SCAMBIO PLASMATICO E PLASMATRATTAMENTO IN EMATOLOGIA: DESCRIZIONE DELLE MALATTIE, INDICAZIONI E PIANI DI TRATTAMENTO

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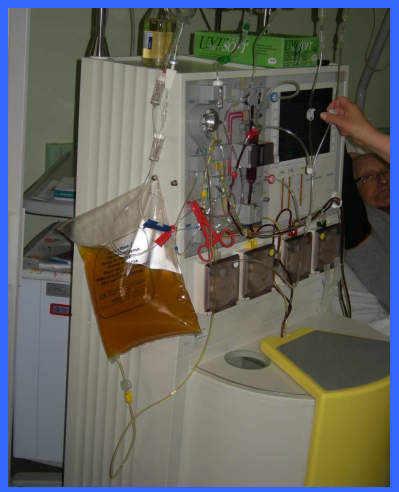
La plasmaferesi in passato è stata usata per svariate patologie senza che vi fossero studi clinici alla base che ne giustificassero il suo utilizzo



1986 prima edizione linee guida ASFA

5° EDIZIONE NEL 2010

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Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

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The American Society for Apheresis (ASFA) Apheresis Applications Committee is charged with a review and categorization of indications for therapeutic apheresis. Beginning with the 2007 ASFA Special Issue (fourth edition), the subcommittee has incorporated systematic review and evidence-based approach in the grading and categorization of indications. This Fifth ASFA Special Issue has further improved the process of using evidence-based medicine in the rec-

Le linee guida sono redatte sulla base del livello di evidenza e del grado di raccomandazione

Livelli di evidenza

Tipo di studio al quale si fa riferimento

Livello I studi clinici controllati e/o revisioni sistematiche di studi randomizzati

Livello III opinioni di esperti basati su esperienze cliniche o studi descrittivi

Gradi di raccomandazione

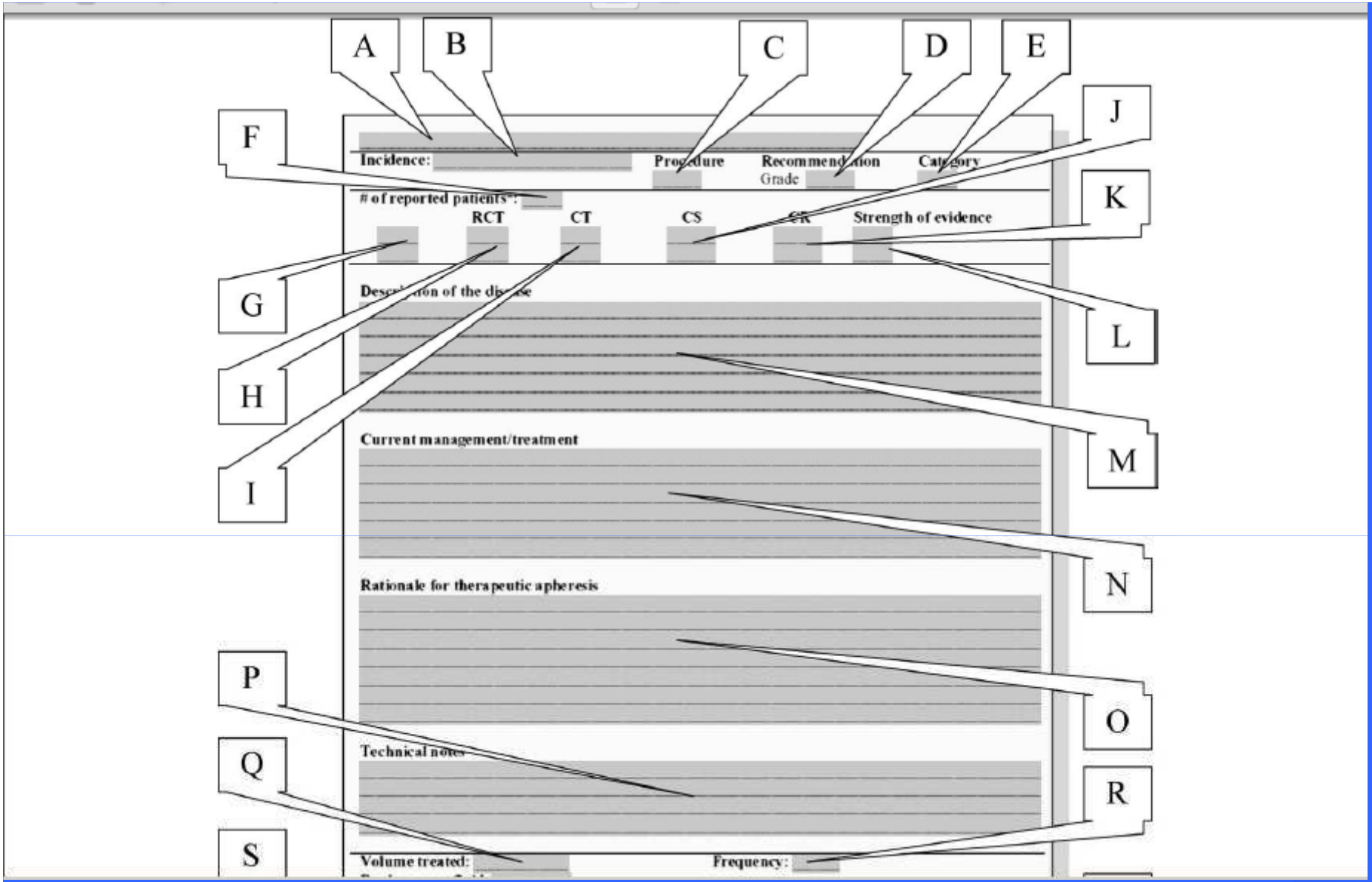
Probabilità che la procedura determini un miglioramento dello stato clinico

Grado I (A,B,C) raccomandazione forte sostenuta da prove scientifiche di buona , media e bassa qualità

Grado II(A,B,C) raccomandazione debole livello evidenza buono, medio, basso

Categorie

I	Terapia di prima scelta
II	Terapia di supporto
III	Quando la terapia tradizionale non è efficace
IV	Non c'è evidenza/ protocolli sperimentali



