



A.Mazzone

*I fondamentali delle Anemie in
 Medicina Interna*

Direttore Dipartimento Area
 Medica Legnano

Presidente Fondazione FADOI

BENEVENTO 12 giugno 2013



Legnano H nuovo



Legnano H storico



Cuggiono



Magenta

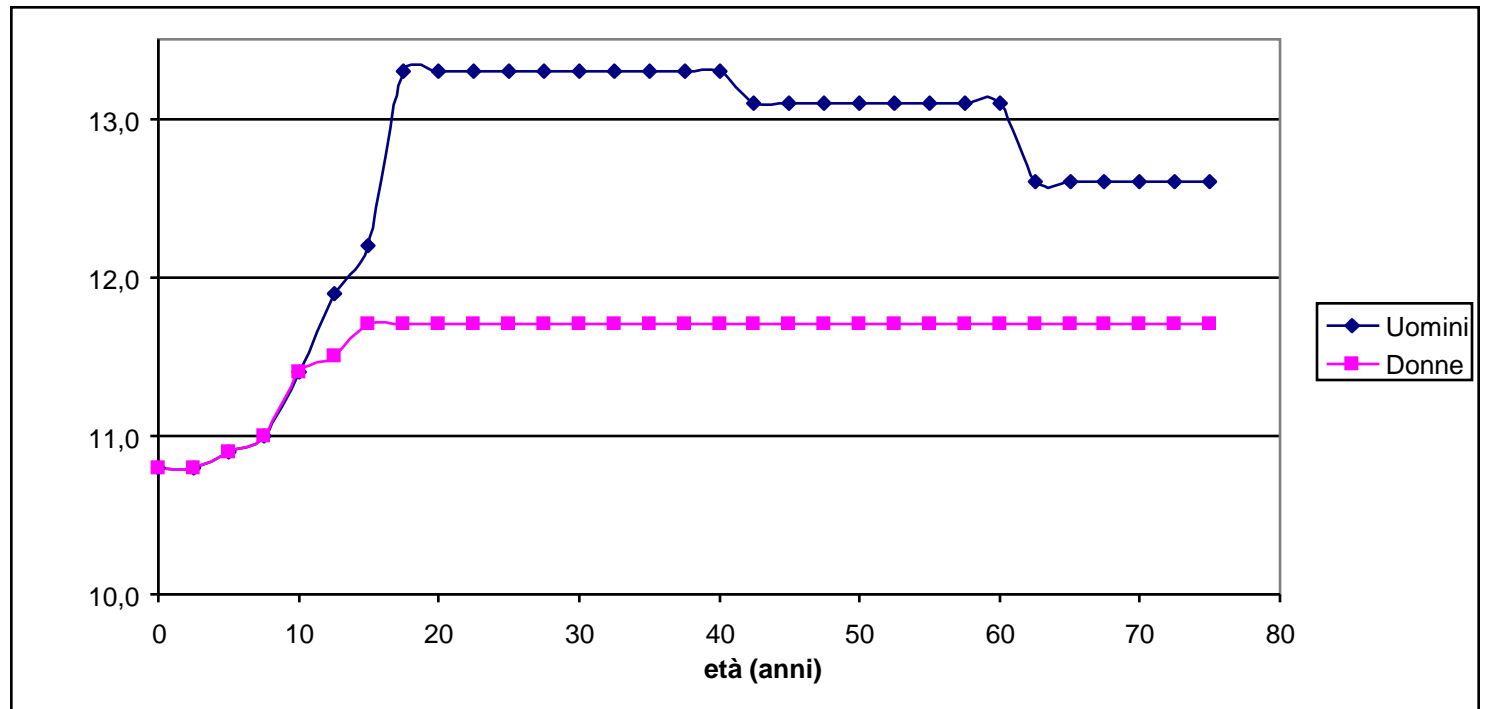


Abbiategrasso

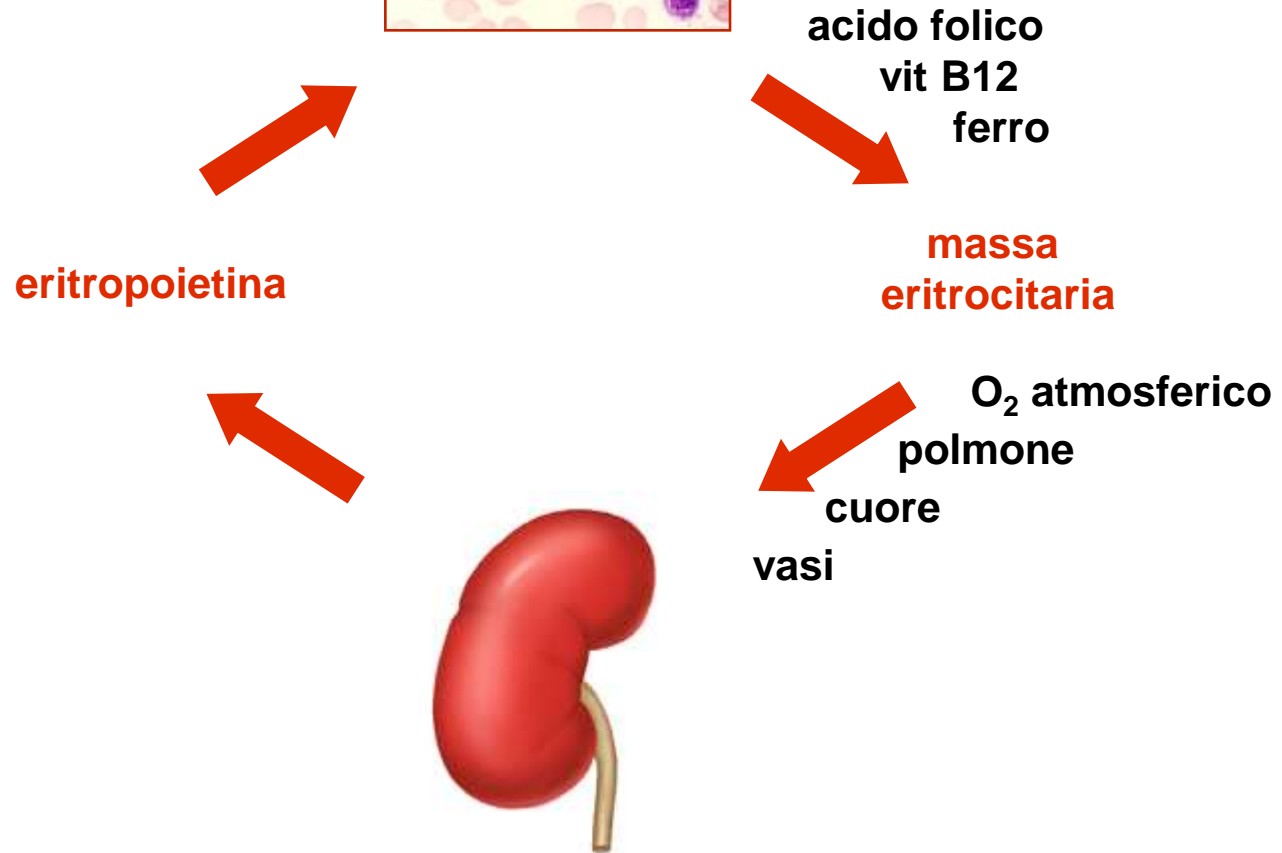
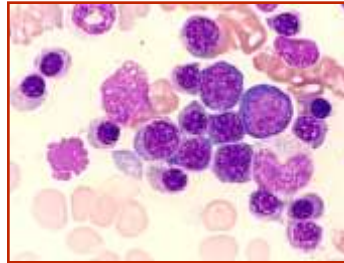


ANEMIA - Definizione

Riduzione della massa eritrocitaria ed in particolare dell'emoglobina al di sotto di 13 g/dL nell'uomo e di 12 g/dL nella donna



Anemia Guidelines – 2008 World Heart Organization (WHO)



Valori di normalità di Hb ed Ht

	Hb (g/dl)	Ht (%)
Alla nascita	17	52
Infanzia	12	36
Adolescenza	13	40
Uomo adulto	16+/-2	47+/-6
Donna adulta fertile	13+/-2	40+/-6
Donna adulta post-menopausa	14+/-2	42+/-6
Gravidanza	12+/-2	37+/-6



ANEMIA – Dato Epidemiologico

WHO global database

Table 3.2 Global anaemia prevalence and number of Individuals affected

Population group	Prevalence of anaemia		Population affected	
	Percent	95% CI	Number (million)	95% CI
Preschool-age children	47.4	45.7-49.1	293	283-303
School-age children	25.4	19.9-30.9	305	238-371
Pregnant women	41.8	39.9-43.8	56	54-59
Non-pregnant women	30.2	28.7-31.6	468	446-491
Men	12.7	8.6-16.9	260	175-345
Elderly	23.9	18.3-29.4	164	126-202
Total population	24.8	22.9-26.7	1620	1500-1740

Worldwide prevalence of anaemia 1993–2005 : WHO global database on anaemia / Edited by Bruno de Benoist, Erin McLean, Ines Egli and Mary Cogswell.

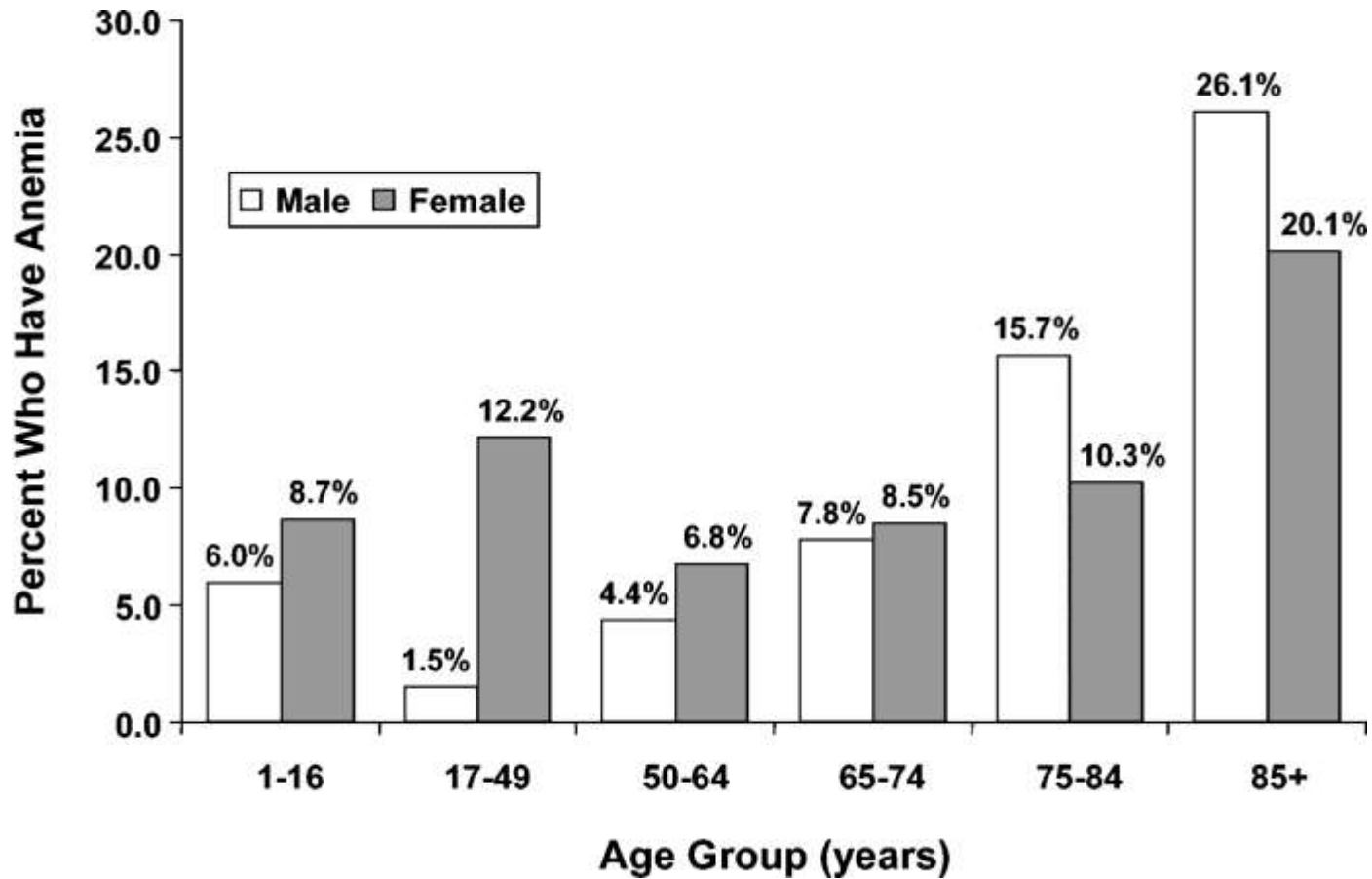
Entità del “problema anemia” nel mondo

Più di 2.000.000.000.000 di soggetti anemici

Il 35% delle donne ed il 43% dei bambini sono anemici

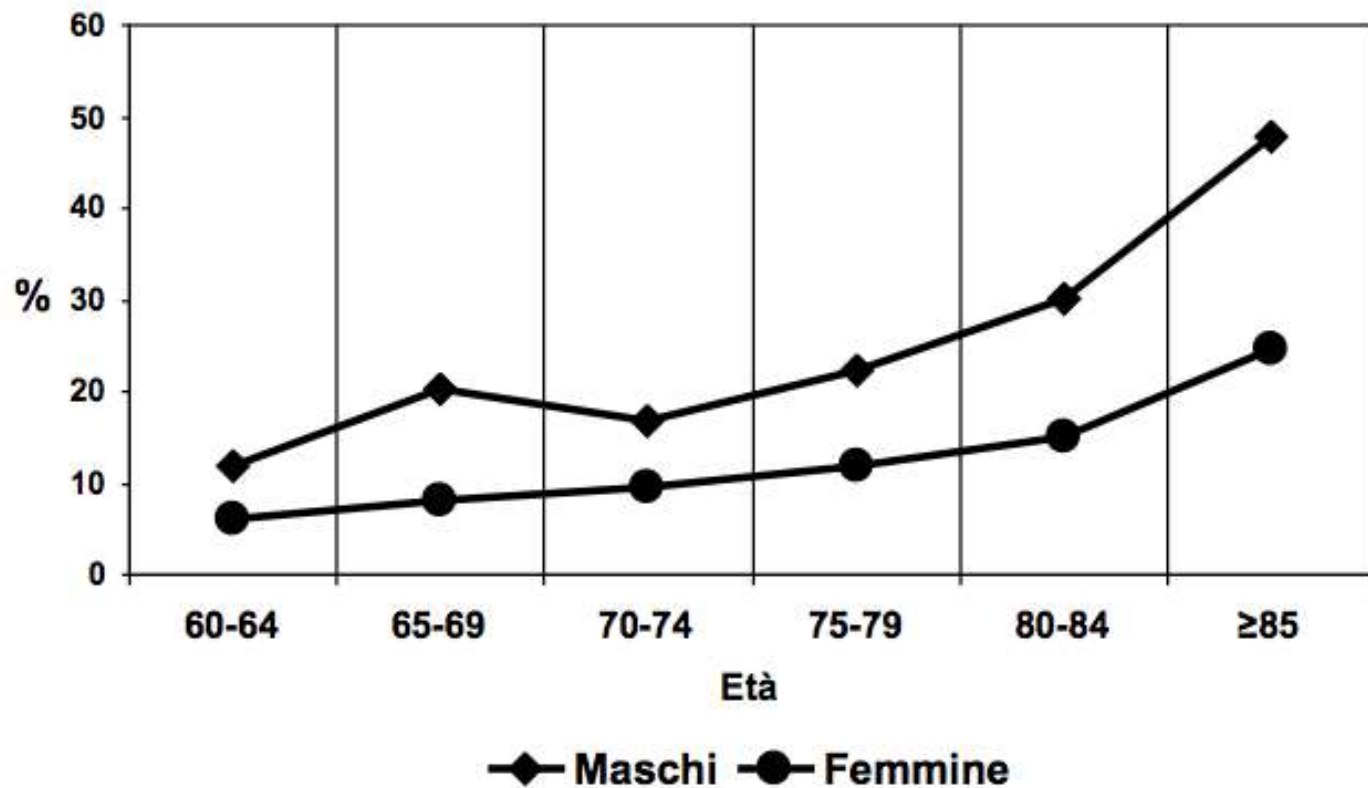


Percentage of persons considered anemic according to age and sex



Guralnik, J. M. et al. Blood 2004;104:2263-2268

Prevalenza dell'anemia in pazienti anziani



ANEMIA – Tipo ed Incidenza In Medicina Interna

ANEMIA in UO Acuti %		ANEMIA in Comunita' %	
Carenza Marziale	15-30		8
Post-emorragica	5-10		0
Deficit B12	5-10		2
Leucemie croniche Linfomi e Mielomi Sindrome mielodisplastica	5-10		0
HF,BPCO,FA, Diabete	15-25		20-40
Origine sconosciuta	15-25		40-60

**MA QUALI SONO I DATI DI PREVALENZA
DELL' ANEMIA NEI REPARTI
DI MEDICINA INTERNA?**





ANEMIA- Prevalenza in Medicina Interna

International Overview

Autore	Stato	Anno	Prevalenza (%)	Note
Nathavitharana RL et al.	Nuova Zelanda	2011	33.3% (1491 pts arruolati)	Criteri WHO
Terrier et al.	Francia	2011	65% (1351 pts. arruolati)	Criteri WHO
Santos IS et al.	Brasile	2011	10.2% (1948 pts. Arruolati)	Criteri WHO
Denny SD et al.	USA	2006	24% (1744 pts. arruolati)	Criteri WHO
Pennix BW et al.	Olanda	2005	11.9% (393 pts. arruolati)	Criteri WHO
Recine(*)	Italia	2011	60%	Criteri WHO (pz. con età >65anni)

(*) http://www.accademia-lancisiana.it/recine_febb_11.htm



ANEMIA- Prevalenza in Medicina Interna

Pazienti con BPCO



Autore	Stato	Anno	Prevalenza (%)	Note
Almagro et al.	Spagna	2012	19.3% (606 pz. arruolati)	Pazienti con BPCO
Barba et al.	Spagna	2012	9.8% (289.007 pz. arruolati)	Pazienti con BPCO
Bouotu AK et al.	Grecia	2011	10.24% (283 pz. arruolati)	Pazienti con BPCO (*)
Rasmussen L et al.	Danimarca	2010	18% (222 pz. arruolati)	Pazienti con BPCO
Shorr AF et al	USA	2008	33% (2404 pz. arruolati)	Pazienti con BPCO
John M et al.	Germania	2006	23.1%. (7337 pz. arruolati)	Pazienti con BPCO



ANEMIA- Prevalenza in Medicina Interna

Pazienti con Diabete

Autore	Stato	Anno	Prevalenza (%)	Note
Bonakdaran S et al.	Iran	2011	19.6% (1962 pz. arruolati)	Diabete di tipo II
Ranil PK et al.	India	2010	12.3% (1414 pz. arruolati)	Diabete di tipo II
Stevens PE. et al.	UK	2010	34% (1205 pz. arruolati)	Diabete di tipo II, Insufficienza renale cronica
Zoppini G et al.	Italia	2010	18.4% (1153 pz. arruolati)	Diabete di tipo II
Thomas MC et al.	Australia	2006	12% (503 pz. arruolati)	Diabete di tipo II



ANEMIA- Prevalenza in Medicina Interna

Pazienti con Scompenso Cardiaco



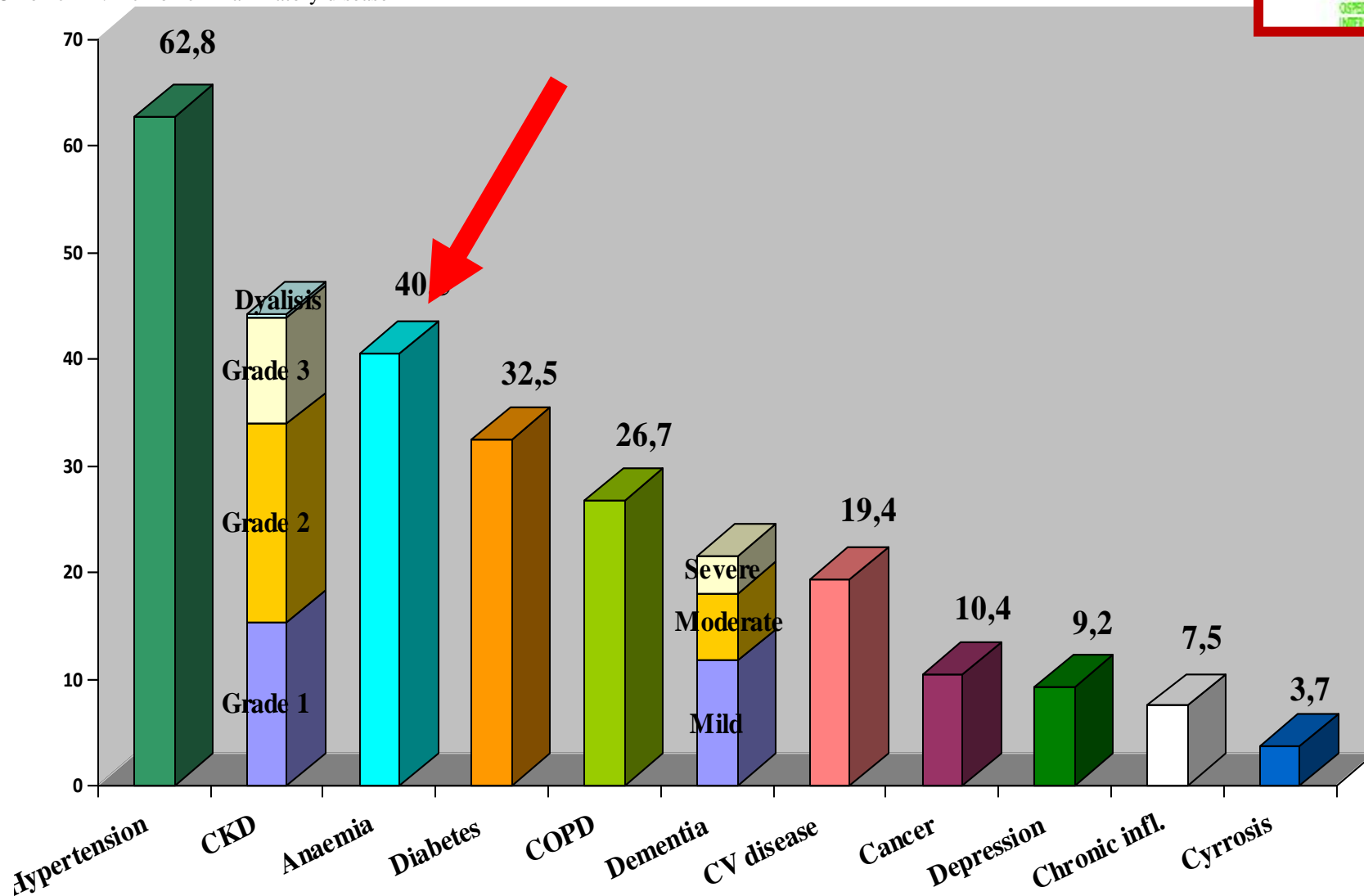
Autore	Stato	Anno	Prevalenza (%)	Note
Waldum B et al.	Norvegia	2012	24% (4144 pz. arruolati)	Pazienti con HF
Saraiva F. et al.	Portogallo	2011	43.2% (391 pz. arruolati)	Pazienti con HF
Von Haehling S. et al.	Germania	2011	10% (2069 pz. arruolati)	Pazienti con HF Trial Clinico randomizzato
Adams KF. et al.	USA	2009	34% (1076 pz. arruolati)	Pazienti con HF
Groenveld HF. et al.	Olanda	2008	37.2% (153180 pz. arruolati)	Pazienti con HF Review sistematica
John M et al.	Germania	2006	23.3%. (7337 pz. arruolati)	Pazienti con HF
Go et al.	USA	2006	42.6% (59772 pz. arruolati)	Pazienti con HF
Ezekowitz JA et al.	Canada	2003	17% (12065 pz. arruolati)	Pazienti con HF Cardiologia

Studio Confine Fadoi Int J of Cardiol 2011

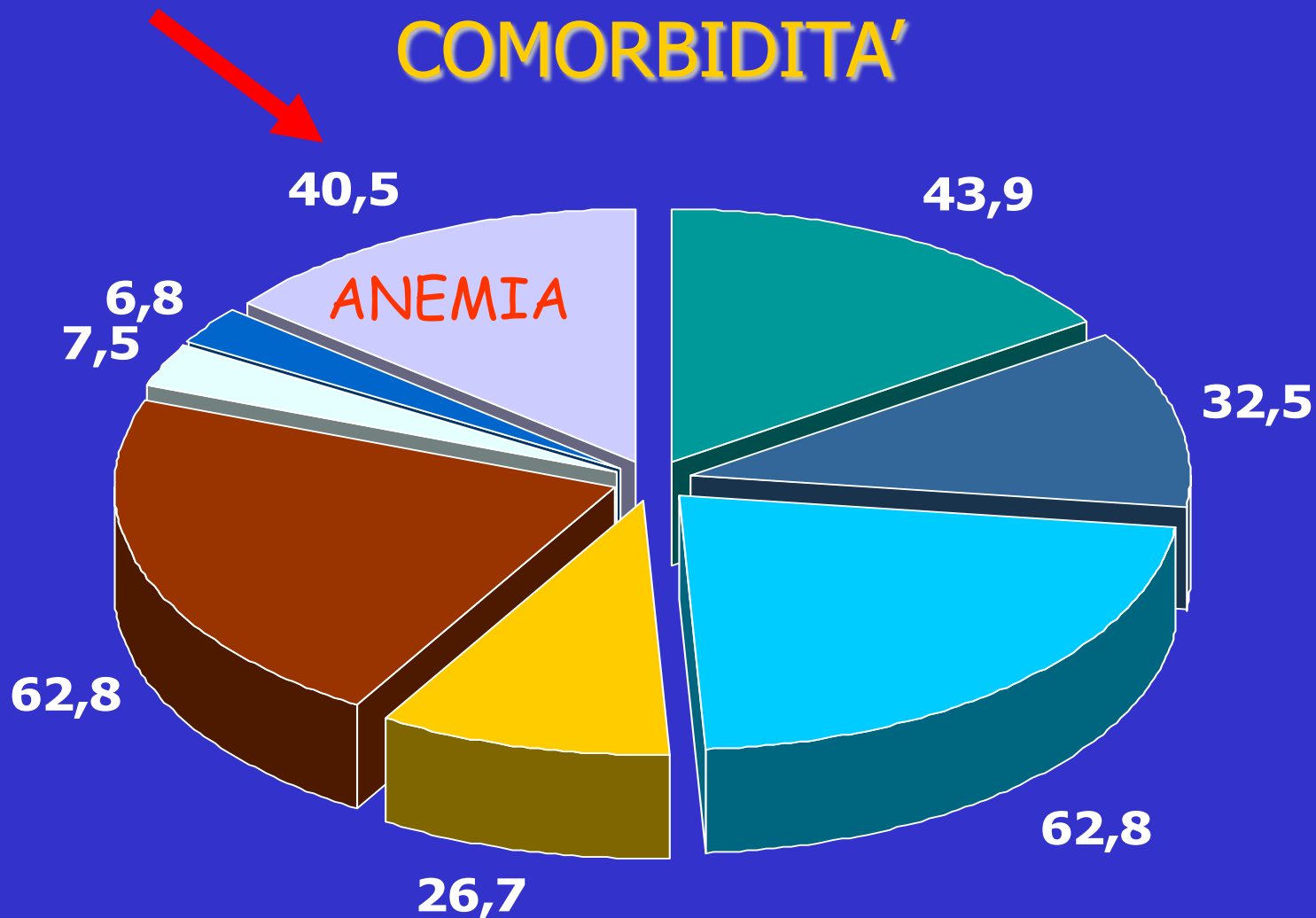


Figure 1. Distribution of comorbidities in the study population.

