CONVEGNO MICROANGIOPATIE TROMBOTICHE UCSC 2016

PRESENTAZIONE E DISCUSSIONE DI CASI CLINICI

Gemelli

Commenti preordinati:

Nicola Piccirillo: aspetti trasfusionali

Venerdì 19 febbraio 2016

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

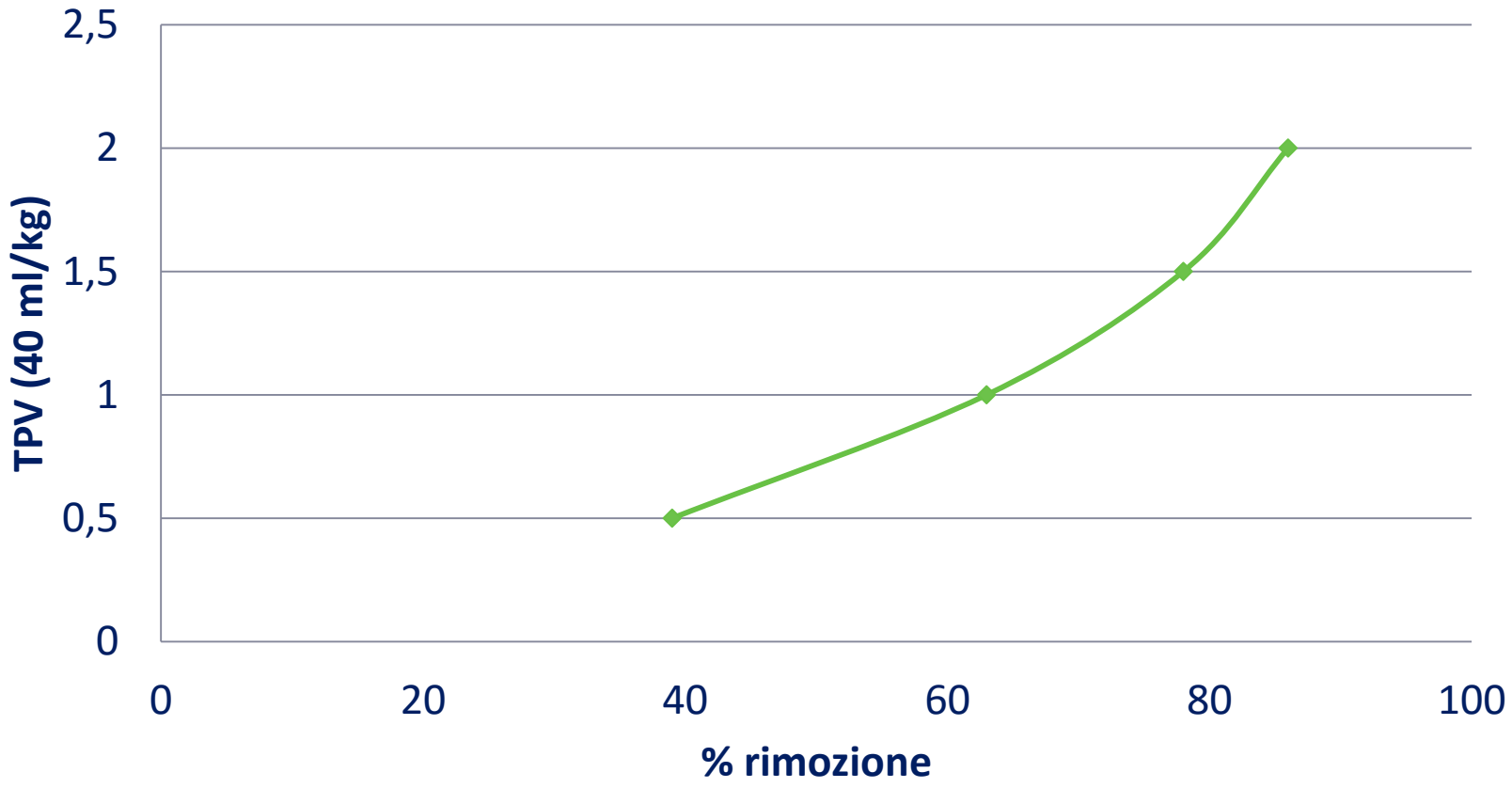
Plasmaexchange

- Cardine del trattamento
- 1-1.5 TPV (40-60 ml/kg)
- Doppio meccanismo d'azione:
    - infusione enzima
    - asportazione multimeri
- Velocità di intervento (aferesi 24h, accesso vascolare)
- Paziente critico (ambiente protetto)

Plasmaexchange

- Mandatorio
- Rock GA, N Engl J Med. 1991 Aug 8;325(6):393-7.
- Aumento della sopravvivenza dal 10% all’80%.

