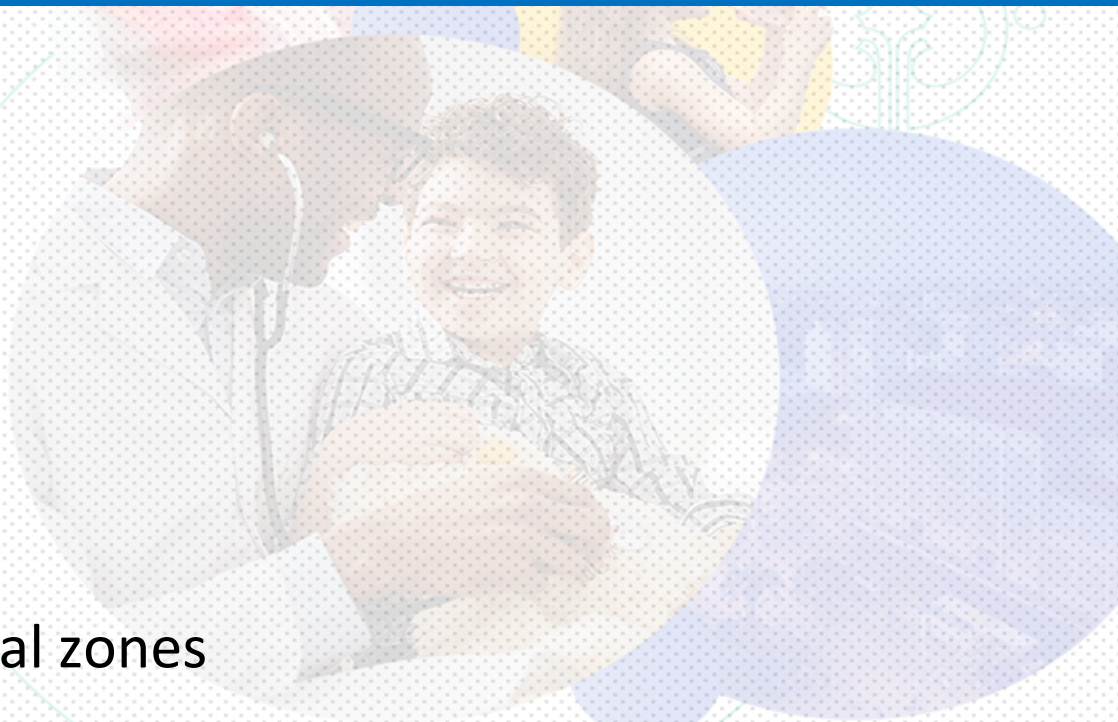
Epidemiology of D+ HUS



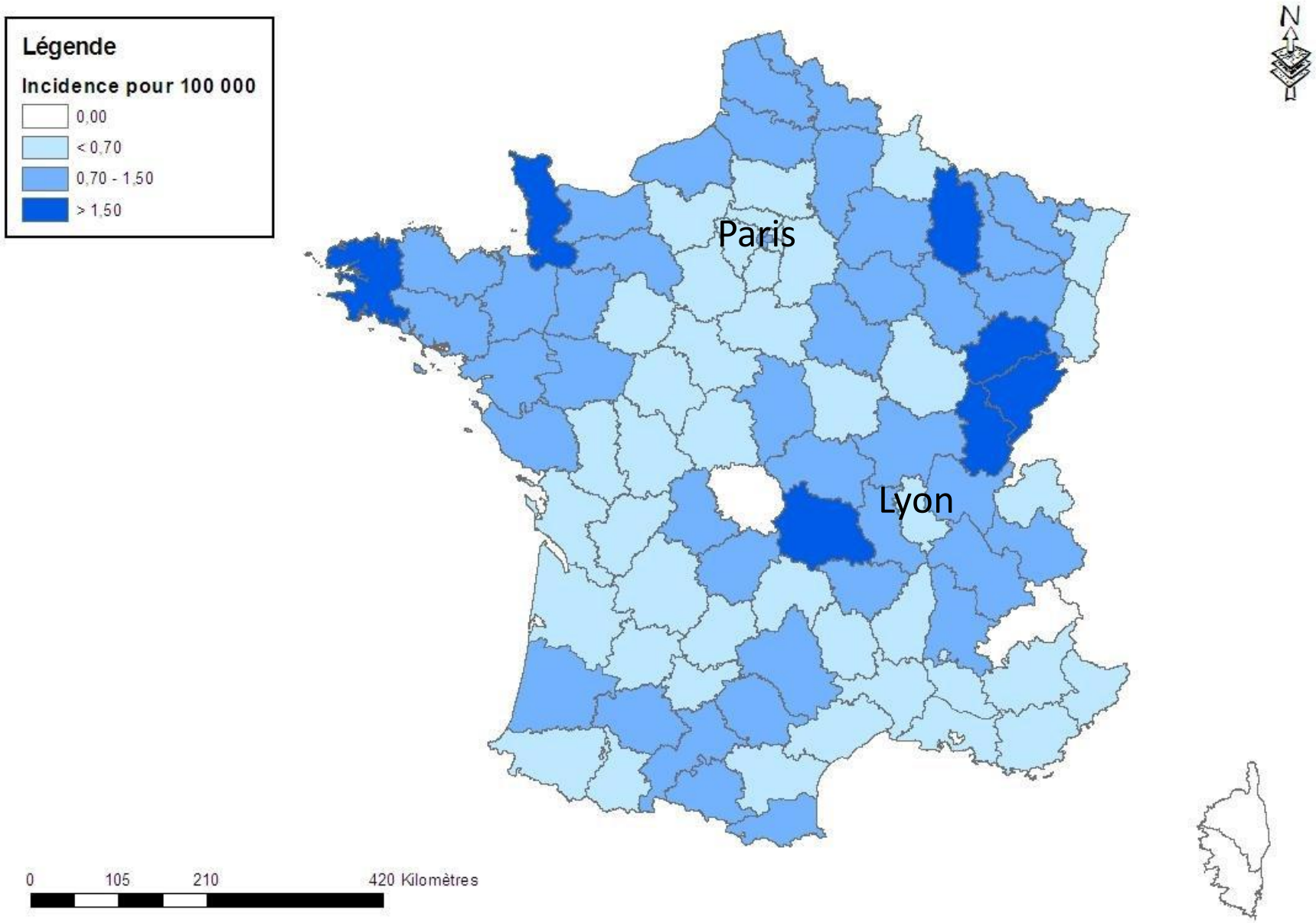
- Mainly isolated cases
- But some outbreaks

- « At-risk » geographical zones

- « At-risk » seasons

- « At-risk » age groups

At-risk geographical areas

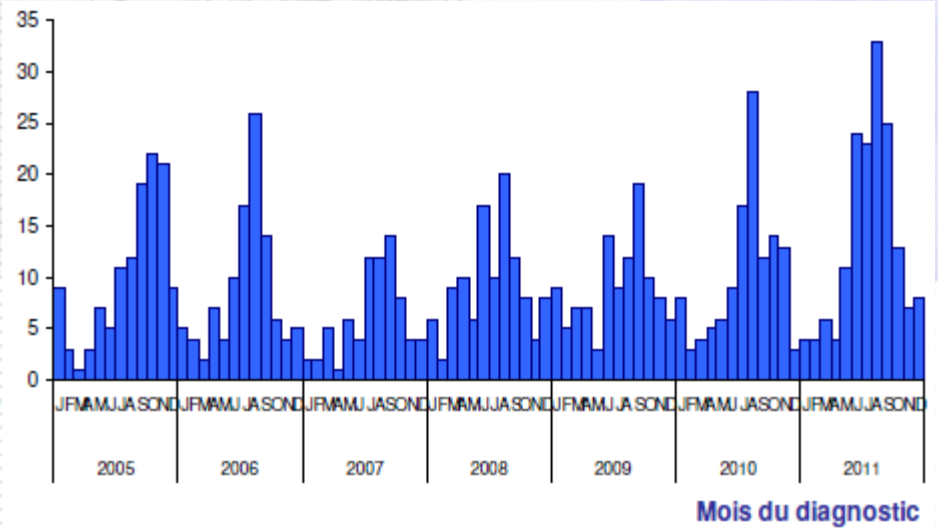


At-risk groups

At-risk age groups: < 3 ans

Groupe d'âge (ans)	Incidence annuelle moyenne (par 100 000 enfants <15ans)
0-2	2,3
3-5	1,0
6-10	0,3
11-15	0,1