Scheda patologia

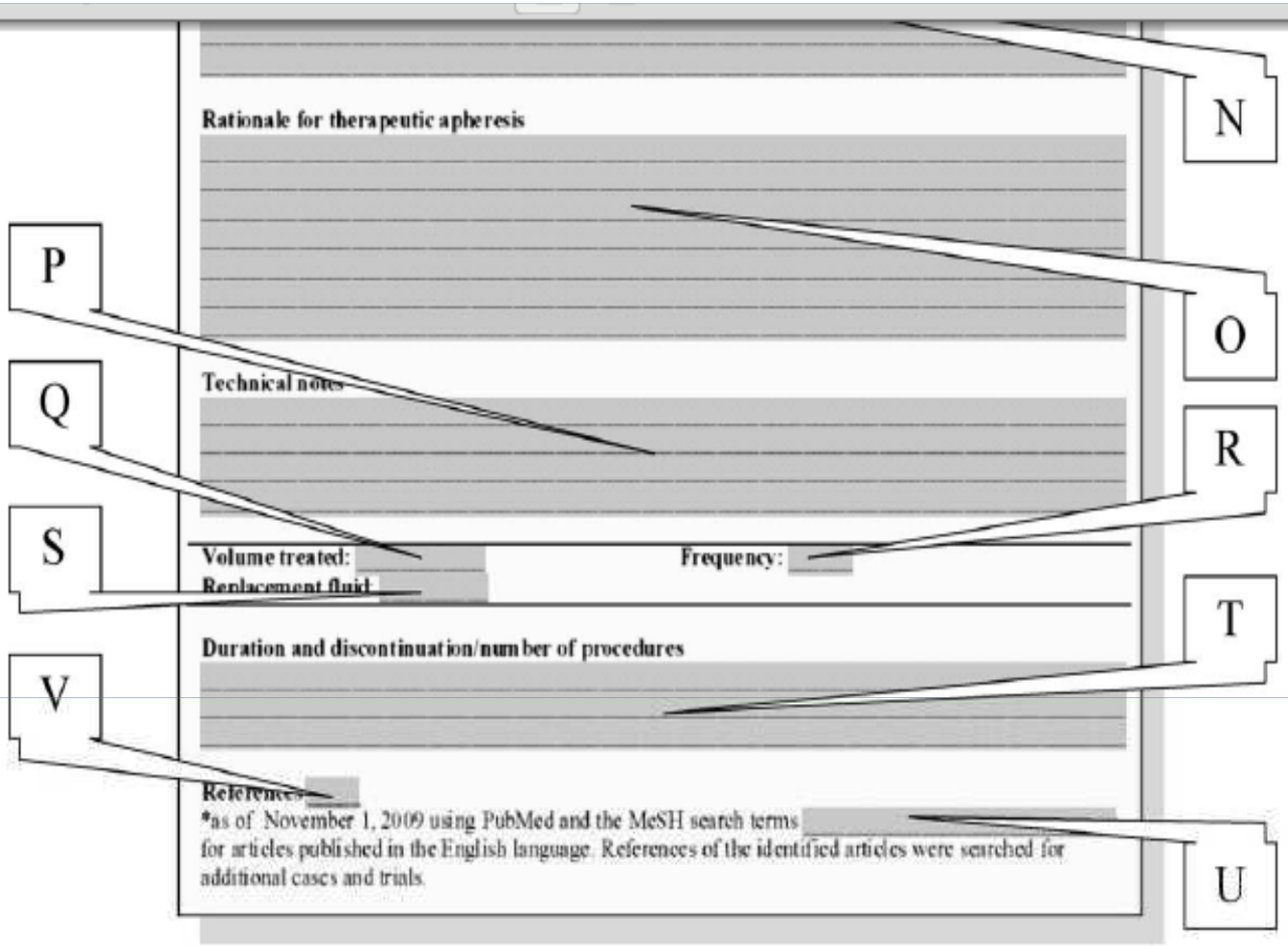


Fig. 1. Explanation of the fact sheet used in the ASFA Special Issue, Fifth Edition (2010).

A The name of the disease as well as its eponym when appropriate.

B This section lists the incidence and/or prevalence of the disease in the US and other selected geographic regions, when appropriate. In some instances when the incidence varies between genders, ethnicity, or race this information was noted as well. For certain diseases with insufficient data on either incidence or prevalence, other terms, such as rare or unknown were used. The reader is cautioned to use this information only as an indicator of disease prevalence. For some diseases, prevalence may vary by geographical area.

C The type of therapeutic apheresis procedure is listed here. Only diseases, which were categorized, are listed. For certain diseases there are several apheresis based modalities available. In such instances (e.g., cardiac allograft rejection) all types of therapeutic apheresis procedures are listed.

D Recommendation grade is assigned to each categorized entity. As noted in the text the authors of this research used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for grading clinical recommendations level. For

Porpora trombotica trombocitopenica

PTT

Sindrome di Moschowitz

- Microangiopatia trombotica occlusiva caratterizzata da aggregazione piastrinica sistemica, ischemia organi, severa trombocitopenia (con aumentato numero di megacariociti nel midollo) e anemia emolitica con presenza di schistociti in circolo.
- Patologia rara (3-7/1.000.000) ma giovane età/decorso fulminante/mortalità elevata (+freq. prime 48 h dalla diagnosi)

Eli Moschowitz

1925 “powerful poison which had both agglutinative and hemolityc properties”

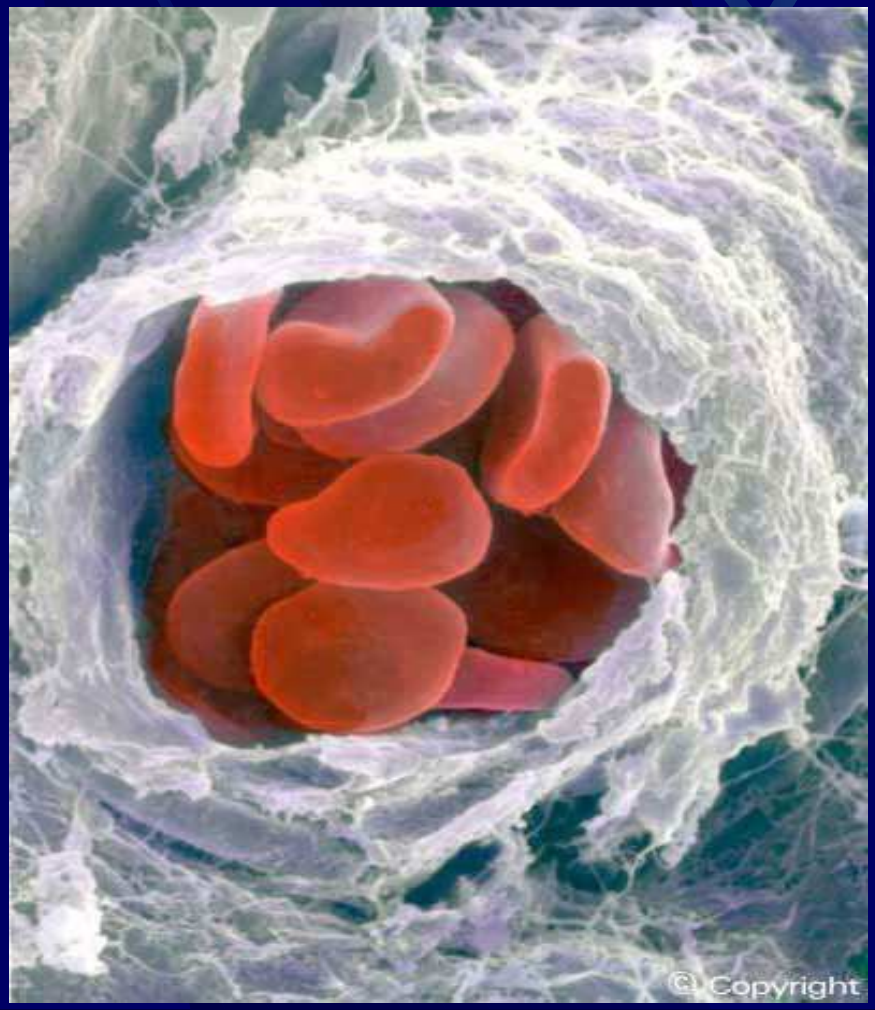
Pentade sintomatologica

- Trombocitopenia
- Anemia emolitica con schistociti e LDH
- Sintomi neurologici
- Funzionalità renale
- Febbre

