ACCADEMIA di FORMAZIONE

SIMTI

Gruppi sanguigni rari: aspetti immunoematologici ed organizzativi per la gestione degli emocomponenti

Livelli di evidenza del matching immunoematologico esteso nei diversi setting clinici

Rachele Montemezzi

UOC Medicina Trasfusionale

Azienda Ospedaliera Universitaria Integrata Verona

La sottoscritta, in qualità di Relatrice
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 mie funzioni al fine di trarne vantaggio.

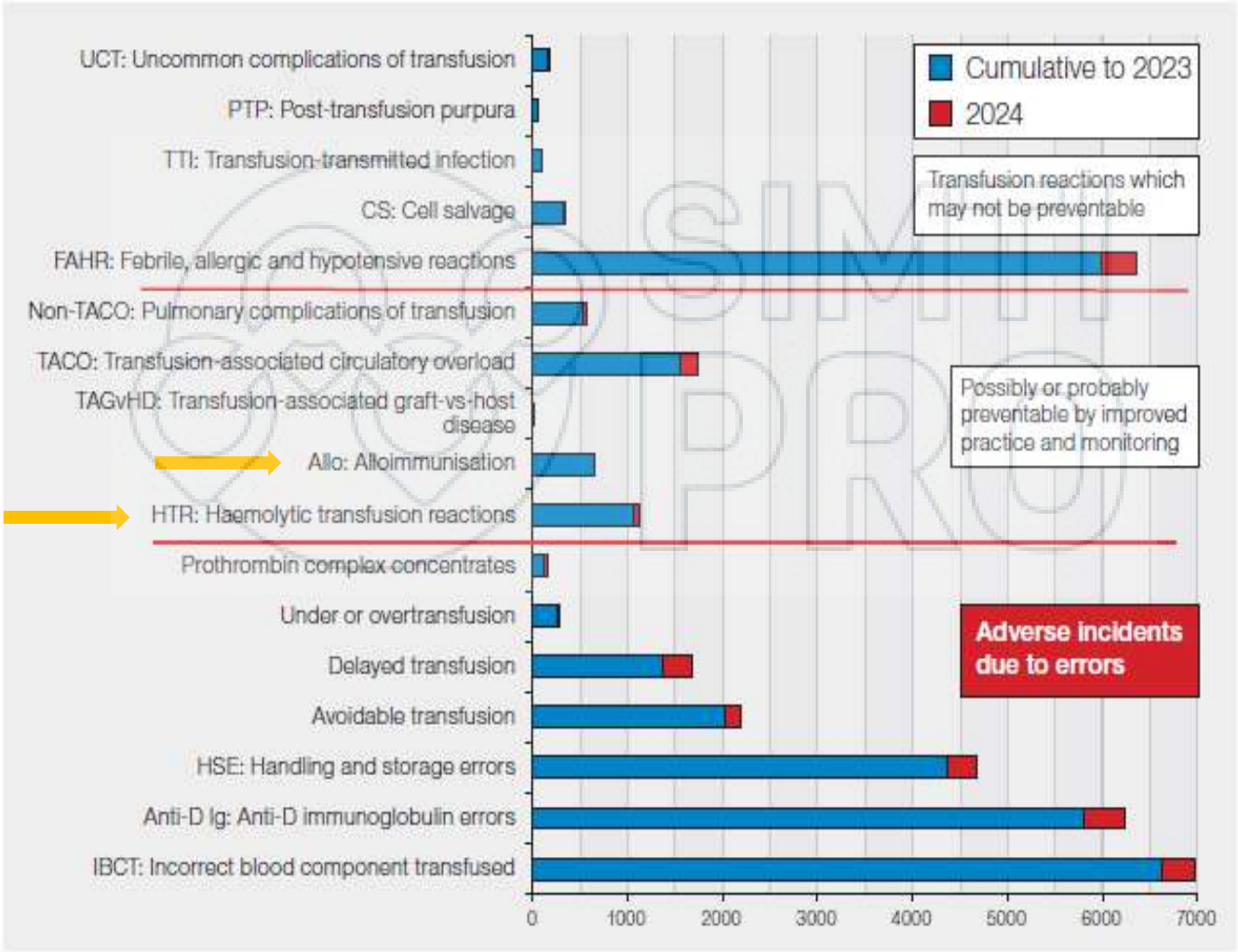
Rachele Montemezzi

Matching immunoematologico esteso

Perchè?

ANNUAL SHOT REPORT 2024

Figure 3.8: Cumulative data for SHOT categories 1996-2024 (n=33343)



Matching immunoematologico esteso

Perchè?

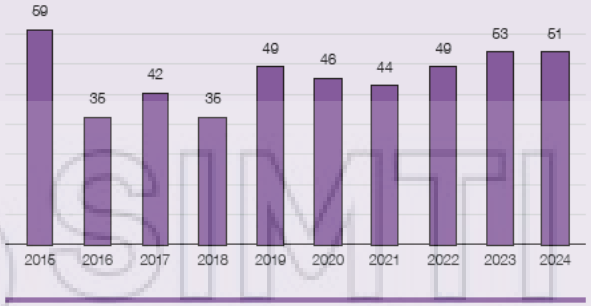
Haemolytic Transfusion Reactions (HTR) n=51

21

Headline data 2024

Number of reports n=51
Deaths n=3
Major morbidity n=14

HTR reports by year



Demographic data

Male n=24
Female n=27
Adults n=45
Paediatric n=6

Blood component data

Red cells n=51
Platelets n=0
Plasma n=0
Multiple components n=0

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Deaths related to transfusion n=3

There were 3 deaths in which the transfusion reaction contributed to the patient death, all in patients with sickle cell anaemia.

