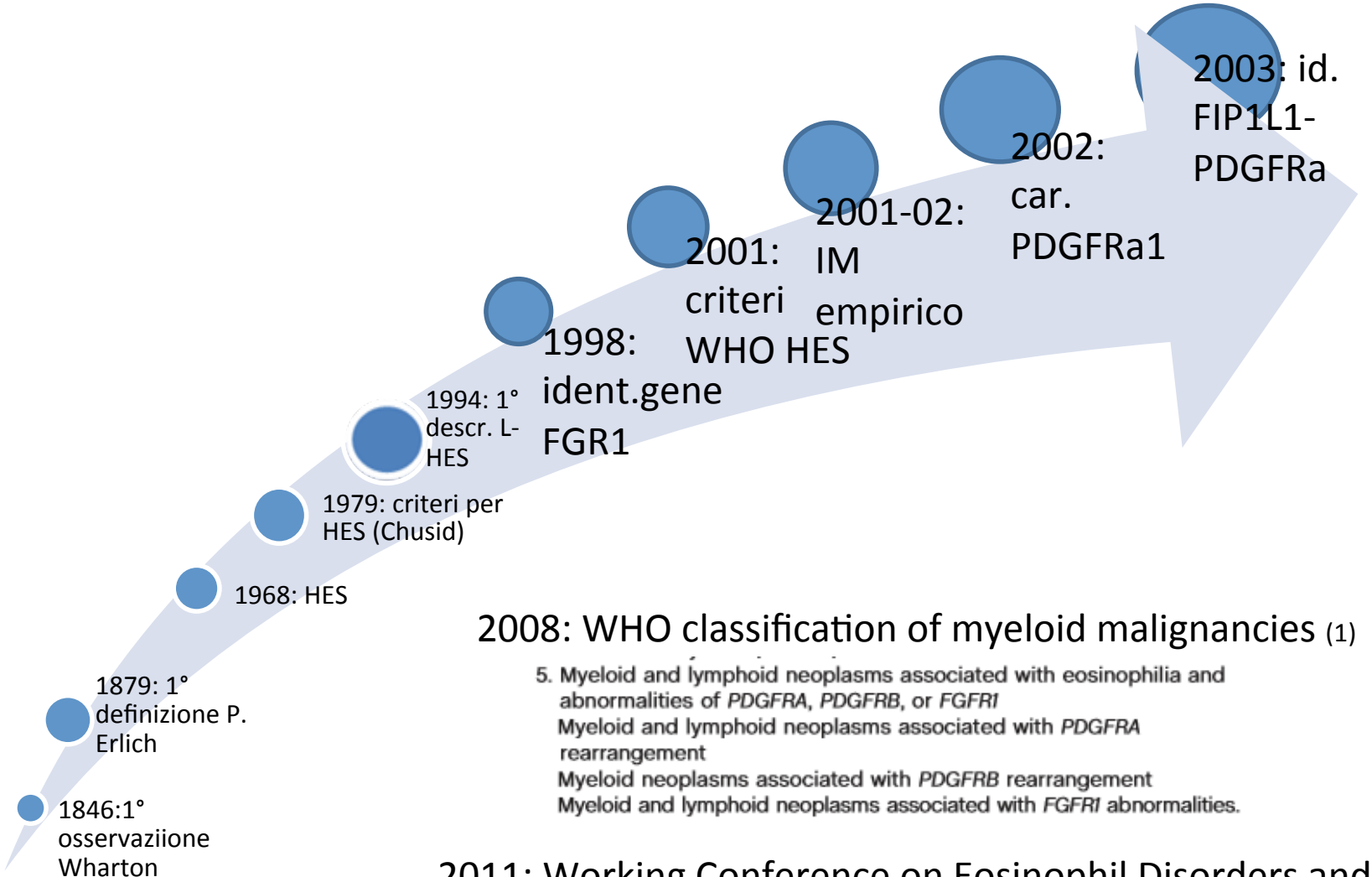
Le sindromi ipereosinofiliche

Eros Di Bona
UOC Ematologia
Vicenza

VII Giornate Ematologiche Vicentine
Vicenza, 10-12 ottobre 2016



2008: WHO classification of myeloid malignancies (1)

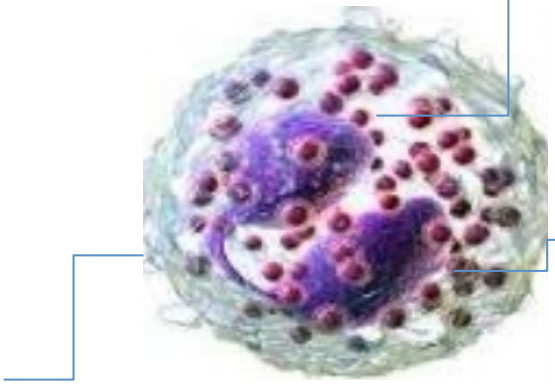
5. Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*
Myeloid and lymphoid neoplasms associated with *PDGFRA* rearrangement
Myeloid neoplasms associated with *PDGFRB* rearrangement
Myeloid and lymphoid neoplasms associated with *FGFR1* abnormalities.

2011: Working Conference on Eosinophil Disorders and Syndromes (2)

HE subtypes were divided into a hereditary (familial) variant (HE_{FA}), HE of undetermined significance (HE_{US}), primary (clonal/neoplastic) HE produced by clonal/neoplastic eosinophils (HE_N), and secondary (reactive) HE (HE_R). HEUS was introduced as a novel term in lieu of "idiopathic HE."

1) Bain BJ et al; World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press;2008. pp 68–73
2) Valent P et al; J Allergy Clin Immunol 2012;130: 607–612.

Che cos'è un eosinofilo?



Eosinophil major basic protein (eMBP)
Eosinphil cation protein (ECP)
Perossidasi
Neurotossina a derivazione eosinofila

Mediatori lipidici
Leucotriene
Fattore attivazione piastrinico

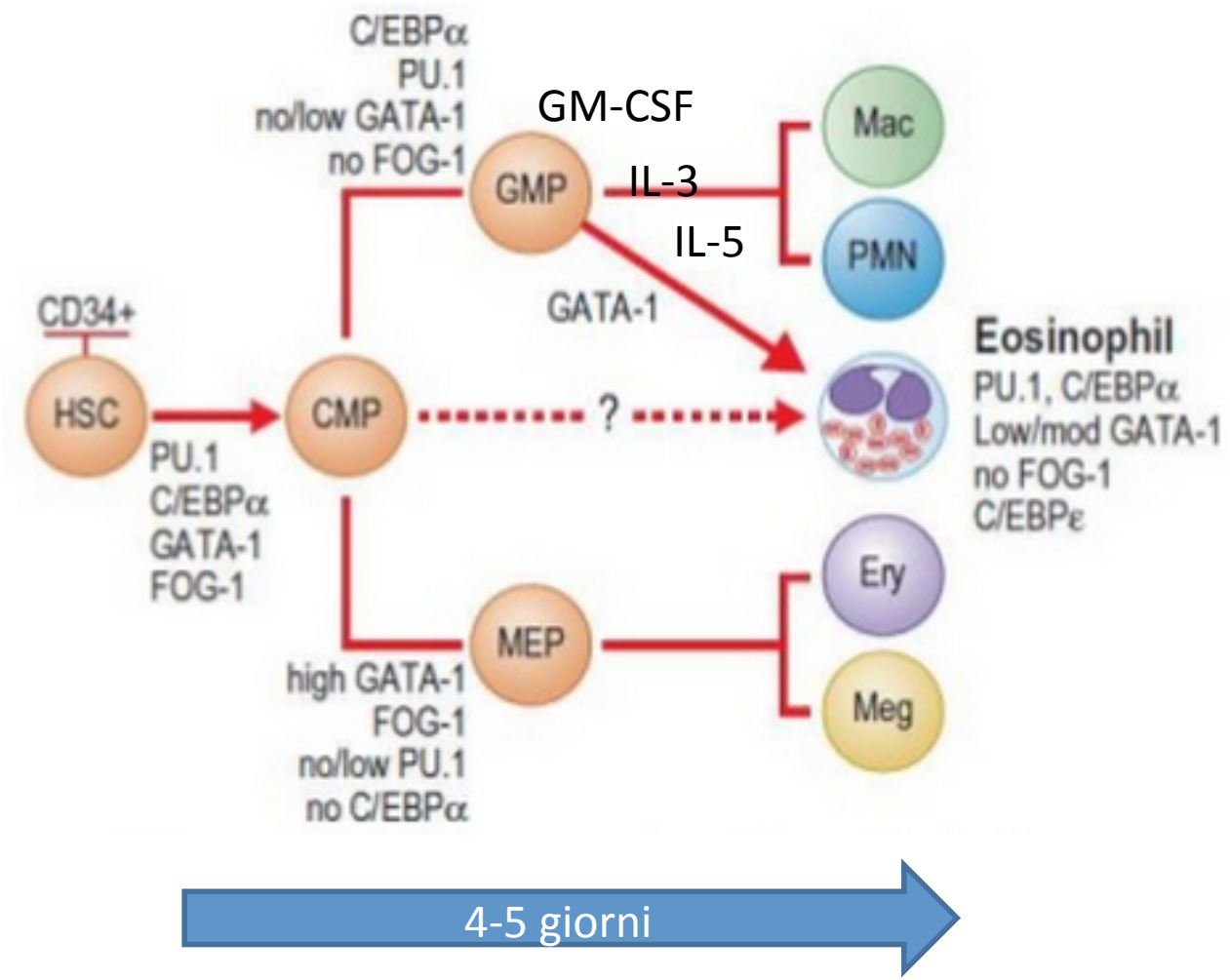
- Recettori per:

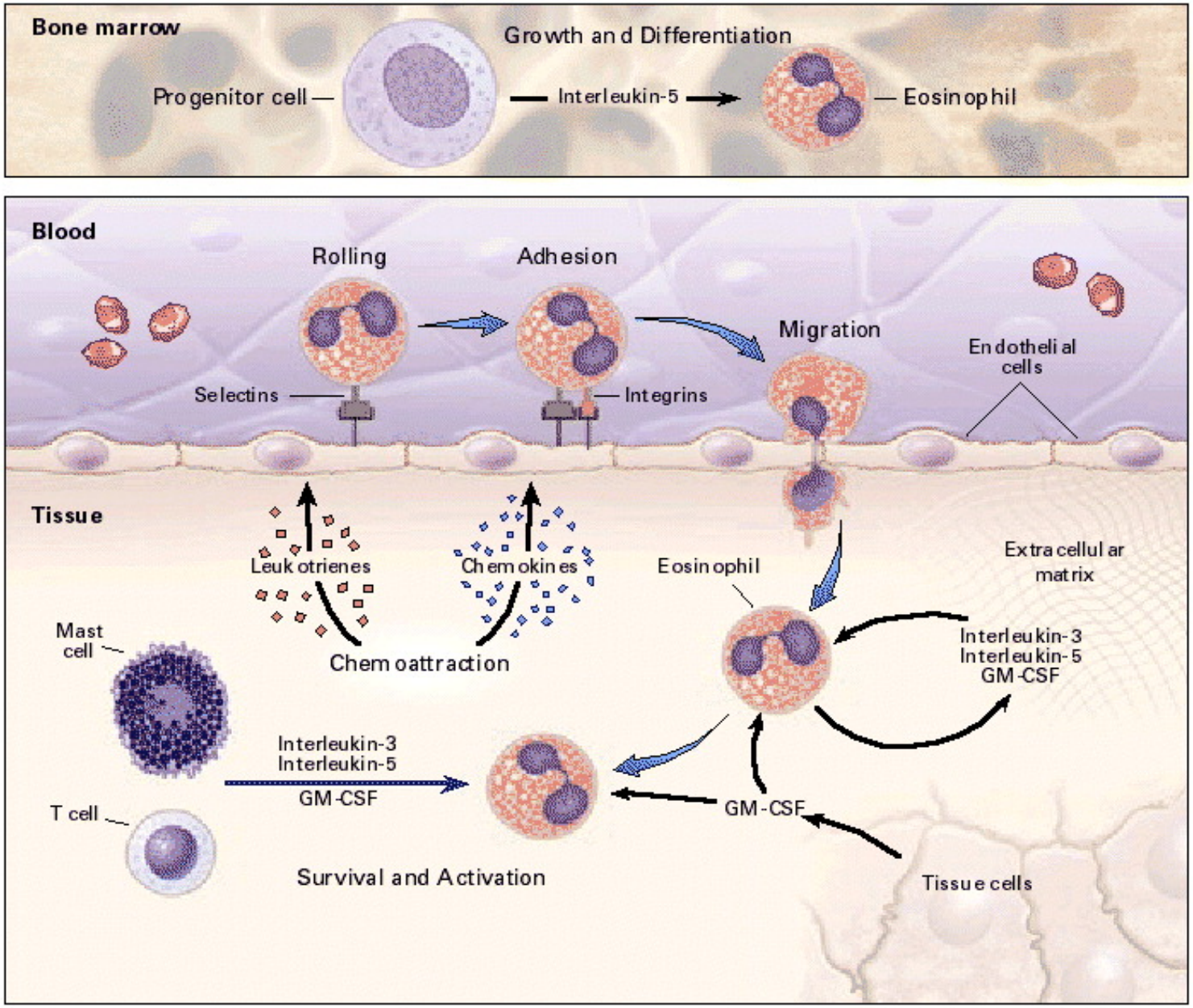
Ig, complemento, citochine (IL2, 3, 5, GM-CSF)
Steroidi, istamina, b-adrenergico, PAF, LTB4, ECF-A
HLA clI, cl II, CD4

