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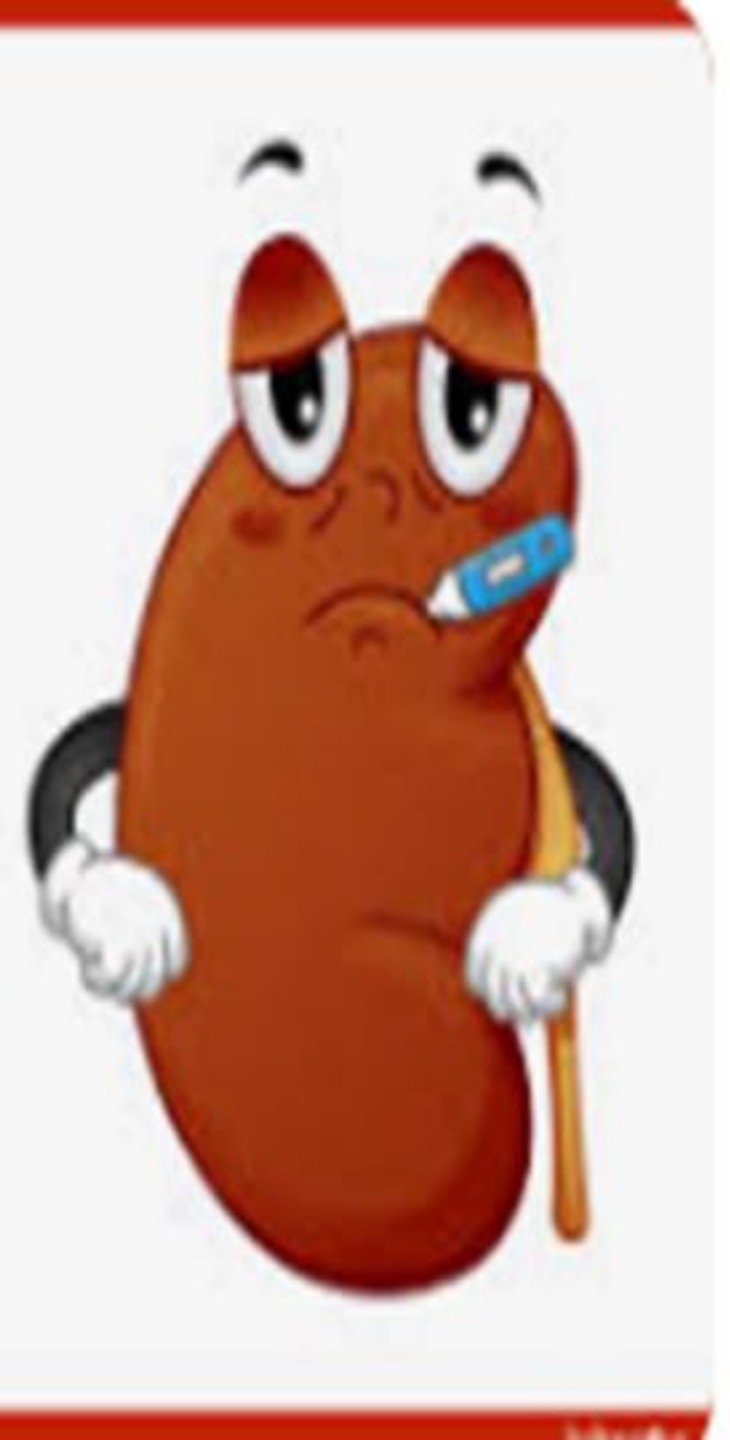
Late sequalae of HUS

