Coexistence of Haemolytic Uremic Syndrome with acute pancreatitis: "The Dilemma of Double Trouble"- An Analysis of Four Cases and Review of Literature

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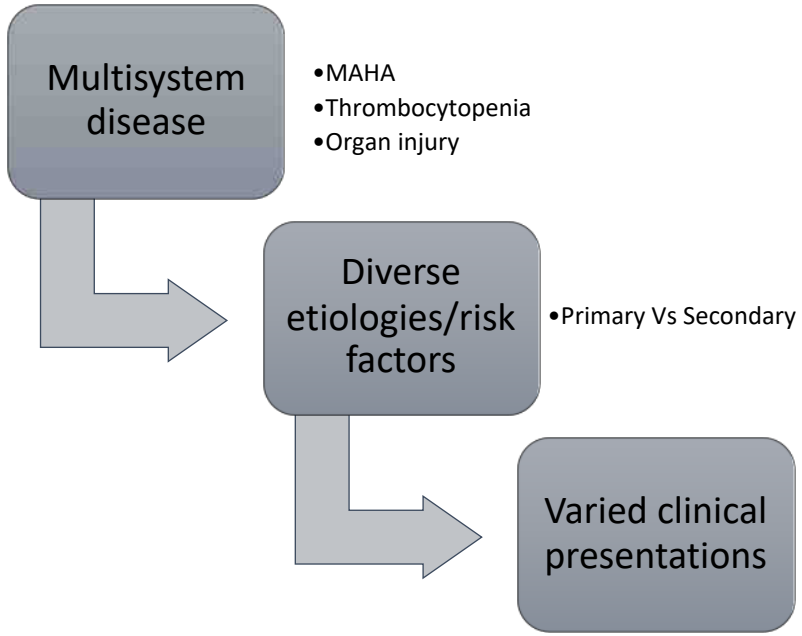
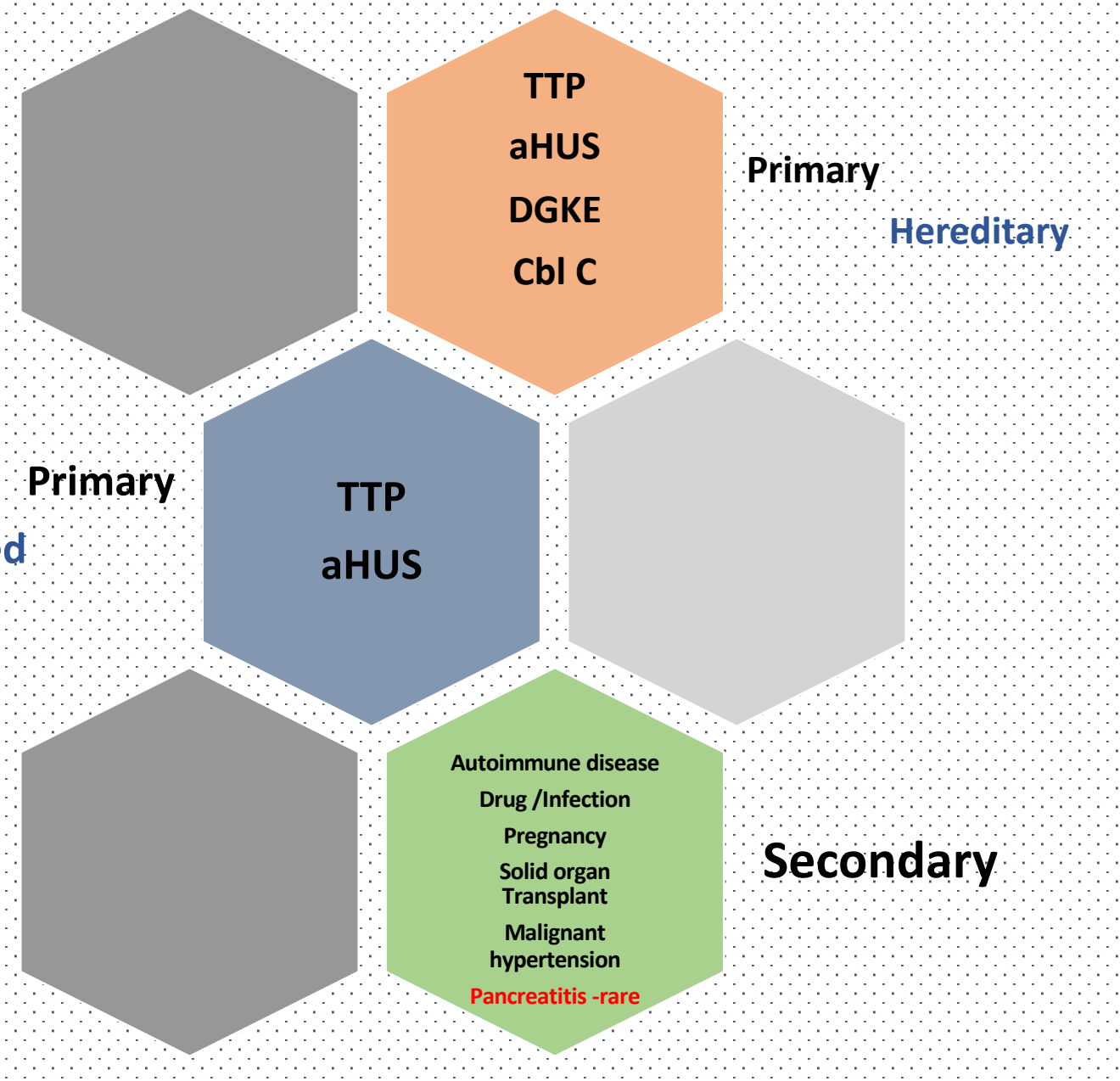
LUCKNOW