- Molecole di adesione

Chemiotassi
Attività pro-infiammatoria
Attività rimodellamento tess.
Adesione all'endotelio
Attivazione coagulazione
Attivazione fibroblasti

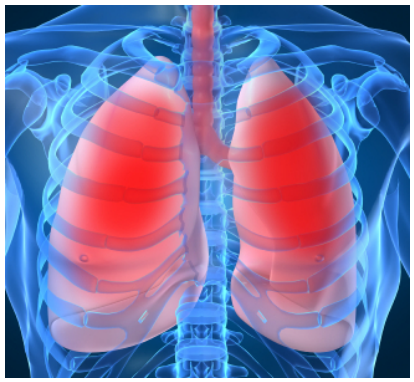
Produzione


C/EBPα
PU.1
no/low GATA-1
no FOG-1
GM-CSF
GMP
IL-3
IL-5
Mac
PMN
GATA-1
CD34+
HSC
CMP
?
PU.1
C/EBPα
GATA-1
FOG-1
Eosinophil
PU.1, C/EBPα
Low/mod GATA-1
no FOG-1
C/EBPε
MEP
high GATA-1
FOG-1
no/low PU.1
no C/EBPα
Ery
Meg
4-5 giorni



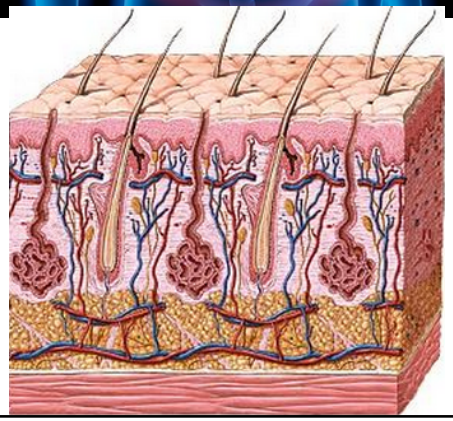
Rothenberg ME. N Engl J Med 1998;338:1592-1600.

Distribuzione degli eosinofili



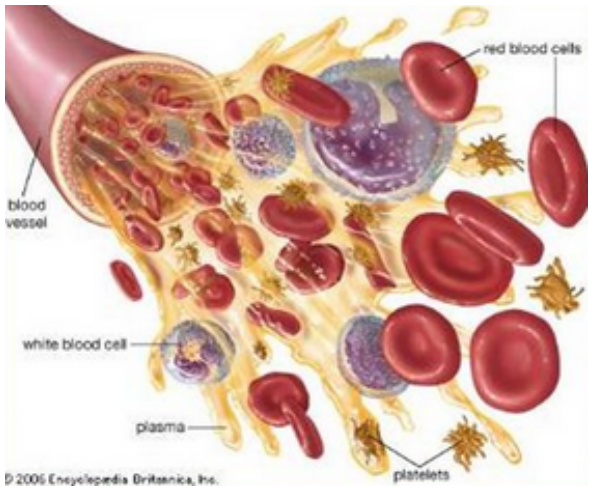
100

eotassina1



2-5 gg

1



8-18 ore

Definizioni

- Eosinofilia: >500/mmc
  - Lieve: >500-1500/mmc
  - Moderata: 1500-5000/mmc
  - Severa: >5000/mmc
- Sindrome ipereosinofilia (Chusid MJ, 1975; Valent P, 2012)
  - >1500/mmc in 2 separati controlli
  - **Danno d'organo**
  - Esclusione di cause secondarie

Definizioni

Infiltrazione tessutale

- >20% eosinofili nel midollo
- Estesa infiltrazione nei tessuti
- Dimostrazione di mediatori di provenienza eosinofila

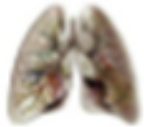
Danno d'organo

- Estesa infiltrazione nei tessuti
- Dimostrazione di mediatori di provenienza eosinofila

Fibrosi
Trombosi (+/-TE)
Cute/mucose
Neuropatia centrale o periferica

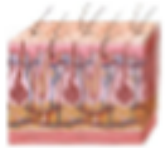
Danno d'organo

•Miocardite, insufficienza cardiaca cronica, insufficienza mitralica e tricuspidale, trombosi endocardica e valvolare, cardiomiopatia restrittiva



•Fibrosi polmonare, polmonite eosinofila, versamento pleurico, embolia polmonare, broncospasmo

•Confusione, atassia, perdita di memoria, neuropatia periferica sensitiva e motoria, ischemia cerebrale da TE



•Angioedema, orticaria, papule eritematose, rash, noduli, ulcere mucose

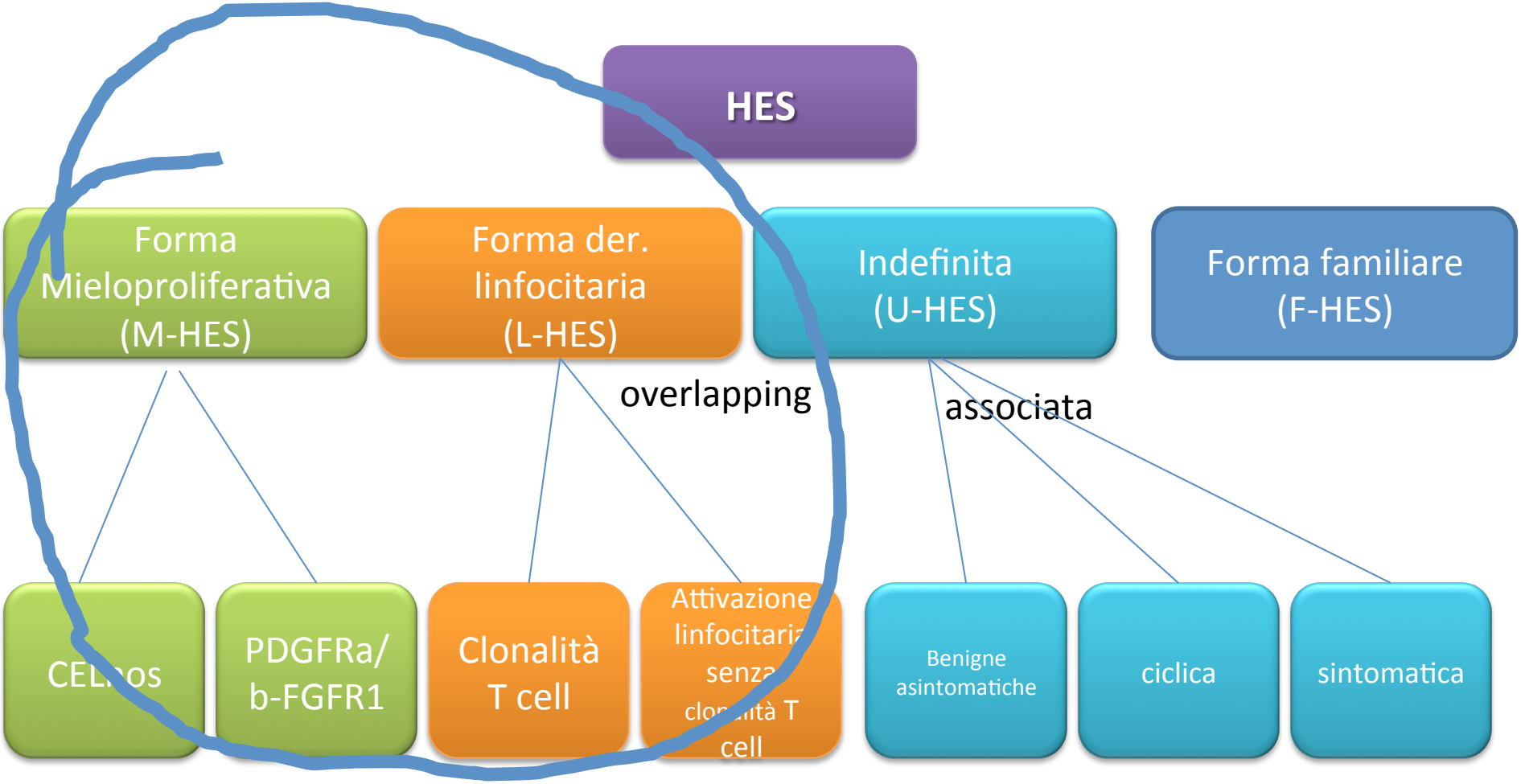
•Splenomegalia, epatomegalia, diarrea, dolore, nausea, vomito, gastrite, ulcerazione, colite, colangite