At-risk season: end of summer time



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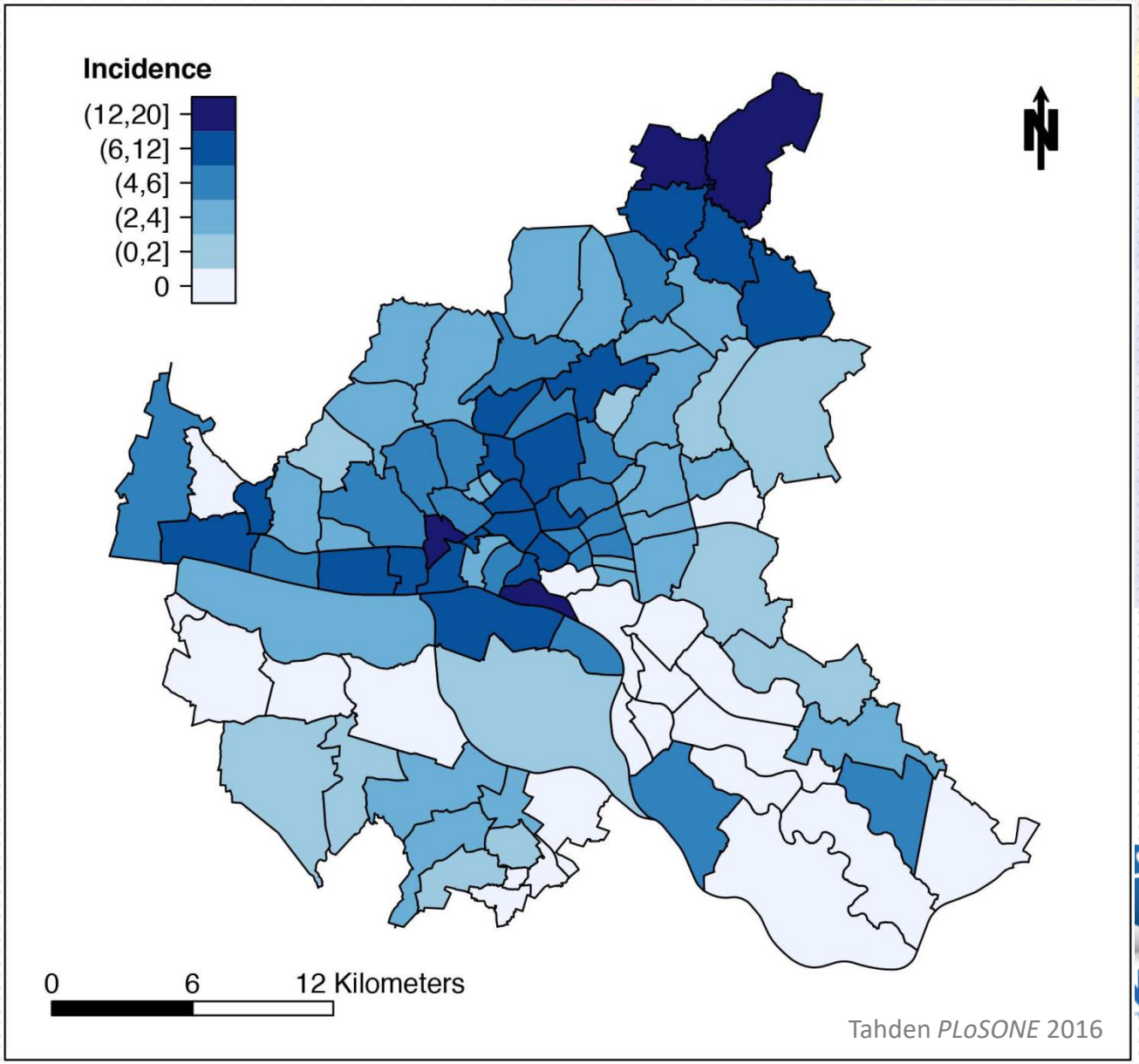
InVS 2011

Example of outbreak: EHEC/HUS incidences

in Hamburg [Germany] during EHEC O104:H4 outbreak 2011



Tahden *PLoSONE* 2016

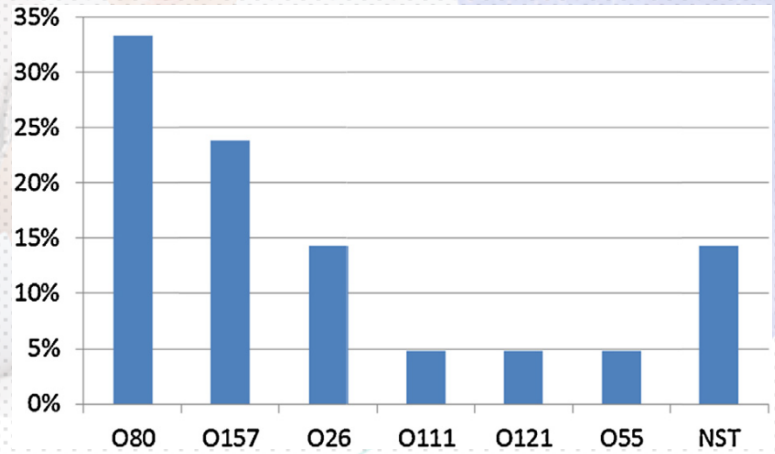
TEACHING COURSE

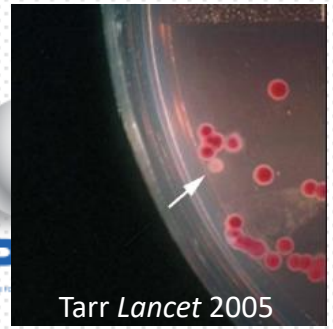
Typical HUS, as a consequence of STEC infection

(*Shiga-like toxin Escherichia coli* or verotoxin)

- Contamination
  - Food
  - Inter-human contacts
  - Infected ruminants
- Diagnosis
  - Antibodies againts STEC
  - Identification of STEC strains
  - Gene PCR encoding shigatoxins in stools (*stx2)*

