ESITI CLINICI: UN IMPEGNO ED UNA RESPONSABILITÀ CONDIVISI

Le patologie del sistema immunitario: gestione multidisciplinare della cronicità con focus sul paziente

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10° CONGRESSO NAZIONALE SIFaCT

24-26 novembre 2022
Centro congressi Fontana di Trevi
Roma

Agenda

LA GESTIONE MULTIDISCIPLINARE

LES

- Perchè parlarne?
- LES-Imitatore
- Manifestazioni clinicghe
- Diagnosi precoce: un unmet need
- Danno d'organo
- Trattamento

ASMA ed EGPA

- Una paziente con asma grave
- Il patient Journey
- Asma o EGPA?
- Diagnosi
- Potevamo pensarci prima?
- Trattamento

Titolo slide

Sifact
SOCIETÀ ITALIANA DI FARMACIA CLINICA E TERAPIA

Mayo Clinic Proceedings
Volume 82, Issue 8, August 2007, Pages 999-1012

SYMPOSIUM ON SOLID TUMORS

A Multidisciplinary Approach to the Management of Breast Cancer, Part 1: Prevention and Diagnosis

Sandhya Pruthi MD [a], Kathleen R. Brandt MD [b], Amy C. Degnim MD [c], Matthew P. Goetz MD [d], Edith A. Perez MD [g], Carol A. Reynolds MD [e], Paula J. Schomberg MD [f], Grace K. Dy MD [d], James N. Ingle MD [d]

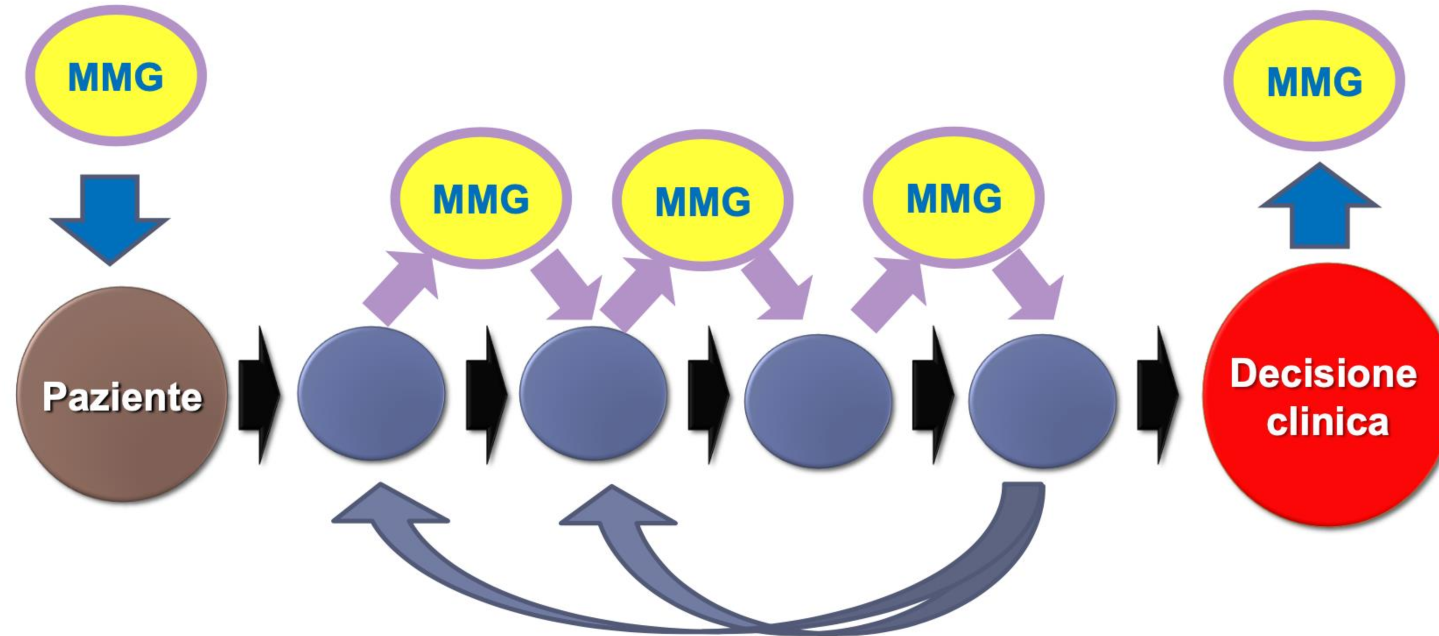
Perché la Multidisciplinarieta?

