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Thrombotic Microangiopathies

Thrombotic thrombocytopenic purpura

EuroBloodNet Topic on Focus

Diagnostic workup for TTP and TMA syndromes; pitfalls

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for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

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ISTH MILAN – JULY 2019

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Disclosures

- Industrial
  - research grant support from Shire
  - and fees for board memberships or symposia from Bayer, BMS, Leo pharma, Sanofi Genzyme, Alexion, GSK, roche chugai
  - and having received travel support from Bayer, Bayer, BMS, Leo pharma, Sanofi Genzyme, Alexion, GSK, roche chugai

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  - Académie Nationale de Médecine
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  - Fondation Charles Nicolle
  - Groupe Pasteur Mutualité

Step 1 : Recognize a TMA- Definition and classifications

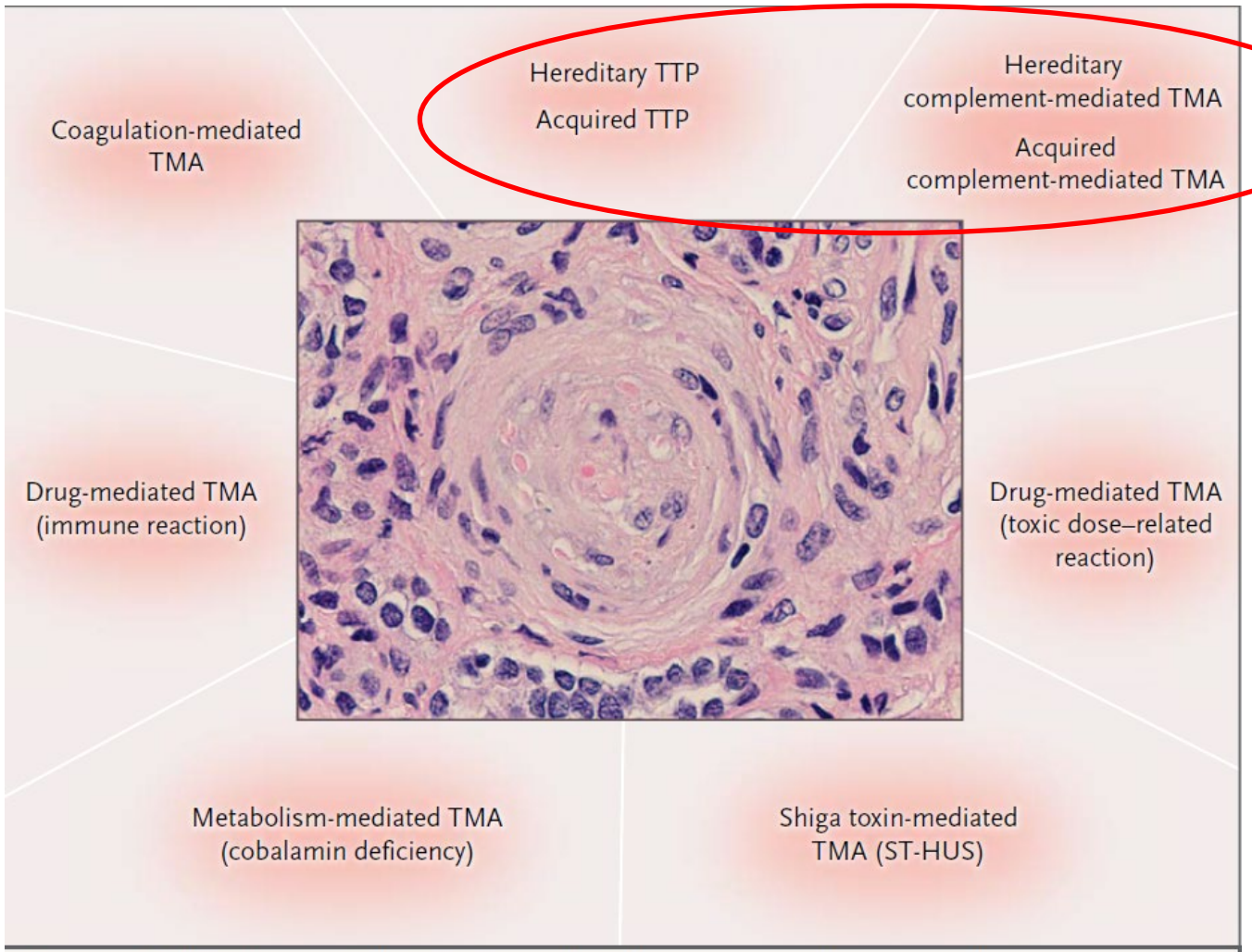
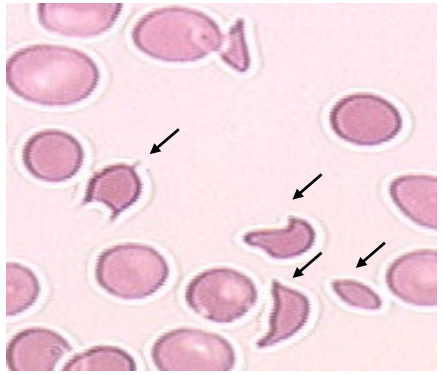


Figure 1. Pathological Features of the Nine Primary Thrombotic Microangiopathy (TMA) Syndromes.