Values are expressed in percentage. CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CV = cerebrovascular; Chronic infl. = chronic inflammatory disease



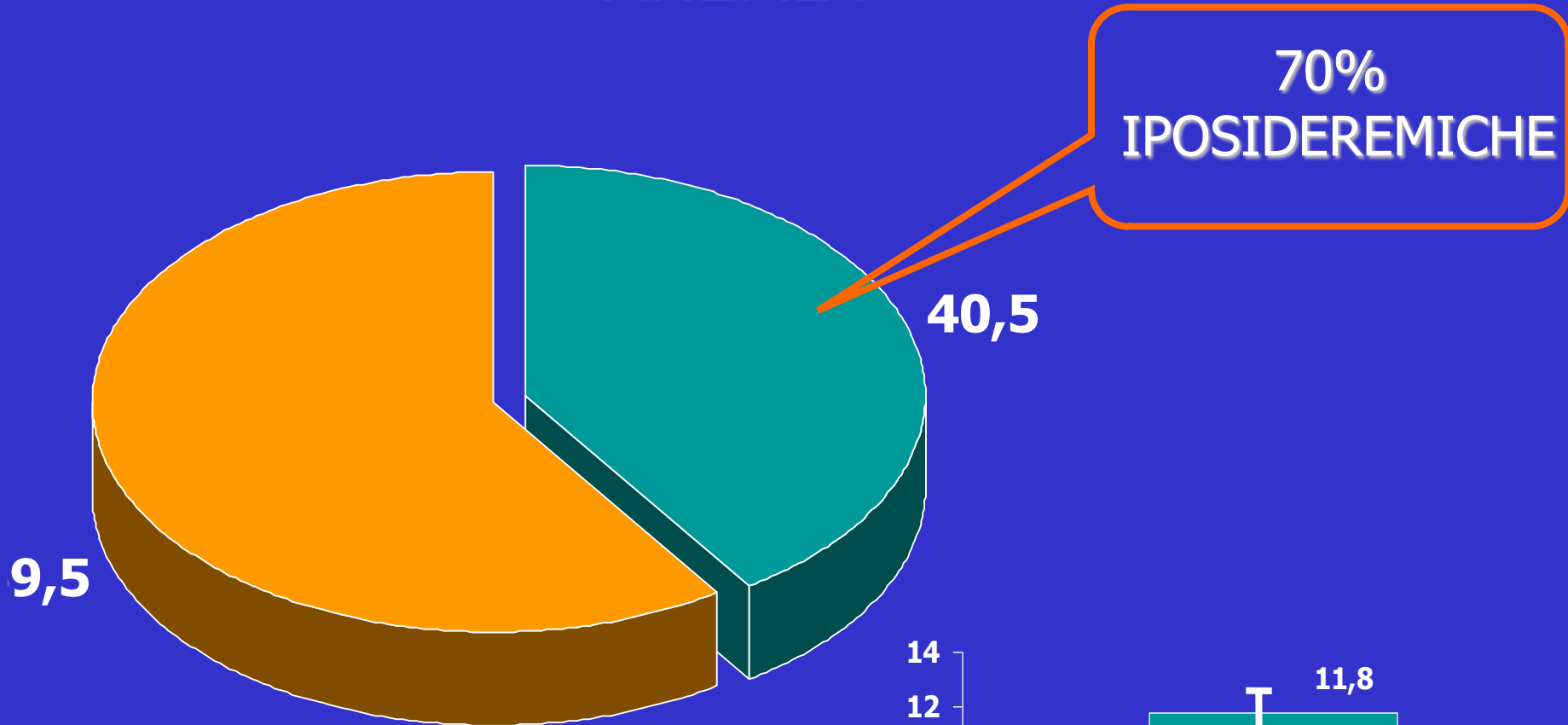
COMORBIDITA'



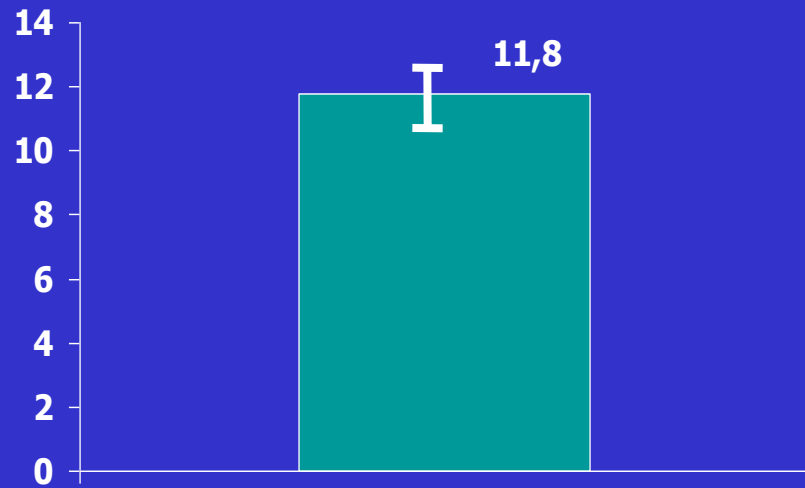
- | | | |
|-----------|----------|-------------------|
| IRC* | DIABETE | IPERTENSIONES§ |
| BPCO | DEMENZA | MAL.INF. CRONICHE |
| CACHESSIA | ANEMIA** | |

* GFR<90; § PA< 135/85;**Hb<13g/L nel maschi e 12g/L nelle femmine

ANEMIA



■ SI ■ NO



■ Mean Hb





ANEMIA- Prevalenza in Medicina Interna

FADOI Overview



Studio FADOI	Autore	Anno	Prevalenza (%)	Note
CONFINE	Biagi et al Int J Cardiol 2011.	2011	40.5% (1411 pts arruolati)	Scompenso Cardiaco
ATA-AF	Di Pasquale et al. (Int J Cardiol 2012 Eur J Int Med 2013)	2012	25.3% (3286 pts. arruolati)	Fibrillazione atriale
DIAMOND	Submitted	2013	7.8% (1588 pts. arruolati)	Diabete di tipo II
AMIL	Franco Bonanni et al.	2002	21.9% (4649 pts. arruolati)	Pazienti non selezionati. Diagnosi di anemia <12 g%

Common causes of anemia based on red blood cell morphology

Microcytic anemia

Iron deficiency
Thalassemia
Lead toxicity

Macrocytic anemia

Low vitamin B₁₂, folate, copper levels
History of alcohol abuse
Medications
Hemolytic anemias
Myelodysplastic syndromes

Normocytic anemia

Chronic kidney disease
Thyroid disorders
Human immunodeficiency virus infection,
other viral infections
Rheumatologic disorders



**Barzi and Sekeres,
Clev Clin J Med 2009**

MEDICINA INTERNA

Malattie Croniche responsabili di anemia (ACD Modificata da Lipschitz 1990 and NEJM 2005)

- 1 Infezioni croniche
- 2 TBC
- 3 Endocardite infettiva
- 4 Infezioni Urinarie Croniche
- 5 Infezioni Micotiche Croniche
- 6 Ulcere da pressione
- 7 Malattie infiammatorie croniche
- 8 Artrite Reumatoide
- 9 Connettivopatie
- 10 Polimialgia Reumatica
- 11 Malattie Infiammatorie Intestinali

MEDICINA INTERNA

Patologie responsabili di anemia

1- Angiodisplasie Intestinali

2-Polipi Digestivi

3-Tumori Maligni

4-Carcinoma Metastatico

5-Emopatie Maligne (leucemie, limfomi)

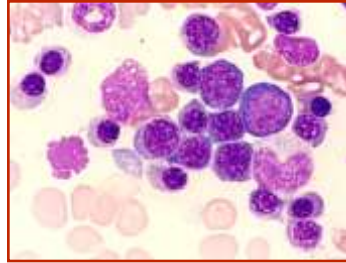
6-Mieloma

7-Malnutrizione proteica

8-Infezioni virali (HBC,HBV,Parvovirus,HIV,HHV8 etc..)

Segni e sintomi di anemia

- Cardiovascolari e respiratori:
Dispnea da sforzo, tachicardia, palpitazioni, angina, claudicatio
- Neurologici:
Cefalea, perdita di concentrazione, fatica, sensibilità al freddo
- Cute:
Pallore, unghie a vetrino di orologio
- Gastrointestinali:
Anoressia, nausea, costipazione, diarrea
- Genitourinari:
Irregolarità mestruali, amenorrea, menorragia, alterazione della sessualità

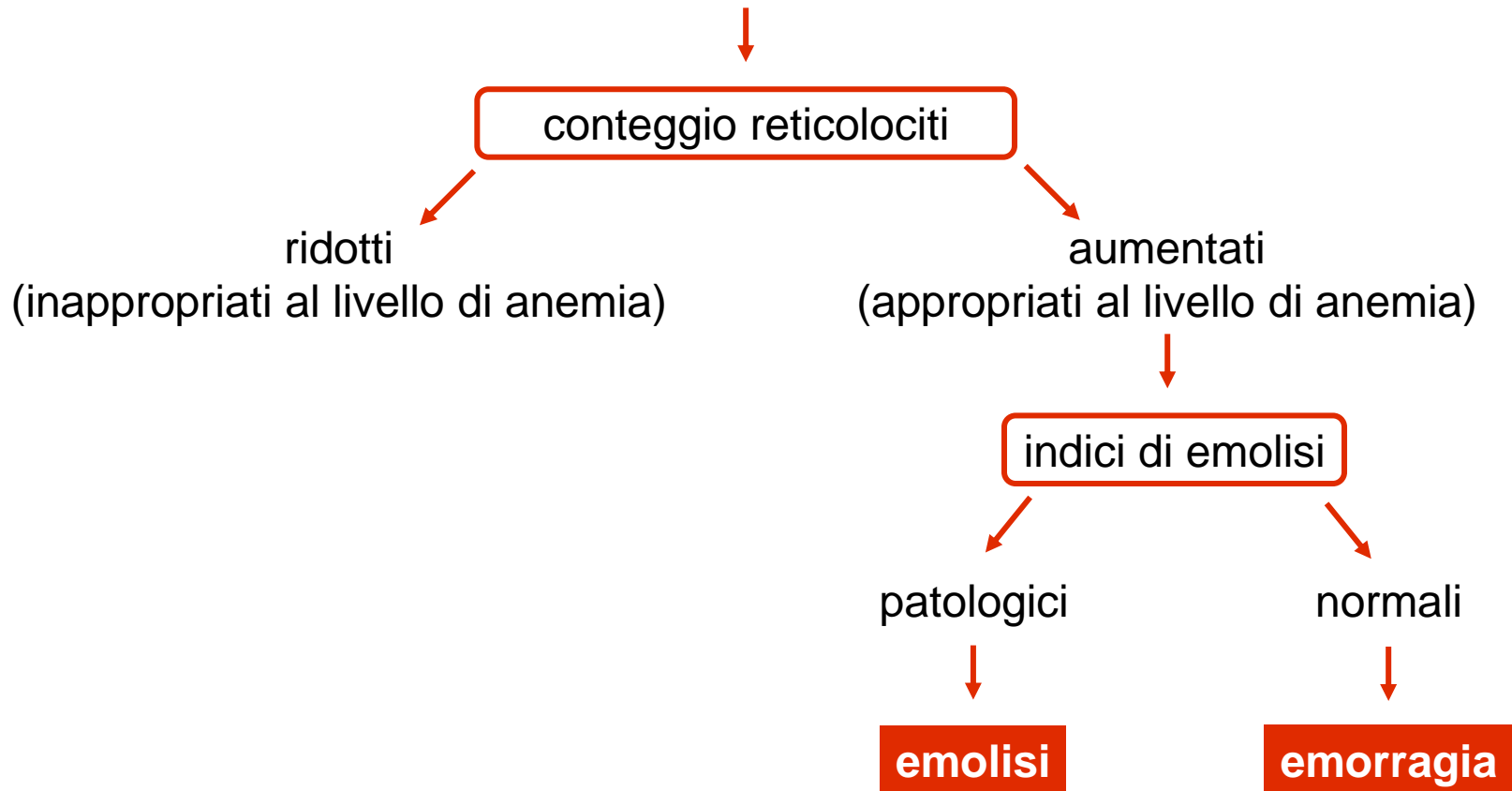


eritropoietina

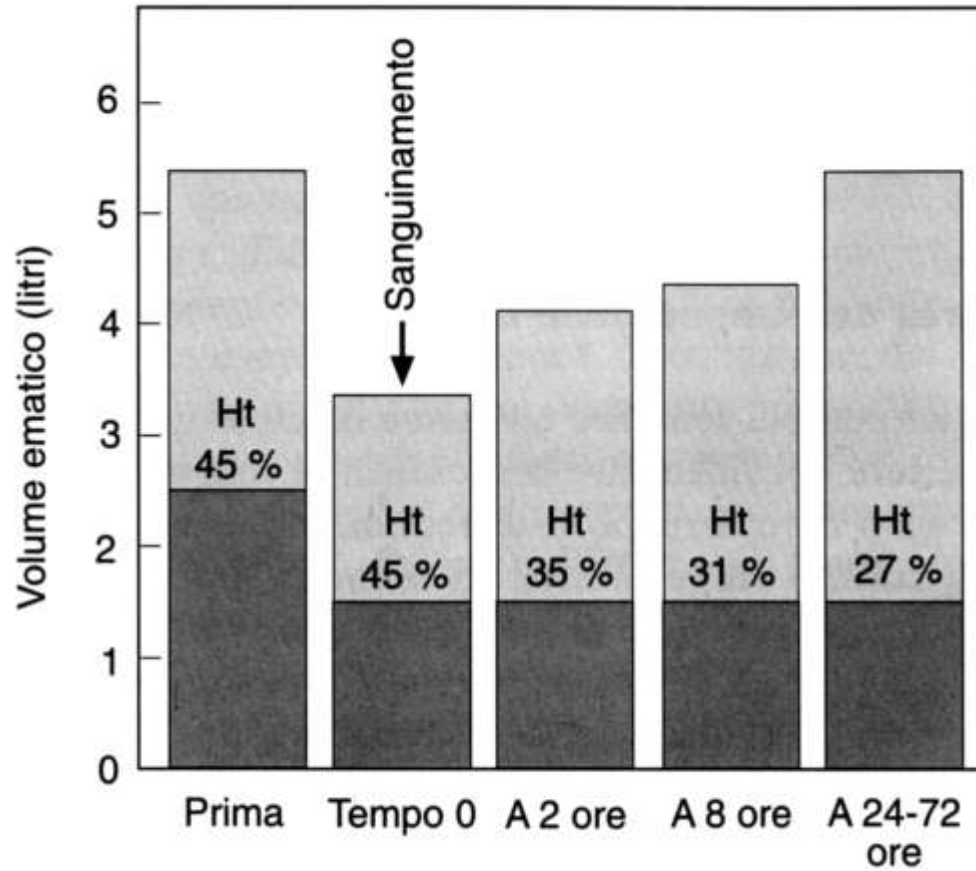
**massa
eritrocitaria**



Anemia



Variazioni dell'Ht dopo sanguinamento acuto



Anemie Ferro-carenziali



la carenza di ferro è la principale forma di malnutrizione nel mondo

Ogni euro speso per arricchire gli alimenti di ferro ha un ritorno di 84 euro in termini di aumento della produttività e decremento degli handicap.

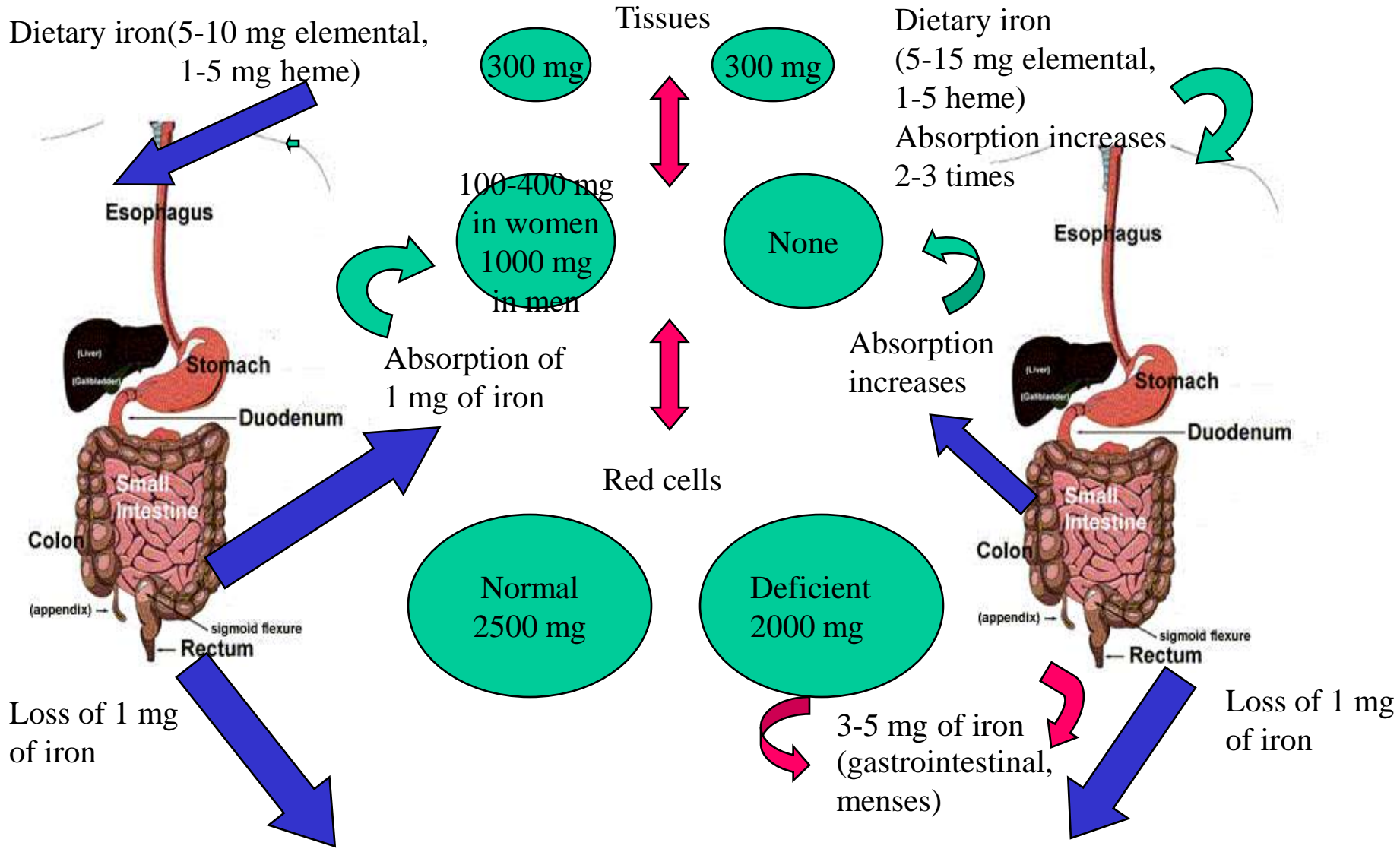
La carenza di ferro è pericolosa soprattutto per le donne in età fertile e per i bambini, per le sue gravi conseguenze sulla salute e sulla capacità di apprendimento.



Normal Balance of Iron

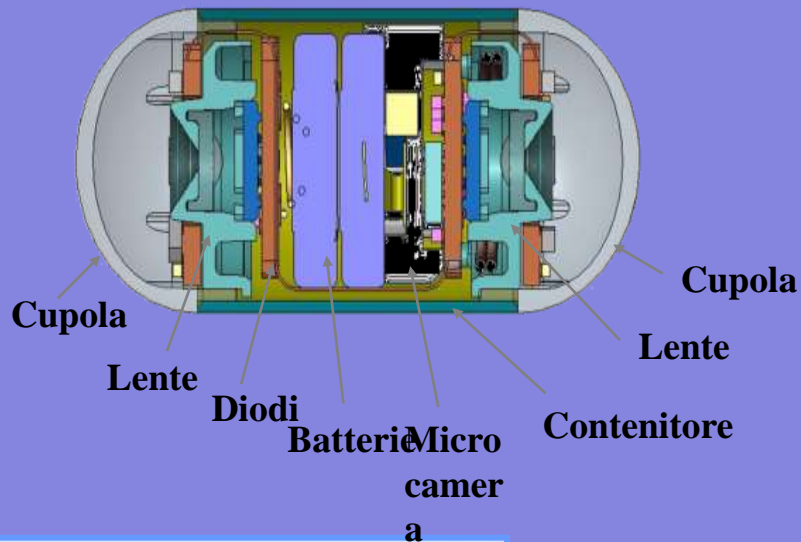
Iron Pool

Iron Deficiency



Obligate loss: 1 mg of iron = 1 ml of blood (0,5 mg of iron) + 0,5 mg of nonblood iron

MECCANISMI PATOGENETICI DELL'ANEMIA SIDEROPENICA



- *Deficit nutrizionali*
- *Malassorbimento*
- *Aumentato fabbisogno*
- *Aumentate perdite*

- *FANS*
- *STEROIDI*



Algoritmo Diagnostico

Anemia sideropenica
e/o FOBT +

Sintomi

-

PCS.
Se negativa, EGDS

+

Indagine mirata:
EGDS o PCS

-

Ciclo di terapia con Fe

Negativi

No risposta

Studio
Piccolo intestino

Negativo

Considerare altri tests diagnostici

TAC e/o Scintigrafia
e/o Angiografua

Rivalutazione



Cancro colon



Esofagite

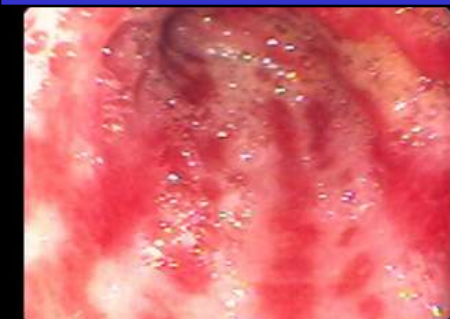


Diverticoli

ID. NO:
SEX: AGE:
D. O. BIRTH:
06/24/03
09:07:56



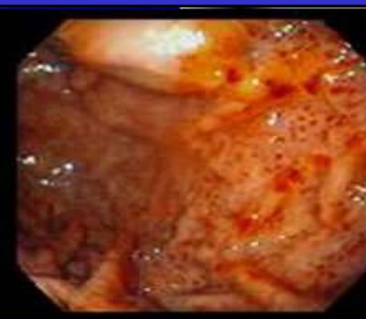
Ulcera g.



G.A.V.E



PHG



PHC



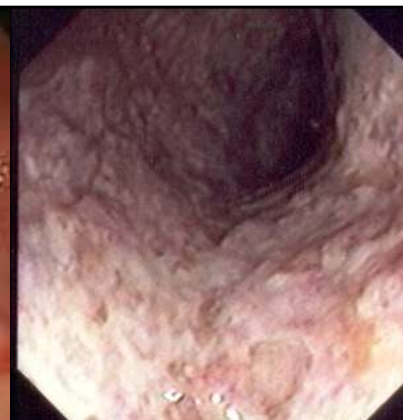
Varici



Mallory-Weiss



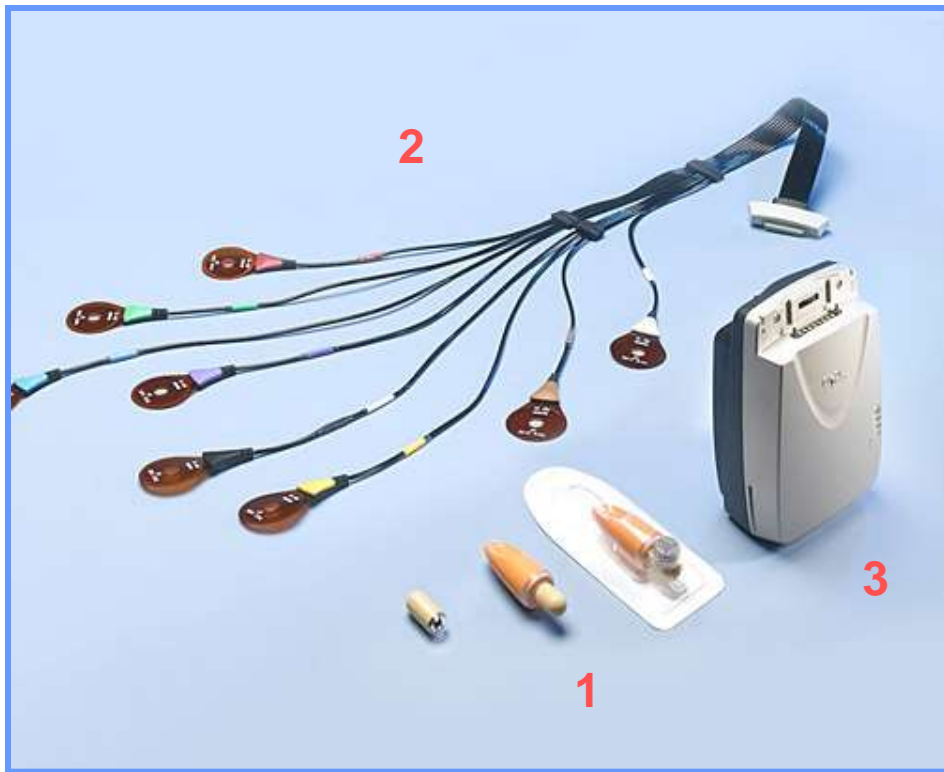
Angiodisplasia



M.di Crohn

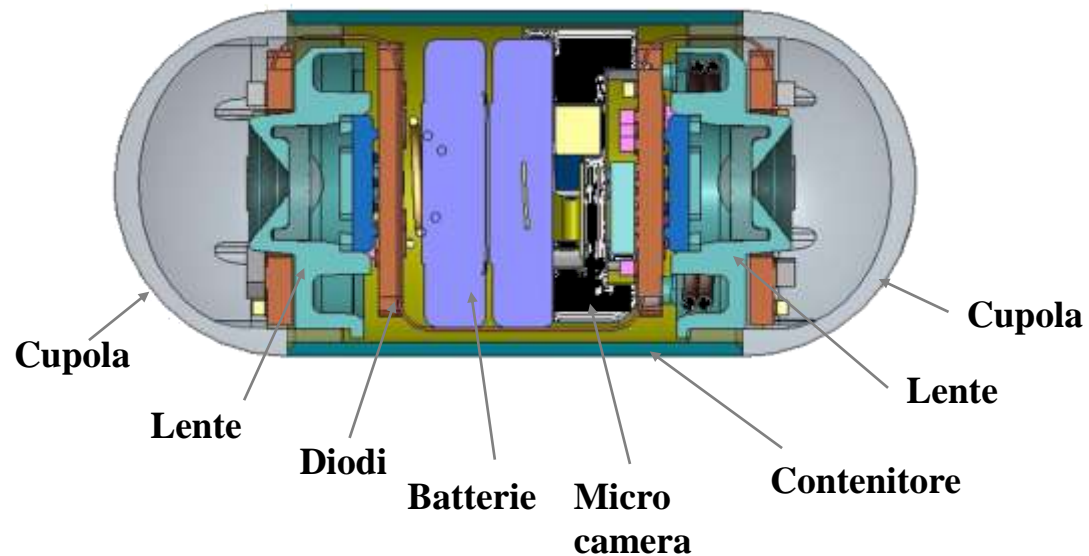


Adenoma colon



1. The PillCam™ Capsule
2. SensorArray™ SB
3. Given® DataRecorder™

diametro: 11 mm
 lunghezza: 26 mm
 peso: 3.7gr
 2 immagini al secondo
 57.000 immagini in 8 ore
 Rileva oggetti < 0,1 mm



NORMALE



01:57:20
XA

06 Oct 05



Given®



MORBO DI CROHN



CELIACHIA



ANGIODISPLASIE ATTIVE

2 (2) – LESIONE VEGETANTE EROSA (→ LINFOMA T TENUE)



A



B

Lesione vegetante del digiuno; successiva diagnosi istologica di linfoma a cellule T, su pezzo operatorio (occlusione).