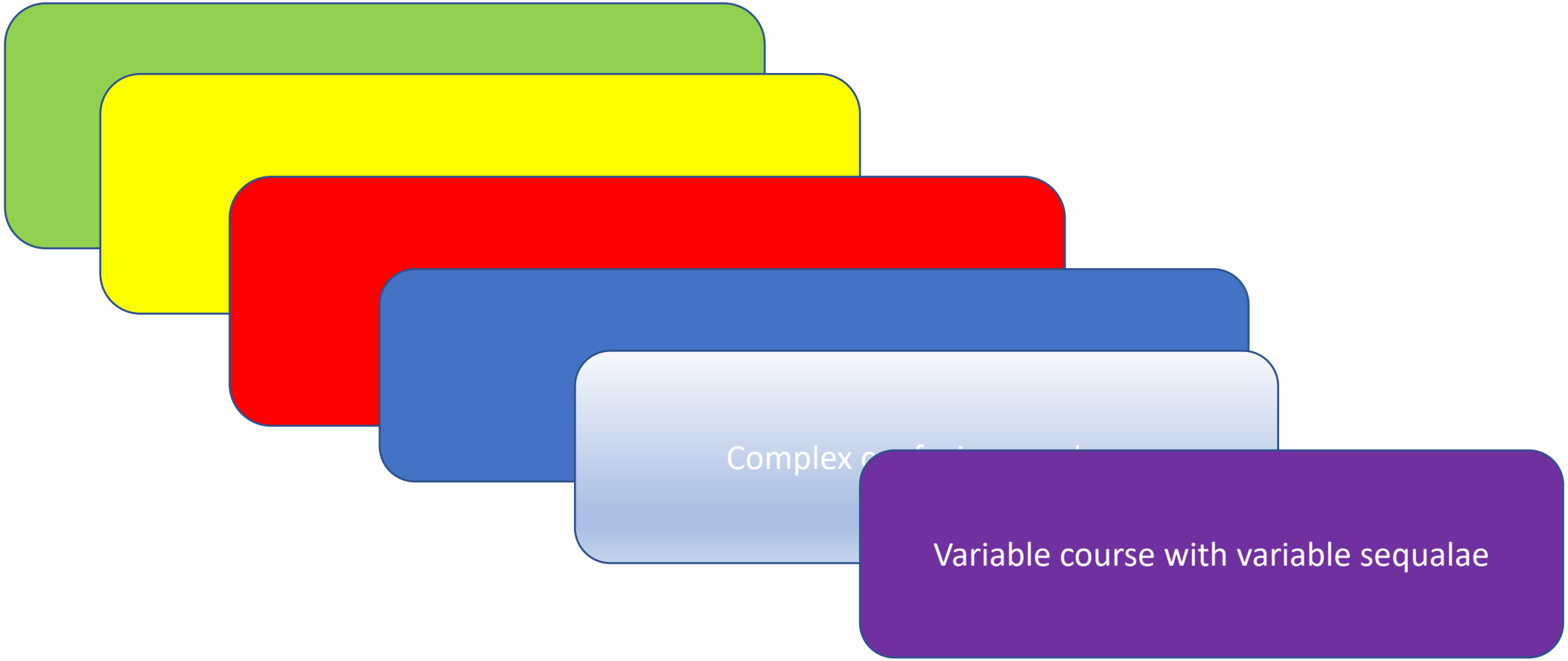
ASS. PROF AHLAM BADAWY

ASSIUT UNVERSITY



AGENDA

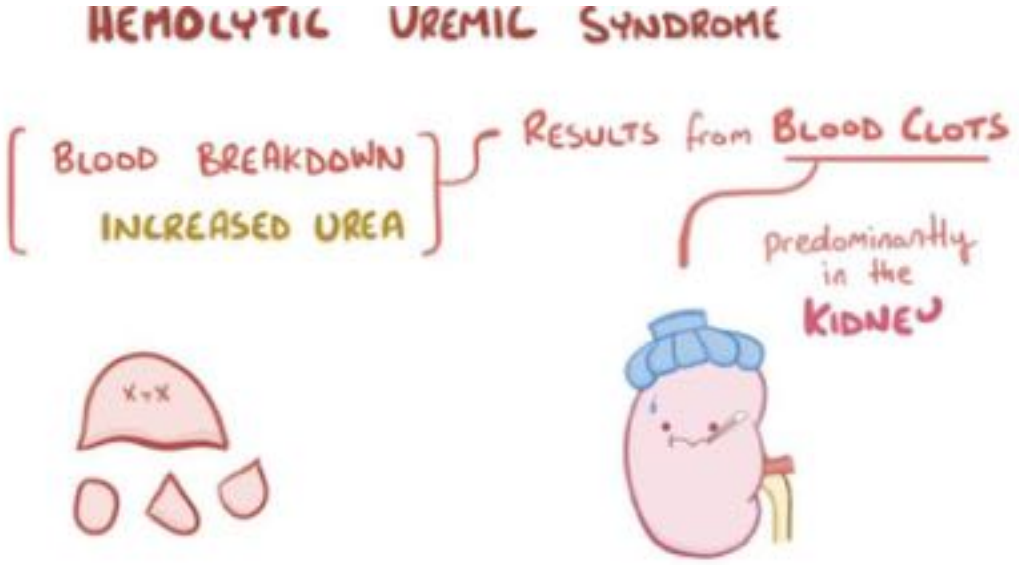
- Dilemma of etiology and and its effects on late sequalae.
- Plasma exchange and its effect on late sequalae.
- Eculizemab and late sequalae



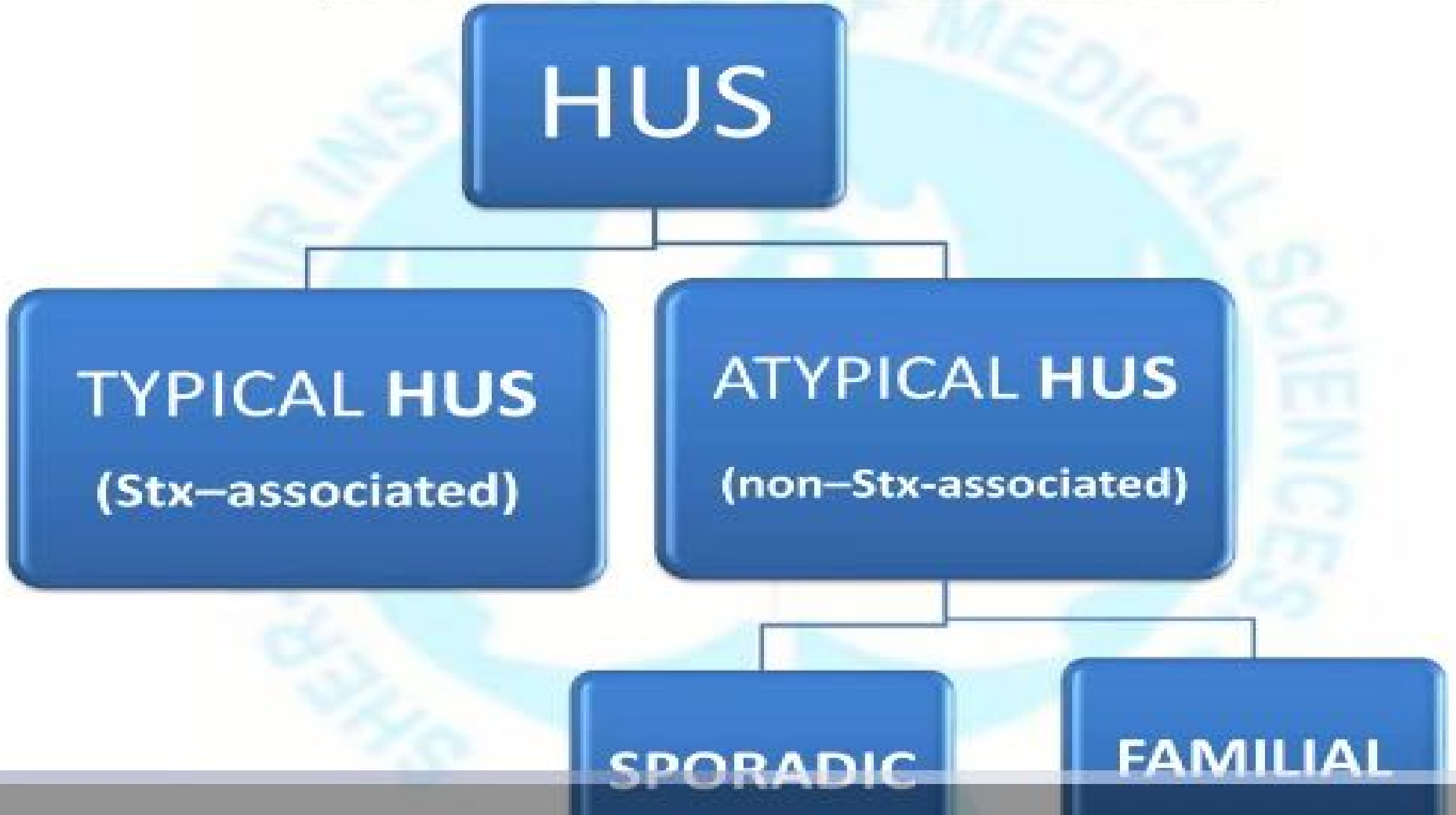
TMA

The percentage of HUS patients presenting with chronic renal complications varies considerably from one series to another

- cohorts were of variable sizes
- large percentages of pts were lost to follow up
- duration of the observation period was too short
- Variable etiological factors