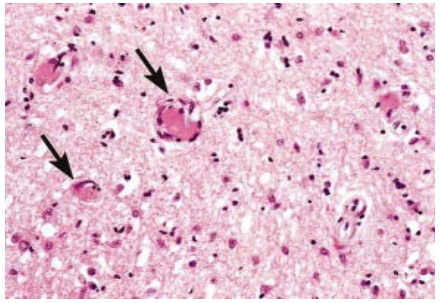
Georges et al, NEJM 2014

TTP: definition – Clinical presentation

- **Mechanical hemolytic anemia**
- **Peripheral thrombocytopenia (< 150 G/L)**
- **Organ failure of variable severity**
- **Severe ADAMTS13 deficiency**



E. Moschcowitz, 1924



Congenital

(Upshaw-Schulman syndrome)

<0.13 cases / 10^6 hab /y

Immune-mediated

(Moschcowitz syndrome)

Women > males

Typically childbearing age

2-3 cases / 10^6 hab /y

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Step 2 : Know the distribution of the different TMAs

Data from a French Retrospective Study including 564 consecutive patients between 2009 and 2016

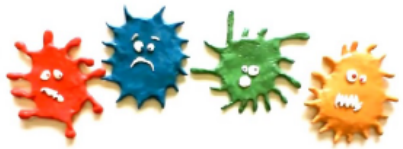
Primary TMA
6%

TTP
3%

aHUS
3%

SECONDARY TMA
94%

35%



33%

26%

19%

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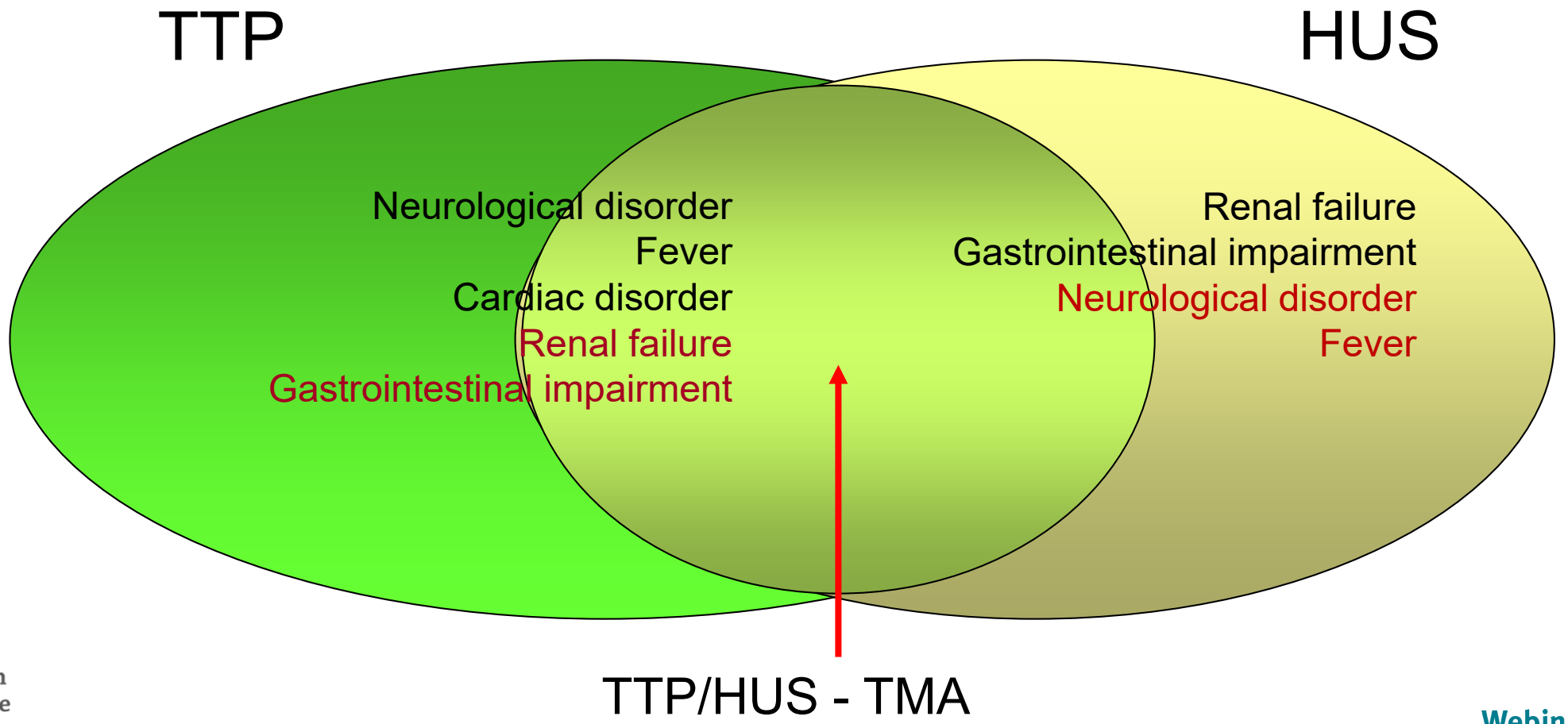
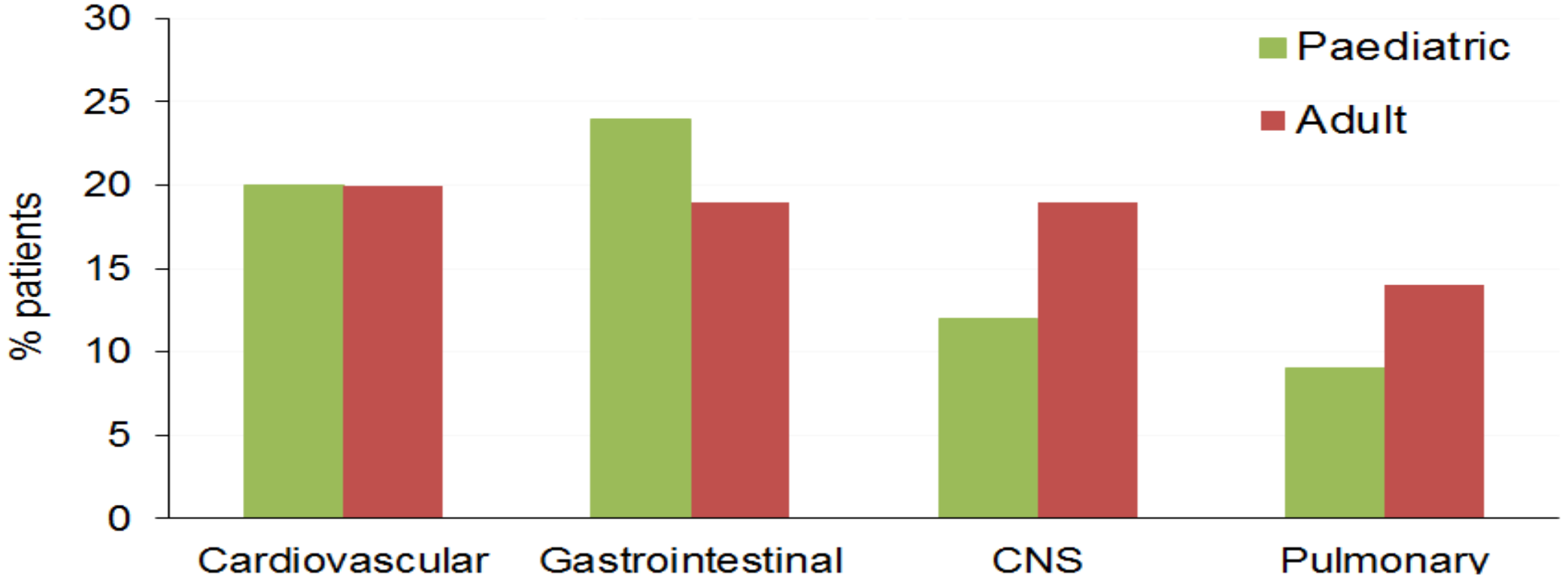
Step 3 : Distinguish between TMAs