Sanguinamento attivo segnalato dal software SBI (A) e dubbia erosione attiva (B)

1₍₁₎ - MAV DIGIUNO



MAV digiunali trattate successivamente con APC

3 (3) - TELEANGECTASIE → R.W.O.

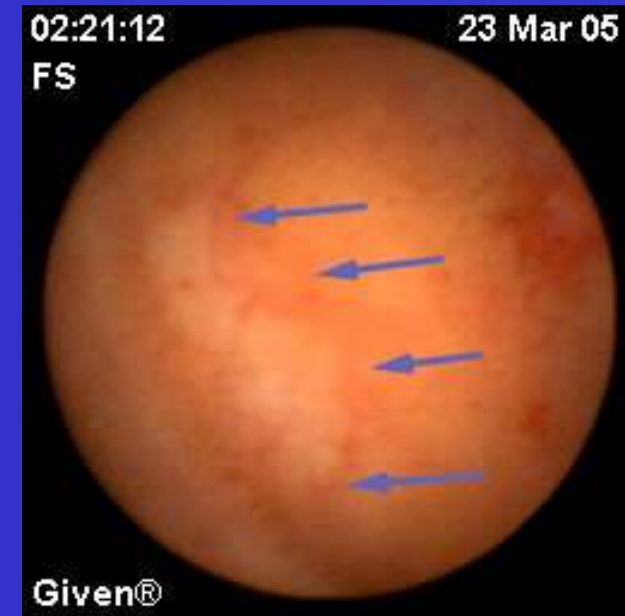
A



B



C



R.W. O. con teleangectasie digiunali

Teleangectasie in varie fasi di attività:

A → attiva, segnalata dal software (SBI)

B → in remissione

C → in fase di cicatrizzazione (fibrina)

4 (4) – EROSIONI ATTIVE (→ ADENOCARCINOMA TENUE)

A



E



B

C

D

F

Lesioni edematose con scomparsa dei villi (A-B), erosioni in parte attive e in parte ricoperte da fibrina (C-D) con sanguinamento attivo e sangue nel lume (E).

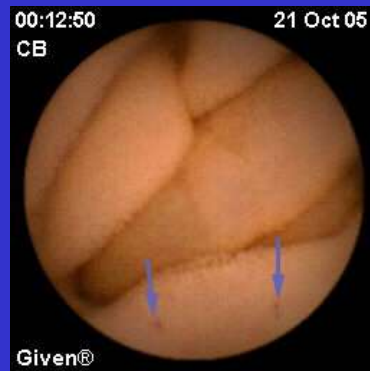
Afte della mucosa ileale (F).

Diagnosi, sul pezzo operatorio, di adenocarcinoma del tenue.

7₍₁₅₎ – POLIPO DUODENO e MAV TENUE



Vegetazione polipoide del duodeno



MAV di digiuno e ileo

QUANTITA' DI Fe da SOMMINISTRARE

DOSE TOTALE DI Fe in mg

Peso corporeo in kg x 2,3

X (15-Hb del paziente in g/dl) +1000

Emoglobina

dose totale mg

>11

5000

9-11

10.000

<9

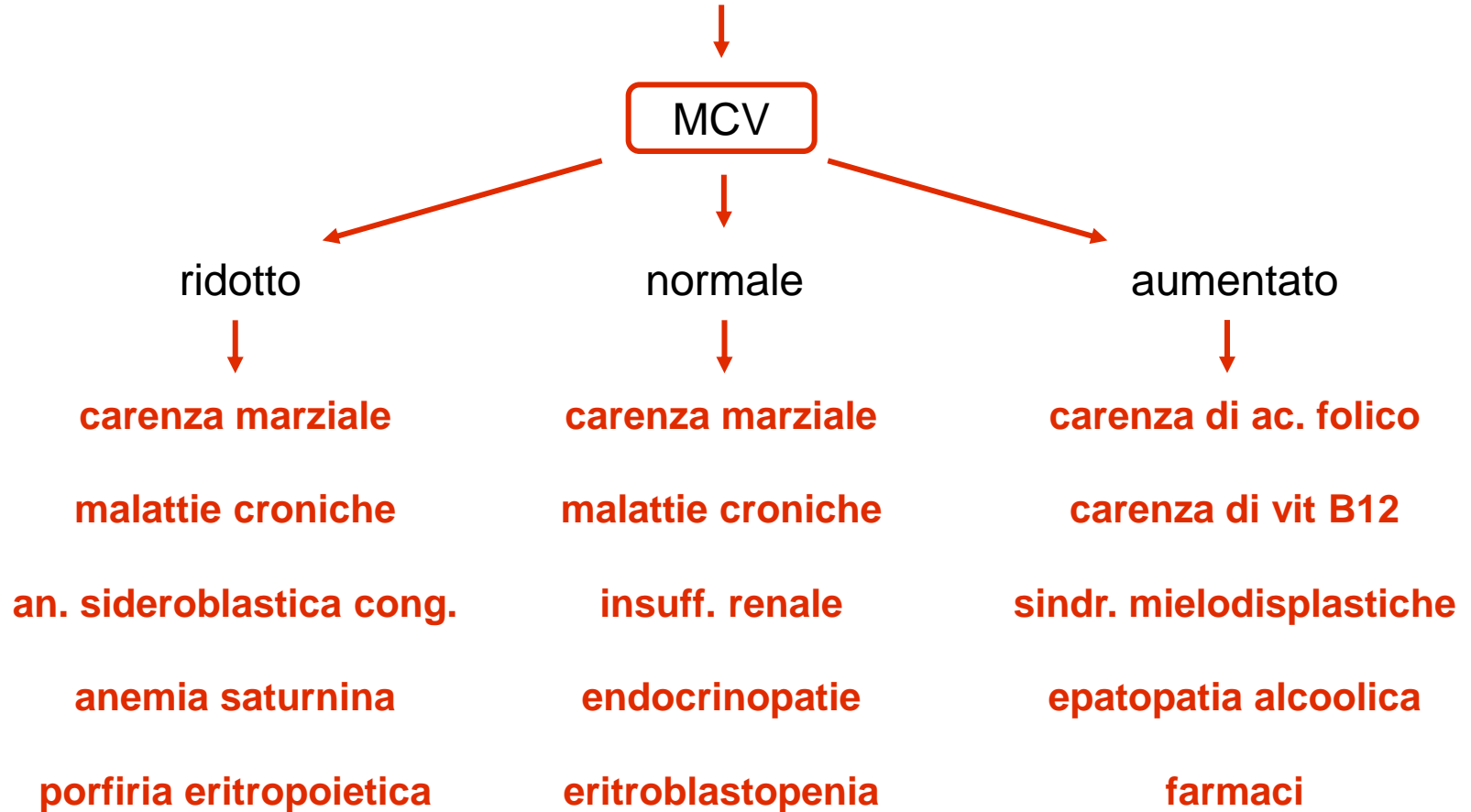
15.000

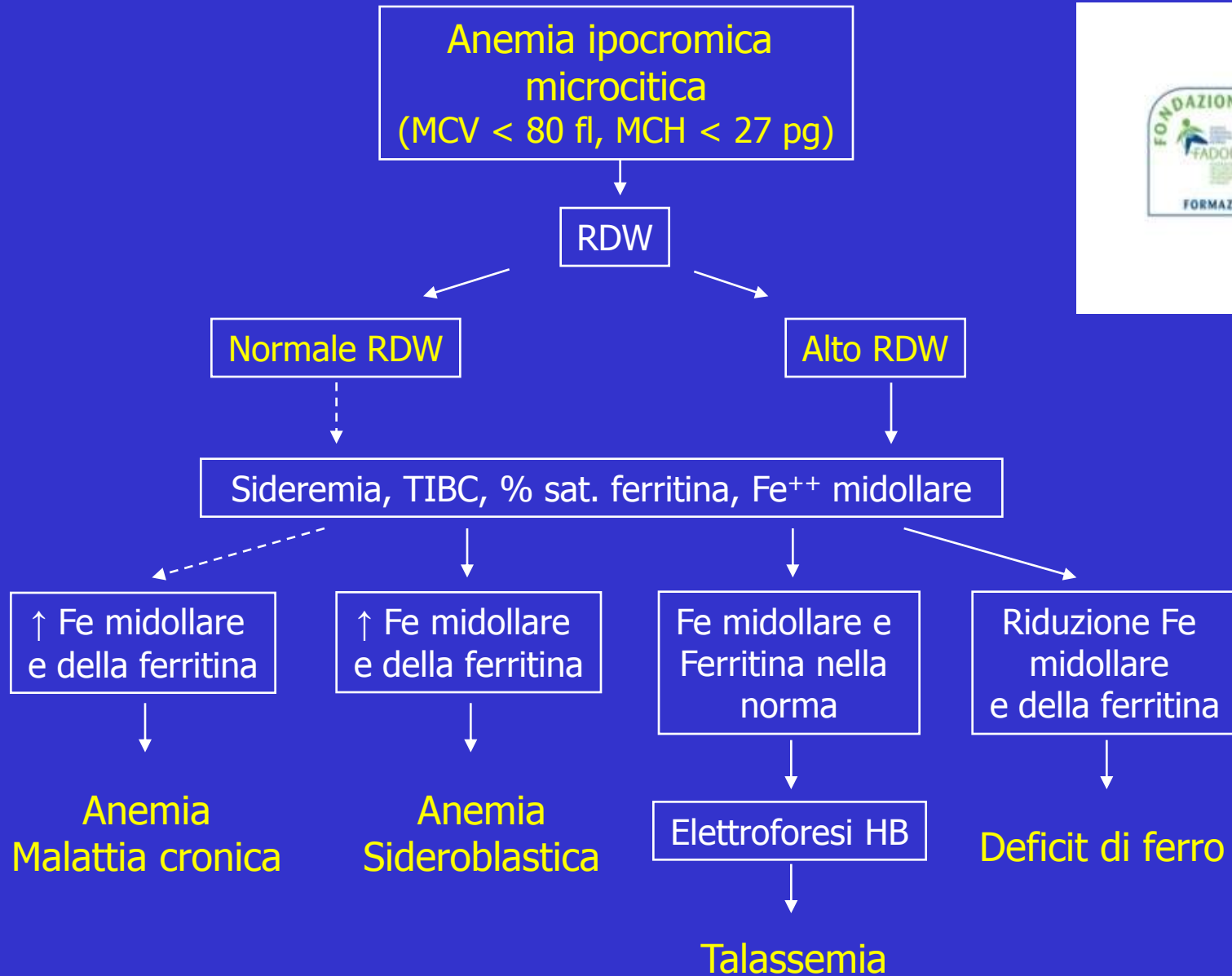


Assorbimento del 10% in un paziente di 60 kg

Solfato ferroso 595 mg (Ferrograd)

Anemia da difetto di produzione





**Anemia normocromica
normocitica**
(MCV = 80-96 fl, MCH = 27-32 pg)

Conta reticolocitaria

Aumentata

Possibile anemia emolitica
o perdita ematica

Bassa/normale

Valutare midollo

Anomalo

- **Metastasi**
- **Mielofibrosi**
- **Mieloma multiplo**
- **Leucemia**
- **SMD**
- **Anemia aplastica**

Normale

Test funzionalità
Rene, fegato, endocrino

**Malattie
sistemiche**

**Malattie
croniche**



Malattie associate all'anemia da malattia infiammatoria cronica

Infezioni Acute

Infezioni Croniche

TBC

Endocardite

Infezioni croniche vie urinarie

Infezioni fungine croniche

Malattie infiammatorie croniche

Artriti

Artrite Reumatoide

Connettiviti sistemiche

Polimialgia Reumatica

Epatite acuta e cronica

Ulcere da decubito

Tumori

Metastasi da carcinoma

Tumori Ematologici

Leucemie

Linfomi

Mielomi

Insufficienza Renale cronica

Ipotiroidismo

Disproteidemia in malnutrizione

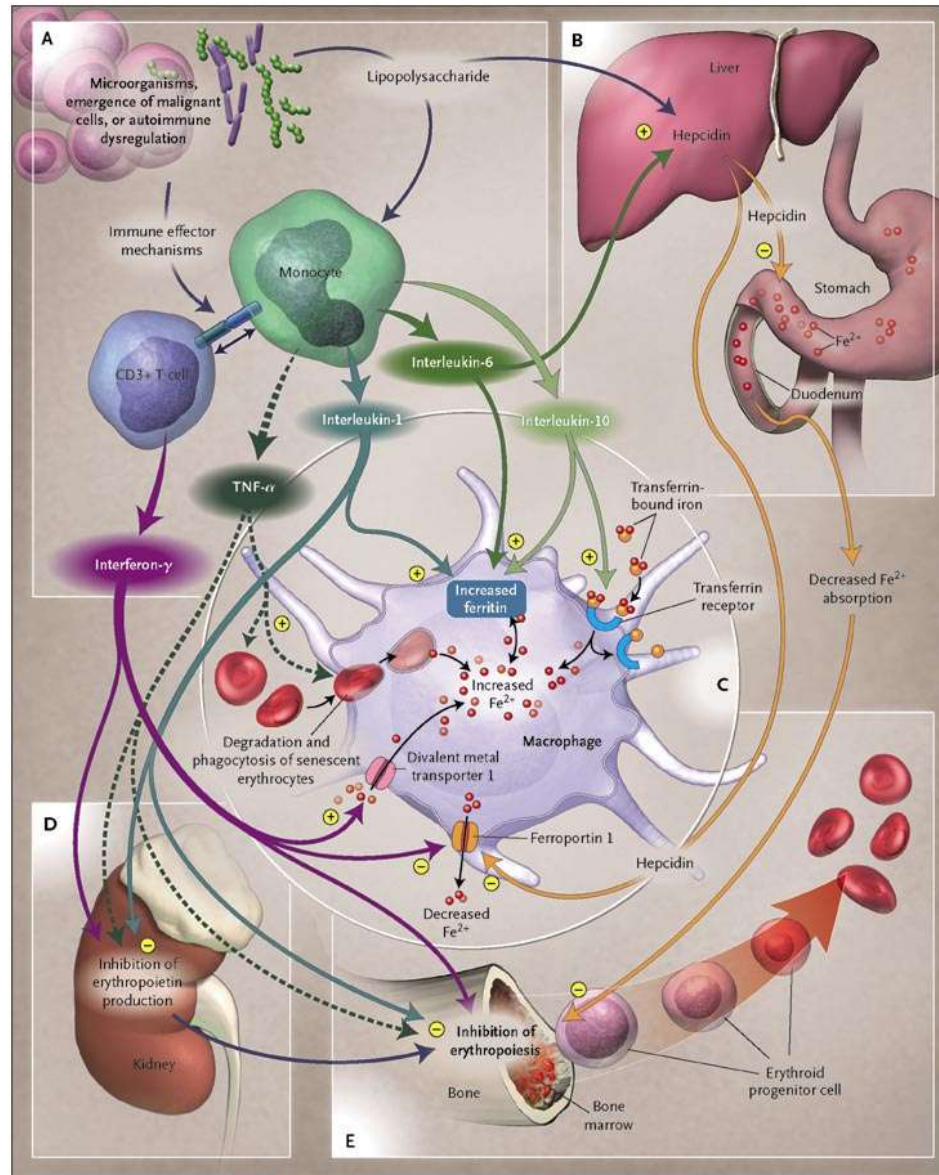




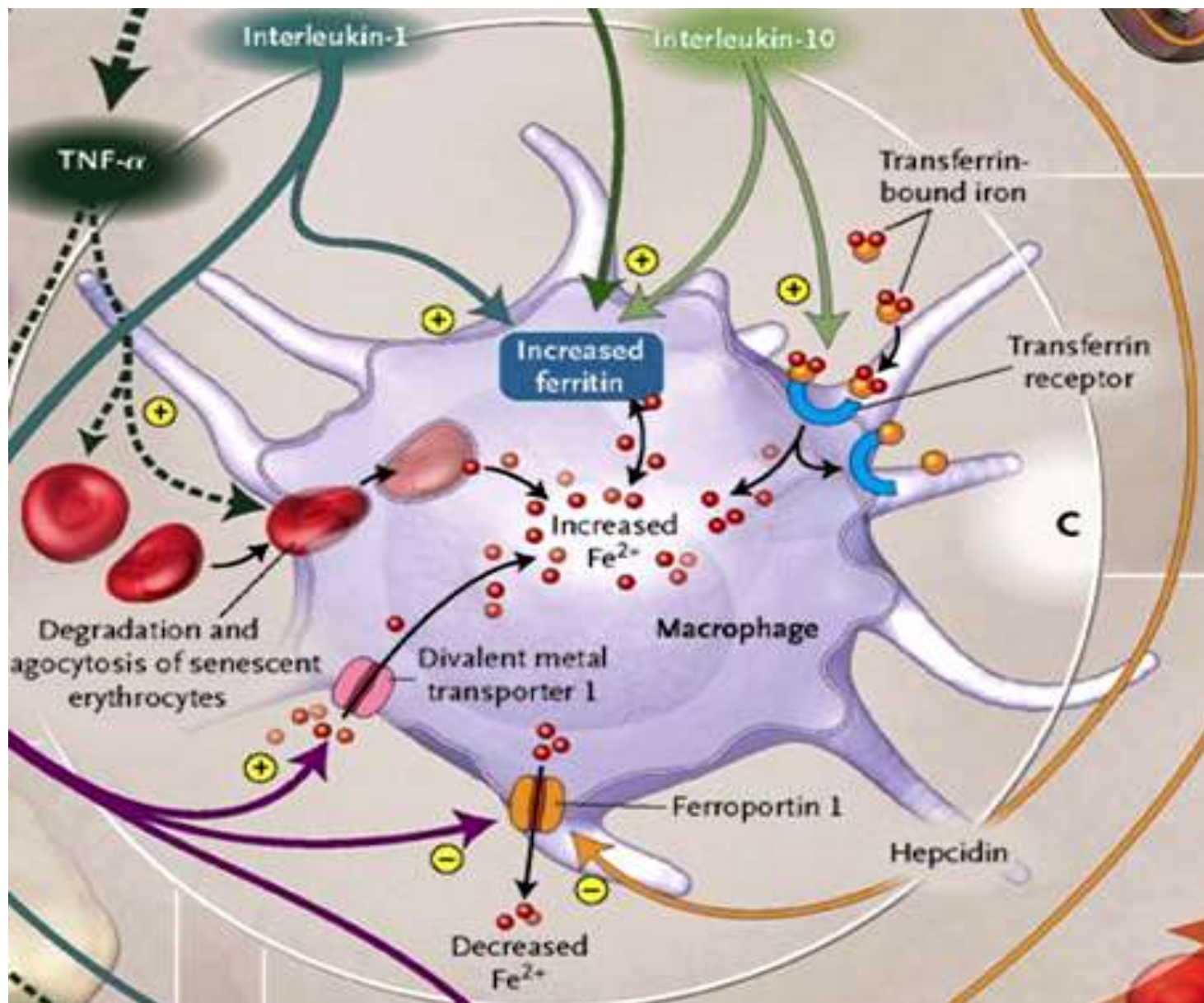
Table 1. Underlying Causes of Anemia of Chronic Disease.

Associated Diseases	Estimated Prevalence* <i>percent</i>
Infections (acute and chronic)	18–95 ⁸⁻¹⁰
Viral infections, including human immunodeficiency virus infection	
Bacterial	
Parasitic	
Fungal	
Cancer†	30–77 ^{9,12-14}
Hematologic	
Solid tumor	
<u>Autoimmune</u>	8–71 ^{5,9,15,16}
<u>Rheumatoid arthritis</u>	
<u>Systemic lupus erythematosus and connective-tissue diseases</u>	
<u>Vasculitis</u>	
Sarcoidosis	
Inflammatory bowel disease	
Chronic rejection after solid-organ transplantation	8–70 ¹⁷⁻¹⁹
Chronic kidney disease and inflammation	23–50 ²⁰⁻²²

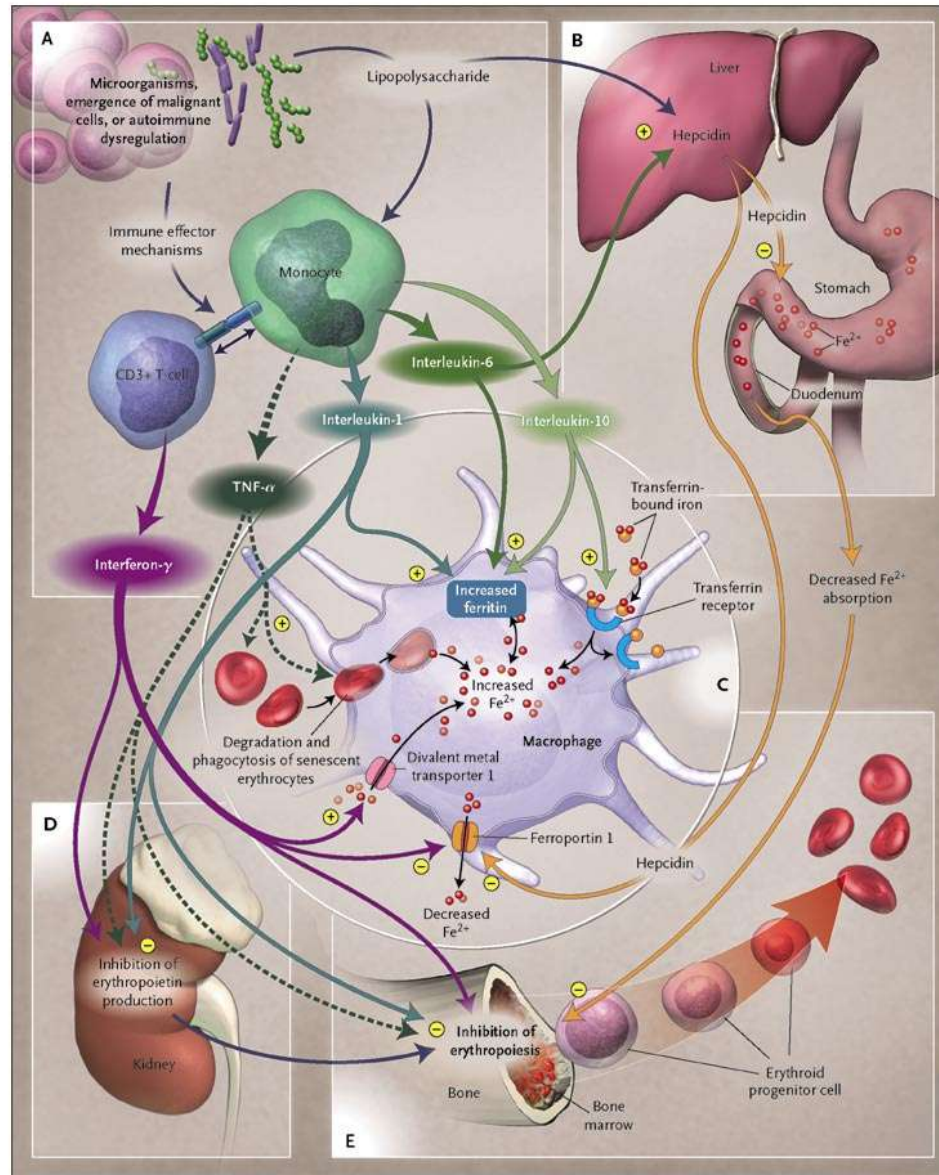
Pathophysiological Mechanisms Underlying Anemia of Chronic Disease



Sovraccarico marziale con anemia sideropenica



Pathophysiological Mechanisms Underlying Anemia of Chronic Disease



Epcidina

Punto cardine della sregolazione del meccanismo fisiologico sia in emocromatosi che in ACD (sono i 2 fenotipi estremi):

- **Emocromatosi:** la sua attività diminuisce e l'assorbimento di ferro aumenta
- **ACD:** la sua attività aumenta e l'assorbimento di ferro diminuisce

Circulating Hepcidin in the Crossroads of Anemia and Inflammation Associated with Rheumatoid Arthritis

Objective To investigate the role of circulating hepcidin, which is a homeostatic regulator of iron metabolism and a mediator of inflammation, in anemia associated with rheumatoid arthritis.

Methods Forty patients with rheumatoid arthritis (19 with anemia and 21 without anemia), 12 patients with iron deficiency anemia and 14 healthy adults were studied. Serum hepcidin levels were analyzed with hepcidin prohormone solid phase enzyme-linked immunosorbent assay.

Results The mean serum hepcidin levels were significantly higher in patients with rheumatoid arthritis with anemia compared to healthy adults and those with iron deficiency anemia. The active rheumatoid arthritis group had significantly higher mean serum hepcidin levels than the inactive rheumatoid arthritis group. In the rheumatoid arthritis group, serum hepcidin levels were positively correlated with disease activity, but inversely correlated with hemoglobin levels. The serum hepcidin level was found to be a significant predictor for hemoglobin level.

Conclusion Serum hepcidin levels are closely associated with disease activity in rheumatoid arthritis patients and might play a role in the pathobiology of chronic disease anemia associated with rheumatoid arthritis.

