Immunosuppressive and HUS

Doaa Youssef

Professor of pediatrics and pediatric nephrology

1- Role in antibody mediated

2- What type of immunosuppressive?

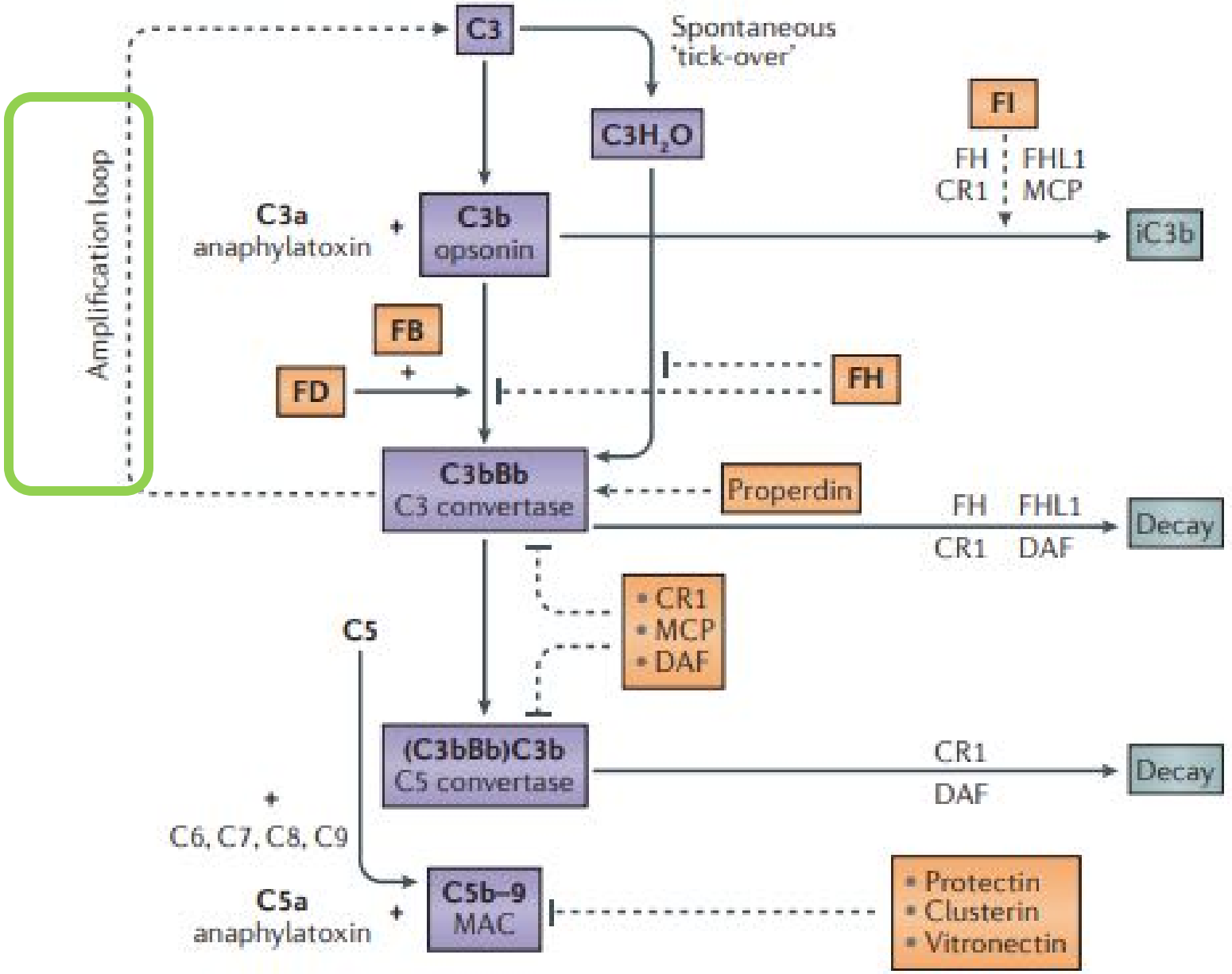
3- Post transplant HUS

4- Immunocompromised or not

5- No antibody available ? To give or not

6- Low c3 ? To give or not

1- Role in antibody mediated


C3
Spontaneous 'tick-over'
C3H2O
FI
FH FHL1
CR1 MCP
iC3b
Amplification loop
C3a anaphylatoxin
+
C3b opsonin
FB
+
FD
FH
C3bBb C3 convertase
Properdin
FH FHL1
CR1 DAF
Decay
• CR1
• MCP
• DAF
C5
(C3bBb)C3b C5 convertase
CR1
DAF
Decay
+
C6, C7, C8, C9
C5a anaphylatoxin
+
C5b–9 MAC
• Protectin
• Clusterin
• Vitronectin

The management of patients across centers was at the discretion of treating physicians, depending on their experience and available facilities.

- **The proportion of children with aHUS who have anti-FH auto antibodies has been reported as 5% to 25% in European cohorts**

Durey MD, Sinha A, Togarsimalemath SK, et al. Anti-complement-factor H-associated glomerulopathies. Nat Rev Nephrol. 2016

- **and as high as 56% in a large Indian cohort.**

Sinha A, Gulati A, Saini S, et al. Prompt plasma exchanges and immunosuppressive treatment improves the outcomes of anti-factor H autoantibody-associated hemolytic uremic syndrome in children. Kidney Int. 2014;85:1151–1160

- **Anti-FH autoantibodies** are also detected in a small proportion of patients with **C3 glomerulopathies**, which are characterized by chronic glomerular injury mediated by activation of the alternative complement pathway and predominant C3 deposits on renal histology

•Combined Plasma exchange (PE) **and** immunosuppression improved long-term outcomes

•***maintenance*** *therapy with* ***corticosteroids and MMF*** or **azathioprine** significantly decreased the risk of relapses, from 87% to 46% at last follow-up

•The **National Renal Complement Therapeutics Centre in the UK recommends initial treatment with eculizumab for anti-FH HUS based upon a more favorable adverse effect profile**

Kidney International (2017) 92, 1261–1271

•Management with **plasma exchange and/or immunosuppression** is remarkably effective in **inducing and maintaining remission in aHUS** associated with FH autoantibodies

•While terminal complement blockade with **Eculizumab** is the first line therapy for atypical HUS

•Lack of its **availability** and **cost** **limits** its use.