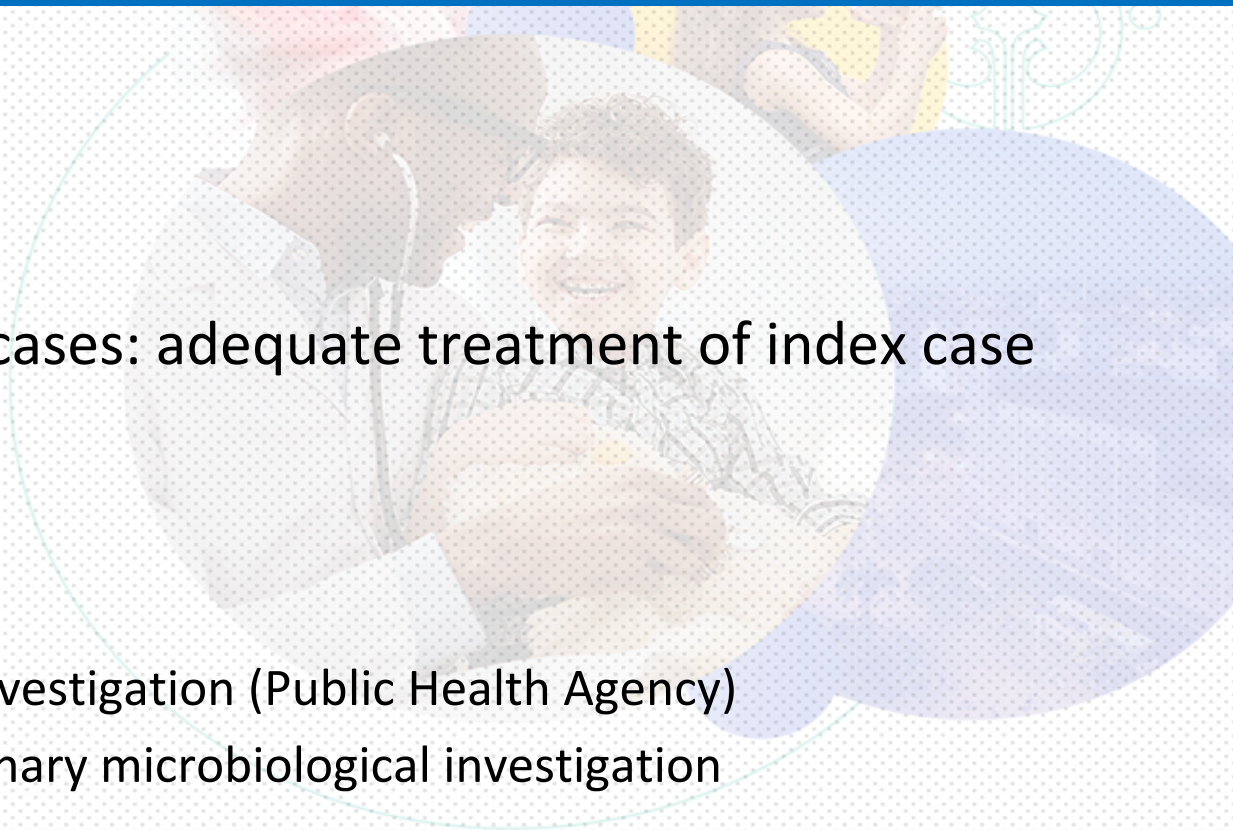
InVS 2015





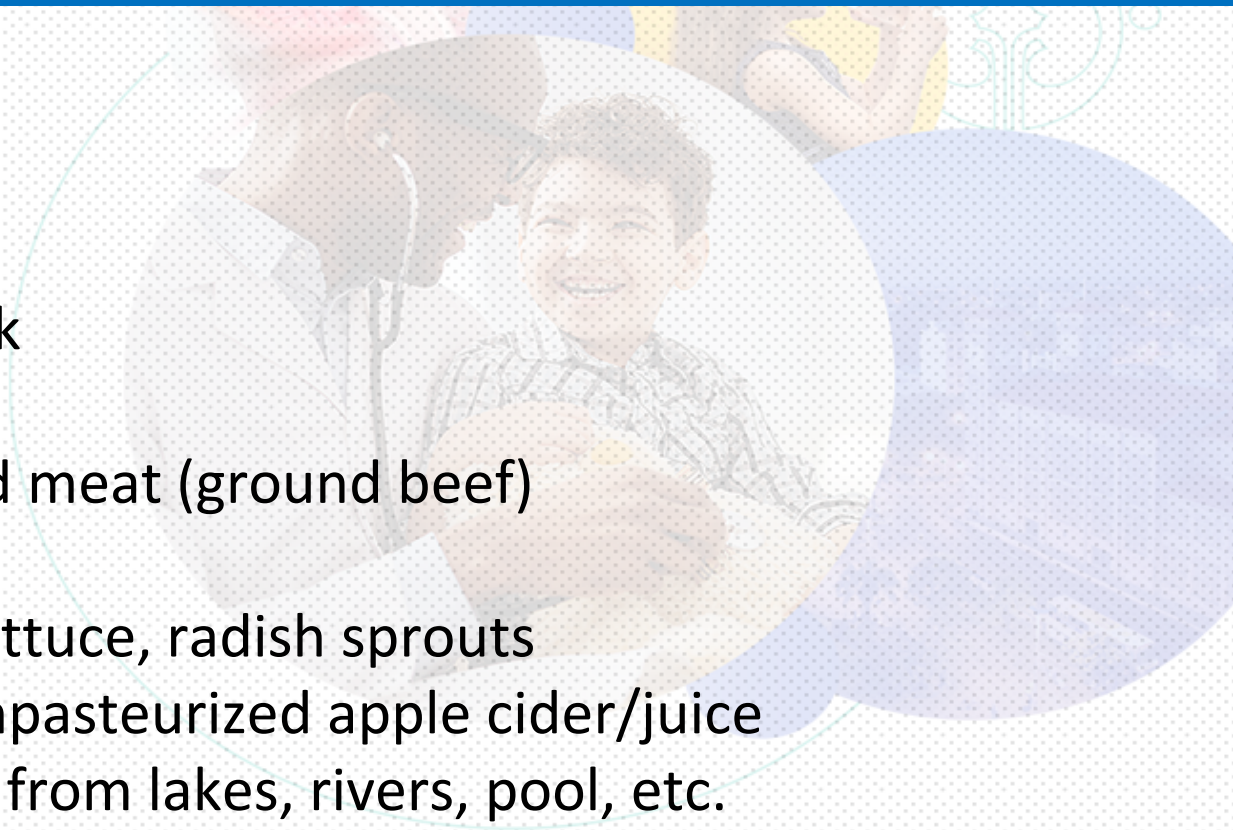
Tarr *Lancet* 2005

Management



- Isolated/sporadic cases: adequate treatment of index case
- Pooled cases
  - Risk of outbreak
  - Epidemiological investigation (Public Health Agency)
  - Human and veterinary microbiological investigation

Risk factors within the previous 2 weeks



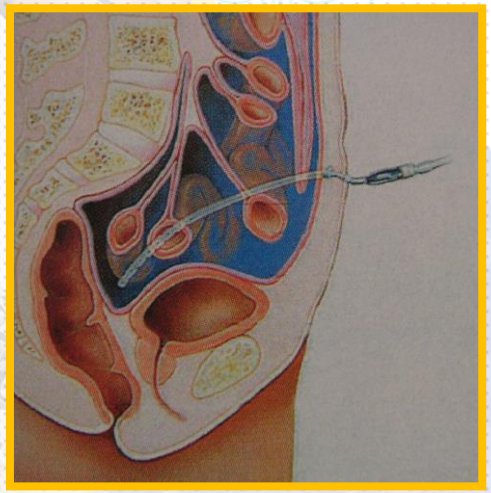
- Unpasteurized milk
- Raw cheese
- Un-/poorly-cooked meat (ground beef)
- Salami
- Raw vegetables, lettuce, radish sprouts
- Fruits with skin, unpasteurized apple cider/juice
- Ingestion of water from lakes, rivers, pool, etc.
- Contacts with farm animals
- Special events (party, marriage, travel)

Treatment: supportive measures

- ± Dialysis (temporary)
- ± Antibiotics (azithromicine)
- ± Blood transfusion
- ± Anti-hypertensive therapy
- ± High-dose frusemide/bumetamide if diuresis
- ± Feeding adapted to digestive conditions

- In case of lifethreatening complication:
  - Plasmapheresis ?
  - Eculizumab (Soliris®) – 3 doses suggested
- Avoid
  - Platelet transfusion
  - Corticosteroids, heparin, aspirin, dipyridamole,

Treatment: supportive measures



- 36 % Dialysis (PD) + blood transfusion
- 47 % Blood transfusion without dialysis
- 2 % Dialysis without blood transfusion
- 16 % Neither dialysis nor blood transfusion