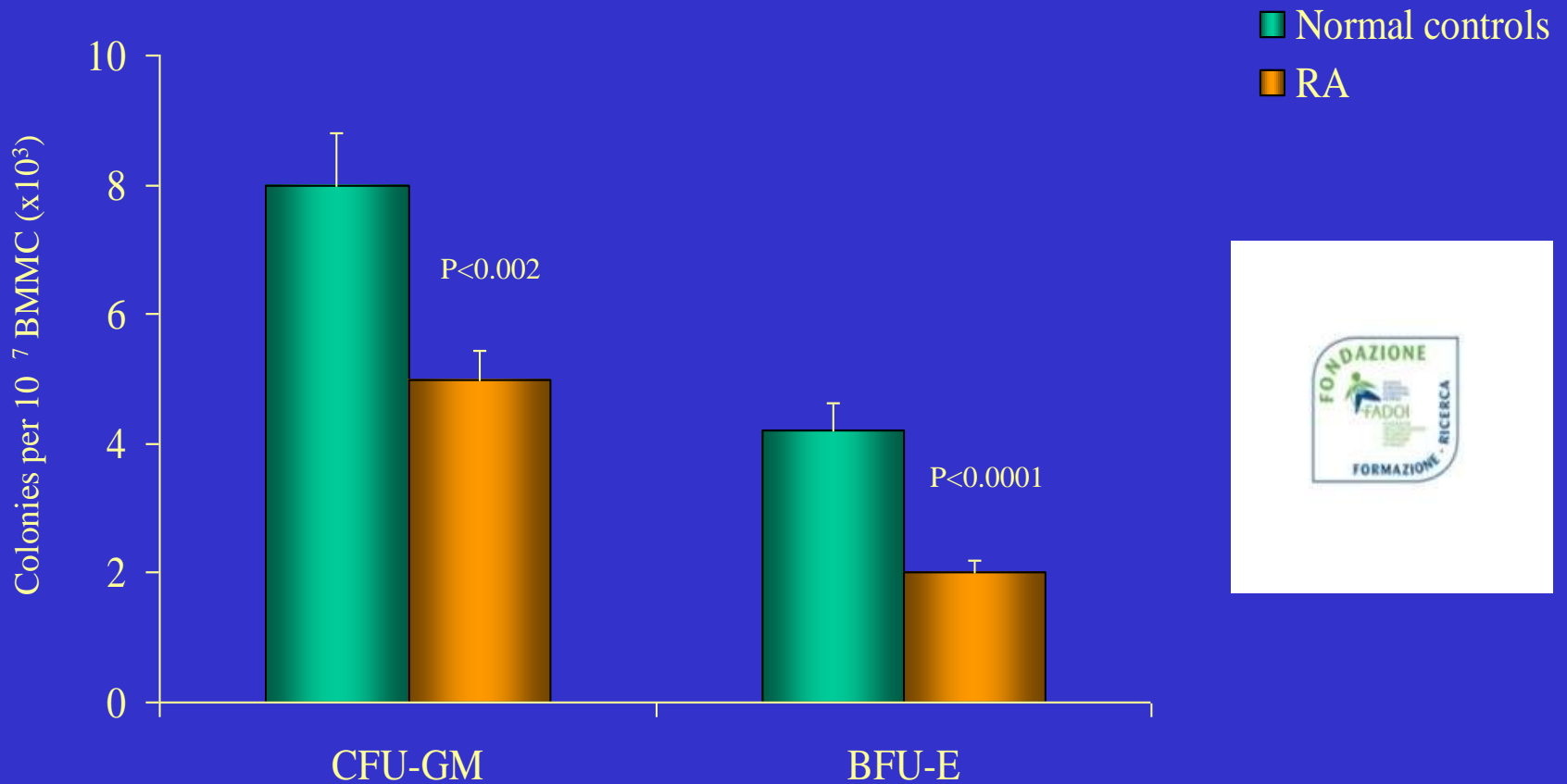
Table 3. Frequencies of Anemia, Levels of Hemoglobin and Serum Hepcidin in Active and Inactive RA Patients

	Active RA (n=17)	Inactive RA (n=23)	p
Frequencies of anemia (%)	58 %	40 %	0.40
Hgb (g/dL)	12±1.6 (11.5)	12.4±1.6 (12.8)	0.24
Hepcidin (ng/mL)	486±101 (449)	393±104 (353)	0.02

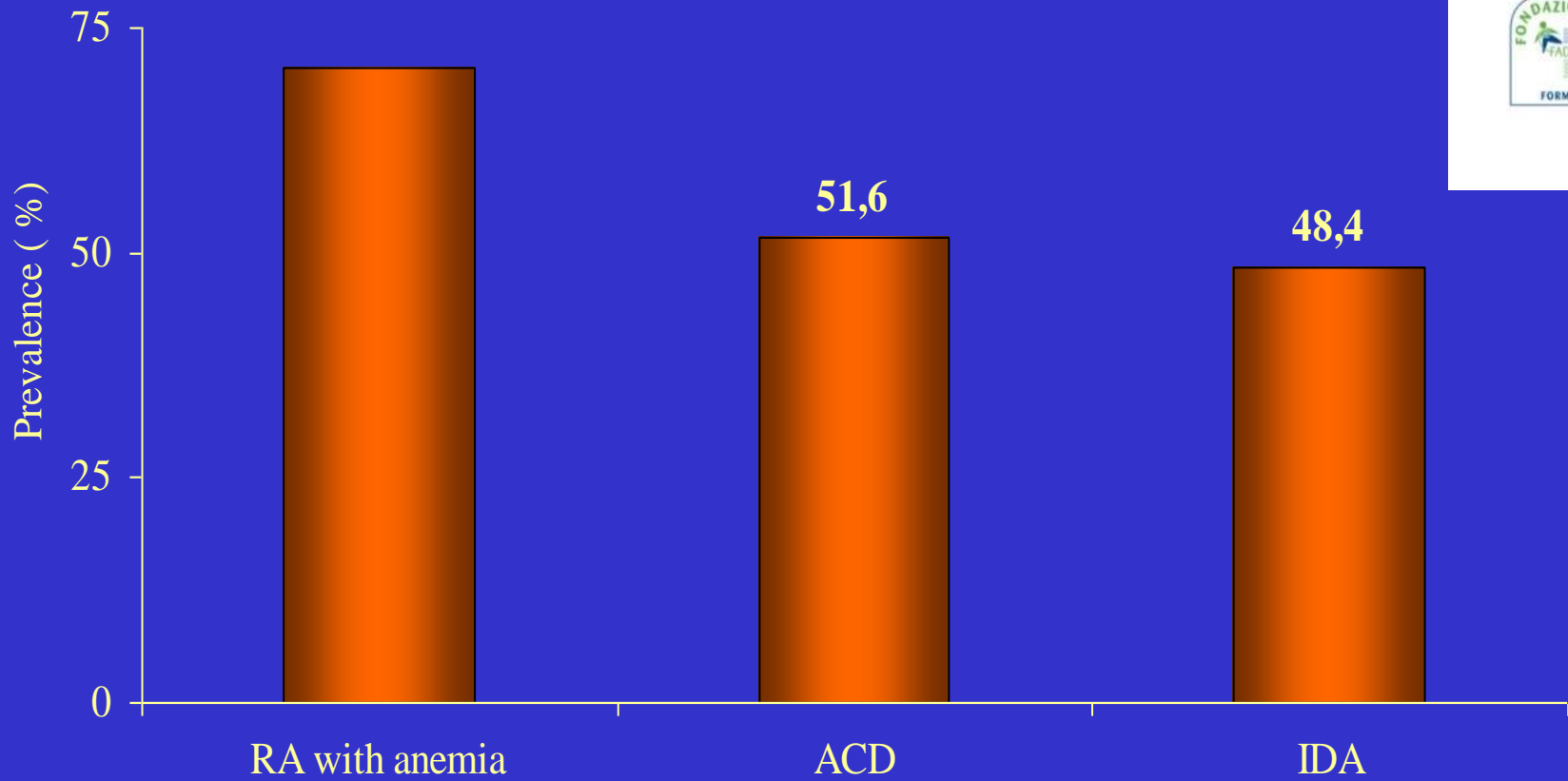
Table 4. Predictors for Hemoglobin Levels in RA Patients

	β coefficient	T value	p
DAS28(CRP) score	0.294	1.519	0.142
Ferritin	0.203	1.202	0.242
Serum Iron	0.459	2.730	0.012
Hepcidin	-0.631	-3.203	0.004

Impaired clonogenic potential of Bone Marrow Progenitor Cells in Rheumatoid Arthritis



High prevalence of iron-deficiency anemia in 214 Indian patients with RA



Diagnosi differenziale tra anemia delle malattie croniche e anemia sideropenica

	<u>Malattia cronica</u>	<u>Anemia sideropenica</u>
<u>Ferro</u>	ridotto	ridotto
<u>Transferrina</u>	ridotta-normale	aumentata
<u>Saturazione transf.</u>	ridotta	ridotta
<u>Ferritina</u>	normale-aumentata	ridotta
<u>Recett. sol. transf.</u>	normale	aumentato



Diagnosi differenziale tra anemia delle malattie croniche e anemia sideropenica

	<u>Malattia cronica</u>	<u>Anemia sideropenica</u>
<u>Ferro</u>	ridotto	ridotto
<u>Transferrina</u>	ridotta-normale	aumentata
<u>Saturazione transf.</u>	ridotta	ridotta
<u>Ferritina</u>	normale-aumentata	ridotta
<u>Recett. sol. transf.</u>	normale	aumentato

Diagnosi differenziale tra anemia delle malattie croniche e anemia sideropenica



	<u>Malattia cronica</u>	<u>Anemia sideropenica</u>	<u>Entrambe</u>
<u>Ferro</u>	ridotto	ridotto	ridotto
<u>Transferrina</u>	ridotta-normale	umentata	ridotta
<u>Saturazione transf.</u>	ridotta	ridotta	ridotta
<u>Ferritina</u>	normale-umentata	ridotta	ridotta-normale
<u>Recett. sol. transf.</u>	normale	umentato	normale-umentato



ANEMIA

VES, PCR

Sat Trasf <16%

Altre Cause Anemia

Ferritina
<30 ng/ml

Ferritina
30-100 ng/ml

Ferritina
>100 ng/ml

Dosaggio recettore solubile della
transferrina sTfR

sTfR/log ferritina <1

sTfR/log ferritina >2

Anemia Infiammatoria
Cronica ed Anemia
Sideropenica

Anemia Infiammatoria
Cronica

**Anemia
sideropenica**

Terapia dell'anemia delle malattie croniche



	<u>Malattia cronica</u>	<u>Malattia cronica + sideropenia</u>
<u>Trattamento malattia di base</u>	sì	sì
<u>Trasfusioni</u>	sì	sì
<u>Terapia marziale</u>	no (sì?)	sì
<u>Eritropoietina</u>	sì	sì ↓

Deficit di B12 sottodiagnosticato nell'anziano

- *I segni e sintomi tipici non sono presenti nell'anziano*
- *Solo il 60% dei pazienti con deficit di B12 è anemico*
- *Un deficit di B12 con anemia è presente nel 5-10% degli anziani*
- *Inadeguato assorbimento nel 10-30%*
- *L'anemia perniziosa è sottodiagnosticata nel 2% degli individui >60anni*
- *I sintomi neurologici spesso precedono l'anemia*



Manifestazioni neurologiche nel deficit di B12

- Parestesie alle dita ed ai polpastrelli
- Pallestesia (riduzione del senso di vibrazione)
- Atassia
- Alterazione dell'olfatto e del gusto
- Atrofia del nervo ottico
- Demenza perdita della memoria e depressione
- “Megaloblastic Madness” – Schizofrenia paranoide
- Alterazioni specifiche in RM



ANEMIA PERNICIOSA (6)

DIAGNOSI:

- Dosaggio vitamina B12 (ridotta) e folati (normali)
- Ricerca APCA
- EGDS: atrofia gastrica (scomparsa delle ghiandole tubulari, metaplasia intestinale, infiltrato linfoplasmocitario)
(Possibile insorgenza di ca gastrico)
- Test di Schilling: somministrazione di vit B12 marcata con cobalto radioattivo e legata o meno a fattore intrinseco(per diagnosticare difettoso assorbimento), oggi sempre meno utilizzato.
- Dosaggio urinario acido metilmalonico (aumentato)

CAUSE DI DEFICIT DI FOLATI

- INSUFFICIENTE INTRODUZIONE

dieta inadeguata (alcolisti, anziani)

- AUMENTATO CONSUMO

gravidanza, allattamento, accrescimento, emolisi cronica, eritropoiesi inefficace, neoplasie

- MALASSORBIMENTO INTESTINALE

malattia celiaca, malattie dell'intestino tenue, farmaci anticonvulsivanti

- ALTERATO METABOLISMO

farmaci inibitori della diidrofolato-reduttasi (methotrexate, pirimetamina, pentamidina)

DISORDINI ESFOLIATIVI CUTANEI

psoriasi diffusa

The NEW ENGLAND JOURNAL of MEDICINE

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Founded by Richard C. Cabot

Nancy Lee Harris, M.D., *Editor*
Jo-Anne O. Shepard, M.D., *Associate Editor*
Sally H. Ebeling, *Assistant Editor*

Eric S. Rosenberg, M.D., *Associate Editor*
Alice M. Cort, M.D., *Associate Editor*
Christine C. Peters, *Assistant Editor*



Case 13-2012: A 62-Year-Old Man
with Paresthesias, Weight Loss, Jaundice,
and Anemia

Alberto Puig, M.D., Ph.D., Mari Mino-Kenudson, M.D.,
and Anand S. Dighe, M.D., Ph.D.

PRESENTATION OF CASE



Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Presentation
Hematocrit (%)	41.0–53.0 (men)	18.7
Hemoglobin (g/dl)	13.5–17.5 (men)	6.3
White-cell count (per mm ³)	4500–11,000	7300
Differential count (%)		
Neutrophils	40–70	73
Lymphocytes	22–44	16
Monocytes	4–11	4
Eosinophils	0–8	7
Platelet count (per mm ³)	150,000–400,000	223,000
Erythrocyte count (per mm ³)	4,500,000–5,900,000	1,510,000
Mean corpuscular volume (fl)	80–100	124
Mean corpuscular hemoglobin (pg/red cell)	26.0–34.0	41.7
Mean corpuscular hemoglobin concentration (g/dl)	31.0–37.0	33.7
Red-cell distribution width (%)	11.5–14.5	21.8
Reticulocytes (%)	0.5–2.5	0.8
Smear description		Anisocytosis 2+, macrocytes 3+
Bilirubin (mg/dl)		
Total	0.0–1.0	3.4
Direct	0.0–0.4	0.7
Lactate dehydrogenase (U/liter)	110–210	1404
Haptoglobin (mg/dl)	16–199	<6

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

Table 2. Causes of Paresthesias.

Cause	Example
Neuropathic	Diabetic neuropathy, alcoholic neuropathy
Genetic	Charcot–Marie–Tooth disease
Vascular	Polyarteritis nodosa
Rheumatologic	Systemic necrotizing vasculitis, rheumatoid arthritis
Immune	Systemic lupus erythematosus, sarcoidosis, amyloidosis, Guillain–Barré syndrome
Inflammatory	Chronic inflammatory demyelinating polyneuropathy, multiple sclerosis
Infectious	Human immunodeficiency virus, Lyme disease, syphilis, leprosy
Malignant	Lymphoma, multiple myeloma
Hematologic	Cryoglobulinemia
Toxic	Drug reactions, lead, organophosphates, arsenic, thallium
Trauma	
Nutritional deficiency	Folate, vitamin B ₁₂
Other disorders	Renal failure, thyroid disease, multisystem atrophy, spinal cord lesion, paraproteinemia

Table 3. Common Causes of Sensory Ataxia.

Hereditary ataxias
Infections (tabes dorsalis, tickborne diseases, leprosy, HIV infection)
Sensory polyneuropathies (diabetes mellitus, alcohol consumption)
Nutritional and vitamin deficiencies (vitamin B₁₂, folate, vitamin E)
Multiple sclerosis
Multisystem atrophy
Toxins

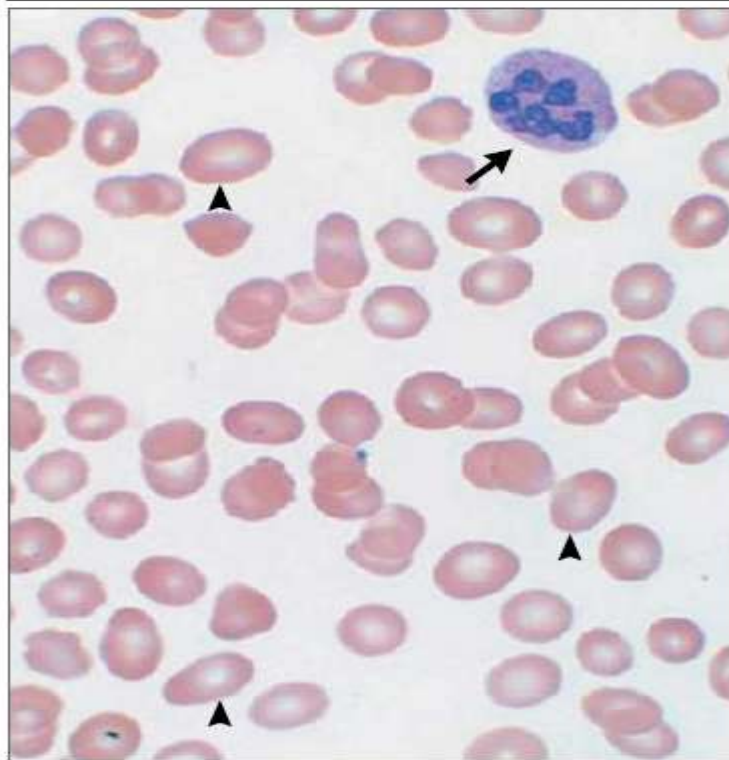


Figure 1. Peripheral-Blood Smear.

A peripheral-blood smear showed anisocytosis with oval macrocytes (arrowheads) and abundant neutrophil hypersegmentation (≥ 6 lobes; arrow). No schistocytes or spherocytes were present.

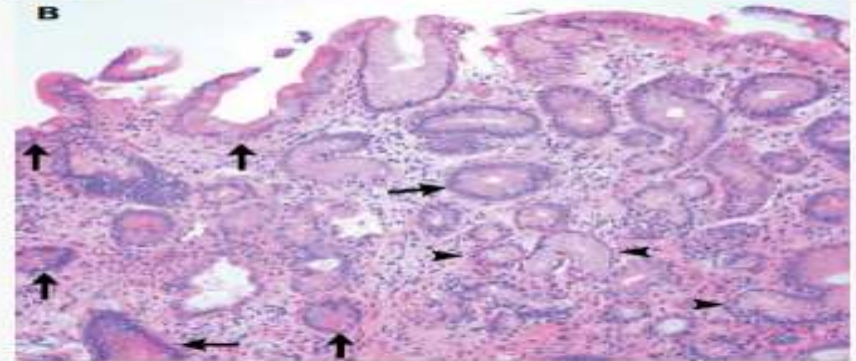


Figure 2. Endoscopic Evaluation and Biopsy Specimen.

Endoscopic examination of the stomach revealed diffuse atrophy of the gastric mucosa (Panel A). A biopsy specimen from the gastric body shows patchy foci of intestinal metaplasia (arrows) and pseudopyloric metaplasia (arrowheads) in the background of chronic inactive gastritis, findings consistent with autoimmune gastritis (Panel B, hematoxylin and eosin). There is no evidence of neuroendocrine hyperplasia, carcinoid, or adenocarcinoma. (Endoscopic image courtesy of Dr. Ashwin Ananthakrishnan, Division of Gastroenterology, Massachusetts General Hospital.)

CLINICAL DIAGNOSIS

Vitamin B₁₂ deficiency (pernicious anemia).

DR. ALBERTO PUIG'S DIAGNOSIS

Vitamin B₁₂ deficiency (pernicious anemia).

PATHOLOGICAL DISCUSSION



ALTRE FORME DI ANEMIA NELL'ARTRITE REUMATOIDE

Rheumatoid arthritis in thalassemia intermedia: coincidence or association?

Giakoumi X et al. Isr Med Assoc J. 2005;7:667-9.

Nel dubbio elettroforesi Emoglobina e dosaggio folati.

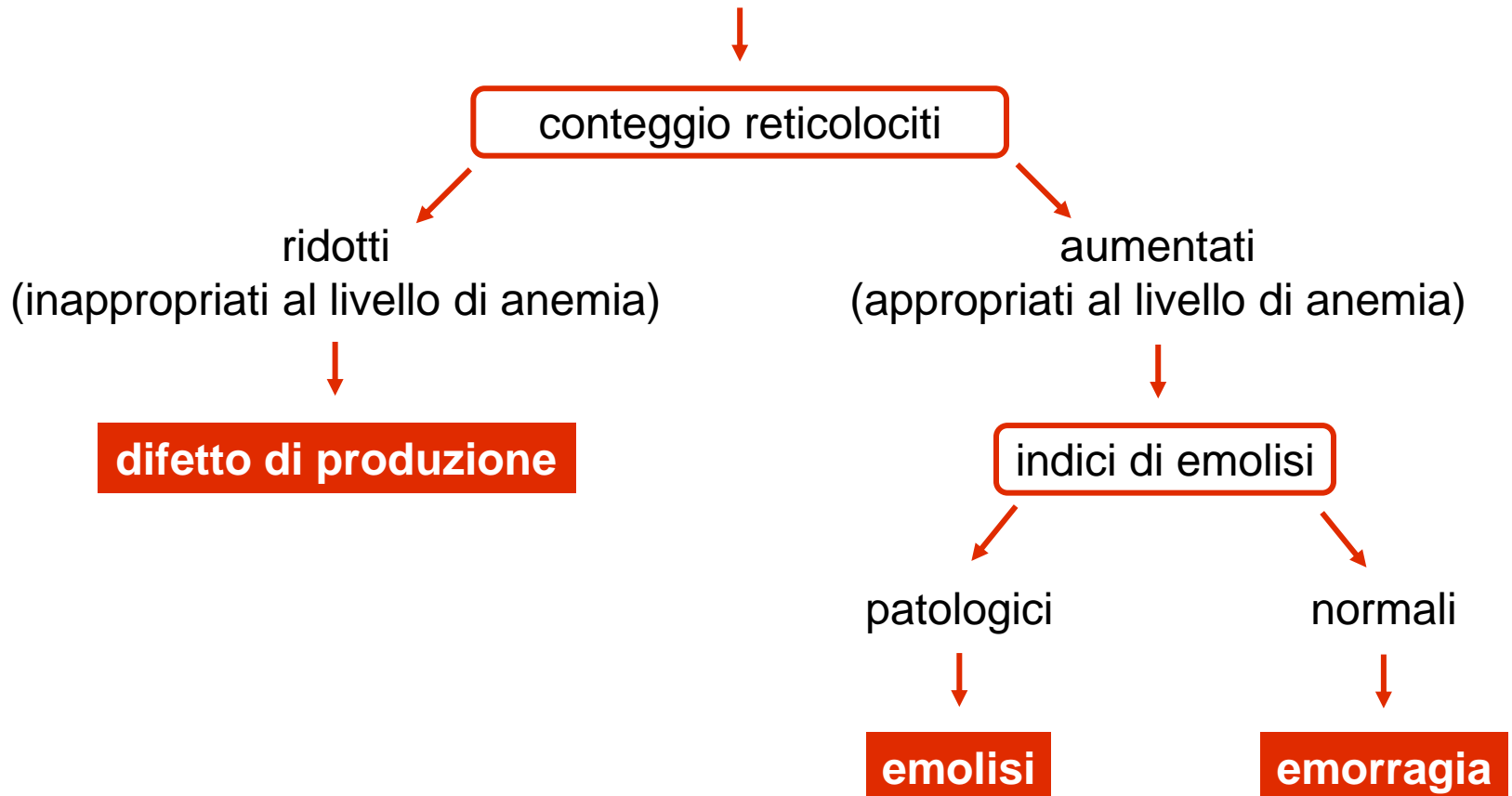
Masked deficit of B(12) and folic acid in thalassemia.

Mazzone A, et al

Am J Hematol. 2001 Aug;67(4):274.



Anemia



Anemie emolitiche



anamnesi



forme ereditarie

difetto della membrana eritrocitaria

difetto emoglobinico

difetto metabolico eritrocitario

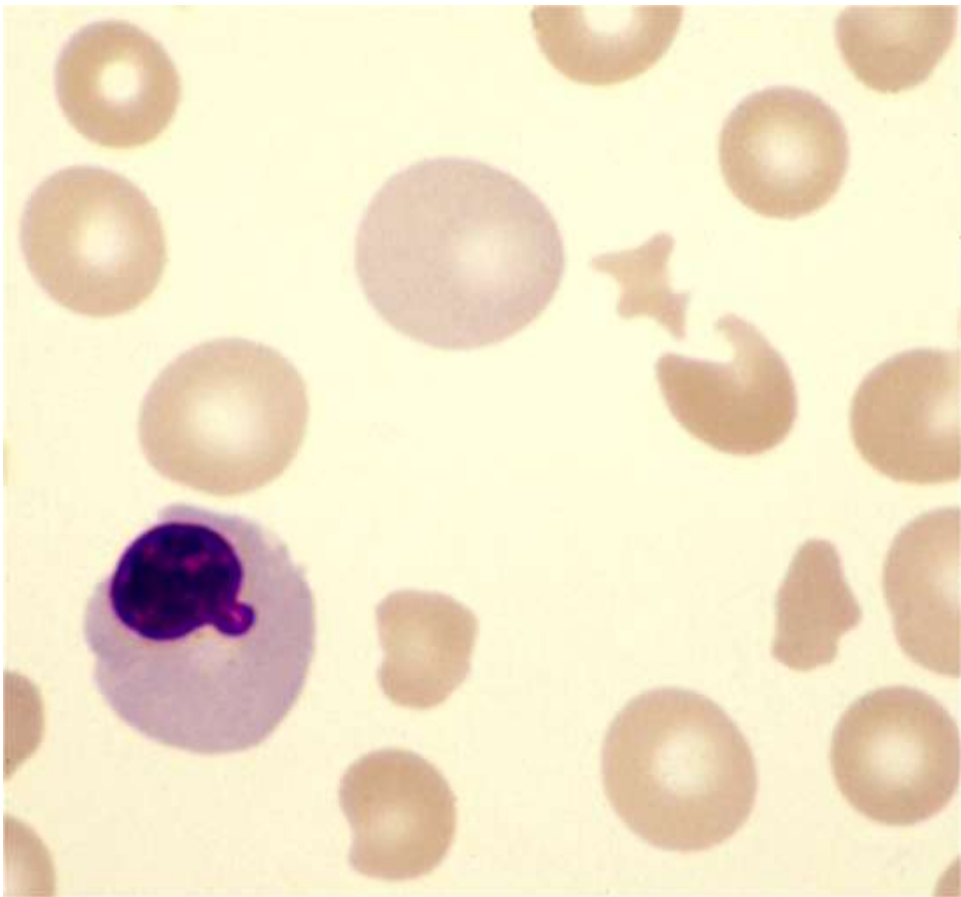


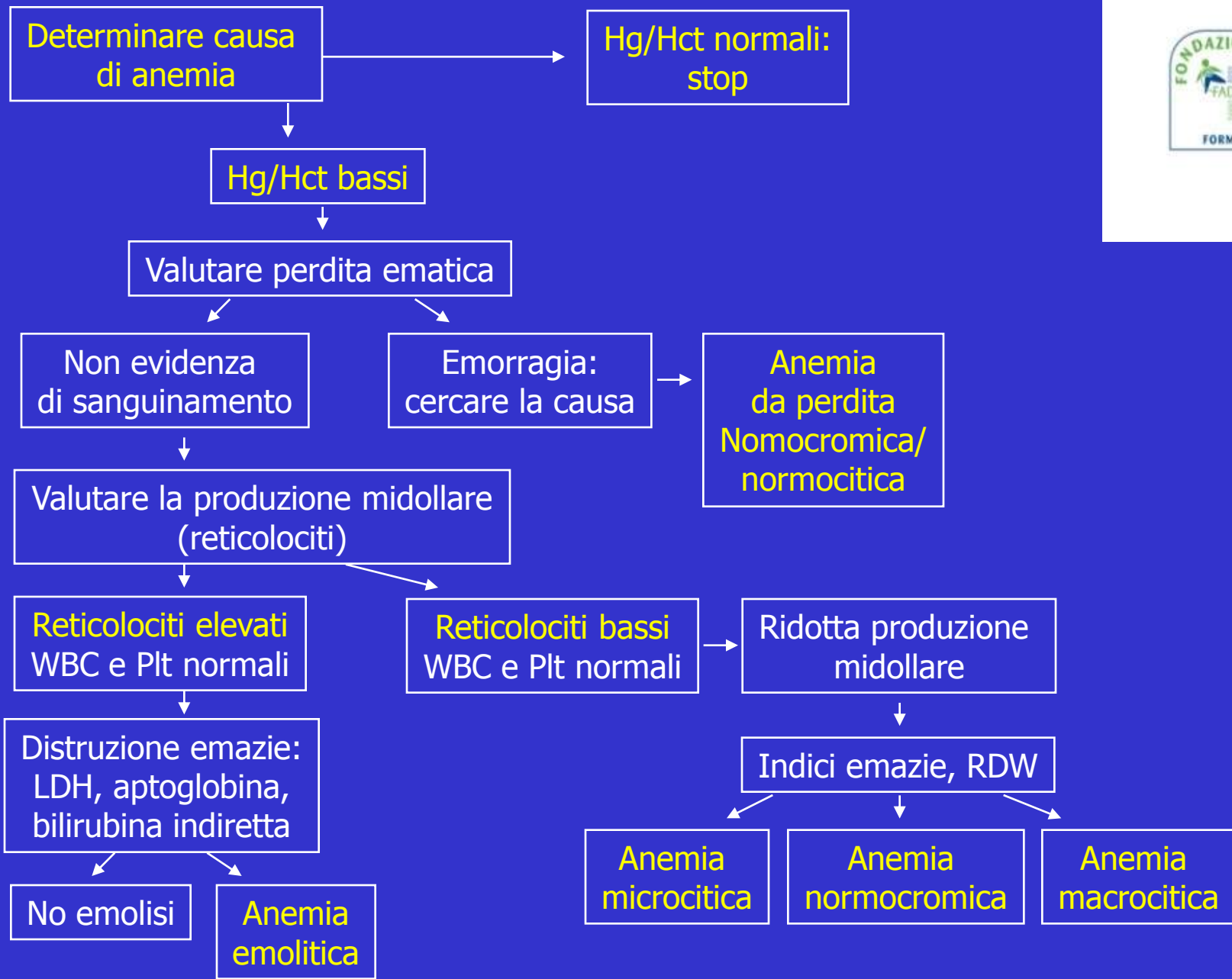
forme acquisite

anemie immuno-emolitiche

emolisi da frammentazione

danni eritrocitari "ambientali"





aumentata distruzione
(emolitica)

