7^ Conferenza Nazionale dei Servizi Trasfusionali
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SIMTI

Terapia aferetica nel trapianto di cuore

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La sottoscritta, in qualità di Presentatrice
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatrice di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le sue funzioni al fine di trarne vantaggio.

I pazienti in attesa di trapianto cardiaco possono sviluppare anticorpi circolanti contro antigeni leucocitari (HLA).
Questo processo, mediante il quale si formano anticorpi, è chiamato ***Sensibilizzazione*.**
La **Sensibilizzazione** può essere determinata da:

- Trasfusioni di sangue
- Gravidanza
- Precedente trapianto di organo
- Cuore artificiale
- Posizionamento di un dispositivo di assistenza ventricolare.
- ECMO (Ossigenazione Extracorporea a Membrana)
- IABP (contropulsatore aortico)

Table 1. Clinical Pearls

General	Any level of detectable antibody may be considered sensitization; however, common thresholds for desensitization therapies are PRA >25% or cPRA >50%.
	Sensitization is associated with posttransplantation mortality, graft loss, CAV, and rejection.
	Sensitization can occur through antigenic exposure or viral infection and as a result of genetic predisposition.
Detection	Antibody screening methods vary in sensitivity and specificity.
	Percent PRA is imprecise, dependent on panel cell construction, not standardized, and not representative of the true donor pool. For these reasons, specificity is now required to determine a cPRA, and the term PRA is now obsolete unless testing is done by CDC or a screening flow bead assay.
	Luminex-based assays, especially with SABs, are the preferred method for pretransplantation and posttransplantation screening, identification, and monitoring of antibodies for all 11 HLA loci.
	Luminex IgG assays cannot determine complement fixation.
	MFI values of HLA antibodies provide a semiquantitative assessment of antibody strength and are not equivalent to antibody titers.
	cPRA is based on specificity determined by Luminex SAB and by entering the specificity in UNOS database to calculate the PRA. cPRA takes into consideration the frequency of the unacceptable HLA in the donor pool.
	Additional testing, such as IgG titers, complement-binding assays, and IgG subtyping assays, can be useful and are often needed to determine the clinical significance of detected DSAs.
	Complement-binding assays detect high-titer HLA antibodies (1:32–1:64) and IgG subtypes that bind complement. They can be used before transplantation for risk assessment in sensitized heart transplant recipients.
Crossmatching	Sensitization to HLA class I and class II antibodies confers a higher risk of rejection and CAV and increases waiting time for heart transplantation candidates.
	Patients exhibiting a positive pretransplantation crossmatch to donor HLA are at high risk for rejection and mortality.
	Avoiding a positive crossmatch and using measures to reduce preformed antibodies may be beneficial in improving posttransplantation outcomes.
	Each center determines the parameters for which HLA should be avoided that are based on level of antibody and, in some cases, biological significance, that is, the type of antibody (eg, complement-fixing capacity). This, in turn, dictates the cPRA, which is based solely on the antigens listed as unacceptable (avoids).
	Virtual crossmatch is recommended to avoid a positive crossmatch. If virtual crossmatch cannot be performed or in the event of recent sensitization, prospective crossmatch is recommended.
	Prospective crossmatch should also be performed, even if the virtual crossmatch is negative, unless the recipient has no DSAs by SABs, no historic DSAs, and no recent sensitizing events.
Management	Highly sensitized patients with cPRA >50%–80% are likely reasonable candidates for desensitization, especially if they have had multiple positive crossmatches.
	TPE is effective in reducing antibodies, although it is associated with rebound by week 1 and may not achieve maximal antibody reduction until week 4.
	IVIG results in early reduction in antibodies but reduction in efficacy by week 4.
	IVIG+rituximab may reduce wait time and may be more effective in preventing rebound that IVIG alone.
	The combination of IVIG, TPE, and rituximab effectively lowers antibody. Recipients who receive this protocol may have more rejection than untreated sensitized patients.
	Bortezomib results in rapid reduction in antibodies, but infection is common.
DSAs	De novo antibodies are associated with graft dysfunction, AMR, and CAV; however, low levels of antibody may be protective and, when detected, could represent accommodation.
	DSAs, particularly class II DSAs, are associated with risk of future AMR.
	Solid-phase assays should be used to characterize DSAs.
	Testing should be considered at the time of suspected or diagnosed acute rejection and periodically for posttransplantation class I and II DSAs to assess the associated risk of transplant rejection, graft loss, and development of cardiac transplant vasculopathy.
LVADs and sensitization	LVADs may result in sensitization; sensitization in patients with a VAD may be complicated by infection and transfusions.
	HLA sensitization after LVAD does not appear to affect rejection rate or survival; however, sensitization with NABs may be associated with graft dysfunction.

