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SÍNDROME HEMOLÍTICO URÉMICO

ETIOLOGIA E DIAGNÓSTICO

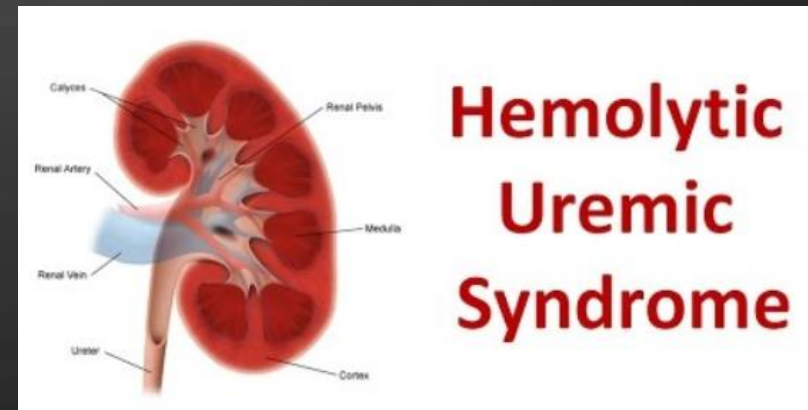
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Porque falar de SHU?

- Doença rara, mas grave

→ Significativa mortalidade e morbidade renal e extra-renal



Porque falar de SHU?

- Uma das causas mais frequentes de LRA na população pediátrica mundial
 ✓ 0,2-4,28 casos/100.000 habitantes/ano

TABLE 39-2 Causes of Pediatric Acute Renal Failure: Demographic Comparison			
Study	Oluwu et al ²³	Arora et al ¹⁹	Hui-Stickle et al ²²
Location	Kenya	India	United States
Number of patients	123	80	248
Causes			
Hemolytic uremic syndrome	2 (1.6%)	25 (31%)	3 (1.2%)
Acute glomerulonephritis	10 (8.1%)	18 (22.5%)	9 (3.6%)
Acute tubular necrosis	—	19 (23.8%)	—
Urology	7 (5.7%)	7 (8.7%)	20 (8.0%)
Renal ischemia or nephrotoxic drugs in the context of the following:			
After cardiac surgery	—	11 (13.4%)	43 (17.3%)
Hematology/oncology	17 (13.4%; renal Burkitt's lymphoma)	—	33 (13.3%)
Hepatic/intestinal transplantation	—	—	11 (4.4%)
Genetic diseases	—	—	19 (7.7%)
Infections (malaria)	37 (30%)	—	—
Sepsis	25 (20.3%)	—	27 (11%)

Geary DF, Schaefer F. Comprehensive Pediatric Nephrology. 1ª edição. Philadelphia. 2008

Porque falar de SHU?

- Importante causa de DRC

Table 1 Selected studies on the causes of chronic kidney disease in children

Study [reference]	Causes of CKD			Causes of ESRD			
	NAPRTCS [12]	Italian Registry [5]	Belgian Registry [13]	ANZDATA [27]	ESPN/ERA-EDTA Registry [28]	UK Renal Registry [29]	Japanese Registry [30]
Population	CKD (GFR <75)	CKD (GFR <75)	CKD (GFR <60)	ESRD (RRT)	ESRD (RRT)	ESRD (RRT)	ESRD (RRT)
Age range	0–20	0–19	0–19	0–19	0–15	0–15	0–19
Patients	Registered 1994–2007	Incident 1990–2000	Incident 2001–2005	Incident 2003–2008	Incident 2008	Incident 2004–2008	Prevalent 1998
Number of cases	7,037	1,197	143	369	499	428	582
Etiology							
CAKUT	3,361 (48%)	689 (58%)	84 (59%)	127 (34%)	182 (36%)	184 (43%)	208 (36%)
Hypodysplasia±reflux nephropathy	1,907	516	66	95		135	198
Obstructive uropathy	1,454	173	18	32		49	10
Glomerulonephritis	993 (14%)	55 (5%)	10 (7%)	108 (29%)	76 (15%)	78 (18%)	130 (22%)
HUS	141 (2%)	43 (4%)	9 (6%)	9 (2%)	29 (6%)		13 (2%)
Hereditary nephropathy	717 (10%)	186 (15%)	27 (19%)		112 (22%)		69 (12%)
Congenital NS	75	13	5	7		15	34
Metabolic disease			5		17	18	
Cystinosis	104	22	2	4			2
Cystic kidney disease	368 (5%)	101 (8%)	13 (9%)	25 (7%)	59 (12%)	49 (11%)	35 (6%)
Ischemic renal failure	158 (2%)	49 (4%)	3 (2%)	8 (2%)	11 (2%)		11 (2%)
Miscellaneous	1,485 (21%)	122 (10%)	10 (7%)	65 (18%)	52 (10%)	19 (4%)	83 (14%)
Missing/unknown	182 (3%)	40 (3%)		16 (4%)	37 (7%)	65 (15%)	34 (6%)

CKD, chronic kidney disease; ESRD, end-stage renal disease; RRT, renal replacement therapy; GFR, glomerular filtration rate (ml/min/1.73 m²); CAKUT, congenital anomalies of the kidney and urinary tract; NS, nephrotic syndrome; HUS, hemolytic uremic syndrome; NAPRTCS, North American Pediatric Renal Trials and Collaborative Studies; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; ESPN/ERA-EDTA Registry, European Registry for Children on Renal Replacement Therapy

Porque falar de SHU?

- Importante causa de DRC



Table 3: PRD distribution at start of RRT in 2015

Cause of renal failure, among patients < 15 years of age, starting RRT in 2015 according to new and old PRD coding.

	N		Percent		Pmarp	
	New	Old	New	Old	New	Old
CAKUT	198	170	37.3	32.0	2.19	1.84
Glomerulonephritis	96	82	18.1	15.4	1.08	0.89
Cystic kidney disease	60	65	11.2	12.2	0.70	0.70
Hereditary nephropathy	-	25	-	4.7	-	0.27
Metabolic and tubulointerstitial disorders	20	7	3.8	1.3	0.21	0.08
Toxic/ischemic renal failure	12	8	2.3	1.5	0.14	0.09
HUS	18	15	3.4	2.8	0.20	0.16
Vascular	5	4	0.9	0.8	0.06	0.04
Miscellaneous	70	75	13.2	14.1	0.78	0.81
Unknown	52	80	9.8	15.1	0.61	0.87

Porque falar de SHU?

- Importante causa de DRC

Etiologia da IRC dos doentes prevalentes com idade <18 anos em TSFR

(31/12/2016)
n=118

Malformações do rim e tracto urinário (CAKUT)	52 (48,5%)
Glomerulonefrite e glomerulosclerose	19 (17,1%)
Doenças quísticas hereditárias	6 (5,7%)
Doenças metabólicas e tubulo-intersticiais	12(10,4%)
Toxico-isquémicas	8 (6,6%)
Síndrome hemolítico urémico (códigos 88)	8(6,6%)
Vascular	-
Outras	7(6,1%)
Desconhecida	6(5,7%)

Porque falar de SHU?

- Novo fármaco inibidor do sistema do complemento aprovado com resultados bastante positivos

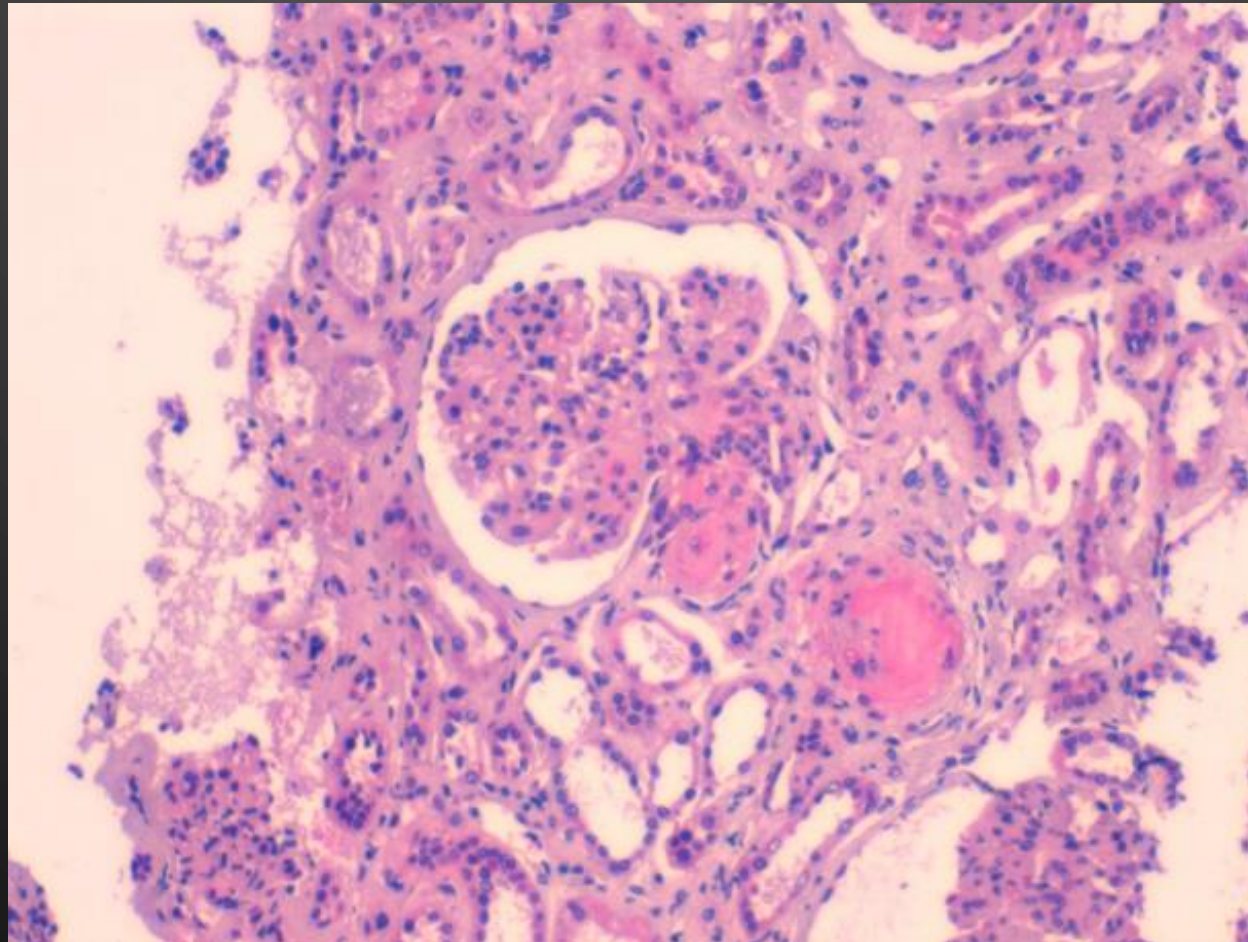
→ Diagnóstico correto e precoce de SHU com desregulação da via do complemento é de extrema importância