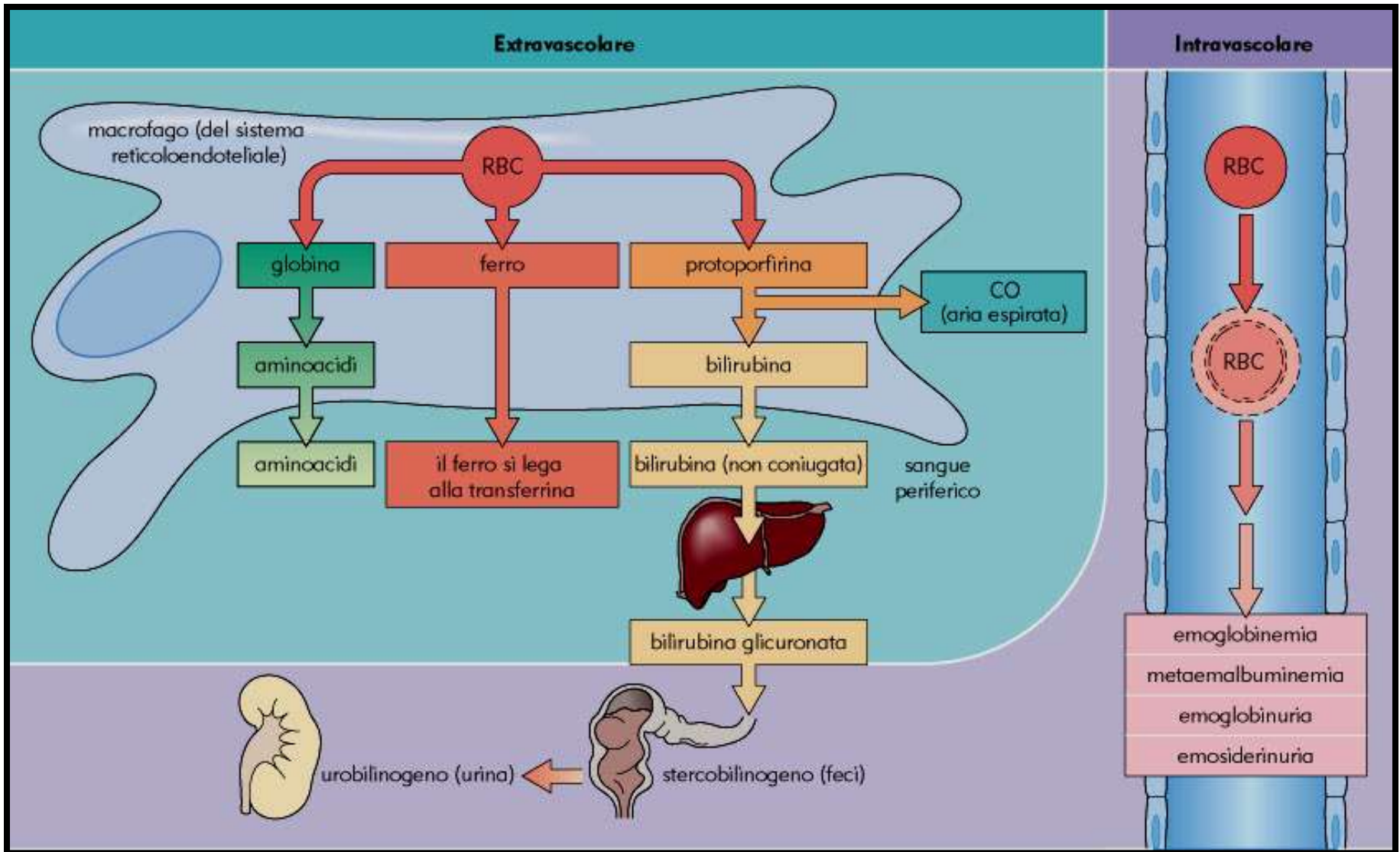
difetto intrinseco

difetti di membrana
difetti enzimatici
porfirie
emoglobinopatie
PNH

difetto estrinseco

AEA
agenti fisici o chimici
infezioni
farmaci
ipersplenismo

emolisi intravascolare ed extravascolare



Anemia emolitica:

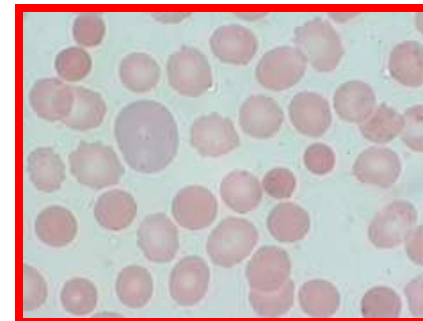
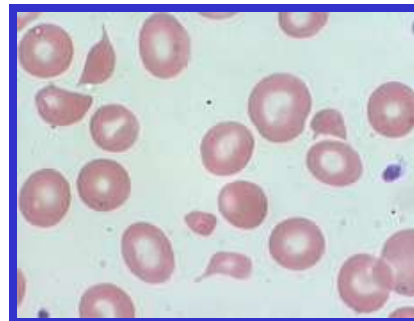
aumentata distruzione a livello periferico dei RBC per:

- *emolisi intravascolare*
- *emolisi extravascolare*

INTRAVASCOLARE

EXTRAVASCOLARE

striscio periferico	schistociti	sferociti
aptoglobina	assente/bassa	normale/lieve riduzione
emoglobina urine	++	assente
emosiderina urine	++	assente
Coombs diretto	negativo	positivo
LDH	aumentata	aumentata
bilirubina indiretta	aumentata	aumentata



Sintomi clinici e di laboratorio

Clinici

secondari all'anemia

Secondari allo stato emolitico (ittero)

splenomegalia

Laboratorio

Ridotta sopravvivenza eritrocitaria (Cr^{51})

Tests di Coombs diretti positivo per Ig e per C3 (forme gravi)

↑ reticolociti, bilirubina indiretta, LDH

↓ aptoglobina

↑ escrezione bilinogeni urinari e fecali

Sferociti, poichilociti, lieve macrocitosi, policromasia

Talora eritroblasti in circolo

Iperplasia eritroide nel midollo osseo

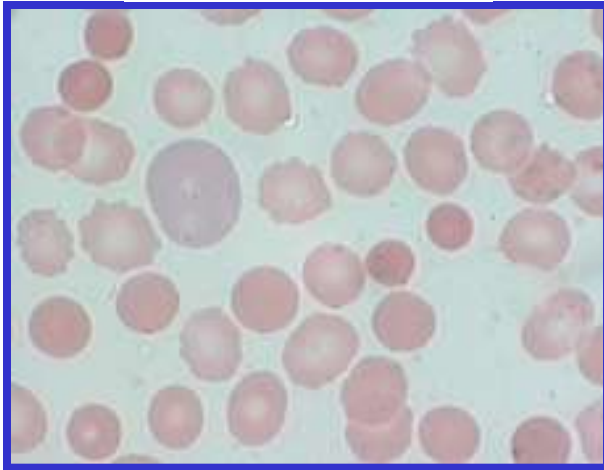
ittero cutaneo



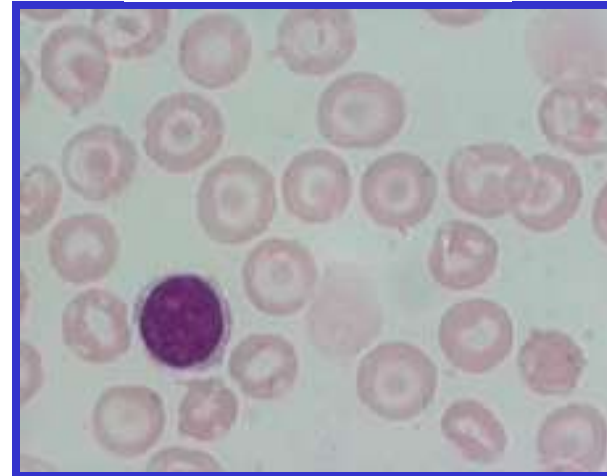
ittero sclerale



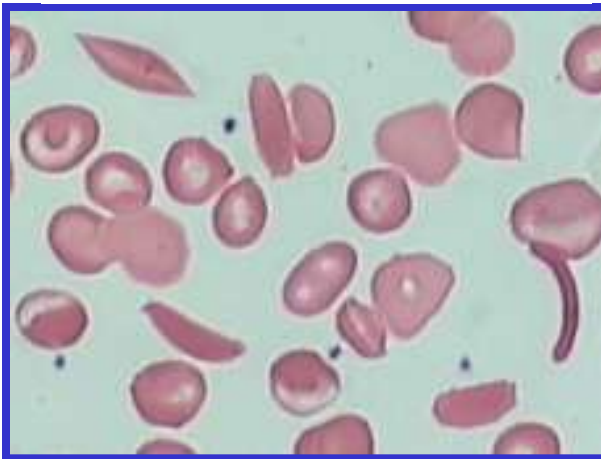
sferocitosi



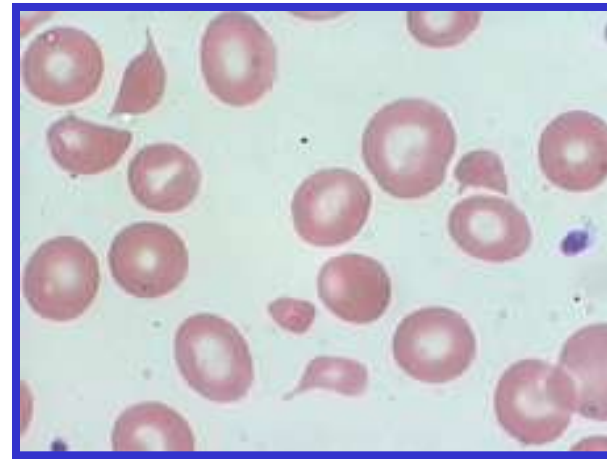
target cells



cellule falciformi



schistociti



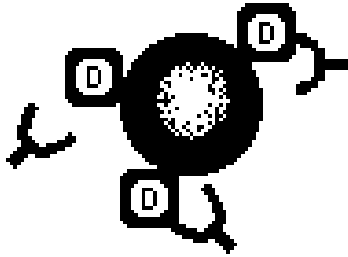
E I FARMACI ?...

tutti gli immunosoppressori



anemia emolitica indotta da farmaci

penicillina



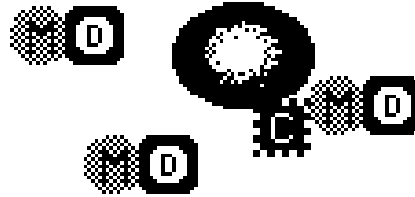
1 haptens formation

Il farmaco si lega alla membrana del GR e induce la produzione di Ac (IgG) che agiscono contro il complesso GR-farmaco. Il C non è attivato.

Coombs diretto + per IgG e - per C

Fagocitosi da parte macrofagi splenici

quinidina



2 immune complex

Il farmaco si lega ad una proteina del plasma e induce la produzione di Ac (IgM). L'IC si fissa alla membrana del GR, attiva il C e causa emolisi.

Spesso l'IC dopo la attivazione del C si stacca dal GR

Coombs diretto + per C e - per IgM

alfa-metil-dopa



3 autoimmune

Il farmaco induce la produzione di Ac diretti contro antigeni della membrana del GR (Rh). Il C non è attivato

Coombs diretto e indiretto + per IG

Lisi per sequestro splenico

Case report

Aplastic anemia following administration of a tumor necrosis factor- α inhibitor

Kuruvilla J, Leitch HA, Vickars LM, Galbraith PF, Li CH, Al-Saab S, Naiman SC. Aplastic anemia following administration of a tumor necrosis factor- α inhibitor.
Eur J Haematol 2003; 71: 396–398. © Blackwell Munksgaard 2003.

Abstract: Upregulation of tumor necrosis factor-alpha (TNF- α) has been implicated in the pathogenesis of several inflammatory conditions, including rheumatoid arthritis. Therapeutic agents such as antibodies or soluble TNF- α receptor analogs, which block TNF- α activity are a recent addition to the therapeutic armamentarium for the conditions. We describe a patient who developed aplastic anemia complicated by sepsis after receiving etanercept, a TNF- α receptor analog, for the treatment of rheumatoid arthritis. Pancytopenia resolved within 3 wk of discontinuing etanercept. To our knowledge, this is the first report of aplastic anemia associated with TNF- α blockade.

**John Kuruvilla¹, Heather A. Leitch¹,
Linda M. Vickars¹, Paul F.
Galbraith¹, Charles H. Li¹, Saad
Al-Saab², Sheldon C. Naiman³**

¹Divisions of Hematology; ²Internal Medicine;

³Laboratory Medicine, St Paul's Hospital, University of British Columbia, Vancouver, BC, Canada

Key words: aplastic anemia; etanercept; tumor necrosis factor- α inhibition

Correspondence: Dr Sheldon C. Naiman, Division of Laboratory Medicine, St Paul's Hospital, 1081 Burrard St, Vancouver BC V6Z 1Y6, Canada
Tel: +604-682-2344
Fax: +604-806-8158
e-mail: snaiman@providencehealth.bc.ca

Accepted for publication 30 May 2003

**EMOPOIESI
NORMALE**

**DISPLASIE
SECONDARIE
REVERSIBILI**

**LE SINDROMI
MIELODISPLASTICHE**

**CITOPENIE
AUTOIMMUNI**

**APLASIE
MIDOLLARI**

**SINDROMI
MIELOPROLIFERATIVE
CRONICHE**

**LEUCEMIE
ACUTE
MIELOIDI**



Studio AMIL

- 1019 pazienti di cui il 21,91% anemici (22,16% donne, 21,61 uomini)
- Anemici anno 8827
- Anemie iporigenerative 791 (77,62%)
- Età media: 75 aa uomini 77 aa donne
- Tra le anemie iporigenerative 36 (4,55%) erano sindromi mielodisplastiche

Risk factors for MDS

Table 1 Risk Factors for Developing Myelodysplastic Syndromes

Risk Factor	Relative Impact
Advanced age	+++++
Exposure to chemotherapy or radiation therapy for another cancer	++++
Male gender	+++
White race	+++
Occupational/environmental exposure to organic solvents	+++
Smoking	++
Agricultural chemicals, pesticides, other solvents	+



SMD

- Gruppo eterogeneo di patologie della cellula staminale totipotente
- Variabile % di trasformazione leucemica
- Difetto mono-bi o trilineare
- Carattere comune: produzione inefficace di cellule nel sangue

Incidenza Di Sindromi Mielodisplastiche

- 0,5 /100000 nei pazienti con < di 50 aa
- 5,3/100000 " " " < di 60 aa
- 15 /100000 " " " < di 70 aa
- 49 /100000 " " " < di 75 aa
- 89 / 100000 " " " > di 81 aa



WHO Classification and Criteria for the Myelodysplastic Syndromes.*

Disease	Blood Findings	Bone Marrow Findings
Refractory anemia	Anemia, no or rare blasts	Erythroid dysplasia alone, <5% blasts, <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts	Anemia, no blasts	Erythroid dysplasia alone, <5% blasts, ≥15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia	Cytopenias (bicytopenia or pancytopenia), no or rare blasts, no Auer rods, <1 billion monocytes per liter	Dysplasia in ≥10% of cells in ≥2 myeloid cell lines, <5% blasts, no Auer rods, <15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts	Cytopenias (bicytopenia or pancytopenia), no or rare blasts, no Auer rods, <1 billion monocytes per liter	Dysplasia in ≥10% of cells in ≥2 myeloid cell lines, <5% blasts, no Auer rods, ≥15% ringed sideroblasts
Refractory anemia with excess blasts, type 1	Cytopenias, <5% blasts, no Auer rods, <1 billion monocytes per liter	Unilineage or multilineage dysplasia, 5–9% blasts, no Auer rods
Refractory anemia with excess blasts, type 2	Cytopenias, 5–19% blasts, occasional Auer rods, <1 billion monocytes per liter	Unilineage or multilineage dysplasia, 10–19% blasts, occasional Auer rods
Myelodysplastic syndrome, unclassified	Cytopenias, no or rare blasts, no Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes, <5% blasts, no Auer rods
Myelodysplastic syndrome associated with isolated del(5q)	Anemia, <5% blasts, platelet count normal to increased	Normal-to-increased megakaryocytes with hypolobated nuclei, <5% blasts, no Auer rods, isolated del(5q)

* Information is from Vardiman et al.²

Le SMD in Medicina Interna

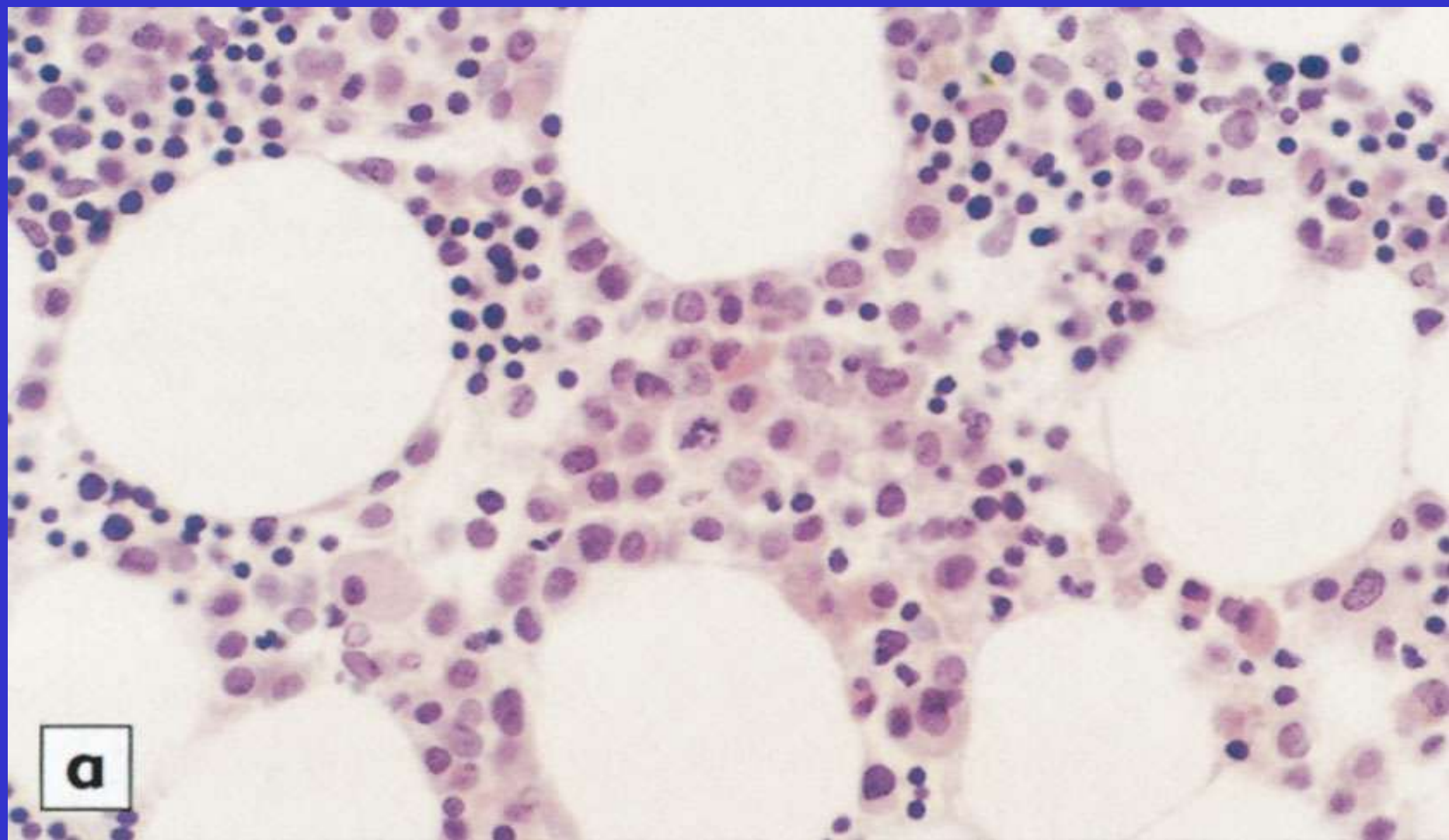
- L'età media dei pazienti in Medicina Interna è di circa 75 anni
- Essendo le SMD patologia che aumenta con l'età, sono di frequente riscontro nelle nostre Divisioni
- La diagnosi si pone se si pensa al problema



Quando sospettare una SMD

- Tutte le volte che ci si trova di fronte ad una anemia non altrimenti spiegabile
- A maggior ragione se
 - 1- normo e macrocitica
 - 2- reticolociti bassi
 - 3- monocitosi
- si deve pensare al sospetto di **Sindrome Mielodisplastica.**





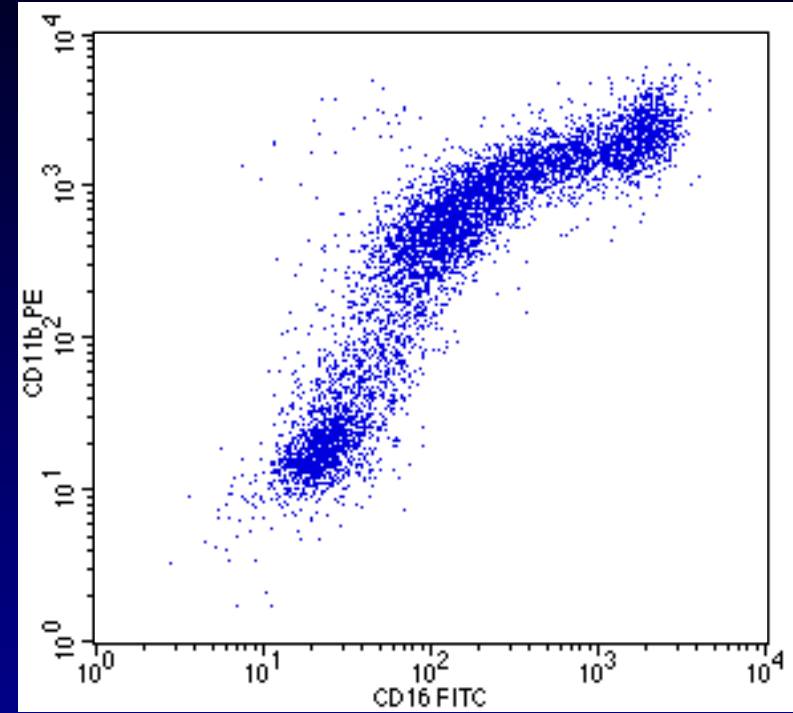
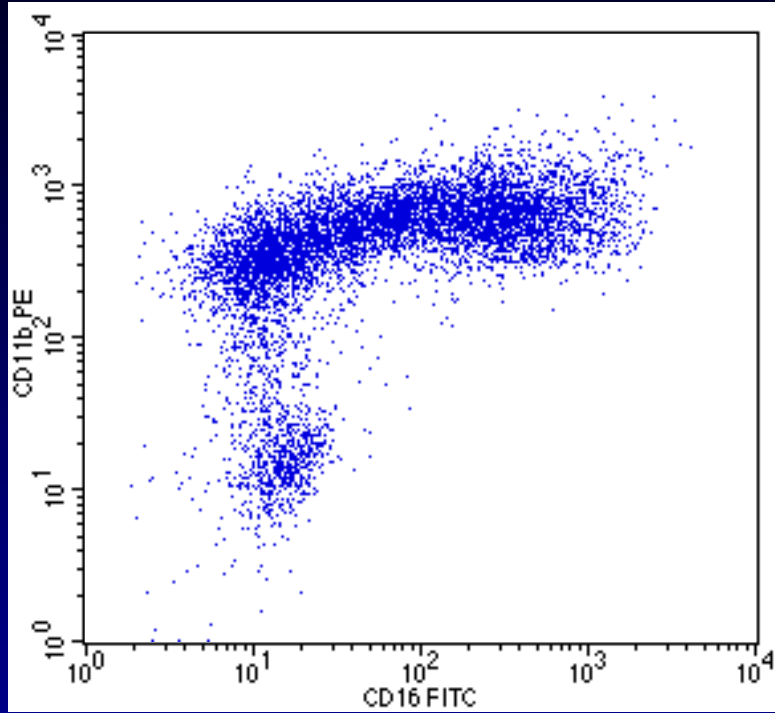
Anomalia di distribuzione dei Granuloblasti Immaturi (ALIP)
differenzia la Sindrome Mielodisplastica da una anemia
secondaria

