Ruolo della PEX/ PI

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RESPONSABILE AFERESI TERAPEUTICA
SIT AZIENDA OSPEDALIERA DI PERUGIA

MICROANGIOPATIE TROMBOTICHE :
DIAGNOSI E TERAPIA
PERUGIA 29SETTEMBRE 2016

TMA

- TMA is a medical urgency and it is important to initiate specific treatment early to avoid irreversible damage to organs

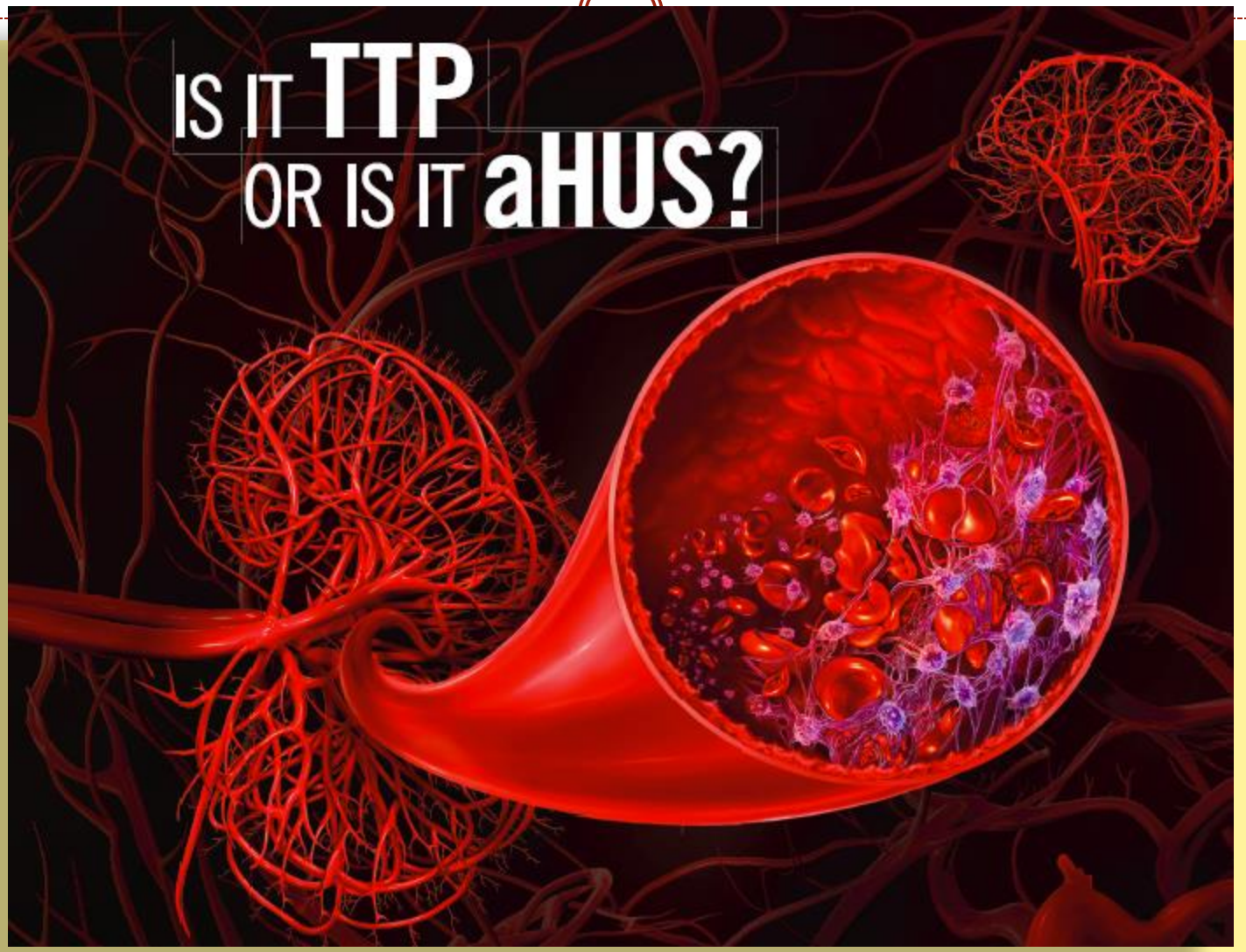
When a patient present TMA

- Prompt diagnosis and intervention with TPE or other plasma therapy is critical because patients can quickly decompensate and untreated mortality is 90%