Step 3 : Extra-renal clinical presentation of atypical HUS



Schaefer et al., Global aHUS registry data, 2015

Step 4 : Know the Areas for improvement in Diagnosis of iTTP

What do we need to improve in TTP ?

To identify patients with ADAMTS13 < 10% from day 1 (Emergency room)

To identify patients at high risk of early death

Step 4 : Identify patients with ADAMTS13 < 10%

Comparison between patients with or without severe deficit in ADAMTS13

	ADAMTS13 < 5% (N=160)	ADAMTS13 ≥ 5% (N=54)	p value
Age	39.9±15	49.6±17.9	<0.001
Weight (Kg)	69.5±18.6	70.8±14.8	NS
Women	73.5%	80%	NS
Fever	32%	42%	NS
Cerebral involvment	53%	56%	NS
Autoimmunity	20%	13%	NS
Hémoglobin (g/dL)	8 ± 2.2	8.4 ± 2.2	NS
LDH (U/L)	6.2 ± 4.5	5.7 ± 3.5	NS
Platelets ($x10^9$/L)	20.4 ± 19.2	56.6 ± 42.9	<0.0001
Créatinin (µmol/L)	127 ± 106	425 ± 335	<0.0001
Antinuclear factors	53%	24%	<0.0001
End stage renal failure	0	10 (21%)	<0.0001

Coppo et al, Medicine 2004; Plos One 2010

Step 4 : Identify patients with ADAMTS13 < 10%

Table 4. Association Between Patient Characteristics and ADAMTS13 Deficiency Using Multivariate Analysis.

Patient Characteristics	Adjusted Odds Ratio	95% CI	*P* Value
Creatinine level ≤200 µmol/L (2.26 mg/dL)	23.4	8.8–62.5	<.001
Platelet count ≤30×10^9/L	9.1	3.4–24.2	<.001
Positive ANA	2.8	1.0–8.0	<.05

Table 5. Internal Validation to Predict Severe ADAMTS13 Deficiency at Clinical Presentation.