Total plasma volume = 40 ml/kg



Plasmaexchange

- 1-1.5 TPV /die fino a risposta
- PEX è superiore alla sola plasma infusione.
- Plasma infusione a dosi massicce (25-30 mL/kg) deve essere considerata fino all'inizio delle procedure aferetiche..

Twice-daily plasma exchange for patients with refractory thrombotic thrombocytopenic purpura: the experience of the Oklahoma Registry, 1989 through 2006

Loan Nguyen, Xiaoning Li, Deanna Duvall, Deirdra R. Terrell, Sara K. Vesely, and James N. George

- Twice-daily PEX is a treatment option in refractory acquired TTP, albeit with limited data on its effectiveness. sometimes initiated when an acutely ill patient, who initially responded to single-volume-daily PEX, has a sudden decline in platelet count or develops new neurologic symptoms.

- In a retrospective review of the Oklahoma registry, only 3 of 28 patients who received twice-daily PEX appeared to obtain any benefit.

- Nguyen L, Transfusion. 2008;48(2):349-357.

Plasma

- PFC
- Crioprecipitato → PFC privato dei multimeri: nessun vantaggio
- PFC inattivato
  - Blu di metilene
  - Psoraleni
  - S/D farmaceutico
  - Riboflavina

→ PFC trattato: abbattimento del rischio infettivo e delle reazioni trasfusionali

TABLE 1. Factor composition of plasma products relative to thawed FFP*

Proteins	FP24	Thawed†	Cryopoor	Cryoprecipitate	S/D	MB	INTERCEPT	Mirasol
Fibrinogen	↔	↔	↓↓	↑↑↑	↔	↓↓	↓	↓↓
FII	↔	↔	↔		↔	↔	↓	↓
FV	↔	↓↓	↔		↓↓	↔	↓	↓↓
FVII	↔	↓↓	↔		↔	↔	↓↓	↓
FVIII	↓↓	↓↓	↓↓	↑↑↑	↓↓	↓	↓↓	↓↓
F IX	↔		↔		↔	↓	↓	↓↓
FX	↔	↔	↔		↔	↔	↓	↓
FXI	↔		↔		↓	↓	↓	↓↓
FXII	↔		↔		↔	↔		↓
FXIII	↔		↓↓	↑↑↑	↔	↔	↓	↔
Antithrombin-III	↔		↔		↔	↔	↓	↔
Protein C	↔		↔		↔	↔	↓	↓
Protein S	↔		↔		↓↓	↔	↓	↓
α_2-Antiplasmin	↔		↔		↓↓	↔	↓	↓
VWF antigen	↔	↔	↓↓	↑↑↑	↔	↓		↔
VWF multimers	↔	↔	Reduced HMW		Reduced HMW			↓↓
VWF protease	↔	↔	↔		↔	↔	↔	↓

* Estimates are approximate, as they represent multiple independent evaluations performed at different times, in various laboratories under varying conditions[5,6,10-15] ↔ = >95% activity; ↓ = 80%-95% activity; ↓↓ = 30%-79% activity; ↓↓↓ = <30% activity.

† On Day 5 after thaw.

HMW = high molecular weight.

S/D plasma

- S/D plasma:
  - Prodotto farmaceutico standardizzato
  - Diminuzione delle reazioni trasfusionali
    - » TRALI, post-transfusion thrombocytopenia, allergic reactions, or GvHD
  - Diminuzione del rischio infettivo
    - » Decreased logs of most enveloped viruses, including human immunodeficiency virus (HIV), hepatitis C virus, and West Nile virus

S/D plasma

- Advantages:
  - standardization (volume, content of proteins)
  - safety regarding infections due to enveloped viruses.
- The frequency of serious adverse reactions is much lower than that after the administration of single-donor FFP
- Pooled S/D-treated plasma does not cause TRALI, post-transfusion thrombocytopenia, allergic reactions, or GvHD which might be induced by single-donor FFP.