When a patient present TMA

- However many causes of TMA do not respond to TPE and prolonged courses of exchange in the absence of underlying diagnosis may cause a detrimental delay in appropriate medical therapy,

When a patient present TMA



J. Schwartz et al. Journal of Clinical Apheresis 28:145–284 (2013)

Esperienza di Perugia 1996/2016

DIAGNOSI	N° PAZIENTI	N° PROCEDURE
TTP	59	780
TMA-TA	24	960
HUS	11	189
ALTRO(EPN,LA.)	20	201

Standards di riferimento

ASFA (AMERICAN SOCIETY FOR APHERESIS) Guidelines in clinical practice-evidence based approach

BCSH (British society for Haematology Committee)

SidEM (SOCIETA' ITALIANA DI EMAFERESI E MANIPOLAZIONE CELLULARE)

ASFA CATEGORIES

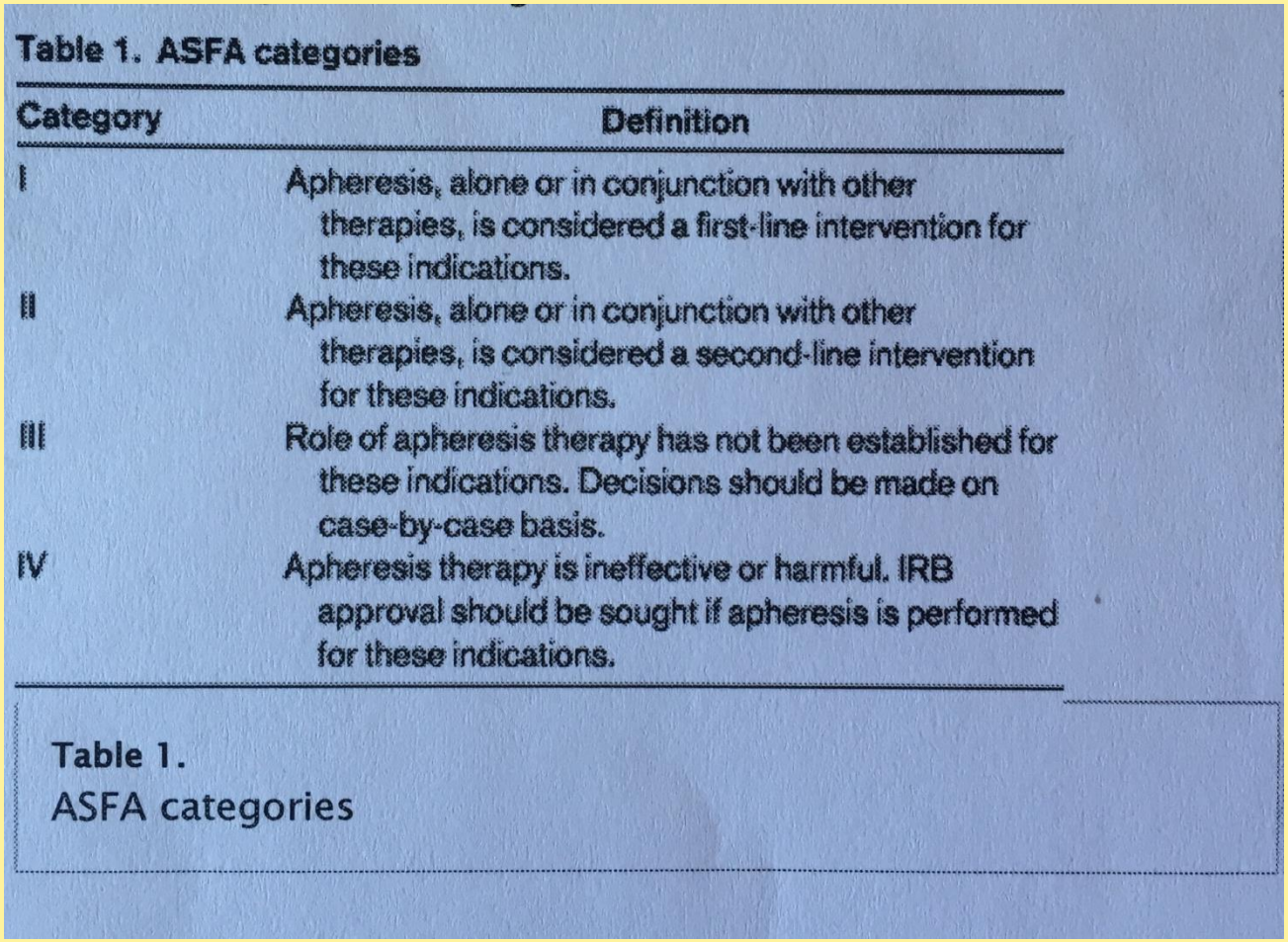


Table 1. ASFA categories

Category	Definition
I	Apheresis, alone or in conjunction with other therapies, is considered a first-line intervention for these indications.
II	Apheresis, alone or in conjunction with other therapies, is considered a second-line intervention for these indications.
III	Role of apheresis therapy has not been established for these indications. Decisions should be made on case-by-case basis.
IV	Apheresis therapy is ineffective or harmful. IRB approval should be sought if apheresis is performed for these indications.

Table 1.
ASFA categories

ASFA GRADING RECOMMENDATIONS

Table 2. Grading recommendations for ASFA guidelines

GRADE	Definition
1A	Strong recommendation with high-quality evidence. Apheresis can be utilized without reservation.
1B	Strong recommendation with moderate-quality evidence. Apheresis can be utilized without reservation.
1C	Strong recommendation with low-quality evidence. Apheresis recommendation may change with additional evidence.
2A	Weak recommendation with high-quality evidence. Apheresis may be considered based on individual circumstance.
2B	Weak recommendation with moderate-quality evidence. Apheresis may be considered based on individual circumstance.
2C	Weak recommendation with low-quality evidence. Alternative therapies may be equally effective.