	At Least 1 Positive Criterion	All 3 Criteria Positive
Sensitivity	98.8 (96.9–100)	46.9 (41.3–53.1)
Specificity	48.1 (38.9–59.3)	98.1 (94.4–100)
Positive predictive value	85.0 (82.6–87.7)	98.7 (96.4–100)
Negative predictive value	93.3 (85.2–100)	38.6 (35.8–41.9)

Platelet count < 30 and creatinine level <200: consistently associated with severe ADAMTS13 deficiency

Coppo et al, Medicine 2004, Plos One 2010

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Step 4 : Predictive features of severe ADAMTS13 deficiency

French score

Platelet count < 30 and creatinine level <2.26

Positive predictive value: 85%
Negative predictive value: 93.3%

CNR-MAT, Medicine 2004
CNR-MAT, Plos One 2010

Platelets/creatinine

	Platelet count (150–400 × 10^9/l)	Creatinine (µmol/l)
ADAMTS13 <10% (n = 40)	12	132·6
ADAMTS13 >10% (n = 14)	66	512·7
P-value	<0·0001	<0·0001

Cataland et al., Br J Haematol 2012

Platelets/creatinine
D-dimers/Reticulocytes
Indirect bilirubin

TABLE 4. Clinical prediction score*

Variable	Assigned points	Total score by model (points)	Probability of TTP (%)
Creatinine >2.0 mg/dL	−11.5	<20	0
PLTs >35 ×10⁹/L	−30	20-30	40
D-dimer >4.0 µg/mL	−10	>30	100
Reticulocytes >3%	21		
Indirect bilirubin >1.5 mg/dL	20.5		

Bentley et al., Transfusion 2010

Plasmic score (7 points)

	β	SE	Odds ratio (95% CI)	p value
Platelet count <29 × 10⁹ per L	2·83	0·58	16·9 (5·4–53·0)	<0·0001
Creatinine <1·8 mg/dL	2·74	0·61	15·5 (4·7–51·2)	<0·0001
INR <1·3	2·69	0·84	14·7 (2·8–76·5)	0·0014
MCV <86·5 fL†	2·29	0·57	9·9 (3·2–30·4)	0·0001
Haemolysis variable‡	1·80	0·74	6·0 (1·4–25·7)	0·015

Bendapudi et al., Lancet Haematol 2017

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Predictive features of severe ADAMTS13 deficiency

TABLE 1 PLASMIC score or French score predicts the likelihood of severe ADAMTS13 deficiency in a suspected TTP

Parameters	French Score	PLASMIC Score
Platelet count	$<30 \times 10^9$/L (+1)	$<30 \times 10^9$/L (+1)
Serum creatinine level	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis		
Indirect bilirubin >2 mg/dL	[a]	+1
or reticulocyte count >2.5%		
or undetectable haptoglobin		
No active cancer in previous year	[a]	+1
No history of solid organ or SCT	[a]	+1
INR < 1.5	[a]	+1
MCV < 90 fL	NA	+1
Likelihood of severe deficiency of ADAMTS13 activity (<10%)	0: 2%	0-4: 0%-4%
	1: 70%	6: 5%-24%
	2: 94%	6-7: 62%-82%

TMA without specific medical context
(pregnancy, cancer, graft, sepsis, chemotherapy)

↓

Severe thrombopénia < 30
+ mild renal failure < 200

↓

TTP > 90% of cases

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Why TTP patients still die at the acute phase?

Main causes of death in acquired TTP in 2021

We learnt how to manage these patients at the acute phase;
but…Mortality is still around 10-15%

Misdiagnosed TTP

Delayed management

Make clinicians more aware of TTP diagnosis

Fulminant cases dying the first days of management

Recognise most severe patients

Intensify those patients from diagnosis

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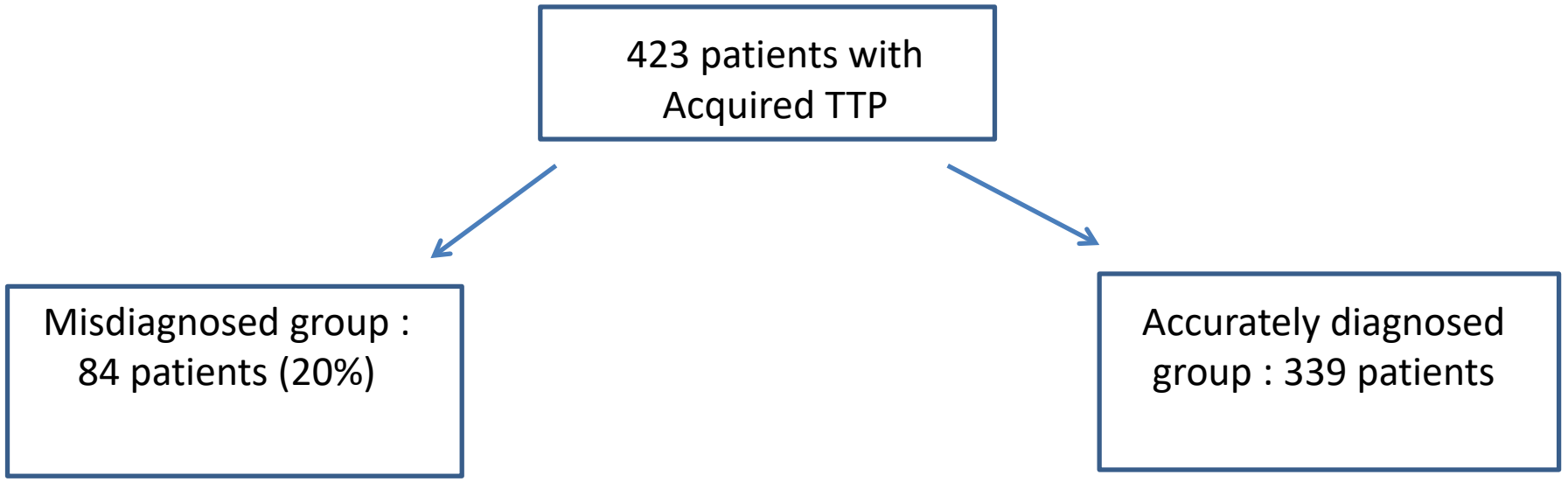
Step 5 : Reduce the Misdiagnosed TTP