Reazioni trasfusionali emolitiche di tipo immunologico (HTR)

Figure 21.3: Antibodies implicated in AHTR in 2024

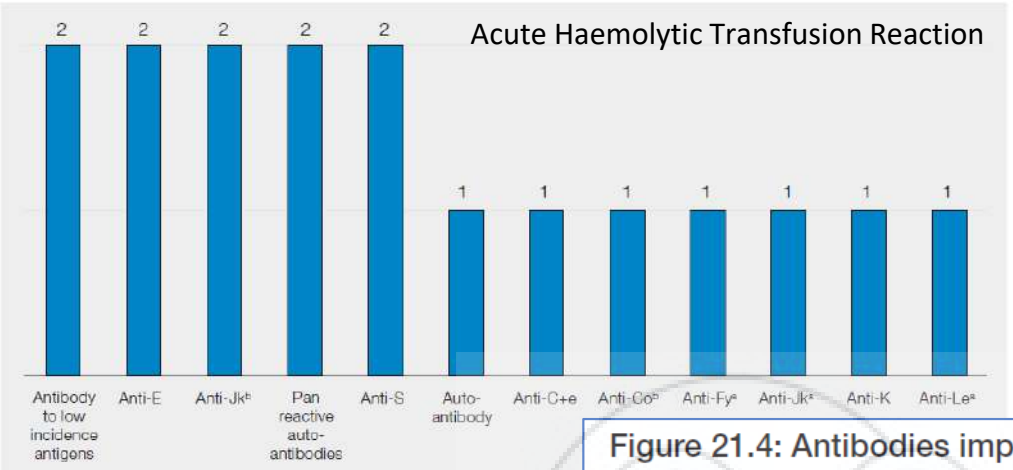

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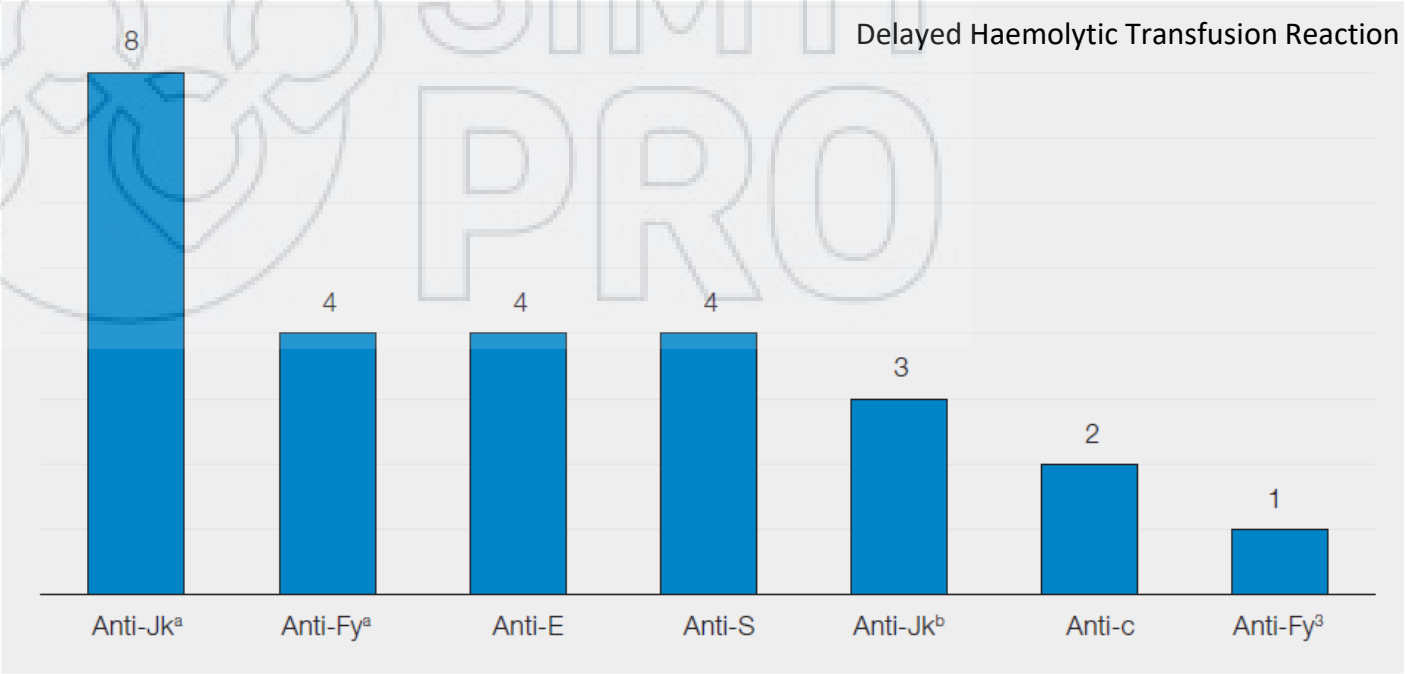
Figure 21.4: Antibodies implicated in DHTR in 2024