•**Plasma exchange** becomes a **first** line modality in the **current scenario**.

• However, exposure to **large volumes of allogenic** plasma and lack of **skilled manpower** are the **limiting factors** associated with it.

•there is a subset of patients who **fail to respond to plasma exchange.**

2- What type of immunosuppressive?

www.kidney-international.org clinical investigation

Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland

Rodney D. Gilbert[4], ivaram Hegde[8], ıth[9], Larissa Kerecuk[10], Sheerin[14],

KD KIDNEY DISEASES

Rituximab to Abbreviate Plasma Exchange in Anti-CFH (Complement Factor H) Antibody Mediated Atypical HUS

Aliza Mittal,[1] Munawer Dijoo,[2] Sandeep Aggarwal,[2] Sanjeev Gulati[2]

ORIGINAL RESEARCH
published: 07 June 2019
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International Journal of Molecular Sciences
MDPI

Communication

Immunosuppressive Therapy of Antibody-Mediated aHUS and TTP

Kata Keleti [1,2], Orsolya Horváth [1,2], Éva Kis [2], Bálint Mikes [1], Péter Sallay [1], Zoltán Prohászka [3], Attila József Szabó [1,4,5] and György S. Reusz [1,*]

OPEN ACCESS
Edited by:
Bradley Patton Dixon,
Children's Hospital Colorado,
United States
Reviewed by:

Clinical and Immunological Profile of Anti-factor H Antibody Associated Atypical Hemolytic Uremic Syndrome: A Nationwide Database

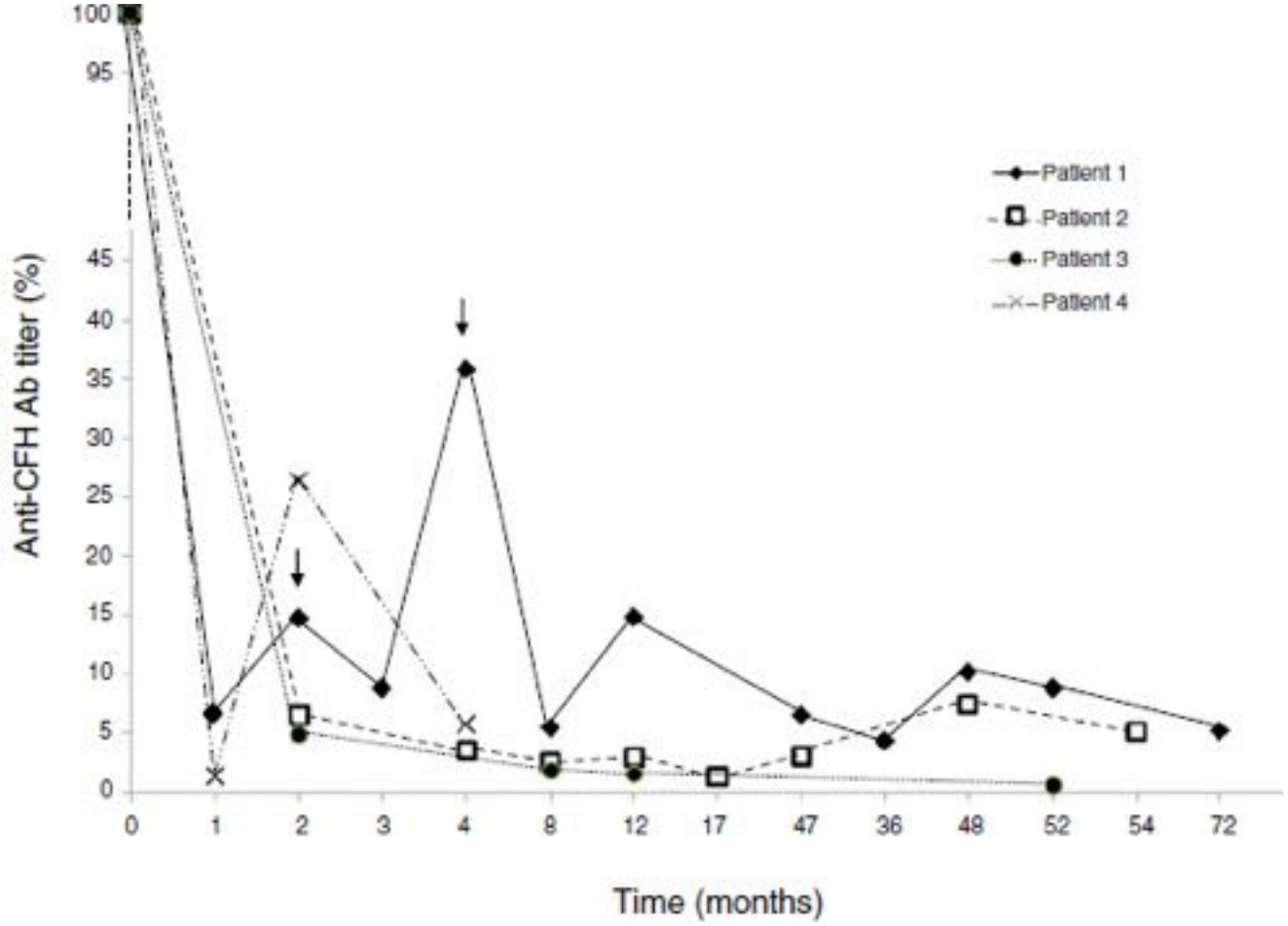
Mamta Puraswani [1†], Priyanka Khandelwal [1†], Himanshi Saini [1], Savita Saini [1], Bahadur Singh Gurjar [2], Aditi Sinha [1], Rajashri Pramod Shende [3], Tushar Kanti Maiti [4], Abhishek Kumar Singh [4], Uma Kanga [5], Uma Ali [6], Indira Agarwal [7], Kanav Anand [8], Narayan Prasad [9], Padmaraj Rajendran [10], Rajiv Sinha [11], Anil Vasudevan [12], Anita Saxena [13], Sanjay Agarwal [14], Pankaj Hari [1], Arvind Sahu [3], Satyajit Rath [3,15] and Arvind Bagga [1]*