Table 2.
Grading recommendations for ASFA guidelines

ASFA GUIDELINES FOR TMAs

Table 3. ASFA guidelines for TMAs

	Category	GRADE
Therapeutic plasma exchange is/may be indicated		
TTP	I	1A
HUS		
Associated with *Streptococcus pneumonia*	III	2C
Atypical HUS		
Factor H antibodies	I	2C
Complement gene mutations	II	2C
Drug-associated TMA		
Ticlopidine	I	2B
Clopidogrel	III	1B
Cyclosporine/tacrolimus	III	2C
Transplantation-associated TMA	III	2C
Therapeutic plasma exchange is NOT indicated		
HUS		
Associated with shiga toxin-producing *Escherichia coli*	IV	1C
Atypical HUS		
Membrane cofactor protein mutations	IV	1C
Drug-associated TMA		
Gemcitabine	IV	2C
Quinine	IV	2C

Table 3.
ASFA guidelines for TMAs

Diagnostic challenges

- Considerable overlap in presenting clinical and laboratory features of TMA associated diseases.
- Diagnostic testing must be performed by specialized reference laboratories and results may not be available for days to weeks after the onset
- There are cases of TMA for which no underlying pathologic insult can be identified.

Evaluating a new patient for TPE

- Rationale
- Impact
- Technical Issues
- Therapeutic Plan
- Clinical and laboratory endpoint
- Timing and location

Suspected TTP

- MAHA ,thrombocytopenia, organ failure in absence of other identifiable cause ?
- Start ASAP (within 4/8 h regardless of the time of day at presentation)PEX.
- Delay in initiation leads to early mortality
- Large volume plasma infusion (20/30 ml /Kg) are indicated if there is to be a delay in arranging PEX.
- (Be careful !!!! Overload)

A baseline prior to plasma exposure.

- Take blood before starting PEX
- To measure ADAMTS 13 level and to detect anti-ADAMTS 13 antibodies.
- Confirm the diagnosis and monitor the course of the disease.

Serial measurement of ADAMTS13 and Inhibitor titers

- Inhibitor boosting recently reported in a study from Japan may explain why some patients who initially appear to respond to treatment,then appear to become refractory.