Introduction

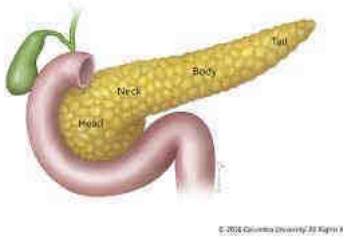
TMA

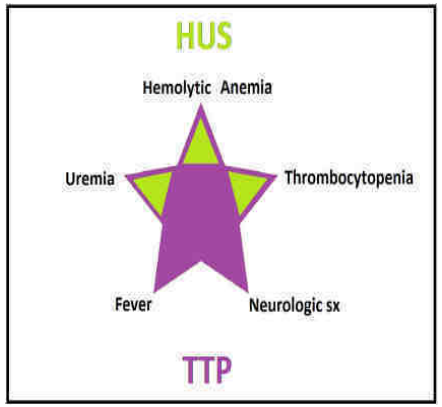




TMA- Thrombotic Microangiopathy
TTP- Thrombotic Thrombocytopenic Purpura
aHUS- atypical hemolytic uremic syndrome
Cbl C- Cobalamin C
DGKE- Diacylglycerol Kinase Epsilon
MAHA-Microangiopathic Hemolytic Anemia

Coexistence of pancreatitis and aHUS/TTP

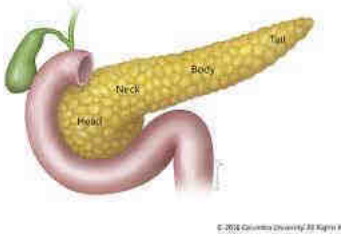




41 cases since 1978
AP→aHUS/TTP
aHUS/TTP→ AP (rarely reported)

AP- Acute Pancreatitis
TTP- Thrombotic Thrombocytopenic Purpura
aHUS- atypical hemolytic uremic syndrome
HUS- hemolytic uremic syndrome

Requires primary management of pancreatitis



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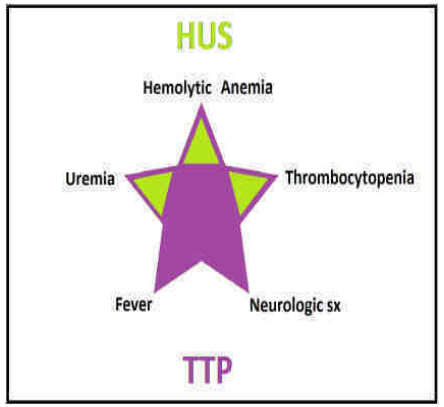

