Pediatric Hemolytic Uremic Syndrome

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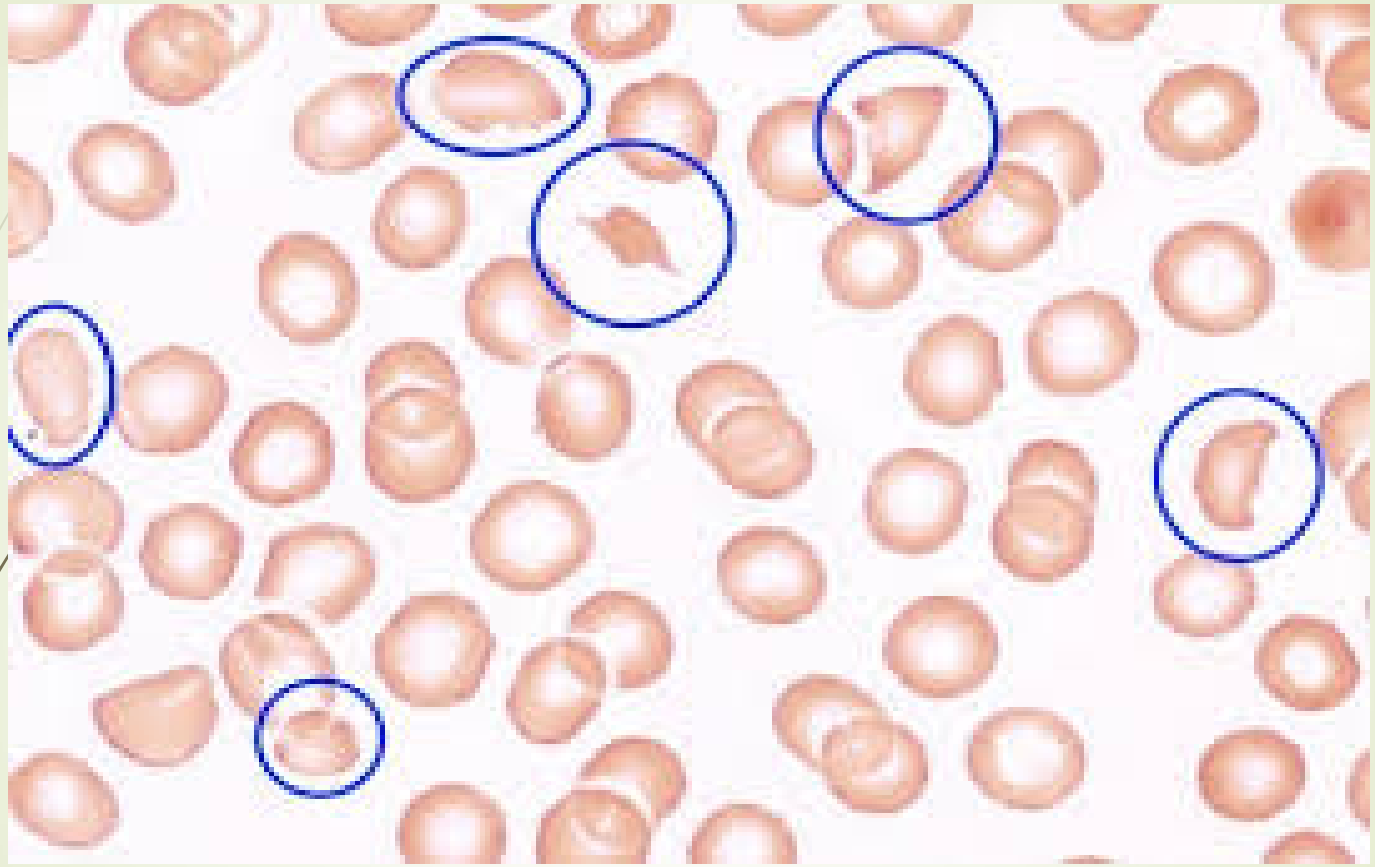
Hemolytic uremic syndrome (HUS)

HUS, is a disease characterized by the classical triad :

- Acute renal failure of varying severity
- Microangiopathic anemia
- Thrombocytopenia of varying severity



Other clinical finding

- Cerebral manifestations (cerebral edema, seizures, leukoencephalopathy, coma, and stroke)
- Cardiac dysfunction
- Gastrointestinal tract and liver dysfunction, including intestinal complications (necrosis, perforation)
- Panceratitis