PTT

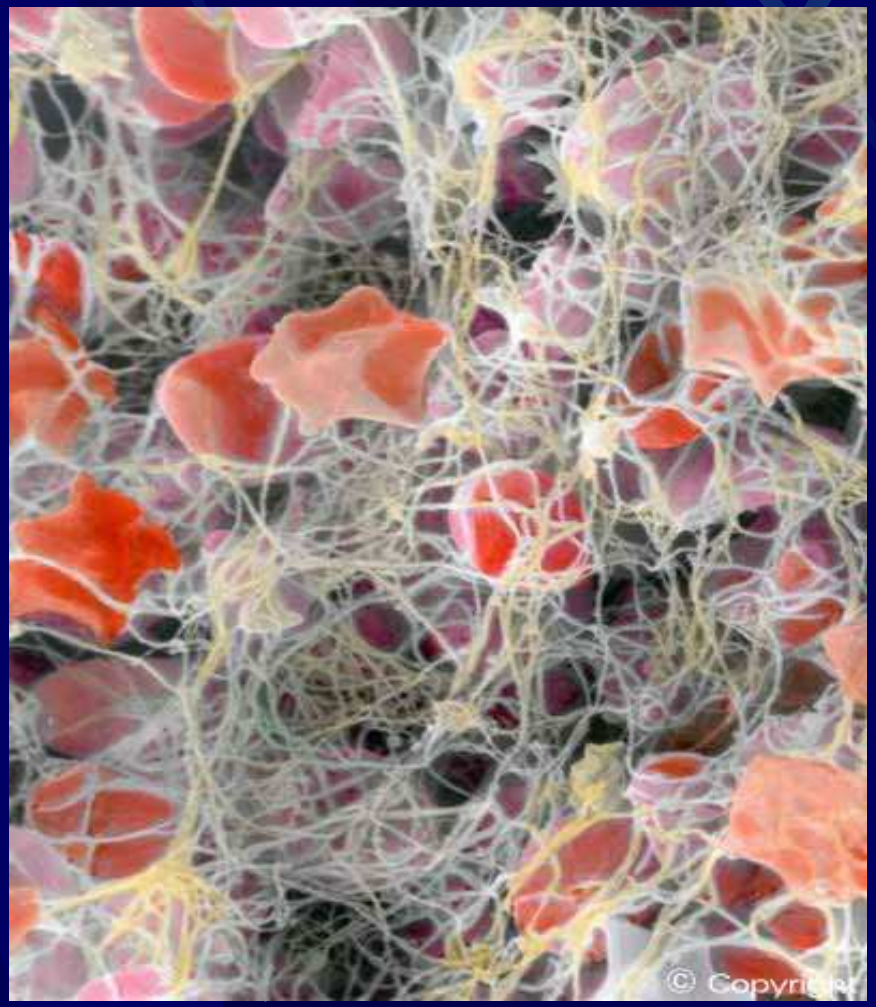
SEU

PTT - FORMAZIONE DEGLI SCHISTOCITI

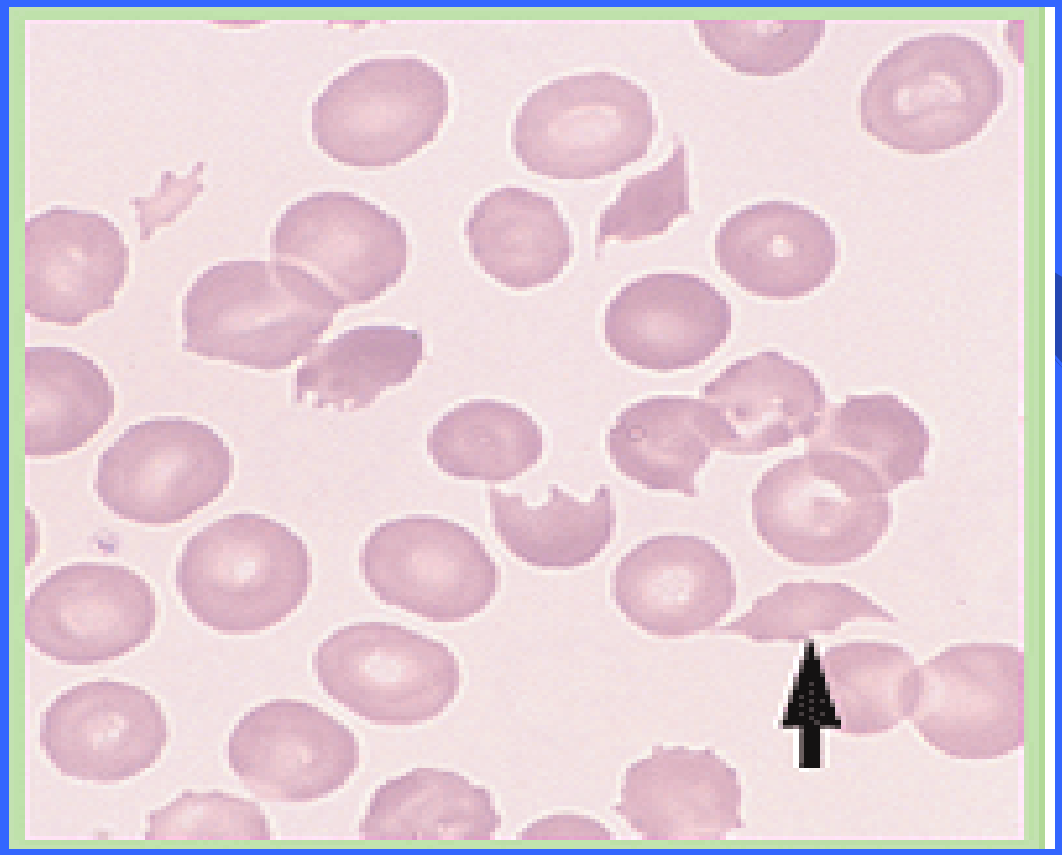


GLOBULI ROSSI CHE SCORRONO IN UN PICCOLO VASO

PTT - FORMAZIONE DEGLI SCHISTOCITI

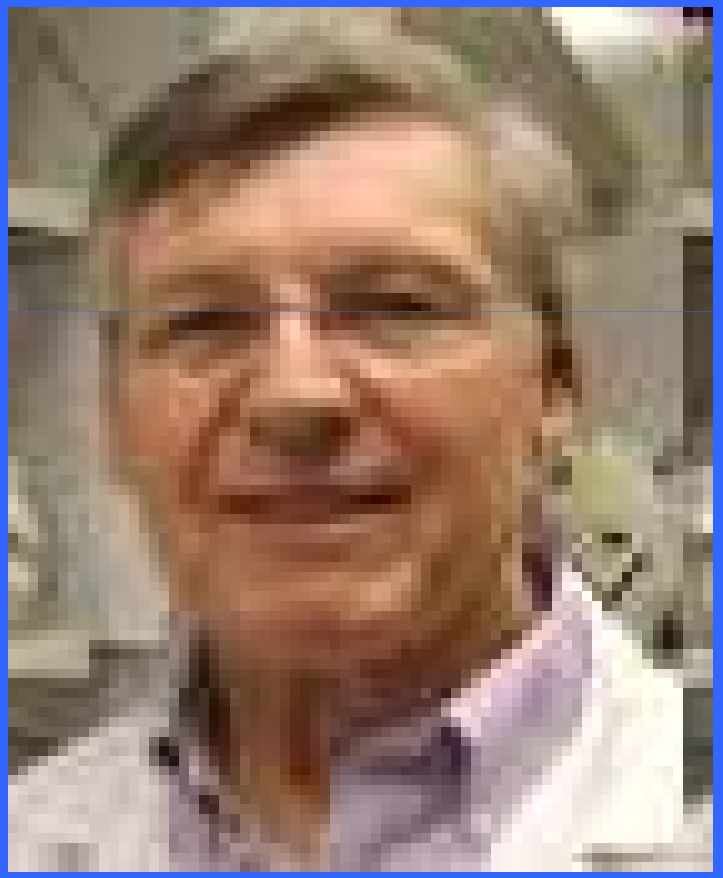


LA ROTTURA DEI GLOBULI ROSSI AVVIENE PER IL TRAUMA CHE SUBISCONO NELLO SCORRERE NEI VASI DEFORMATI DAI TROMBI



SCHISTOCITI ALLO STRISCIO PERIFERICO

Perché si formano i trombi piastrinici?