CLASSIFICATION OF HUS



CLASSIFICATION OF HUS / TTP ACCORDING TO ETIOPATHOGENESIS

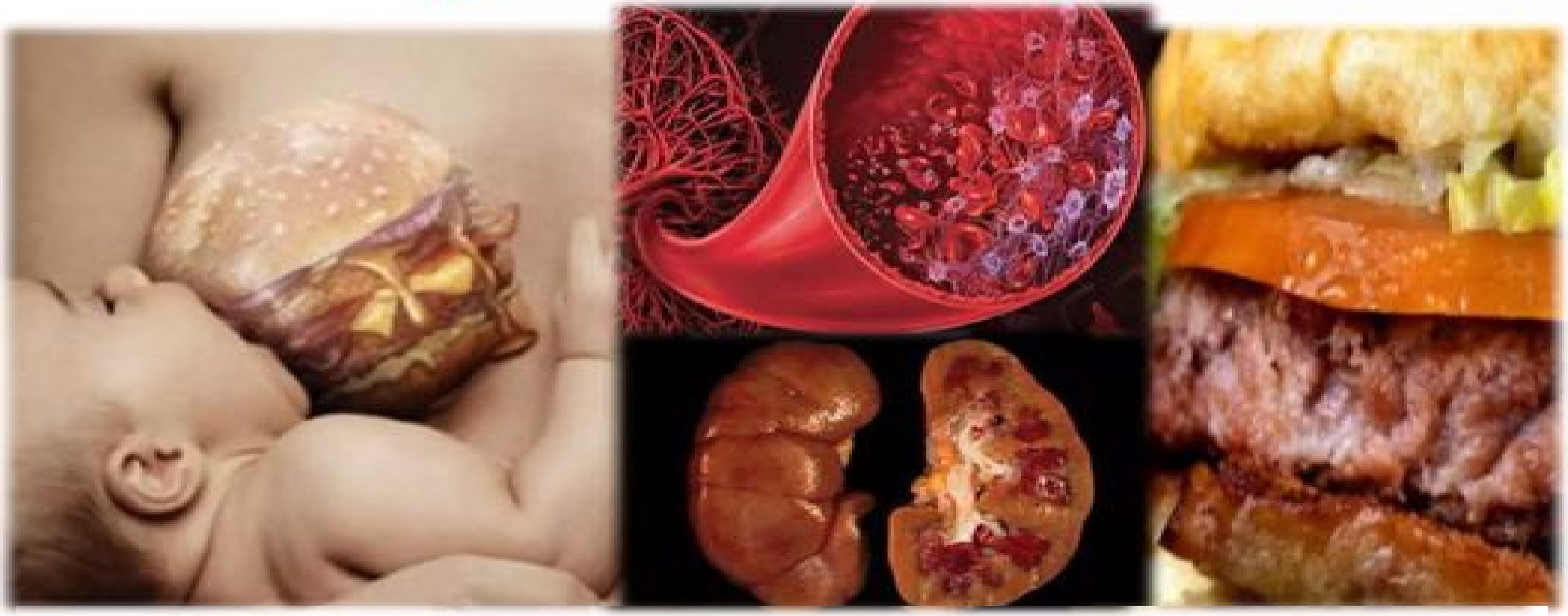
➢ **Type of HUS / TTP → Specific Cause**

- Infection related
  - Shiga toxin producing E.coli/Shigella
  - Pneumococcal infection
  - HIV
  - Other viral or bacterial infections

  → **Typical**
- Complement factor abnormality
  - Factor H deficiency
  - Factor I deficiency
- Miscellaneous
  - CTD
  - Drugs
  - Malignancy

  → **Atypical**

Hemolytic-uremic syndrome



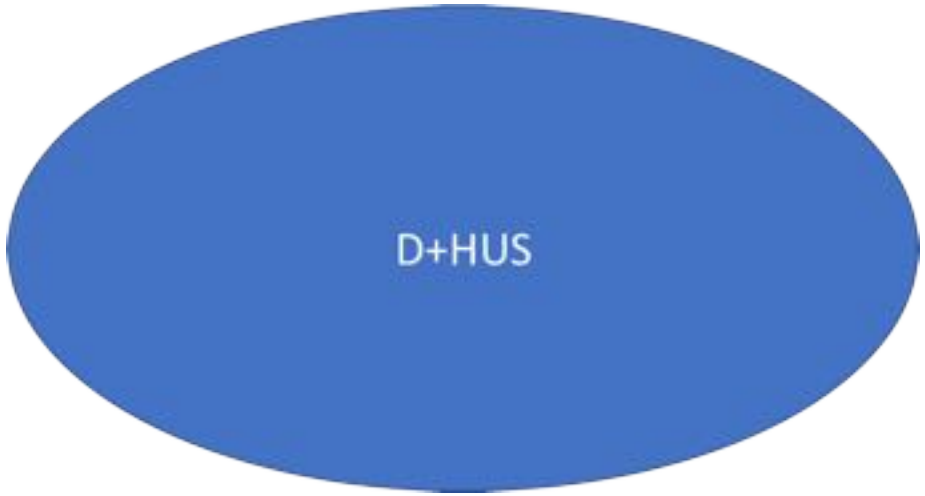
Post-infectious hemolytic uremic syndrome (HUS)

Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression

Amit X Garg [1], Rita S Suri, Nick Barrowman, Faisal Rehman, Doug Matsell, M Patricia Rosas-Arellano, Marina Salvadori, R Brian Haynes, William F Clark

Affiliations + expand

PMID: 12966129 DOI: 10.1001/jama.290.10.1360



2003

Death or ESRD occurs in about 12% of patients with diarrhea-associated HUS, and 25% of survivors demonstrate long-term renal sequelae.

Home › European Journal of Pediatrics › Article

Hemolyti… syndrome in Sy… …ide surveillance

D+HUS

D - HUS

…an Knowledge Bank

Among the children with D- HUS

two patients (50%) were in end-stage renal failure

one s…

Two c…

No se…

After the acute episode all patients must be followed for at least 5 years, and severely affected patients should be followed indefinitely if there is proteinuria, hypertension or a reduced glomerular filtration rate (GFR).

BMC Infectious Diseases

BMC Infect Dis. 2016; 16: 285.
Published online 2016 Jun 13. doi: 10.1186/s12879-016-1627-7

10 years

Clinical features, therapeutic interventions and long-term aspects of haemolytic-uremic syndrome in Norwegian children: a nationwide retrospective study from 1999–2008

Gaute Reier Jenssen,✉ Line Vold, Eirik Hovland, Hans-Jacob Bangstad, Karin Nygård, and Anna Bjerre

D+HUS

D - HUS

- 8/21 of D+HUS and 4/7 of D-HUS had persistent proteinuria
- 5/19 D+HUS and 4/5 D−HUS had persistent hypertension
- Two D+HUS and one D−HUS patient were diagnosed with chronic kidney disease
- one D+HUS patient required a renal transplantation.

Scientifica

Scientifica (Cairo). 2012; 2012: 341860.
Published online 2012 Dec 31. doi: 10.6064/2012/341860

PMCID: PMC3820622
PMID: 24278685

Hemolytic Uremic Syndrome: Late Renal Injury and Changing Incidence—A Single Centre Experience in Canada

Pierre Robitaille,* Marie-José Clermont, Aïcha Mérouani, Véronique Phan, and Anne-Laure Lapeyraque

Ten years or more after-HUS :
(9.4%) patients demonstrated serious complications and (25.9%) mild-to-moderate, including (16%) microalbuminuria
total sequelae, 35.3%.