Prevalenza

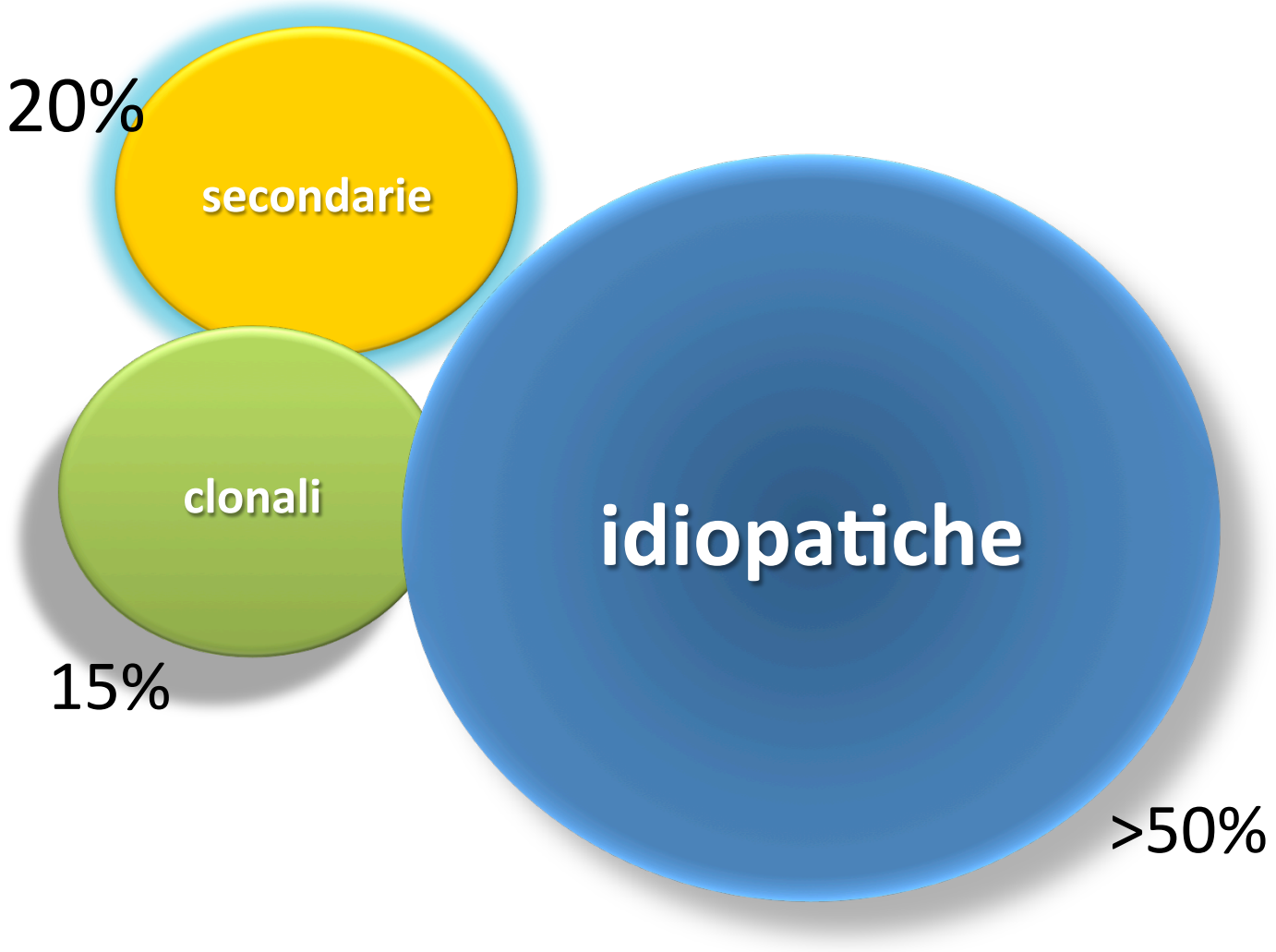
SEER: 2010

- 0.3-6.3 casi/100.000 persone/anno
- 52 aa età mediana
- M>F

Classificazione



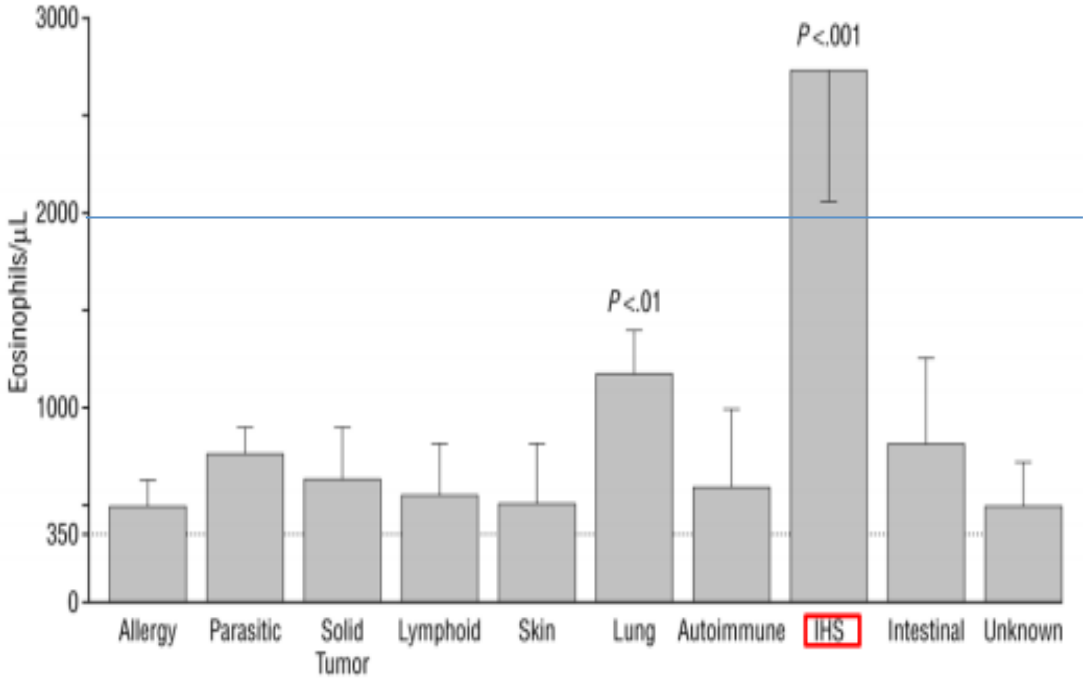
Diagnosi



Distribution of Diseases in 1862 Patients With Eosinophilia

Disease	Patients, No. (%)
Allergic diseases	1485 (79.7)
Asthma	492 (26.4)
Rhinitis	755 (40.5)
Rhinoconjunctivitis	215 (11.5)
Allergic GE	23 (1.2)
Parasitic infections	152 (8.2)
Helminths	146 (7.8)
Protozoa	6 (0.3)
Hemolymphoid neoplasms	44 (2.4)
Hodgkin disease	23 (1.2)
Non-Hodgkin lymphoma	12 (0.6)
IgA myeloma	2 (0.1)
Idiopathic hypereosinophilic syndrome	7 (0.4)
Solid tumors	35 (1.9)
NSCL cancer	14 (0.8)
Gastric cancer	6 (0.3)
Colorectal carcinoma	10 (0.5)
Pancreatic cancer	3 (0.1)
Other	2 (0.1)
GI diseases	29 (1.6)
Ulcerative colitis	11 (0.5)
Crohn disease	5 (0.3)
Celiac disease	9 (0.5)
Eosinophilic GE	4 (0.2)
Skin diseases	40 (2.1)
Chronic idiopathic urticaria	25 (1.3)
Atopic dermatitis	14 (0.8)
Well syndrome	1 (0.05)
Lung diseases	14 (0.8)
Pulmonary aspergillosis	5 (0.3)
Churg-Strauss syndrome	2 (0.1)
Wegener disease	1 (0.05)
Sarcoidosis	5 (0.3)
Eosinophilic pneumonia	1 (0.05)
Autoimmune diseases	12 (0.6)
Rheumatoid arthritis	6 (0.3)
Sjögren syndrome	3 (0.1)
Rheumatic polymyalgia	2 (0.1)
Behçet syndrome	1 (0.05)
Eosinophilia of unknown significance	51 (2.7)
Total	1862 (100)

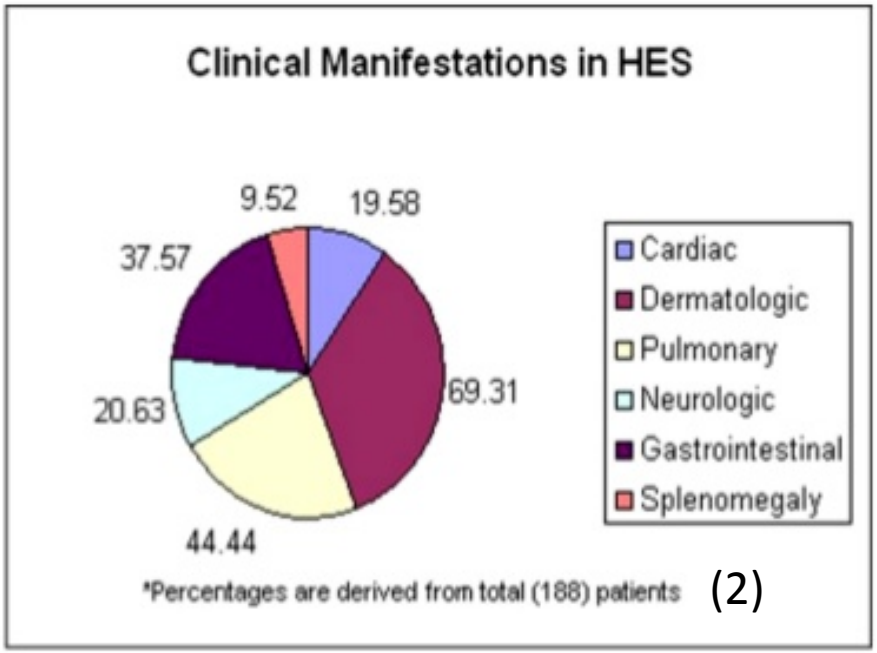
Abbreviations: GE, gastroenteritis; GI, gastrointestinal; NSCL, non–small cell lung.



Lombardi C, Passalacqua G. Eosinophilia and diseases: clinical revisions of 1862 cases. Arch Intern Med.2003;1

Clinica

50 pazienti (1)	
Astenia	26%
Tosse	24%
Dispnea	16%
Mialgie e angioedema	14%
Rash e febbre	12%
Lesioni retiniche	10%
ASINTOMATICI	12%

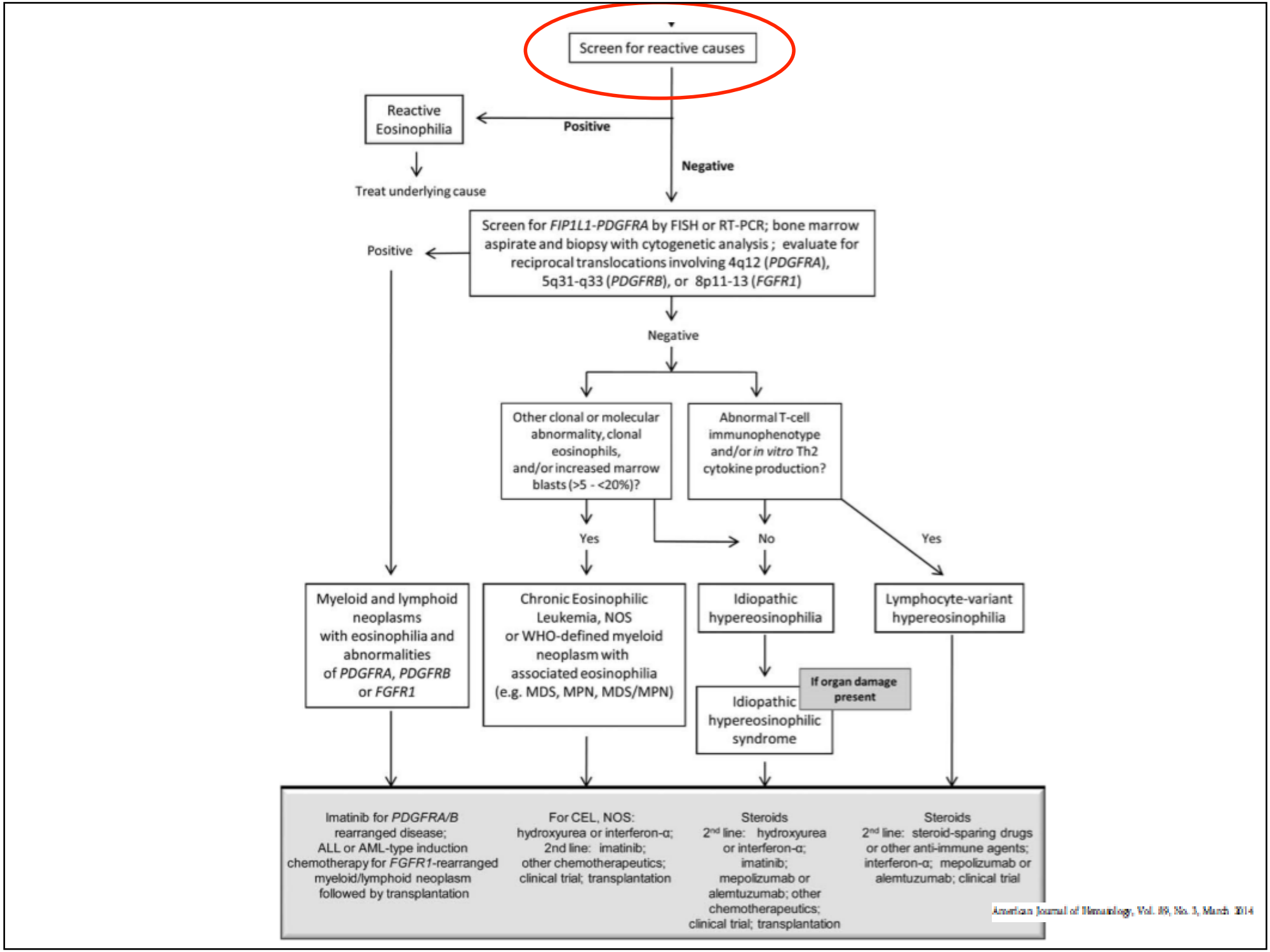


(2)

6% asintomatici

Asintomatici per anni
Sintomi insidiosi per lungo tempo
Raramente morte improvvisa

1) *Fauci et al. Ann Intern Med97:78,1982*
2) *Ogbogu PU et al, J Allergy Clin Immunol 2009;124:1319–1325.*



American Journal of Hematology, Vol. 89, No. 3, March 2014

Diagnosi

Escludi la secondarietà

Cause non neoplastiche

Allergie
Malattie polmonari (da ipersensibilità, Loeffler, Churg & Strauss)
Vasculiti e collagenopatie

Infezioni: batteri, funghi, **elminti** (cisticercosi, echinococco, filiariosi, strongiloide,….)