Profilo a L rovesciata

normale

MDS

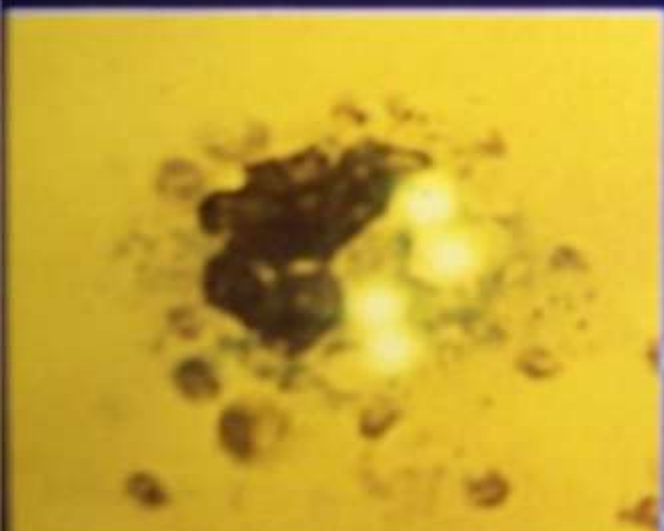
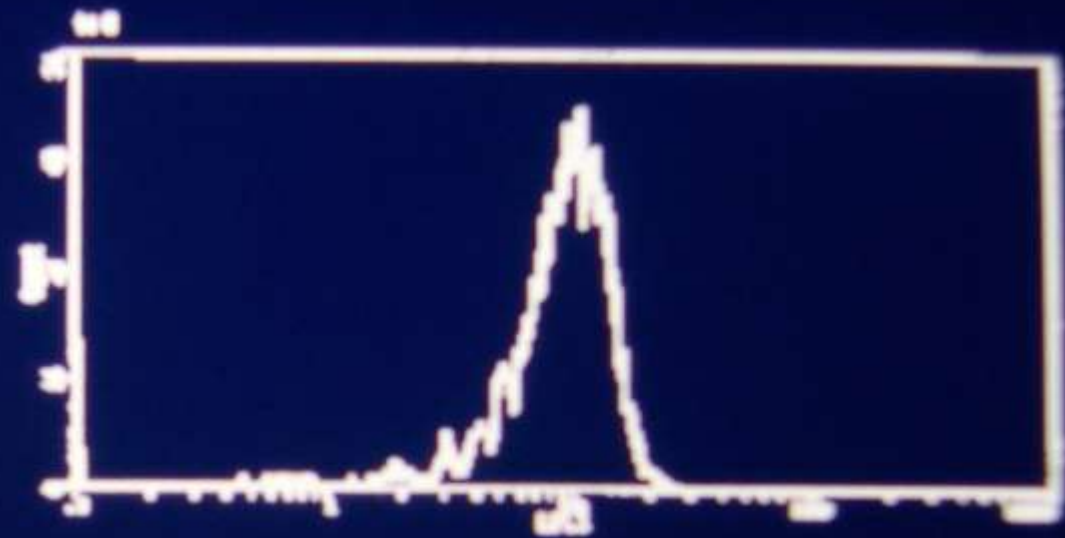
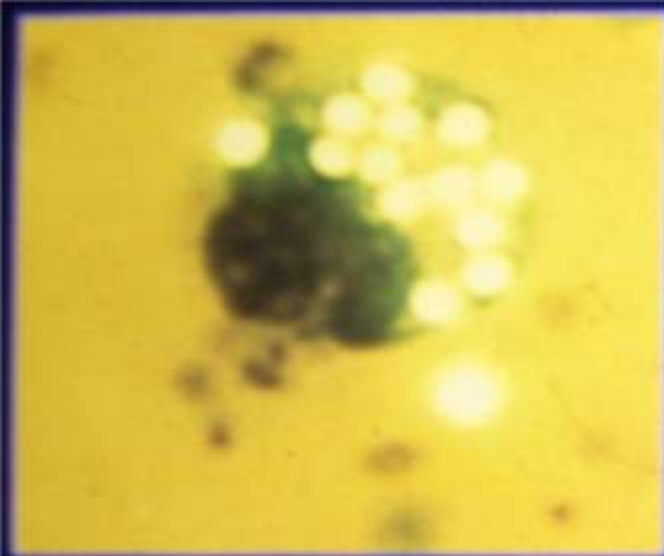
CD11b



CD16

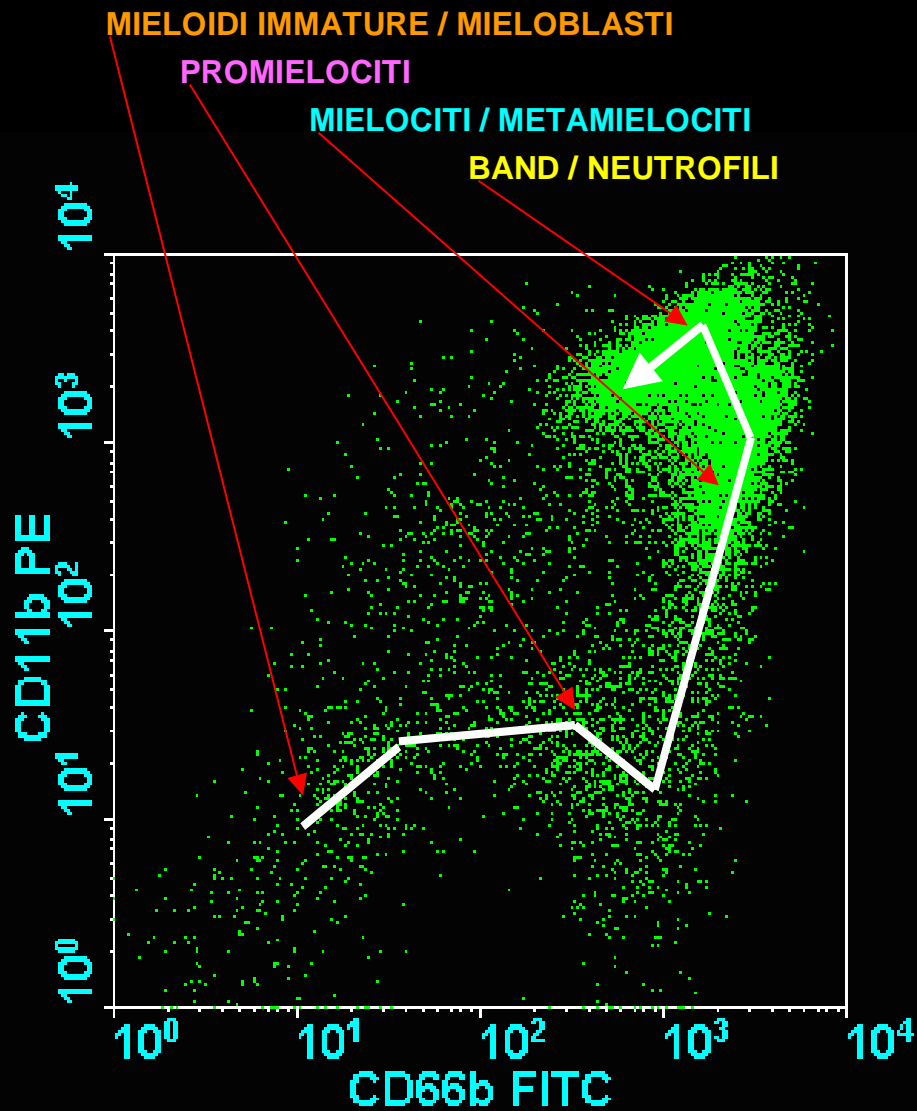


Mazzone A et al. The CD11b/CD18 granulocyte Adhesion Molecules in Myelodysplastic Syndromes. Br J Haematology, 1993;83:245-252

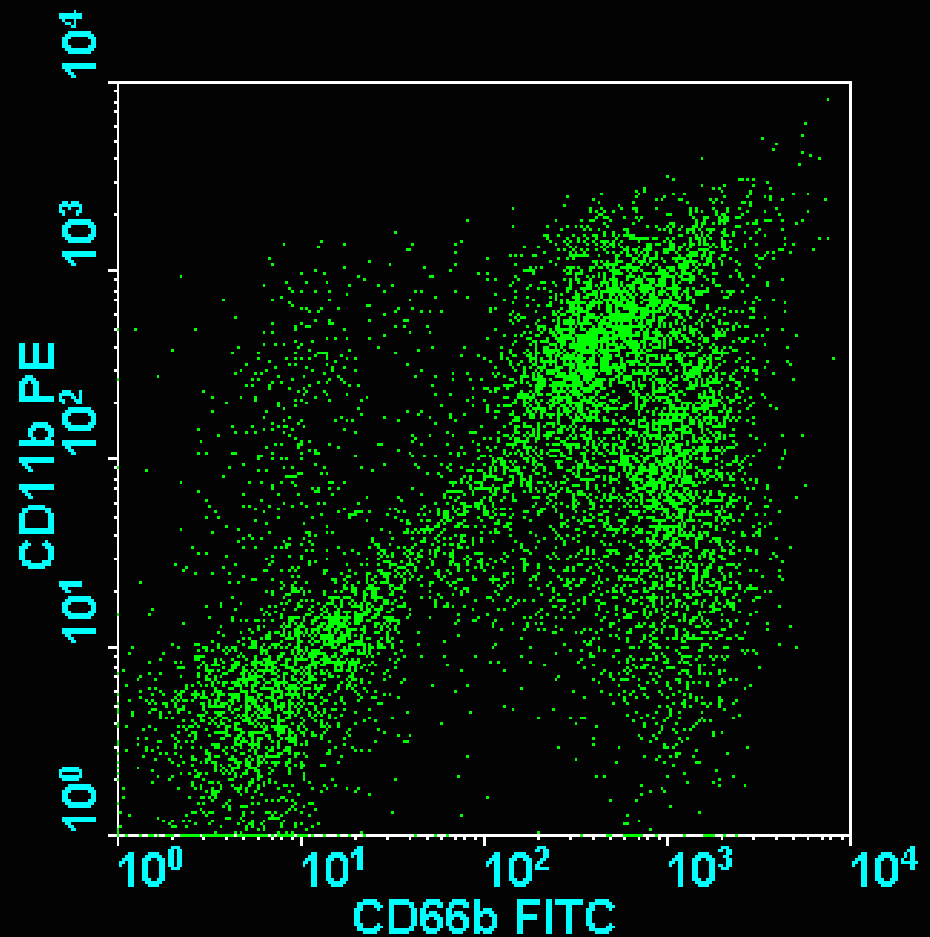


Mazzone A et al. The role of integrins in granulocyte dysfunction in myelodysplastic syndrome. Leukemia Research 1993;17:609-619

CD66b/CD11b profilo normale a “gamberetto”



Midollo normale



AREB-1

Citofluorimetria MIDOLLO

RUOLO DEL CD34+ E PROGNOSI

Ribeiro E et al. Flow cytometric analysis of the expression of Fas/Fasl in bone marrow CD34+ cells in myelodysplastic syndromes: relation to disease progression, Leuk lymphoma 2004;45:309-13.

Prognostic value of circulating CD34+ cells in myelodysplastic syndromes.

*Cesana C, Klersy C, Brando B, Nosari A, Scarpati B, Scampini L, Molteni A, Nador G, Santoleri L, Formenti M, Valentini M, Mazzone A, Morra E, Cairoli R.
Leuk Res. 2008 Nov;32(11):1715-23.*



IMPORTANZA CLINICA DELLA ANALISI CITOGENETICA

Sindrome da Monosomia 7 (-7; 7q)

5% delle Sindromi Mielodisplastiche

Prognosi Severa

Trasformazione leucemica

I difetti della funzione dei granulociti che facilitano le infezioni batteriche.

Mazzone A. et al. Presence of monoclonal-antibody -defined protein complex on human granulocytes in dysmyelopoietic syndromes with monosomy 7 and altered chemotaxis. Med Sci Res.1987;15:1035-1036.

Da Internisti considerare sempre le forme rare di anemia e le associazioni con altre patologie



**Pseudo
Pelger**

Mazzone A et al. Neutrophil Defects are a prognostic factor in Myelodysplastic Syndromes. Haematologica 1988;73:293-6.

The del 5q story so far

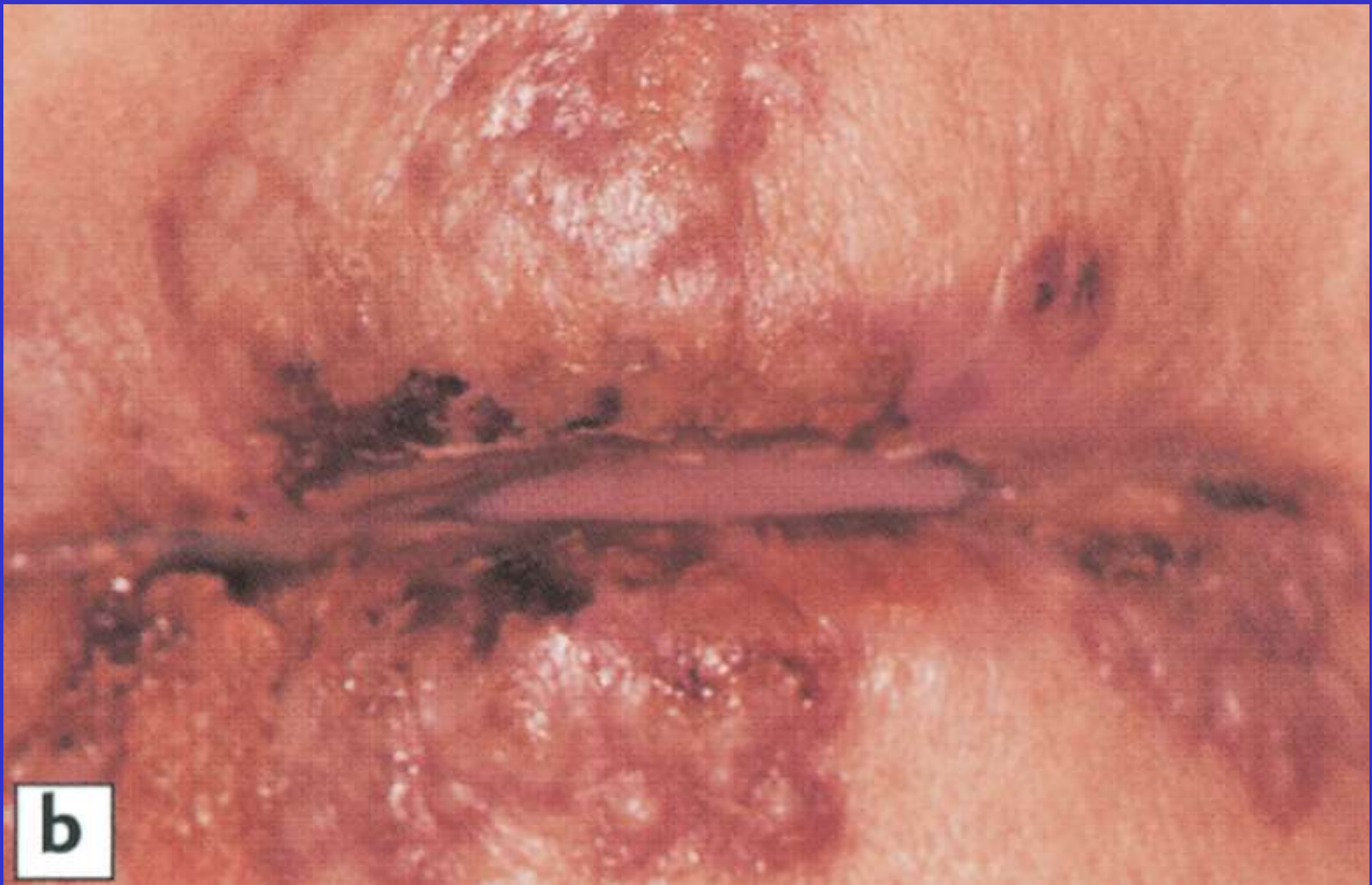
- Cytogenetics of MDS and detection of del 5q-.
- >50% of MDS patients have a clonal cytogenetic abnormality at presentation
- Partial or complete deletion of 5q is the commonest identified abnormality in de-novo MDS (10-15%)
- There is a hierarchy of prognosis relating to del 5q: Isolated 5q- / < 5% blasts >> additional cytogenetic abnormalities & increased blasts



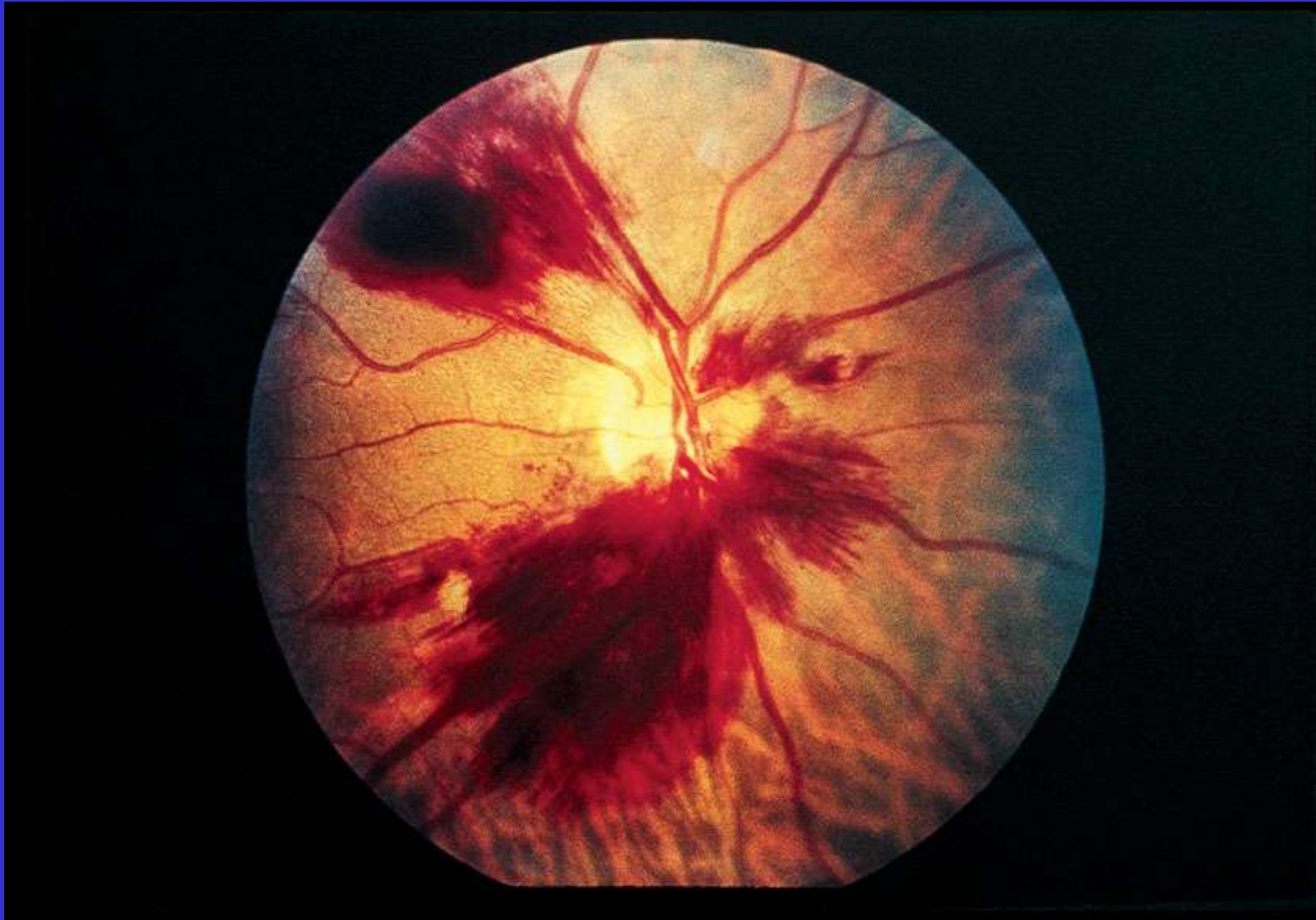
**INFEZIONE CONGIUNTIVALE E FLEMMONE
CUTANEO PERIORBITARIO IN SMD DI ANNI 76**



INFEZIONE ERPETICA IN SMD



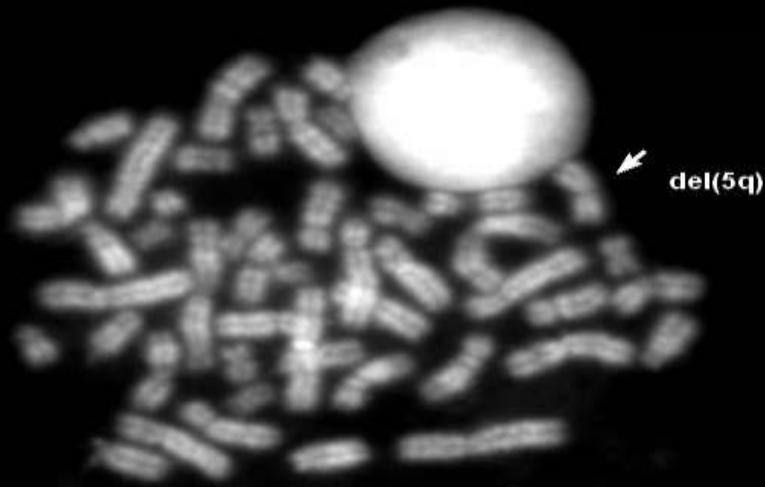
INFEZIONE VIRALE E BATTERICA IN SMD



EMORRAGIA RETINICA IN PIASTRINOPENIA DA
SMD

Giagoudinis AA et al. Autoimmune disorders in two patients with Myelodysplastic Syndrome and 5q deletion. Acta Haematol 2005;113:146-9.

Caratteristica AR con Anemia e Trombocitosi

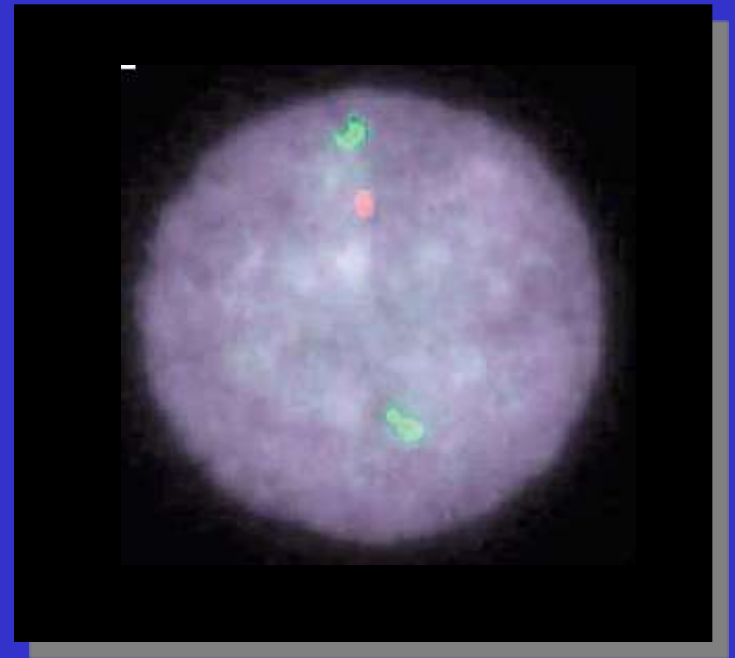
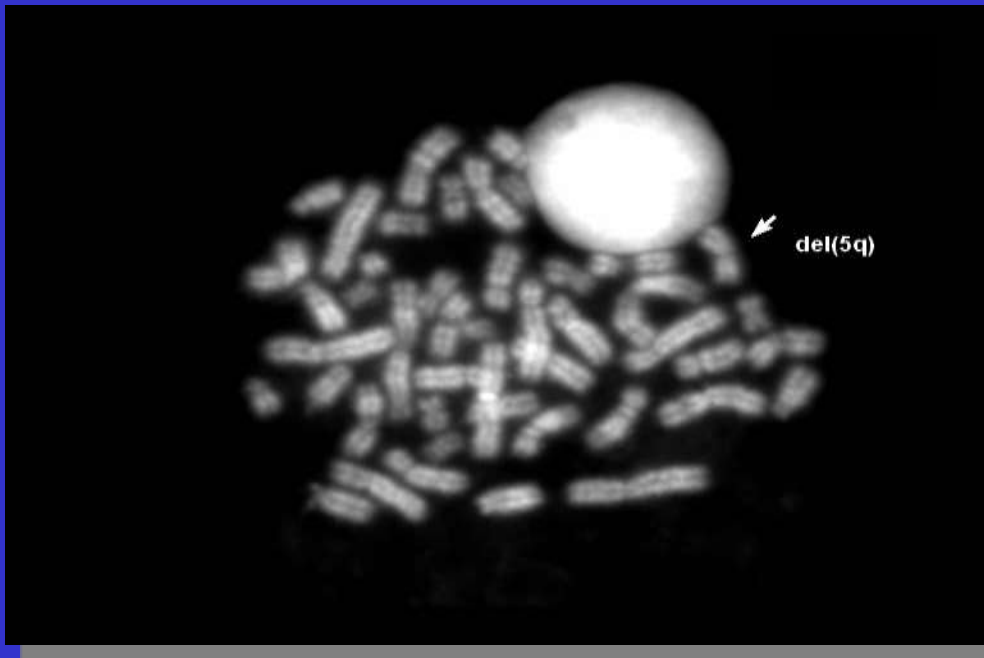


V.I. 76 AR + SMD Delezione 5q.