STEC HUS

Review > Pediatr Nephrol. 2013 Nov;28(11):2097-105. doi: 10.1007/s00467-012-2383-6. Epub 2013 Jan 4.

Long-term outcomes of Shiga toxin hemolytic uremic syndrome

Joann M Spinale [1], Rebecca L Ruebner, Lawrence Copelovitch, Bernar

Affiliations + expand

PMID: 23288350 DOI: 10.1007/s00467-012-2383-6

STEC-HUS

70% of patients recover completely from the acute episode
15-30% proteinuria;
5-15% hypertension

Most renal sequelae are minor abnormalities, such as treatable hypertension and/or variable proteinuria.
Most of the patients who progress to ESKD do not recover normal renal function after the acute episode.
Length of anuria (more than 10 days) and prolonged dialysis are the most important risk factors for a poor acute and long-term renal outcome.

Pediatric Kidney Disease. 2016 Jun 17 : 653–731.
Published online 2016 Jun 17. doi: 10.1007/978-3-662-52972-0_26

PMCID: PMC71

Postinfectious Hemolytic Uremic Syndrome

Guest Editor (s): Denis F. Geary[1] and Franz Schaefer[2]
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Denis F. Geary, Phone: +11(416) 813-6283, Email: Denis.Geary@sickkids.ca.
Contributor Information.

Martin Bitzan[✉3] and Anne-Laure Lapeyraque[4]

Post-infectious hemolytic uremic syndrome (HUS) is caused by specific pathogens in patients with no identifiable HUS-associated genetic mutation or autoantibody.

The outcome of STEC-HUS is generally favorable, but chronic kidney disease, permanent extrarenal, mainly cerebral complication and death (in less than 5 %) occur

long-term follow-up is recommended.

There is emerging evidence of (transient) complement activation in post-infectious forms of HUS

Pediatr Nephrol. 2020; 35(9): 1749–1759.
Published online 2020 Apr 22. doi: 10.1007/s00467-020-04560-0
PMCID: PMC7385025
PMID: 32323005

Hemolytic uremic syndrome caused by Shiga toxin–producing *Escherichia coli* in children: incidence, risk factors, and clinical outcome

Elisa Ylinen,[✉1] Saara Salmenlinna,[2] Jani Halkilahti,[2] Timo Jahnukainen,[1] Linda Korhonen,[3,4] Tiia Virkkala,[1] Ruska Rimhanen-Finne,[2] Matti Nuutinen,[3,4] Janne Kataja,[5] Pekka Arikoski,[6] Laura Linkosalo,[7] Xiangpin[illegible][8] Andreas Matussek,[8,9] Hannu Jalanko,[1] and Harri Saxén[1]

- The overall outcome of children with HUS was good, with no mortality.
- 10% had mildly decreased kidney function (GFR 60–90 mL/min/1.73 m2)
- 2.6% had more severely affected GFR (31 and 45 mL/min/1.73 m2) at the end of follow-up.
- 2.6% [illegible]dney tran[illegible]
- 13% [illegible]
- 10% had persistent hypertension at the end of follow-up.
- 2.6% suffered from neurological long-term complications.

Finally, approximately one quarter of the patients develop long-term renal or neurological sequelae.

ATYPICAL HUS

COMPLICATIONS

Mortality/Morbidity - Atypical HUS

- patients have poor outcomes
- 50% progressing to ESRD (50% - sporadic , 60% in familial forms) or irreversible brain damage.
- As many as 25% die during the acute phase
- Recurrence rate in patients receiving renal transplants is as high as 50%; (with graft loss >90%)

Clin J Am Soc Nephrol. 2013 Apr 5; 8(4): 554–562.
Published online 2013 Jan 10. doi: 10.2215/CJN.04760512
PMCID: PMC3613948
PMID: 23307876

Genetics and Outcome of Atypical Hemolytic Uremic Syndrome: A Nat vide French Series Comparing Children and Adults

Véronique Fremeaux-Bacchi, Fadi Fakhouri, Arnaud Garnier, Frank Bienaimé, Marie-Agnès stéphanie Ngo, Bruno Moulin, Aude Servais, François Provot, Lionel Rostaing, Stéphan es Deschênes, Yv Julien Zuber, and Chantal Loirat

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45 ms

Pediatrics

Adults

214

- ❑ Renal involvement was more severe in adults
- ❑ The mortality rate was significantly higher in children than in adults
- ❑ 56 % of the adults and 29% of the children required renal replacement therapy or died within 1 year of follow-up
- ❑ Relapses occurred in 43% of children and 35% of adults who survived the first aHUS episode without reaching ESRD

Pediatr Nephrol. 2012; 27(8): 1283–1291.
Published online 2012 Mar 13. doi: 10.1007/s00467-012-2131-y

7.5

Atypical hemolytic uremic syndrome in children: complement mutations and clinical characteristics

Lianne M. Geerdink ✉1 Dineke Westra,[1] Joanna A. E. van Wijk,[2] Eiske M. Dorresteijn,[3] M[illegible]rc R. Lilien,[4]
Jean-C[illegible] [7] [8] [9] [illegible]s P. van den Heuvel,[1,10]
an[illegible]

[illegible]netics and outcome a cohort of 45 Dutch and Belgian children pediatric aHUS patients

50% of this pediatric aHUS cohort, a genetic defect in complement-regulating genes

50% of this pediatric aHUS cohort, without a gentic defect in complement-regulating genes

Complete remission: normalization of hematologic parameters (Hb >10 g/dl, thrombocytes >150x109/l, LDH <450U/l) and renal function [glomerular filtration rate (GFR) >80 ml/min/1.73 m2, no proteinuria].

partial remission : hematologic normalization was seen, but with renal sequelae (GFR <80 ml/min/1.73 m2 and/or proteinuria and/or hypertension).

- **outcome of first episode:**

  15% with a genetic defect was complete remission reached after the first episode, compared with 38% in the other group.