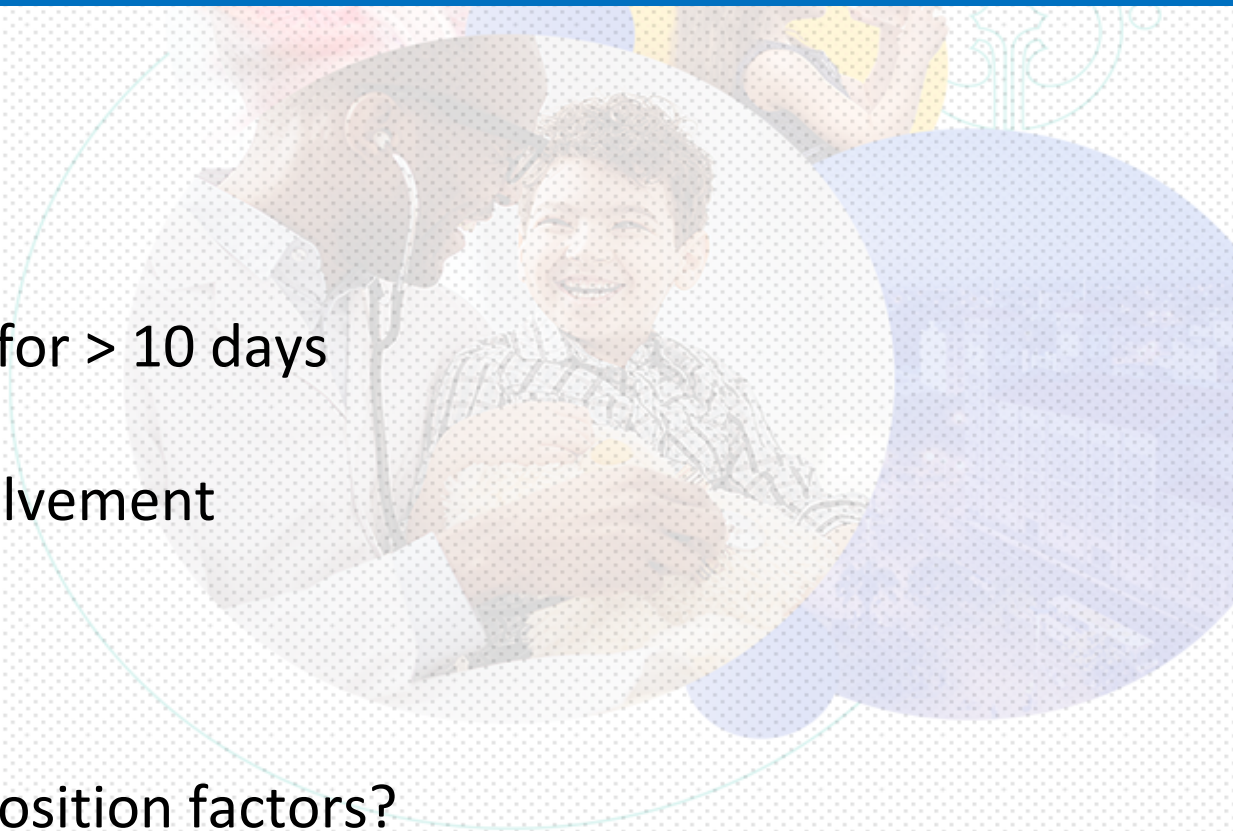
Median duration for hospital stay: 10 days [2 – 48]

Outcomes

- Death (neurological/cardiac) 1-4 %

- Long-term renal sequellae 30-40 % !
  - Proteinuria – HTN – CKD
  - ESRD : 5 to 10 % (no recurrence after kidney Tx)
  - At least 1 work-up per year
  - Recommend normal-low sodium/protein diet, avoid overweight
  - In some cases, start ACEi/ARB

Prognostic factors



- Dialysis required for > 10 days
- Neurological involvement
- Leukocytosis
- Inherited predisposition factors?

Prevention

Les viandes, et surtout la viande hachée de bœuf, doivent être bien cuites à cœur

Le lait cru et les fromages à base de lait cru ne doivent pas être consommés par les enfants de moins de 3 ans [illegible]rer les fromages à pâte pressée cuite (type Emmental, Comté, etc.), les fromages fondus à tartiner et les fromages au lait pasteurisé

Les légumes, les fruits et les herbes aromatiques, en particulier ceux qui vont être consomm[illegible] soigneusement lavés

Les aliments crus doivent être conservés séparément des aliments cuits ou prêts à [illegible]

Les restes alimentaires et les plats cuisinés doivent être suffisamment réc[illegible]es rapidement

Les ustensiles de cuisine (surtout lorsqu'ils ont été en contact [illegible]de la viande crue), ainsi que le plan de travail, doivent être soigneusement lavés

Le lavage des mains doit être systématique av[illegible]anger et en sortant des toilettes

En cas de gastro-entérite, il convient d'év[illegible]gner dans des lieux de baignades publics et de préparer des repas

Les enfants ne doivent pas boire d'eau non traitée (eau de puits, torrents, etc.) et éviter d'en avaler lors de baignades (lac, étang, etc.)

Enfin, il faut éviter le contact des très jeunes enfants (moins de 5 ans) avec les vaches, veaux, moutons, chèvres, daims, etc., et leur environnement

IPNA recommendations coming soon

- Antibiotic prophylaxis in sibs (azithromycin)
- Antibiotic treatment of any *E coli* O157 infection
- Avoid treatment of diarrhoea with antimotility agents
- Immunisation anti-*shiga-like toxins*?

Conclusions

- Think of HUS!
- Mainly in children < 5 yrs of age
- Prevention ++
- Online epidemiological survey
- Early treatment in specialized unit
- Long-term follow-up


aHUS

Dual role of complement

Courtesy Dr V Fremeaux-Bacchi

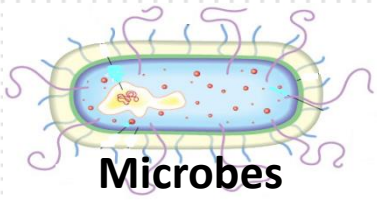
Defense against infection

C3

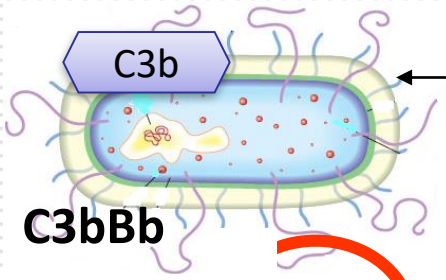
24h/24

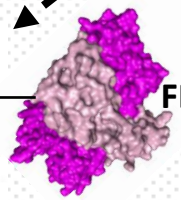
C3b

Protection of host cell membranes



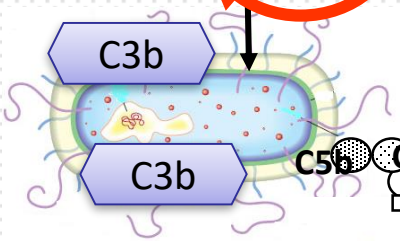
Microbes

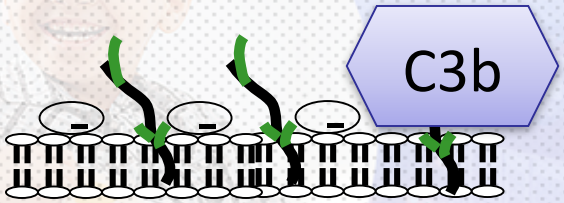




C3bBb

Amplification loop



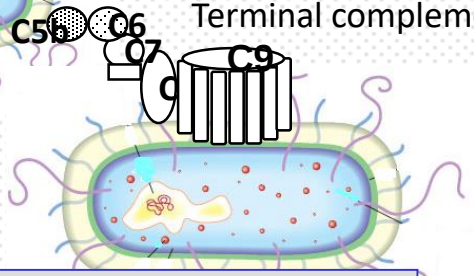


Self

Negatively charged cell surface polyanions (heparin, sialic acid, GAGs)

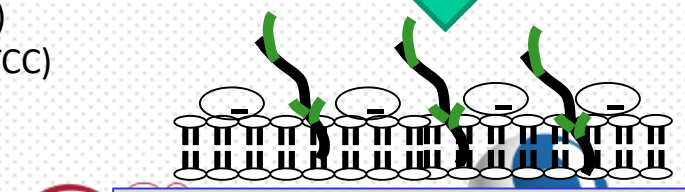
Complement regulatory proteins

C5b-9
Membrane attack complex (MAC)
Terminal complement complex (TCC)