[1] Division of Nephrology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, [2] Immuno Biology

•The largest experience with the approach to decrease anti-FH antibodies with immunosuppressive treatment comes from **India**, where **55.8% of their 781** aHUS patients presented with **anti-FH antibodies**

•In a cohort of **17 patients with anti-CFH antibody associated aHUS**

Kidney International (2017) 92, 1261–1271



Pediatr Nephrol
DOI 10.1007/s00467-013-2558-9

ORIGINAL ARTICLE

Long-term remission of atypical HUS with anti-factor H antibodies after cyclophosphamide pulses

Gwenaëlle Sana · Marie-Agnès Dragon-Durey · Marina Charbit · Karim Bouchireb · Caroline Rousset-Rouvière · Etienne Bérard · Rémi Salomon · Véronique Frémeaux-Bacchi · Patrick Niaudet · Olivia Boyer

In case of positive anti-FH antibodies,

additional immunosuppression is administered, starting with **prednisolone 1 mg/kg daily** for 4 weeks followed by **alternate** day dosing for another 4 weeks and tapering down for 1 year.

Cyclophosphamide (**500 mg/m2 q 4 weeks, 3–5 doses**)

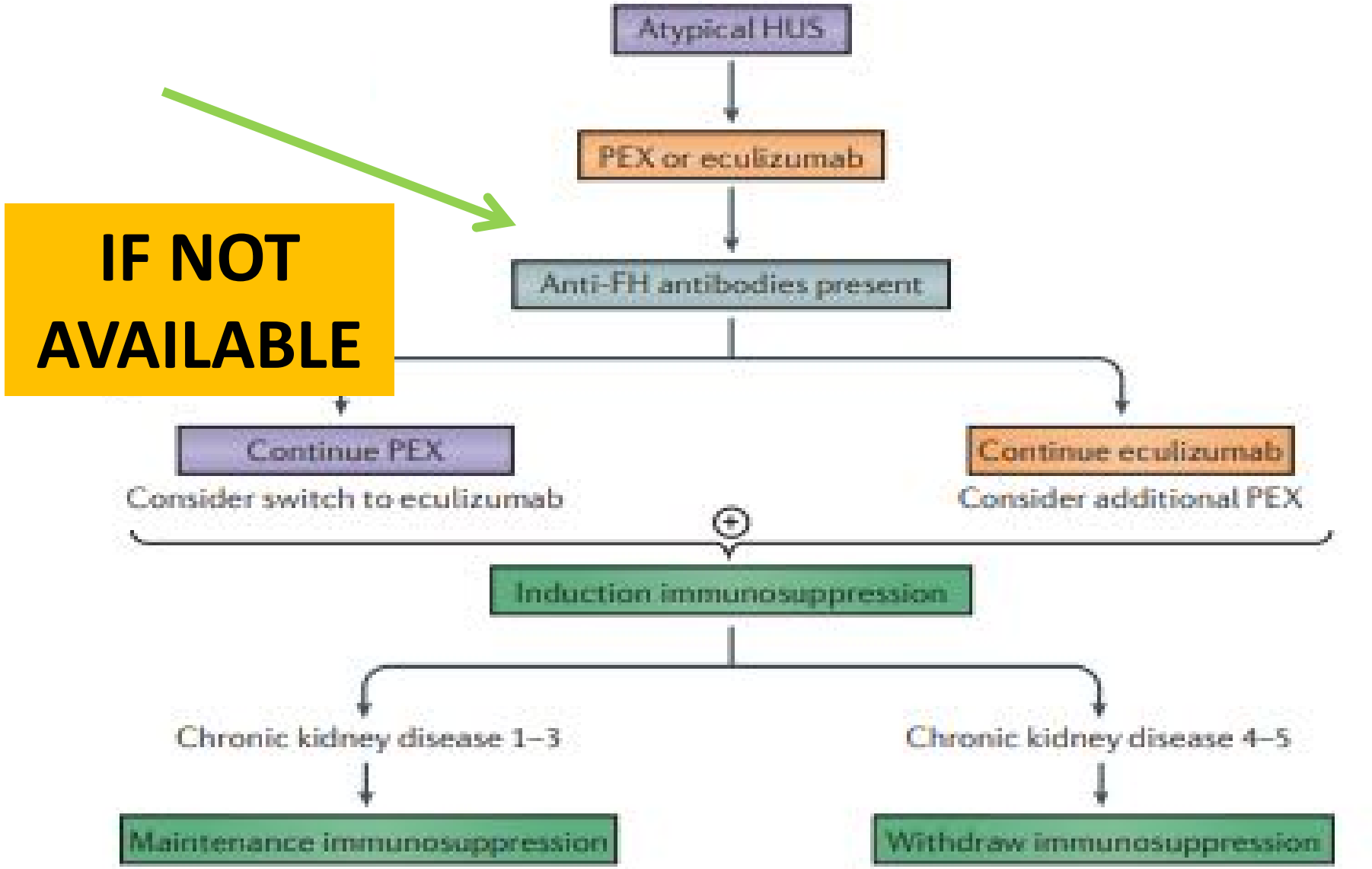
or Rituximab (**500 mg/m2 q 7 day, 2 doses**)

are given to further decrease the production of antibodies.