- **Long-term outcome:**

- **Almost half of the aHUS patients (n = 21) had a relapse.**
- **In the group with a genetic anomaly, 65% of patients relapsed versus 32% in without known anomalies.**
- **Most relapses occurred after a viral infection**
- **Time between aHUS onset and the first relapse varied widely, a maximum of 8.5 years.**
- **Ten patients with a relapse were initially treated with plasma therapy, eight of whom received chronic plasma therapy.**
- **Seven patients received a total number of 13 renal transplants, but in 10/13 grafts, aHUS recurred. Three of these patients had familial aHUS.**

- **54% chronic hypertension**
- **47%, proteinuria sustained.**
- **In four patients, neurological involvement was seen later during the course of disease. (seizures ,reduced consciousness , one patient had dysphasia and sensibility disorders).**
- **Another patient developed necrotizing pancreatitis with transient diabetes mellitus 10 years after first presentation,**

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Blood. 2006 Aug 15; 108(4): 1267–1279.
Prepublished online 2006 Apr 18. doi: 10.1182/blood-2005-10-007252
PMCID: PMC1895874
PMID: 16621965

Genetics of HUS: the impact of *MCP*, *CFH*, and *IF* mutations on clinical presentation, response to treatment, and outcome

Jessica Caprioli, Marina Noris, Simona Brioschi, Gaia Pianetti, Federica Castelletti, Paola Betti
Elena Bresin, Linda Cassis, Sara Gamba, Francesca Porrati, Sara Bucchioni, Giuseppe Montef
M. K. Liszewski, David Kavanagh, John P. Atkinson, Giuseppe Remuzzi, and for the Internation
and Familial HUS/TTP

156 Non STEC HUS

- MCP had a better prognosis than CFH-mutated and nonmutated patients.
- Kidney transplantation outcome was favorable in patients with MCP mutations, whereas the outcome was poor in patients with CFH and IF mutations due to disease recurrence.

- In MCP-mutated patients: plasma treatment did not impact the outcome significantly.
- This study documents the outcome of the disease are influenced by the genotype so we need tailored treatments.

Atypical HUS

Outcome of Atypical Hemolytic Uremic Syndrome According to Associated Genetic Abnormality					
Affected Gene	Affected Protein (Main Effect)	Frequency in aHUS (%)	Rate of Remission with Plasma Exchange* (%)	Mortality (5-10 yr) or ESRD (%)	Rate of Recurrence After Kidney Transplant (%)
CFH	Factor H (no binding to endothelium)	30	60 (dose and timing dependent)	70-80	60-70
CFHL1, CFHL3	Factor HR1, R3 (anti–factor H antibodies)	5-10	70-80 (combined with immunosuppression)	30-40	40
MCP	Membrane cofactor protein (no surface expression)	10-15	No indication to plasma exchange	<20	15-20
CFI	Factor I (low levels/low cofactor action)	4-10	30-40	60-70	70-80
CFB	Factor B (C3 convertase stabilization)	1-2	30	70	One case reported
C3	Complement C3 (resistance to C3b inactivation)	8-10	40-50	60	40-50
THBD	Thrombomodulin (reduced C3b inactivation)	4-5	60	60	One case reported

Table 29-3 **Outcome of atypical hemolytic uremic syndrome (aHUS) according to the associated genetic abnormality.** *Complete remission or hematologic remission with renal sequelae.

PLoS One. 2017; 12(5): e0177894.
Published online 2017 May 18. doi: 10.1371/journal.pone.0177894
PMCID: PMC5436831
PMID: 28542627

Predictive features of chronic kidney disease in atypical haemolytic uremic syndrome

Matthieu Jamme,[1,2] Quentin Raimbourg,[3] Dominique Chauveau,[1,4] Amélie Seguin,[1,5] Claire Presne,[1,6] Pierre Perez,[1,7] Pierre Gobert,[1,8] Alain Wynckel,[1,9] François Provôt,[1,10] Yahsou Delmas,[1,11] Christiane Mousson,[1,12] Aude Servais,[1,13] Laurence Vrigneaud,[1,14] Agnès Veyradier,[1,15] Eric Rondeau,[#1,2] Paul Coppo,[#1,16,*] and French Thrombotic Microangiopathies Reference Centre[¶]

Giuseppe Remuzzi, Editor

Patients with mutations of CFH have the poorest prognosis with an up to 79% mortality or ESRD rate at 3 years

patients with MCP mutations mortality/ESRD rate is 20%

So identification of genetic mutation is imp to identify sequalae

LIMITATIONS

However, the assessment of aHUS prognosis from complement mutational analysis has limitations.

1. First, more than half of patients with poor renal outcome have no identifiable complement abnormalities
2. genetic analysis in aHUS still requires skill and time.
3. The results are not rapidly available for clinical practice

PLoS One. 2017; 12(5): e0177894.
Published online 2017 May 18. doi: 10.1371/journal.pone.0177894
PMCID: PMC5436831
PMID: 28542627

Predictive features of chronic kidney disease in atypical haemolytic uremic syndrome

Plasma therapy and renal sequalae

Plasma therapy and renal sequalae

- It has been proven difficult to retrospectively assess the effect of such treatment in patients
  - who present with variable severity of renal failure;
  - who have various types of complement dysregulation;
  - who received plasma therapy with a highly variable delay, intensity, and duration.
- Finally, the efficiency of plasma therapy remains unproven in aHUS today,

PLoS One. 2017; 12(5): e0177894.
Published online 2017 May 18. doi: 10.1371/journal.pone.0177894
PMCID: PMC5436831
PMID: 28542627

Predictive features of chronic kidney disease in atypical haemolytic uremic syndrome

so what?

Eculizumab and renal sequalae

Clinical Trial > N Engl J Med. 2013 Jun 6;368(23):2169-81. doi: 10.1056/NEJMoa1208981.

Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome

enbaum, S Babu, C Bedrosian, C Bingham, D J Cohen, p, D Fouque, R R Furman, O Gaber, M Herthelius, Mariat, J Menne, B Moulin, J Nürnberger, M Ogawa, B Severino, N S Sheerin, A Trivelli, L B Zimmerhackl,

Abstract

Background: Atypical hemolytic-uremic syndrome is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy. Plasma exchange or infusion may transiently maintain normal levels of hematologic measures but does not treat the underlying systemic disease.

Methods: We conducted two prospective phase 2 trials in which patients with atypical hemolytic-uremic syndrome who were 12 [illegible] long-term extension phases [illegible] those with renal damage but no d[illegible] during plasma exchange or infusio[illegible] e in the platelet count (in trial 1)[illegible] the platelet count of >25%, no [illegible]

FDA 2011

Results: A total of 37 patien[illegible] of 64 and 62 weeks, respectively. Eculizumab resulted in increases in the platelet count; in trial 1, the mean increase in the count from baseline to week 26 was 73×10(9) per liter ($P<0.001$). In trial 2, 80% of the patients had thrombotic microangiopathy event-free status. Eculizumab was associated with significant improvement in all secondary end points, with continuous, time-dependent increases in the estimated glomerular filtration rate (GFR). In trial 1, dialysis was discontinued in 4 of 5 patients. Earlier intervention with eculizumab was associated with significantly greater improvement in the estimated GFR. Eculizumab was also associated with improvement in health-related quality of life. No cumulative toxicity of therapy or serious infection-related adverse events, including meningococcal infections, were observed through the extension period.