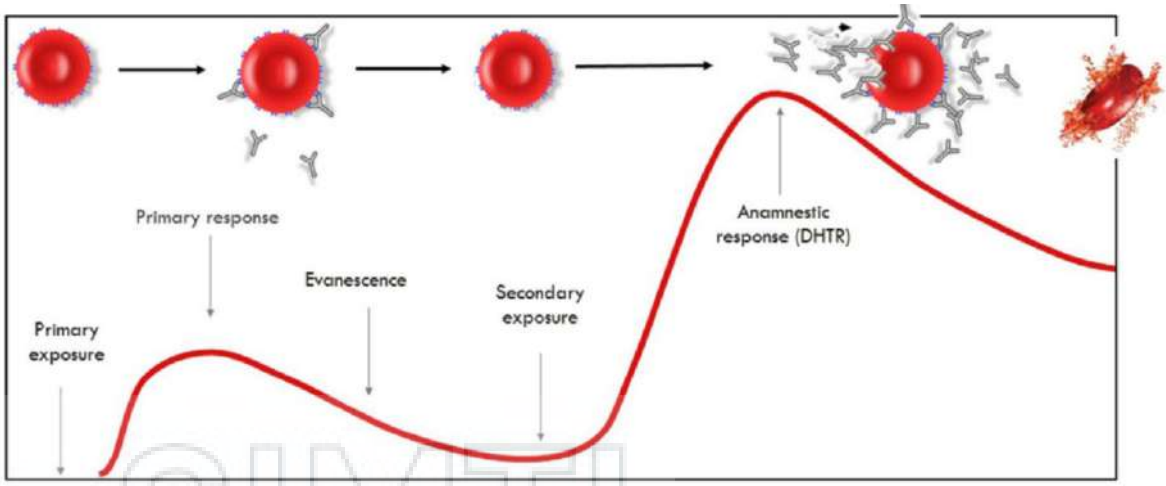


In 8/21 DHTR cases, the patient had multiple red cell antibodies detected post transfusion. In cases

Reazioni trasfusionali emolitiche ritardate (DHTR)

PATOGENESI IMMUNE

1. **Alloimmunizzazione**
2. **Evanescenza anticorpale** (Ab non più rilevabile allo screening)
3. **Riesposizione all'antigene** → rapida (3 a 10 giorni) produzione di anticorpi IgG ed emolisi extravascolare ritardata.



Da Fasano et al, 2019, Transfusion Clinique et Biologique

DIAGNOSI

- Comparsa tra 1-2 settimane ed entro 30 giorni dall'evento trasfusionale.
- Anemia, ittero, urine scure, febbre, dolore lombare ed addominale, dispnea, brivido, ipertensione
- Lab:
  - diminuzione o mancato incremento dell'Hb, ↑ indici emolisi
  - TCI: positivo, specificità alloAb evanescente
  - TCD+ (emazie trasfuse) monospecifici: IgG+, eluato: alloAb evanescente
  - crossmatch incompatibile non rilevabile prima della trasfusione

PREVENZIONE

Anamnesi immunoematologica
Matching esteso

Alloimmunizzazione

Sistema	Antigene	Immunogenicità
Rh	**D**	*70%*
	c	*4%*
	E	*3,3%*
	e	*1,1%*
	C	*0,2%*
Kell	**K**	*10%*
	k	*1,5%*
Duffy	**Fy^a**	*0,5%*
Kidd	**Jk^a**	*0,1%*
	Jk^b	*0,03%*
MNSs	**S**	*0,08%*
	s	*0,06%*

Matching immunoematologico esteso

In quali setting?

Prevalenza alloimmunizzazione nei vari setting

Donatori di sangue *(Kaur, 2017)*	0,2 - 0,9 %
Pazienti occasionalmente trasfusi *(Hendrickson, 2016)*	1 - 7 %
Pazienti poli-trasfusi *(Kaur, 2017)*	9 - 30 %
Patologie oncoematologiche *(Pattarakosol, 2024)*	2,5 - 9,1%
Talassemia trasf-dipendente (TDT) *(TIF Guidelines, 2025)*	10 - 20 %
Anemia falciforme (SCD) *(Fasano, 2014)*	18 - 47 %