Gestione della complessità

Competenze multiple

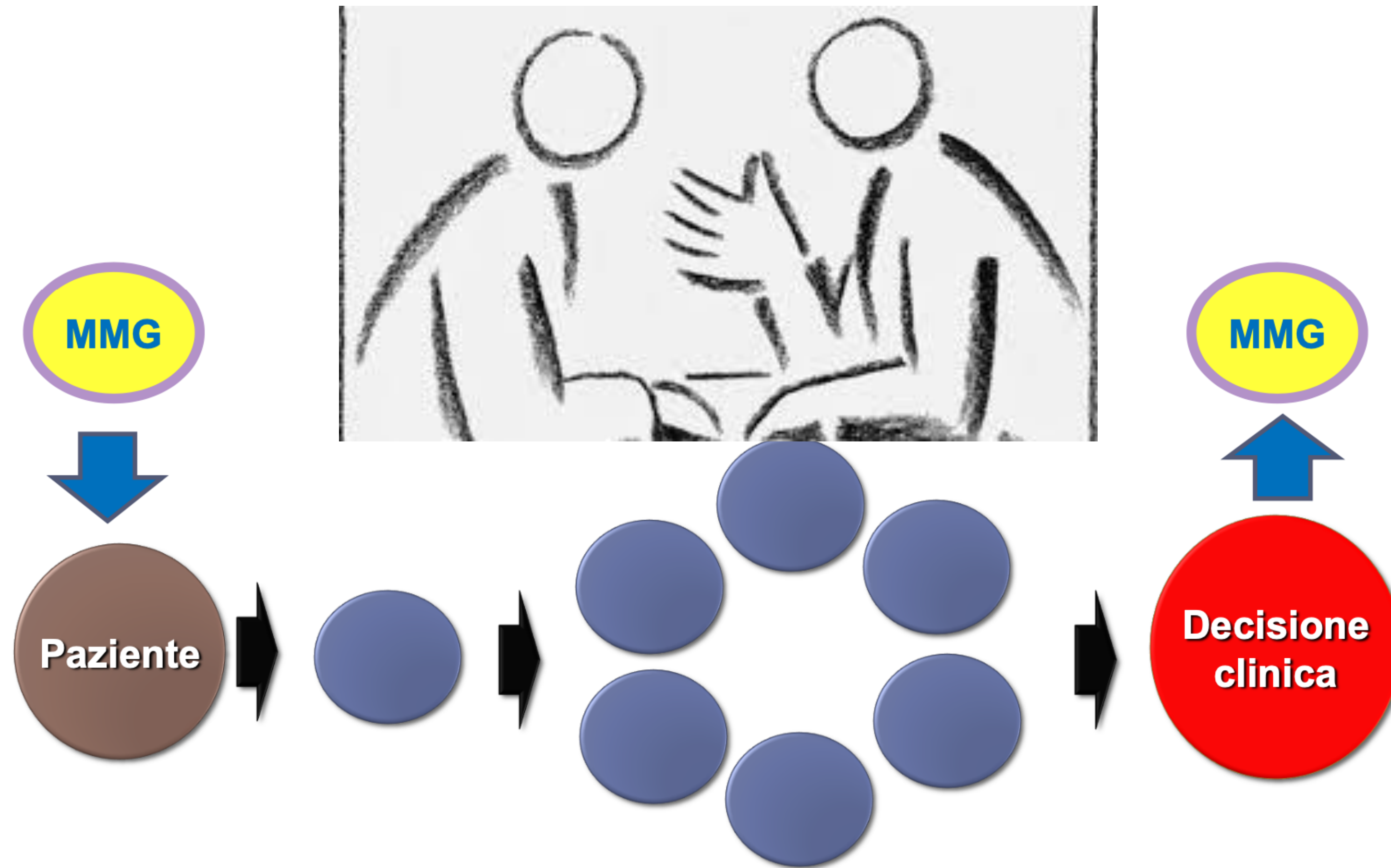
Razionalizzazione delle risorse

INTERAZIONE SEQUENZIALE



- **Tempo**
- **Trasmissione multipla di informazioni**
  - **Rischio di errore**
- **Esclusione di attori rilevanti**
- **Ripetizione di procedure**

INTERAZIONE MULTIDISCIPLINARE



- Riduzione del tempo
- Trasmissione efficace delle informazioni
  - Riduzione del rischio di errore
- Coinvolgimento degli attori necessari
- Unificazione delle procedure

Lupus Eritematoso sistemico:

LES

Perché la Multidisciplinarieta?