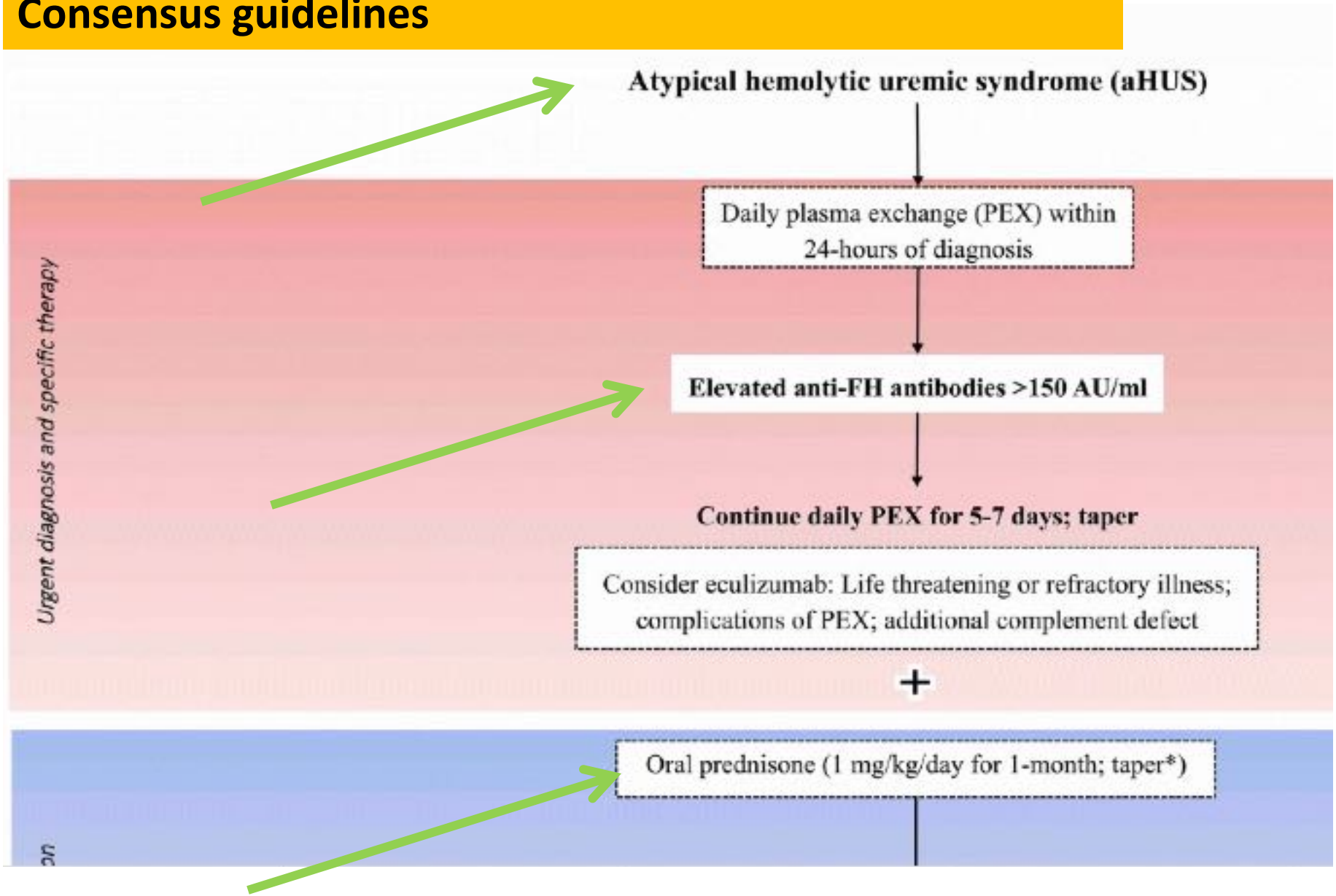
Mycophenolate mofetil (**500–750 mg/m2/day**)

or azathioprine (**1–2 mg/kg/day**)

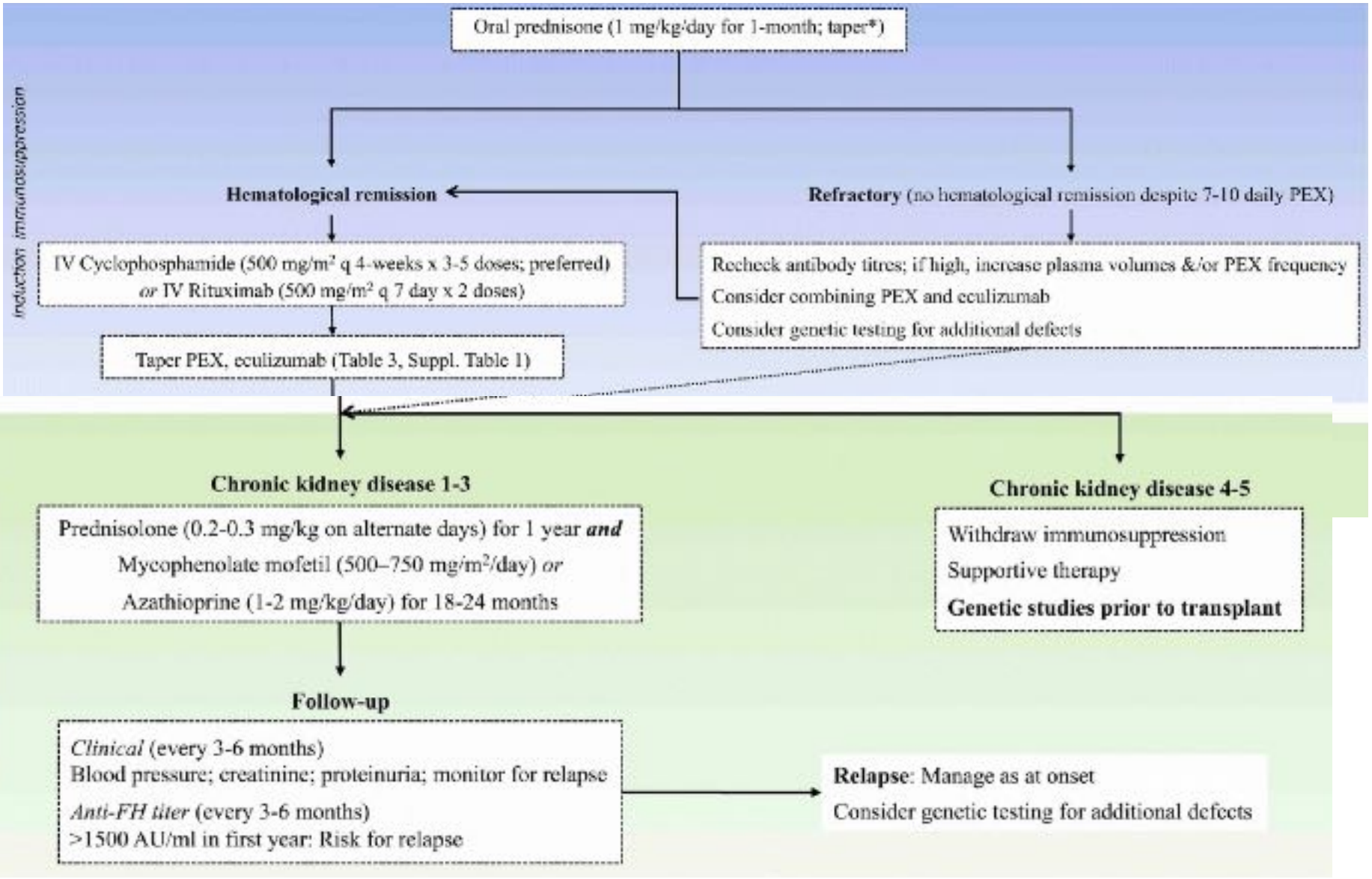
are used as additional long-term immunosuppression