Conclusions: Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic-uremic syndrome. (Funded by Alexion Pharmaceuticals; C08-002 ClinicalTrials.gov numbers,

- **Dialysis was discontinued in four of five patients (80%) who had required dialysis at the time of initiation of eculizumab, and these patients remained dialysis-free throughout eculizumab treatment.**
- **Earlier initiation of eculizumab was associated with a significantly greater improvement in the estimated GFR throughout the treatment period**

KIDNEY INTERNATIONAL
An open access paper
www.nature.com

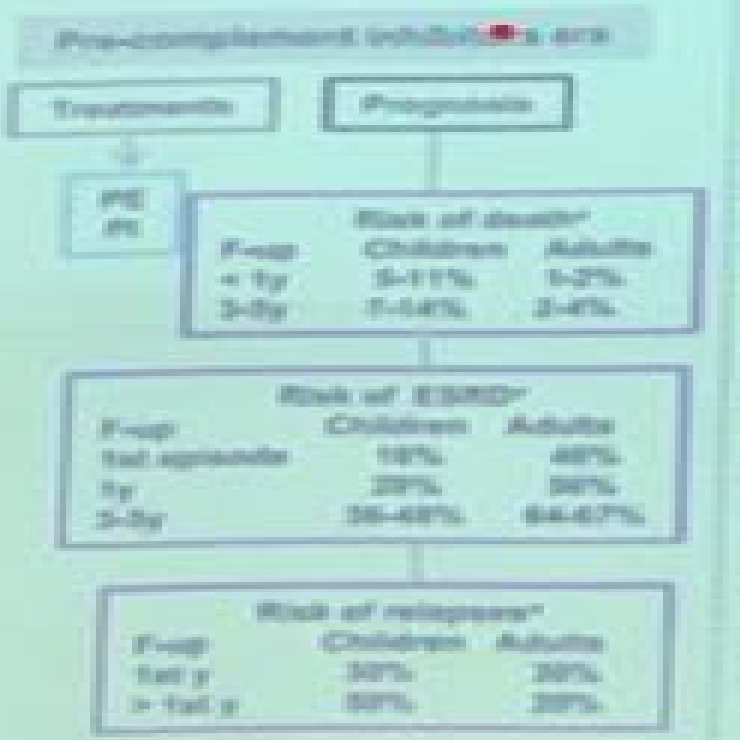
Kidney Int. 2015 May; 87(5): 1061–1073.
Published online 2015 Feb 4. doi: 10.1038/ki.2014.423
PMCID: PMC4424817
PMID: 25651368

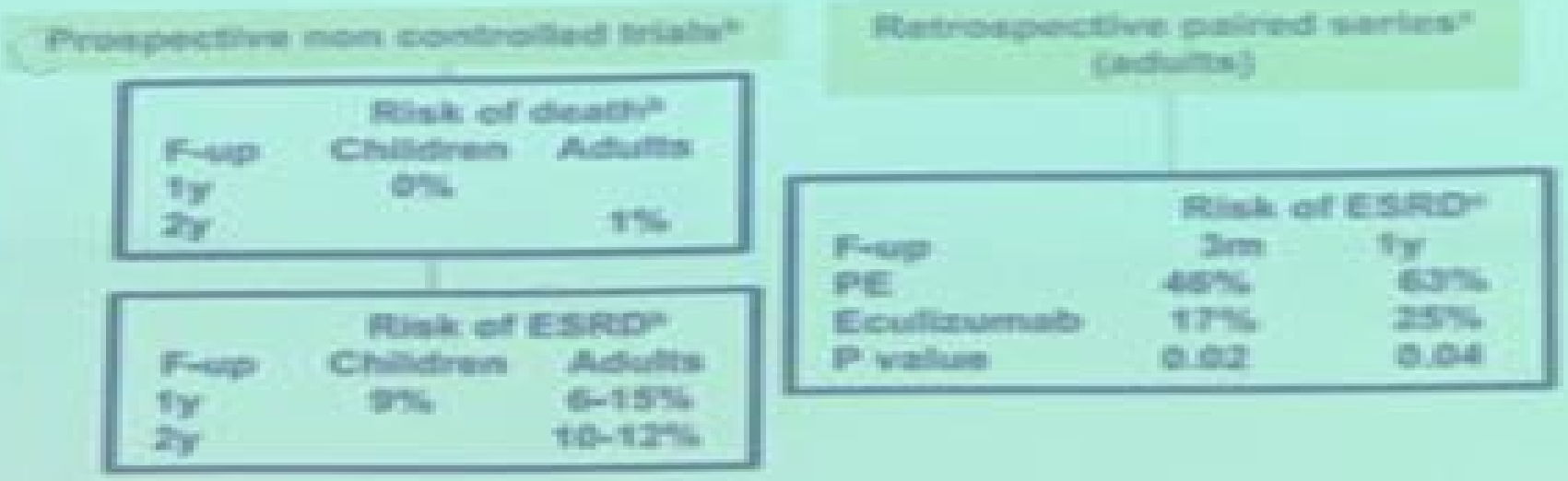
Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies

Christoph Licht,[1,*] Larry A Greenbaum,[2] Petra Muus,[3] Sunil Babu,[4] Camille L Bedrosian,[5] David J Cohen,[6] Yahsou Delmas,[7] Kenneth Douglas,[8] Richard R Furman,[9] Osama A Gaber,[10] Timothy Goodship,[11] Maria Herthelius,[12] Maryvonne Hourmant,[13] Christophe M Legendre,[14] Giuseppe Remuzzi,[15] Neil Sheerin,[16] Antonella Trivelli,[17] and Chantal Loirat[18]

2-year analysis found that the earlier clinical benefits achieved by eculizumab treatment of aHUS were maintained at 2 years of follow-up.

aHUS outcome before and after eculizumab





Fakhouri F, Loirat C. Semin Hematol. 2018

Eculizumab discontinuation and renal sequalae

Avoid Injury

Clinical Trial > Blood. 2021 May 6;137(18):2438-2449. doi: 10.1182/blood.2020009280.

Eculizumab discontinuation in children and adults with atypical hemolytic-uremic syndrome: a prospective multicenter study

- They conducted a prospective national multicenter open-label study to assess eculizumab discontinuation in children and adults with aHUS.
- Fifty-five patients (including 19 children) discontinued eculizumab (mean treatment duration, 16.5 months). (51%) had rare variants in complement genes, mostly in MCP (n = 12; 22%), CFH (n = 6; 11%), and CFI (n = 6; 10%).
- On follow-up, 13 patients (23%; 6 children and 7 adults) experienced aHUS relapse.
- female sex , presence of complement gene abnormality , increased sC5b-9 plasma level were associated with an increased risk of aHUS relapse
- Of the 13 relapsing patients, all of whom restarted eculizumab, 11 regained their baseline renal function and 2 had a worsening of their preexisting chronic kidney disease
- A strategy of eculizumab discontinuation in aHUS patients based on complement genetics is reasonable and safe.