Definição de SHU

- O SHU faz parte de um grupo etiológicamente muito heterogêneo de doenças
→ Microangiopatias trombóticas
- Ocorre trombose de pequenos e micro vasos, tanto arteriais como venosos, na presença de dano endotelial
- Compartilham:
 - ✓ Histologia
 - ✓ Tríade Clínica

Microangiopatias Trombóticas

- Histologia



Microangiopatias Trombóticas

- Tríade Clínica

- ✓ Anemia hemolítica microangiopática não autoimune
- ✓ Trombocitopenia
- ✓ Lesão de órgão



Microangiopatias Trombóticas

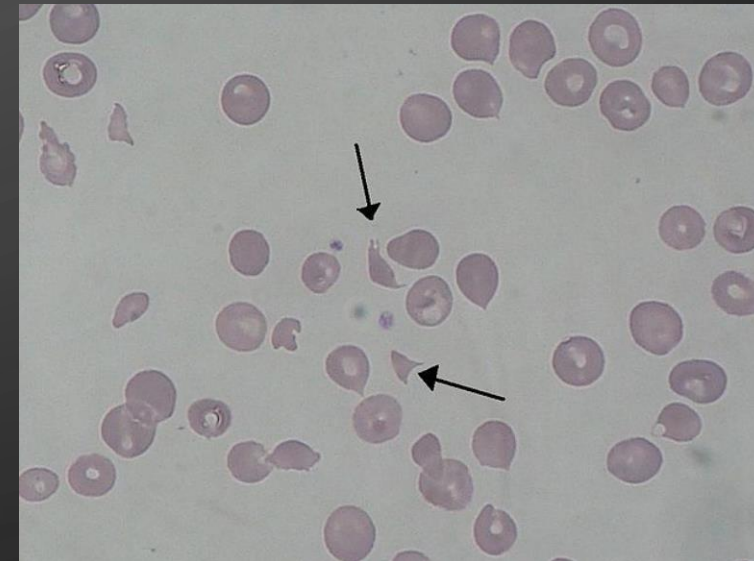
- Tríade Clínica

- ✓ Anemia hemolítica não autoimune microangiopática

- Hb <10g/dl
 - Reticulocitose
 - Teste de Coombs direto negativo
 - Esquizócitos no sangue periférico
 - ↓ Haptoglobina
 - ↑ LDH

- ✓ Trombocitopenia

- <150.000/mm³
 - ↓ >25% em relação ao anterior



Microangiopatias Trombóticas

- Tríade Clínica

- ✓ Lesão de órgão

- Rim

- Hematúria
 - Proteinúria
 - Edema
 - Oligoanúria
 - HTA
 - ↑ ureia e creatinina
 - Acidose
 - ↑ K^+ , ↑ PO_4^{3-}

- Depósito no glomérulo de frações do complemento circulantes ativadas
 - Produção e ativação local do complemento



Microangiopatias Trombóticas

- Tríade Clínica

- ✓ Lesão de órgão

- SNC

- Alteração do estado de consciência
 - Convulsões
 - Sinais neurológicos focais
 - Alterações visuais
 - + comum em idade pediátrica

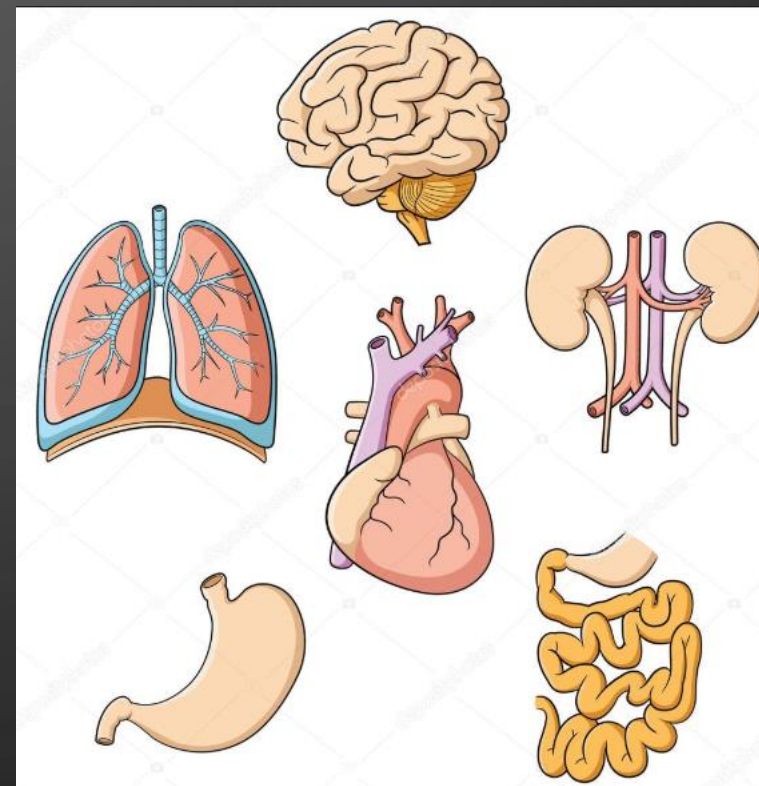


Microangiopatias Trombóticas

- Tríade Clínica

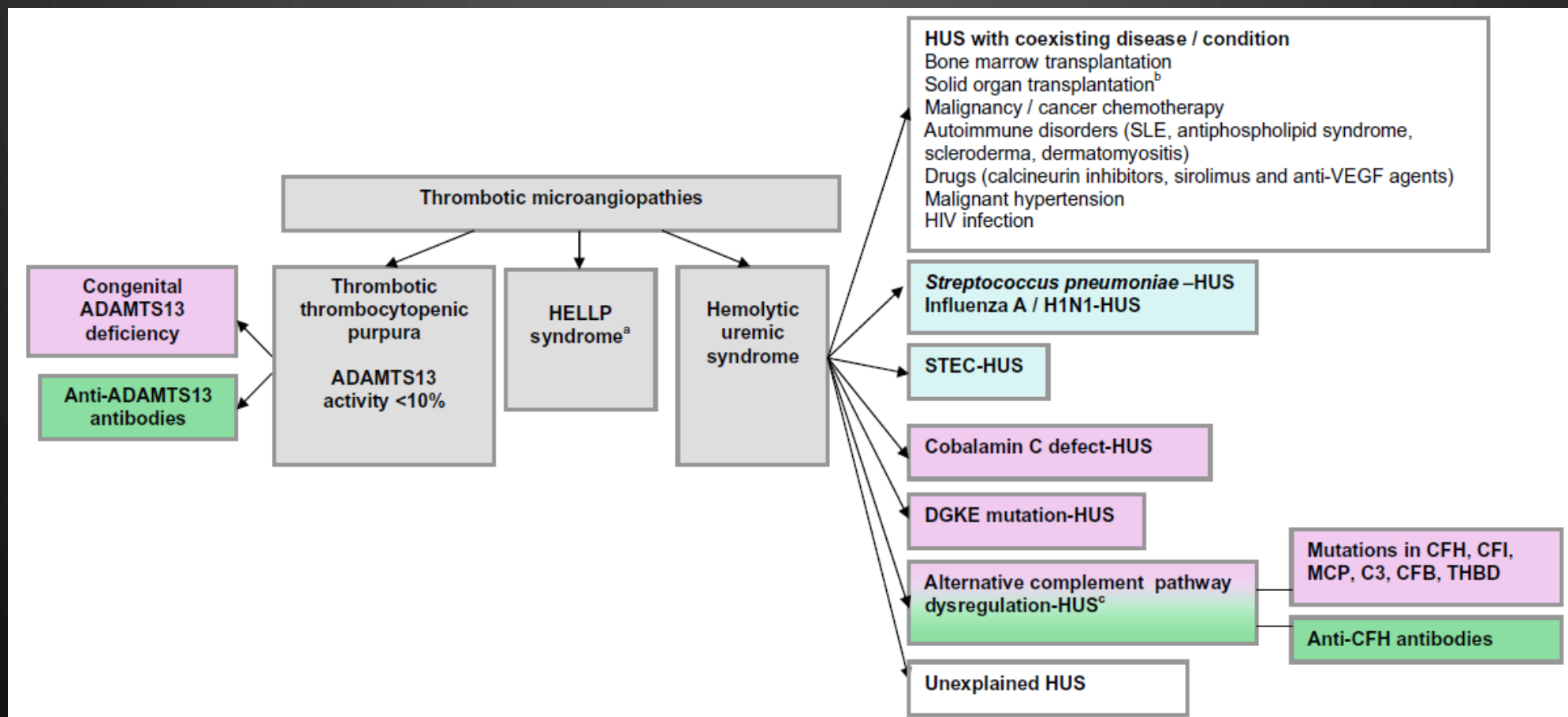
- ✓ Lesão de órgão

- Trato gastrointestinal
 - Coração
 - Pâncreas
 - Fígado
 - Sistema respiratório
 - ...