IF NOT AVAILABLE
Atypical HUS
PEX or eculizumab
Anti-FH antibodies present
Continue PEX
Consider switch to eculizumab
Continue eculizumab
Consider additional PEX
Induction immunosuppression
Chronic kidney disease 1–3
Chronic kidney disease 4–5
Maintenance immunosuppression
Withdraw immunosuppression

Hemolytic uremic syndrome in a developing country: Consensus guidelines

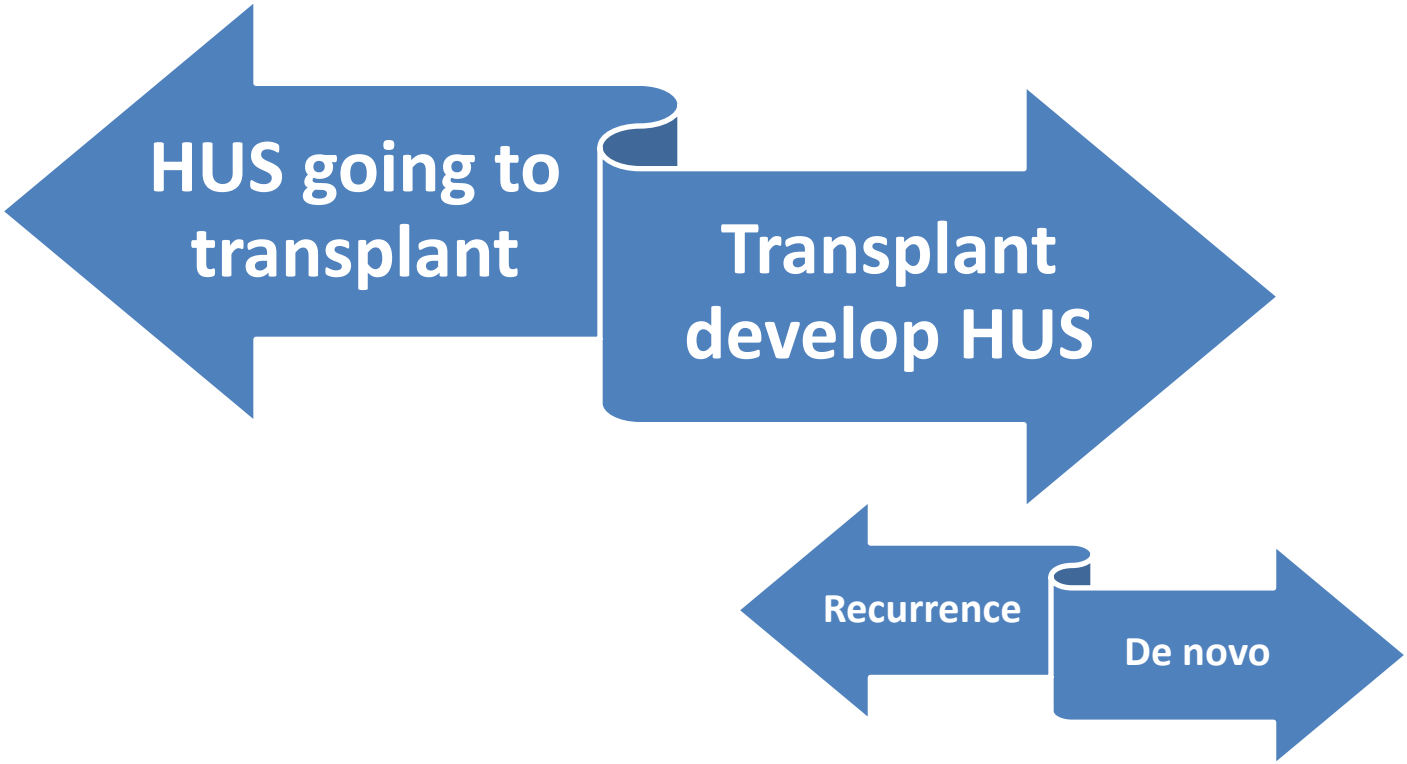


Pediatric Nephrology (2019) 34:1465–1482



Pediatric Nephrology (2019) 34:1465–1482

3- Post transplant HUS



HUS going to transplant

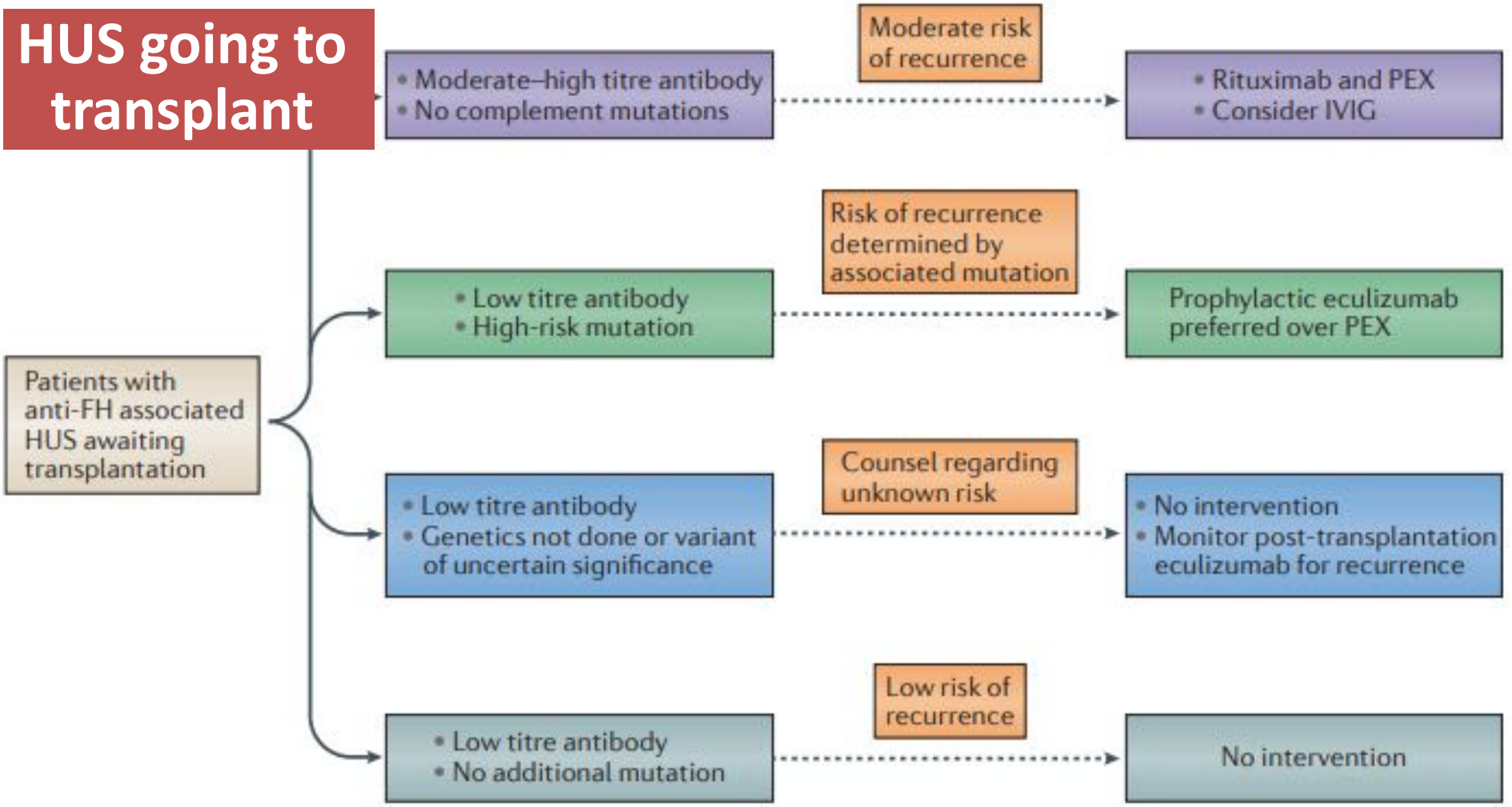


Figure 3 | **Strategies for peri-transplant management of patients with anti-factor H (FH)-associated haemolytic uraemic syndrome (HUS).** Recipient and donor are screened for coexisting mutations in the genes encoding FH, FI, C3,

Transplant develop HUS

Front. Med., 08 April 2021
Sec. Nephrology
Volume 8 - 2021 |
https://doi.org/10.3389/fmed.2021.642864

This article is part of the Research Topic
Management of Patients with Non-Dialysis Dependent Chronic Kidney Disease (ND-CKD)
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Thrombotic Microangiopathy After Kidney Transplantation: An Underdiagnosed and Potentially Reversible Entity

Ana Ávila* Eva Gavela* Asunción Sancho*

Nephrology Department, University Hospital Dr. Peset, Valencia, Spain

•It appears in **0.8–14%** of transplanted patients and negatively affects graft and patient survival.

•It can appear in a **systemic** form, with hemolytic microangiopathic anemia, thrombocytopenia, and renal failure, or in a **localized** form, with progressive renal failure, proteinuria, or arterial hypertension.