1982

Moake scopre nel plasma di questi pazienti fattore Von Willebrand ad alto PM

FORMAZIONE DI TROMBI PIASTRINICI

1997

ULVW

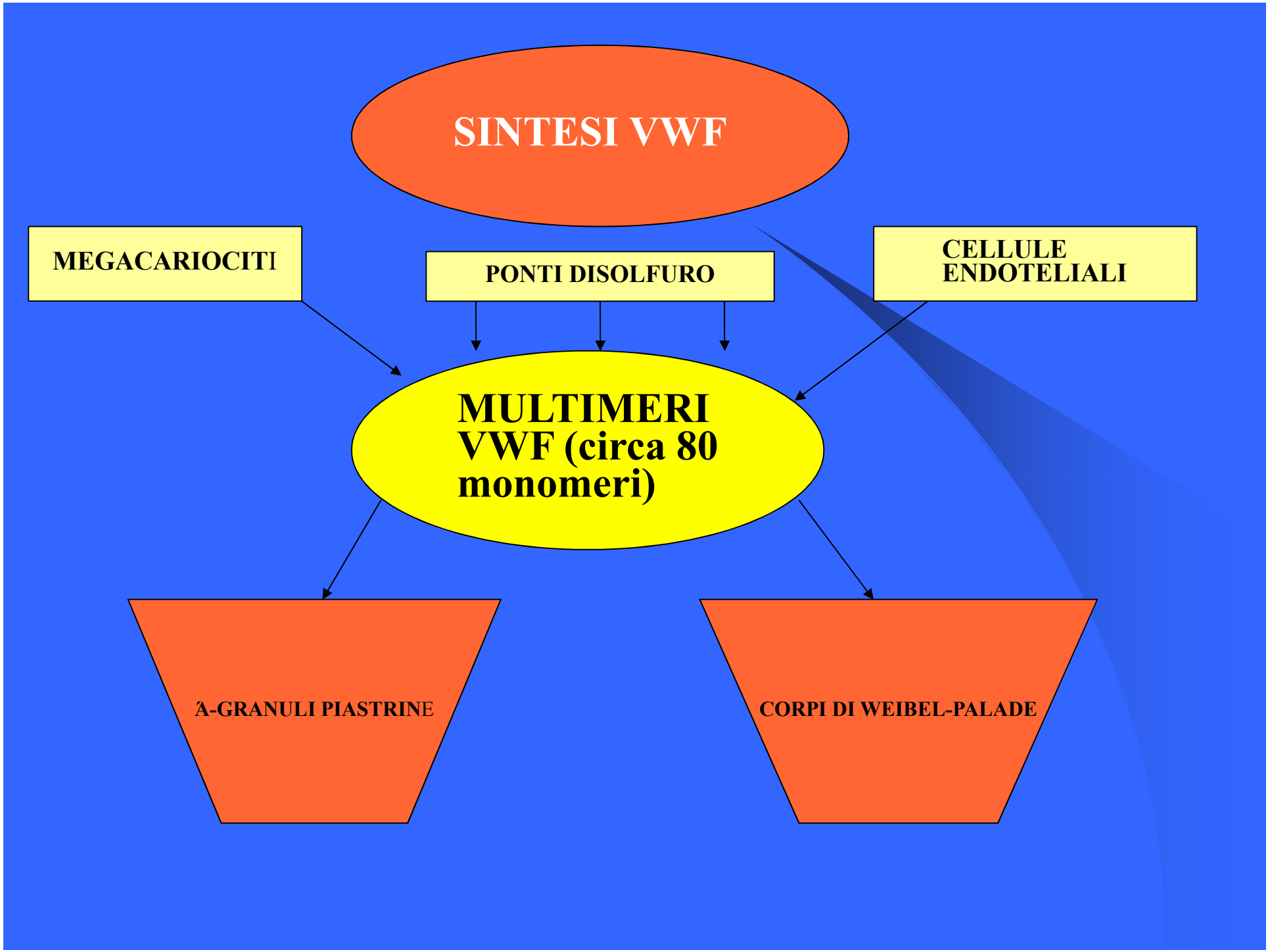
ADAMTS 13

FATTORE VON WILLEBRAND

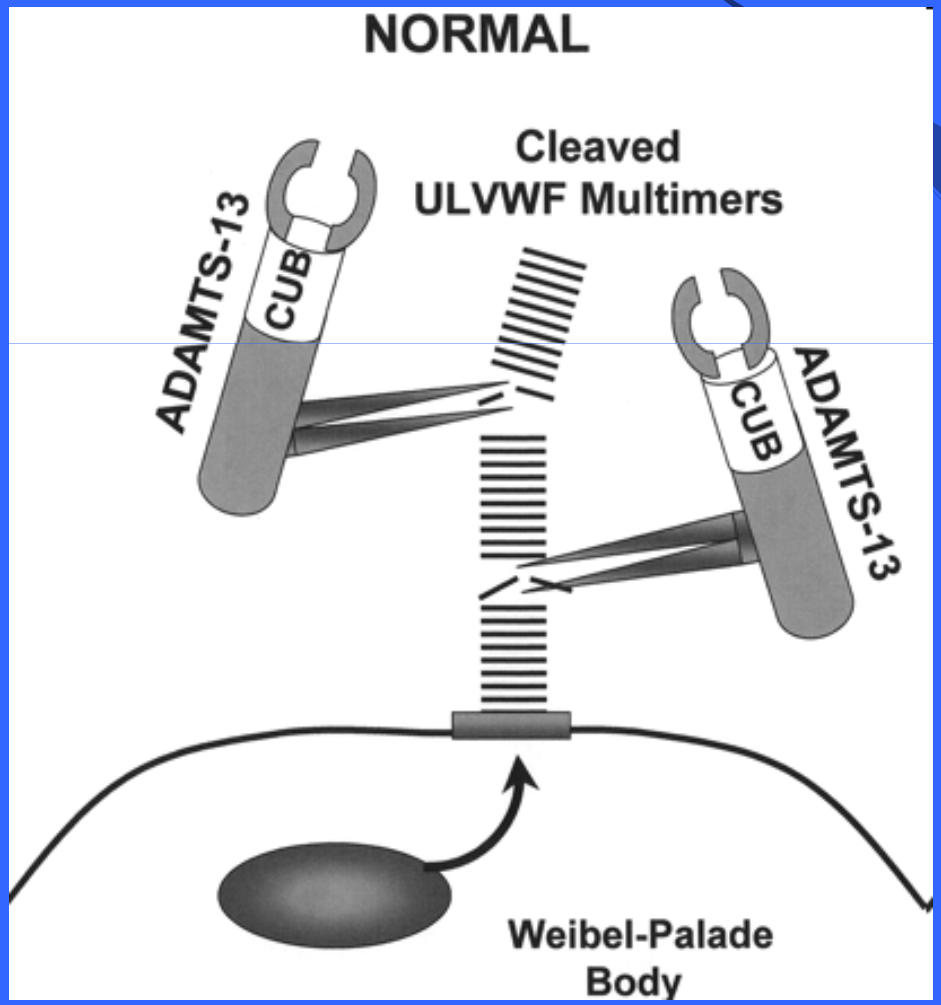
- Interviene nell'adesione piastrinica al sottoendotelio in caso di lesione endoteliale
- Interviene nell'aggregazione piastrinica
- I multimeri sono più attivi – hanno più siti di legame (circa 80 monomeri)

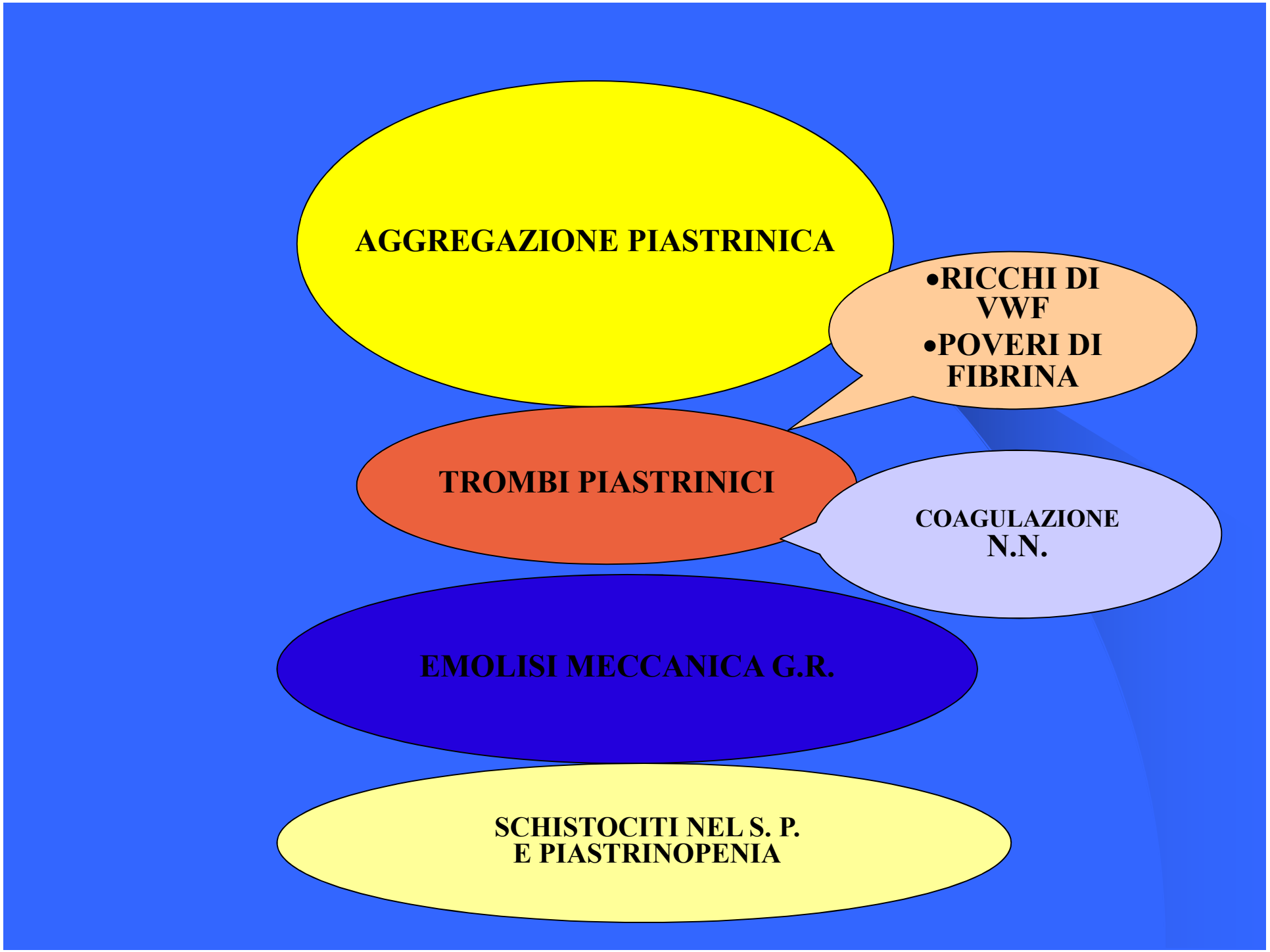
In condizioni normali non si stacca dalle cellule endoteliali viene degradato dall'Adamts 13