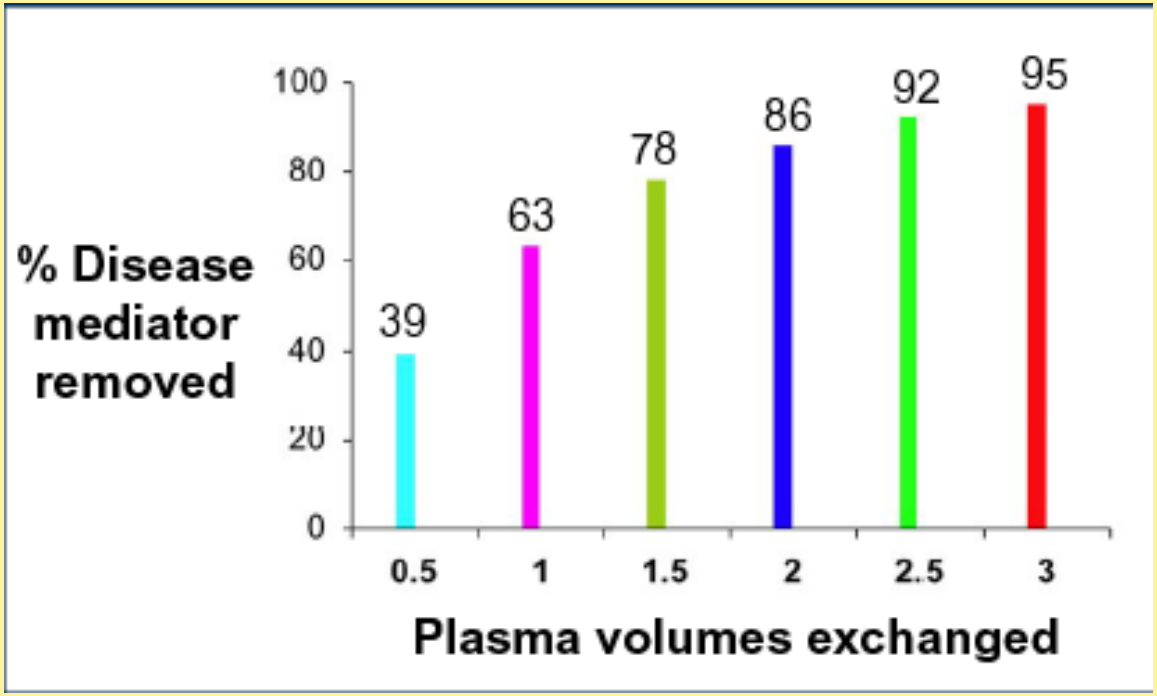
- Transfusion 2015 PMID

Plasmaexchange

- Mandatory
- Reduced mortality rates from over 90% to 10-20%.
- It allows:
- Removal of autoantibodies and ULvWF multimers
- Replacement ADAMTS-13

Therapeutic effectiveness of TPE

Plasma Vol. exchanged = % of Dis.mediator removed



Recommendation

- **Start** :1.5 PV exchange (S/D plasma)
- **Reduce** to 1.0 when clinical conditions and laboratory results are stabilizing.
- **Intensification** in frequency and volume should be considered in life threatening cases.
- **Daily** PEX for a minimum of 2 d after platelet count has been >150x109/l .
- And then ?????????????

Different opinions

- .....**Then STOP**
- (Scully et al BJH Guidelines 2012)

- .....**Then TAPERING**
- (George et al Oklahoma Registry 2008)

Canadian Apheresis Group Survey

AMBIGUOUS AREAS INCLUDE:

- The role of TPE taper
- Replacement fluid
- Concomitants drugs

37 th Annual Meeting ASFA July 2016

How long ?

- The number of procedures required to achieve remission is highly variable, but is longer in mediated TTP
- From <5 to > 70 treatments over several months.
- Coppo et al. 2006

Esperienza di Perugia

- 5-8 sedute per indurre la remissione
- 6-10 mantenimento

Refractory TTP

- Progression of clinical symptoms or persistent thrombocyopenia despite PEX ?
- RULE OUT ANOTHER ETIOLOGY

Twice a daily PEX ?
(Oklahoma Registry 1989-2006)

- A treatment option in refractory acquired TTP, with limited data on its effectiveness in acutely ill patients, who have a sudden decline in platelet count or develops new neurologic symptoms.
- Retrospective review only 3/28 patients appeared obtain benefit
- Nguyen L, Transfusion 2008

Exacerbation

- Worsening ,recurrent thrombocytopenia following a response of daily plasma exchange treatment after < 30 days of no TPE

Relapse

- An episode of acute TTP >30 days after remission in 20-50% of cases,
- Relapse is unpredictable in its onset, severity and outcome

Over a 10 years follow up 36% of patients should relapse. (Canadian Apheresis Group)