Evanescenza anticorpale

Transfusion-related red blood cell alloantibodies: induction and consequences

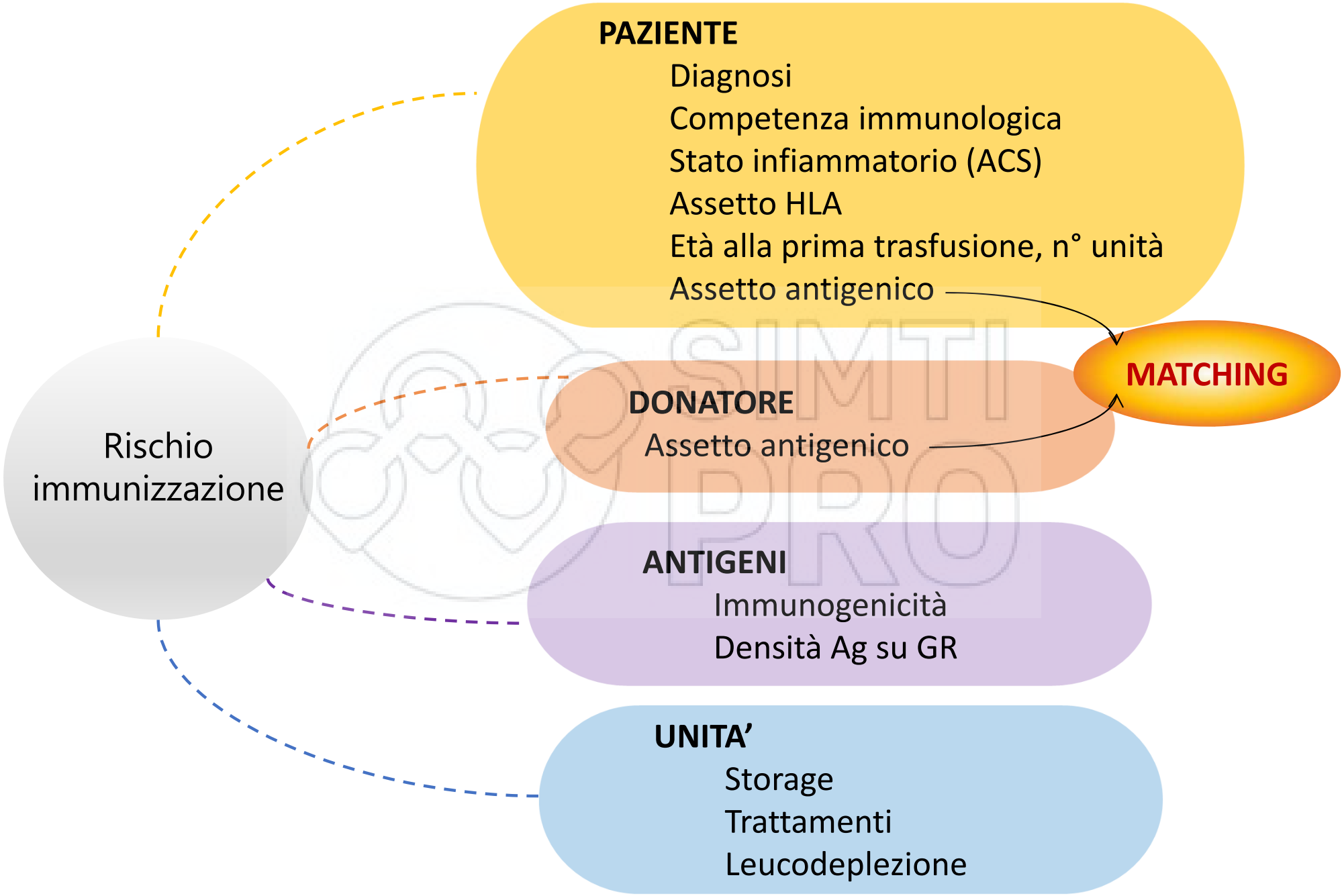
Christopher A. Tormey[1,2] and Jeanne E. Hendrickson[1,3]

Blood, 2019;133(17):1821-1830

Table 1. Mean evanescence rates by RBC alloantibody specificity

Blood group system	General patient groups (%)*	Sickle cell disease groups (%)*
Duffy		
Fy^a	17	51
Fy^b	—	78
Kell		
K	32	41
Js^a	—	80
Kidd		
Jka	49	—
Jkb	54	58
Lewis		
Le^a	48	—
Le^b	52	—
Lutheran		
Lu^a	65	—
MNS		
M	30	38
S	30	66
P		
P1	50	—
Rh		
D	12	36
C	19	47
c	27	0
E	38	41
C^w	61	—
V	—	39

Cosa influenza l'alloimmunizzazione?



Diverse frequenze antigeniche in diversi gruppi etnici

TABLE 13-2. Prevalence of the Principal Rh Haplotypes

Fisher-Race Haplotype	Modified Wiener Haplotype	Prevalence (%)		
		White	Black	Asian
Rh positive				
DCe	R_1	42	17	70
DcE	R_2	14	11	21
Dce	R_0	4	44	3
DCE	R_z	<0.01	<0.01	1
Rh negative				
ce	r	37	26	3
Ce	r′	2	2	2
cE	r″	1	<0.01	<0.01
CE	r^y	<0.01	<0.01	<0.01

AABB Technical Manual

TABLE 14-5. Kidd Phenotypes in Three Populations

Phenotype	Frequency (%)		
	Whites	Blacks	Asians
Jk(a+b–)	26	52	23
Jk(a+b+)	50	40	50
Jk(a–b+)	24	8	27

TABLE 14-4. Duffy Phenotypes and Genotypes in Selected Populations

Phenotype	Genotype		Frequency (%)		
	European or Asian Ethnicity	African Ethnicity	Whites	Blacks	Japanese
Fy(a+b–)	Fy^a/Fy^a	Fy^a/Fy^a or Fy^a/Fy	20	10	81
Fy(a+b+)	Fy^a/Fy^b	Fy^a/Fy^b	48	3	15
Fy(a–b+)	Fy^b/Fy^b	Fy^b/Fy^b or Fy^b/Fy	32	20	4
Fy(a–b–)	Fy/Fy	Fy/Fy	0	67	0

Matching immunoematologico esteso

Quanto esteso?