Thrombotic thrombocytopenic purpura misdiagnosed as autoimmune cytopenia: Causes of diagnostic errors and consequence on outcome. Experience of the French thrombotic microangiopathies reference centre



What about misdiagnosed patients ?

Grall et al., Am J Hematol 2017

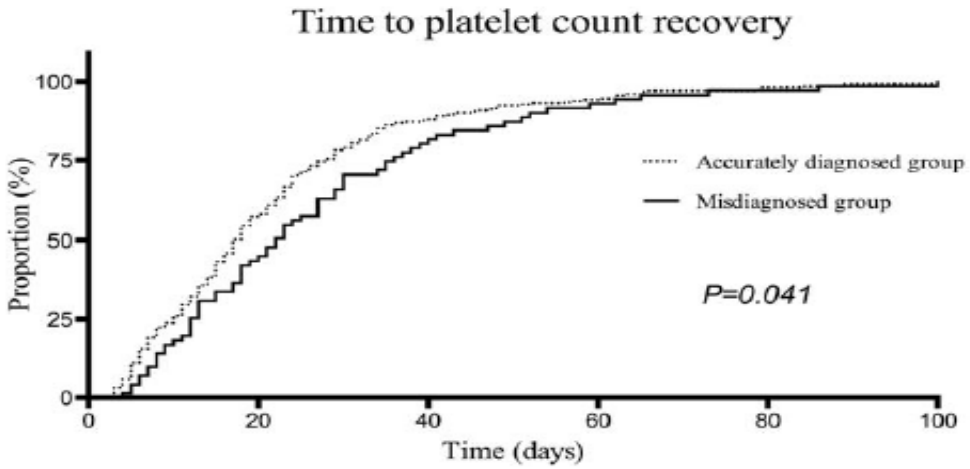
Step 5 : Reduce the Misdiagnosed TTP

Association between patient's characterisitcs and diagnostic error

Parameters	Odds ratio	95% CI	*P* value
Sex (female)	2.33	1.12–5.12	0.02
AID on diagnosis	1.56	0.73–3.34	0.25
Hemoglobin level (per unit increased)	1.20	1.02–1.43	0.03
Positive DAT	6.88	1.84–33.82	0.004
Low or undetectable schistocytes	3.17	1.73–5.93	<0.001
Positive ANA	1.68	0.89–3.23	0.11

The main alternative diagnoses :

- ✓ Evans Syndrome in 43 cases (51%)
- ✓ Immune thrombocytopenia in 31 cases (38%)
- ✓ Antiphospholid syndrome



Grall et al., Am J Hematol 2017

But no more deaths

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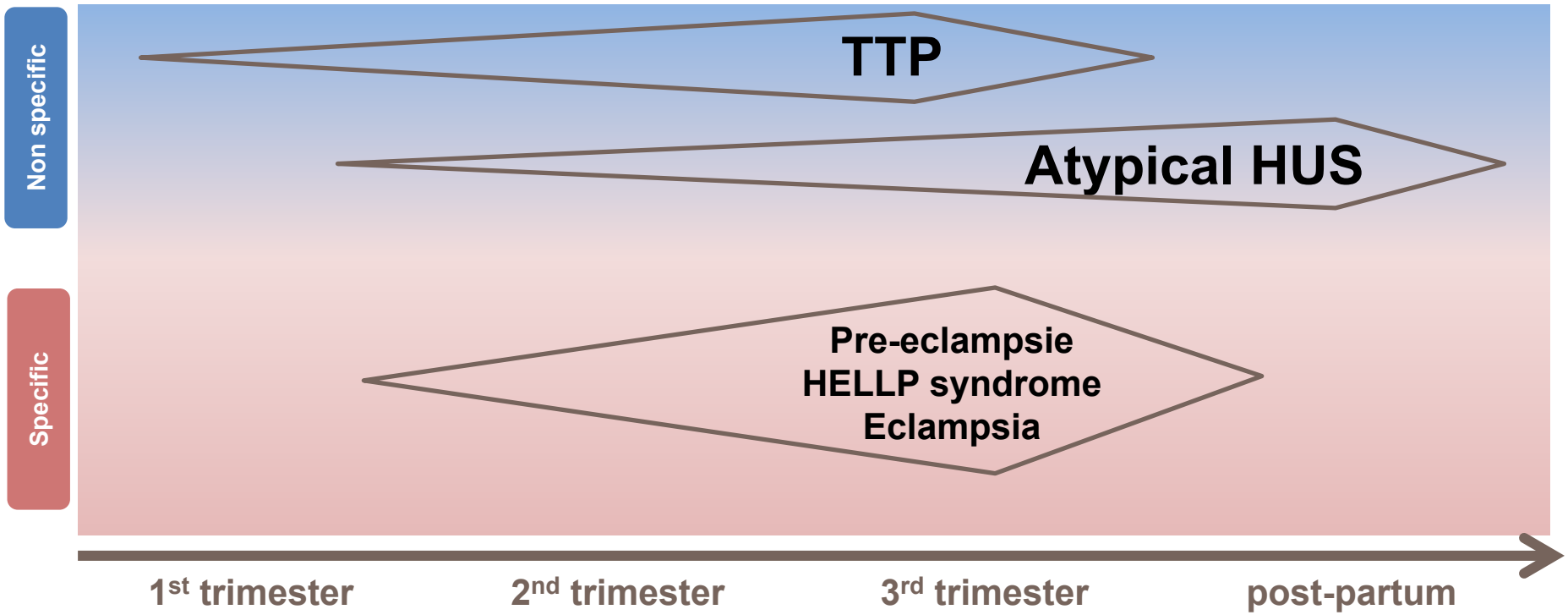
Various TMAs with similar presentations during pregnancy