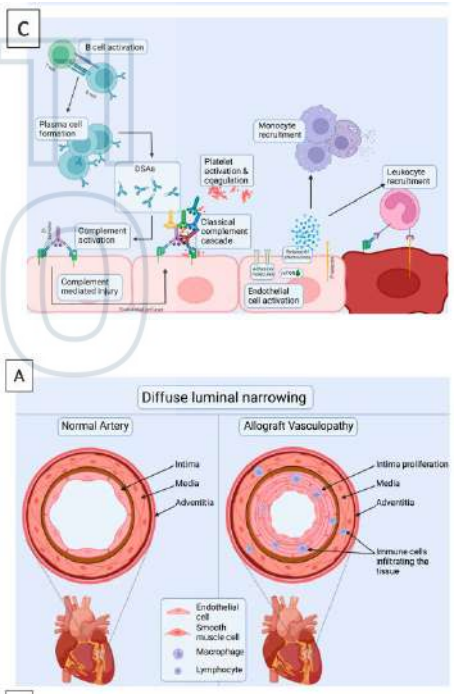
AMR indicates antibody-mediated rejection; CAV, cardiac allograft vasculopathy; CDC, complement-dependent cytotoxicity; cPRA, calculated panel-reactive antibody; DSA, donor-specific antibody; HLA, human leukocyte antigen; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; LVAD, left ventricular assist device; MFI, mean fluorescence intensity; NAB, natural antibodies; PRA, panel-reactive antibody; SAB, single-antigen bead; TPE, therapeutic plasma exchange; UNOS, United Network of Organ Sharing; and VAD, ventricular assist device.

Colvin M *et al*
Circulation 2019 Mar 19;139(12)
Sensitization in Heart Transplantation: Emerging Knowledge: A Scientific Statement From the American Heart Association

- Rigetto Cellulare
  - Infiammazione interstiziale
  - Graft antigeni/APC -> **Cellule Effettrici Tcell** -> Attivazione Mieloide -> Danno del miocita

- Rigetto Anticorpo-Mediato
  - Infiammazione Intracapillare innescata dagli Anticorpi circolanti

- Vasculopatia Cardiaca graft correlata
  - Vasculite cronica associata a fibrosi



Hurskainer M *et al* Failing Heart Transplants and Rejection—A Cellular Perspective *J. Cardiovasc. Dev. Dis.* 2021, *8*(12), 180

Accepted Manuscript

The clinical impact of donor-specific antibodies in heart transplantation

Markus J. Barten, Uwe Schulz, Andres Beiras-Fernandez, Michael Berchtold-Herz, Udo Boeken, Jens Garbade, Stephan Hirt, Manfred Richter, Arjang Ruhpawar, Tim Sandhaus, Jan Dieter Schmitto, Felix Schönrath, Rene Schramm, Martin Schweiger, Markus Wilhelm, Andreas Zuckermann

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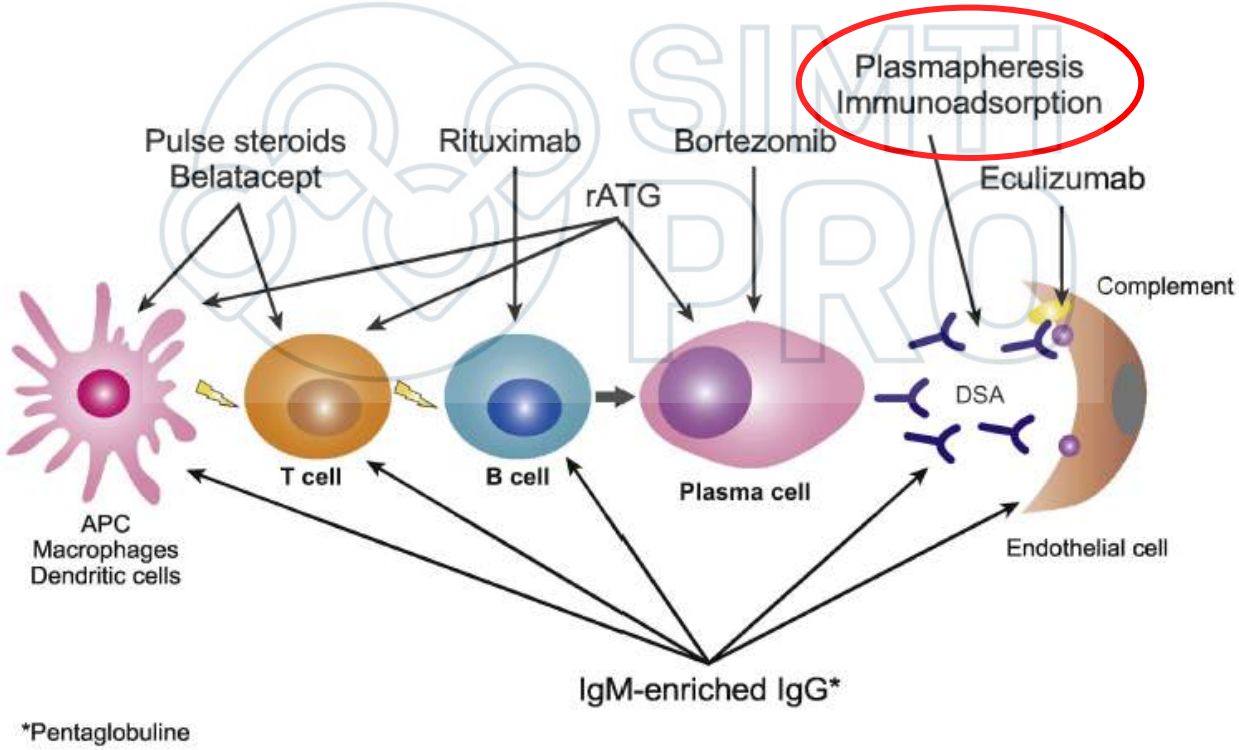
Reference: YTRRE 477