LE STRATEGIE TRASFUSIONALI NELLE EMOGLOBINOPATIE

Buone pratiche SITE-SIMTI-SIdEM

Novembre 2024

LIVELLO	Matching antigenico Ricevente – Unità Trasfusionali
LIVELLO 1	ABO; RhD
LIVELLO 2	C, c, E, e; K, k
LIVELLO 3	Fya, Fyb; Jka, Jkb; M, N, S, s

Matching immunoematologico esteso

Livelli di evidenza

Impact of Red Blood Cell Antigen Matching on Alloimmunization and Transfusion Complications in Patients with Sickle Cell Disease: A Systematic Review

Fasano RM, Transfusion Medicine Reviews 2019, (33) 12–23

Table 4
Serologic antigen RBC matching transfusions

Author, Year	Alloimmunization Prevalence %			Alloimmunization Rate		
	ABO/D Unit Transfusions	Limited-Match Unit Transfusions	Extended-Match Unit Transfusions	ABO/D Unit Transfusions	Limited-Match Unit Transfusions	Extended-Match Unit Transfusions
Agasa, 2010						
Ambruso, 1987						
Ameen, 2009						
Castellino, 1999	a					
Chou, 2013						
Cox, 1988						
Fasano, 2015	b	b	b			
Godfrey, 2010						
Kacker, 2014		c	c			
Lasalle-Williams, 2011	d					
Murao, 2005						
Roberts, 2012						
Tahhan, 1994			e			
Telen, 2015	e					
Vichinsky, 2001						

a) Castellino et al examined autoimmunization rate and then alloimmunization rate from those already autoimmunized.
b) Fasano et al examined probability of alloimmunization not prevalence.
c) Kacker et al used a Markov-based model to predict alloimmunization events.
d) Lasalle-Williams et al used Ambruso et al data for historic regarding ABO/D alloimmunization.
e) Telen et al did not specify types of units transfused as patients were surveyed with regard to transfusion history.

ABO/D = Livello 1 Limited-Match = +C,c,E,e = Livello2 Extended Match = +Duffy, Kidd, MNSs = Livello 3

Matching immunoematologico esteso

Impatto sull'alloimmunizzazione

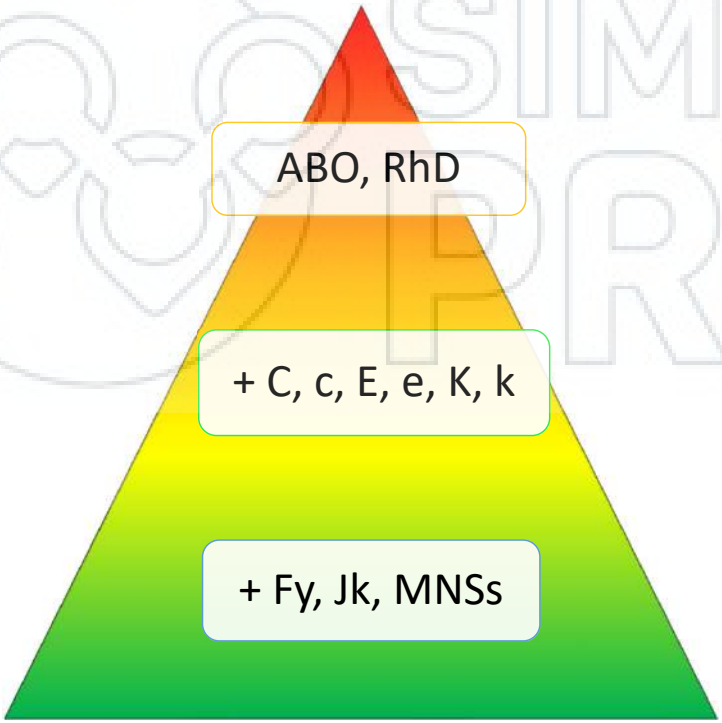
Impact of Red Blood Cell Antigen Matching on Alloimmunization and Transfusion Complications in Patients with Sickle Cell Disease: A Systematic Review

Fasano RM, Transfusion Medicine Reviews 2019, (33) 12–23

Red cell transfusion and alloimmunization in sickle cell disease

Linder e Chou, Haematologica | 2021; 106(7)

Alloimmunization prevalence		**Alloimmunization rate** (antibodies per 100 units)
58 – 66 %	ABO, RhD	1,7 - 3,9
2,3 – 23,6 % 15% se donatori afroamericani	+ C, c, E, e, K, k	0,26 - 0,5
0,7 %	+ Fy, Jk, MNSs	0,1 - 0,3



Matching immunoematologico esteso

Livelli di evidenza

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support

Chou ST et al, Blood Adv (2020) 4 (2): 327–355.

Prophylactic red cell antigen matching for transfusion

Matching di Livello 2

Recommendation 2

The ASH guideline panel *recommends* prophylactic red cell antigen matching for Rh (C, E or C/c, E/e) and K antigens over only ABO/RhD matching for patients with SCD (all genotypes) receiving transfusions (strong recommendation based on moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks:

- The extended red cell antigen profile may be determined by genotype or serology.
- Extended red cell antigen matching (Jk^a/Jk^b, Fy^a/Fy^b, S/s) may provide further protection from alloimmunization.
- Patients who have a GATA mutation in the *ACKR1* gene, which encodes Fy antigens, are not at risk for anti-Fy^b and do not require Fy^b-negative red cells.
- Patients identified by genotype with the hybrid *RHD*DIIIa-CE (4-7)-D* or *RHCE*CeRN* alleles, which encode partial C antigen, and no conventional *RHCE*Ce* or **CE* allele should be transfused with C-negative red cells to prevent allo-anti-C development.