MANIFESTAZIONE MULTISISTEMICA

Manifestazione primaria

Perché la Multidisciplinarieta in Immunologia?

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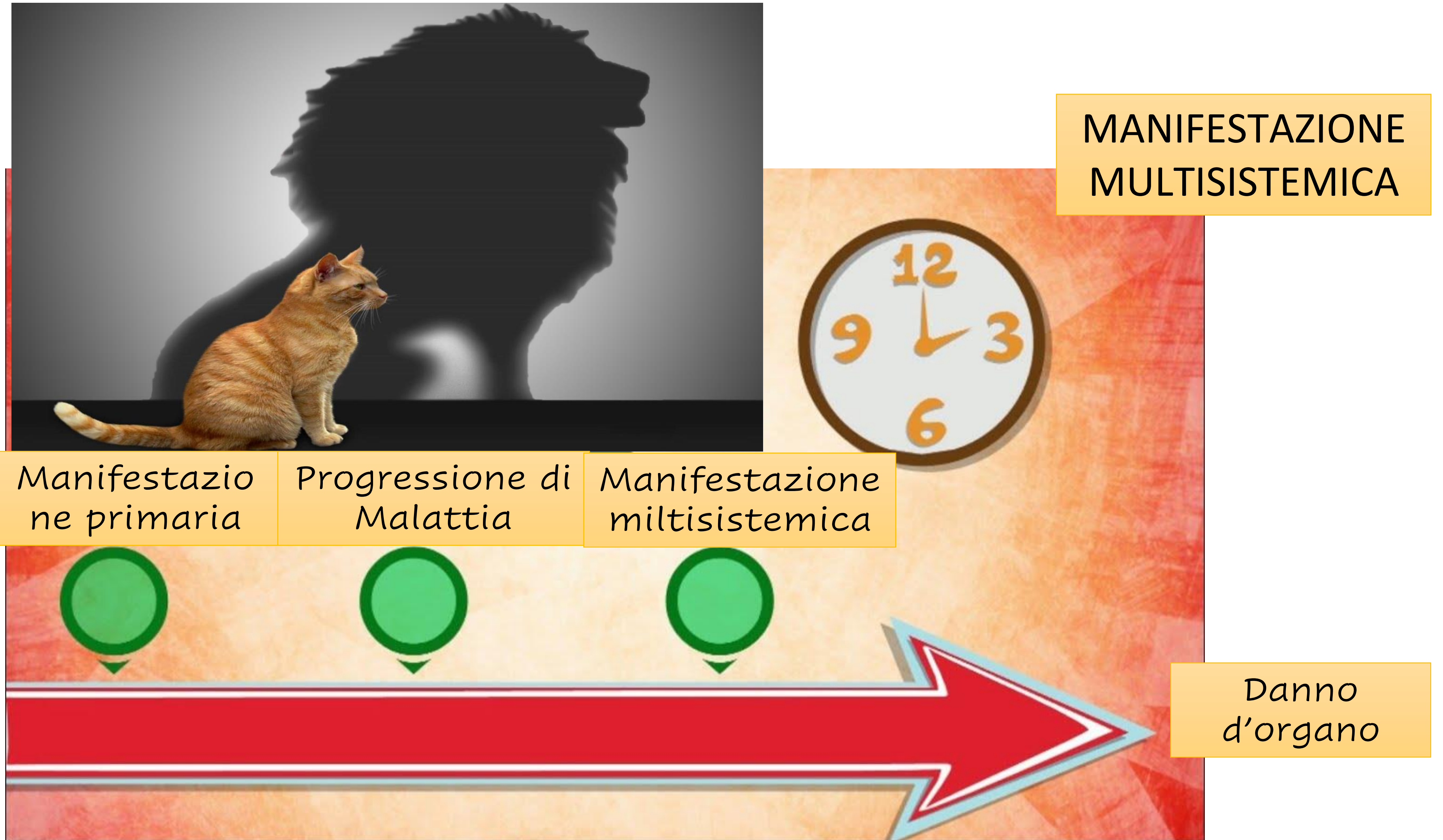

MANIFESTAZIONE MULTISISTEMICA

Manifestazione primaria

Progressione di Malattia

Manifestazione miltisistemica

Danno d'organo

Perché la Multidisciplinarieta in Immunologia?