Opsonisation
Phagocytosis
Chemotactic factors

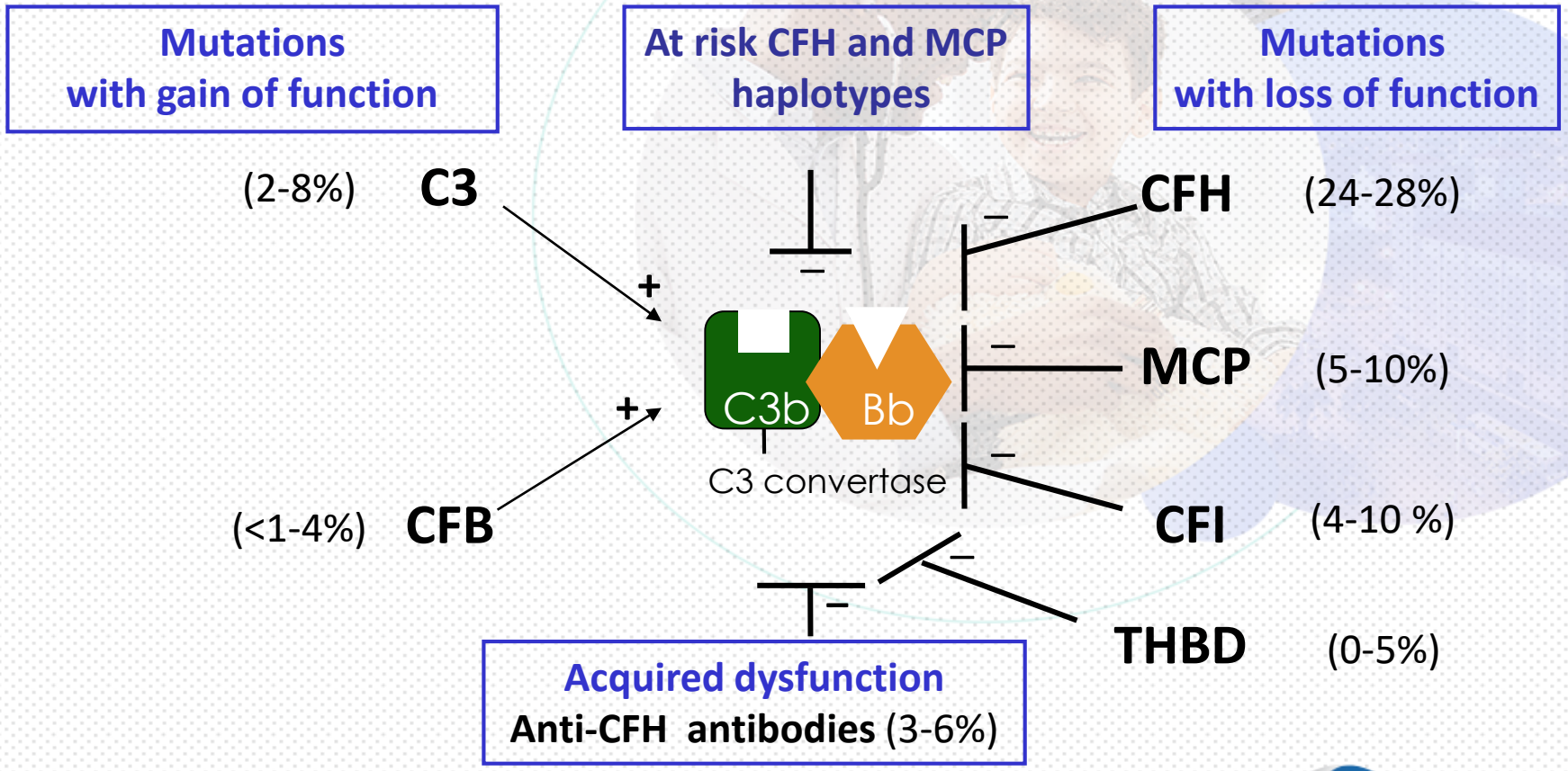
Clearance of microbes



Protection of cell surface from C3b deposits and complement activation

aHUS: a disease mostly of complement alternative pathway dysregulation

More than 1000 patients studied in Europe and the USA

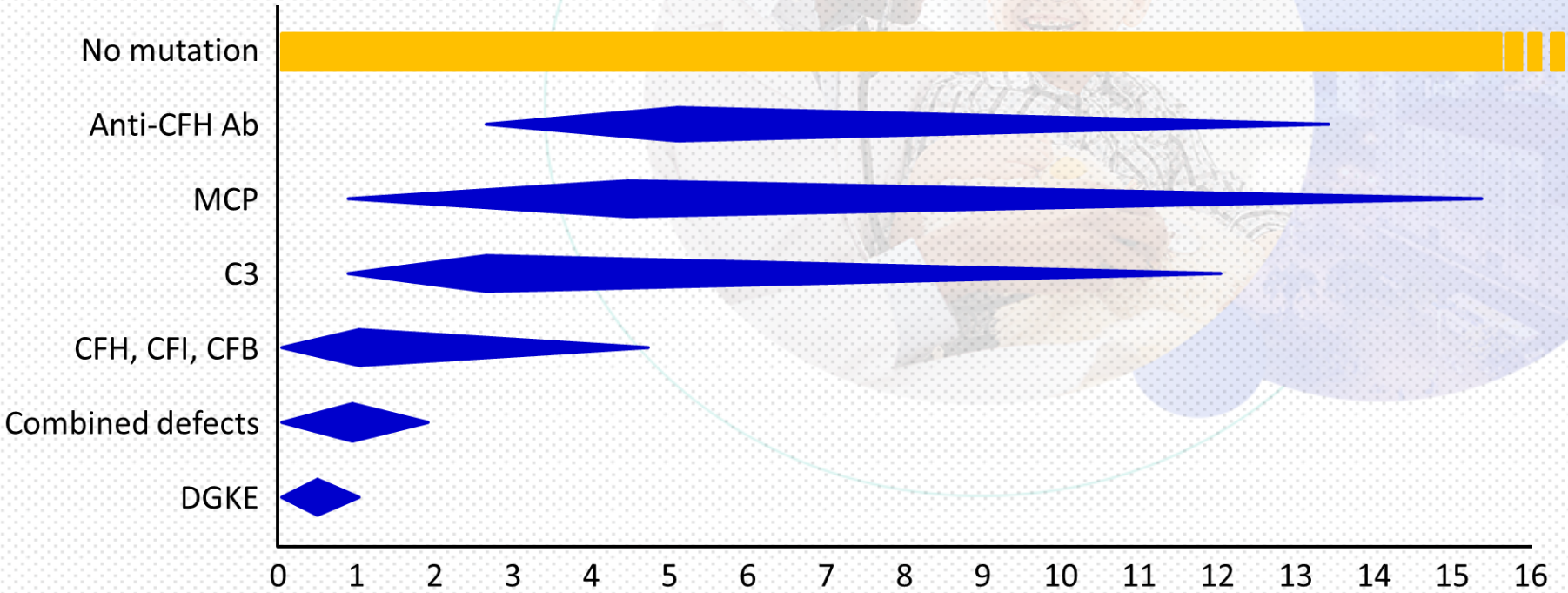


In 30 to 40% of patients, no complement abnormality could be identified, including DGKE mutations

Noris *Clin J Am Soc Nephrol* 2010; Maga *Human Mut* 2010; Fremeaux-Bacchi *Clin J Am Soc Nephrol* 2013; Lemaire *Nat Genet* 2013

(Courtesy V. Fremeaux-Bacchi)

Age at onset of atypical HUS



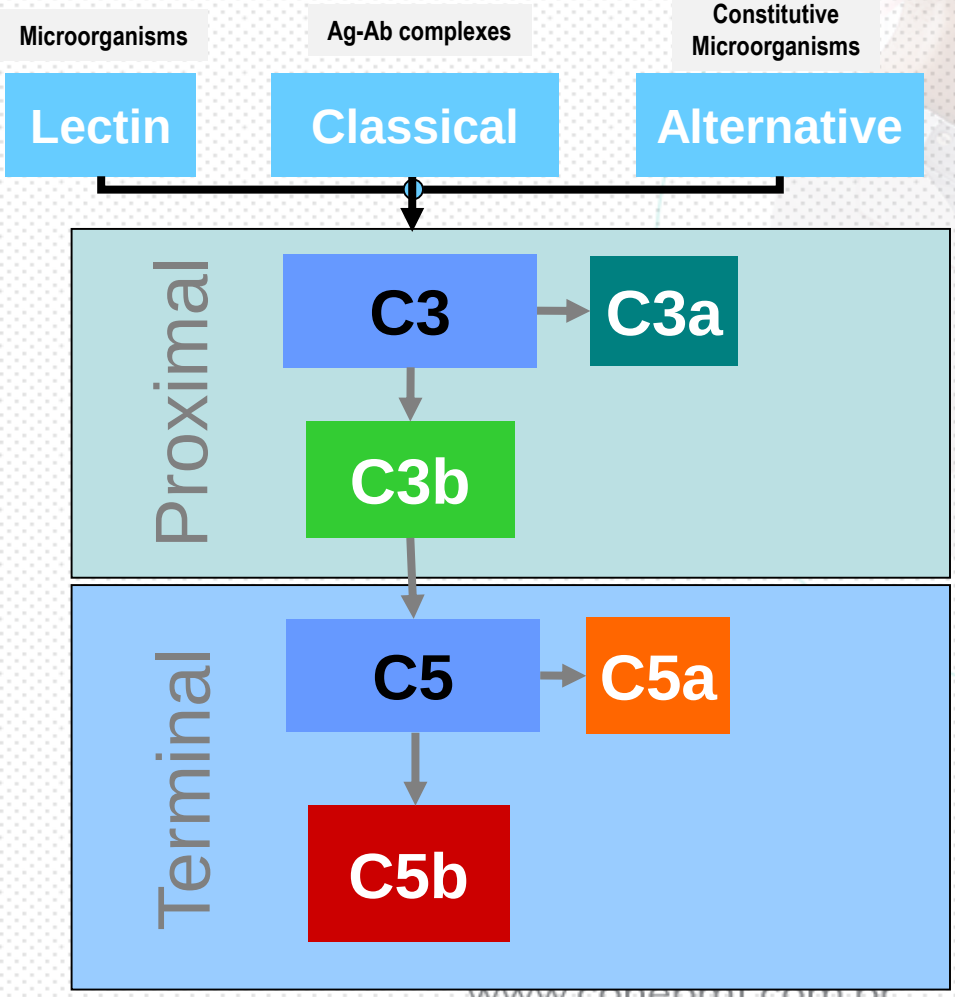
Genetic abnormalities and clinical outcomes in aHUS