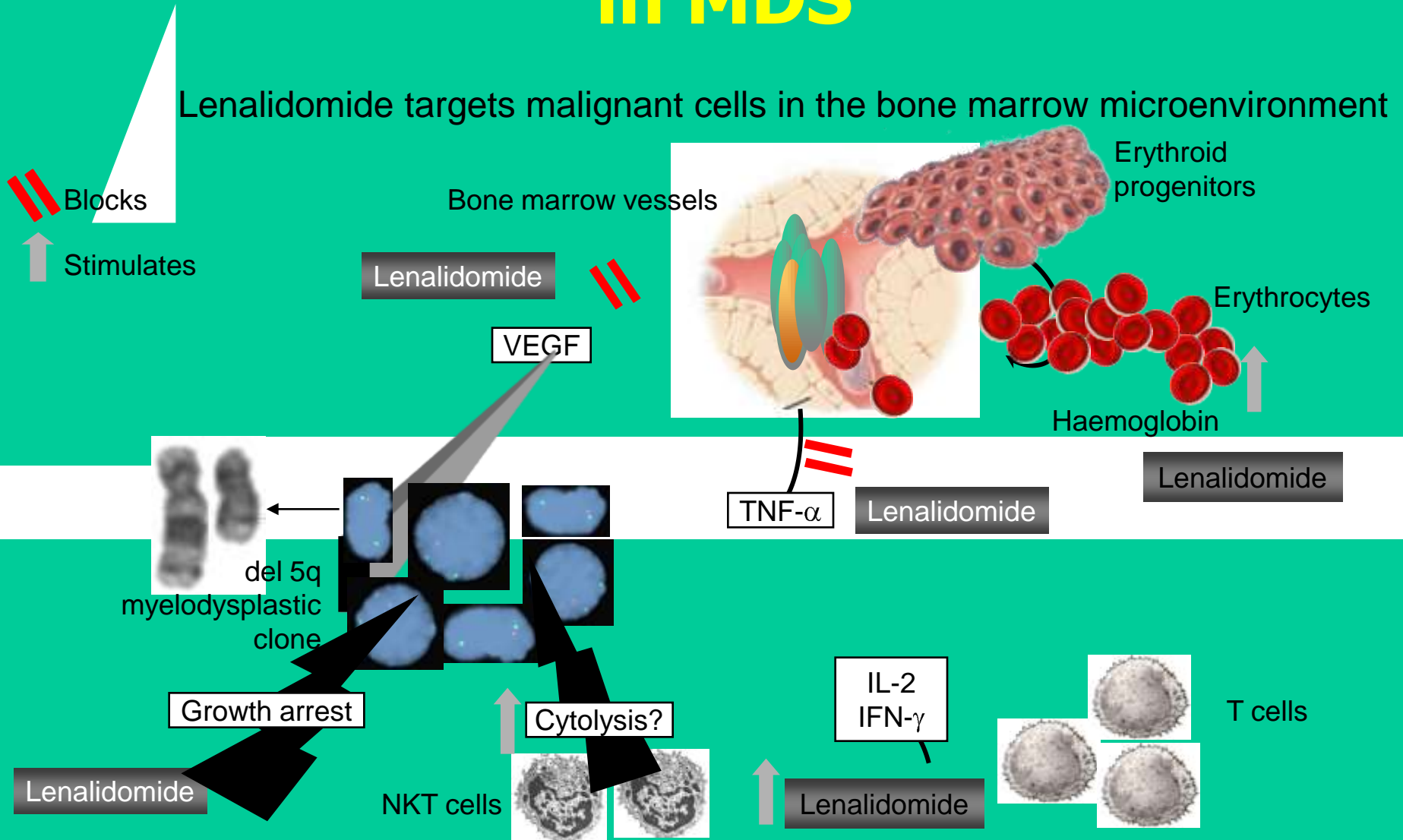
Caso clinico 2

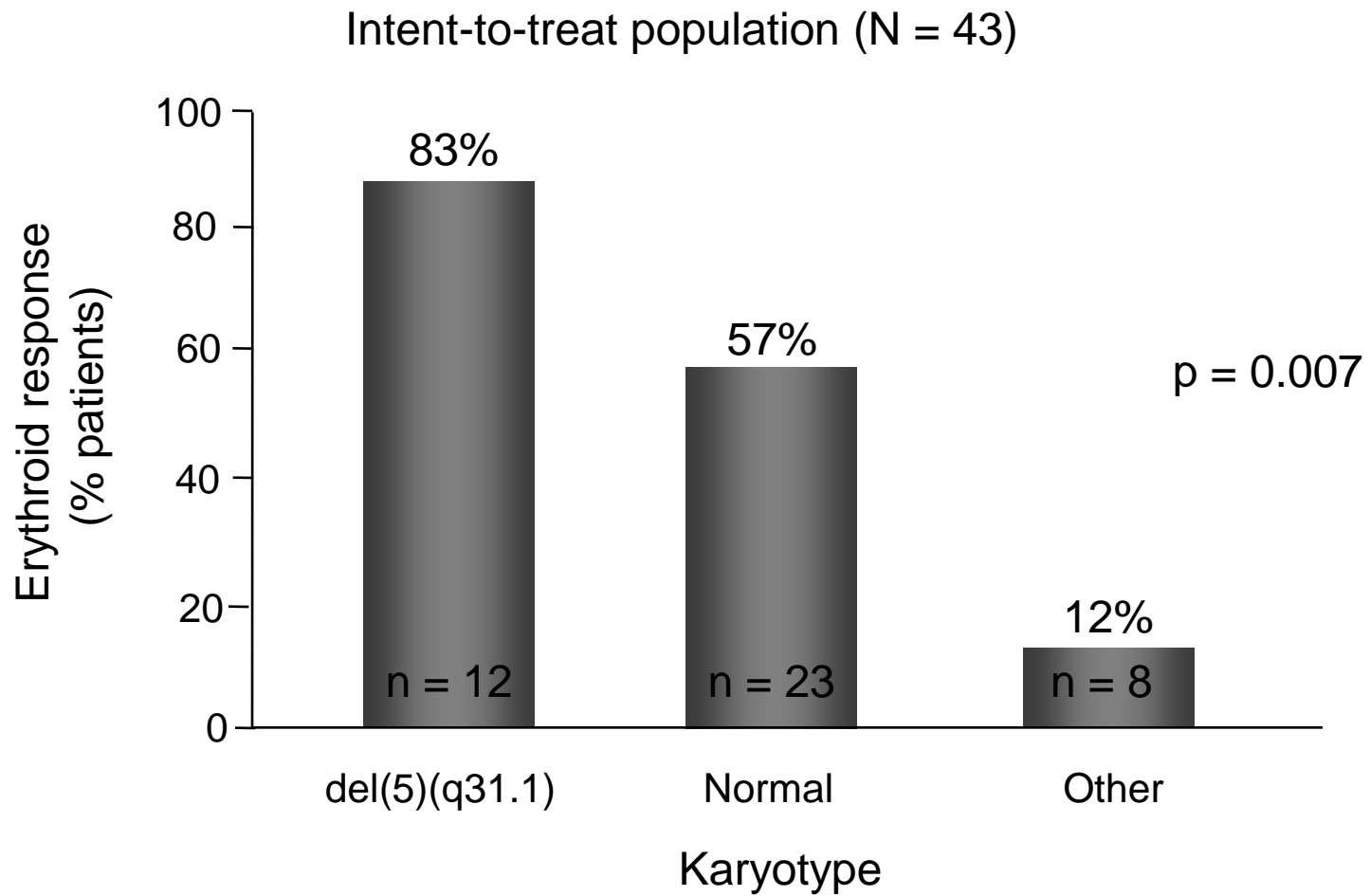
- Citogenetica: 46,XX,del(5)(q22q35)[5 metafasi]/46,XX,[15 metafasi]



Modes of action of lenalidomide in MDS

Lenalidomide targets malignant cells in the bone marrow microenvironment



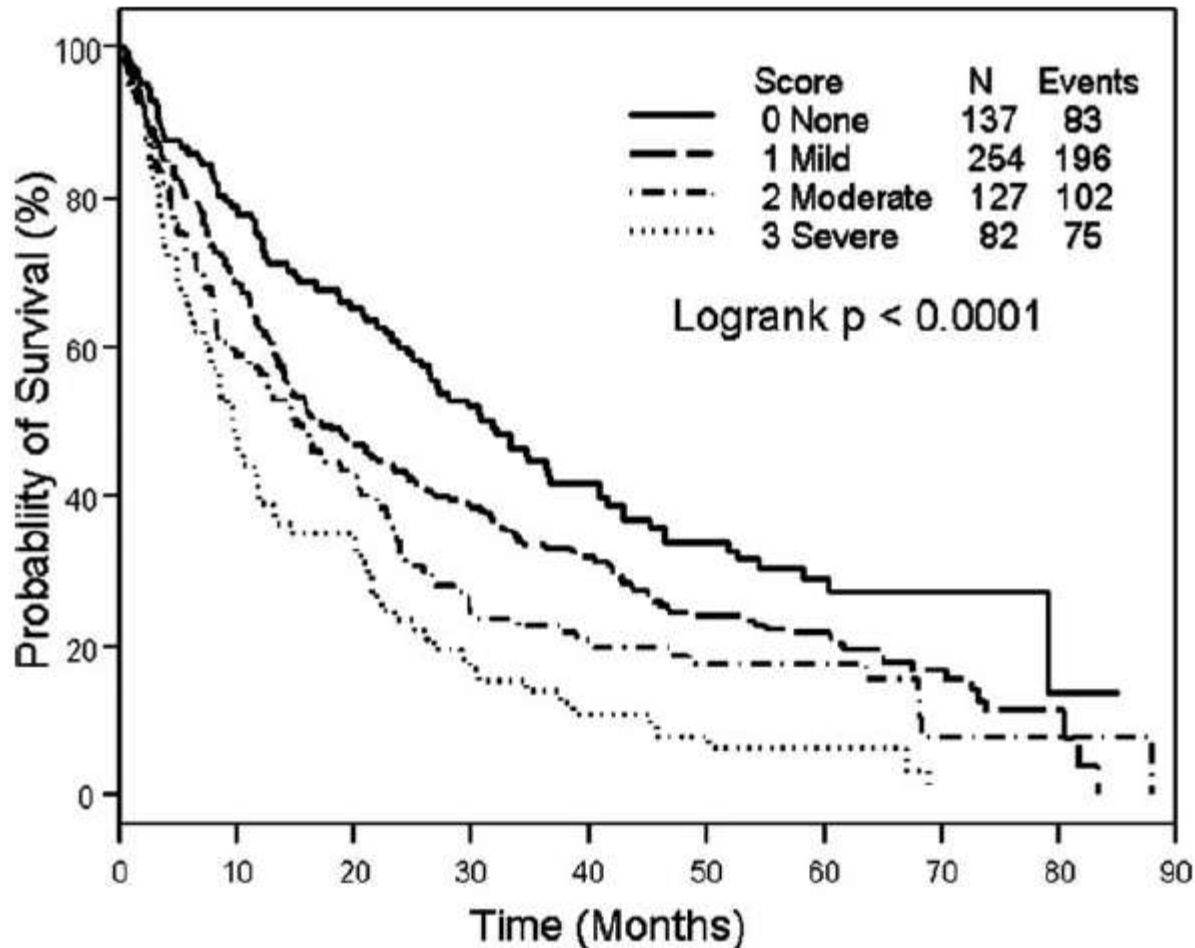


CLASSI DI GRAVITA' IPSS

Rischio	Punteggio	Sopravvivenza (anni)
BASSO	0	5,7
INTERMEDIO 1	0,5 – 1	3,5
INTERMEDIO 2	1,5 – 2	1,2
ALTO	> 2,5	0,4

Effect of comorbidity on survival of MDS patients

Comorbidity ACE-27 score



**Sindrome mielodisplastica
Età > 65 anni**

Valutazione complessiva:
sintomi, performance status, qualità di vita, comorbidità

IPSS basso-intermedio 1

IPSS intermedio 2-elevato

Sindrome 5q-

Ipocellularità

Anemia refrattaria
Eritropoietina
< 250 mU/mL
Basso fabbisogno
trasfusionale

ARS
RCMD
Alto fabbisogno
trasfusionale

Agenti
ipometilanti
As

s LMA:
chemio LMA like

Lenalidomide

ATG, CyA

Eritropoietina

Eritropoietina,
fattori di crescita
granulocitari

Assenza di risposta

Assenza di risposta

+ Talidomide

Assenza di risposta

Trasfusioni
+ terapia ferrochelante

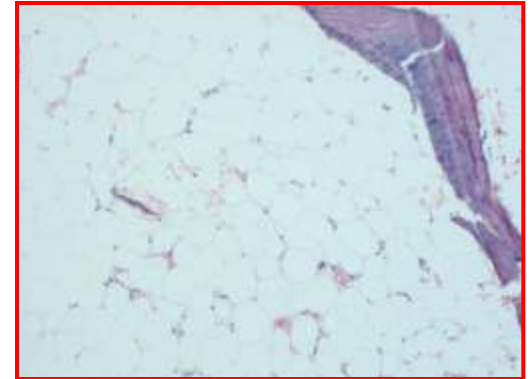
PNH – Clinical Features



Haemolytic anaemia
Haemoglobinuria



Thrombosis
Budd-Chiari

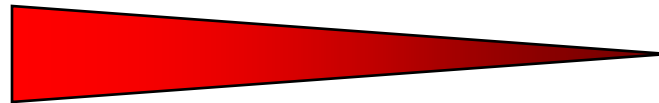


Bone Marrow Failure
Aplastic anaemia

Wide spectrum of presentations and clinical disease courses

Haemolysis ±
Thrombosis

Large PNH clones



Aplastic anaemia
minimal haemolysis

Small PNH clones

Historical Classification of PNH

- Stem cell disorder/molecular mutation

Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 3193
© 2009 American Society of Hematology

Poster Session

BONE MARROW FAILURE POSTER II

Co-Existence of *JAK^{V617F}* and *PIG-A* mutations in Primary Budd-Chiari Syndrome.

Chiharu Sugimori, MD^{*1}, Kenneth H Shain, MD, PhD²,
Gisela Caceres, PhD^{*3}, Lubomir Sokol, MD, PhD³,
David Araten, MD⁴, Jaroslaw P. Maciejewski, MD, PhD⁵,
JianXiang Zou, MD^{*6}, P.K. Epling-Burnette, PhD⁷ and
Alan F List, MD³

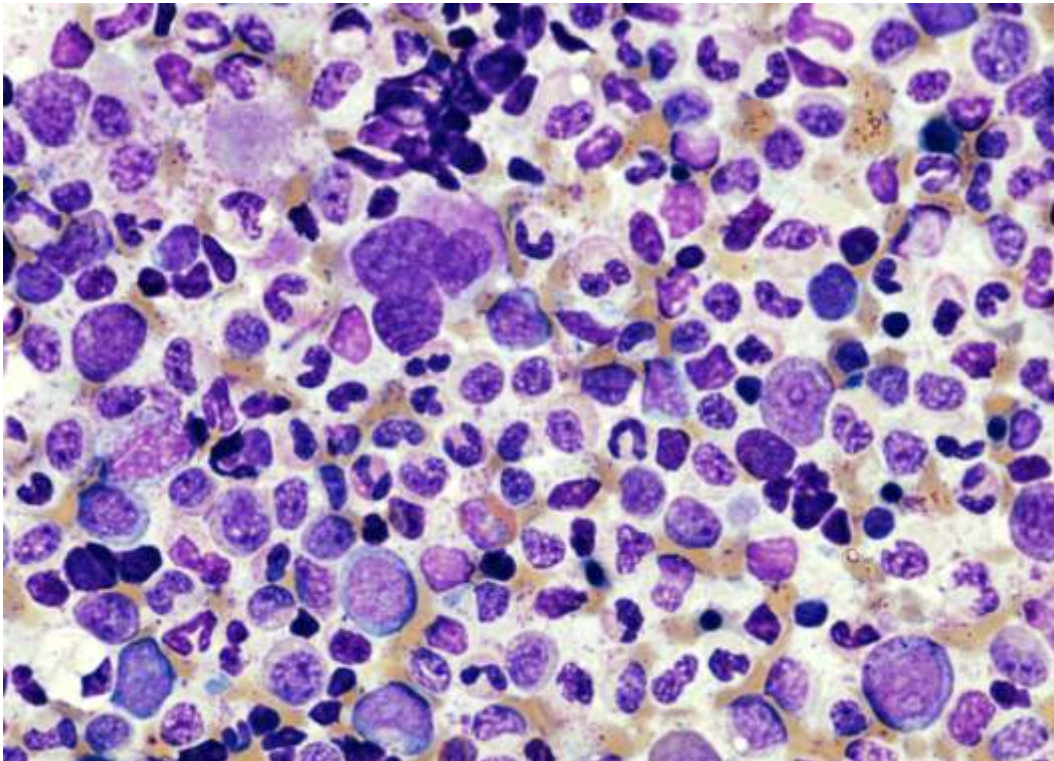
Detection of paroxysmal nocturnal hemoglobinuria clones in patients with myelodysplastic syndromes and related bone marrow diseases, with emphasis on diagnostic pitfalls and caveats

Sa A. Wang,^{1,4} Olga Pozdnyakova,² Jeffrey L. Jorgensen,² L. Jeffrey Medeiros,¹ Dariusz Stachurski,³ Mary Anderson,⁴ Azra Raza,⁵ and Bruce A. Woda⁴

¹Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX; ²Department of Pathology, Brigham and Women Hospital, Harvard Medical School, Boston, MA; ³Department of Pathology, Rhode Island Hospital, Brown University, Providence, RI; ⁴Department of Pathology, UMass Memorial Medical Center, University of Massachusetts School of Medicine, Worcester, MA. and ⁵MDS Program, St. Vincent's Comprehensive Cancer Center, New York, NY, USA

PMF IN LEUKEMIC TRANSFORMATION?

BONE MARROW ASPIRATE



MYELOID HYPERPLASIA

BLASTS <5%

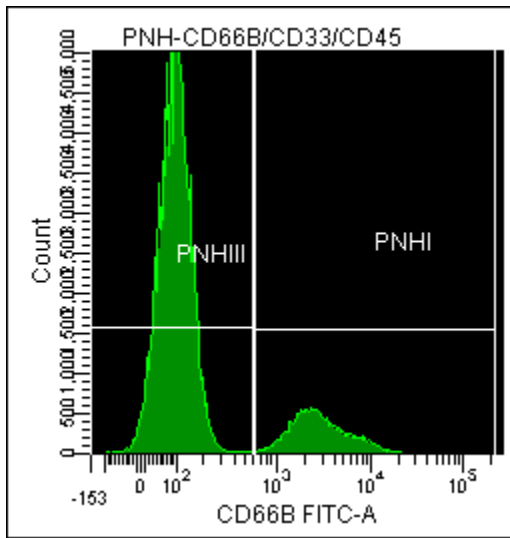
ERYTHROID HYPOPLASIA

ABNORMAL MEGAKARYOCYTES

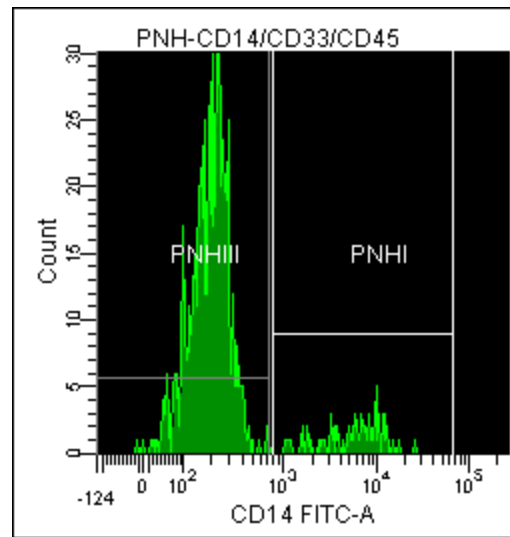
PNH?

PERIPHERAL BLOOD

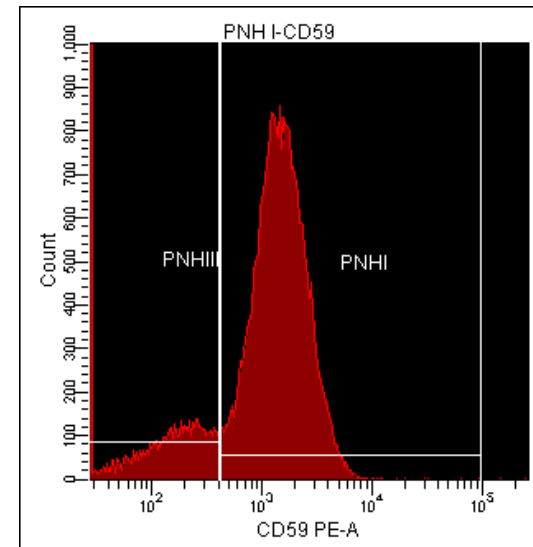
GRANULOCYTES



MONOCYTES



ERYTHROCYTES



Experiment Name: SAMPLE PNH

Population	#Events	%Parent
R2	137,194	82.9
PNHIII	143,935	87.0
PNHI	21,480	13.0

Experiment Name: SAMPLE PNH

Population	Parent Name	#Events	%Parent
PNHIII	P2	674	89.0
PNHI	P2	83	11.0

Experiment Name: SAMPLE PNH

Population	#Events	%Parent
PNHI	30,622	77.9
PNHIII	8,463	21.5

Original Article

The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Neal S. Young, M.D., Jörg Schubert, M.D., Robert A. Brodsky, M.D., Gerard Socié, M.D., Ph.D., Petra Muus, M.D., Ph.D., Alexander Röth, M.D., Jeffrey Szer, M.B., B.S., Modupe O. Elebute, M.D., Ryotaro Nakamura, M.D., Paul Browne, M.B., Antonio M. Risitano, M.D., Ph.D., Anita Hill, M.B., Ch.B., Hubert Schrezenmeier, M.D., Chieh-Lin Fu, M.D., Jaroslaw Maciejewski, M.D., Ph.D., Scott A. Rollins, Ph.D., Christopher F. Mojcik, M.D., Ph.D., Russell P. Rother, Ph.D., and Lucio Luzzatto, M.D.

N Engl J Med
Volume 355(12):1233-1243
September 21, 2006

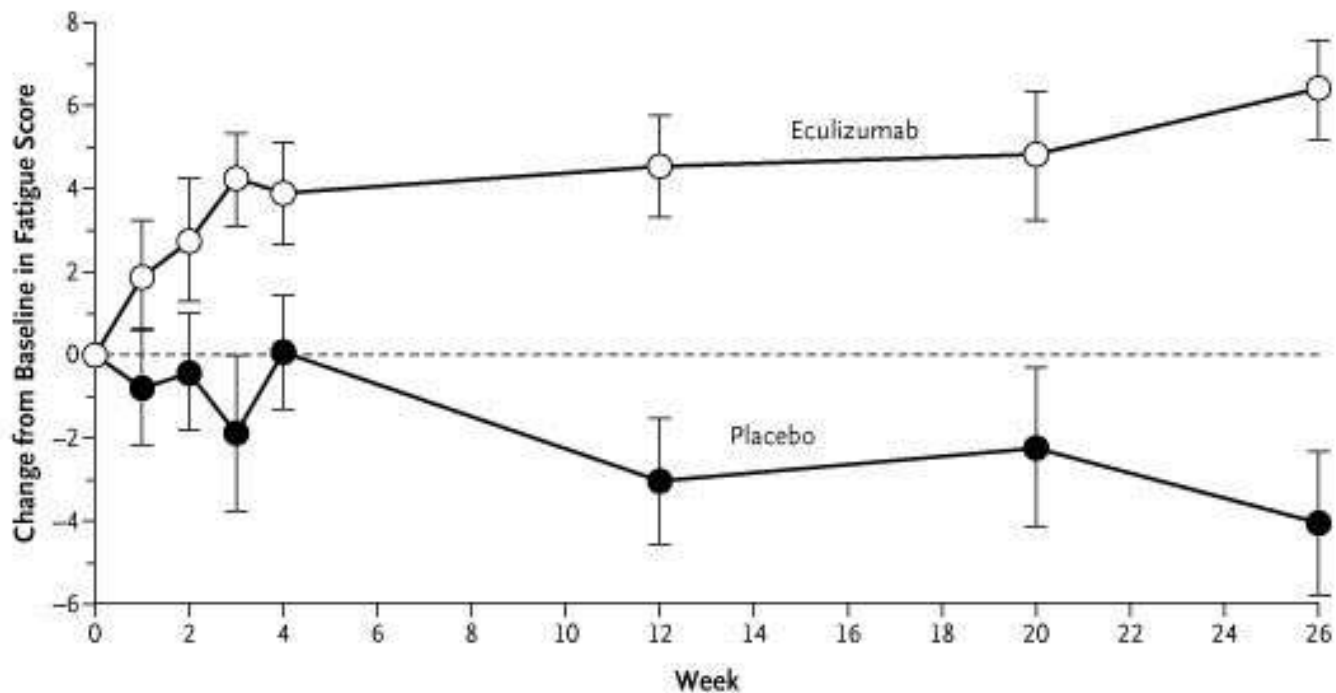


The NEW ENGLAND
JOURNAL of MEDICINE

Study Overview

- In this randomized trial, eculizumab, a humanized monoclonal antibody against C5 that inhibits terminal complement activation, was compared with placebo as a treatment for paroxysmal nocturnal hemoglobinuria
- The antibody stabilized hemoglobin levels, decreased the need for transfusions, and improved the quality of life by reducing intravascular hemolysis





No. of Patients

Placebo group	41	39	41	41	40
Eculizumab group	43	41	43	43	43

	40		36	39
	42		36	41



Mechanical Trauma

- A. Prosthetic Heart Valve
- B. Vasculitis
- C. Malignant Hypertension
- D. Eclampsia
- E. Renal graft rejection
- F. Giant Hemangioma
- G. Scleroderma
- H. Thrombotic thrombocytopenic Purpura
- I. Hemolytic Uremic Syndrome
- J. Disseminated Intravascular Coagulation (DIC)
- K. March Hemoglobinuria (Marathon runners)



ORIGINAL ARTICLE

Terminal Complement Inhibitor Eculizumab in Atypical Hemolytic–Uremic Syndrome

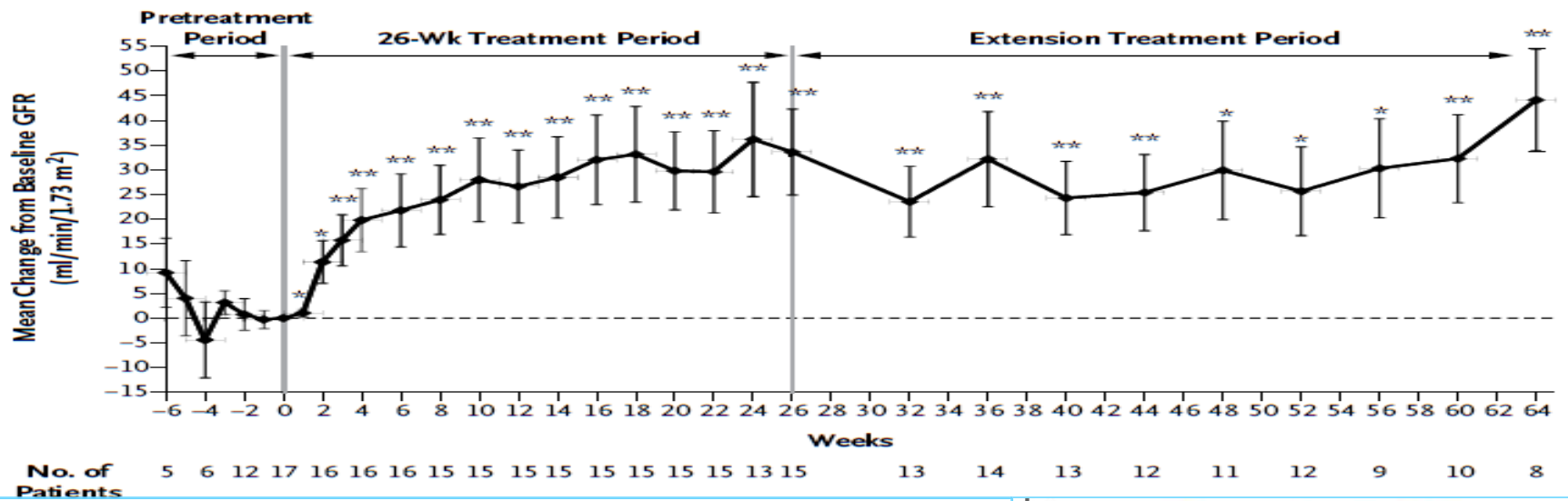
C.M. Legendre, C. Licht, P. Muus, L.A. Greenbaum, S. Babu, C. Bedrosian, C. Bingham, D.J. Cohen, Y. Delmas, K. Douglas, F. Eitner, T. Feldkamp, D. Fouque, R.R. Furman, O. Gaber, M. Herthelius, M. Hourmant, D. Karpman, Y. Lebranchu, C. Mariat, J. Menne, B. Moulin, J. Nürnberger, M. Ogawa, G. Remuzzi, T. Richard, R. Sberro-Soussan, B. Severino, N.S. Sheerin, A. Trivelli, L.B. Zimmerhackl,* T. Goodship, and C. Loirat

ABSTRACT

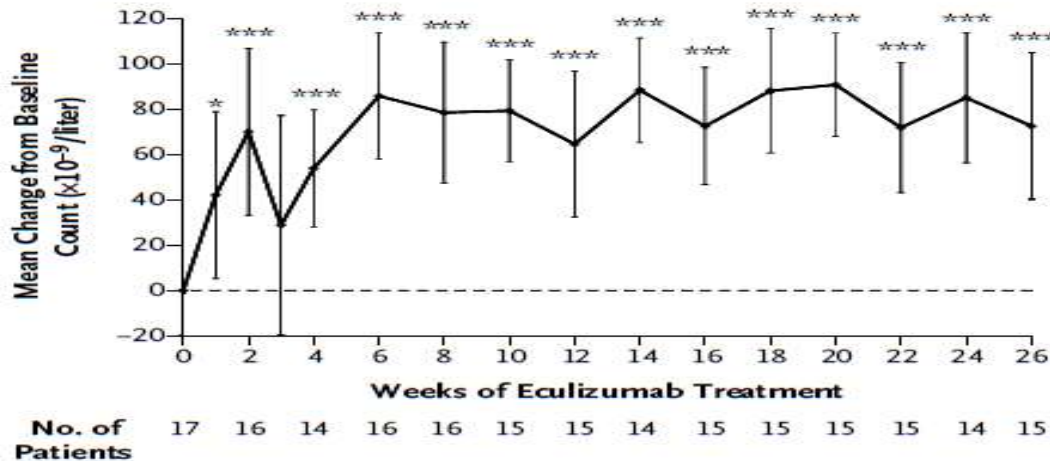
BACKGROUND

Atypical hemolytic–uremic syndrome is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy. Plasma exchange or infusion may transiently maintain normal levels of hematologic measures but does not treat the underlying systemic disease.