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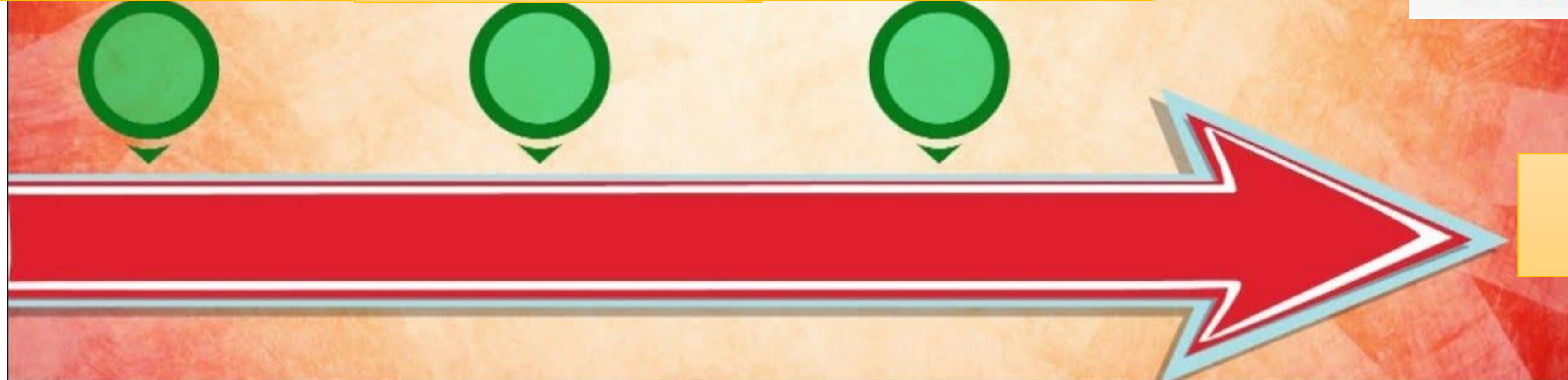
Manifestazione primaria