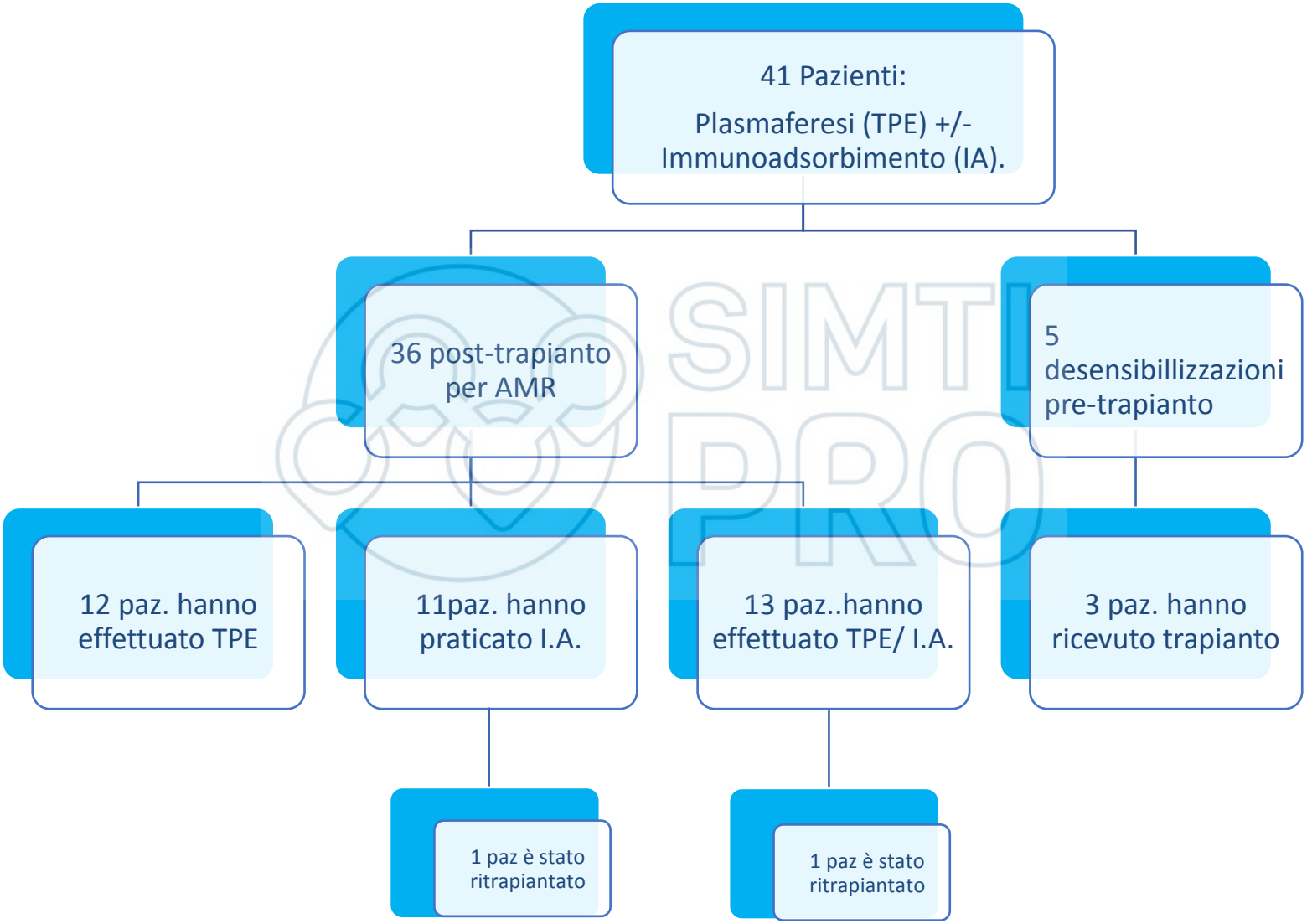
*Pentaglobuline

TRANSPLANTATION, CARDIAC

Incidence: ~3200 transplants performed per year (US); Cellular rejection: 21-30% in 1st post-transplant yr; Rejection prophylaxis: rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	Cellular/recurrent rejection	ECP	Grade 1B	II
	Rejection prophylaxis	ECP	Grade 2A	II
	Desensitization	TPE	Grade 1C	II
	AMR	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Cellular/recurrent rejection	0	0	4(58)	2(4)
Rejection prophylaxis	1(60)	2(38)	1(2)	NA
Desensitization	0	4(76)	8(124)	NA
AMR	0	0	>10(>200)	NA

AMR = Antibody mediated rejection

Esperienza con aferesi terapeutica (TPE/IA) dal 2015 al 2022



Caso clinico 1

- Luglio 2020: paziente di 36 anni, affetta da cardiopatia ipertrofica familiare, già in lista per trapianto con un PRA classe II del 91 % veniva ricoverata con urgenza per insufficienza cardiaca bi-ventricolare e con i primi segni di insufficienza epatica.
- Dopo 8 giorni di inotropi in infusione continua, inserimento in Emergenza Macroarea
- **Agosto 2020: comincia desensibilizzazione:**

  5 IA consecutivi seguiti da 6 IA a giorni alterni seguiti da somministrazione di Rituximab
- **PRA Classe II 5% MFI 1000**
- Inserimento in lista Emergenza Nazionale
- 29 settembre TPE seguito il 30 settembre da trapianto (virtual cross match negativo)
- Terapia immunosoppressiva standard: IVIG, ATG, Tacrolimus, Micofenolato e steroidi

Caso clinico 2

- Paziente di 40 anni, cardiotrapiantato nel maggio 2021
- Gennaio 2022 scompenso cardiaco acuto in seguito ad episodio di colangite. BEM: rigetto cellulo mediato e immuno mediato di grado severo. Inizia terapia con CCS
- **DSA MFI >7000**
- **Inizia sedute di IA , 7 trattamenti consecutivi**
- **DSA dopo 48 ore dall'ultima seduta: NEGATIVI**