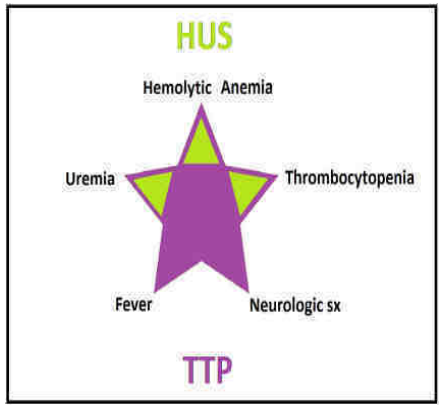

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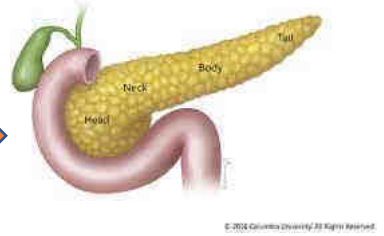
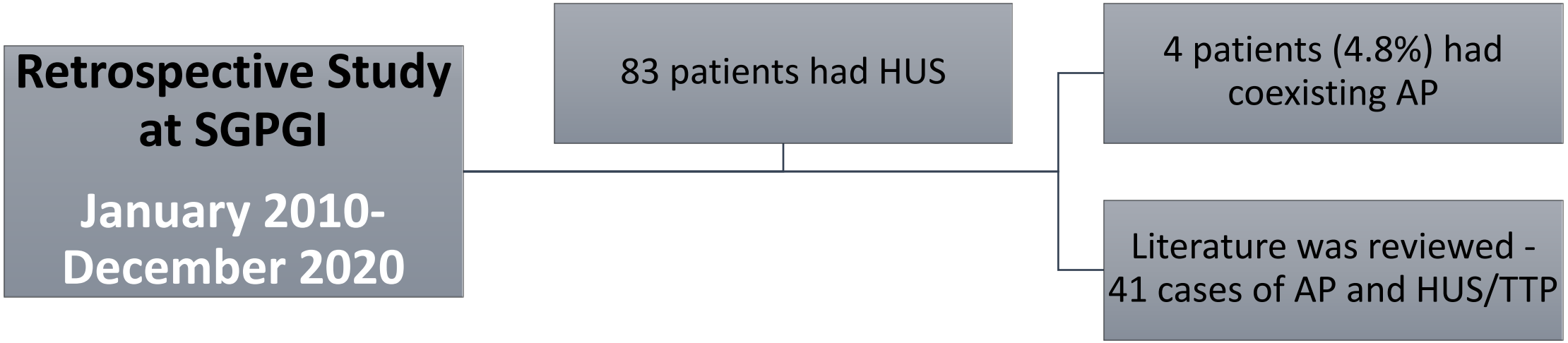


Requires primary management of HUS/TTP

Material and methods: Study design



AP- Acute Pancreatitis
TTP- Thrombotic Thrombocytopenic Purpura
HUS- hemolytic uremic syndrome

Material and methods: Definitions

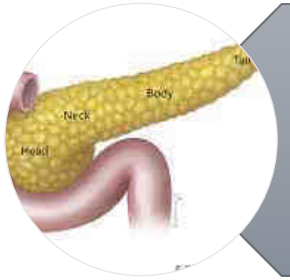
- TMA-defined clinically as MAHA, thrombocytopenia and organ dysfunction
- Pancreatitis and its severity-according to the 2012 Atlanta classification
- AKI- defined as per KIDGO criteria

- HUS- aHUS due to complement dysregulation, due to shiga toxin, other genetic causes
- TTP – ADAMTS13 < 10%, inherited or acquired
- Secondary HUS-HUS associated with co-existing diseases (drugs, infection, malignancy,transplant,systemic diseases)

AP- Acute Pancreatitis
TTP- Thrombotic Thrombocytopenic Purpura
HUS- hemolytic uremic syndrome
TMA- Thrombotic Microangiopathy

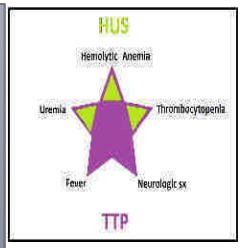
AKI- Acute Kidney Injury
MAHA-Microangiopathic Hemolytic Anemia
ADAMTS-13 – an enzyme that cleaves vWF