S/D plasma

- S/D plasma is generally considered as effective as FFP
- Improved safety of a virally inactivated product, despite the pooling of multiple units.
- Nevertheless, the specter of an association with venous thrombosis has been raised (one retrospective study of TTP patients in Europe and in liver transplant case reports): decreased antithrombotic protein S and observational study evidence of thrombosis .
- In Europe, S/D plasma continues to be utilized after studies that failed to detect thrombotic complications in similar patient groups;

ASFA guidelines nella aHUS

Rationale for therapeutic apheresis

The application of TPE as first-line therapy is largely based on anecdotal reports. The rationale is that it can effectively remove the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators. Despite conflicting reports of the effectiveness, the European Group as well as others recommend TPE over plasma infusion because of potential therapeutic benefits of TPE without risk of volume overload, development of hyperproteinemia, or refractoriness to regular plasma infusion in a disease with the high risk of rapid progression to ESRD.

Technical notes

Since the majority of affected patients with aHUS are children, establishment of vascular access, RBC prime, and calcium supplementation are of special concern.

Volume treated: 1–1.5 TPV **Frequency:** Daily
Replacement fluid: Plasma; albumin (T activation associated HUS)

Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment of TTP have been empirically adopted to treat aHUS. European Group recommends that TPE be performed daily for 5 days after urgent initiation of TPE, 5 times per week for 2 weeks, then 3 times per week for 2 weeks with outcome evaluated at day 33 (*Sanchez*). These guidelines address neither continued treatment after initial therapy failure nor ongoing prophylactic treatment for patients with remission. As shown in a recent case series of three patients with *CFH* mutation, acute and prophylactic TPE in the pre- and post-renal transplant periods were effective in maintaining long-term native and allograft kidney function. Decisions of duration or to discontinue should be made based upon patient response and condition.

Cambiamenti in gravidanza

- Emodiluizione
  - Aumento volume plasmatico (fino al 45%)
  - Aumento della massa eritrocitaria (fino al 30%)
  - Aumento della volemia (fino al45%) con conseguente emodiluizione
- Alterazioni cardiovascolari:
  - Aumento della gittata cardiaca (30%–50%)
  - Aumento del volume cardiaco, frequenza con edema periferico.
  - Diminuzione della pressione arteriosa
  - Diminuzione delle resistenze periferiche
- Alterazioni renali:
  - Aumento delle dimensioni renali, dilatazione dei calici degli ureteri
- Alterazioni immunologiche:
  - Attivazione dei monociti e granulociti in circolanti
  - Inibizione della immunità cellulomediata con diminuzione della risposta Th1con aumento della suscettibilità alle infezioni virali

Perché aferesi terapeutica in gravidanza?

a) TA is a priority and has no alternative equally effective treatment:
   - thrombotic thrombocytopenic purpura

b) TA is a priority, but there are alternative therapies not contraindicated in pregnancy (e.g. IVIg):
   - myasthenia gravis

c) TA is an effective tool of saving/avoiding drug/alternative medications contraindicated in pregnancy (immunosuppressants, antiviral drugs, chemotherapy):
   - systemic lupus erythematosus

Perché aferesi terapeutica in gravidanza?

a) TA is a treatment of specific conditions/complications of pregnancy with maternal and/or fetal risks:
   - preeclampsia
   - HELLP syndrome
   - antiphospholipid syndrome
   - acute fatty liver
   - intrahepatic cholestasis
   - peripartum cardiomyopathy
   - hypertriglyceridemia/pancreatitis
   - thyrotoxicosis gravidarum/hyperthyroidism
b) TA is a treatment of specific conditions of pregnancy with exclusive fetal risk:
   - hemolytic disease of the newborn
   - fetal heart block by anti-SSA/SSB
c) TA is a treatment of diseases in which is indicated and can exceptionally occur during pregnancy:
   - Goodpasture's syndrome

Considerazioni tecniche

- Condizioni emodinamiche con ripercussioni sul flusso placentare.
- Monitoraggio fetale.
- Il volume di circolazione extracorporea inferiore al 10%.
- Sottrazione dei fattorie della coagulazione da tenere presente in relazione al periodo periparto.

TTP in gravidanza

aTTP is described in 7–11.5% of women in childbearing age.