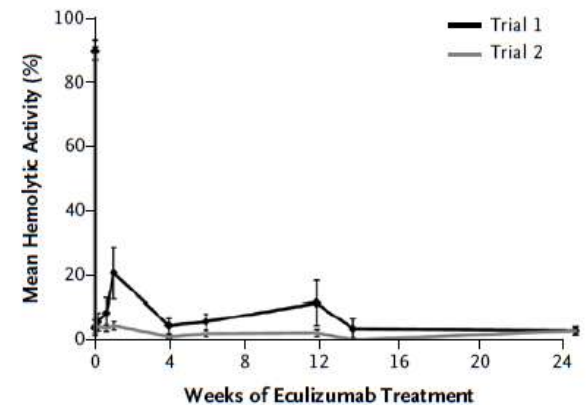
B Estimated GFR, Trial 1



A Platelet Count, Trial 1



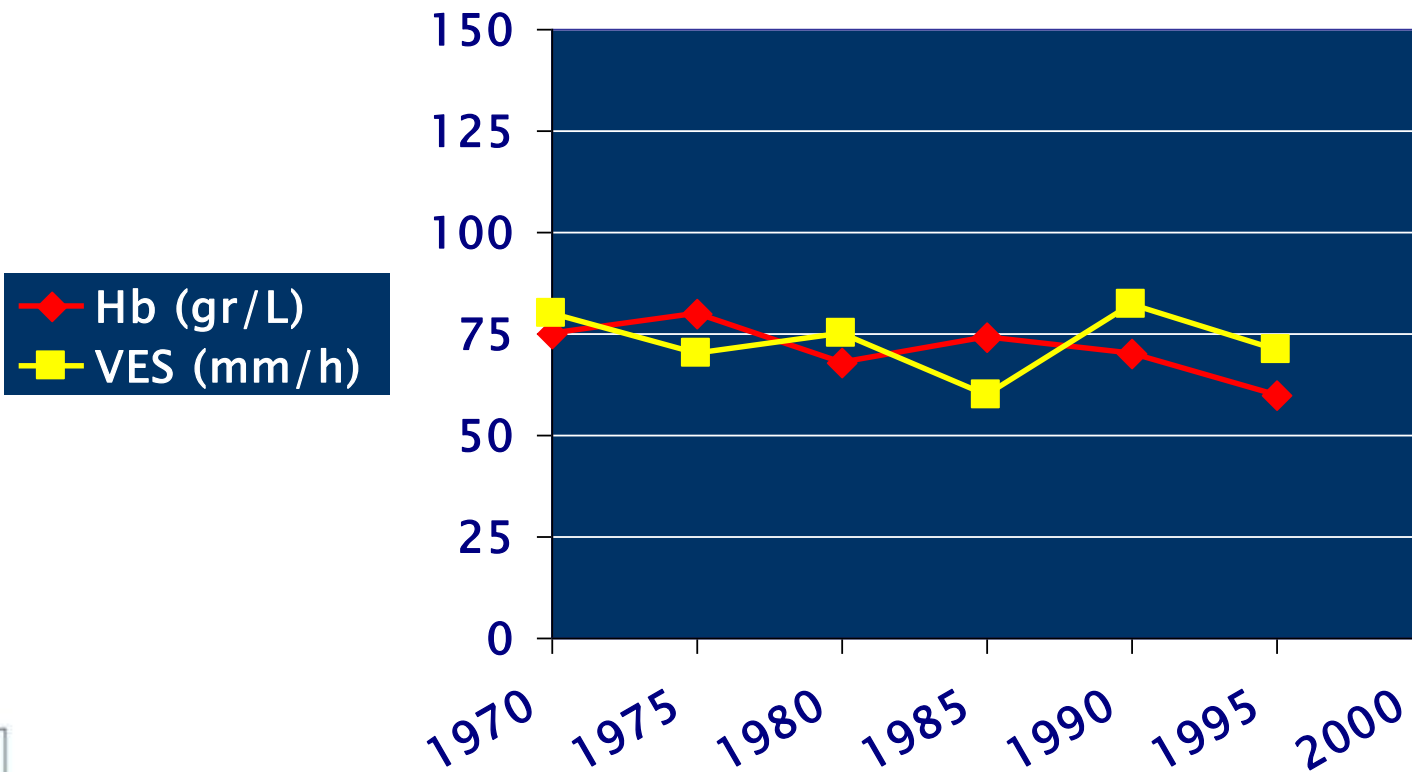
D Inhibition of Complement Activity, Trials 1 and 2



**Caterina M, donna di 56 anni, “da sempre” anemica
e con elevazione degli indici della fase acuta**



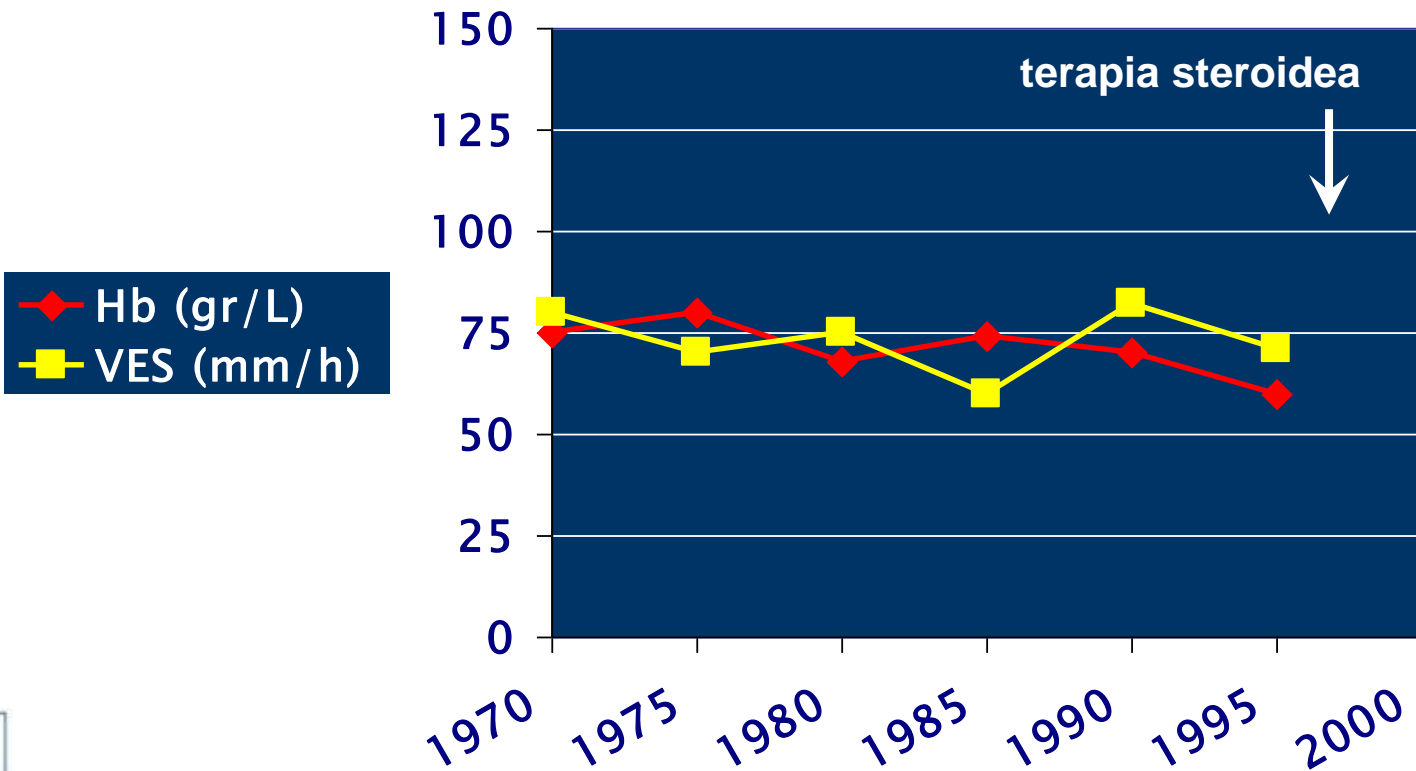
Caterina M, donna di 56 anni, “da sempre” anemica e con elevazione degli indici della fase acuta



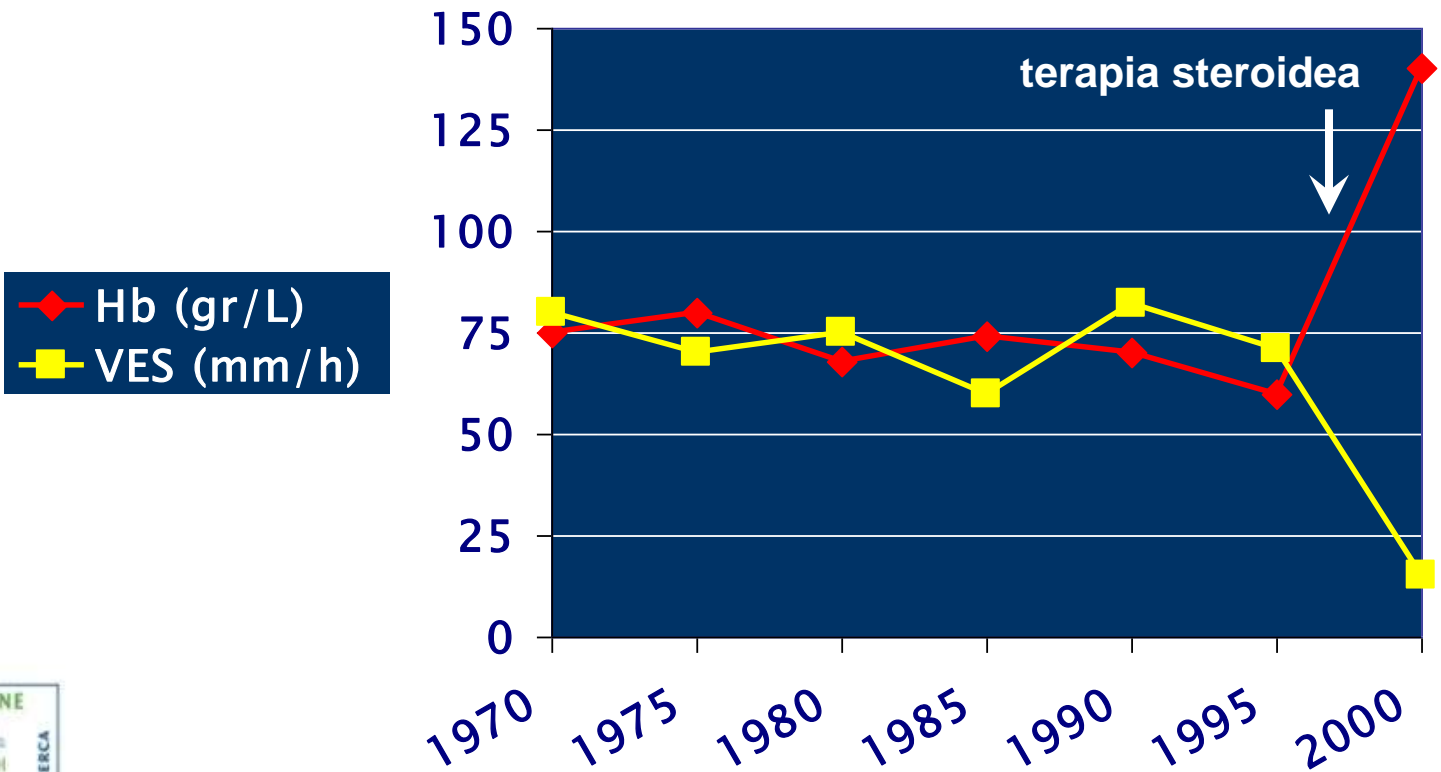
**Caterina M, donna di 56 anni, “da sempre” anemica
e con elevazione degli indici della fase acuta**



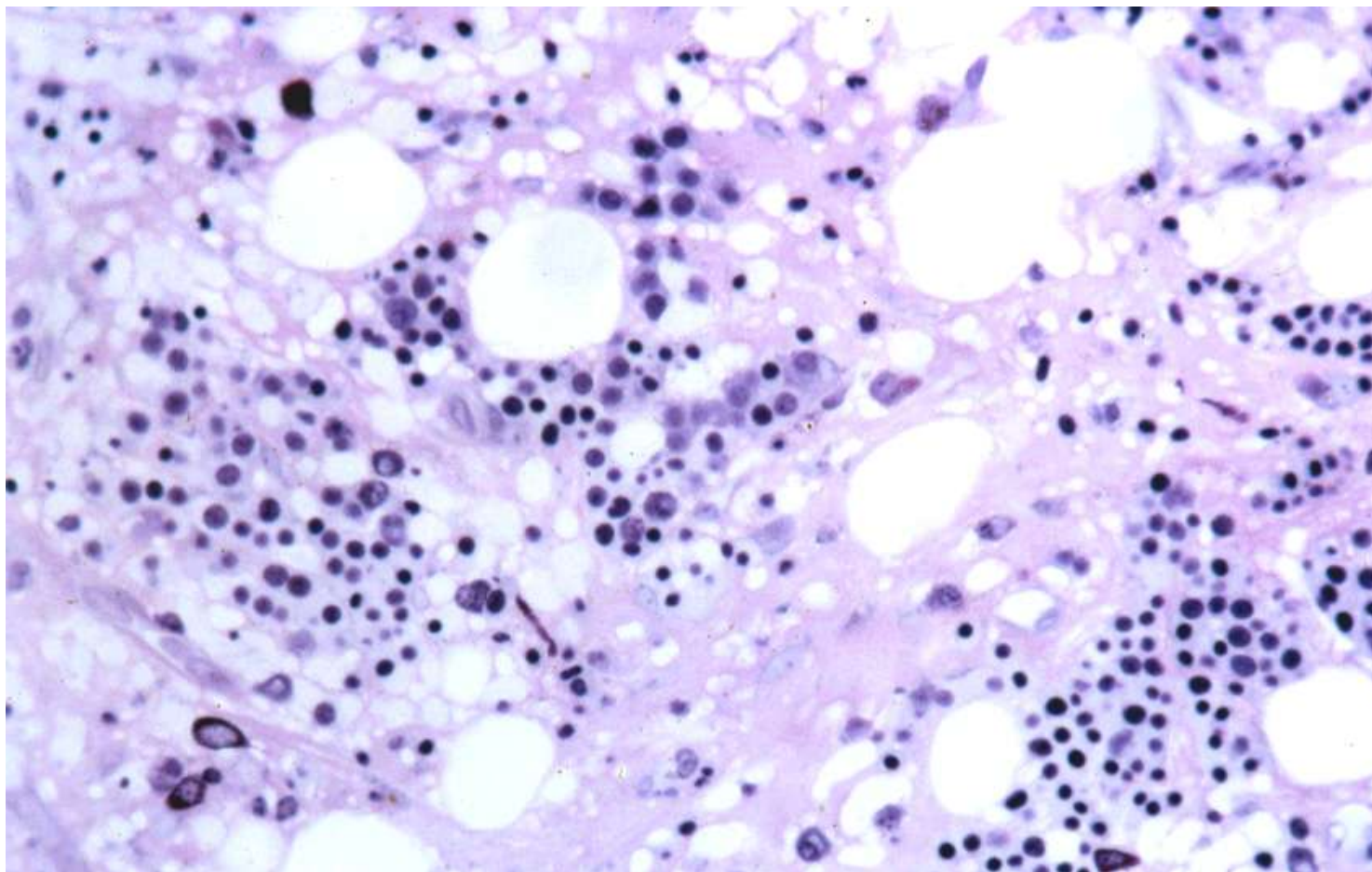
Caterina M, donna di 56 anni, "da sempre" anemica e con elevazione degli indici della fase acuta



Caterina M, donna di 56 anni, "da sempre" anemica e con elevazione degli indici della fase acuta



**Caterina M, donna di 56 anni, “da sempre” anemica
e con elevazione degli indici della fase acuta**



REVIEW

Camurati-Engelmann disease: review of the clinical, radiological, and molecular data of 24 families and implications for diagnosis and treatment

K Janssens, F Vanhoenacker, M Bonduville, L Verbruggen, L Van Maldergem, S Ralston, N Guañabens, N Migone, S Wientroub, M T Divizia, C Bergmann, C Bennett, S Simsek, S Melançon, T Cundy, W Van Hul

J Med Genet 2006;43:1–11. doi: 10.1136/jmg.2005.033522



Figure 1 Clinical picture of the patient from family 14 at the age of 15. Note the absence of subcutaneous fat (weight 27 kg), muscle hypotrophy, and vulva deformity of the lower and feet. Muscle weakness restricts her maximum walking distance to 20 to 50 m. Secondary sex characteristics (breast development, menarche) were delayed. Written permission of the patient for reproduction of this photograph was obtained.



Figure 2 Whole body bone scintigraphy of a patient from family 13 showing the characteristic distribution of the disease. Increased uptake is visible in the diaphyseal portions of the long bones of the lower, lower leg, humeri and forearms, clavicles, and frontal bones. There is also increased uptake at the parietal and occipital bones. Also note the slight valgus deformity of the knees.

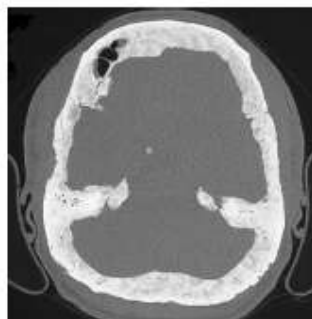


Figure 3 Axial computed tomography (bone window) of the head of a patient from family 11, showing massive sclerosis and obliteration of the calvaria and petrous bones with loss of the diploë. Note also obliteration of the left frontal sinus.



Most clinical features of CED—such as bone pain in the limbs, walking gait, and a radiolytic impairment—are secondary to the hyperostosis and sclerosis of the skeleton. However, the reduction in fat and muscle mass, observed in a significant percentage of the patients (21% and 39%, respectively, in this population), seems to be unrelated to the sclerosis of the skeleton. We sought to clarify these additional symptoms on the basis of the mutations detected. TGF β 1 is a known inhibitor of myogenesis, impairing fusion of myoblasts into myotubes and myofibers.¹⁶ Indeed, recent evidence points to a role for the TGF β pathway in suppressing the expression of two important myogenic transcription factors.¹⁷ TGF β 1 also inhibits adipogenesis,¹⁸ at least partly through the transcriptional repression of genes important in

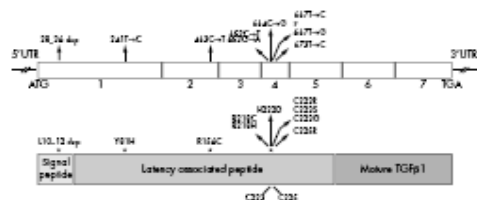


Figure 5 Position of Camurati-Engelmann disease (CED) mutations identified in TGFB1 at DNA and protein level. Numbering of the mutations starts from the ATG start codon. Numbers indicate the TGFB1 exon. TGF, transforming growth factor.

Camurati M.

*Di un raro caso di osteite simmetrica ereditaria degli arti inferiori.
Chirurgia degli Organi in Movimento 1922;6:662-5.*

Mutazione del gene TGFbeta1



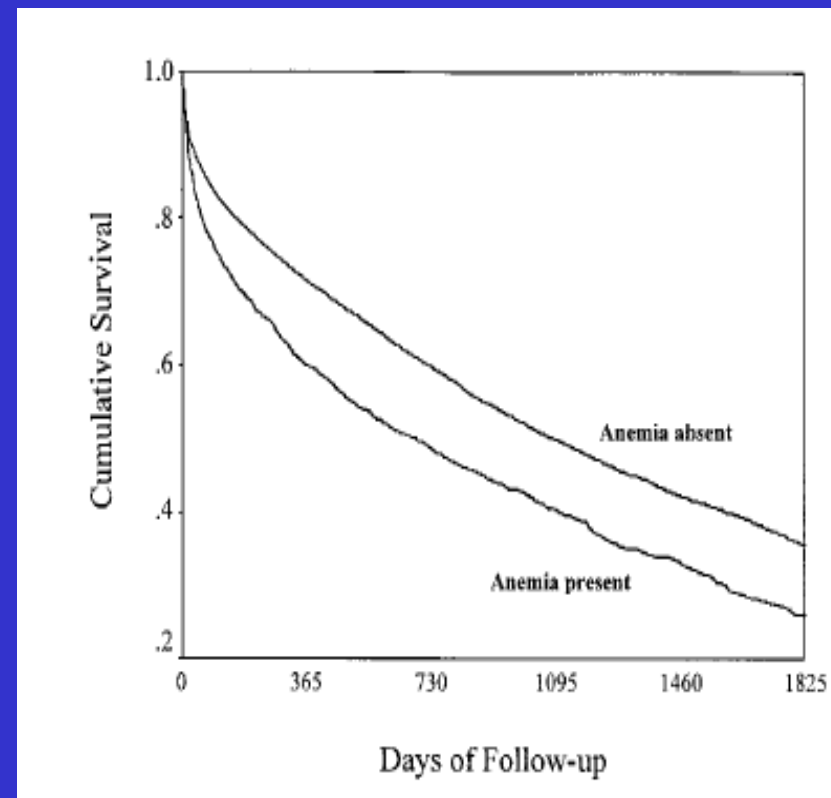
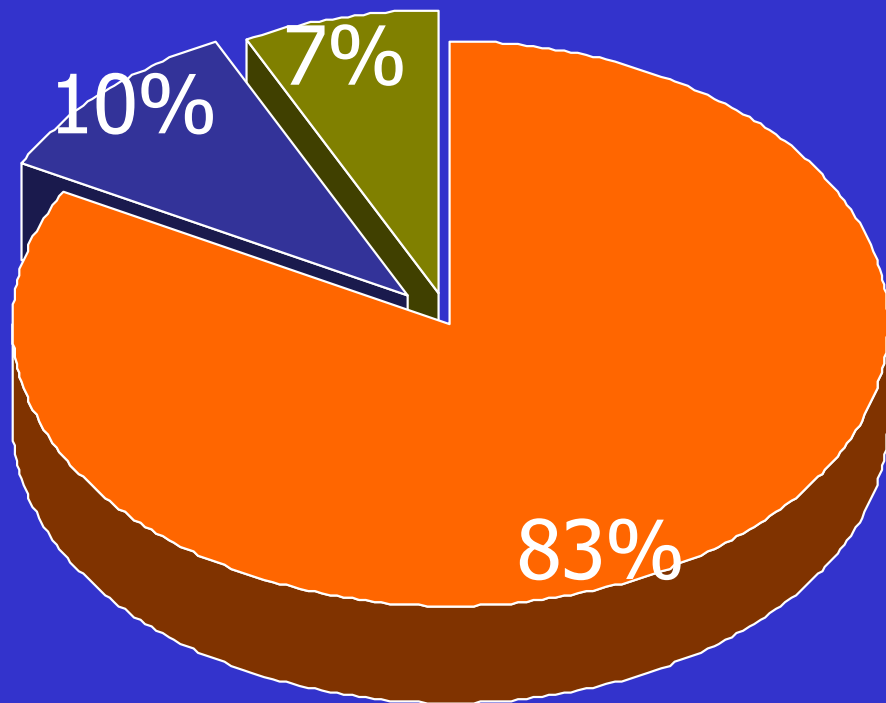
Camurati-Engelmann disease: review of the clinical, radiological, and molecular data of 24 families and implications for diagnosis and treatment

K Janssens, F Vanhoenacker, M Bonduelle, L Verbruggen, L Van Maldergem, S Ralston, N Guañabens, N Migone, S Wientroub, M T Divizia, C Bergmann, C Bennett, S Simsek, S Melançon, T Cundy and W Van Hul

J. Med. Genet. 2006;43:1-11; originally published online 13 May 2005;

doi:10.1199/jmgen.2005.000500

Anaemia in a cohort of 12,065 patients with new-onset heart failure.



- No Anaemia
- Anaemia Chronic Disease
- Anaemia other causes



Hb e SaO₂



Emoglobina g/dl	N	709	709		
	Media	11.8	12.1	0.35	
	SD	2.3	6.0	5.8	T-test: p=n.s
SaO ₂ %	N	417	417		
	Media	90.6	94.3	3.6	
	SD	6.5	5.7	7.9	T-test: p<0.0001



Anemia e mortalità

Nella popolazione generale la mortalità è maggiore nei soggetti anemici

Nello scompenso cardiaco la presenza di anemia ha valore prognostico negativo

Nei pazienti con infarto del miocardio, la mortalità è maggiore nei soggetti anemici



Anemia e mortalità

Nella popolazione generale la mortalità è maggiore nei soggetti anemici

Nello scompenso cardiaco la presenza di anemia ha valore prognostico negativo

Nei pazienti con infarto del miocardio, la mortalità è maggiore nei soggetti anemici

Negli infartuati con Ht <33% la trasfusione di emazie riduce la mortalità



Anemia e qualità di vita

Nelle donne in post-menopausa, la qualità di vita (misurata con parametri obiettivi) è migliore nei soggetti con livelli di Hb nel range alto della normalità (13-15 gr/dl) rispetto a quelli nel range basso (12-13 gr/dl).

PERCHE' E' FONDAMENTALE UN APPROCCIO SISTEMATICO ALLA DIAGNOSI DI ANEMIA IN MEDICINA INTERNA

- Necessario effettuare una diagnosi corretta***
- Terapia adeguata nelle dosi e nei tempi di somministrazione***
- Miglioramento della prognosi in qualsiasi Patologia cronica e/o comorbidity***
- Miglioramento della qualita' di vita***
- Migliora la Mortalita'***





RELATIVE TO MEDICINE IN ITALY,

IN A LETTER FROM A GENTLEMAN ON A TOUR IN THAT COUNTRY, 1812.

At Pavia, the residence of the celebrated M. Scarpa, is one of the best institutions I have visited. The Medical Professors at this place are ten in number; the Professorships are thirteen. They are as follow :

The Institutes of Surgery ;
Clinical Medicine ;
Botany ;
Clinical Surgery ; by SCARPA.
Human Anatomy ; by FATTORI.
Operative Surgery ; by SCARPA.
Pathology and Legal Medicine ;
Chemistry ; by BRUGNATELLI.
Materia Medica ;
Physiology and Comparative Anatomy ;
Pharmaceutic Chemistry ; by MARABELLI.
Midwifery ;

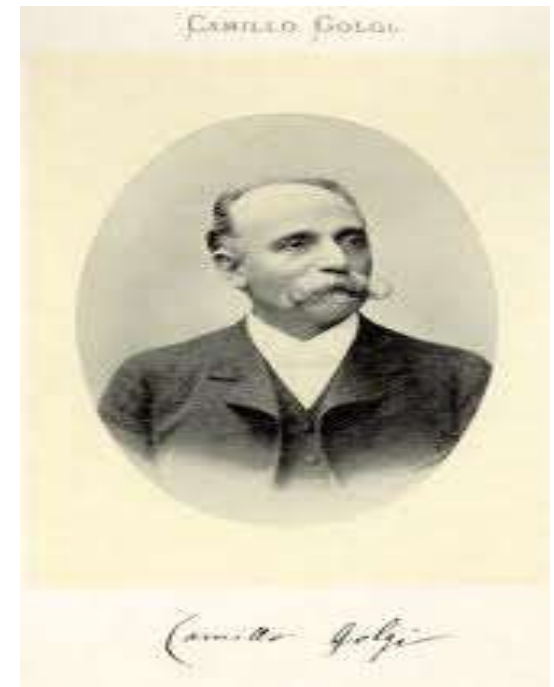
Biblioteca
Clinica Medica
Adolfo Ferrata
Pavia



In addition to these are Professors in the following departments :

Agriculture ;
Experimental Philosophy ; by VOLTA and CONFIGLIACHI.
Natural History ;
General Physics ;

An extensive Library belongs to the School, and a splendid Museum of Anatomy and the various branches of Natural History. These are contained in a building much like the medical school in Paris, but twice as large. The hospital is an excel-



*E' meglio avere un
laboratorio povero
con tante idee
Che un laboratorio
ricco senza idee*



*Camillo Golgi Premio
Nobel per la Medicina
1906 Pavia*