Matching di Livello 3

Matching immunoematologico esteso

Livelli di evidenza

Sickle cell disease

For this reason, it is recommended (Grade of recommendation: **1C**) to select the units of erythrocyte concentrate to be transfused respecting at least the match for ABO, Rh, K antigen systems (level 2 match)[24,25,36,46,64,66]:

Extended erythrocyte antigen profile including typing for C/c, E/e, K/k, Fya/Fyb, Jka/Jkb, M/N, and S/s, should be defined for all sickle cell patients (as soon as possible and before transfusion). Direct Coombs Test should also be evaluated.

In non-Caucasic sickle cell patients it is recommended to perform genotypic characterization, which is more specific regarding the identification of antigenic variations affecting the RHD gene and the expression of C and Duffy antigens (Grade of recommendation: **1B**).

In alloimmunized sickle cell subjects, in whom transfusion is anyway considered essential, it is strongly advised to assign erythrocyte concentrates that respect the antigenic pattern of the recipient as much as possible, for the greatest number of antigenic systems[70] (Grade of recommendation: **4**).

Transfusion strategies in thalassemia and sickle cell disease SITE-SIMTI-SIdEM Good Practice

Gian Luca Forni[1,2], Aurora Vassanelli[3], Lucia De Franceschi[4,5], Piero Marson[6], Roberto Lisi[7], Angelo Ostuni[8,9], Antonia Gigante[2], Raffaella Origa[10,11], Francesco Fiorin[12]

Blood Transfusion 2025 Jun 20. doi: 10.2450

Transfusion dependent thalassemia (TDT)

TDT patients sometimes develop a sort of immunological tolerance, leading to a low incidence of alloimmunization. The specificity of the alloantibodies that develop, however, is almost always linked to differences in the Rh and Kell system between donor and recipient[24,67].

For this reason, it is recommended (Grade of recommendation: **1C**) to select the units of erythrocyte concentrate to be transfused respecting the match for ABO, Rh, K antigen systems (level 2 match)[24].

Prevenzione: secondaria vs primaria

Matching immunoematologico esteso

Livelli di evidenza

Effects of prophylactic red blood cell (RBC) transfusion with extended antigen matching on alloimmunization in patients with Sickle Cell Disease (SCD)

Ianca Leal, Tamires Delfino dos Santos, Simone Gilli, Lilian Castilho*

Transfusion and Apheresis Science 62 (2023) 103813

Methods: This is a 20-year retrospective study of patients with SCD transfused with RBCS that were prospectively matched for D, C, c, E, e, K, Fy^a/Fy^b, Jk^a/Jk^b and S antigens. Our study included 95 patients, and none had antibodies documented before their first transfusion. Patients and donors were phenotyped and molecular typing was performed in all patients who had recent transfusions or a positive direct antiglobulin test to predict their antigen profile. Unexpected antibodies to the Rh system, meaning anti-Rh antibodies in patients whose serologic phenotype was Rh positive, were investigated by molecular genotyping for RH variant alleles.

Results: During this study-period, 12 (12.6%) were alloimmunized and 83 (87.4%) were not. Among the 12 patients who alloimmunized, 7 (58.3%) developed antibodies to Rh antigens and 5 (41.7%) produced antibodies to low prevalence antigens. All patients who developed Rh antibodies had RH variant alleles. Autoantibodies were found in 16 (16.8%) transfused patients.

Matching immunoematologico esteso

Che metodica?

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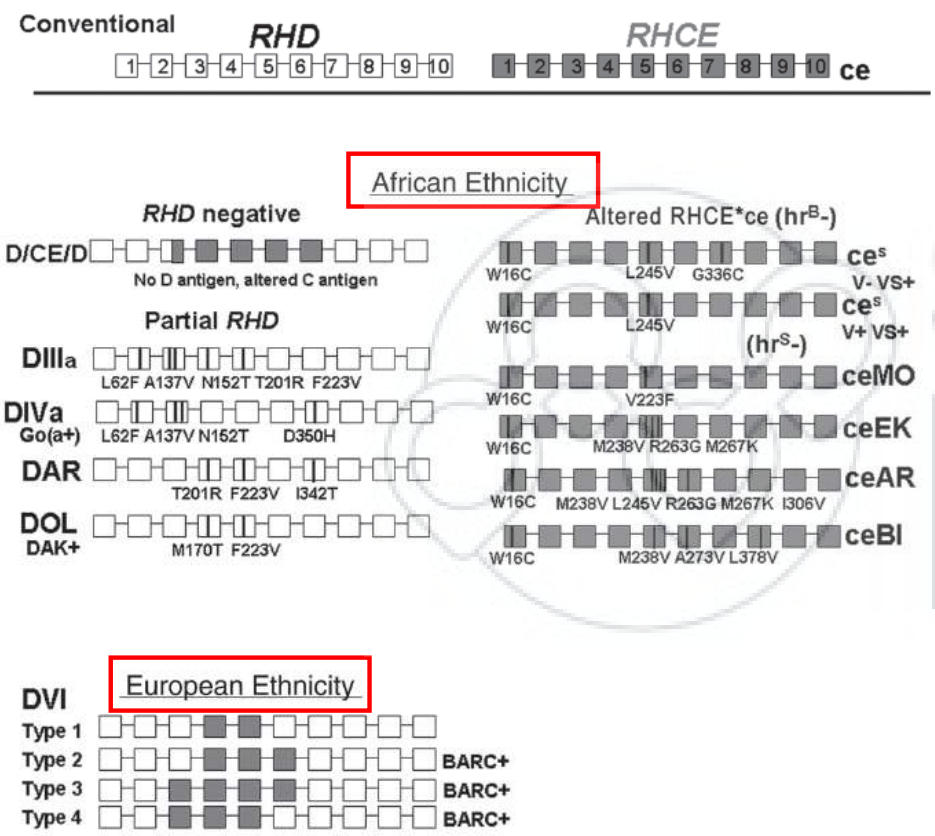


FIGURE 13-3. *RHD* and *RHCE* genes. The 10 exons of *RHD* and *RHCE* are depicted as white and grey boxes, respectively. Also shown are some examples of *RHD* encoding partial D and of *RHCE* with mutations often found in people of African ethnicity. These mutations complicate transfusions in patients with sickle cell disease.