Progressione di Malattia

Manifestazione miltisistemica



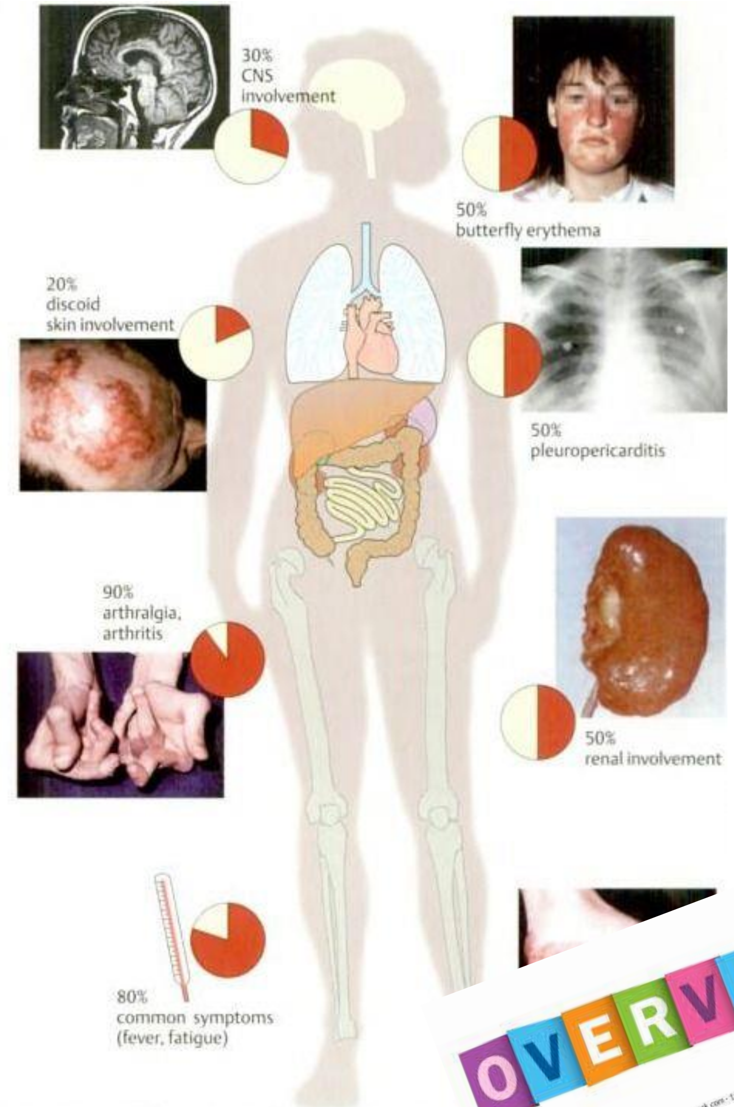
Danno d'organo

Manifestazioni cliniche

Manifestazioni cliniche molteplici e variabili

Presentazione non sincrona

Gravità variabile



A. Clinical manifestations of systemic lupus erythematosus