In cTTP, the role of pregnancy as a trigger for an acute disease manifestation is well recognized. Affected women can display the initial, delayed presentation of cTTP during their first pregnancy and, in the absence of prophylactic plasma infusion, in almost all pregnancies

- hemolytic uremic syndrome (HUS),
- secondary TTP (mainly in the context of connective tissue diseases)
- preeclampsia (PE),
- HELLP syndrome,
- acute fatty liver (AFL) of pregnancy,
- obstetric antiphospholipid antibody syndrome (APL),
- sepsis with disseminated intravascular coagulation (DIC)

TTP in gravidanza

- Therapeutic Plasma Exchange (TPE) is the standard of care in idiopathic TTP, and previous undiagnosed congenital TTP A short course of TPE can also be offered to atypical HUS patients before complement inhibitory treatment with eculizumab

- British Guidelines on TTP recommend that TPE should be started “ASAP”, preferably within 4–8 hours from presentation.
- Large volume plasma infusion is indicated if there is a delay in arranging TPE.
- TPE treatment can be harmful and apheresis related adverse events during pregnancy can involve both the mother and the fetus.

TTP in gravidanza

- Vital signs of mother and fetus must be monitored constantly
- Solvent/Detergent has been used more frequently than fresh frozen plasma because of a lesser incidence of allergic reactions, moreover S/D plasma is associated with a reduced risk of transfusion transmitted infections.
- The only concern regarding S/D plasma is the reduced content in protein S, possibly related to an increased thrombotic risk (not demonstrated in TTP patients).

TTP in gravidanza

- TTP onset in first/second trimester may require periodic TPE (weekly or fortnightly) throughout pregnancy and postpartum based on hematological parameters and ADAMTS13 Levels
- In previously diagnosed congenital TTP patients, plasma infusion (PI) may be the only therapy for the whole pregnancy. The suggested protocol includes PI at the dose of 10 mL/kg every two weeks starting from 8 to 10 weeks of GA. The frequency should then be increased to weekly PI from the second/early third trimester to delivery or if the platelet count drop below 150 × 109/L.

Indicazione trasfusione di emazie

Valutazione clinica e laboratoristica che tenga conto della necessità di circolazione extracorporea, peso corporeo, livello hb, condizioni cardiorespiratoria.

Indicazione trasfusione di piastrine

Questione controversa: PubMed 2015

- Otrock ZK,**Vox Sang. 2015 Aug**;109(2):168-72.
- Riviere E,**Transfusion. 2015** Jul;55(7):1798-802.
- Benhamou Y, **Am J Hematol. 2015 Jun;**90(6):E127-9.
- Zhou A, **Ann Hematol. 2015 Mar**;94(3):467-72.
- Goel R, **Blood. 2015 Feb** 26;125(9):1470-6.

Alcuni report anni ’80:

4 decessi in seguito a trasfusione plt, prima di exchange sistematico

- Gottschall JL, Semin Thromb Hemost. 1981 Winter;7(1):25-32.
- Harkness DR, JAMA. 1981 Oct 23-30;246(17):1931-3.
- Gordon LI, Semin Hematol. 1987 Jul;24(3):194-201.

Successivamente report di non peggioramento

- Coppo P, Am J Hematol. 2001 Nov;68(3):198-201.
- de la Rubia JTransfusion. 2002 Oct;42(10):1384-5.
- Lozano M, Transfusion. 2005 Dec;45(12):1984.

Linee guida

- Allford SL, Br J Haematol. 2003 Feb;120(4):556-73.

Recommendation. Red cell transfusion should be administered according to clinical need (Grade B, level III). Folate supplementation is required in all patients. Platelet transfusions are contraindicated in TTP unless there is life-threatening haemorrhage. Hepatitis B vaccination is recommended in all patients (Grade C, level IV).

Perché trasfondere piastrine?

- Sanguinamento
- Necessità di CVC
  - Bleeding related to central venous catheter insertion is a major cause of morbidity and mortality in TTP.
    - Rizvi MA, Transfusion. 2000 Aug;40(8):896-901.
    - McMinn JR JrTransfusion. 2003 Mar;43(3):415-6.

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2015) 109, 168–172
© 2015 International Society of Blood Transfusion
DOI: 10.1111/vox.12274

ORIGINAL PAPER

Platelet transfusion in thrombotic thrombocytopenic purpura

Z. K. Otrock, C. Liu & B. J. Grossman
Department of Pathology and Immunology, Washington University, St Louis, MO, USA

- 10 anni 2004-2014: 110 paz TTP
- 23 paz ricevono PLT: 15 pltpenia severa, 3 sanguinamento, 5 apposizione cvc
- Evento: convulsioni, accidenti cerebrovasc, sanguinamento, trombosi, infarto, morte entro 30 giorni.