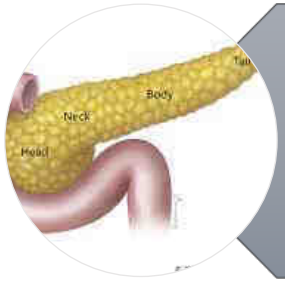
We defined coexistence as:



Type I coexistence- AP- associated secondary TMA

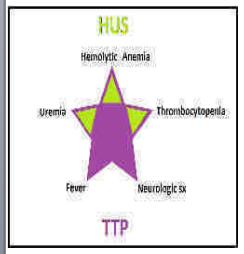
TMA is associated and preceded by AP

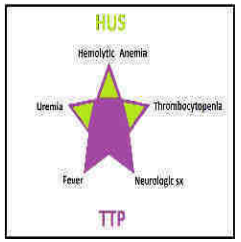


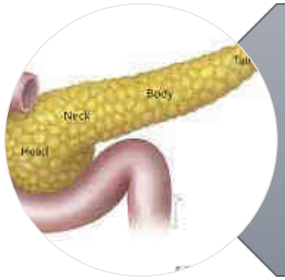


Type II coexistence-TMA triggered by AP

TMA is triggered by and preceded by AP in patients who had underlying inherited complement dysregulation or ADAMTS-13 deficiency

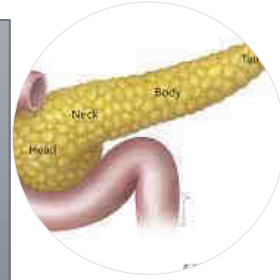






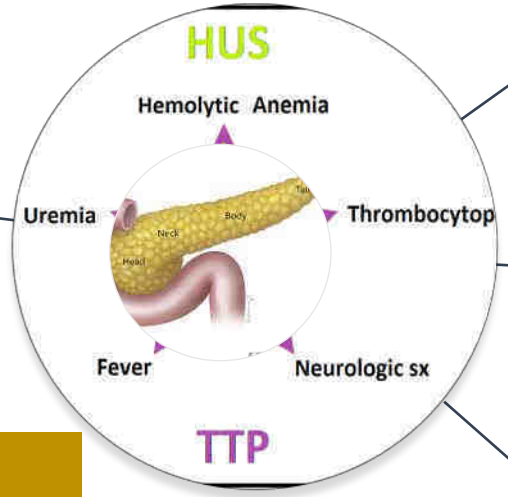
Type III coexistence- TMA associated with HUS and AP

HUS is associated either with concurrent AP or AP occurs late in the course, which was demonstrated to have ADAMTS-13 deficiency, antibody to complement proteins, inherited complement dysregulation or mutation of diacylglycerol kinase ε, cobalamin C defect, etc.



Concurrent **or** **AP occurs late**

Results- Demographic details



Patient 1

AP→TMA

Severe, non recurrent pancreatitis

19 year old male
Interval between AP and TMA= 21 days

Patient 2

TMA→AP

Mild, non recurrent pancreatitis

13 year old male
Interval between TMA and AP = 15 days

Patient 3

TMA→AP

Mild, recurrent pancreatitis

22 year old male
Interval between TMA and AP = <1 day

Patient 4

AP→TMA

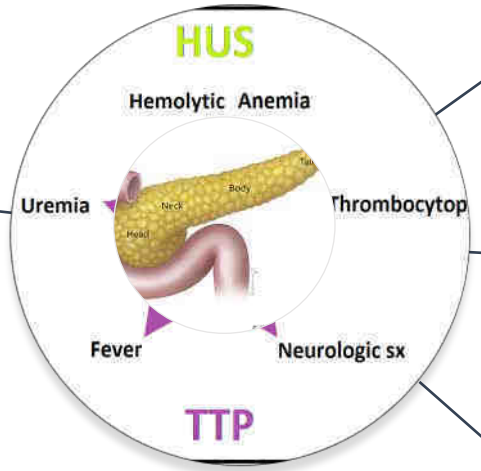
(Concurrent)

Moderate, recurrent pancreatitis

15 year old male
Interval between TMA and AP = <1 day

Red circles- partial recovery of renal function
Green circles- full recovery of renal function