HUS: Pathophysiology

- Infection related
  - Shigella/E.coli toxin (Typical HUS, Most common)
  - Pneumococcal infection
  - Viral infections (HIV)
- Complement abnormalities
  - Factor H deficiency
  - Factor 1 deficiency
- Miscellaneous (Drugs, Malignancy)

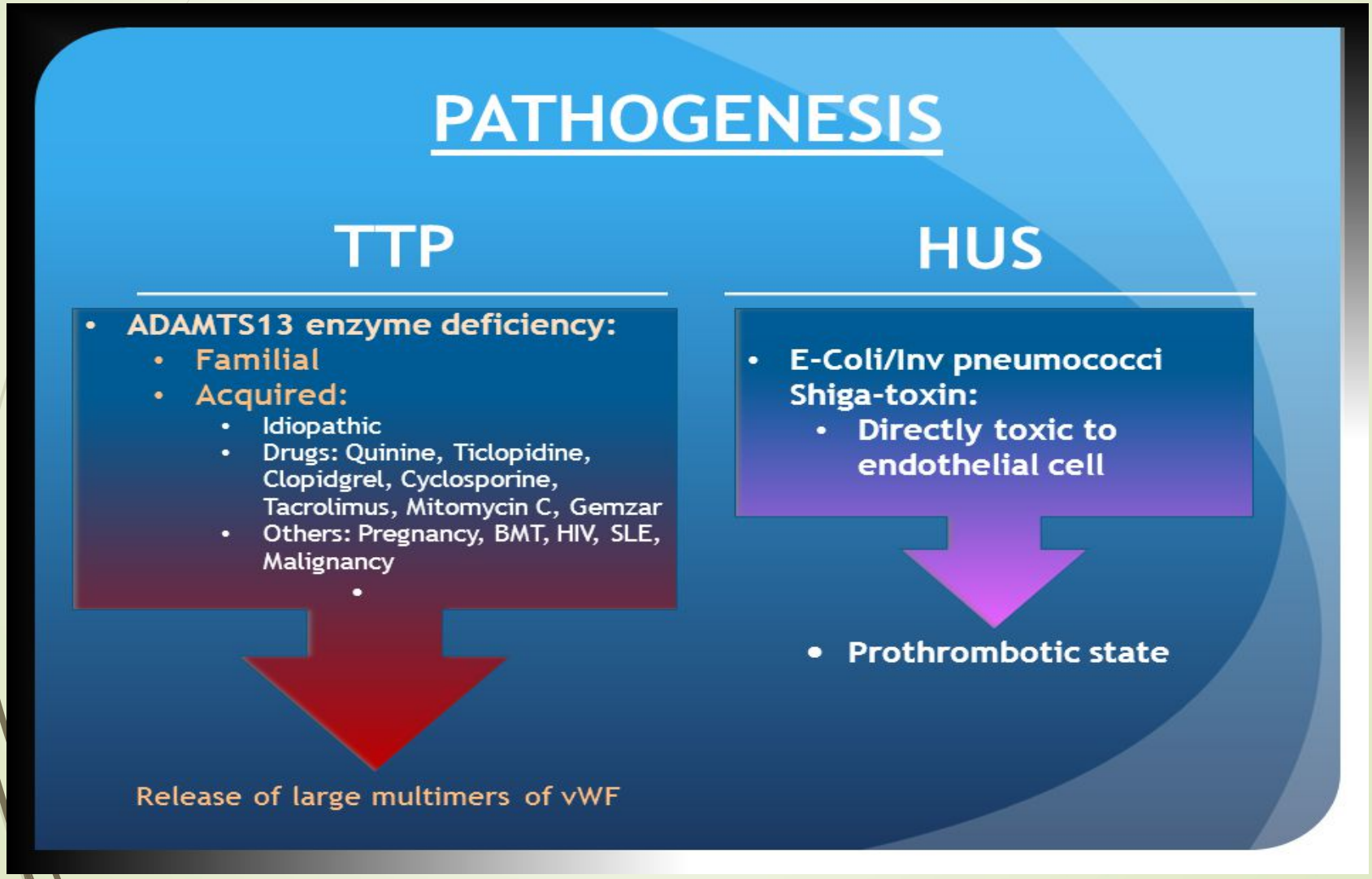
Other classification:

- Typical (Diarrhea positive , D+HUS)
- Atypical (5-10%) D-HUS

Typical HUS

- Diarrhea positive (D+ HUS)
- Usually occurs after intestinal infection with Shiga-toxin-producing bacteria
- E.coli O157:H7 (shigatoxins 1 and 2)
- Shigella dysenteriae serotype 1, Salmonella
- Food borne disease: uncooked / unpasteurized
- products contaminated by animal wastes
- Most patients are <3 years of age though can occur in adults
- Pathophysiology : shigella-toxin binding protein on the surface of glomerular endothelium and **inactivating a metalloproteinase called ADAMTS13.**

Pathogenesis



Pathogenesis

Coppo and Veyradier
Thrombotic Microangiopathies: Towards a Pathophysiology-Based Classification
Cardiovascular &Haematological Disorders – Drug Targets, 2009, Vol 9, No.1, pp36-50.

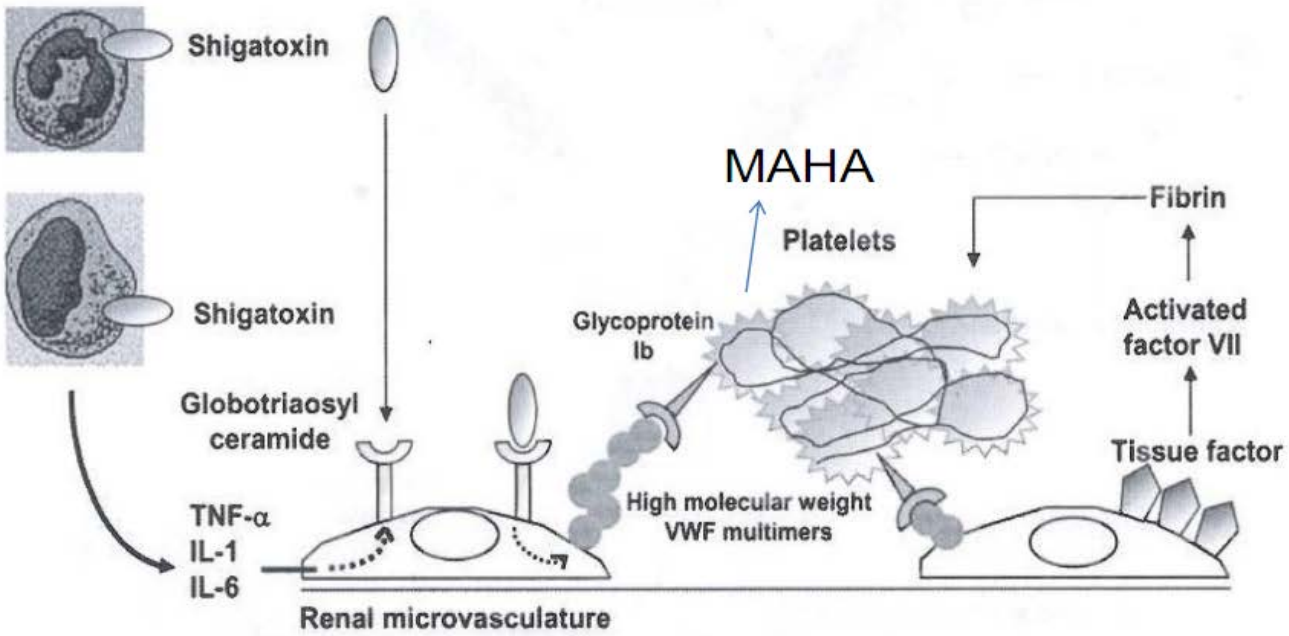


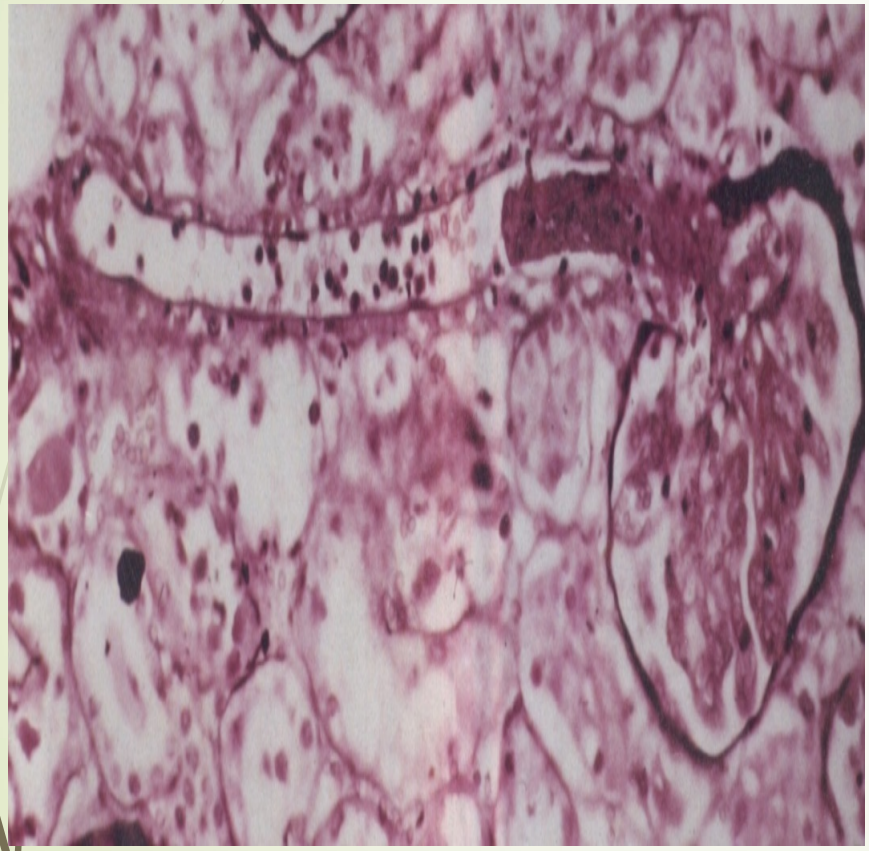