Chou ST, British Journal of Haematology, 2012, 159, 394–404

Table I. Common variant *RH* genes in African-Americans and associated alloimmunization risk.

	Gene	Serological phenotype	Alloimmunization risk*
RHD	DAU0, DAU3, DAU4, DAU5	D+	Anti-D
	DIIIa	D+	Anti-D
	DIVa	D+	Anti-D
	Weak partial D type 4.0	D+	Anti-D
	DAR	D+	Anti-D
	DOL	D+	Anti-D
	DIIIa-DE(4–7)-D	D–, C+	Anti-C
RHCE	CeRN	C+	Anti-C, -e, -Rh46
	ce^S	c+, e+, hr^B–	Anti-e, -c, -hr^B
	ceJAL	c+, e+, hr^B–	Anti-e, -c, -hr^B
	ceMO	c+, e+, hr^S–, hr^B–	Anti-e, -c, -hr^S, -hr^B
	ceAR	c+, e+, hr^S–	Anti-e, -c, -hr^S
	ceEK	c+, e+, hr^S–	Anti-e, -c, -hr^S
	ceBI	c+, e+, hr^S–	Anti-e, -c, -hr^S
	ceCF	c+, e+, hr^B–, hr^S–/+^{w}	Anti-e, -c
	ceTI	c+, e+	Anti-e, -c
	ce (733G)	c+, e+, hr^B–	Anti-e, -hr^B
	ce (48C,733G)	c+, e+, hr^B–	Anti-e, -hr^B
	ce (254G)	c+, e+, hr^B–	Anti-e, -hr^B
	ce (48C)	c+, e+	Anti-e

*If other *RH* allele does not encode conventional corresponding RH antigen.

Breaking down barriers: Recruiting donors of African ancestry in Ireland

Waters A et al, Vox Sanguinis. 2025; 120:765–775.

TABLE 2 Barriers and motivators to recruiting blood donors of African ancestry in Ireland.

Blood donation	Theme	*n*	%
Barriers	Lack of information	33	70.2
	Donor qualification criteria	20	42.6
	Trust in the institution	18	38.3
	Accessibility	16	34.0
	Atmosphere in the donation clinic	16	34.0
	Assumptions of replacement donation	14	29.8
	Negative association with hospitals	14	29.8
	Spiritual/religious beliefs	15	31.9
	Time	8	17.0
	Concern about the effect blood has on donor/patients	7	14.9
	Fear of needles	6	12.8
	Iron deficiency	5	10.6
Motivators	Specific information for Black donors	24	51.1
	Help family or friends, especially if have a rarer blood type that can help	22	46.8
	Emotional connection to the need for blood donors	10	21.3
	Small incentives—easy access, food, time-in-lieu from work	10	21.3
	Advertisements	8	17.0
	Social media markets	4	8.5

Matching immunoematologico esteso

Che metodica?