If ADAMTS 13 activity was >15% at the remission, only 5% relapsed *(Ferrari 2007*)

Congenital TTP Upshaw Schulman Syndrome

- **Current treatment consists of** :
- plasma infusion
- **or**
- a virally inactivated intermediate purity factor VIII concentrate containing ADAMTS 13 (8Y-BPL)

Advantages: small infusion volume , so good for outpatient or home setting

Problem: No guaranteed constant quantity of ADAMTS 13

PI infusion

- Despite the ADAMTS 13 half life of only 2-3 days,the clinical effects of PI or 8Y BPL are such that infusion are required every 10-20gg to achieve a normal platelet and haemoglobin level.

- PI 10-15 ml/Kg
  8Y BPL 15-30 u /kg

TPE in congenital TTP

- Patients do not need plasma exchange unless they have volume sensitive comorbidities.

- Half of all patients with congenital TTP are asymptomatic until they suffer from a physiologic stress event as adults , pregnancy, surgery or inflammatory disorder.

HIV related TTP

- PEX in conjunction vith HAART (triple or quadruple therapy) should be started as soon as the diagnosis of HIV associated TTP is made
- HAART should be given immediately after PEX therapy to maximize time for absorption.
- HAART should be continued after remission to prevent further relapse.
- In resistant patients Rituximab could be considered.
- Mortality 60% despite PEX

TTP in pregnancy

- Onset in first/second trimester may require periodic TPE (weekly or fortnightly) throughout pregnancy and postpartum based on haematological parameters and ADAMTS 13 levels.

- WARNING !!
- TPE treatment can be harmful and apheresis related adverse events ,during pregnancy ,can involve both the mother and the fetus

Technical notes

- Vital signs of mother and fetus must be monitored constantly.
- S/D plasma is better (if available)
- Extracorporeal circulation as small as possible (<10%)

TTP in pregnancy

- In previously diagnosed congenital TTP patients, plasma infusion may be the only therapy for the whole pregnancy.

- Suggested protocol: PI 10ml/kg every two weeks starting .Then increase the frequency weekly from second third trimester to delivery

Atypical HUS

- Anti CFH autoantibodies cat I 2c
- Other Complement mutations cat II 2c
- Membrane Cofactor Mutations cat IV

- 50-60% of cases die or progress in ESRD

aHUS Rationale for TPE

- Remove the defective complement proteins and autoantibodies against CFH
- Provides normal exogenous complement factors.
- In contrast to older guidelines, empiric PEX in all forms is recommended, pending genetic testing.

HUS Infection associated

- STEC-HUS: Shiga toxin –producing Escherichia coli associated (cat IV 1c)
- P HUS : Streptococcus pneumoniae associated HUS (cat III 2c)

Shiga toxins injury and TPE

- Proinflammatory and prothrombotic effects on the vascular endothelium
- May attach to,vehicled by neutrophils, and stimulate endothelial cells to release ULvWF multimers which activate and promote adhesion and aggregation of platelets.

- **TPE could remove the toxins or factors damaging endothelium**
- Adamski J ASH Education Book 2014

OVERLAP STEC HUS and aHUS

Shiga toxin has direct toxic effects on renal endothelium and the majority of cases of e. coli infection associated HUS are self limited, but **infection** is also a well known complement-amplifying condition and may uncover aHUS.

- Patients did not recover renal function with supportive care should be evaluated for complement mediated TMA .

- Yamada et al. Case Report University of Michigan 2016

S.Pneumoniae injury and TPE

- Produces a neuraminidase which cleaves sialic acid residues from cell surface glycoprotein exposing Thomsen Friederich (T) antigen.
- pHUS occurs by binding of naturally IgM anti T antibody to exposed T antigen on erythrocytes, platelets and endothelium.