Results



Patient 1

AP→TMA

Severe, non recurrent pancreatitis

- Antibody and ADAMTS13 levels not done
- Plasmaphresis only

Patient 2

TMA→AP

Mild, non recurrent pancreatitis

- **High titres of anti-CFH Ab**
- Normal ADAMTS13
- Plasmaphresis→ **steroids**

Patient 3

TMA→AP

Mild, recurrent pancreatitis

- Normal anti-CFH Ab
- Normal ADAMTS13
- Plasmaphresis→**plasma infusions**

Patient 4

AP→TMA

Moderate, recurrent pancreatitis

- Normal anti-CFH Ab
- Normal ADAMTS13
- Plasmaphresis→ **hydroxycobalamine**

Complement level- normal for all patients

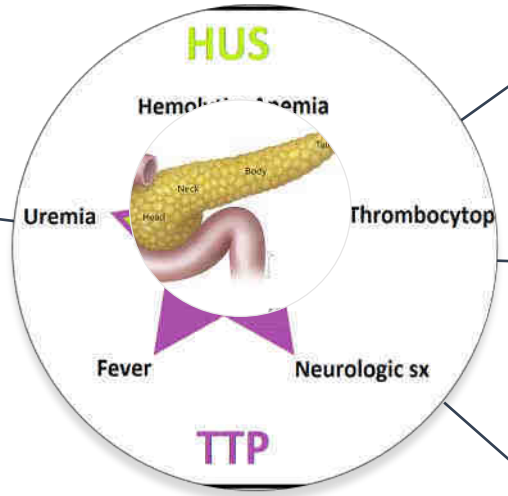
Renal biopsy done for patient 3 and 4 –suggestive of TMA

All are idiopathic pancreatitis

Genetic analysis- MMACHC mutation associated with Cobalamin C deficiency

Red circles- partial recovery of renal function
Green circles- full recovery of renal function

Results-Type of coexistence



Patient 1

AP→ TMA

Severe, non recurrent pancreatitis

AP associated secondary HUS

Patient 2

TMA→AP

Mild, non recurrent pancreatitis

TMA associated with HUS and AP due to Anti CFH Ab

Patient 3

TMA→AP

Mild, recurrent pancreatitis

TMA associated with HUS and AP due to ? inherited complement dysregulation

Patient 4

AP→TMA

(Concurrent)

Moderate, recurrent pancreatitis

TMA associated with HUS and AP due to genetic MMACH deficiency

Red circles- partial recovery of renal function
Green circles- full recovery of renal function

Review of literature

Variables /Total patients N=45	AP associated secondary HUS N= 37 {36 + 1(our series)}	HUS triggered by AP N= 4	TMA associated with HUS and AP N=4{1+ 3 (our series)}
Age	37 years (18-74 years)	49 years (35-61 years)	18.5 years (13-29 years)
Gender	**Males-30(81%),** Females-7 (29%)	Males-1(25%), **Females-3(75%)**	**Males-3 (75%),** Female1(25%)
Etiology of AP / TMA	**Alcohol 20 (54%)** **Idiopathic 7 (19%)** Gall stones 5 (13.5%) Post ERCP 3 (8.1%) Others 1 (2.7%) Drugs 1 (2.7%)	Alcohol 2 (50%) Gall stone 2 (50%)	Primary TMA-1 Hereditary-2 (1suspected, 1-proven) Acquired 1 (Anti CFH Ab)
Time between AP and TMA	Median-3 days (1 – 15 days)	3 days (2-4 days)	5.5 days (<1 -15 days)
Recurrent AP or TMA	**Recurrent AP-4** (2 alcohol, 2 Idiopathic)	**Recurrent AP-1** (1 Idiopathic)	**Recurrent AP-2** due to recurrent TMA (1 MMACH mutation, 1heriditary TMA)
Treatment	PI-6 (16.2%) PLEX-6 (16.2%) PI and PLEX-1 (2.7%) **Steroids-10 (27%)** Only fluid therapy- 2 (5.5%) RTx-0, Eculizumab-3 (8.1%) Combination-6 (16.2%) No information 3 (8.1%) cases.	PI-0 **PLEX- 4 (100%)** PI and PLEX- 0 Steroids-2 (50%) Only fluid therapy 0 RTx-1 (25%), Eculizumab- 0 Combination of Tx -2 (50%)	Plasma infusions- 1 **PLEX- 4 (100%)** Plasma infusions and PLEX- 0 Steroids-1 (25%) Only fluid therapy- 0 Rituximab- 0, Eculizumab-0, Combination of therapies- 0