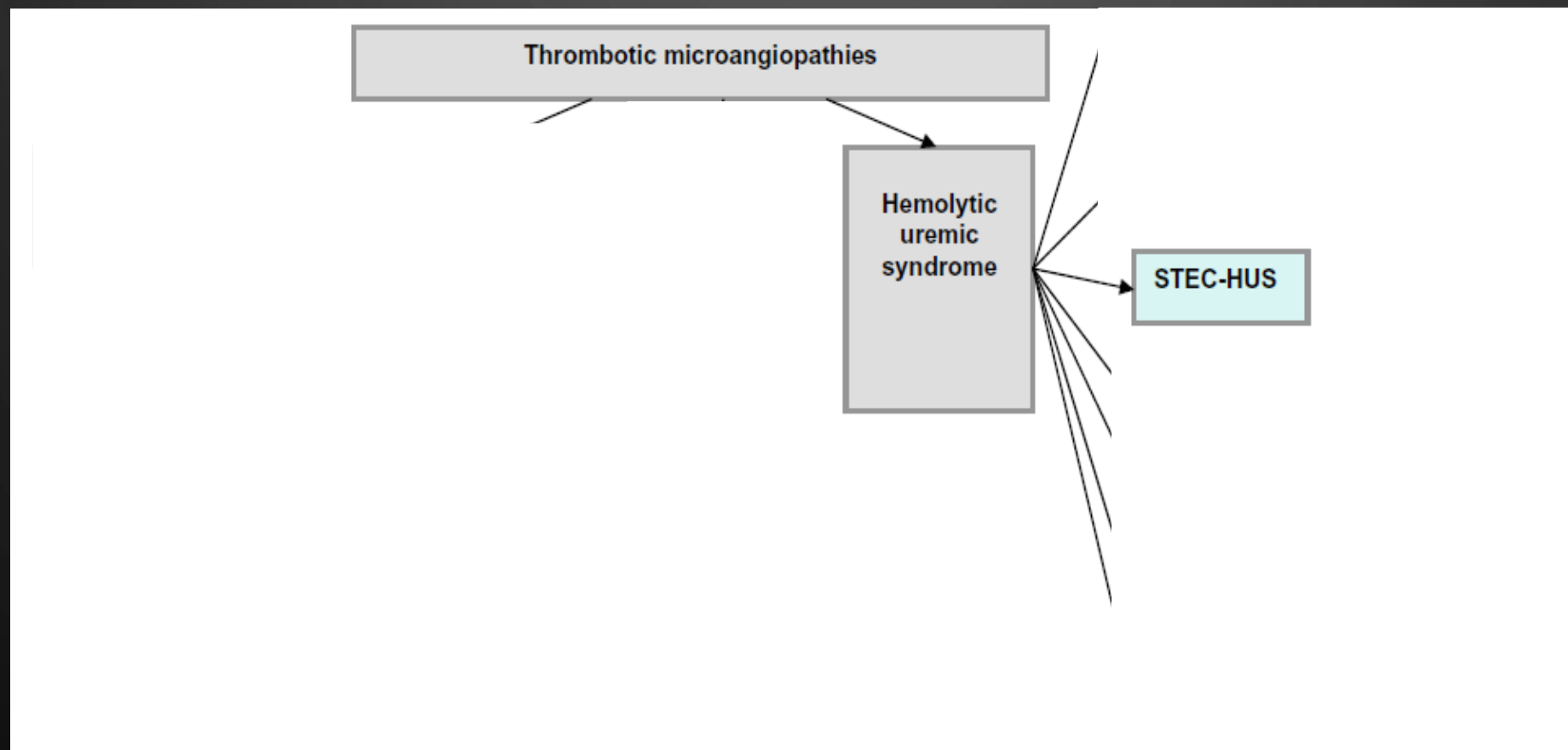
Microangiopatias Trombóticas

• Classificação etiológica



Microangiopatias Trombóticas

- Classificação etiológica



STEC-SHU

- 90% dos casos de SHU
- Incidência: 0,7-8 casos/100.000 habitantes/ano
- ++ 2-6 anos (rara antes dos 12M)
- Verão e Outono
- Zonas rurais
- Maioria casos esporádicos



STEC-SHU

- Etiologia

- ✓ *Escherichia coli* produtora de toxina Shiga (STEC)
- ✓ *Shigella dysenteriae* tipo 1
- ✓ *Campylobacter*

- Transmissão

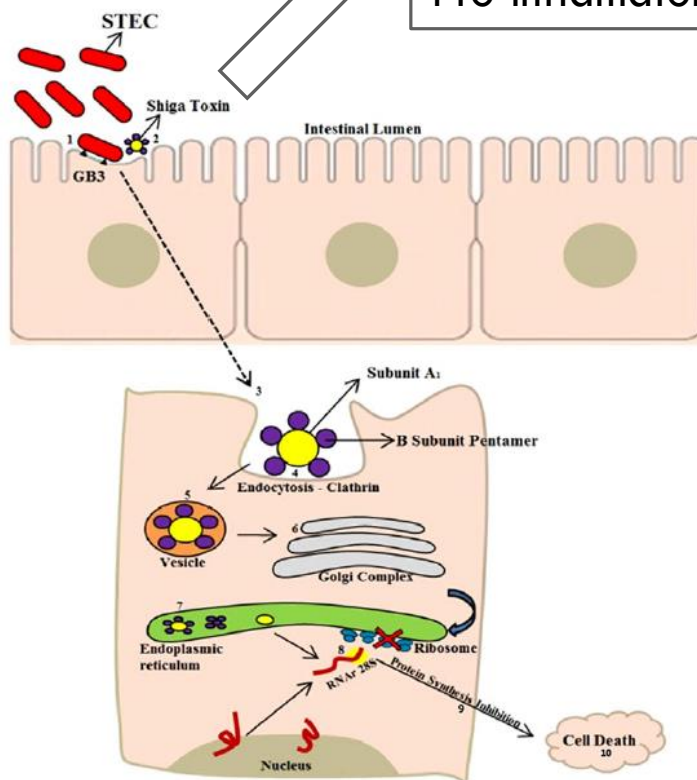
- ✓ Via fecal-oral pelo consumo de alimentos ou água contaminados
- ✓ Contacto direto com animais ou pessoas infetadas



STEC-SHU

- Fisiopatologia

Vasoconstritor
Pro-adesivo
Pro-inflamatório



Morte das células endoteliais

Exposição do espaço subendotelial

Ativação da cascata trombótica e do complemento

Trombose microangiopática intravascular extensa

Hemólise por fragmentação
Consumo de plaquetas
↓ perfusão glomerular

STEC-SHU

- Clínica

- ✓ Incubação: 3 a 8 dias (1-12)
- ✓ Dor abdominal intensa
- ✓ Diarreia aquosa → hemorrágica

10-15%

5-10 dias

Anemia hemolítica
Trombocitopenia
LRA

Perfuração intestinal
Hemorragia massiva

STEC-SHU



- 10-15% dos pacientes com infecção pela STEC desenvolvem SHU – porquê?
 - ✓ Serotipo bacteriano (++ O157:H7, O104:H4, O111:H8, O103:H2, ...)
 - ✓ Idade do hospedeiro (++ crianças pequenas)
 - ✓ Antibióticos
 - ✓ Predisposição genética (?)

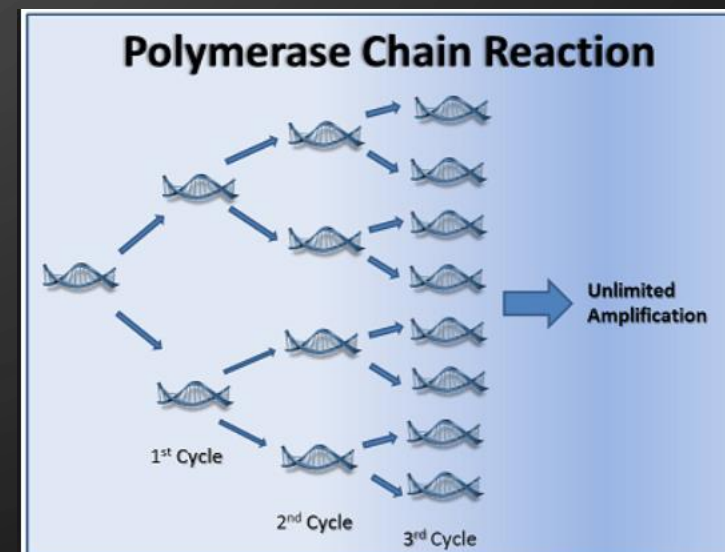
STEC-SHU

- Diagnóstico

- ✓ Coprocultura
- ✓ Pesquisa de Toxina Shiga por imunoensaio
- ✓ PCR
- ✓ Serologia

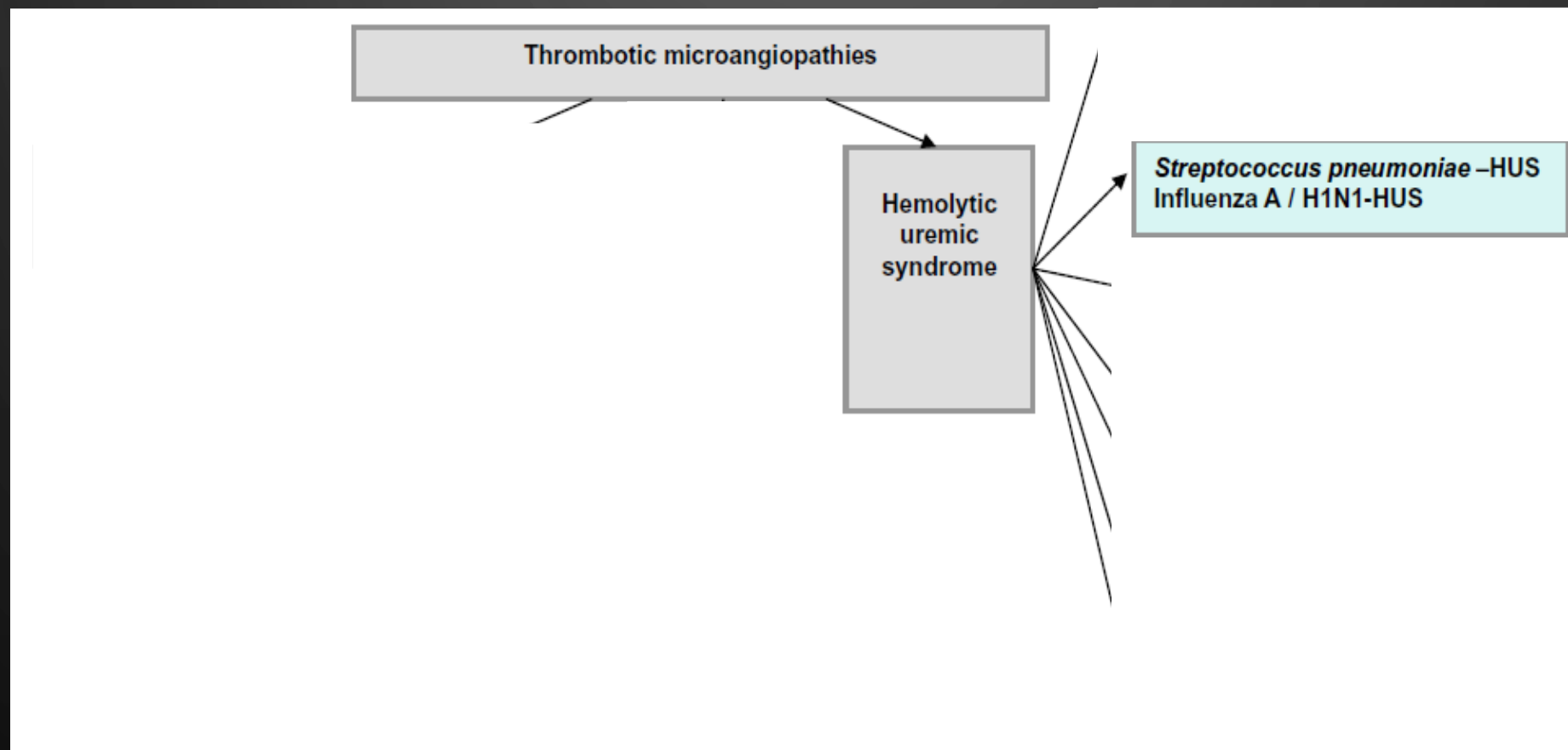


Amostra de fezes
Zaragatoa rectal



Microangiopatias Trombóticas

- Classificação etiológica



SHU associada à doença invasiva pelo pneumococo

- 5% dos casos de SHU
- 40% dos casos de SHU não STEC
- Incidência após infecção pneumocócica invasiva: 0,4-0,6%
- Idade < 2 anos
- SHU 3-13 dias depois infecção
- Pior prognóstico que o STEC-SHU
 - ✓ > duração da oligúria
 - ✓ > duração da trombocitopenia
 - ✓ + complicações extra-renais



SHU associada à doença invasiva pelo pneumococo

- Fisiopatologia

Streptococcus pneumoniae produz
a enzima neuraminidase



Enzima une-se ao ácido N-acetilneuramínico da
membrana das células endoteliais, plaquetas e GV