In carenza di Adamts 13 le piastrine aderiscono, si distaccano/embolizzano fino a formare trombi nei piccoli vasi


SINTESI VWF
MEGACARIOCITI
PONTI DISOLFURO
CELLULE ENDOTELIALI
MULTIMERI VWF (circa 80 monomeri)
Α-GRANULI PIASTRINE
CORPI DI WEIBEL-PALADE

MECCANISMO D'AZIONE ADAMTS 13




AGGREGAZIONE PIASTRINICA
•RICCHI DI VWF
•POVERI DI FIBRINA
TROMBI PIASTRINICI
COAGULAZIONE N.N.
EMOLISI MECCANICA G.R.
SCHISTOCITI NEL S. P.
E PIASTRINOPENIA

PTT

Forma familiare (Upshaw-Schulman)

- Rara
- Quadri clinici diversi
- Sempre bassi livelli Adamts 13
- No anticorpi anti-Adamts 13
- Recidive frequenti

PTT idiopatica acquisita

- Bassi livelli Adamts13 solo in fase acuta
- Livelli normali in fase di remissione
- Si anticorpi anti-Adamts 13
- Recidive (11-36%)

PTT SECONDARIE

- Post trapianto midollo
- Farmaci : Chinino, chemioterapici, ticlopidina,clopidogrel
- Gravidanza,post partum
- Patologie autoimmuni
- Infezioni batteriche, virali, fungine
- Neoplasie
- Ipertensione maligna

FORME SECONDARIE

Minor chiarezza sulla patogenesi

Ruolo Adamts 13 ?

Disequilibrio di molteplici fattori

Danno endoteliale

Iter diagnostico

Emocromo

Ricerca schistociti nello s.p.

Ldh

Bilirubina Diretta e indiretta

Coagulazione(nn)

Test di Coombs diretto

Aptoglobina

Reticolociti (se assenti es. midollo)

Funzionalità Adamts 13 e presenza inibitore

RUOLO PLASMAFERESI

Cat.I

Livello di evidenza 1

Grado di raccomandazione 1A

TERAPIA SALVAVITA

PTT

MORTALITA'

Pre-plasma exchange	Attuale
90% (1966)	**15-20%**

La maggior parte entro 48 ore dalla diagnosi

Importante intervento tempestivo

PTT - PLASMA-EXCHANGE

Razionale

Sottrazione di anticorpi anti ADAMTS13.
Apporto di nuovo ADAMTS13 con il plasma infuso

Volume di scambio

1 volume plasmatico per procedura (circa 2-4L)

PTT - PLASMA-EXCHANGE

Frequenza

Quotidiana

Durata

Fino a normalizzazione stabile (da almeno 3 gg) del conteggio piastrinico e dell'LDH sierico)

In casi di particolare gravità il volume plasmatico può essere raddoppiato oppure si possono eseguire 2 aferesi al giorno

THROMBOTIC THROMBOCYTOPENIC PURPURA

Incidence: 0.37 per 100,000/year in the US	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 1A	I

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
7 (301)	2 (133)	17 (915)	28 (48)	Type I

Description of the disease

Thrombotic Thrombocytopenic Purpura (TTP) is a systemic thrombotic illness affecting mostly small vessels. When initially described, TTP was defined by a pentad of clinical findings: thrombocytopenia, microangiopathic hemolytic anemia (MAHA; fragmented red cells on blood smear and elevated lactate dehydrogenase), mental status changes, renal failure and fever. In current practice, however, the clinical findings of unexplained thrombocytopenia and MAHA are sufficient to diagnose TTP. Treatment should not be initiated until other causes of systemic thrombotic microangiopathy (TMA) such as disseminated intravascular coagulopathy severe malignant hypertension, hemolytic uremic syndrome (HUS) and post-transplant TMA are ruled out. Recently TTP has been shown to be associated with a severe (<5%) deficiency of plasma ADAMTS13 (*Adisintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)* enzyme activity, which is responsible for maintaining normal distribution of vWF multimers by cleaving ultralarge multimers released from the endothelium. The severe deficiency of ADAMTS13 is documented in 100% of patients with idiopathic TTP in 7 out of 12 studies and in 37% to 83% of patients in the remaining 5 studies. An autoantibody is identified in the majority of patients with idiopathic acquired TTP. In a recent study, IgG4 was found to be most common anti-ADAMTS13 subclass and was suggested to be related to recurrence of the disease. Congenital TTP is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Severe ADAMTS13 deficiency appears to be an important proximal step in the pathophysiology of TTP. However, as noted above, some patients with idiopathic TTP have no defect in ADAMTS13 function. The role of laboratory assays that measure protease activity and anti-ADAMTS13 antibody level in medical decision-making in TTP is still evolving. At this time TTP remains a clinical diagnosis. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Work to differentiate TTP from HUS (characterized by TMA, thrombocytopenia, and renal failure) is currently underway. Better understanding of which individuals suffer from HUS or TTP may result in improved treatment by identification of patients who would benefit from emergent TPE. Pregnancy, connective tissue disease, medications, infection, cancer, and transplantation are all associated with TTP, HUS TMA syndromes (see HUS, TMA Drugs and TMA HSCT-associated Fact Sheets).

Current management/treatment

TPE has decreased the overall mortality of idiopathic TTP from uniformly fatal to <10%. TPE should be initiated emergently once TTP is recognized. If TPE is not immediately available, plasma infusions may be given until TPE can be initiated. Both fresh frozen plasma (FFP) and plasma

been practiced. Other adjuncts include vincristine and splenectomy. Although platelet counts can be very low, patients with TTP have thrombotic rather than hemorrhagic tendency. Bleeding, if present, is typically limited to skin and mucous membranes. Platelets should not be transfused unless clinically indicated. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10 to 15 mL/kg) or cryoprecipitate (which contains ADAMTS 13) or plasma derived von Willebrand factor concentrates (used to treat von Willebrand disease) have been used.

Rationale for therapeutic apheresis

TPE with plasma replacement has significantly improved patients' clinical outcomes. No other intervention has had as significant impact on the treatment of TTP. One hypothesis is that TPE removes the anti-ADAMTS13 autoantibody, while restoring ADAMTS 13 protease activity. Clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor and/or levels.