- Aprile 2022 BEM compatibile con rigetto cellulo mediato grado 1R. Inizia protocollo di fotoaferesi.

Rigetto anticorpo – mediato
Protocollo

BEM, dosaggio DSA, emocromo, funzione renale compresi elettroliti (Ca2+), troponina, BNP,,QPE + dosaggio albumina,,funzione epatica, coagulazione, dosaggio Ig (comprese sottoclassi), tampone nasale MRSA e tampone rettale (ricerca germi MDR). Valutazione settimanale CMV DNA, EBV DNA. Posizionamento catetere per dialisi possibilmente non in femorale . In questa fase preparatoria, condizionamento con Solumedrol 0.5-1 gr/die per 3 gg. ATG (quanto prima dell' aferesi ?)

↓

TPE/ Immunoadsorbimento (5 trattamenti consecutivi) → a 48 h dall' ultima seduta eseguire dosaggio DSA. Dopo ogni seduta dosaggio IgG (eventuale supplementazione se IgG < 200 mg/dl) → Valutazione successive sedute in base a DSA ed ecocardio / clinica

Riduzione DSA (MF I < 5000)

↓

Rituximab 500mg/settimana per 4 settimane

Eseguire conta linfociti CD19+ e IgG a T0 e dopo ogni infusione

Tamponi di sorveglianza microbiologica e emocoltura da CVC e vena periferica + CMV-DNA settimanale

↓

Fotoaferesi (durata ed intervalli da decidere in itinere)

Mancata riduzione DSA

↓

Continua Plasma Exchange e/o IA fino a riduzione DSA

↓

Ig 2g/Kg (dosaggio totale suddivisibile in due /tre giorni)

↓

Rituximab 500 mg/settimana per 4 settimane (una volta ridotti i DSA seguito da fotoaeferesi)

Conclusioni

La sensibilizzazione rimane un importante limite per i pazienti candidati al trapianto

I dati sulle terapie attualmente disponibili sono limitati

TPE/IA sono procedure sicure, con dimostrata efficacia

TPE/IA rappresentano il primo step terapeutico: la rimozione degli anticorpi deve essere seguita da terapie che prevengono l'ulteriore formazione


GRAZIE!