• Post-transplant thrombotic microangiopathy is classified **as recurrent atypical hemolytic uremic syndrome or *de novo* thrombotic microangiopathy**

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DOI: 10.12659/AOT.909781

Effect of Immunosuppressive Therapy on the Occurrence of Atypical Hemolytic Uremic Syndrome in Renal Transplant Recipients

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Natasha Kesav[3]
Mustafa Ascha[5]
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Treatment of aHUS Recurrence

•**Prophylactic** treatment or **recurrence** treatment are the two alternatives.

•**Prophylactic** treatment based on **plasmapheresis <u>does not</u>**

<u>effectively</u> prevent recurrence in patients with **high or moderate risk**

mutations, and subclinical complement activation have been reported in

these patients.

•**Excellent** results with **eculizumab** as the first-line therapy have been

reported n the treatment of **recurrence**

Treatment of *de novo* Post-transplant Thrombotic Microangiopathy

•should be based on correcting the **potential cause** of the disease and varies depending on the **time of onset**.

•Given the extreme **heterogenicity of the mechanisms** related to the appearance of TMA, therapeutic maneuvers must be individualized.

•**The first step is to avoid complement over-activation** before donation, preventing renal hypoperfusion during organ procurement, and reducing cold ischemia time.

•In cases of **PT-TMA secondary to immunosuppressive medications**, the first step is to reduce or stop the offending agent, by **switching** from **a CNI to another CNI or to an mTOR**i., the effectiveness of this strategy is controversial.