Manifestazioni cliniche

Asintomatica	**Fase attiva**	**Danno d'organo**
Ab ++ NO Sintomi	Ab ++ Sintomi	Ab ++ Danno irreversibile

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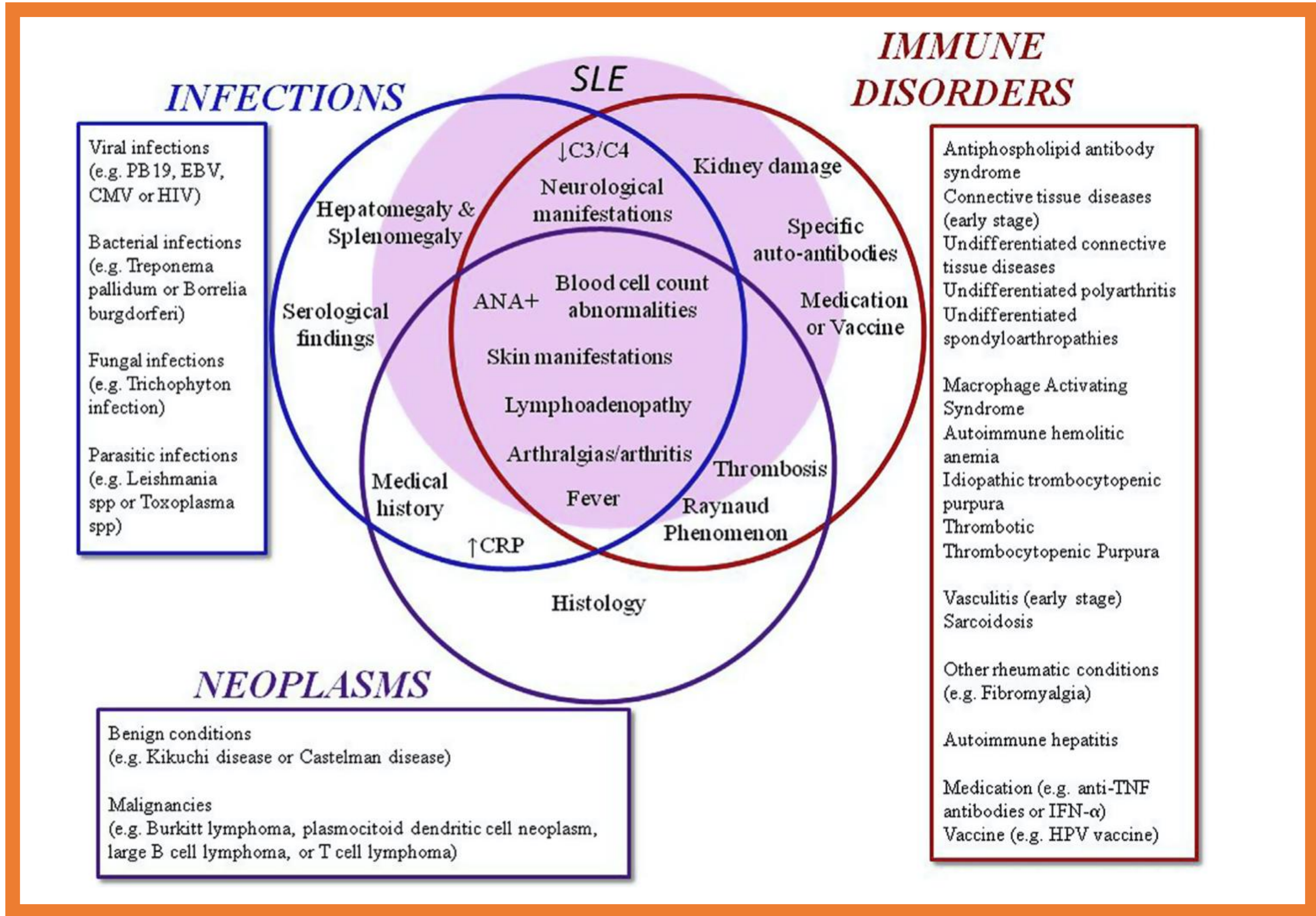
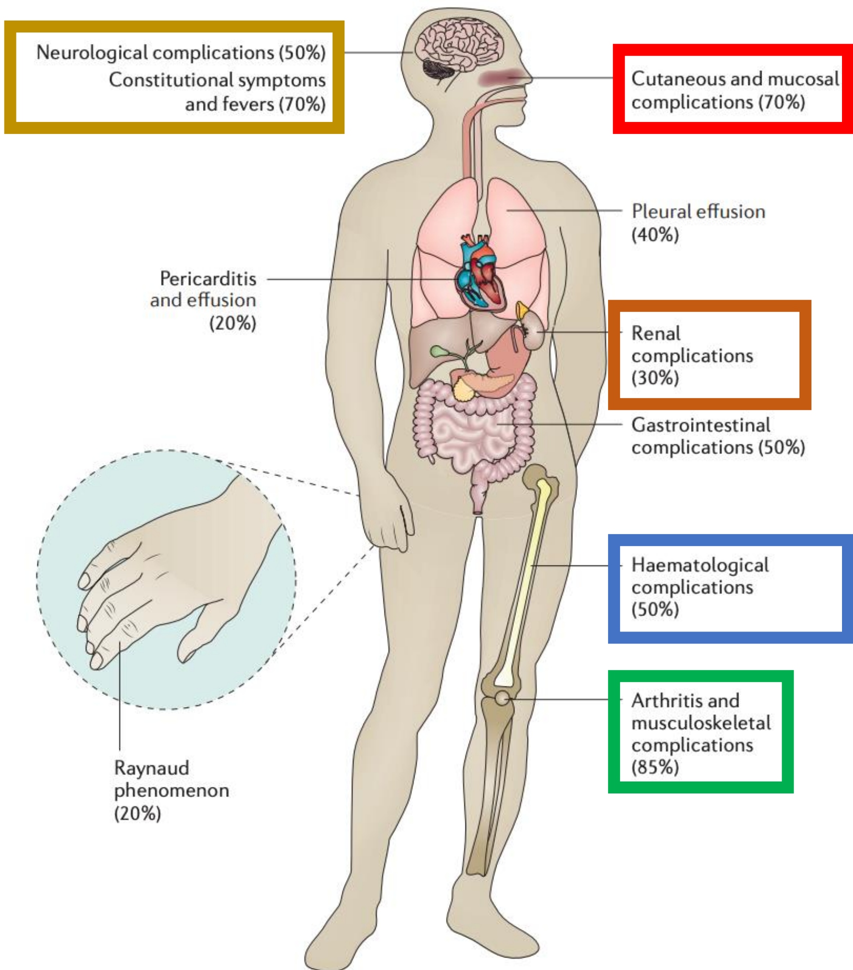
SLE: the «great imitators»