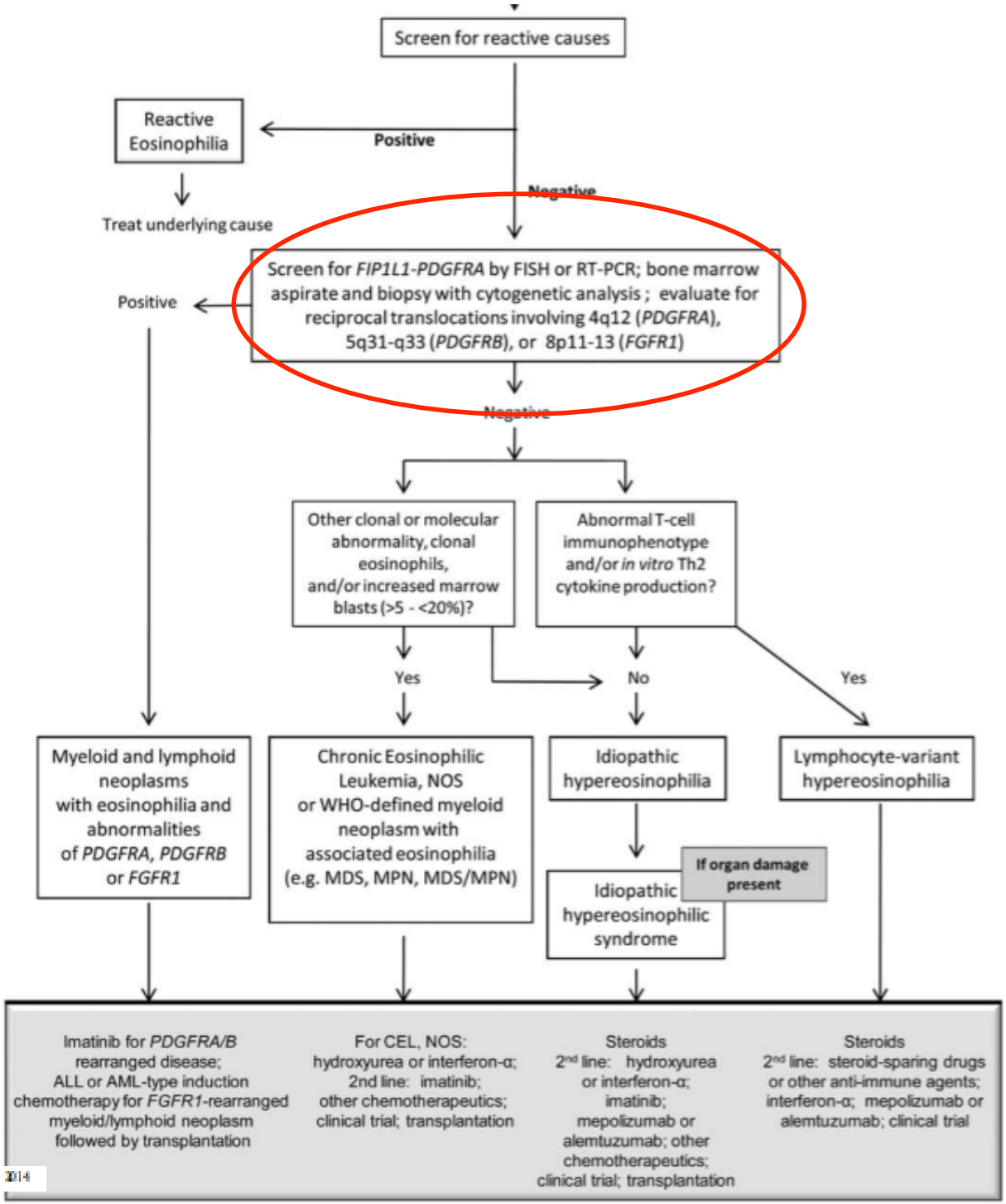
Farmaci:
con danno d'organo(polmoni: nitrofurantoina, FANS, sulfamidici; fegato: tetracicline; muscoli: L-triptofano; nefrite interstiziale: cefalosporine; rash cutaneo con ss. sistemici: antiepilettici)
senza danno d'organo (chinina, cefalosporine, quinolone)

Diagnosi

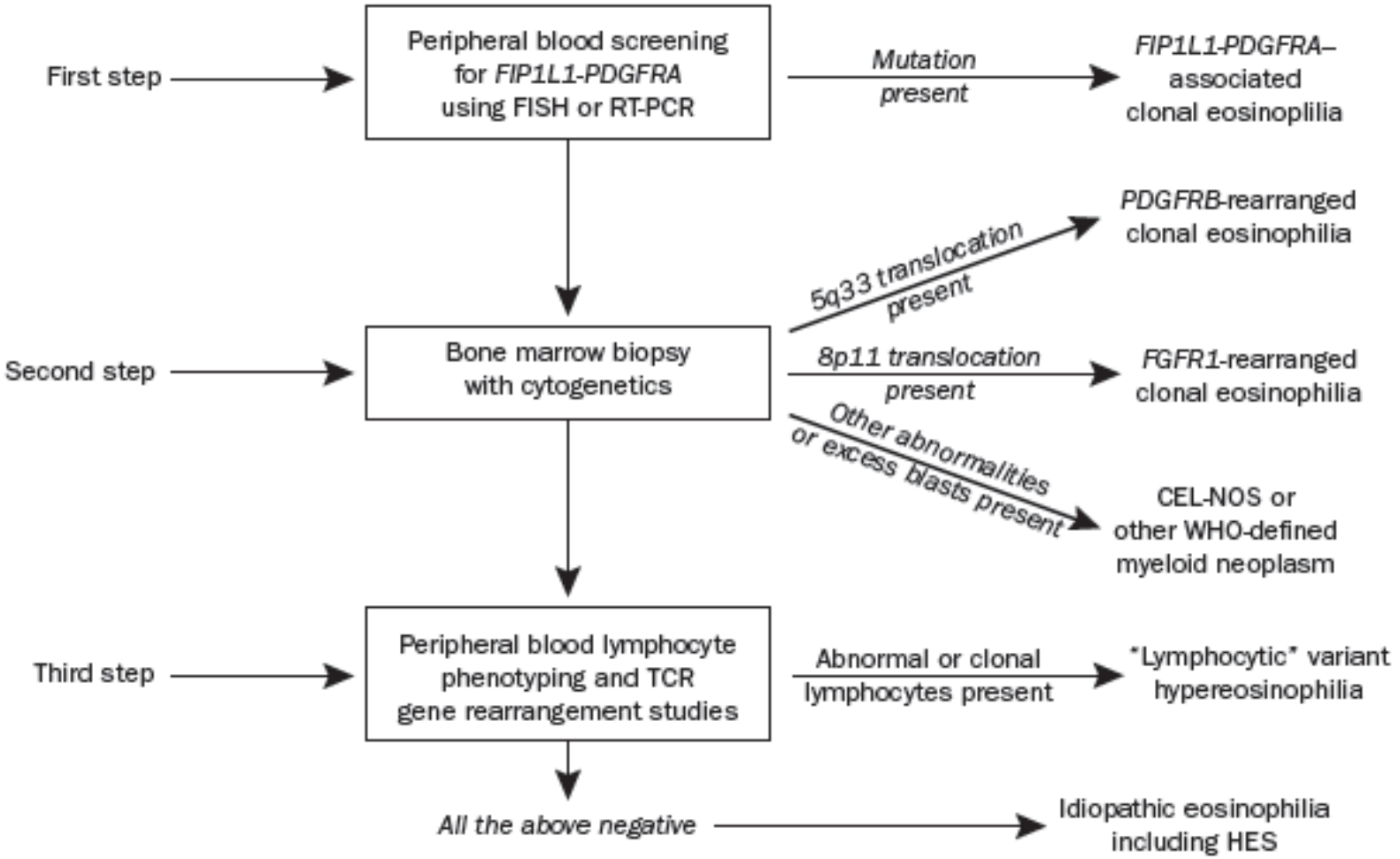
Escludi la secondarietà

Cause neoplastiche

- Linfomi a cellule T (inclusa micosi fungoide e Sezary)
- Linfoma di Hodgkin
- Leucemia linfoblastica
- Mastocitosi
- Leucemia mieloide cronica Ph/BCR-ABL positiva
- Leucemie mieloidi acute con inv(16), t(6;16)
- Altre malattie mieloproliferative croniche (PV, TE, MF)
- Sindromi mielodisplastiche


Screen for reactive causes
Reactive Eosinophilia
Positive
Negative
Treat underlying cause
Screen for FIP1L1-PDGFRA by FISH or RT-PCR; bone marrow aspirate and biopsy with cytogenetic analysis ; evaluate for reciprocal translocations involving 4q12 (PDGFRA), 5q31-q33 (PDGFRB), or 8p11-13 (FGFR1)
Positive
Negative
Other clonal or molecular abnormality, clonal eosinophils, and/or increased marrow blasts (>5 - <20%)?
Abnormal T-cell immunophenotype and/or in vitro Th2 cytokine production?
Yes
No
Yes
Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1
Chronic Eosinophilic Leukemia, NOS or WHO-defined myeloid neoplasm with associated eosinophilia (e.g. MDS, MPN, MDS/MPN)
Idiopathic hypereosinophilia
Lymphocyte-variant hypereosinophilia
If organ damage present
Idiopathic hypereosinophilic syndrome
Imatinib for PDGFRA/B rearranged disease; ALL or AML-type induction chemotherapy for FGFR1-rearranged myeloid/lymphoid neoplasm followed by transplantation
For CEL, NOS: hydroxyurea or interferon-α; 2nd line: imatinib; other chemotherapeutics; clinical trial; transplantation
Steroids 2nd line: hydroxyurea or interferon-α; imatinib; mepolizumab or alemtuzumab; other chemotherapeutics; clinical trial; transplantation
Steroids 2nd line: steroid-sparing drugs or other anti-immune agents; interferon-α; mepolizumab or alemtuzumab; clinical trial

Ricerca della clonalità



Diagnosi

M-HES/CELnos

Epatosplenomegalia, anemia, piastrinopenia, forme immature, ritardo maturativo, B12 aumentata

PDGFRa	Aumento triptasi e mastcellule midollari	Del criptica 4q12 FIP1L1-PDGFRa Almeno altri 66 geni partner
PDGFRb	monocitosi	T(5;12)(p13.2;q32) ETV-PDGFRb altri 22 gene partner
FGFR1	T-ALL o AML	T 8p11.2 vari geni partner
PCM1/JAK2	Aumento eritroide spostato a sinistra; aggregati linfoidi	T(8;9)(p22;q24.1)