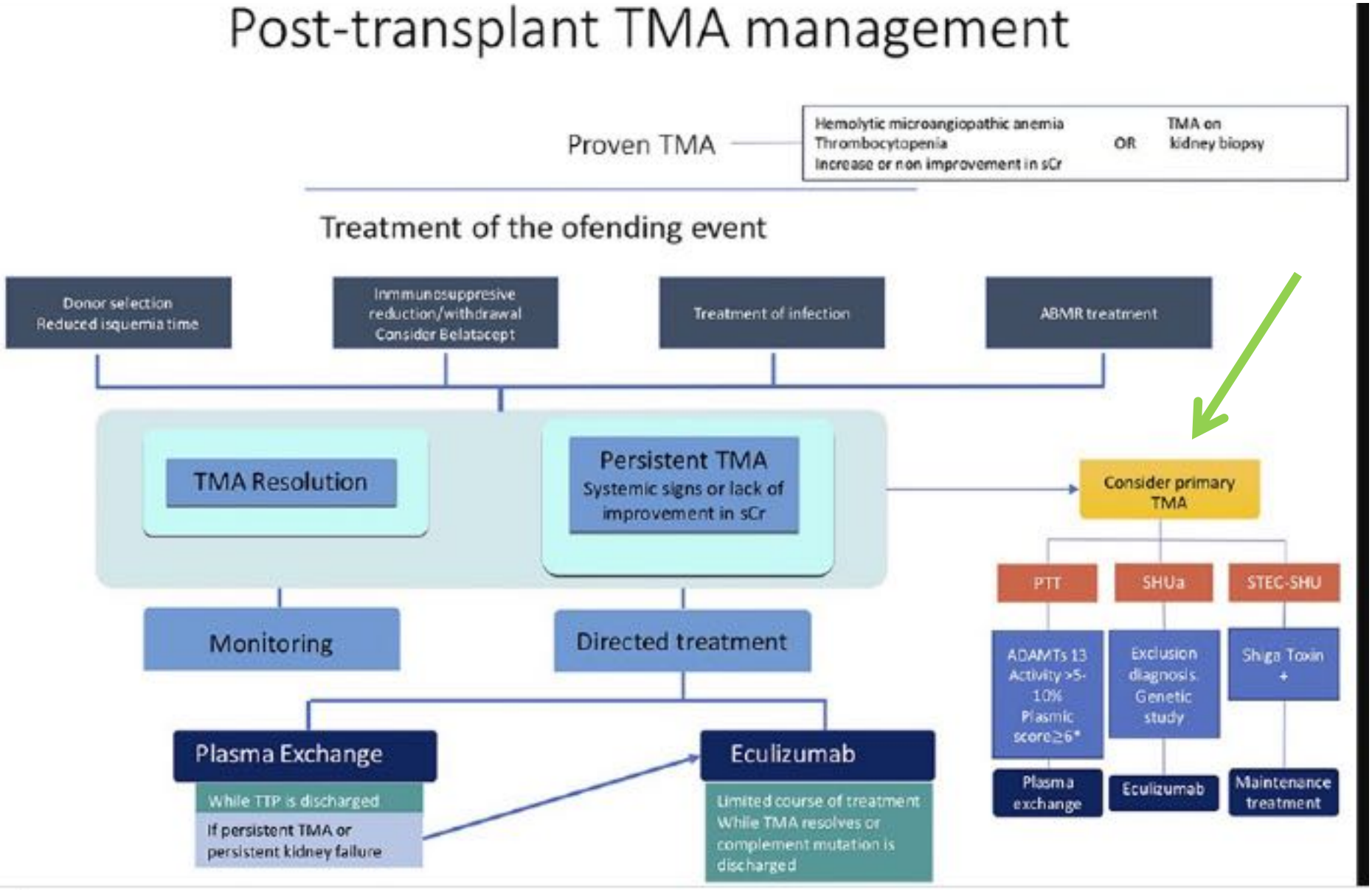
•**Belatacept**, a cytotoxic T lymphocyte antigen 4-immunoglobulin fusion protein that inhibits T cell function, allows the minimization or discontinuation of endothelial toxic immunosuppressants such as CNIs and mTORis

•However, a **higher risk of acute kidney transplant rejection** compared with current standard immunosuppressive therapy has been observed after conversion to **belatacept** in kidney transplant rejection.

•treatment is **plasmapheresis** (PP), with or without **IVIg** and additional **immunosuppression** is difficult to assess with current clinical data and is yet to be established.

• Instead, **eculizumab** use is currently **recommended** as a rescue therapy

Post-transplant TMA management



4- Immunocompromised or not

Immunocompromisation- is it aHUS?

Len Woodward - October 20, 2023 - News - 0 Comments

Immunocompromisation is a hall mark of aHUS. For those who are predisposed to it and for those who have had it and are in treatment. It is just a matter of the degree of compromise.

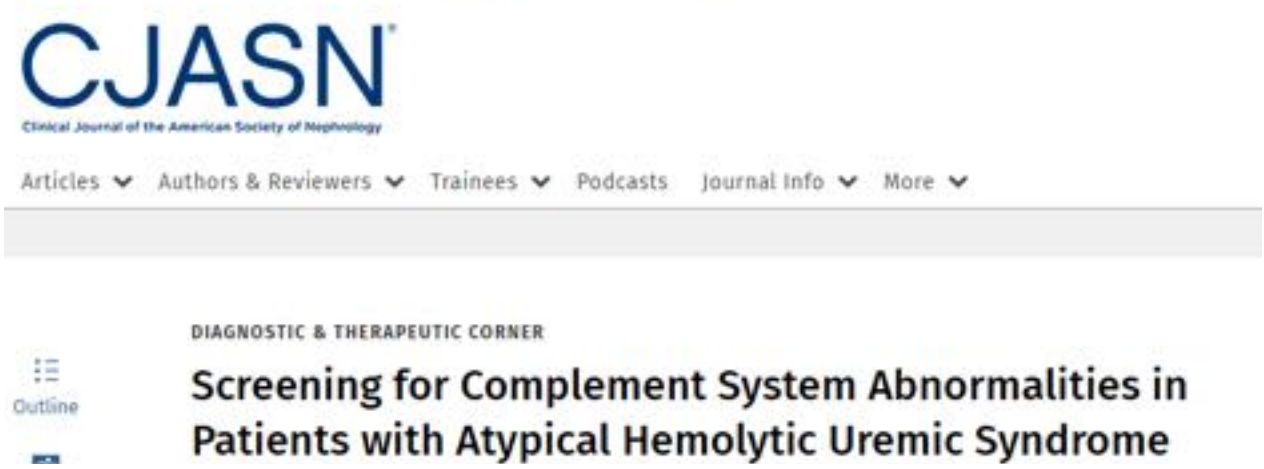
aHUS – degrees of immunocompromisation of patients and predisposed

	Transplant Immunosuppression	No transplant
Complement Inhibitor	Extremely Immunocompromised	Very immunocompromised
No Complement Inhibitor	Very immunocompromised	Compromised

5- No antibody available ? To give or not

6- Low c3 ? To give or not

No evidence



•**Low C3** levels are commonly seen in patients with mutations in *CFH*, *CFI*, and *MCP*.