Fig. (4). Pathophysiological mechanisms leading to microthrombi formation in diarrhea-associated HUS. Shigatoxins are transported in blood flow by neutrophils, platelets and monocytes, and bind their receptors (globotriaosyl ceramide) at the surface of renal endothelial cells. IL-1, IL-6 and TNF-α up-regulate expression of shigatoxins receptors on endothelial cells surface. After internalization, they interfere with protein traduction machinery and thereby induce endothelial cell apoptosis. Damaged cells express surface high molecular weight VWF, which initiates platelet clumping through interaction with glycoprotein Ib. Shigatoxins also induce tissue factor expression on endothelial cells, leading to factor VII activation and fibrin formation. VWF: von Willebrand factor.

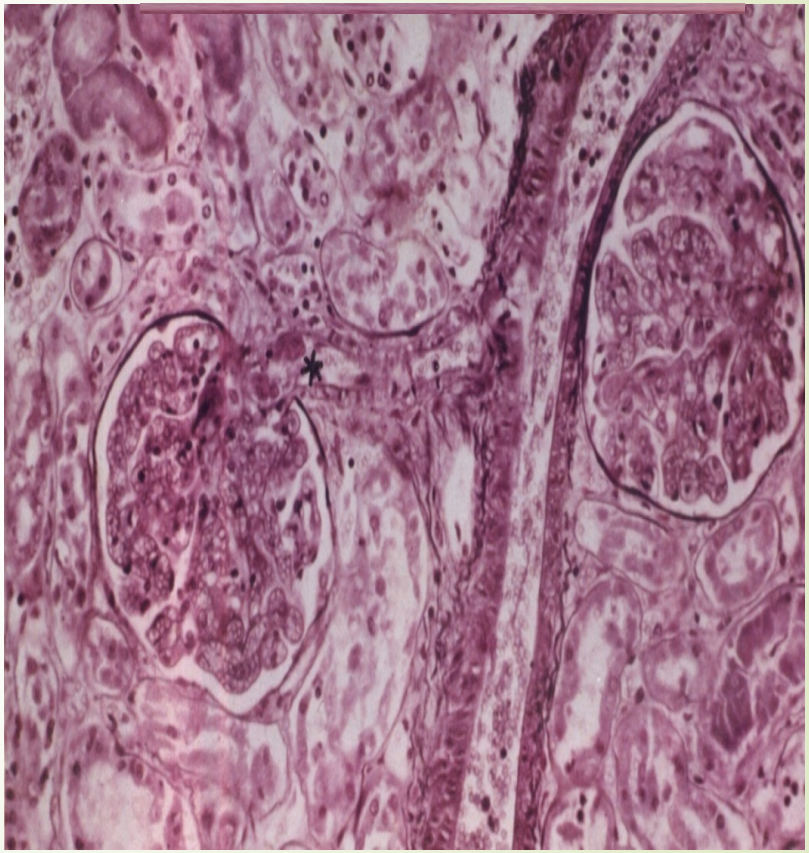
Long term results (10-20 years after HUS*)