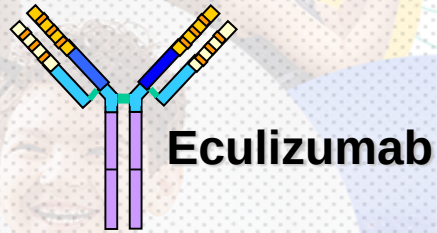
Table 2. Genetic Abnormalities and Clinical Outcome in Patients with Atypical Hemolytic–Uremic Syndrome.*

Gene	Protein Affected	Main Effect	Frequency	Response to Short-Term Plasma Therapy†	Long-Term Outcome‡	Outcome of Kidney Transplantation
			%			
CFH	Factor H	No binding to endothelium	20–30	Rate of remission: 60% (dose and timing dependent)	Rate of death or ESRD: 70–80%	Rate of recurrence: 80–90%§
CFHR1/3	Factor HR1, R3	Anti–factor H antibodies	6	Rate of remission: 70–80% (plasma exchange combined with immunosuppression)	Rate of ESRD: 30–40%	Rate of recurrence: 20%¶
MCP	Membrane cofactor protein	No surface expression	10–15	No definitive indication for therapy	Rate of death or ESRD: <20%	Rate of recurrence: 15–20%¶
CFI	Factor I	Low level or low cofactor activity	4–10	Rate of remission: 30–40%	Rate of death or ESRD: 60–70%	Rate of recurrence: 70–80%§
CFB	Factor B	C3 convertase stabilization	1–2	Rate of remission: 30%	Rate of death or ESRD: 70%	Recurrence in one case
C3	Complement C3	Resistance to C3b inactivation	5–10	Rate of remission: 40–50%	Rate of death or ESRD: 60%	Rate of recurrence: 40–50%
THBD	Thrombomodulin	Reduced C3b inactivation	5	Rate of remission: 60%	Rate of death or ESRD: 60%	Recurrence in one case

Noris *N Engl J Med* 2009

Eculizumab blocks terminal complement pathway



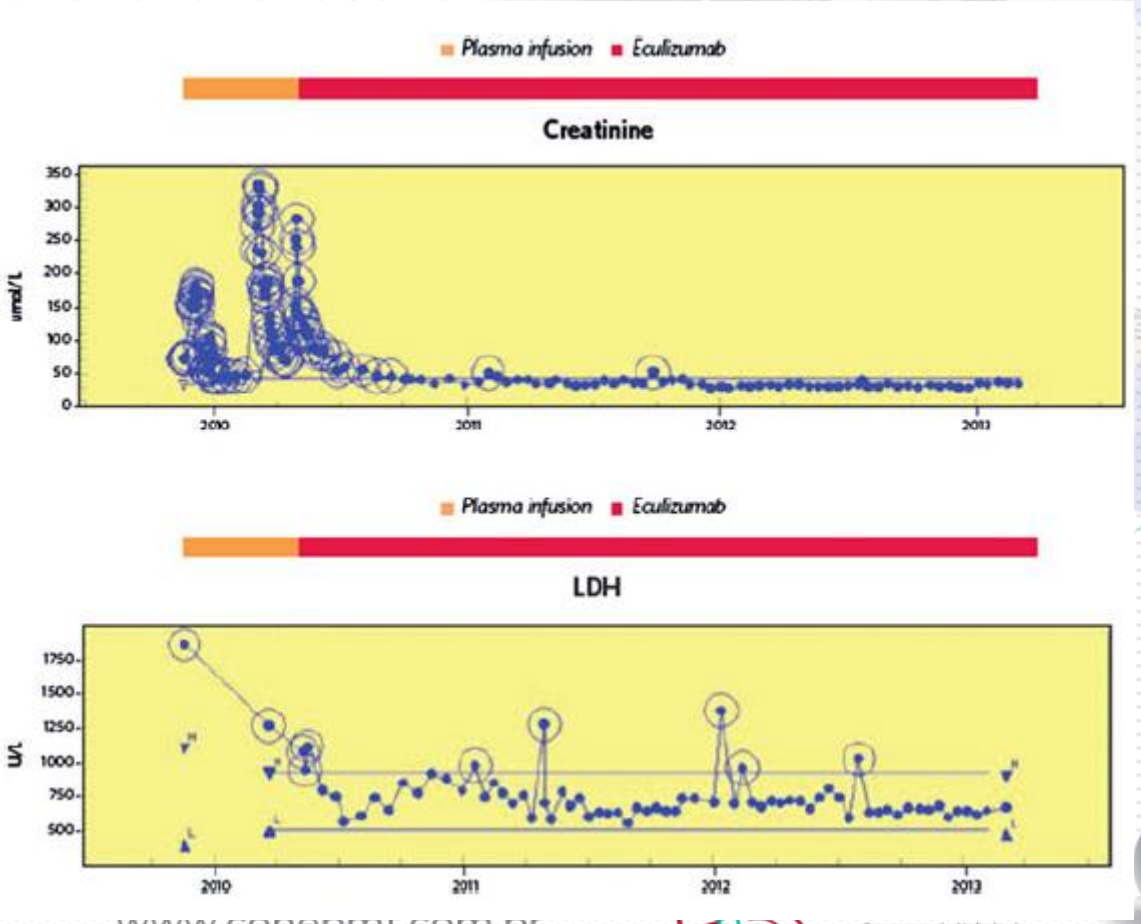


- Eculizumab binds with high affinity to C5
- Terminal complement activity is blocked
- Proximal functions of complement remain intact
  - Weak anaphylatoxin
  - Immune complex and apoptotic body clearance
  - Microbial opsonization

Figueroa *Clin Microbiol Rev* 1991 - Walport *N Engl J Med* 2001

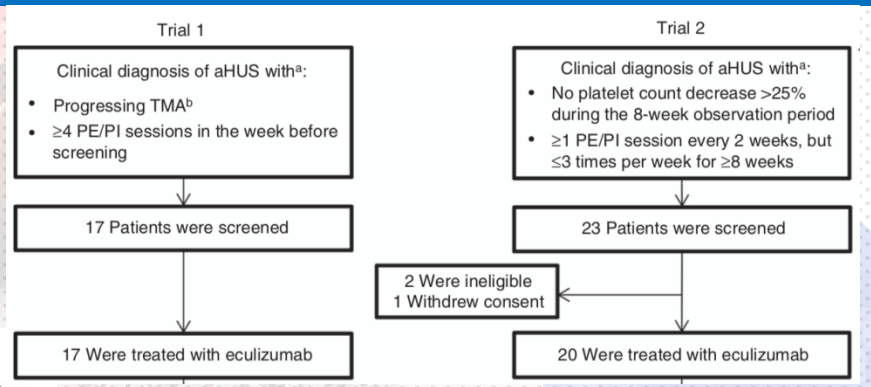
Efficacy of eculizumab in aHUS: Case report