Pediatr Nephrol. 2019; 34(11): 2261–2277.
Published online 2018 Nov 6. doi: 10.1007/s00467-018-4091-3
PMCID: PMC6794245
PMID: 30402748

Eculizumab in atypical hemolytic uremic syndrome: strategies toward restrictive use

Kioa L. Wijnsma,[#1] Caroline Duineveld,[#1,2] Jack F. M. Wetzels,[2] and Nicole C. A. J. van de Kar[✉1]

- **Initial guidelines suggested lifelong treatment and recommended prophylactic use of eculizumab in aHUS patients receiving a kidney transplant.**
- **Worldwide, there is an ongoing debate regarding the optimal dose and duration of treatment,**
- **Our current treatment protocol is based on restrictive use of eculizumab.**
- **Prospective monitoring will provide more definite proof of the feasibility of such restrictive treatment**

Close Monitoring

Ravulizumab and Renal sequalae

Clinical Trial > Kidney Int. 2020 Jun;97(6):1287-1296. doi: 10.1016/j.kint.2020.01.0

Epub 2020 Ma

The lon effectiv hemolytic uremic syndrome naïve to comple nt inhibitor treatment

treatment with ravulizumab resulted in rapidly improved hematologic and renal endpoints with no unexpected adverse events in adults

> Kidney Int Rep. 2021 Mar 24;6(6):1603-1613. doi: 10.1016/j.ekir.2021.03.884. eCollection 2021 Jun.

Long-Term Efficacy and Safety of the Long-Acting Comp Treat in Ad

Thomas Barbour [1], Marie Scully [2], Gema Ariceta [3], Spero Cataland [4], Katherine Garlo [5], Nils Heyne [6], Yosu Luque [7], Jan Menne [8], Yoshitaka Miyakawa [9], Sung-Soo Yoon [10], David Kavanagh [11] [12]; 311 Study Group Members

FULL TEXT LINKS

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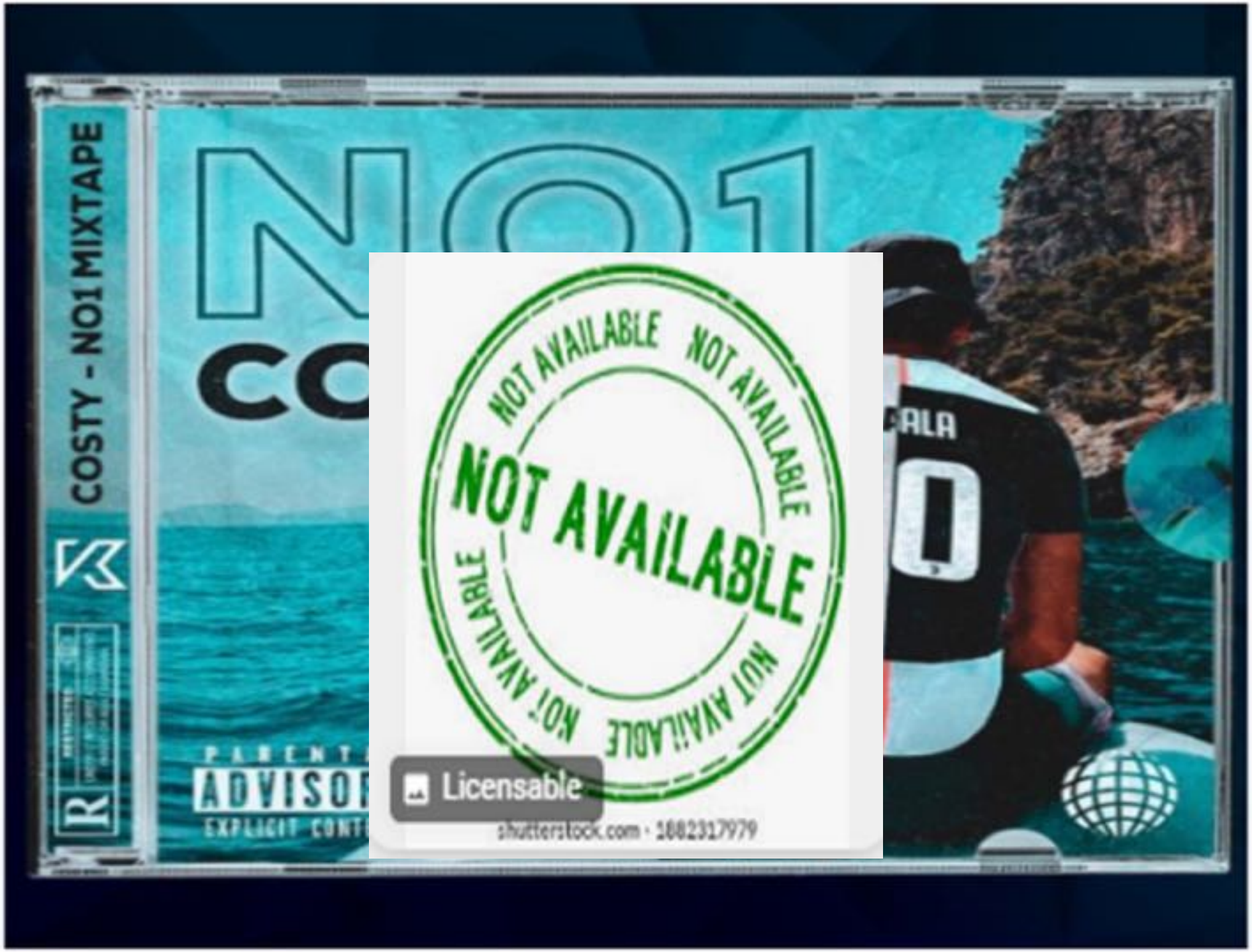
PMC