Sierologia

- Più disponibile
- Più economico

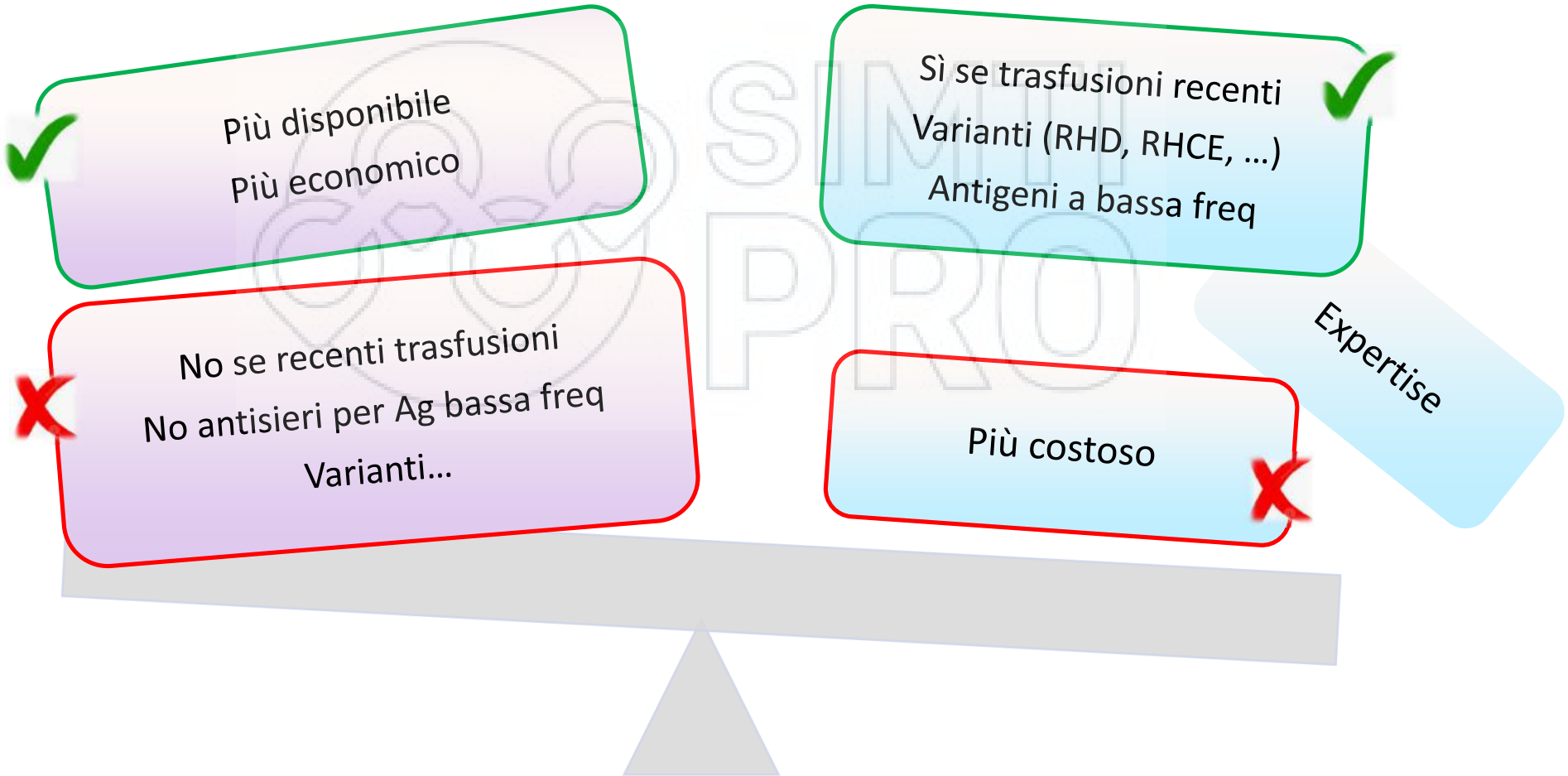
- No se recenti trasfusioni
- No antisieri per Ag bassa freq
- Varianti…

Molecolare

- Sì se trasfusioni recenti
- Varianti (RHD, RHCE, …)
- Antigeni a bassa freq

- Più costoso

Expertise



Matching immunoematologico esteso

Riassumendo

GUIDELINE

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

Red cell specifications for blood group matching in patients with haemoglobinopathies: An updated systematic review and clinical practice guideline from the International Collaboration for Transfusion Medicine Guidelines

Br J Haematol. 2025;206:94–108.

- It also should also be recognised that disparity in donor/ recipient RBC antigens may vary globally. If, for example, donor and recipient populations are well matched, recipients might be more likely to get antigen-matched units by chance, which might dilute the apparent benefit of a formal extended matching strategy
- It should however be noted that alloantibody formation can occur despite extended RBC matching
- Potential advantages of genotyping over serological phenotyping may include the detection of weakly-expressed or variant antigens, detection of antigens for which no commercial antisera are available
- However, the cost implications are unclear, and savings generated by avoiding the need for complex serological work-ups need to be balanced against costs for blood centres (genotyping donors) and for hospitals (genotyping patients).

La realtà veronese

Centro Anemie emolitiche congenite ed anemie rare

Talassemie (circa 50 TDT)

Anemie falciformi (circa 30 pz)

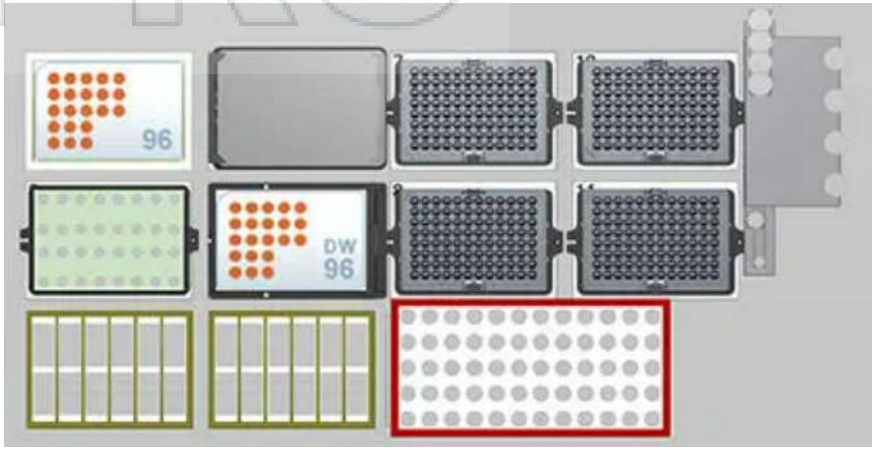
UOC Medicina Trasfusionale

(dati 2024)

Consegnate 2764 unità GRC

2-3 GRC ogni 2-3w (≈1700 GRC/anno)

511 EEX (≈2000 GRC/anno)



Considerazioni finali

NECESSARIA PIANIFICAZIONE

- Studio della propria popolazione di pazienti e donatori
- ‘’Scegliere’’ strategia:
  - sierologia/molecolare
  - per quali pazienti (SCD, TDT, ematologici…)
  - prevenzione secondaria/primaria
- Ampio quantitativo di unità tipizzate (quali?)
- Fattibilità (studio dei costi e della sostenibilità)
- Approfondire conoscenze (!!!)

Grazie per l'attenzione