Carter *Nephrology* 2017

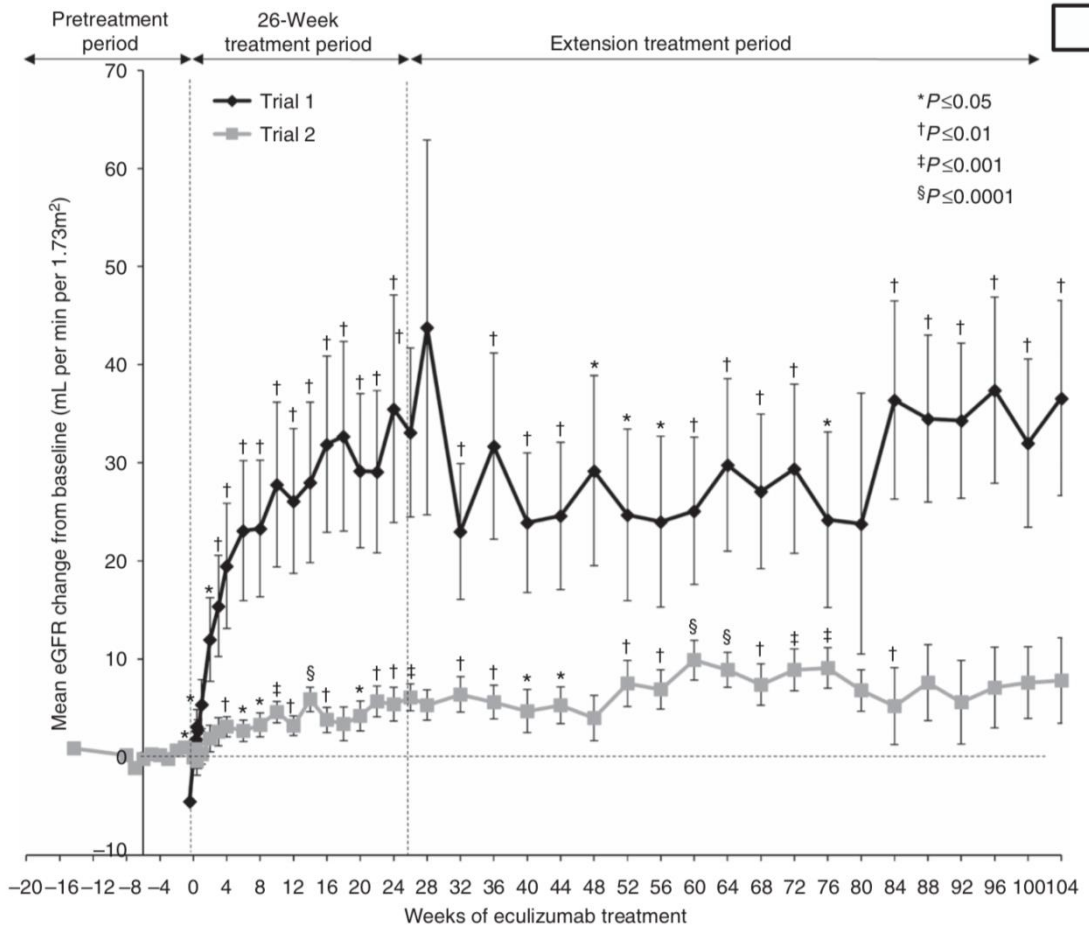


Efficacy of eculizumab in aHUS: Case series

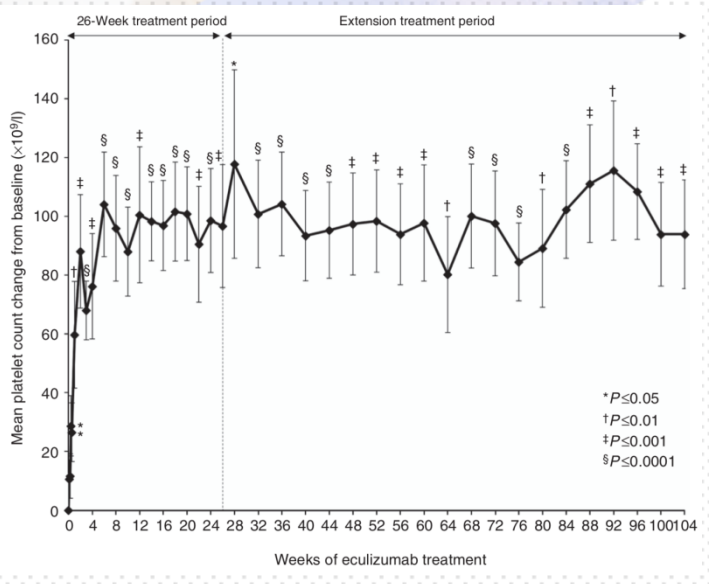
Licht *Kidney Int* 2015



Evolution of GFR change from baseline

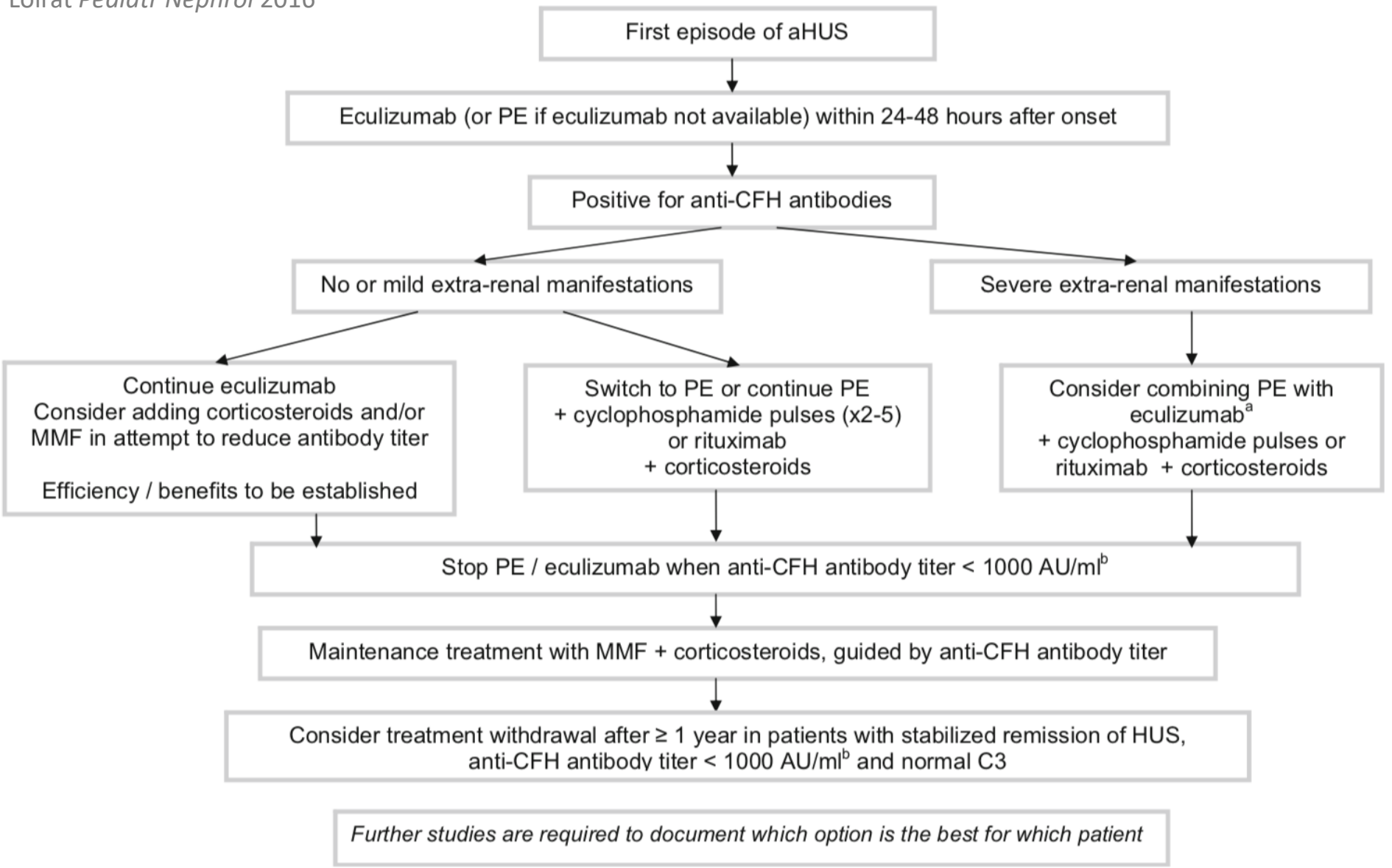


Evolution of platelet count



Proposed treatment algorithm for anti-CFH antibody-associated HUS

Loirat *Pediatr Nephrol* 2016



Comments on eculizumab

Table 4 Recommended eculizumab dosing regimen for patients with atypical HUS (aHUS)

Patient body weight	Induction regimen	Maintenance regimen
40 kg and over	900 mg weekly x 4 doses	1,200 mg at week 5; then 1,200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

- Eculizumab offers to children with aHUS the best chance of sustained remission and full rescue of renal function
- The best way to monitor eculizumab treatment in the clinical practice has yet to be established (CH50 level?)
- Prospective trials are required to establish if eculizumab withdrawal is safe, in which patients according to genetic background, and when.