- A severe condition: acute mortality (2.5%) associated with significant morbidity
- Complete recovery 63%
- Recovery with proteinuria 12%
- Recovery with proteinuria and HTN 6%
- Recovery with low GFR ± proteinuria or HTN, 16%
- ESRD, 3%

*** Diarrheal or URI- related only, pediatric**

Acute Kidney Injury





Laboratory tests

- CBC, peripheral smear, renal function studies, electrolytes, LDH, and urinalysis
- Coagulation studies including PT and PTT
- Testing for Shiga toxins (eg, ELISA) in the stool, stool cultures, and serologic testing for IgM and anti-lipopolysaccharide antibodies against the most frequent STEC serotypes.
- C3 levels should be part of every HUS evaluation(Save blood from before plasma exchange)
- ADAMSTS13 / auto-Ab analysis if TTP not ruled out

Treatment

- **The initial management of HUS is supportive**
- Red blood cell transfusions for anemia when clinically indicated (HB 6 to 7 g/dL or HT <18 %).
- Platelet transfusion for patients with significant clinical bleeding or if an invasive procedure is required.
- Appropriate fluid and electrolyte management.
- Stopping nephrotoxic drugs.
- Management of hypertension
- Initiation of dialysis: symptomatic uremia, severe fluid overload, or electrolyte abnormality , refractory to medical therapy.
- Provision of adequate nutrition.

Atypical HUS

- Usually due to disorders of complement regulation.
- **About 50%-60% of aHUS cases are associated with a mutation in a complement-related gene.**
- Empiric plasma therapy can delay or prevent ESRD in many of those cases.
- Risk of post-transplant recurrence depends on the specific disorder of complement regulation.
- Clinically very severe
  - 15% died
  - 25% ESRD
  - 15% renal insufficiency
- 1/3 recover without significant renal disease
  - Most (75%) have a single episode
  - Few (25%) have recurrent aHUS

Complement and Atypical HUS

Protein	Gene	Source	Location	% of aHUS
Factor H	*CFH*	Liver	circulates	~ 15-30%
Factor I	*CFI*	Liver	circulates	~ 5-10%
Membrane Cofactor Protein	*MCP*	Widespread	Membrane bound	~ 10-15%
Factor B	*CFB*	Liver, ?	circulates	<5%
C3	*C3*	Liver, ?	circulates	~ 5-10%
Anti-FH-Ab	*CFHR1/ CFHR3*	Lymphocyte	circulates	~ 10%
Unknown				~ 40-50%

Jozsi et al. Blood 2008, Frémeaux-Bacchi V et al. Blood 2008, Goicoechea de Jorge 2007, Caprioli, et al Blood 2006, Kavanagh Curr Opin Nephrol Hypertens, 2007