• this is **not a sensitive** screening test,

• and **normal C3 levels do not exclude** the presence of mutations in complement regulation

•In those with **mutations in *CFH*,** approximately **50% have normal C3** levels, For ***CFI***, this figure is **40**% and for ***MCP*** approximately **70**%

• There is also a group with **low C3 levels** (approximately 30%) and **no** mutations in *MCP*, *CFH*, or *CFI* ; **This group likely represents a cohort with mutations in an as-yet-unidentified complement gene.**

•In those **without** detectable mutations in *CFH*, *CFI*, or *MCP*, **autoantibodies** to CFH have been identified in a small percentage of cases approximately 6%

Front Med (Lausanne). 2020; 7: 357.
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PMCID:
PM

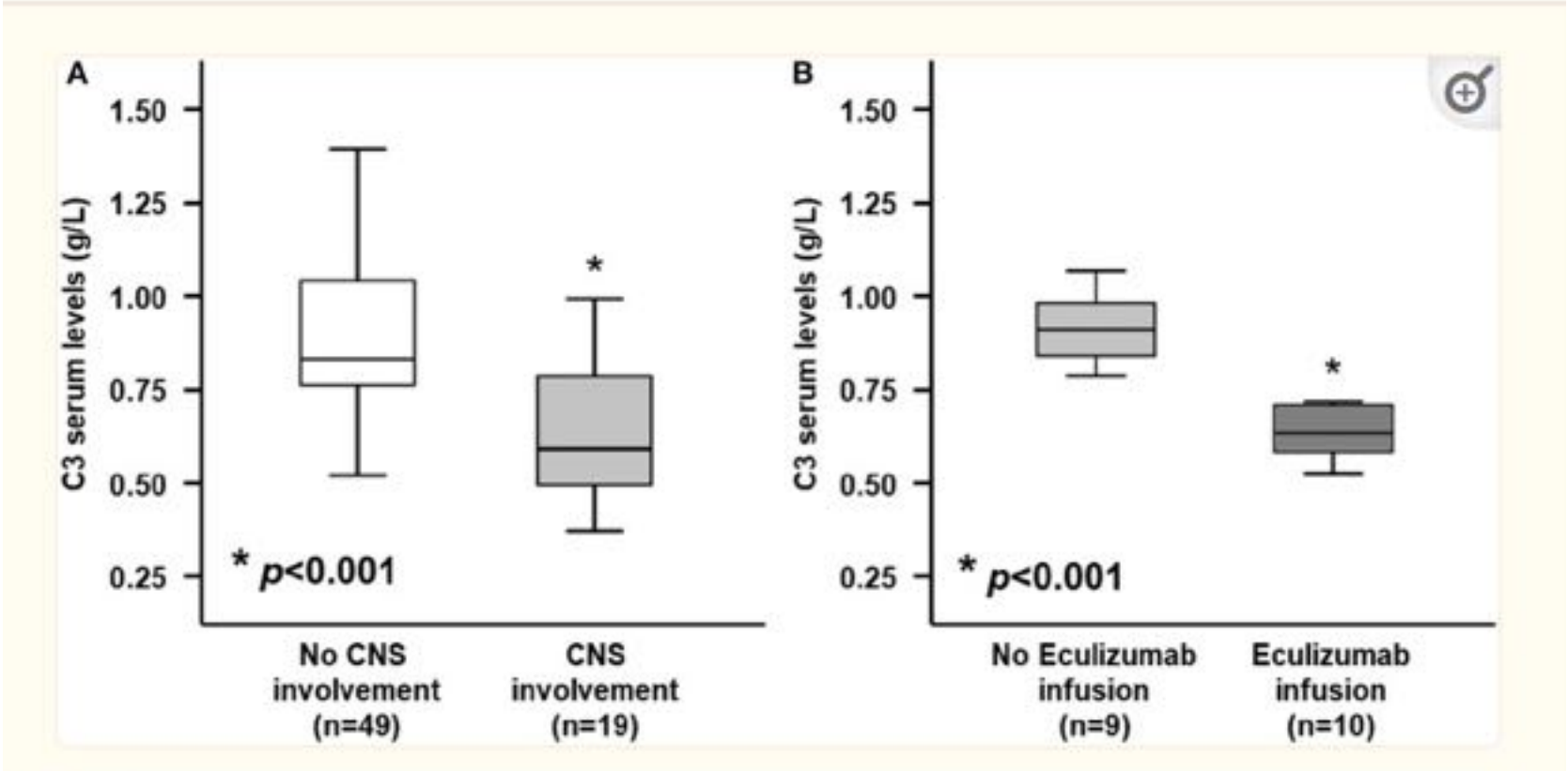
Low C3 Serum Levels Predict Severe Forms of STEC-HUS With Neurologic Involvement

Giuseppe Stefano Netti,[1,†] Luisa Santangelo,[2,†] Leonardo Paulucci,[2] Giovanni Piscopo,[2] Diletta D. Torres,[2] Vincenza Carbone,[2] Paolo Giordano,[3] Federica Spadaccino,[1] Giuseppe Castellano,[4] Giovanni Stallone,[4] Loreto Gesualdo,[5] Maria Chironna,[6] Elena Ranieri,[1,*] and Mario Giordano[2,*]

Front Med (Lausanne)

• Several reports during last decades have described low plasma C3 concentrations and **augmented complement products' degradation in children affected by STEC-HUS**

•Recently an *in **vitro*** study showed that high doses of STX2 are able to **induce direct activation of complement alternative pathway (AP) and to bind factor H**, decreasing its activity on the cell surface .



•children with **STEC-HUS** with **decreased C3** concentrations at admission are more likely to develop neurologic involvement and are at increased risk of having severe clinical complications

Thank you