- **TPE would remove antibodies against T-antigen as well as neuraminidase.**

Technical notes

- Volume treated 1-1.5 TPV
- Replacement fluid:
- Albumin in pHUS (no natural IgM anti T)
- Plasma in STEC HUS and aHUS
- Frequency : Daily
- Duration and discontinuation:
- No standardized approach : schedule for treatment of TTP empirically adopted .
- Special concern in children (vascular access, RBC prime, anticoagulation and calcium suppl)

TA-TMA

- Absence of ADAMTS 13 deficiency and inhibitors undetectable
- Management is difficult
- No benefit has been shown with TPE
- In a retrospective review it was associated with an increased mortality

- George et al 2004
- Ruutu et al 2007
- Scully et al BJH 2012

TA- TMA Rationale for TPE

- Cat III 2c
- Rationale is undefined and consistent with the uncertain clinical efficacy.
- Because some patients appear to respond a trial of TPE could be considered as salvage therapy for selected patients with persistent/progressive TA TMA

Technical notes

- Volume treated 1-1,5 Plasma volume
- Frequency similar to idiopathic TTP
- Replacement fluid :Plasma
- Duration and discontinuation ????????
- Difficult endpoint:
- -Platelet count and LDH levels could be affected by incompleted engrafment and post transplant complications
- -Persistent schistocytes may be due to drugs and others complications post Transplant

WHICH PLASMA ?

- **FFP**
- **Cryosupernatant** :depleted of vWF multimers
- No differences. Canadian Apheresis Group

- **Safe FFP**:

- a) MB FFP
- b) Psoralen treated
- c) Solvent/detergent
- d) Riboflavin

MB –FFP Methylene blue treated

- In the UK , single donor MB FFP is recommended in patients born after 1° st January 1996 to minimize the risk of prion transmission.
- However MB-FFP has been associated with increased number of TPE and longer hospital stay in TTP patients.
- (Rio Garma et al 2008)

Solvent detergent Plasma

- Standardized(volume, content of proteins)
- Safe regarding infections due to enveloped viruses
- It does not cause TRALI, post transfusion thrombocytopenia, allergic reactions, GVHD
- BUT ??????

Solvent detergent plasma

- It contains reduced levels of protein S
- An association with venous thrombosis was evidenced in an European Observational study .
- Thromboprophylaxis with LWMH and a low dose aspirin was used once PLT count was > 50X109/l
- Scully et al 2007

OPEN QUESTION

- None of the currently applied methods inactivate all types of pathogens and all have some effect on plasma quality when compared to fresh frozen plasma

Platelet transfusion in TTP

- Open question.

- Otrock ZK Vox sanguinis 2015
- Riviere E Transfusion 2015
- Benhamou Y Am J Hematology 2015
- Zhou A Ann Hematol 2015
- Goel R. Blood 2015

Platelet transfusion in TTP

- The incidence of heart failure is increased in patients who have been given a recent platelet transfusion.

Platelet transfusion in TTP

- Fourteen patients were transfused with PLT prior to catheter placement.
- Six (43%) in the transfused group died
- Two (5%) in the non transfused
- Were patients transfused more acutely ill ???????
- (No objective data)

- Duffy SM J Clin Apher 2013 Oct.

Platelet transfusion in TTP

- PLT should not be transfused without a clinical indication such as a intracranial hemorrage.
- Bleeding if present is limited to skin and mucous membrane.
- In TTP is thrombotic tendency rather than hemorragic
- ASFA Guidelines 7° edition 2016

CVC in aferesi

Non tunnellizzato
Non valvolato
No silicone
Calibro 12 french

ECG abnormalities emerging during TPE

- (> 5% of patiens)
- Synus tachycardia, QT interval prolongation,synus bradycardia,premature atrial contraction, right bundle branch block,T wave changes.
- (Corash et al 37 th Annual Meeting ASFA 2016)

- Raised troponin levels are a sinister finding for coronary artery occlusion.
- (Brazelton et al J of Clinical Apheresis **26/9/2016**)

Complications of TPE

Relatively safe.

Mortality 2,4%

Severe adverse reactions :Risks associated with central line placement, (Hemorragic , pneumothorax, sepsis, thrombosis.)
Anaphylactic reaction to plasma,atrial fibrillation, severe synus bradicardia, cardiac tamponade.

Mild adverse reactions: Hypovolemia,Hypotension,cytrate intolerance, vasovagal reaction. ortycarioid reactions.

Oklahoma Registry

MODELLO ORGANIZZATIVO AUSPICABILE

- PERCORSO DIAGNOSTICO TERAPEUTICO CONDIVISO MULTIDISCIPLINARE IN ACUTO E IN FOLLOW UP
- Attenzione rischio recidive non controllate nel paziente dimesso.!!!!
- Ridefinire e/ o ridisegnare il ruolo della Sezione Aferesi nella gestione dei pazienti trattati con TPE

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