Technical notes

Transfusion of RBC, when medically necessary, may be given emergently during TPE. Clinical response with clearing of mental status usually precedes recovery of platelet count and normalization of LDH. The median number of TPE procedures to establish hematologic recovery is 7 to 8 days. The pattern of platelet response is variable and platelet count may fluctuate during treatment. Allergic reactions and citrate reactions are more frequent due to the large volumes of plasma required. Since plasma has citrate as an anticoagulant, ACD-A can be used in a higher ratio to minimize citrate reactions, especially with moderate to severe thrombocytopenia. Fibrinogen levels may decrease following serial TPE procedures with PCR as replacement. In patients with severe allergic reactions to plasma proteins or limited supply of ABO compatible plasma, 5% albumin may be substituted for the initial portion (up to 50%) of replacement. Albumin alone however has never shown efficacy.

Volume treated: 1 to 1.5 TPV **Frequency:** daily
Replacement fluid: plasma; plasma cryoprecipitate removed

Duration and discontinuation/number of procedures:

TPE is generally performed daily until the platelet count is above 150×10^9/L, and LDH is near normal for 2 to 3 consecutive days. LDH is removed during TPE, therefore, may not reflect response to TPE. The role of tapering TPE over longer duration has not been studied prospectively. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment.

References [786–795]

*As of November 8, 2009 using PubMed and the MeSH search terms thrombotic thrombocytopenic purpura, plasma exchange, plasmapheresis and rituximab reports published in the English language. References of the identified articles were searched for additional cases and trials.

Forme secondarie

L’indicazione nelle forme secondarie, tranne in quelle nei pz in terapia con ticlopidina o clopidogrel, è molto debole, in quanto i meccanismi alla base sono diversi , sembra prevalere la componente del danno endoteliale

THROMBOTIC MICROANGIOPATHY: HEMATOPOIETIC STEM CELL TRANSPLANT-ASSOCIATED

Incidence: HPC TA-TMA 3%–15% (recent studies)	**Procedure** TPE	**Recommendation** Grade 1B	**Category** III

# of reported patients*: >300

	RCT	CT	CS	CR	Strength of evidence
HSCT-associated TMA [TA-TMA]	0	0	22 (322)	6 (6)	Type II-3

Description of the disease

Thrombotic microangiography (TMA) refers to the histopathological appearance of arteriolar microthrombi with associated intimal swelling and fibrinoid necrosis of the vessel wall. A variety of conditions and drugs can activate platelets causing their intravascular deposition as microthrombi, resulting in the clinicopathologic hallmarks of TMA: microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. TMA following allogeneic hematopoietic stem cell transplantation (also called transplant associated [TA]-TMA) appears to be primarily triggered by mechanisms of endothelial cell injury, including high-dose conditioning chemotherapy, irradiation, graft-versus-host disease (GVHD), mTOR (mammalian target of rapamycin) and calcineurin inhibitor drugs (used to prevent and treat GVHD) and infections. Damaged and apoptotic endothelial cells generate microparticles, release of von Willebrand factor (vWF) and induce platelet adhesion/aggregation and a procoagulant state. In contrast to idiopathic thrombotic thrombocytopenic purpura (TTP), the plasma ADAMTS13 protease level is not severely deficient nor is ADAMTS13 inhibitor activity detectable. The incidence of TA-TMA varies based on the diagnostic criteria and transplant-associated risk factors. Incidence rates in older studies ranged from 0.3-63.6%; however, the rates in more recent studies range from 3-15%. Risk factors associated with TA-TMA include higher dose conditioning regimens, acute GVHD, female sex, active infections, unrelated donor transplants and the combination of mTOR and calcineurin inhibitor drugs. Controversy exists whether non-myeloablative conditioning regimens are associated with greater risk. Kidneys are the major target organs of TA-TMA. Renal function test elevation is common and renal failure is a poor prognostic feature. Diagnostic criteria require MAHA (with high LDH or low haptoglobin) with or without unexplained thrombocytopenia, renal and/or neurologic dysfunction. Because MAHA can be due to other causes and drugs, the published criteria for TA-TMA diagnosis are relatively insensitive. TA-TMA carries a poor prognosis. Mortality rates range from 44-90%, including those patients who respond to interventions, due to renal failure, cardiac or brain ischemia, bleeding and complications of concur-

THROMBOTIC MICROANGIOPATHY: DRUG-ASSOCIATED

Incidence:	**Procedure**	**Recommendation**	**Category**
Ticlopidine/Clopidogrel: 50 in 100,000 users	TPE	Grade 2B	I (ticlopidine; clopidogrel)
Cyclosporine/Tacrolimus: rare	TPE	Grade 2C	III (cyclosporine; tacrolimus)
Gemcitabine: 15 in 100,000 (0.015%) users	TPE	Grade 2C	IV (gemcitabine)
Quinine: rare	TPE	Grade 2B	IV (quinine)

# of reported patients*: >300

	RCT	CT	CS	CR	Strength of evidence
Ticlopidine/ Clopidogrel	0	0	4 (152)	5 (5)	Type II-3
Cyclosporine/ Tacrolimus**	0	0	6 (90)	7 (7)	Type II-3

Volume di scambio plasmatico

Il volume di scambio viene calcolato in termini di 1 o più volumi plasmatici del paziente

1 volume plasmatico = 40-50mL/Kg

Volume di plasma

Volume di plasma scambiato	Percentuale di rimozione
0	100%
0.5	39.3%
1.0	63.2%
1.5	77.7%
2.0	86.5%
2.5	91.8%
3.0	95.0%

Trattamento

Scambio 1-2 V fino a 2 aferesi die

Frequenza giornaliera

Durata fino a normalizzazione del quadro per almeno 3 gg consecutivi (plts e LDH)

Liquido di sostituzione : plasma fresco

Tempestività

In caso di a. emolitica microangiopatica e piastrinopenia in assenza di cause apparenti iniziare pex

Importante > mortalità entro 48 h dalla diagnosi

Patologie alternative:

A. megaloblastica

Virosi

Sepsi

Parassitosi

Neoplasie

Ipertensione maligna

Malattie autoimmuni

SINDROME EMOLITICO-UREMICA

P T T **S E U**

C O N S I D E R A T E C O M E U N I C A E N T I T A C L I N I C A A S E C O N D A D E L L A P R E V A L E N Z A D I S I N T O M I N E U R O L O G I C I (P T T) O R E N A L I (S E U) F I N O A L L A S C O P E R T A D E I M E C C A N I S M I P A T O G E N E T I C I

SEU

FORMA TIPICA POST-INFETTIVA

- **Bambini <2 aa**
  Prognosi severa
  Mortalità 25%
- **Adulti 85/90%**
  Prognosi buona
  Mortalità <5%

FORMA ATIPICA

- **F.CONGENITE:**
  Mutazioni sui geni complemento
- **F. acquisite:**
  Auto anticorpi anti- fattore H H

Forme SEU

F. tipica post-infettiva adulto 85-90% di tutte le SEU è preceduta da episodio enterite + freq. da E. coli

F. tipica bambini: in corso di sepsi, meningiti, polmoniti da S. pneumoniae

F. atipica congenita e acquisita: il fattore scatenante ipotizzato è l'insulto alle strutture endoteliali

Indicazioni PEX

Cat.I : Gruppo con auto-anticorpi

Cat. II: F. atipiche congenite

Cat. IV: F. tipiche post-infettive tranne in alcuni casi f. infettive da S. pneumoniae

RAZIONALE PLASMAFERESI

Rimozione autoanticorpi o forme mutate regolatori complemento e rimpiazzo con forme normali

Nonostante pareri controversi sull'indicazione a effettuare pex o plasmainfusione il Gruppo Europeo consiglia pex per evitare rischi di sovraccarico

Modalità

Linee guida ASFA indicano

pex giornaliere x 5gg

poi 5 pex /sett x 2 sett.

poi 3 vv./sett x 2 sett.

valutazione risultati al giorno +33

L'efficacia della pex è sul quadro emolitico generale non sul rene

Alcuni pz con mutazioni specifiche hanno un'alta % di recidiva post-trapianto

SINDROME DA IPERVISCOSITA’

Condizione clinica dovuta a un incremento della viscosità ematica che si manifesta con sintomi derivanti dalla ipoperfusione e dalla stasi vascolare.