Diagnosi

CEL-NOS
WHO2008

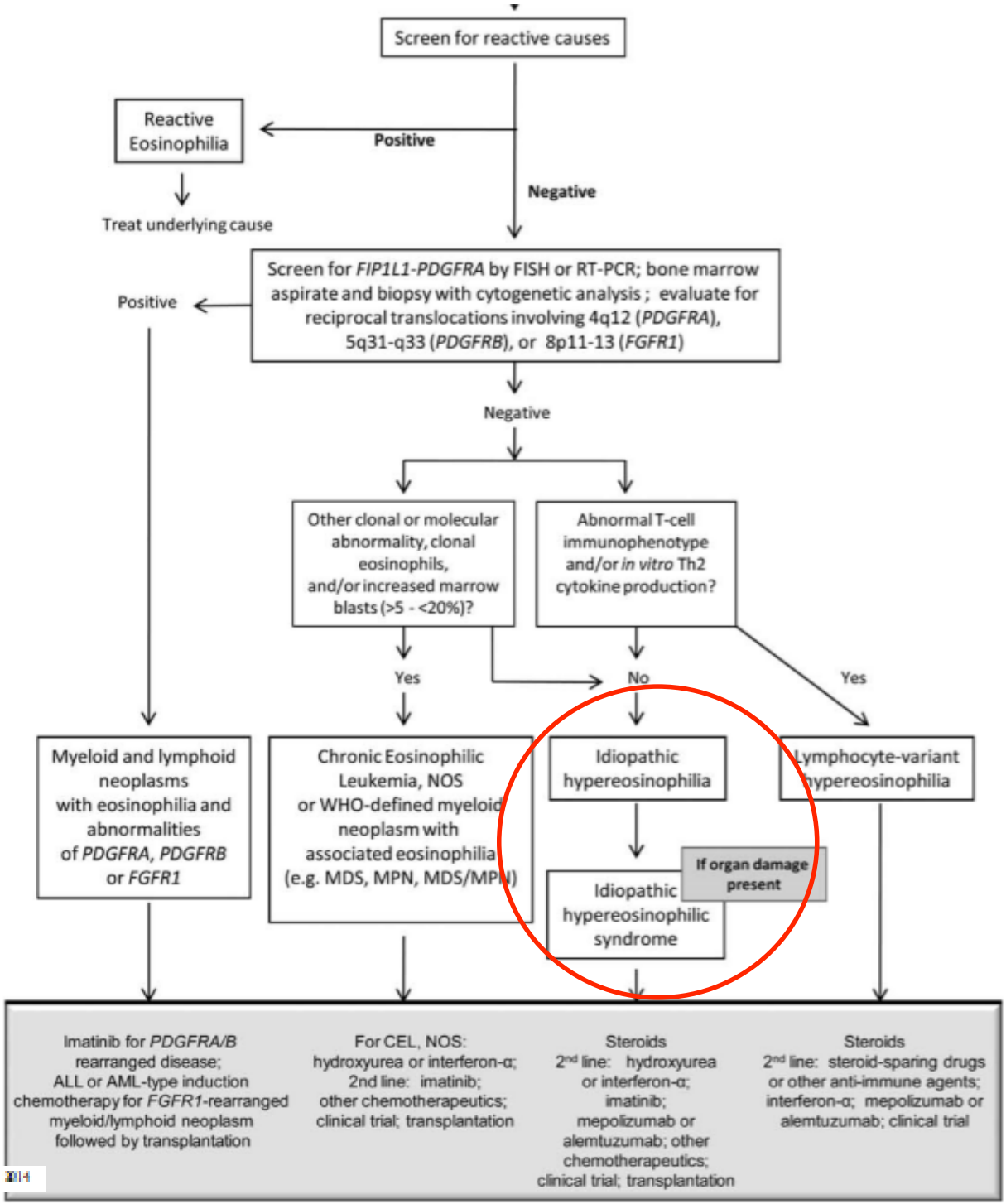
- Eosinofilia > 1.5 x 10^9/L
- **No** cromosoma Philadelphia, BCR-ABL1, altre MPN (PV, ET, PMF) o MDS
- **No** t(5;12) o altri riarrangiamneti di PDGFRa
- **No** FIP1L1-PDGFRb o altri riarrangiamenti di PDGFRb
- **No** riarrangiamnti di FGFR1
- **No** inv(16) o altri indicatori di AML
- Può esserci una anomalia citogenetica o molecolare non ricorrente e blasti <2% nel SP e <20% nel midollo;

Diagnosi

Lv-HES

Spesso segni cutanei

CD3+CD4-CD8-	Aumento IgE, IL5, TARC (Thymus and Activation-Regulated Chemokine)	Profilo Th2
CD3-CD4+ CD5+/CD7-	EBV?	
TCR		


Screen for reactive causes
Reactive Eosinophilia
Positive
Negative
Treat underlying cause
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Positive
Negative
Other clonal or molecular abnormality, clonal eosinophils, and/or increased marrow blasts (>5 - <20%)?
Abnormal T-cell immunophenotype and/or in vitro Th2 cytokine production?
Yes
No
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Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1
Chronic Eosinophilic Leukemia, NOS or WHO-defined myeloid neoplasm with associated eosinophilia (e.g. MDS, MPN, MDS/MPN)
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Esami per la diagnosi

anamnesi e visita accurata (compresa tutta la cute)

emocromo, formula leucocitaria, fosfatasi alcaline leucocitarie

ricerca parassiti nelle feci su più campioni, sierologia per toxo, toxocara, stongiloide, trichinella, HIV

dosaggio IgE totale e specifico, LDH, vitamina B_{12}, CPK, aldolasi, VES, proteina C reattiva, fattore reumatoide, funzione epatica e renale, anticorpi anti nucleo, anticorpi anti-DNA, ANCA, triptasi, troponina

Rx torace, eventuale TAC

ECG, ecocardiografia, RMN

ecografia addome, eventuale TAC

se richiesti, esofagogastroduodenoscopia, pancolonscopia

agoaspirato midollare, citogenetica e FISH, BCR-ABL, JAK2, FIP1L1-PDGFa, altri studi molecolari

biopsia osteomidollare

Diagnosi: morfologia

Criterio utile?

sangue periferico	sangue midollare
eosinofili maturi granulazioni sparse vacuoli citoplasmatici iper/iposegmentazione del nucleo taglia aumentata neutrofilia/monocitosi basofilia blasti<2%	eosinofilia prevalente in vari stadi di maturazione blasti <5% Fibrosi (BOM)

Nella diagnosi differenziale vanno ricercati gli aspetti caratteristici delle MDS, della MMM

Decorso clinico-prognosi

- 57 casi: sopravv mediana 9 mesi; a 3 anni 12% (Chusid MJ Medicine1975;54:1–27). Cardiopatia come causa principale di morte
- 40 casi: sopravv a 5 anni 80%, 42% a 15 anni; fattori prognostici negativi: elevati GB ed eos, loc.cardiaca, refrattarietà a steroide, maschi (Lefebvre C, Ann Med Interne 1989;140:253–257)
- 247 casi: 23 decessi in 19 anni compresi nella revisione (Podjasek JC, Leuk Res 2013;37:392–395)
- CEL-NOS: 10 pz, sopravv mediana 22 mesi (Helbig G, Am J Hematol 2012;87:643–645.

Quali test prognostici?

Triptasi sierica

Klion A et al. Blood 101:4660, 2003

Table 2. Characteristics of HES patients with increased and normal tryptase levels

Patient group	Serum tryptase level 11.5 ng/mL or greater	Serum tryptase level less than 11.5 ng/mL	*P*
Number of patients	9	6	
Median age, y (range)	38 (28-77)	36 (17-57)	NS
Sex, M/F	9/0	1/5	< .01
WBC, × 10^9/L, median (range)	18.1 (13.3-31.6)	8.2 (6.2-16.4)	.04
Eosinophils, × 10^9/L, median (range)	8.352 (2.425-27.550)	1.792 (.707-6.216)	< .01
Basophils, × 10^9/L, median (range)	.001 (0–.072)	.026 (.009–.057)	NS
Splenomegaly	7/9	0/6	< .01
Myeloid precursors on peripheral smear	8/9	0/6	< .01
Bone marrow biopsy cellularity, greater than 50%	7/9	1/4	NS
Dysplastic mast cells*	7/9	0/4	.02
Myelofibrosis†	5/9	0/4	NS
Median hemoglobin, g/dL (range)	12.2 (6.9-13.8)	13.8 (11-15)	.08
Median platelet count, 10^9/L (range)	165 (95-223)	283 (192-531)	< .01
Median serum IgE level, kU/L (range)	15 (0-4862)	137 (11-544)	.08
Median serum B_{12} level, pM (range)	4255 (2315-20 316)	592 (276-838)	< .01

NS indicates not significant.

*More than 25% of mast cells in bone marrow biopsy are spindle-shaped.

†Presence of antireticulin antibody staining on bone marrow biopsy.

Esistono succedanei alla biopsia per definire il danno d'organo?

Troponina
(Sato Y et al. Internal Medicine 39, 350, 2000)

Approccio terapeutico

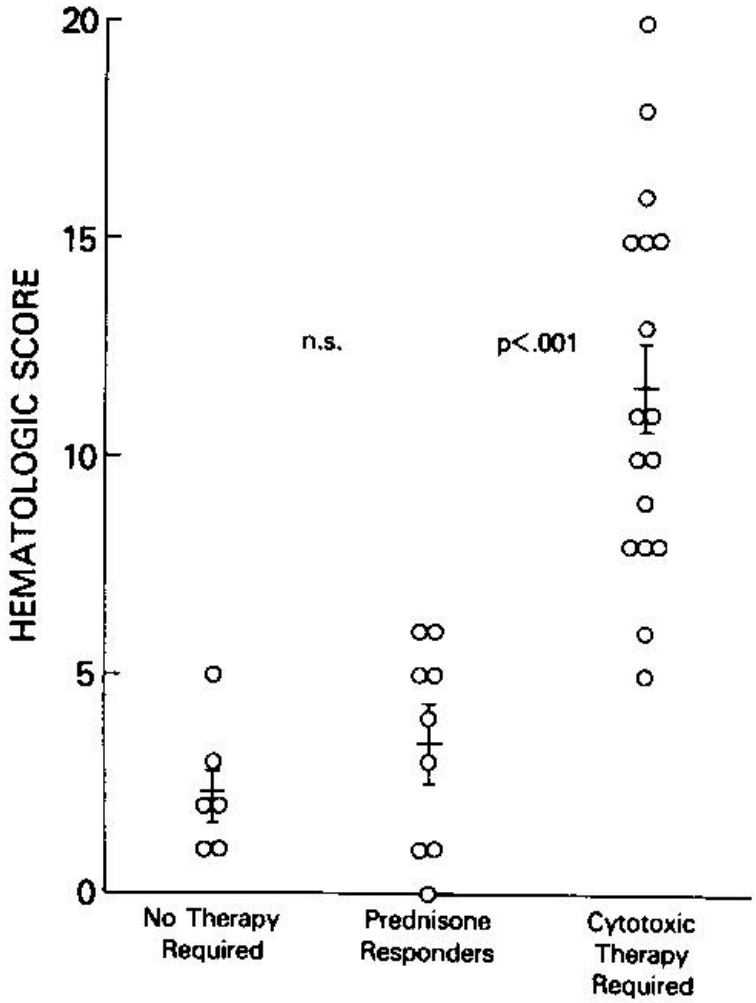
- Non vi sono dati per definire l'inizio ideale della terapia, perché mancano dati sul rilievo dell'entità e della durata dell'eosinofilia
- Nella CEL-HES, dai dati storici, è indicata terapia anche in assenza di danno d'organo
- Per U-HE è possibile il monitoraggio clinico

Grading system

Flaum et al. Blood 58: 1012, 1981

Table 1. Hematologic Grading System

Peripheral blood	
Anemia	2
Moderate to severe red blood cell morphological abnormalities	1
Increased platelets	1
Decreased platelets	2
Myeloid dyspoiesis or hypersegmentation	1
Basophilia (>200 cells/cu mm)	2
Immature WBCs	
Myeloblasts or progranulocytes	2
Metamyelocytes or myelocytes	1
Bone marrow	
Hypercellularity	
Mild-moderate	1
Marked	2
Decreased megakaryocytes	1
Myelofibrosis	2
Myeloid dyspoiesis	2
Basophilia (>1% of differential)	2
Myeloblasts-progranulocytes (>5% of differential)	2
Abnormal cytogenetics	2
Increased B_{12}	1
LAP-abnormal	1



Vicenza, 1993-2015

Epidemiologia

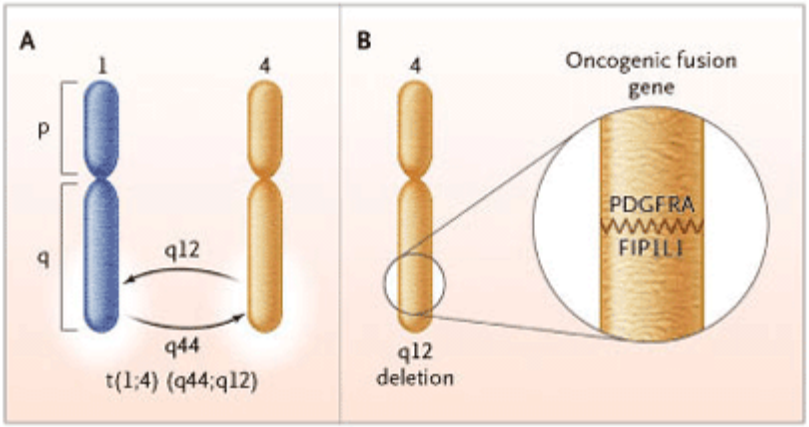
174 casi riferiti per eosinofilia

- 3 linfomi
- 2 sierologie positive per toxocara canis
- 1 strongyloides
- 4 mielodisplasie
- 76 con conta <1500/mmc o reattive

88 considerati come possibili HES

- 34 con screening per PDGFRa
- 9 (26%) F/P positivi
  - 1 LAL
  - 1 LAM

Terapia:imatinib



All fusion transcripts were found to be in frame and involved use of cryptic splice sites within PDGFRA exon 12 (defined as type A breakpoint) or within intronic sequence of FIP1L1 (type B).