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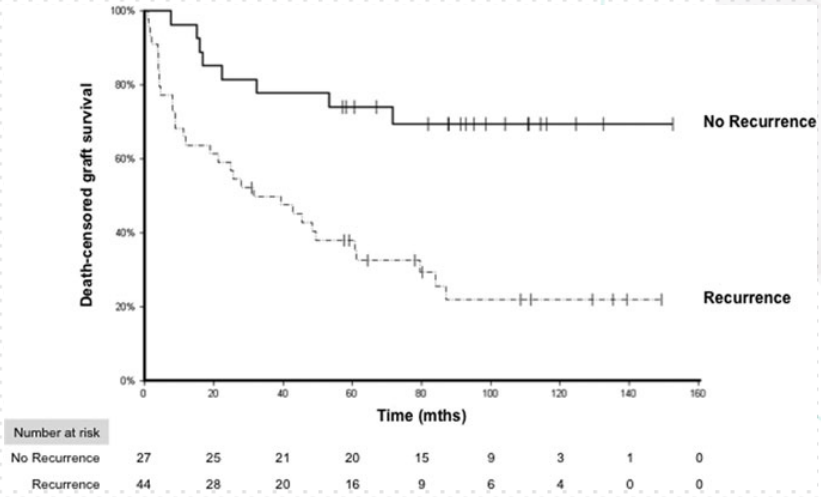
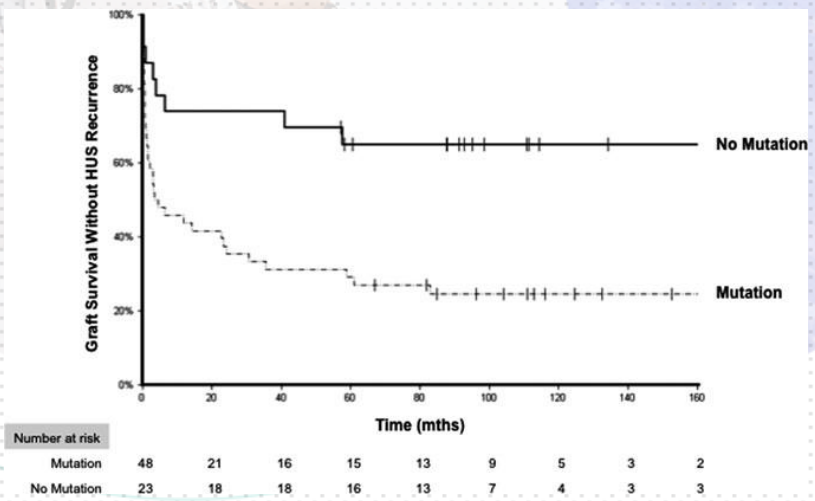
aHUS - Transplantation

aHUS carries a >50% risk of ESRD
aHUS is responsible for 2% to 5 % of ESRD in children
Overall recurrence rate: 50-80%
Median time to recurrence: 30 days [0 day – 16 yrs]

Biological defect	*% of aHUS*	*% disease recurrence*	*% graft loss*
ADAMTS-13 deficiency	<5	+++	
Methylmalonic aciduria		++	
DGKE mutation		0	
Anti-factor H antibodies	5-10	Low	
Factor H mutation	20-30	**50-100**	**75-95**
MCP/CD46 mutation	10-15	<20	
Factor I mutation	10-15	**80-90**	**100**
Factor B mutation	<5	**100**	
C3 mutation	5-10	**50**	
THBD (thrombomodulin) mutation	<5	5	
No gene mutation	30-40	**60**	**85**

Death-censored graft survival after renal Tx





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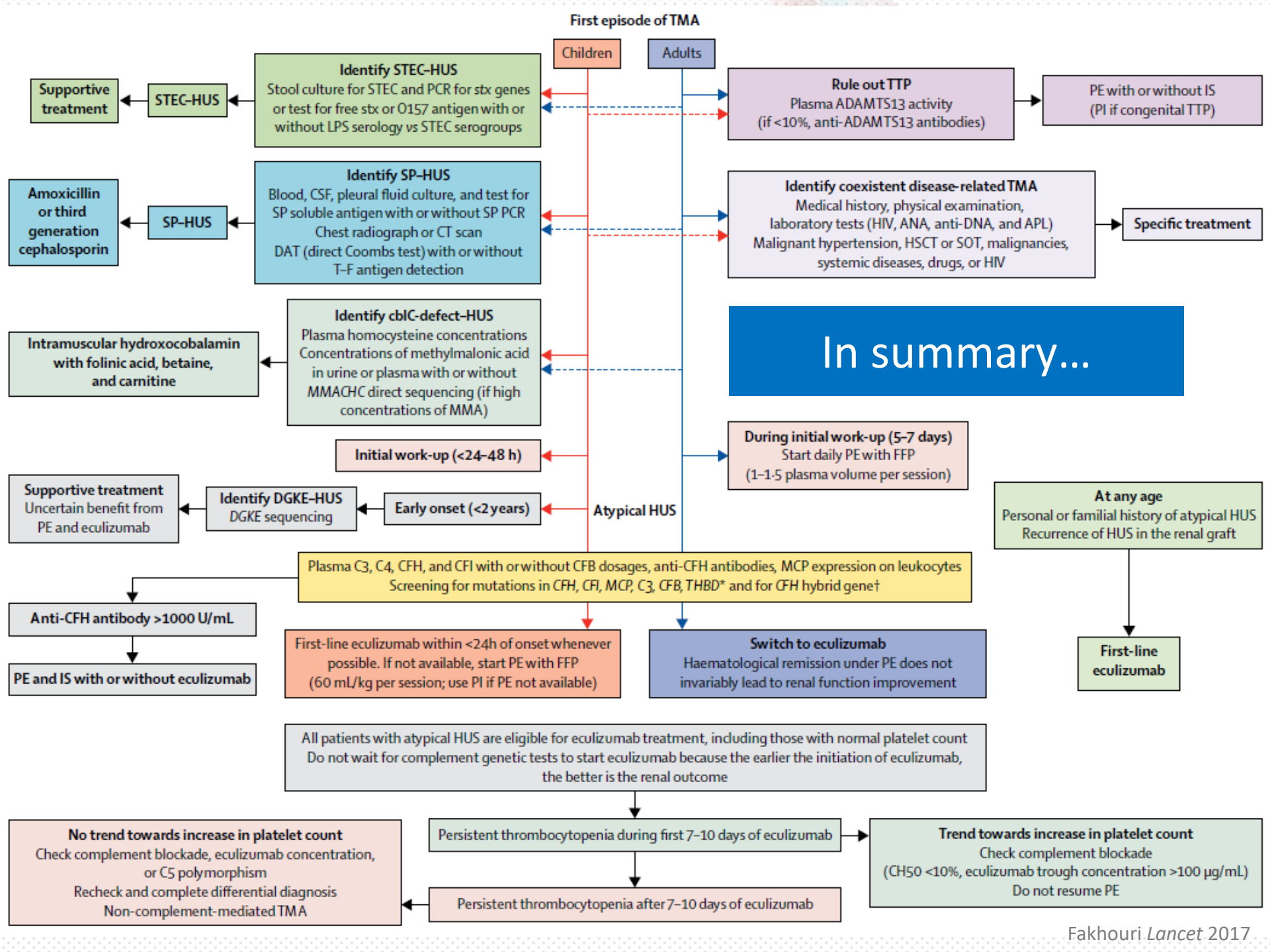
IPNA TEACHING COURSE

Le Quintrec *Am J Transplant* 2013

Use of Eculizumab post-Tx

- Anti-meningococcal immunization
- 375 mg/m^2 - Initially 1x week, then 1x 2 weeks
- To be continued lifelong?
- Individualized management according to
  - CH50 levels
  - Free eculizumab levels?



Fakhouri *Lancet* 2017


Thank you for your attention!