CAUSE

MACROGLOBULINEMIA DI WALDESTROM → **IGM**

MIELOMA MULTIPLO → **IGA**
IGG

SINTOMI

EMORRAGIE MUCOSE

CEFALEA

VERTIGINI, NISTAGMO

IPOACUSIA

DISTURBI VISUS

TORPORE PSICHICO

CRISI COMIZIALI

COMA

PLASMAFERESI

Generalmente si effettuano un paio di procedure

Si usa albumina diluita o PPS come liquido di sostituzione

HYPERVISCOSITY IN MONOCLONAL GAMMOPATHIES

Incidence: 0.1-0.3 per 100,000/year	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 1B	I** (treatment of symptoms)
	TPE	Grade 1C	I** (prophylaxis for rituximab)

# of reported patients*: >300

	RCT	**CT**	**CS**	**CR**	**Type of evidence**
treatment of symptoms	0	3 (46)	18 (253)	12 (12)	Type II-1
prophylaxis for rituximab	0	0 (0)	3 (45)	2 (2)	Type II-3

Description of the disease

Whole blood viscosity varies as a function of hematocrit, red blood cell aggregation, plasma proteins, and interactions between the blood and the blood vessel wall. As blood viscosity rises, a nonlinear increase in shear stress in small blood vessels, particularly at low initial shear rates, produces damage to fragile venular endothelium of the eye and other mucosal surfaces. The term ''hyperviscosity syndrome'' refers to the clinical sequelae of mucous membrane bleeding, retinopathy, and neurological impairment. Specific signs and symptoms include headache, dizziness, vertigo, nystagmus, hearing loss, visual impairment, somnolence, coma, and seizures. Other manifestations include congestive heart failure (related to plasma volume overexpansion), respiratory compromise, coagulation abnormalities, anemia, fatigue (perhaps related to anemia), peripheral polyneuropathy (depending on specific properties of the immunoglobulin), and anorexia. This syndrome occurs most typically in Waldenström's macroglobulinemia, a lymphoplasmacytic lymphoma associated with the elaboration of ≥3 g/dL of monoclonal IgM immunoglobulin (M-protein) in the plasma. It also occurs in multiple myeloma, a plasma cell dyscrasia, when there is ≥6–7 g/dL of monoclonal IgA or ≥4 g/dL of monoclonal IgG3 in the plasma. In vivo whole blood viscosity is not necessarily identical to in vitro serum viscosity (relative to water; normal range being 1.4–1.8 centipoise [cp]). Therefore, serum viscosity measurement does not consistently correlate with clinical symptoms among individual patients. Almost all patients will be symptomatic when their serum viscosity rises to between 6 and 7 cp. Some may be symptomatic at a viscosity as low as 3–4 cp, others not until their viscosity reaches 8–10 cp. Recent data indicate that early manifestations of hyperviscosity-related retinopathy in Waldenström's macroglobulinemia can be detected in the peripheral retina at a serum viscosity as low as 2.1 cp and IgM levels below 3 g/dL, using indirect opthalmoscopy. Finally, the tendency of many hospitals to outsource serum viscosity to reference laboratories renders this test potentially less useful than it once was due to uncertainties related to specimen integrity while in transit and to turnaround time.

Current management/treatment

Plasma removal has been successfully employed in the treatment of hyperviscosity syndrome in Waldenström's macroglobulinemia since 1959. Manual plasmapheresis

CRIOGLOBULINEMIE

Condizione clinica determinata dalla presenza in circolo di immunoglobuline che precipitano reversibilmente alle basse temperature, aderendo ai piccoli vasi e causando danni conseguenti all'attivazione del complemento e al richiamo di leucociti.

SINTOMATOLOGIA

Fenomeni ischemici a carico dei distretti periferici , in particolare estremità distali degli arti

CLASSIFICAZIONE

Tipo I : Ig monoclonali (Ig M Waldestrom, IgG mieloma multiplo)

Tipo II : IgG policlonali e IgM monoclonali con attività di FR (epatite C)

Tipo III: IgM e IgG policlonali (malattie infettive o autoimmuni)

80% tipo misto (II e III)
80% (epatite B e C)

CRYOGLOBULINEMIA

Incidence: 1-2% of patients with chronic hepatitis C, approximately 80% of patients with cryoglobulinemia have hepatitis C	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 1B	I (severe/symptomatic)
	IA	Grade 2B	II (secondary to hepatitis C)

# of reported patients*: 100–300

	RCT	**CT**	**CS**	**CR**	**Type of evidence**
TPE	0	0	18 (195)	>50	Type II-3
IA	1 (17)	0	1 (4)	0	Type I

Description of the disease

Cryoglobulins are immunoglobulins that reversibly precipitate below body temperature. The aggregates of cryoglobulins can deposit on small vessels and cause damage by activating complement and recruiting leukocytes. This most likely occurs on the skin of lower extremities because of exposure to lower temperatures. The end-organ complications secondary to cryoglobulinemia range from none to severe. Cryoglobulinemia is associated with a wide variety of diseases including lymphoproliferative disorders, autoimmune disorders, and viral infections (e.g. hepatitis B and C). Mild symptoms include purpura, arthralgia, and mild sensory neuropathy.

Severe symptoms include glomerulonephritis, neuropathy, and systemic vasculits. Cryoglobulins are classified into three types: type I consist of monoclonal immunoglobulins, usually due to multiple myeloma (IgG) or Waldenström's macroglobulinemia (IgM), type II contain polyclonal IgG and monoclonal IgM rheumatoid factor usually due to hepatitis C infection, and type III contain polyclonal IgG and IgM usually due to inflammatory disorders, autoimmune disease, or hepatitis C infection. About 80% of individuals with mixed cryoglobulinemia (types II and III) have hepatitis C. The diagnosis of cryoglobulinemia is made by history, physical findings, low complement levels and detection and characterization of cryoglobulins (cryocrit).

Current management/treatment

Management is based on the severity of symptoms and treating the underlying disorder. There is no correlation between the severity of disease and cryocrit. Individuals with type I have a higher cryocrit than individuals with type II or III. Asymptomatic individuals do not require treatment of their cryoglobulinemia. Mild symptoms can be treated with cold avoidance and analgesics. More severe disease warrants the use of immunosuppressive therapy such as corticosteroids, cyclophosphamide, and rituximab (anti-CD20). Additionally, interferon and ribavirin are used for the treatment of cry-

Plasmaferesi

Solo nei soggetti sintomatici, coadiuvata dalla terapia specifica

I sintomi non sono correlati con il valore del criocrito

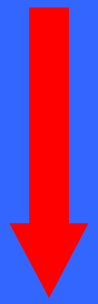
Albumina come liquido di sostituzione

Numero di procedure variabile (da 3 a 8), alcune volte si fa una terapia di mantenimento

Attenzione alla temperatura dei liquidi di reinfusi one!

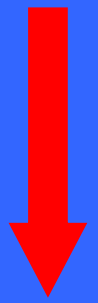
TRAPIANTO DI MIDOLLO OSSEO ABO INCOMPATIBILE

Trapianto organo solido ABO incompatibile



RIGETTO IPERACUTO

Trapianto midollo ABO incompatibile



EMOLISI INTRAVASCOLARE

TRAPIANTO DI MIDOLLO OSSEO ABO INCOMPATIBILE

La problematica è identica a quella della trasfusione del sangue:

INCOMPATIBILITA' MAJOR Gli anticorpi anti A/B del ricevente reagiscono con le emazie presenti nelle cellule emopoietiche (HPC) del donatore

INCOMPATIBILITA' MINOR Gli anticorpi presenti nel plasma delle HPC del donatore reagiscono con le emazie del ricevente

INCOMPATIBILITA' AB0 NEL TRAPIANTO DI MIDOLLO

Manipolazione raccolta
(deplasmatizzazione, deeritrocizzazione)

Diminuzione titolo anticorpi nel ricevente
(plasmaferesi)