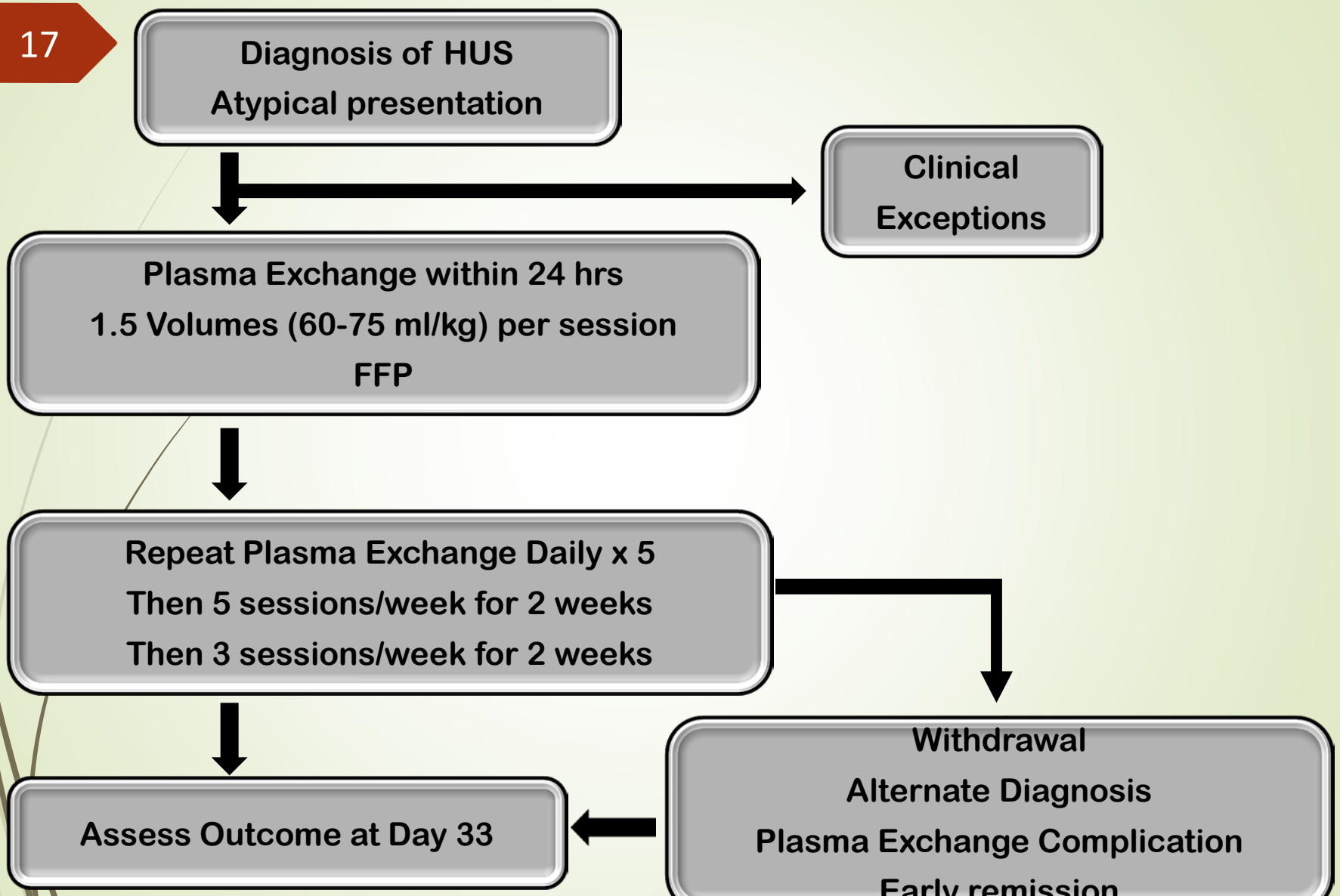
DIFFERNCES BETWEEN "ATYPICAL HUS" and "REGULAR" HUS

	ATYPICAL HUS	HUS
Caused by a Bacteria or Virus	No	Yes
Initial Symptoms are severe	No	Yes
Accompanied by Severe Diarhea	No	Yes
Dialysis often needed	Yes	Yes
Blood Pressure Regulation Problems	Yes	Yes
Temporary Kidney Failure is Common	Yes	Yes
Permanent Kidney Failure is Common	Yes	No
Disease is often Recurring	Yes	No
Complications throughout life may occur	Yes	No
May be caused by a Gene Problem	Yes	No

Treatment

- Plasma exchange is indicated for non-Shiga toxin-associated HUS
- Follow response with platelet count and LDH
- Platelet transfusion contraindicated
- Childhood E.coli-associated HUS does not warrant plasma therapy as it usually resolves spontaneously
  - Plasmapheresis
  - Plasma infusion (especially ADAMTS13)
  - Eculizumab (binds to C5 and blocks C5 convertase)

Empiric Plasma Exchange



Ariceta et al. Ped Neph 2009

Eculizumab

- A monoclonal antibody to complement factor C5
- Blocks complement activation, in treatment of patients with complement-mediated HUS.
- May also be beneficial in patients with STEC HUS and CNS involvement.
- The first report of three children with severe neurologic symptoms, resolution of neurologic symptoms 7 to 12 days after starting eculizumab.
- The possible complication of meningococcal infection needs appropriate vaccination before its use.