PI – plasma infusion
PLEX- plasmapheresis
RTX- Rituximab
ECZ- eculizumab

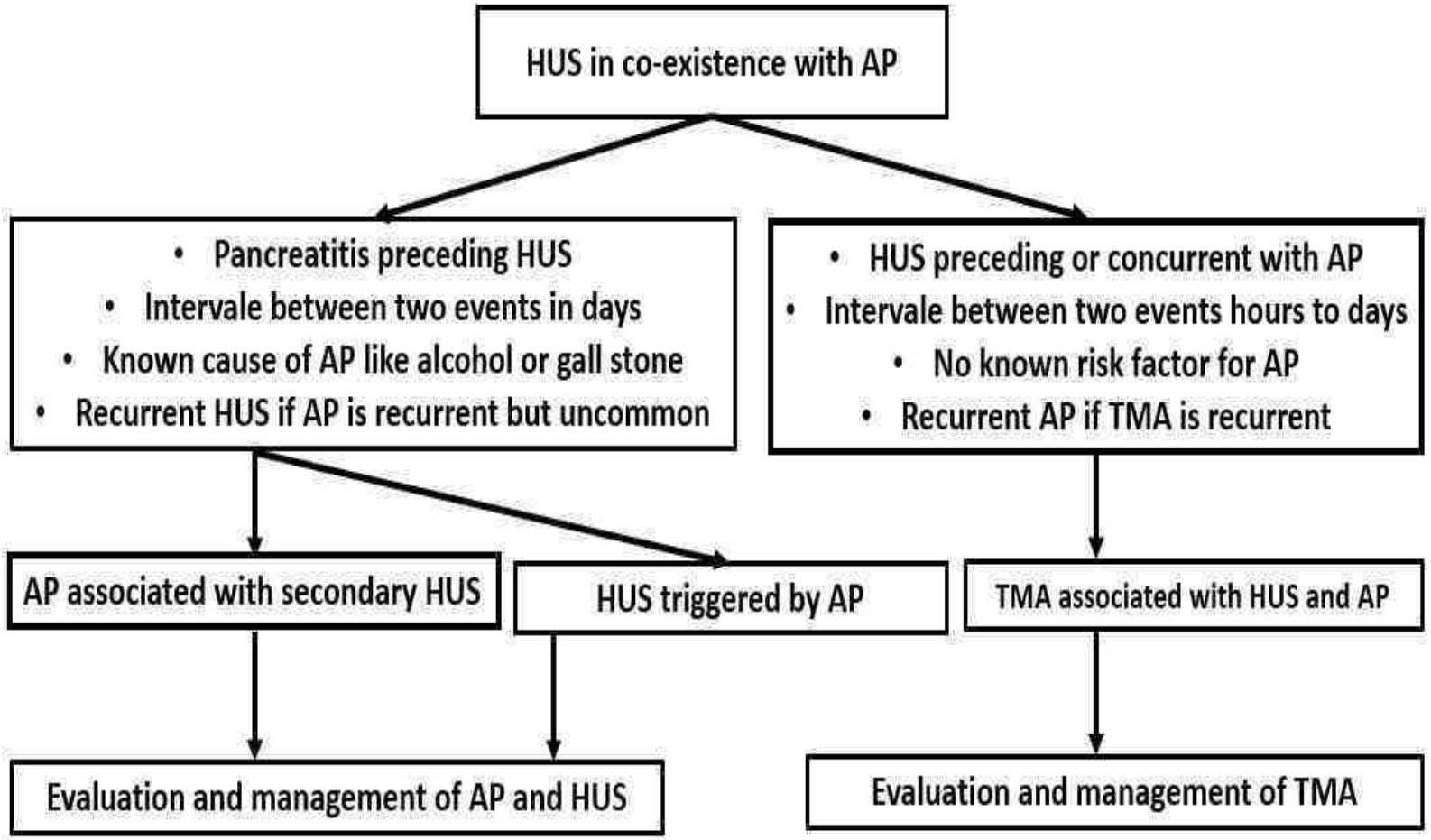
Review of literature

Variables /Total patients N=45	AP associated secondary HUS N= 37 {36 + 1(our series)}	HUS triggered by AP N= 4	TMA associated with HUS and AP N=4{1+ 3 (our series)}
Complement levels Done in 7 patients	**Not done in 33 (89.1%) cases,** Normal levels in 4 (11.9%) cases	**Not done in any case**	**Normal- 3 (75%)** Not done -1 (25%)
ADAMTS13 levels Done in 9 patients	**Not done in 34 (91.8%) cases** Normal levels in 3 (8.2%) cases	**Low in 100% patient** ADAMTS13 antibody 1. Absent in 2 cases (50%) 2. Present in 2 cases (50%).	Normal-2 (50%) Not done -2 (50%)
Anti-CFH antibody levels Done in 3 patients	**Not done in 36 (97.2%) cases**, Normal levels in 1 (2.8%) case	Not done in any case	**Normal- 2 (50%),** High titres- 1(25%) Not done- 1(25%)
Genetic analysis Done in 6 patients	**Not done in 32 (86.5%) cases** Done in 5 (13.5%) case which was normal	Not done in any case	**Not done- 3 (75%),** MMACHC mutation in one case (25%)
Diagnosis Renal biopsy done in 10 patients	**Clinical 30 (81%)** Biopsy done in 7 (19%) cases	**Made clinically in all cases.** Biopsy not done in any case	**Made Clinically in all cases.** Post-mortem biopsy - 1 Biopsy is done in 2 (50%) cases

Review of literature

Variables /Total patients N=45	AP associated secondary HUS N= 37 {36 + 1(our series)}	HUS triggered by AP N= 4	TMA associated with HUS and AP N=4{1+ 3 (our series)}
Outcome (Renal + Hematological), **Full recovery 30/45** **Partial recovery 7/45** **No recovery 2/45 Death 3/45**	**Full recovery-26 (70.2%)** Partial recovery-4 (10.8%) No recovery- 2 (5.4%) No information about 3 (8.2%) Death 2 (5.4%) case	**Full recovery-3 (75%)** Partial recovery- 1 (25%)	**Full recovery-1 (25%)** Partial recovery- 2 (50%) Death in 1 case (25%)