Terapia: Imatinib

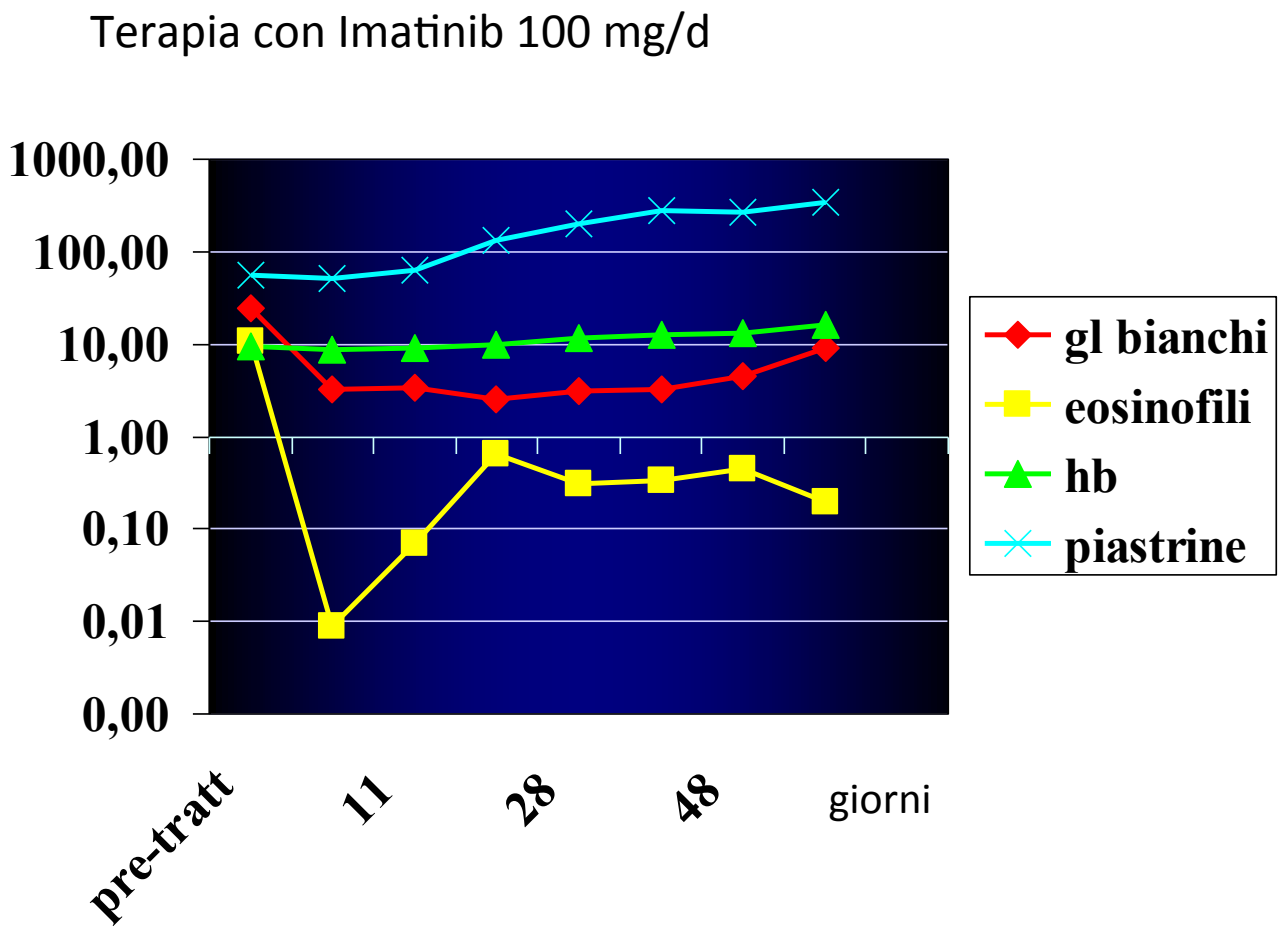
- Imatinib è stato usato in 5 pazienti con HES idiopatica (Gleich et al, Lancet 2002)
- 4 risposte, con 100 mg die, ridotti a 200 mg/sett

Terapia: Imatinib

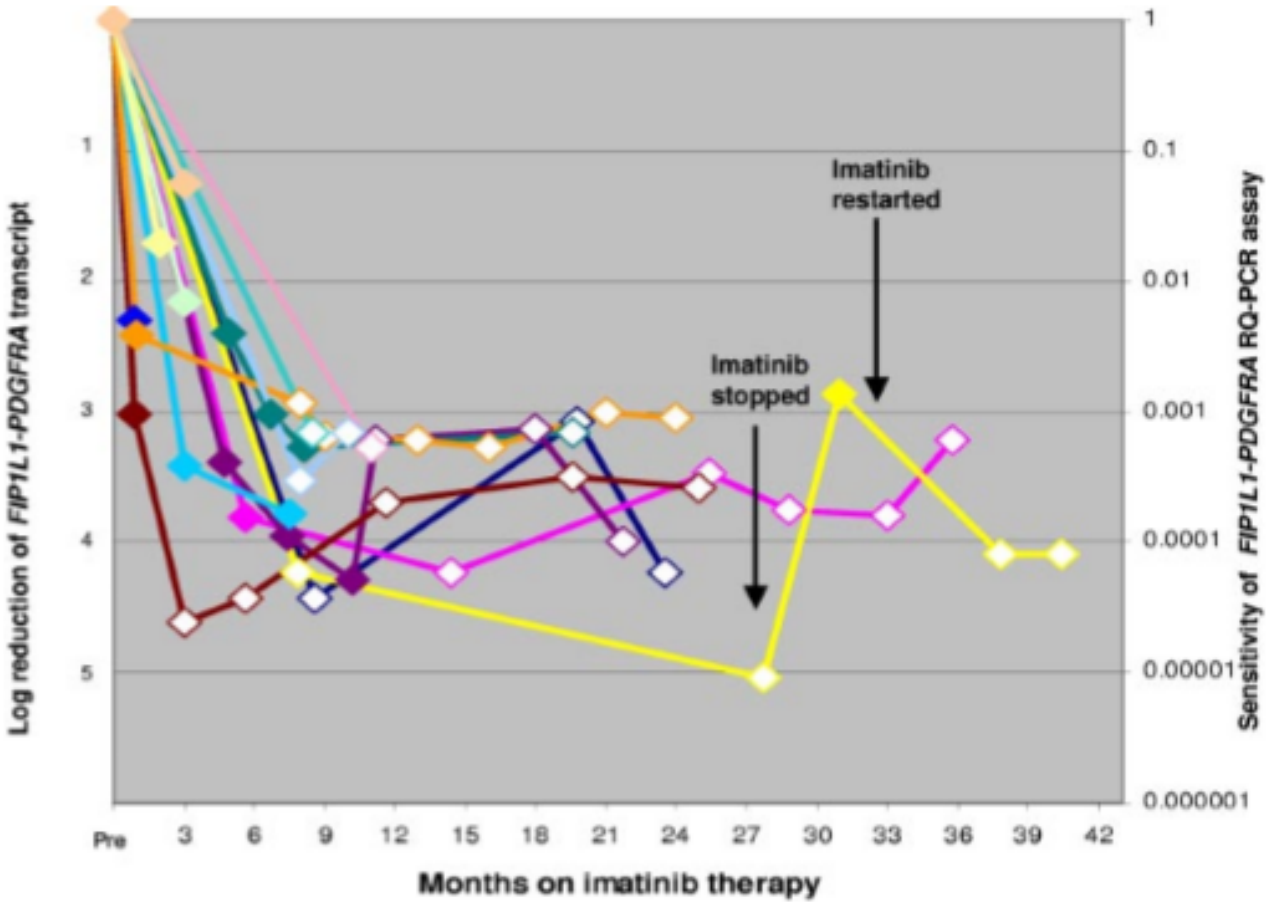
Cools et al. NEJM 2003

- 11 pt: imatinib 100-400 mg die
- 9 di 11 remissione >3 mesi, dopo terapia mediana 4 settimane
- dall'analisi di 1 pt con t(1;4)(q44;q12) viene definito per la prima volta il gene di fusione FIP1-like1 (FIP1L1), evidenziando la delezione interstiziale in 4q12
- 9 ptt sequenziati: 5 avevano il gene di fusione
- 1 pt sviluppa resistenza a imatinib: definita nuova mutazione T647I (nella regione di legame ATP) di PDGFRA, nella stessa posizione di BCR-ABL T315I

VG, 66 aa, M, resistente a steroide e HU

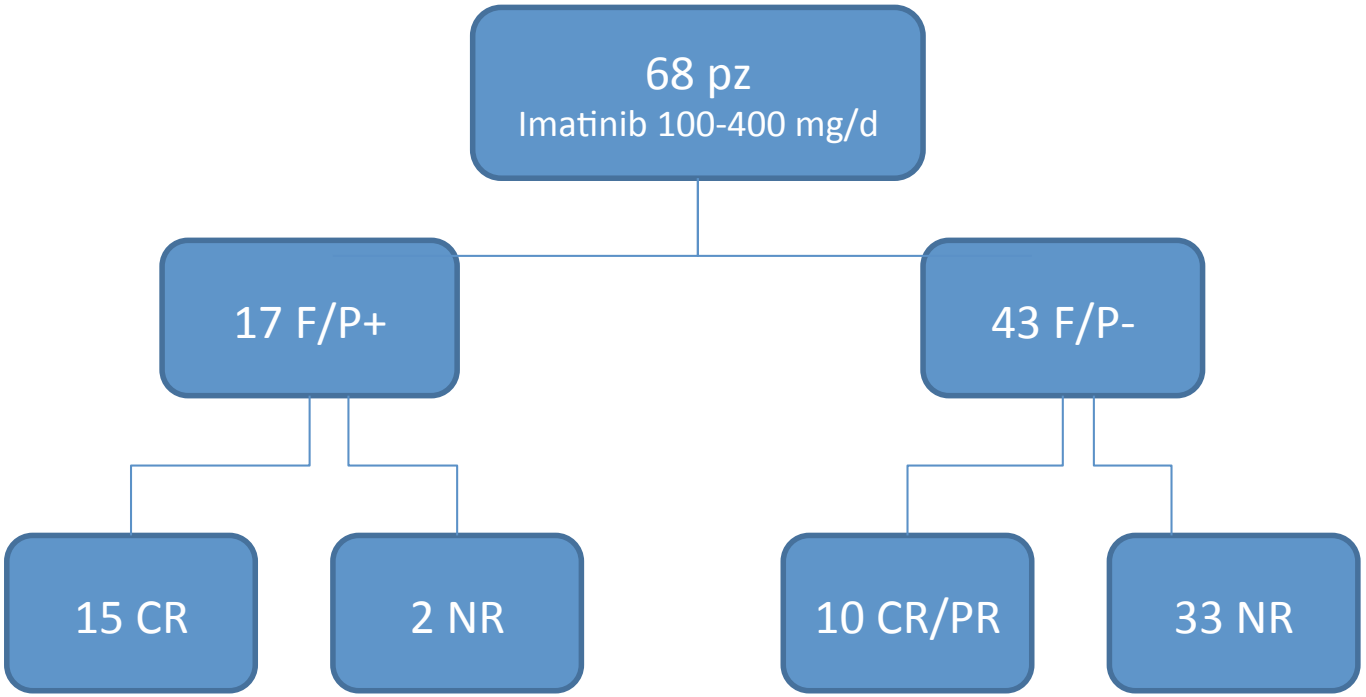


Terapia: f-up imatinib



Jovanovic JV, BLOOD, 2007,109, 4635

Terapia: Imatinib



Ogbogu PU et al, J Allergy Clin Immunol 2009;124:1319–1325

Che significato dare alla risposta ad Imatinib in F/P negativi?