Similar clinical presentation

Despite a distinct pathophysiology

Specific management

Need to be distinguished to avoid important therapeutic errors

Rehberg et al., Obstetrics Gynecol 2006

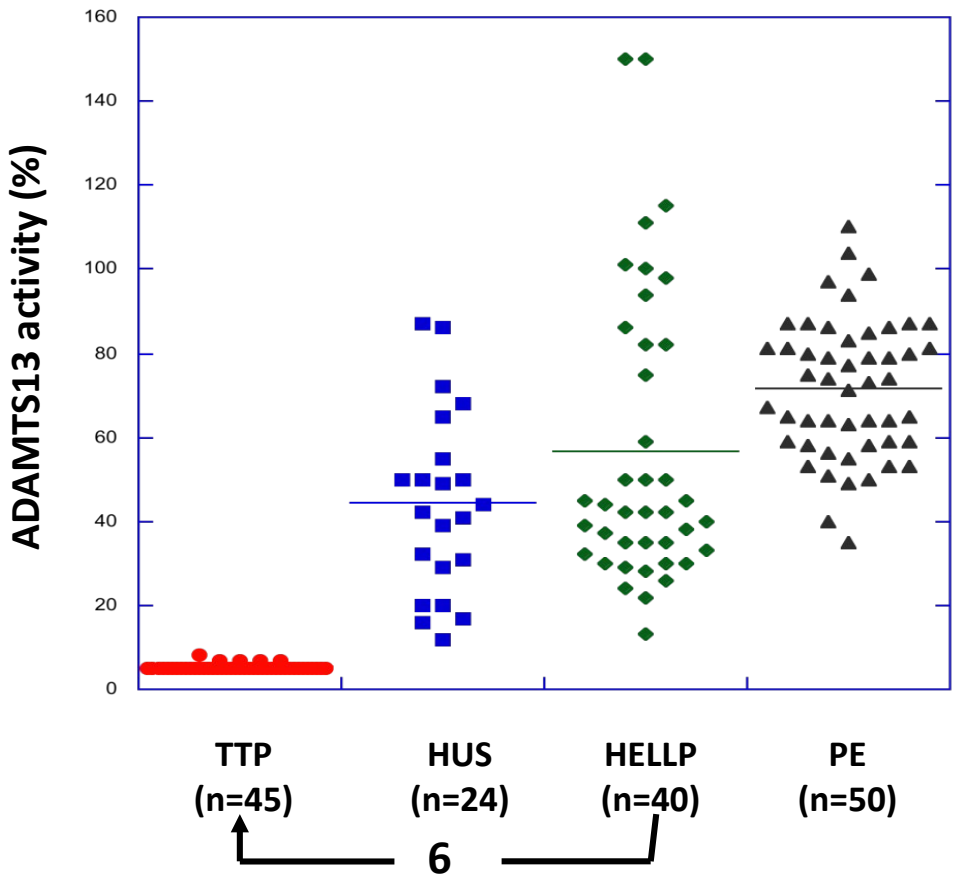
ADAMTS13: the most reliable marker to distinguish TTP from severe HELLP

Comparison between iTTP patients (N = 45) and HELLP syndromes (N = 40)

PTT *vs* HELLP
Fever 24% *vs* 9%
Anemia 7.3±1,6 g/dl *vs* 9.2±2.2
Platelets/creatinine comparable

LDH/ASAT comparable+++

No reliable clinical surrogate marker



ADAMTS13 activity is the reliable marker: allowed revisiting the diagnosis of HELLP for TTP in 6/46 (13%) patients

CNR-MAT, unpublished data

Step 5 : Recognize a frequent pitfall - PSEUDO TMA

Lettres À La Rédaction

Faux Moskowitz, vrai Biermer

P.L. Blanc[1], E. Legrand[1] and J.M. Marc[1]

[1]Service de médecine D, centre hospitalier, 07103 Annonay, France

Received 30 April 1999; accepted 7 July 1999. Available online 27 March 2000.

Am J Med. 2003 Apr 1;114(5):423-5.

Schizocytosis in pernicious anemia mimicking thrombotic thrombocytopenic purpura.

Garderet L, Maury E, Lagrange M, Najman A, Offenstadt G, Guidet B.