Expõe Ag de Huebner-Thomsen-
Friedenreich (Ag T)



Ag T + Ac circulantes



Ativação da via clássica do complemento



Aglutinação GV
Hemólise
Trombocitopenia
Trombose microvascular

SHU associada à doença invasiva pelo pneumococo

- Diagnóstico

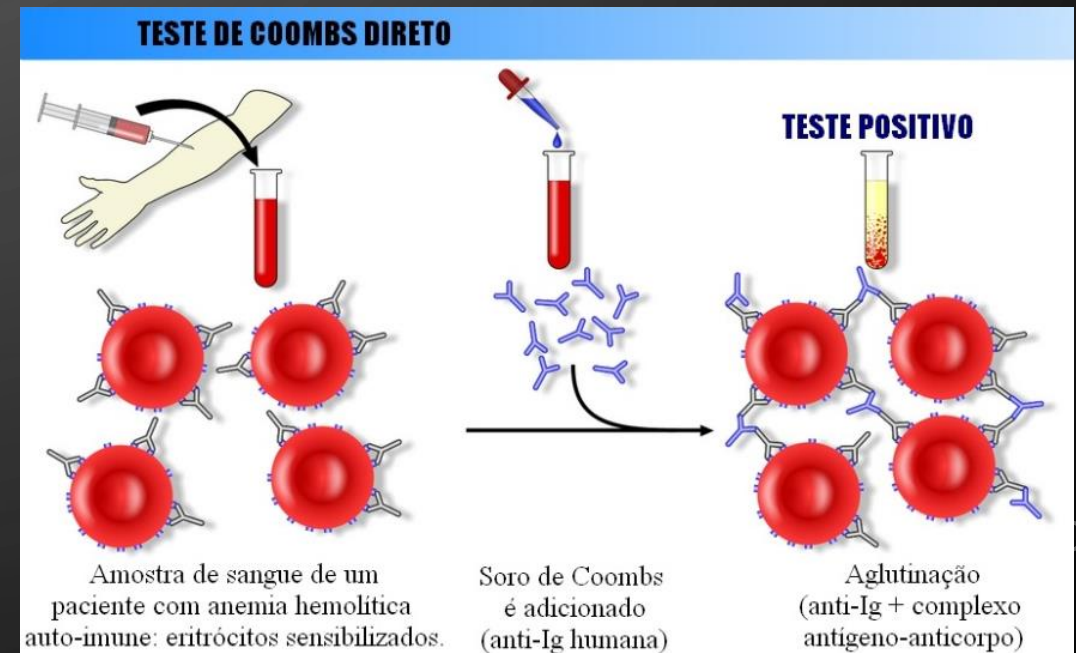
- ✓ Culturas (sangue, LCR, urina, LBA)

- ✓ Detecção do Ag T urinário

- ✓ Teste de Coombs direto positivo

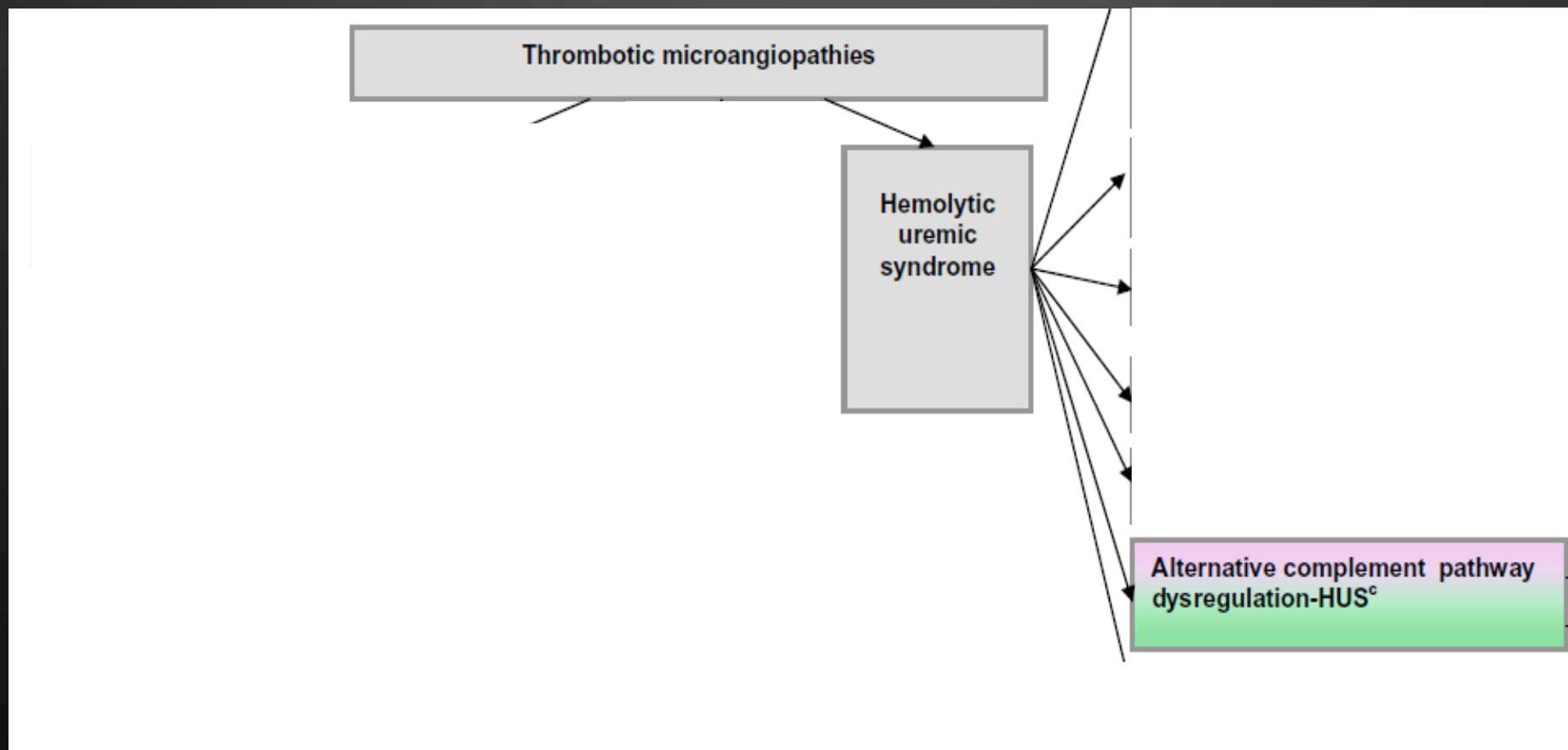
- ✓ Ativação das vias clássica e alternativa do complemento → ↓ CH50, C3, C4