Novel imatinib-sensitive PDGFRA-activating point mutations in hypereosinophilic syndrome induce growth factor independence and leukemia-like disease

Elling C, Blood.2011;117(10):2935-2943

•Sequencing of 87 FIP1L1-PDGFRA–negative HES patients revealed several novel PDGFRA point mutations (R481G, L507P, I562M, H570R,H650Q,N659S,L705P,R748G,and Y849S) in 7 patients

•Mutations (…) possess transforming potential (…) injected into
•mice (…) found that they induced a leukemia-like disease

•Oral imatinib treatment significantly decreased leukemic growth in vivo and prolonged survival

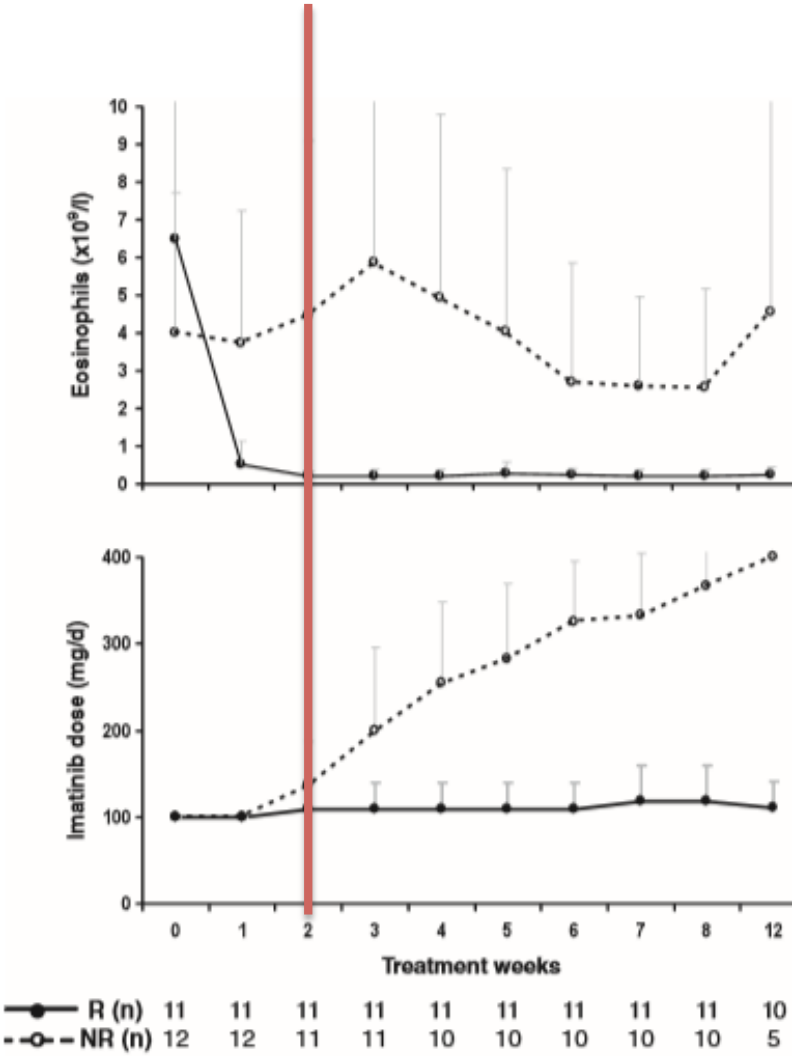
Terapia: f-up imatinib

	FIP1L1-PDGFRα rearrangement	*No FIP1L1-PDGFRα rearrangement*
No. of cases	27	36
Gender, Male/Female, no. of cases	27/0	25/11
Age, years, median (range)	50 (17-75)	58 (18-81)
Hemoglobin, g/L, median (range)	137 (94-165)	138 (84-180)
Platelet count, $\times 10^9$/L, median (range)	191 (29-365)	228 (27-668)
WBC count, $\times 10^9$/L, median (range)	10.7 (1.8-57.5)	12.2 (6.7-47.0)
Eosinophils %, median (range)	43 (20-85)	27 (13-38)
Eosinophil count $\times 10^9$/L, median (range)	4.8 (1.6-16.5)	3.4 (1.5-34.9)
Serum creatinine ≥20 mg/L, no. of cases	1/27	1/37
Serum uric acid ≥60 mg/L, no. of cases	6/27	6/37
Serum LDH ≥460 U/mL, no. of cases	5/27	6/37
Organ or tissue involvement, no. of cases		
Lung	5/27	10/37
Spleen	5/27	1/37
Skin	0/27	5/37
Heart	2/27	2/37
Liver	1/27	1/37
Soft tissues	2/27	0/37
Waldeyer's ring	0/27	1/37
Intestine	0/27	1/37
Prior disease duration, months, median (range)	16 (6-125)	25 (6-209)
Prior treatment, % of cases	66%	66%

	Complete hematologic response	
Time on treatment	*FIP1L1-PDGFRα rearrangement (n=27)*	*No FIP1L1-PDGFRα rearrangement (n=36)*
1 month	27 (100%)	4 (11%)
3 months	27 (100%)	3 (8%)
6 months	27 (100%)	3 (8%)
12 months	27 (100%)	1 (3%)
Last contact	27 (100%)	0 —

Baccarani M et al. Haematologica, 2007; 92, 1173

E’ necessario conoscere F/P per imatinib?



Primary endpoint: definition of the dose-response relationship over time.

Imatinib 100 mg/d, weekly reassessment for step-up dosing (100 mg/d per week, up to 400 mg/d) for suboptimal response (stable disease or less)

25 patients.
CR rate 42% in HES (5/12), 67% in CEL (4/6) and 40% in CIH (2/5)
100% in pts FIP1L1 pos (6/6) vs 29% in FIP1L1 neg (5/17) (P =0.0006).
CR rate 100% in PDGFRA-associated HES (6/6), 60% in CEL (3/5), 33% in HES complex (2/6) and 0% in benign HES (0/2) and the lymphocytic variant (0/4).

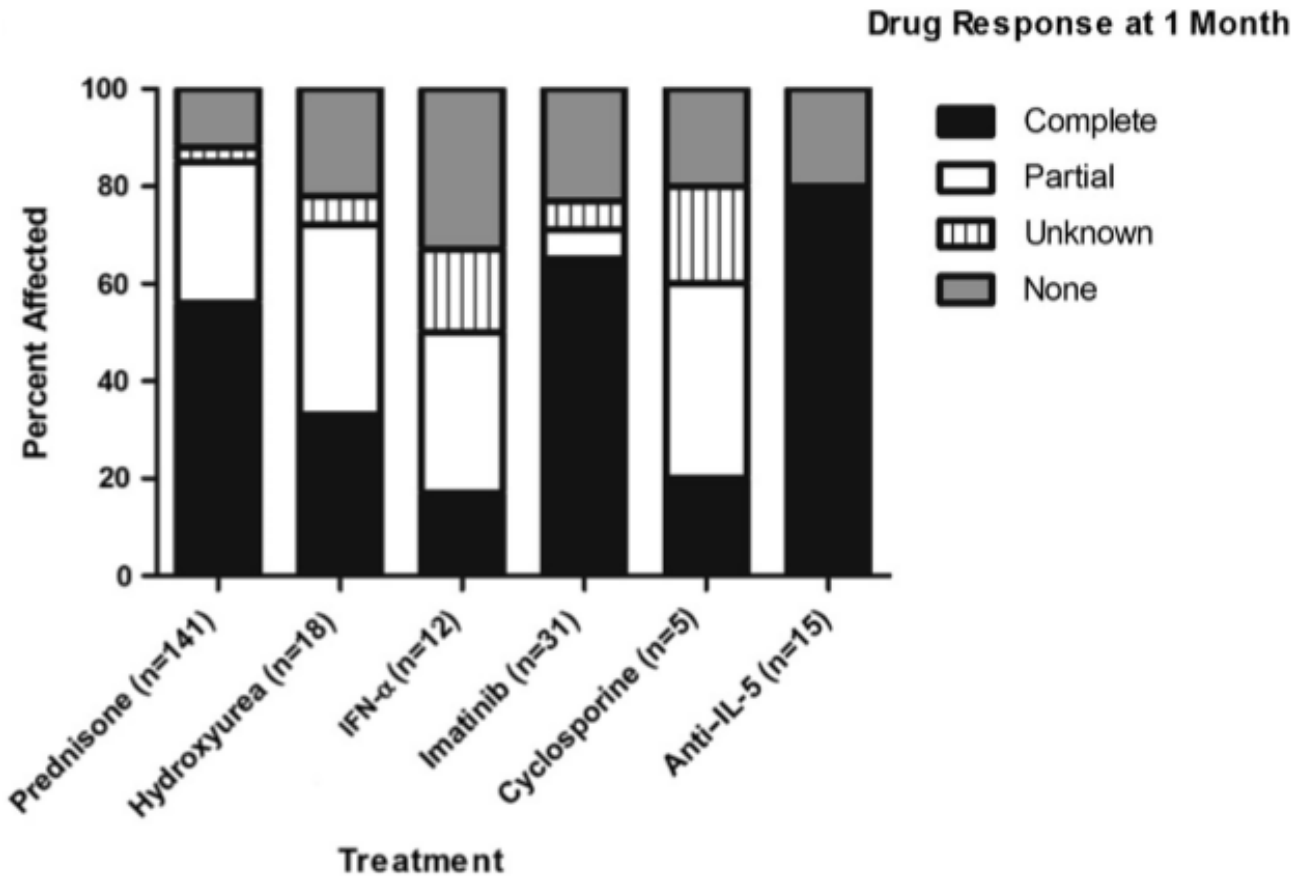
With the exception of T cell variants and selected benign cases, a short low-dose IM trial (100 mg/d for 2 weeks) can be recommended to rapidly confirm the diagnosis of IM-sensitive hypereosinophilia.
Genetic screening for IM-sensitive rearrangements should not greatly affect this decision because many of these rearrangements would remain undetected, whereas an early clinical response is an unequivocal indicator of drug sensitivity.

Intermesoli T, 2009, Br Journal Haematol, 147, 681–685

Esiste resistenza a Imatinib?

- In 13 anni circa di esperienza pochi singoli casi di resistenza acquisita riguardante la mutazione T674I
- 1 caso riportato di resistenza primaria con mutazione S601P e L629P