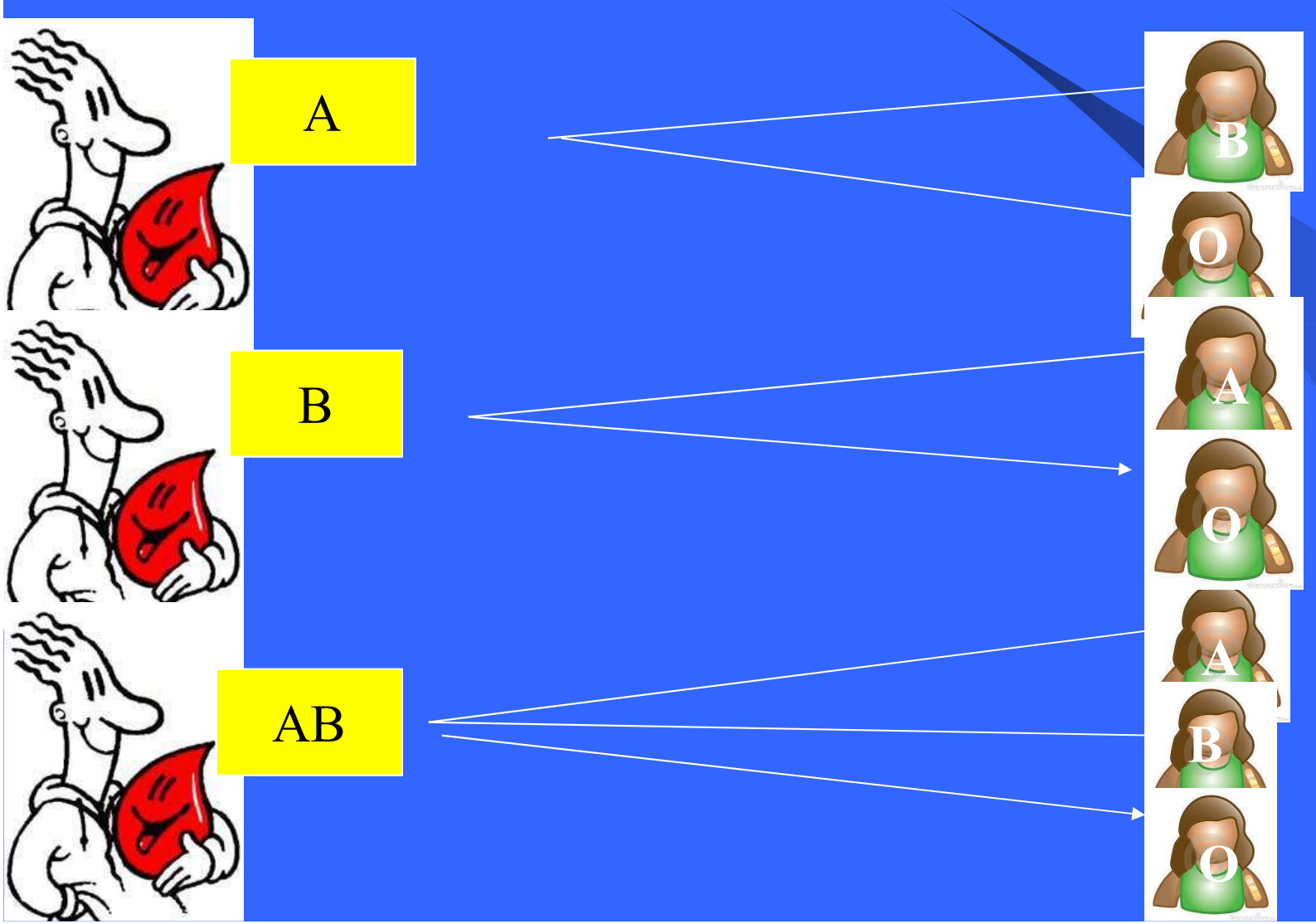
RISCHI EMOLISI

Rischio di emolisi > per midollo

Quantità globuli rossi > 20 ml

Titolo anticorpale ricevente > 1:16

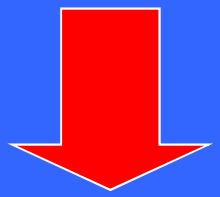
Incompatibilita’ AB0 major



TRAPIANTO DI MIDOLLO OSSEO ABO INCOMPATIBILE

INCOMPATIBILITA' MAJOR

Se concomitano una quantità di globuli rossi superiore a 20 mL ed un titolo anti A/B superiore a 1:16



Deeritrocizzazione (eventuale plasmaexchange al ricevente)

PLASMAFERESI

- Obiettivo: titolo anticorpale < 1:16
- Plasmaferesi ravvicinate nei giorni precedenti il trapianto
- Albumina o plasma come liquido di sostituzione

INCOMPATIBILITA' ABO MINOR

COMPLICANZE

Severa emolisi acuta intravascolare (a volte mortale) dopo 7-10 giorni dal trapianto dovuta alla produzione di anticorpi anti A/B da parte dei linfociti del donatore.

Trasfusione intensiva di emazie 0

Plasmaexchange

Eritrocitoexchange con emazie 0

ABO INCOMPATIBLE HEMATOPOIETIC STEM CELL TRANSPLANTATION

Incidence: ABO incompatibility exists in about 20%–40% of HLA-matched allogeneic hematopoietic stem cell and bone marrow transplants	**Procedure**	**Recommendation**	**Category**
	TPE	Grade 1B [HPC(M)]	II
	TPE	Grade 2B [HPC(A)]	II

# of reported patients*: >300

RCT	CT	CS	CR	Type of evidence
0	0	4 (465)	10 (21)	Type II-3

Terminology: HPC, Apheresis [HPC(A)]; HPC, Marrow [HPC(M)]; HPC, Cord Blood [HPC(CB)].

Description of the disease

Major incompatibility refers to the presence of natural antibodies in the recipient against the donor's A or/and B blood group antigens. These isoagglutinins may cause acute hemolysis of the red cells present in the transplanted stem cell product. Blood hematopoietic progenitor cell (HPC) products collected by apheresis (HPC, Apheresis) carry a lower risk of hemolysis due to reduced red cell contamination (2-8%) as compared to bone marrow HPC products, which contain 25-35% red cells. In the latter case, either the product needs to be red cell-reduced (easier to perform) or the patient's isoaglutinin titer needs to be lowered (to <32) to prevent an acute hemolytic reaction. Delayed erythrocyte engraftment occurs in 20% of patients after major ABO mismatched transplantation. Pure red cell aplasia (PRCA) occurs rarely due to persistence of anti-A that destroys donor erythroid precursors (e.g. with an O recipient and A donor). In minor incompatibility, the HPC donor product has antibodies against the recipient's A and/or B antigen. These products should be plasma-reduced if the titer is >256 when the plasma volume is >200 mL to prevent an acute hemolytic transfusion reaction. In addition, donor lymphocytes (passenger B cells) are capable of mounting an antibody response against the recipient's A or B antigens, which can result in severe and even fatal hemolysis (generally occurring 7-10 days post HPC infusion). Peripheral blood stem cell (PBSC) transplantation has greater risk of this complication than bone marrow transplantation, since HPC, Apheresis products have 16-fold more CD3+T lymphocytes and 11-fold more CD19+ B lymphocytes than HPC, Marrow products. T cell depletion and cyclosporine-A are risk factors for this complication, whereas methotrexate reduces this risk by suppressing the proliferation of donor lymphocytes.

Current management/treatment

In major incompatibility, red cell reduction of the HPC product can be performed to prevent acute hemolytic transfusion reaction. In minor incompatibility, plasma reduction may prevent the same complication. For delayed erythroid engraftment or PRCA post transplantation, various management strategies have been reported including high-dose erythropoietin, plasma exchange (TPE), immunoadsorption, rituximab, donor lymphocyte infusions, discontinuation of cyclosporine, and antithymocyte globulin. The optimal treatment is currently not well defined. Acute hemolysis due to passenger

La plasmaferesi viene ancora oggi eseguita in patologie in cui non vi è alcun riscontro positivo in letteratura

Opzioni terapeutiche terminate

Casi complicati con diagnosi incerta

“Ultima ratio”

Conclusioni

Sicuramente le linee guida che abbiamo a disposizione rappresentano un valido strumento nei casi difficili; è bene comunque valutare sempre il rapporto rischio/beneficio tenendo presenti i rischi legati alla procedura, che molto spesso sono sottovalutati e il fatto che , essendo una metodica di rimozione meccanica , la sua azione è temporanea e deve quindi essere sempre supportata da una congrua terapia farmacologica.


Grazie