- ✓ Mutações em fatores do complemento



Microangiopatias Trombóticas

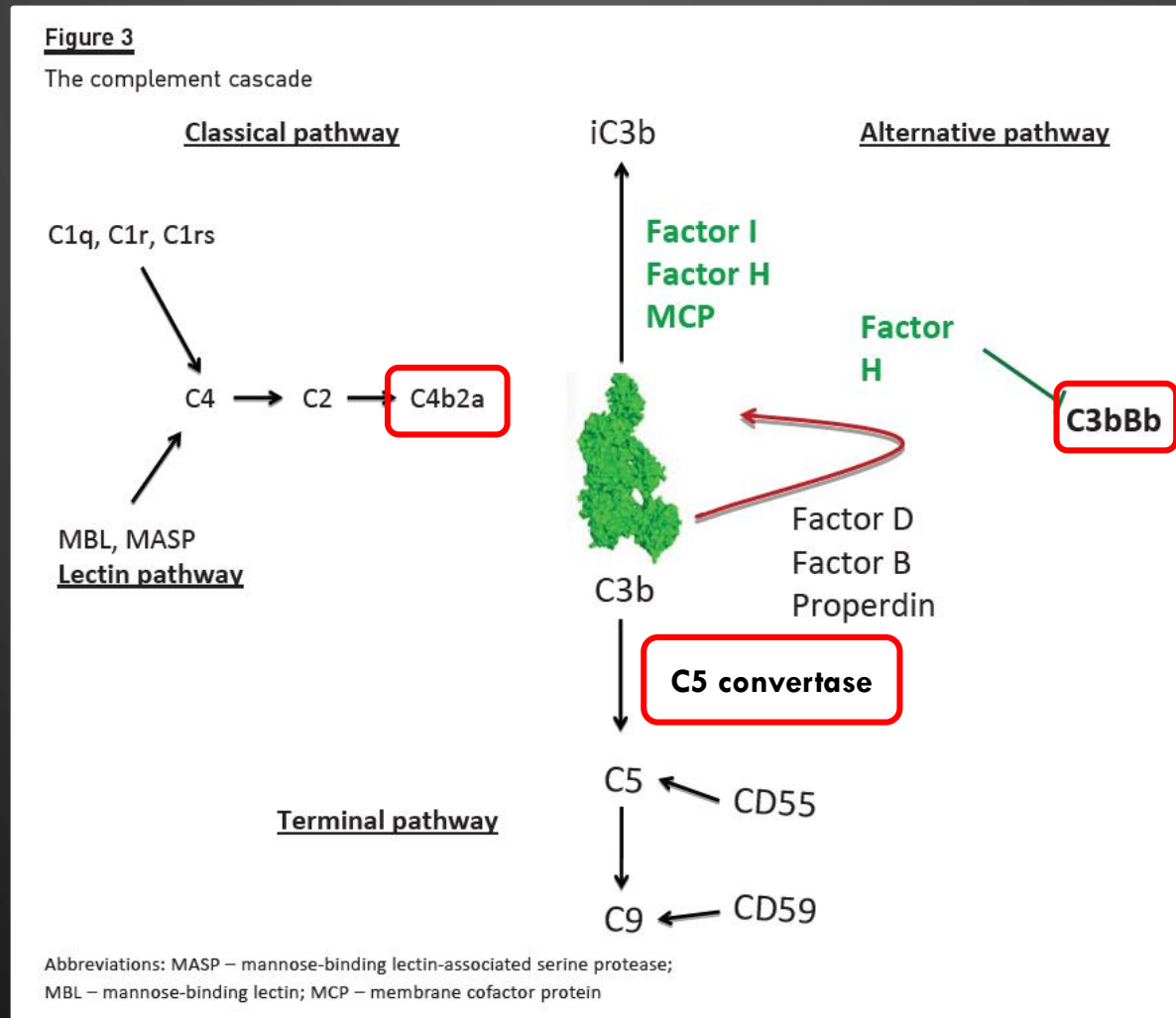
- Classificação etiológica



SHU com desregulação da via alternativa do complemento

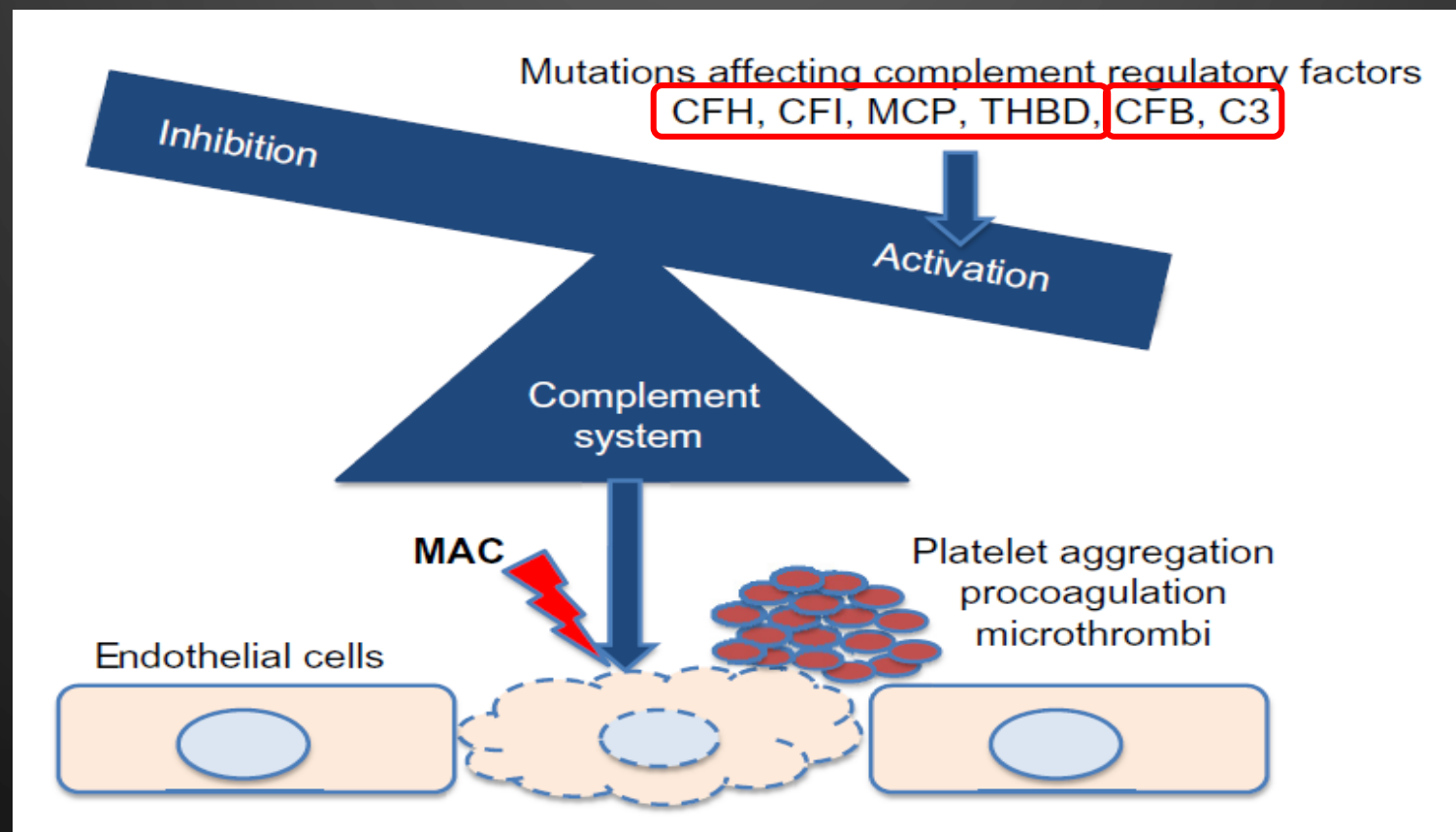
- 5-10% dos casos de SHU
- Incidência: 0,5-2 casos/1.000.000 habitantes/ano
7 casos/1.000.000 crianças/ano
- Em qualquer idade (70% <2 anos)
- Sem predominância de sexo em idade pediátrica
- Esporádico ou familiar

SHU com desregulação da via alternativa do complemento



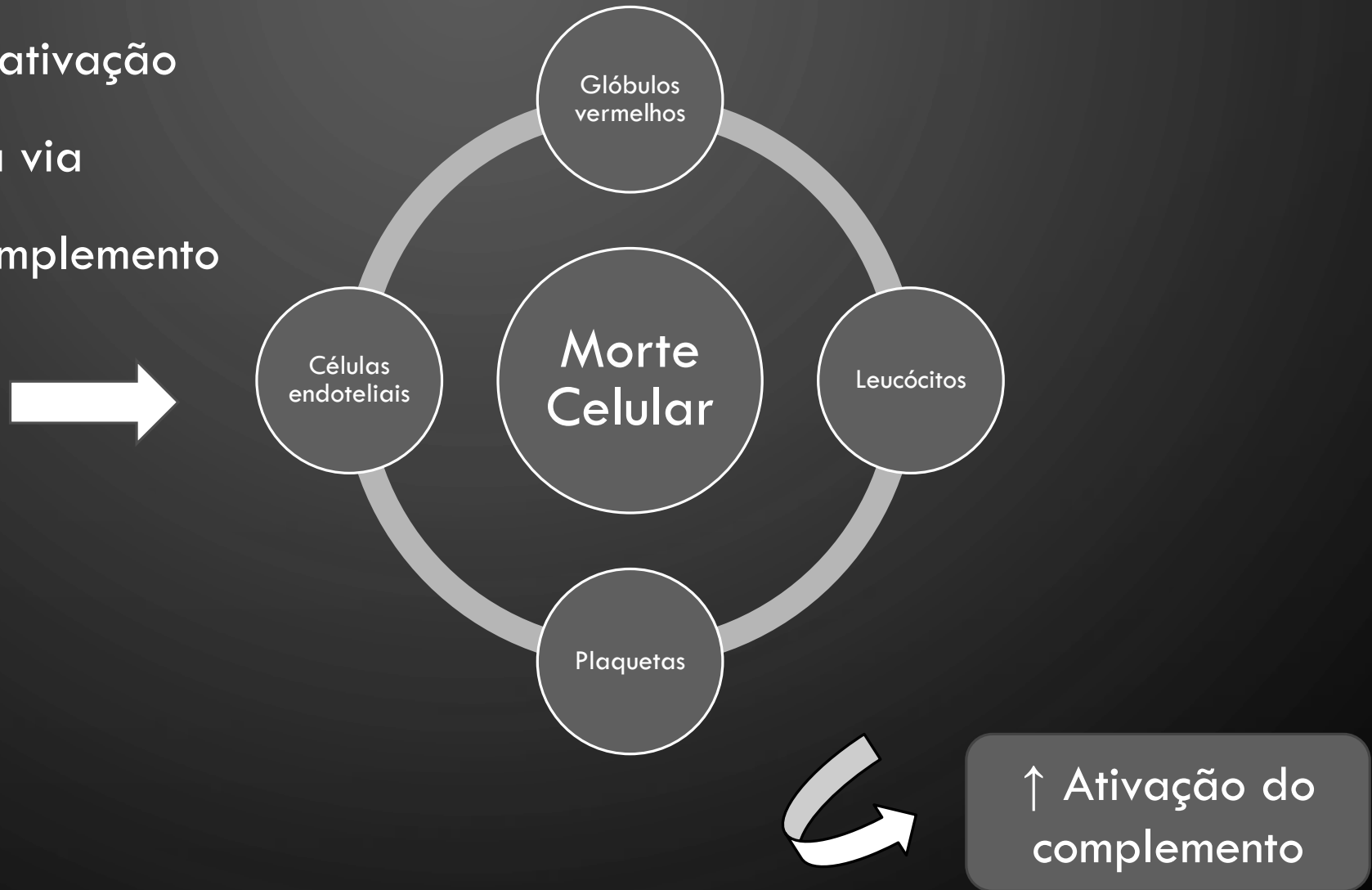
SHU com desregulação da via alternativa do complemento

- Fisiopatologia



SHU com desregulação da via alternativa do complemento

- Fisiopatologia: ativação descontrolada da via alternativa do complemento



SHU com desregulação da via alternativa do complemento

- Anormalidades genéticas foram identificadas em 60-70% pacientes
- 80% das mutações são esporádicas
- Penetrância incompleta: apenas 50% portadores desenvolverão doença
- 3-6% dos pacientes têm >1 mutação

Table 1. Frequencies of the most common mutations identified in aHUS patients

Mutated gene/protein	Type	Frequency (%) [*]	Death or end-stage renal disease 3-10 y after onset (%) [†]
Factor H (including <i>CFH/CFHR1</i> hybrid genes)	Loss of complement regulation	24-28	70-80
<i>MCP</i> (CD46)	Loss of complement regulation	5-9‡	<20
Factor I	Loss of complement regulation	4-8	60-70
<i>C3</i>	Gain of complement activation	2-8	60-70
Factor B	Gain of complement activation	0-4	70
Thrombomodulin	Possibly loss of complement regulation and procoagulative state	0-5	50-60
<i>CFHR1/3</i> deficiency with anti-factor H autoantibodies	Loss of complement regulation	3-10§	30-70
Diacylglycerol kinase ϵ	Prothrombotic	0-3	46
None identified		30-48	50

SHU com desregulação da via alternativa do complemento

- Clínica

- ✓ Início habitualmente insidioso
- ✓ Pode ser precedido de infeção respiratória ou diarreia (50-80%)
- ✓ Manifestações extra-renais em 20%
- ✓ Recidivas frequentes

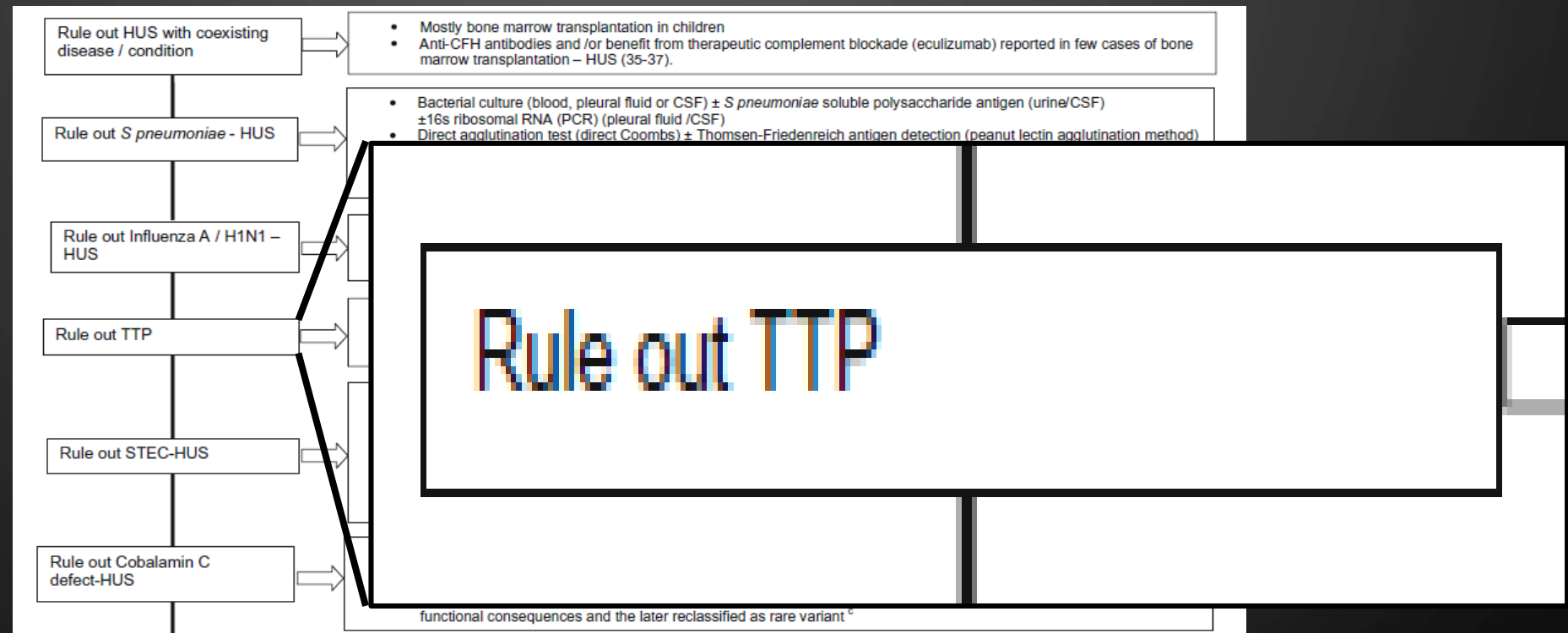
SHU com desregulação da via alternativa do complemento