PMID: 12714141 [PubMed - indexed for MEDLINE]

Step 5 : Recognize a frequent pitfall - PSEUDO TMA

Table 1 Comparison of pseudo-TMA and TTP groups

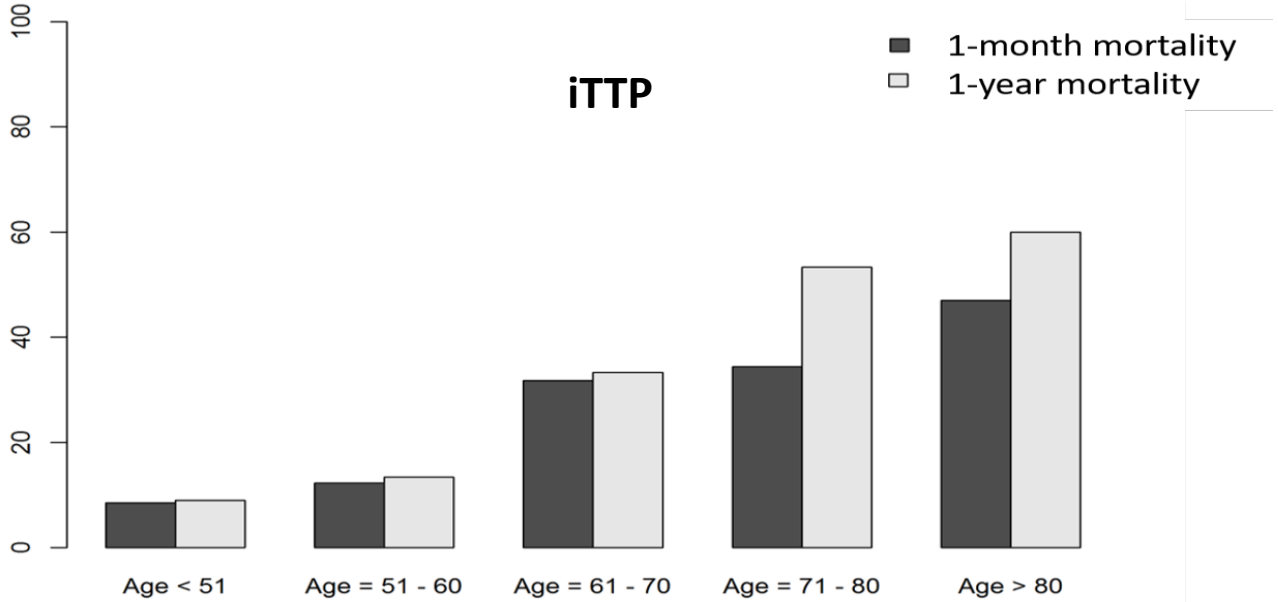
	Pseudo-TMA ($n=7$)	TTP ($n=6$)	*P*-value
Clinical characteristics			
Male, *n* (%)	5 (71.4)	2 (33.3)	0.17
Age at hospitalization (years)	72 (43–78)	35.2 (23.4–74)	0.05
Caucasian origin, *n* (%)	3 (42.9)	4 (66.7)	0.59
Neurological symptoms, *n* (%)	2[a] (28.6)	4 (66.6)	0.17
Acute kidney failure, *n* (%)	0 (0)	2 (33.3)	0.10
Hematological characteristics			
Hemoglobin (g/l)	42 (35–79)	69 (49–110)	0.07
Schistocytes, *n* (%)	7 (100)	6 (100)	1
Reticulocyte count (10^9/l)	13.1 (6.3–39.8)	265.5 (134–500)	0.0012
Mean corpuscular volume (fl)	110.6 (96.3–130)	92 (82–118)	0.05
Platelet count (10^9/L)	73 (38–145)	12.5 (8–41)	0.0023
White blood cell count (10^9/l)	3.4 (1.3–6.2)	7.0 (5.8–13.3)	0.0047
Neutrophil count (10^9/l)	1.3 (0.5–3.6)	5.1 (3.4–10)	0.0023
Neutropenia (<1 10^9/l), *n* (%)	2 (28.6)	0 (0)	0.15
Pancytopenia, *n* (%)	2 (28.6)	0 (0)	0.15
Hemolysis and biochemical patterns			
LDH (IU/l, Normal <480)	7310 (1084–16520)	1460 (866–2976)	0.01
Haptoglobin (g/l, Normal >0.2)	0.1 (0.1–0.9)	0.08 (0.06–1.06)	0.75
Bilirubin (µmol/l, Normal <10)	21 (16–49)	25 (5–85)	0.72
Outcome			
Length of hospital stay (days)	14 (5–26)	34 (9–45)	0.03

Noel et al, QJM 2013

TTP in the elderly: Keep your mind open for unusual presentations

	Age < 60 n = 340		Age ≥ 60 n = 71		*p*-value
Delirium	61	18 %	21	30 %	0.034
Seizures	25	7 %	11	15 %	0.038
Behaviour abnormalities	46	14 %	17	24 %	0.045
Plasma creatinine (µmol/L)	89	[73;120]	124	[89;198]	<0.0001
Platelets count (G/L)	13	[9;21]	22	[9;57]	0.002
Haemoglobin level (g/dL)	8	[7;10]	9	[8;11]	0.0007
High French score predictive of a severe ADAMTS13 deficiency (score=2)	273	80 %	43	61 %	< 0.0001
Time from hospital admission to diagnosis (days)	1	[1;3]	3	[1;7]	0.0001

Prevel et al., Blood 2019



iTTP in older patients has atypical clinical features that may not be alarming at this age but delaying diagnosis, with higher 1-month and 1-year mortality rates; it also negatively impacts life expectancy in survivors

Recognize the most severe forms of TTP

Most deaths occurred in the first two weeks after diagnosis mainly in a context of multiple organ failure in relation with uncontrolled TTP : Is there a profile of patients whose outcome is worse ?