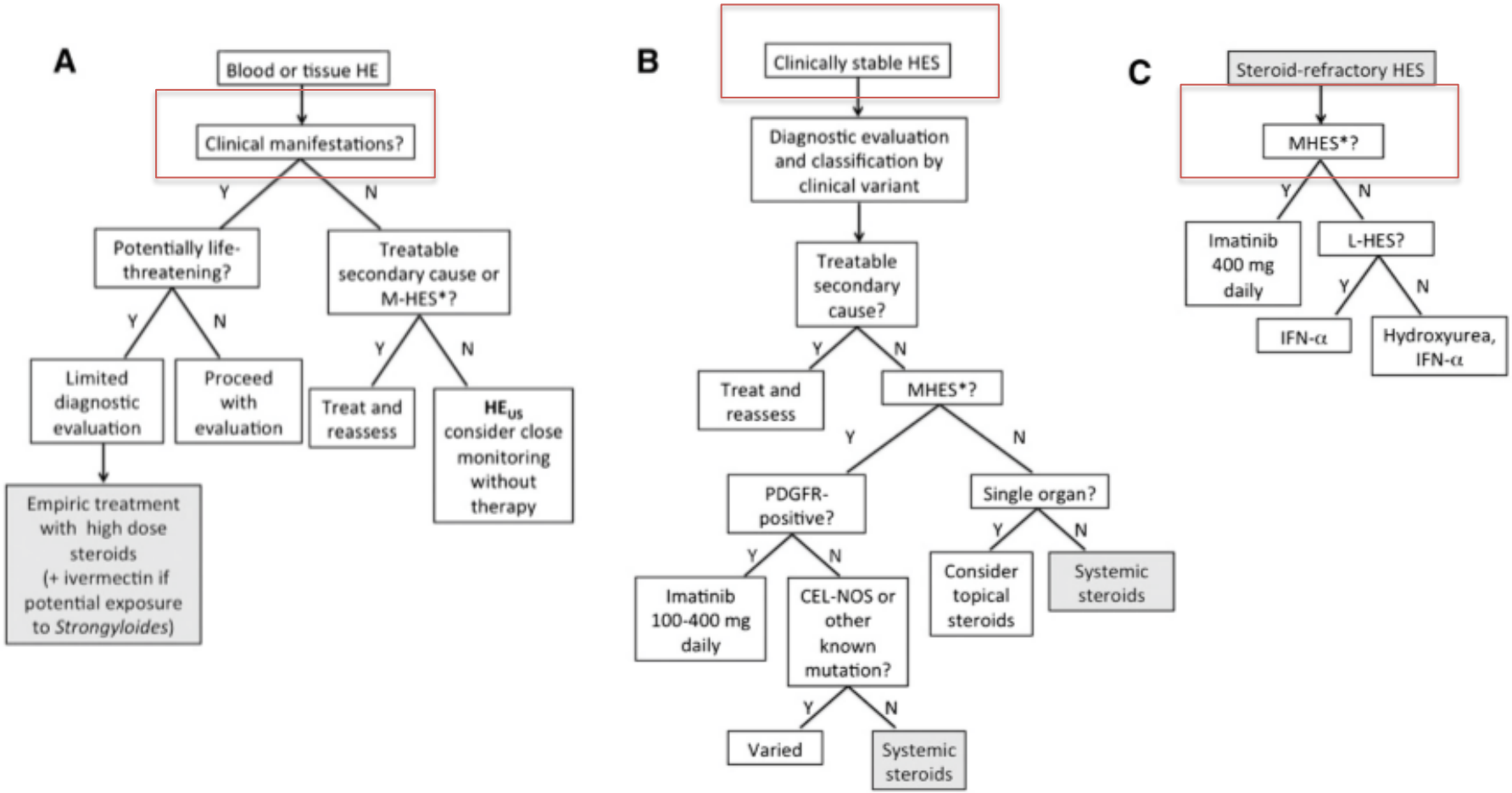
Approccio terapeutico



Ogbogu PU et al, J Allergy Clin Immunol 2009;124:1319–1325

HES: algoritmi terapeutici

KLION AD, BLOOD, 2015, 126, 1069



U-HES

Elbig G, Med Oncol (2014) 31:815

Parameter	HE^{US} (*n*)
Number of patients	40
Gender: male/female	12/28
Median age (range; years)	61 (17–85)
WBC[a] count ($\times 10^9$/L)	11.2 (5.5–70.1)
WBC > 10 ($\times 10^9$/L)	52 %
Hemoglobin (g/dL)	13.0 (8.7–19.1)
Hemoglobin <12 (g/dL)	22 %
Platelet count ($\times 10^9$/L)	289 (68–605)
Platelet count <150 ($\times 10^9$/L)	2 %
AEC[b] ($\times 10^9$/L)	4.2 (1.5–55.4)
AEC >3 $\times$ 10^9/L	42 %
Eosinophils in bone marrow (%)	30.5 (11–78.2)
Serum IgE (IU/mL)[c]	528 (11.9–4,089)
Serum IgE > N[c]	67 %
Serum B12 vitamin (pg/mL)[c]	333 (149–1,431)
Serum B12 > N[c]	2 %

[a] *WBC* white blood cell, [b] *AEC* absolute eosinophil count, [c] normal ranges (N): IgE < 100 IU/mL; for vitamin B12 level: 157–1,057 pg/mL

12 pazienti iniziano steroide, asintomatici, per un valore alto di eosinofili.

Buona riduzione, terapia dipendente, necessità di dosi ridotte continuative

Quale il livello di eosinofili a cui trattare?
Per impedire le complicanze d'organo?

U-HES

Il trattamento di U-HES consiste in **steroide**

se non responsivo o troppo prolungato (evidenze di grado 2b)

breve tentativo con imatinib (4-6 settimane)

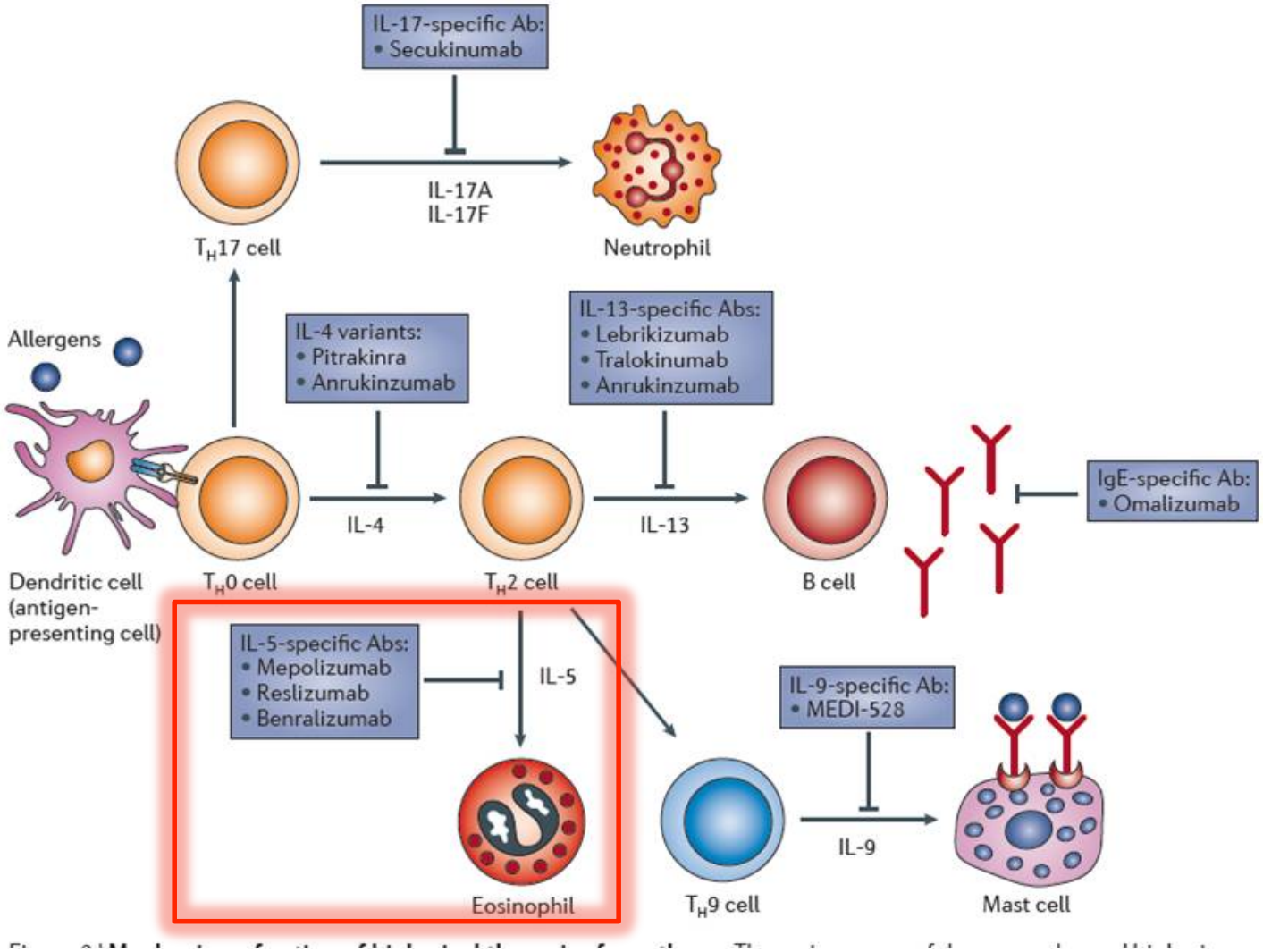
interferone a, ciclosporina, azatioprina (come nelle L-HES)

idrossiurea (nelle forme con leucocitosi marcata)

mepolizumab (nelle forme con interessamento d'organo grave/refrattario)

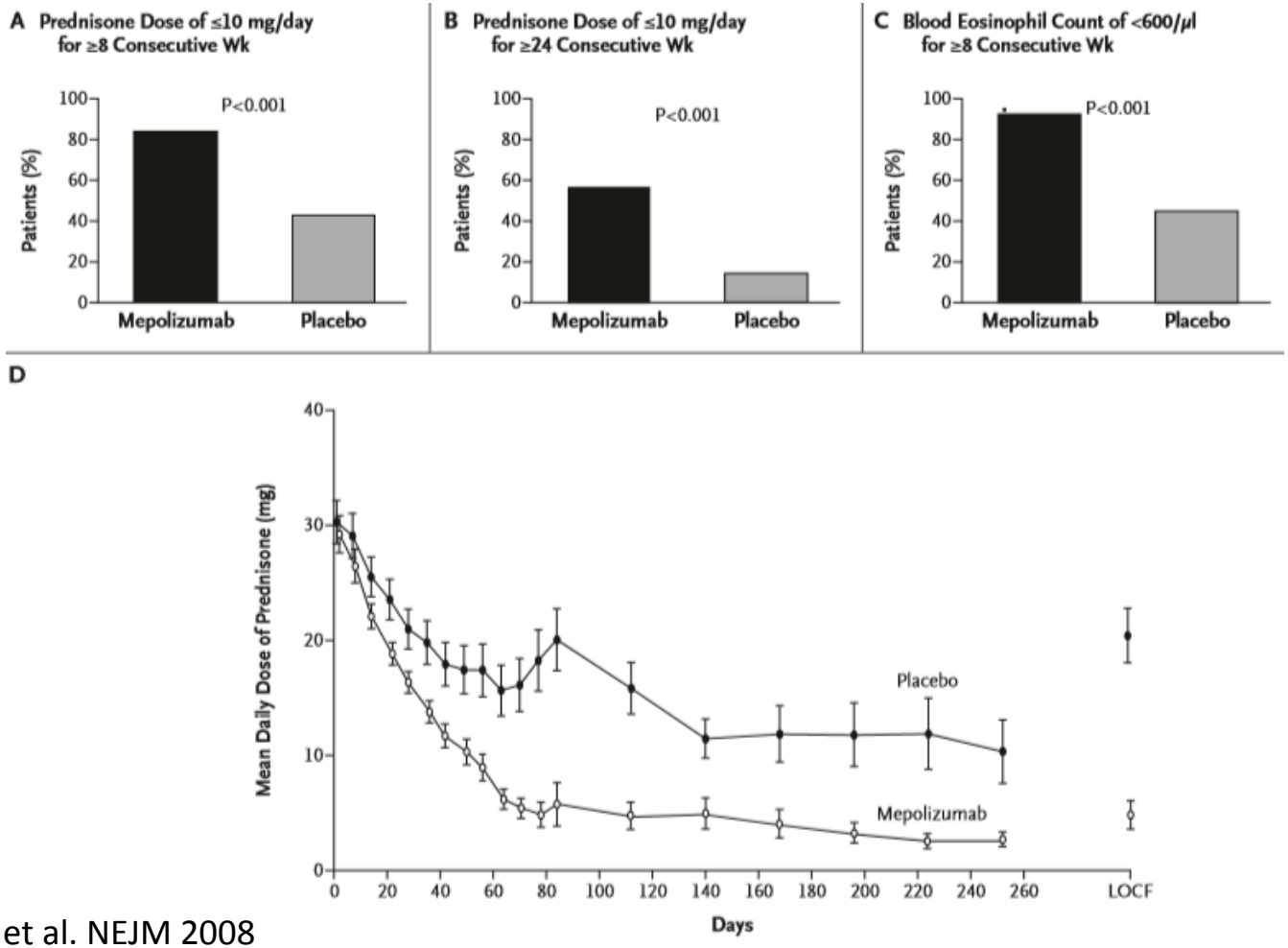
alentuzumab (forme con danno cardiaco o neurologico)

Altri approcci terapeutici



Terapia: mepolizumab

End point primario la riduzione di prednisone a 10 mg o meno per >8 settimane consecutive



Rothenberg et al. NEJM 2008

CONCLUSIONI

- Sindromi eosinofiliche: gruppo eterogeneo di malattie
  - maggiore studio nelle forme US-HES
  - necessità di raccolta dati clinici
- Imatinib: controllo clinico e molecolare (15%? dei pazienti)
- Altri inibitori TK?
- Anti -L5: controllo dell'espressione clinica