- Diagnóstico

- ✓ Identificação da anomalia genética
- ✓ Exclusão de outras causas de MAT

SHU com desregulação da via alternativa do complemento

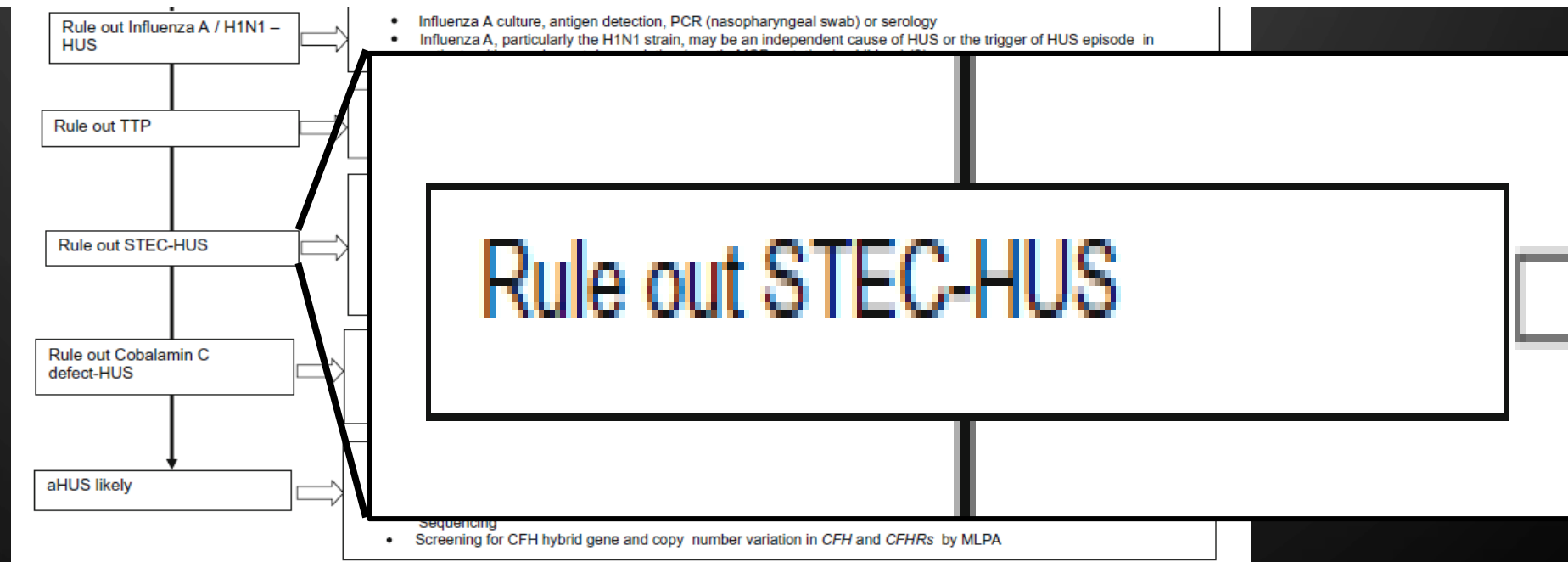
- Diagnóstico: exclusão de outras causas de MAT



- Plasma^a ADAMTS13 activity (Frets VW 73 (40); commercial kits (41,42) only partially reliable)
- Anti-ADAMTS13 antibodies
- No association of congenital TTP with complement mutation (single case associated with a CFH rare variant (43^b))

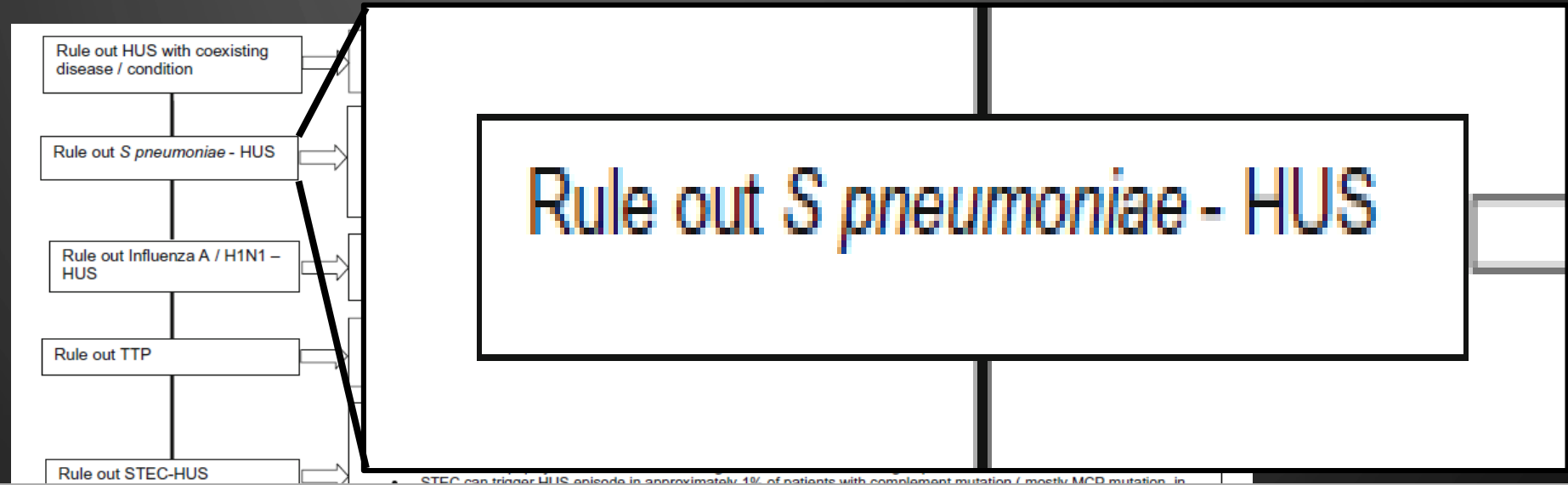
SHU com desregulação da via alternativa do complemento

- Diagnóstico
 - Stool or rectal swab at admission: culture for STEC (sorbitol MacConkey agar for O157:H7; selective media for non-O157 STEC) ; real time PCR for Stx genes; immunologic tests for free Stx, Stx genes or O157 LPS antigen (commercial kits): confirmation by culture or PCR desirable
 - Serum: anti-lipopolysaccharides antibodies against common STEC serogroups
 - STEC can trigger HUS episode in approximately 1% of patients with complement mutation (mostly MCP mutation in children) (3)
 - The alternative complement pathway can be transiently activated during the acute phase of STEC-HUS (44,45)



SHU com desregulação da via alternativa do complemento

- Diagnóstico: exclusão de outras causas de MAT

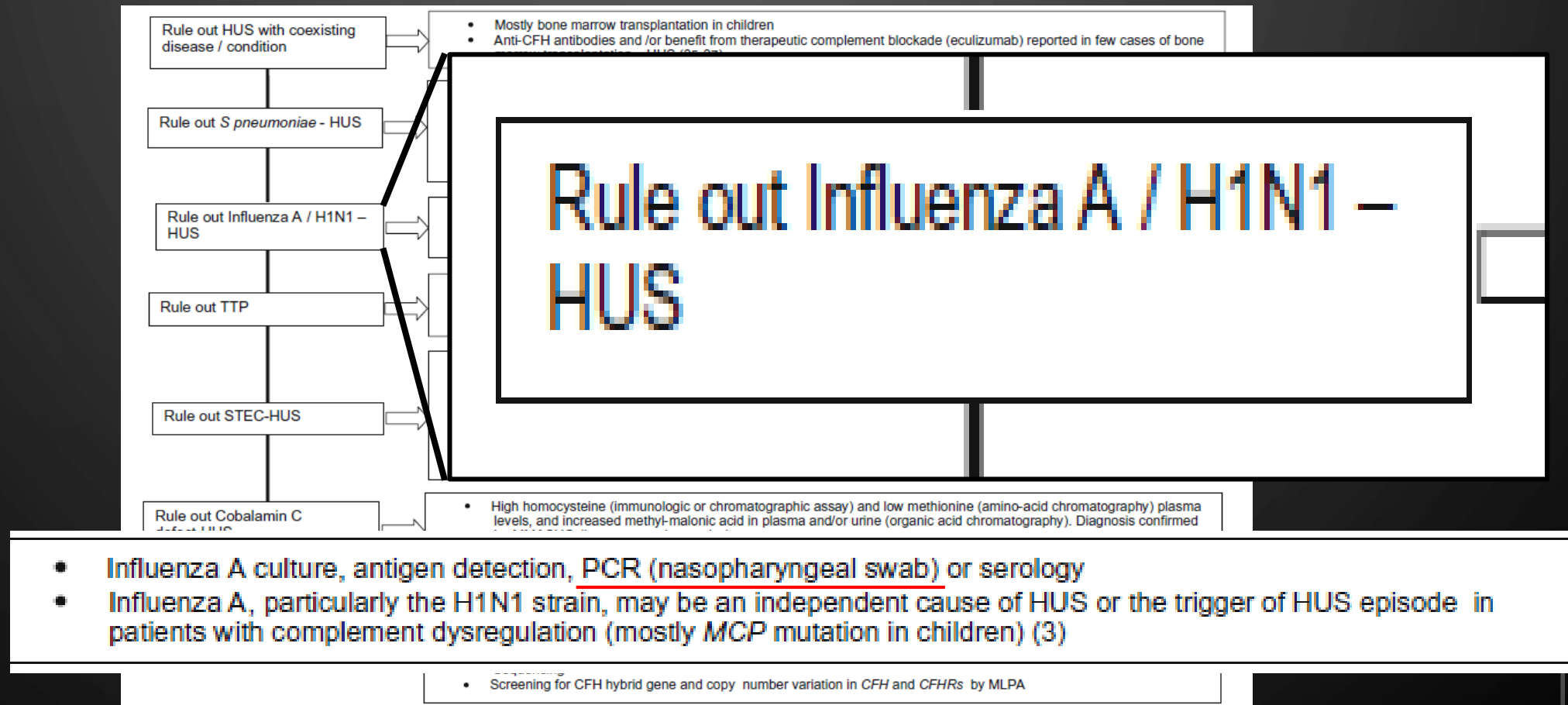


- Bacterial culture (blood, pleural fluid or CSF) ± *S pneumoniae* soluble polysaccharide antigen (urine/CSF) ± 16s ribosomal RNA (PCR) (pleural fluid /CSF)
- Direct agglutination test (direct Coombs) ± Thomsen-Friedenreich antigen detection (peanut lectin agglutination method) confirm neuraminidase activity
- *S pneumoniae* infection may be a complication of influenza A infection
- There is a transient activation of the alternative complement pathway at the acute phase of *S pneumoniae* –HUS (38,39)