Etiology of co-existence	**AP associated secondary HUS**	**HUS triggered by AP** Auto-antibody to ADAMTS-13- 2 Familial ADAMTS-13 def - 2	**TMA associated with HUS and AP** Anti CFH Ab mediated-1 Inherited complement dysregulation-1 MAMCH mutation-1

Discussion-



Proposed algorithm suggesting approach to patients of HUS in co-existence with AP

Pathogenesis of the coexistence

Co-existence of AP + HUS

Type 1 Co-existence AP associated with secondary HUS	IL-6, IL-8, TNF-α, and other cytokines/enzymes causing direct endothelial injury → HUS
Type 2 Co-existence TMA triggered by AP	Patients with ADAMTS-13 deficiency or Congenital HUS due to complement dysregulation → TMA/HUS
Type 3 Co-existence TMA associated with HUS and AP	Patients of TMA due to ADAMTS-13 deficiency, complement dysregulation or mutation of diacylglycerol kinase ε, cobalamin C defect etc. → TMA/HUS → Involvement of different organ in TMA

Salient features:

Type 1-AP associated secondary HUS

- Most common scenario
- Cytokines released by AP cause endothelial injury
- If AP patients develop MAHA & renal dysfunction→ high suspicion of HUS
- Relapse is infrequent
- Needs to correct AP etiology and to treat TMA

Type2-HUS triggered by AP

- AP unmasks the underlying etiology of TMA
- Circulating high MW vWF triggered by AP
- Not cleared due to underlying ADAMTS13 deficiency/complement dysregulation
- Relapse is frequent
- Needs to correct underlying etiology to prevent recurrent episodes

Type3-TMA associated with HUS and AP

- AP occurs as extrarenal manifestation of TMA
- AP develops concurrently or later in the course
- If TMA patients develop characteristic pain abdomen→ high suspicion of AP
- Relapse is frequent
- TMA etiology needs correction