- Duffy SM, J Clin Apher. 2013 Oct;28(5):356-8.
- Fifty-five patients were included, and they underwent 57 catheter insertion attempts. Fourteen patients were transfused with PLT prior to catheter placement. Six (43%) patients in the transfused group died versus 2 (5%) in the non-transfused group. Patients receiving PLT transfusion were reported to be more acutely ill, but no objective data were shown

- 3 morti (paz neoplastici, no trombosi)
- Morti non trombotiche ma tutti neoplastici

Although there are no randomized controlled trials evaluating the safety of PLT transfusion in TTP, the available evidence consisting of registry based and retrospective studies shows that PLT transfusions in TTP do not appear harmful. Our case series provides further information to support this finding.

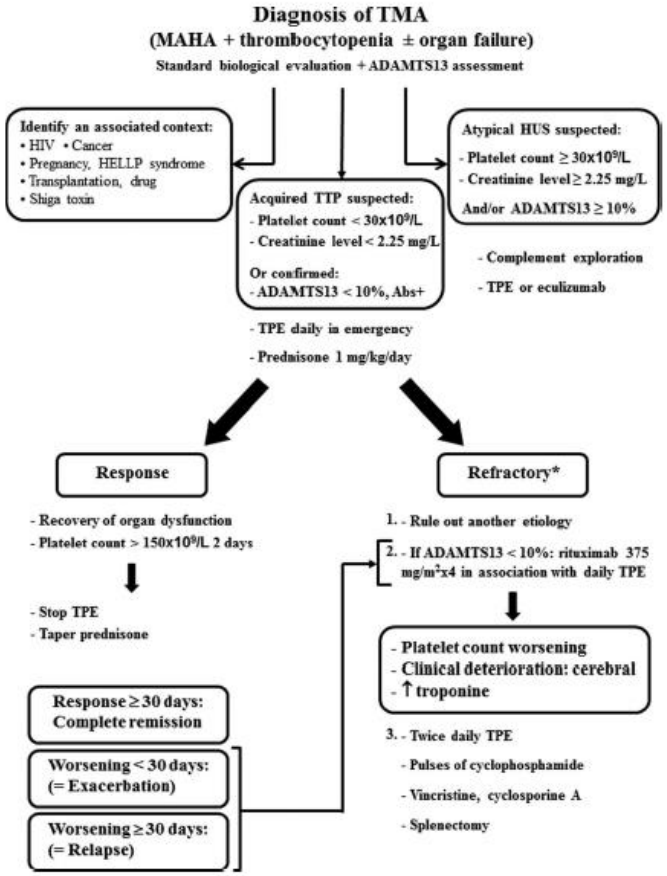
conclusioni

- Meglio non trasfondere
- Ma non sembra essere una causa certa di morte!!!

Treatment of thrombotic thrombocytopenic purpura beyond therapeutic plasma exchange

Paul Coppo[1-4] and Antoine Froissart,[1,5] for the French Reference Center for Thrombotic Microangiopathies

[1]Centre de Référence des Microangiopathies Thrombotiques, AP-HP, Paris, France; [2]Service d'hématologie, Hôpital Saint Antoine, Paris, France; [3]Inserm U1170, Institut Gustave Roussy, Villejuif, France; [4]Université Pierre et Marie Curie, Paris, France; and [5]Service de médecine interne, CHI Créteil, Paris, France



- S/D plasma and qFFP can be safely proposed in clinical practice in patients with acquired idiopathic TTP for PE, since major outcomes were found comparable and tolerance was acceptable.
- The faster response when S/D plasma was used, specifically observed in younger patients, warrants confirmation in larger prospective studies.

Toussaint Transfusion 2015

- The risk of recurrence in subsequent pregnancies differs between women with congenital and acquired TTP. Pregnancy associated cTTP patients have a relapse risk of almost 100% but regular plasma infusion can prevent acute TTP flare up and fetal IUGR.
- Conversely, the risk of recurrence during an ensuing next pregnancy is not well defined in patients recovered from acute aTTP although earlier studies and case reports reported a risk of about 50%
- The recent analysis of the TTP/HUS Oklahoma Registry [42] showed that, among 16 pregnancies (in 10 women), only two relapsed suggesting that relapses in pregnancy following recovery from acquired, severe ADAMTS13-deficient TTP may be uncommon. In this group 81% of pregnancies resulted in live births in the third trimester and there were no maternal death. Five (31%) out of 16 pregnancies were complicated by preeclampsia and the relative frequency of preeclampsia per pregnancy in TTP women was significantly greater than US population estimates