• Screening for C3H hybrid gene and copy number variation in C3H and C3HHS by MLPA

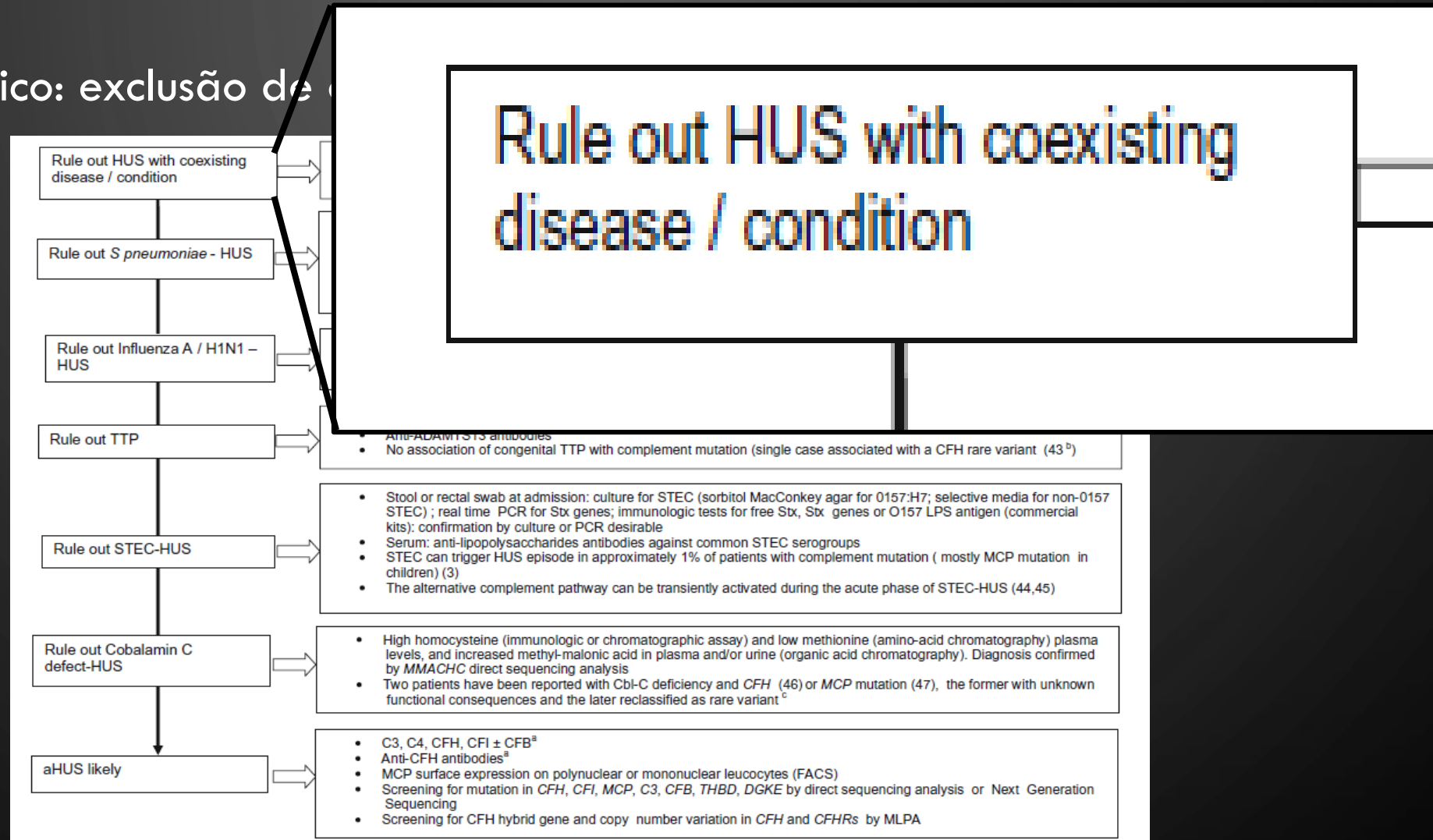
SHU com desregulação da via alternativa do complemento

- Diagnóstico: exclusão de outras causas de MAT



SHU com desregulação da via alternativa do complemento

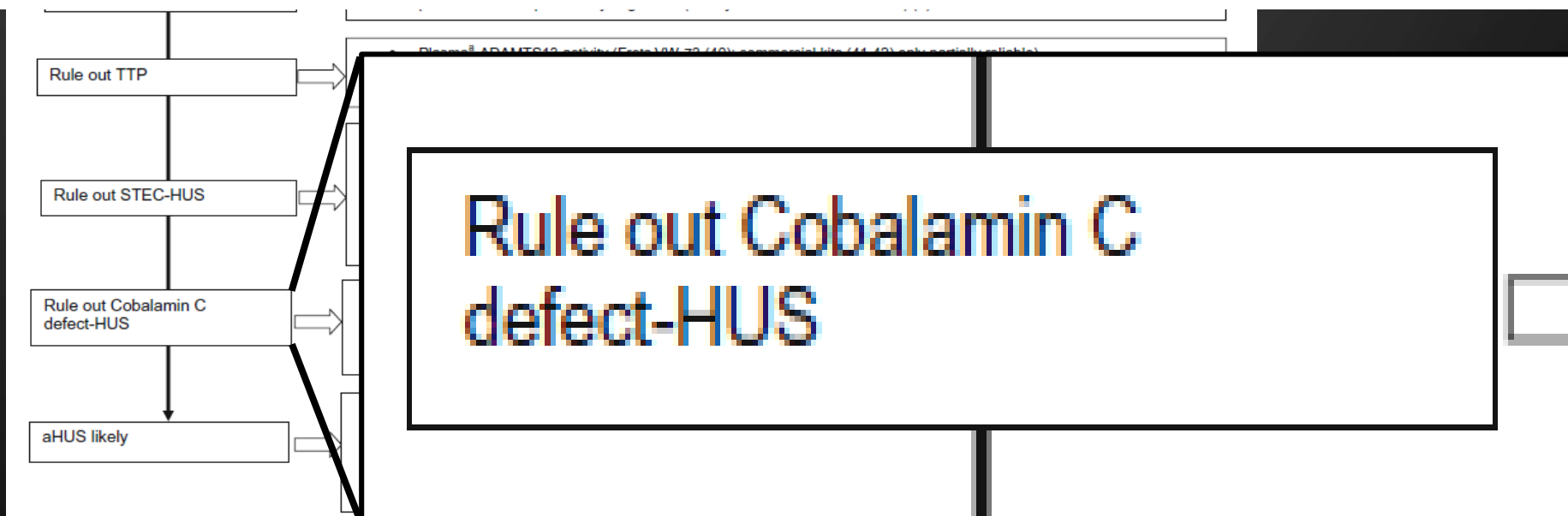
- Diagnóstico: exclusão de



SHU com desregulação da via alternativa do complemento

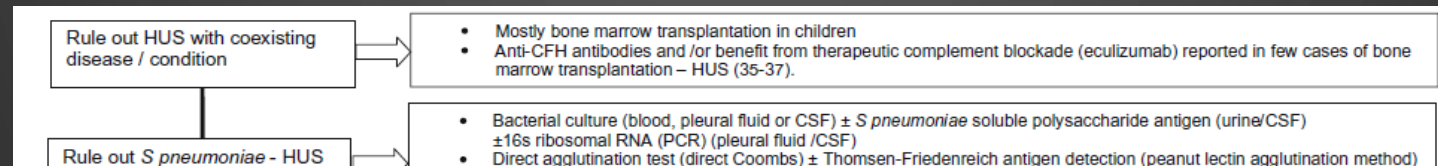
- Diagnóstico: exclusão de outras causas de MAT

- High homocysteine (immunologic or chromatographic assay) and low methionine (amino-acid chromatography) plasma levels, and increased methyl-malonic acid in plasma and/or urine (organic acid chromatography). Diagnosis confirmed by MMACHC direct sequencing analysis
- Two patients have been reported with Cbl-C deficiency and *CFH* (46) or *MCP* mutation (47), the former with unknown functional consequences and the later reclassified as rare variant^c



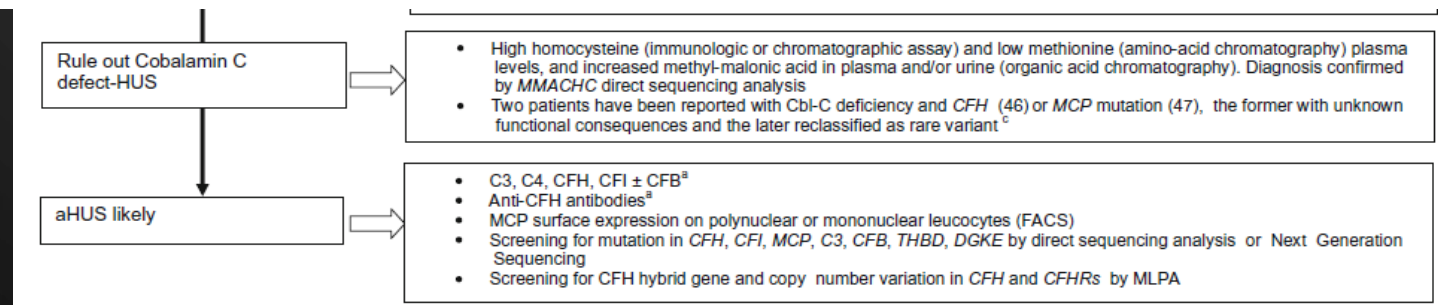
SHU com desregulação da via alternativa do complemento

- Diagnóstico: Identificação da anomalia genética



aHUS likely

- C3, C4, CFH, CFI ± CFB^a, CH50, AH50
- Anti-CFH antibodies^a
- MCP surface expression on polynuclear or mononuclear leucocytes (FACS)
- Screening for mutation in CFH, CFI, MCP, C3, CFB, THBD, DGKE by direct sequencing analysis or Next Generation Sequencing
- Screening for CFH hybrid gene and copy number variation in CFH and CFHRs by MLPA



SHU com desregulação da via alternativa do complemento

- Quando e porquê realizar estudo genético?