248 patients – idiopathic TTP (ADAMTS13 < 10%; antibodies +)

27 early deaths (30 days) and 221 survivors (~ 90 %)

Factors associated with early death (< 30 days):
Multivariate analysis

Table 4. Association between patients' characteristics and outcome by multivariable analysis.

	Odds Ratio	95% CI	*P*	Score
Cerebral involvement	2.6	[1.0, 6.9]	0.05	+1
Age			8.10^{-6}	
≤40	1	-		+0
41-60	3.4	[1.2, 9.7]		+1
> 60	10.6	[2.0, 32.0]		+2
LDH level ≥ 10N	3.0	[1.3, 11.6]	0.014	+1

CI, confidence interval; N: number of times the upper normal value.

Mortality rate

Patients with 2 points : 32%
Patients with 3 points : 39%
Patients with 4 points 66%

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Benhamou et al., Haematologica 2012

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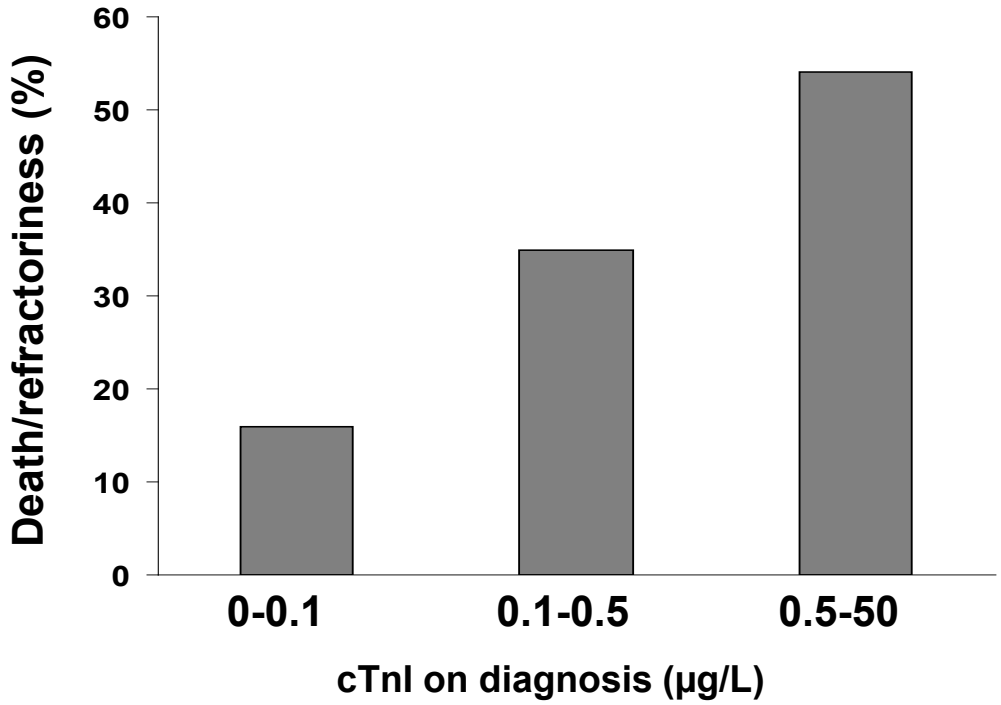
Prognostic value of cardiac troponin I (cTnI)

133 patients – Acquired idiopathic TTP (ADAMTS13 < 10%; Abs +)

cTnI: independent factor for death/refractoriness

	Odds ratio	95%CI	P-value
cTnI >0.25 µg/L	**2.86**	**[1.13,7.22]**	**0.024**
Age (y) ≤40	1		0.7
[41,60]	1.54	[0.49,4.87]	
>60	1.76	[0.48,6.54]	
Neurologic involvement	1.66	[0.58,4.78]	0.4
eGFR	0.61	[0.23,1.63]	0.32

Higher levels = worse outcome



Reliable marker of severe disease

Hugues C et al., J Thromb Haemost 2009;
Benhamou et al., J Thromb Haemost 2015

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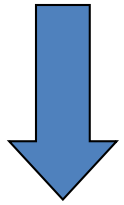
Take home message

- ✓ TMA is a common medical disorder with a severe prognosis when specific treatment is delayed
- ✓ Predicitve rules are available to identify patients with severe deficit in ADAMTS 13
- ✓ Prognosis assessment based on age, cerebral involvement, LDH and Troponin levels is useful for personalized treatment
- ✓ Be aware of certain clinical situation (pregnancy) and certain pitfalls that can induce misdiagnosis

Learning by experience can be painful…



…but it is still more painful not to learn from experience…

Discussion