Cite

Collections

Ravulizumab provides additional clinical benefit beyond 6 months of treatment.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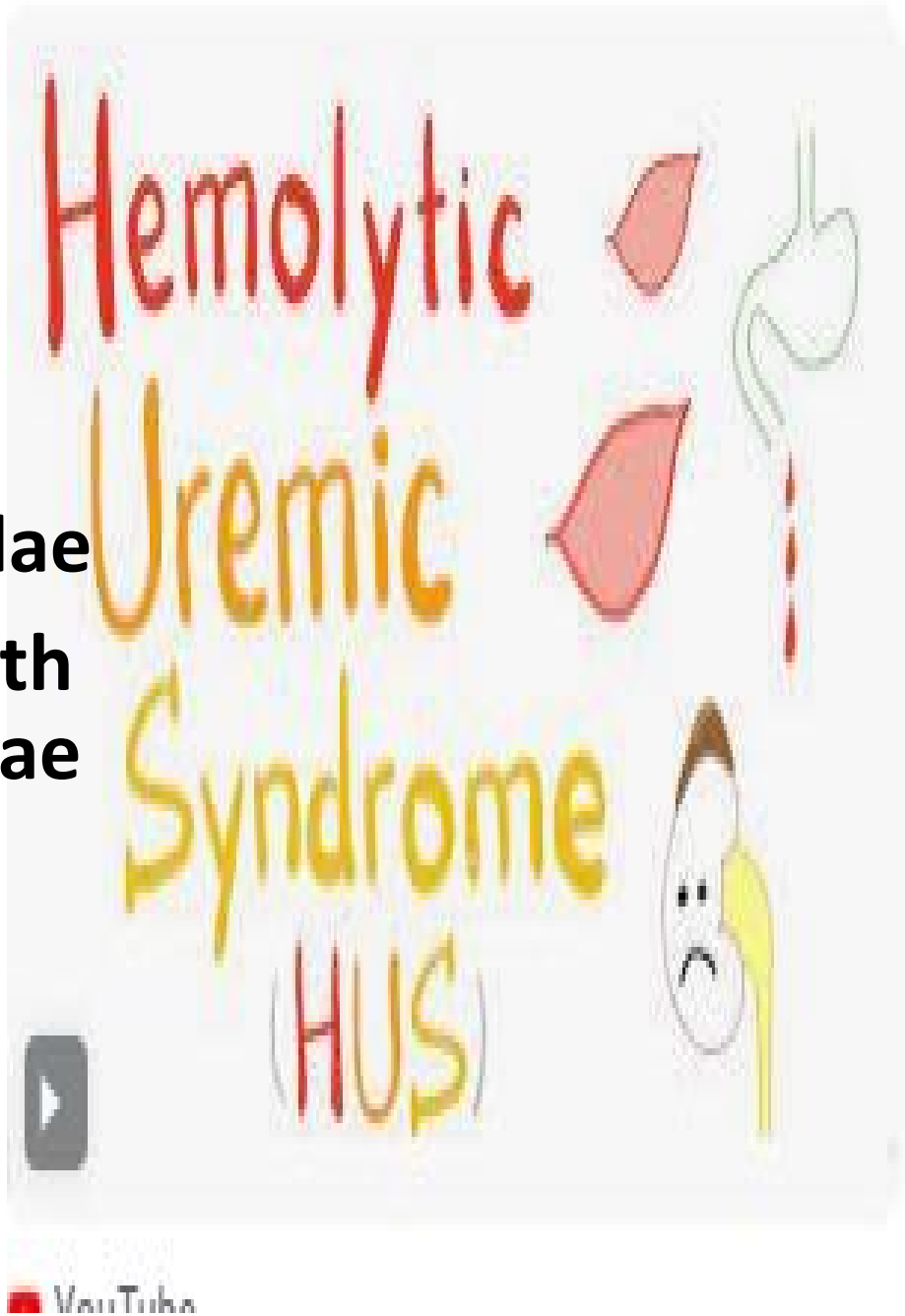
- REAL LIFE SEQUALAE

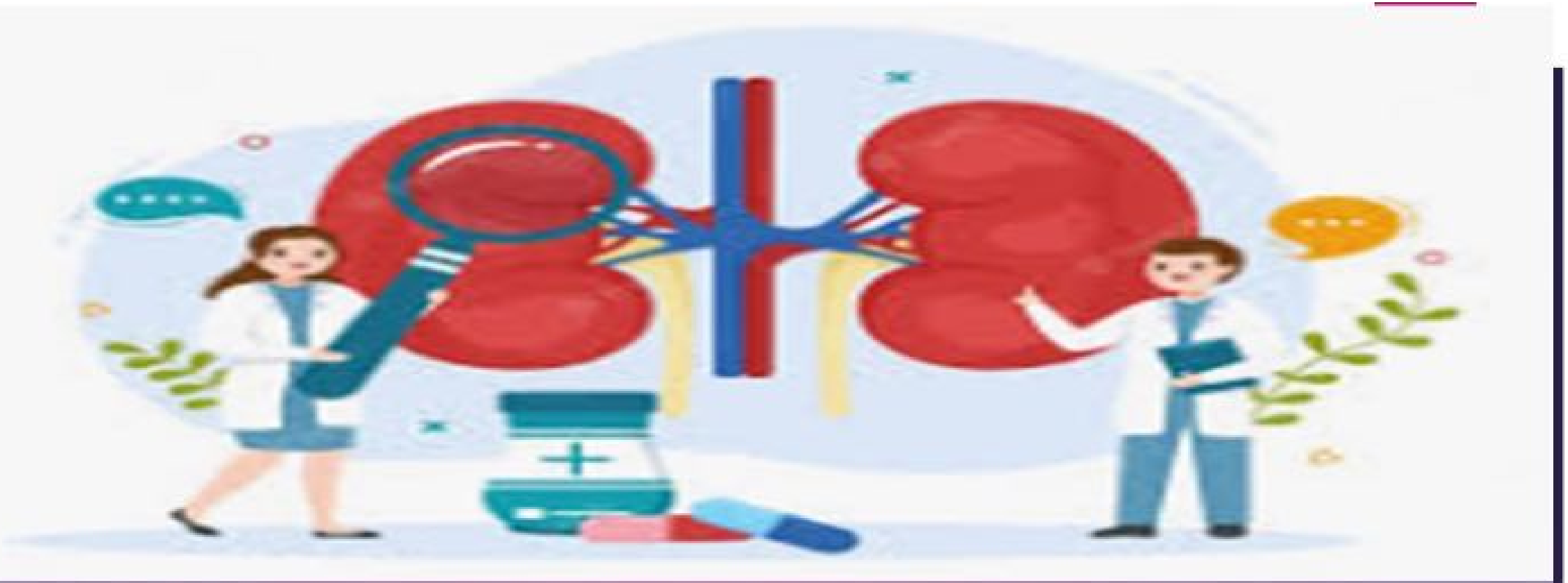
- Female pt with confirmed character of HUS
- Pt has history of GE
- Mother has proven history and biopsy and TMA and on regular dialysis
- PD was started on creatinine 4.5
- Pt received 2 BT
- Pt was advised to receive PE
- Parents refused due to familial issues
- 2 weeks later after 2 PD session , serum creatinine was decreased to 0.7 with good hematological response

- Male pt 2 years with confirmed picture of HUS with anuria
- History of GE
- Pt received 2 sessions of PD
- Pt start hematological response
- UOP start to increase
- Serum creatinine start to normalize up to 0.4
- Nephrotic range proteinuria was present
- Pt was discharged for regular follow up
- Proteinuria starts to normalize
- Parents stopped follow up from their self
- 1 year later pt presented with NS
- Renal biopsy early FSGS

Take home massage

- **Late sequalae is not uncommon in both Typical and atypical**
- **Early identification of etiology affect sequalae**
- **Early diagnosis and proper management with target therapy have decreased renal sequalae much**
- **Last but not the least you should follow up your pt throughout his pediatric life**





Thank you