When

- First episode of aHUS: Start genetic screening after confirmation that there is no causative disease, no STEC infection, no severe ADAMTS 13 deficiency and no hyperhomocysteinemia /methyl-malonic aciduria.
- Start genetic screening without delay if
 - Relapse of HUS
 - Familial history of non synchronous HUS
 - Pregnancy/post-partum-HUS
 - De novo post-transplant HUS
- Genetic screening required before kidney transplantation for aHUS. Not justified before transplantation for STEC-HUS, unless this diagnosis was uncertain/unproven.

Why

- Genetic characterization necessary for
 - Confirmation that the disease is complement-dependent or not
 - Establishing prognosis, risk of relapses and of progression to ESRD
 - Genetic counselling to parents and family
 - Decisions for kidney transplantation: choice of the donor, treatment schedule to prevent or treat post-transplant recurrence, decision of combined kidney-liver transplantation
 - Further prospective studies are required to establish the safety of complement blockade treatment discontinuation, according to the genetic background

SHU com desregulação da via alternativa do complemento

• Onde realizar?

Table 1

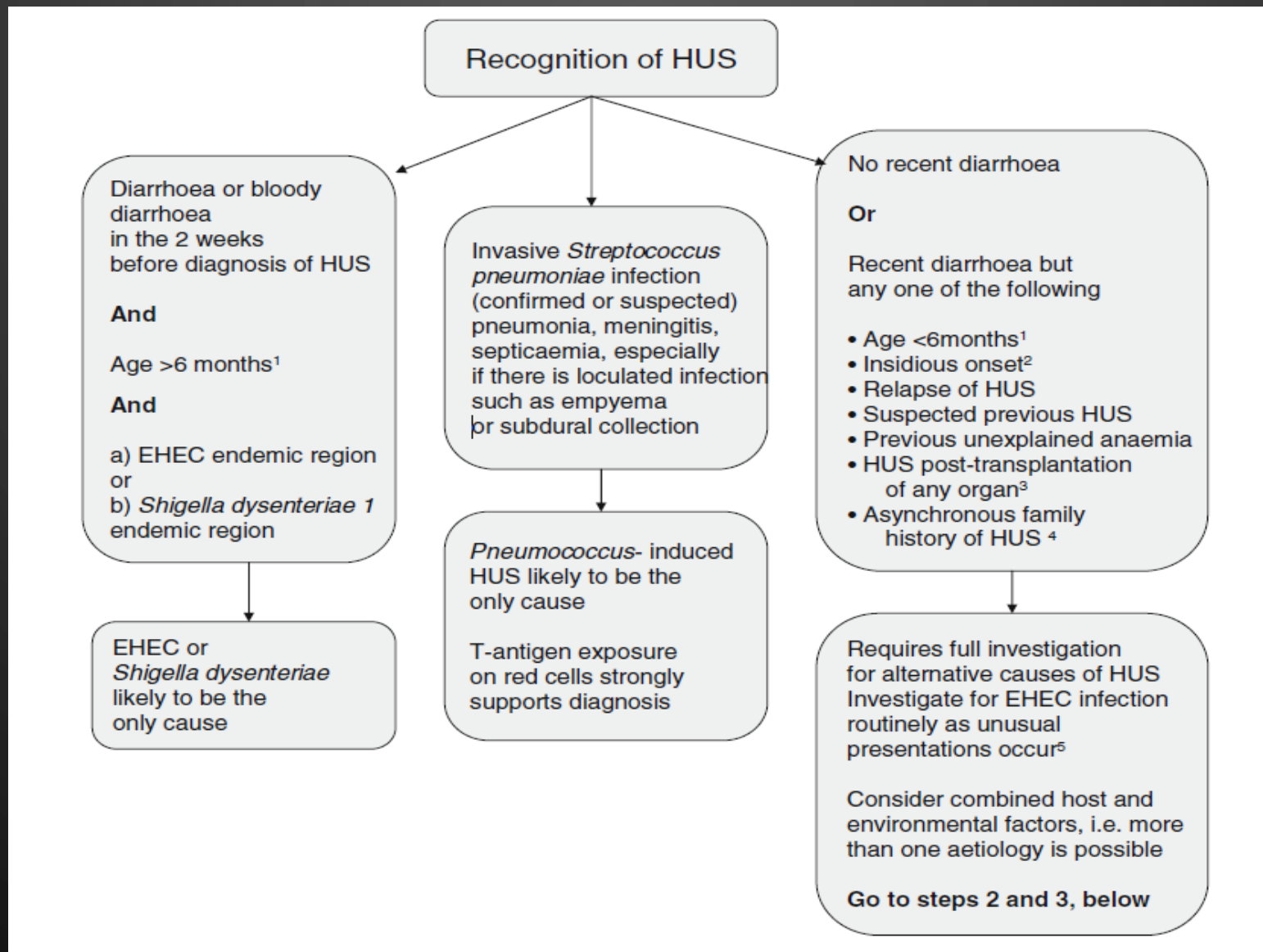
Information for sample collection for analyses in thrombotic microangiopathies

Analyses	Sample	Transport conditions	Aliquots	Lab
• C3; C4	• serum	• frozen sample (sample should arrive frozen at the Lab)		• All labs perform these tests
• Factor H, B, I	• serum	• frozen sample (sample should arrive frozen at the Lab)	2 (10µl each)	• CHLC – Immunology lab – Clinical Pathology
• CH50; AH 50	• serum	• frozen sample (sample should arrive frozen at the Lab)	2 (10µl each)	• CHP; CHLC, HBA, HSM; Terceira;
• Antibodies • Anti factor H	• serum	• frozen sample (sample should arrive frozen at the Lab)	2 (10µl each)	• CHLC; CHP
• MCP (CD46) • Flow cytometry	• all blood • sample with EDTA	• Sample with EDTA (should arrive in the same day)		• No lab performs this test in Portugal
• ADAMTS13 Activity and Antigen • Antibodies Anti ADAMTS13	• Plasma	• Sample with citrate (sample should arrive frozen at the Lab)	3 (20µl each)	• CHUC – Haemostasis and Molecular Haematology Lab • CLHC – Immunology lab
• Shiga Toxin detection • ELISA	• Fresh stool sample	• Sterile container • For solid phase immunodetection of shiga toxins in diluted fecal samples (without the need of stool cultures);		• Local microbiology lab (see text for indications for sending samples to Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa)
• Real-time PCR	• Standard stool culture enrichment	• Requires stool culture enrichment before bacterial DNA extraction and PCR amplification;		
• Sorbitol-MacKonkey (SMAC)	• Stool culture with selective media	• Requires stool culture enrichment with SMAC: solely identifies the E. coli O157:H7 serotype.		

Estudo genético



CHUC
Laboratório de Hematologia
Molecular e Hemostase



Em resumo



Table 1. Laboratory features of the three forms of thrombotic microangiopathy are presented.

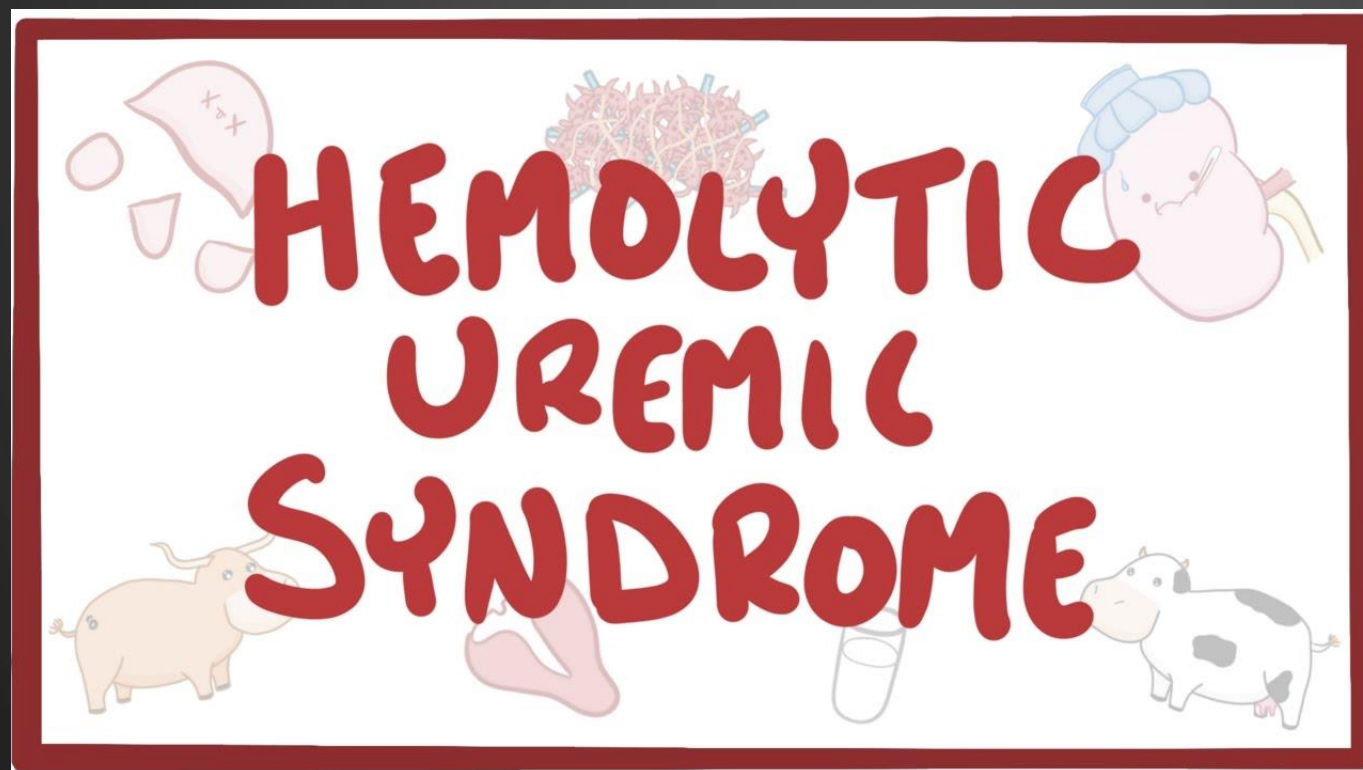
Thrombocytopenia + anemia + target organ injury	ADAMTS13	Shiga-Toxin	Diagnosis
Present	>5%	Negative	aHUS
Present	<5%	Negative	TTP
Present	Normal	Positive	STEC-HUS

aHUS: atypical hemolytic uremic syndrome, TTP: Thrombotic thrombocytopenic purpura, STEC-HUS: hemolytic uremic syndrome associated with Shiga-toxin producing *Escherichia coli*.

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