I comuni «lupus-imitatori» devono essere esclusi alla diagnosi



M. Gatto et al. / Best Practice & Research Clinical Rheumatology 33 (2019) 101422

LES: manifestazioni cliniche



Clinical heterogeneity

70%

30%

Pleurisy and pericarditis

Photosensitivity

70%

Immunological heterogeneity

B cell

Plasmablast

Weight change

NK cell

T cell

Lymphocytes

Cutaneous rash (i.e., malar)

70%

Cytokine profile

Type I interferon response

Ulcers

Patient heterogeneity

Neuropsychiatric

Neutrophils/ myeloid cells

Fever

Hematological

70%

85%

50%

Musculoskeletal

Raynaud's phenomenon

Fatigue

Trends in Molecular Medicine

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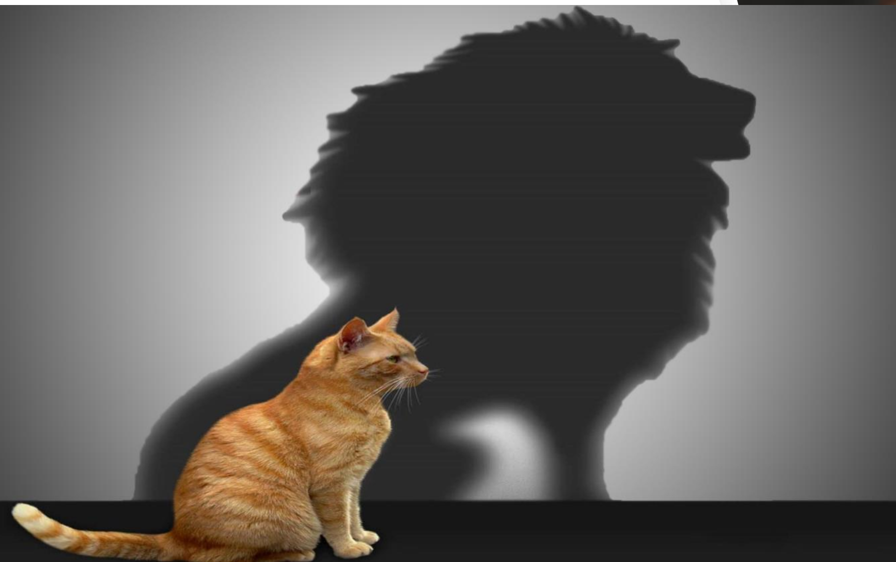
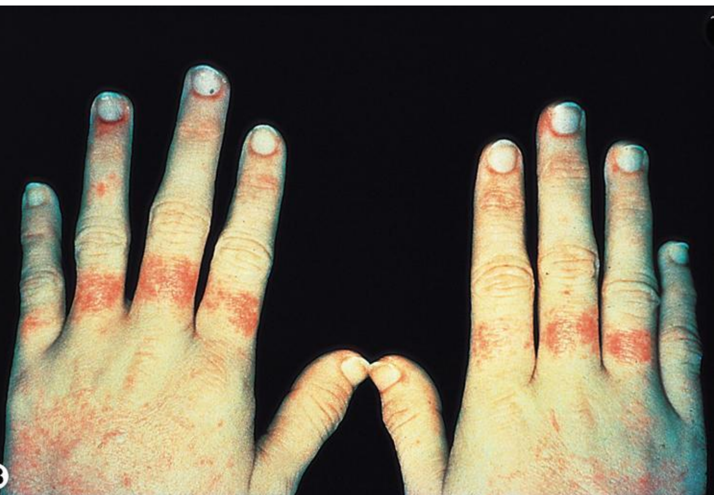
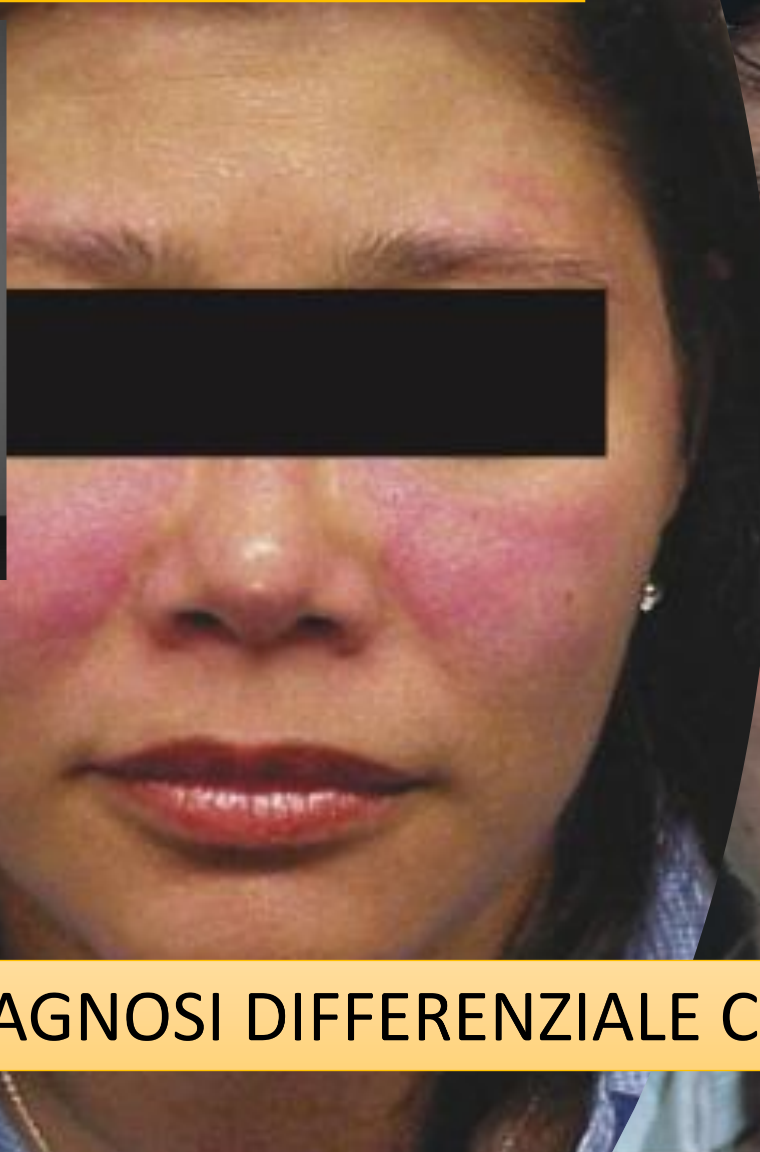
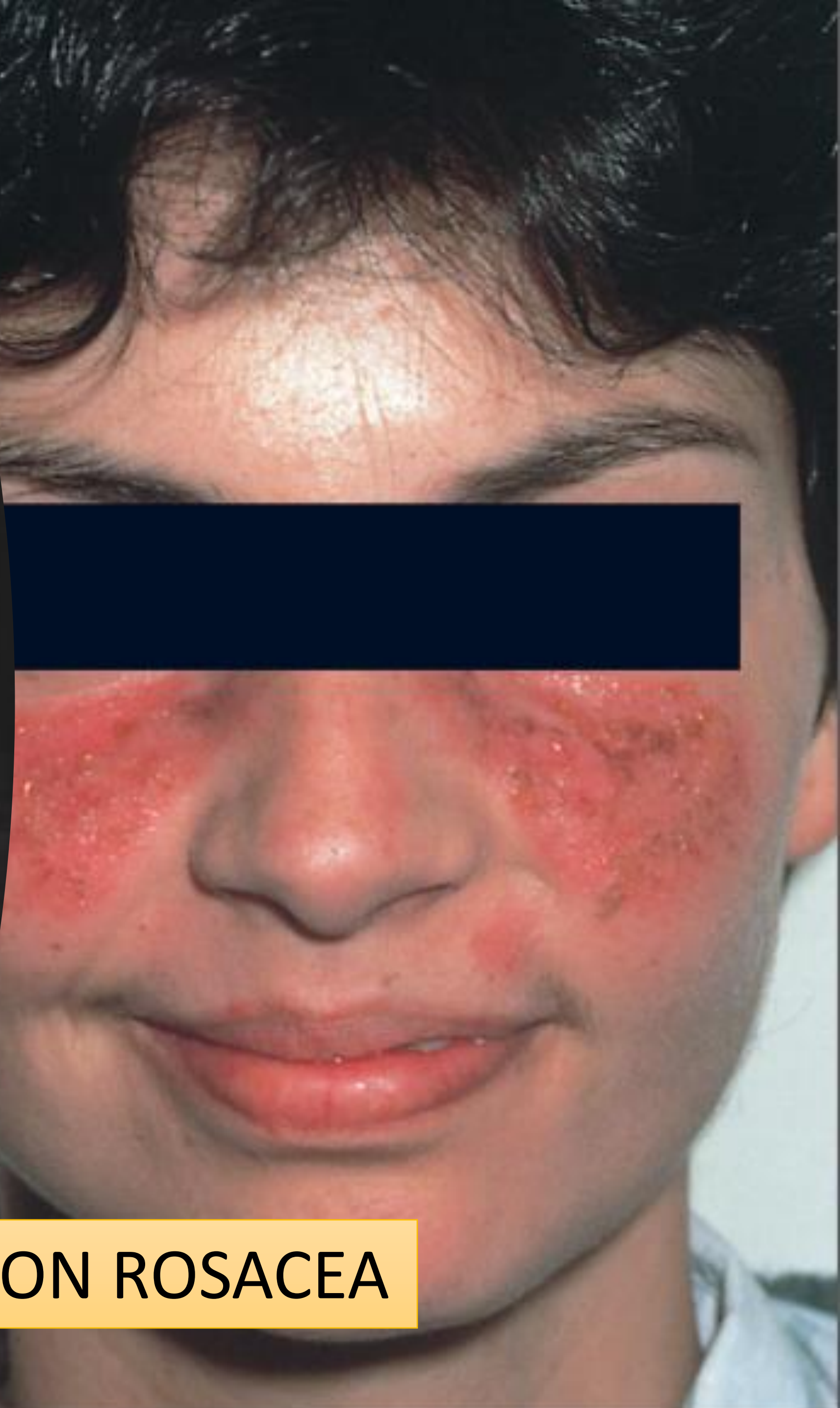
CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)







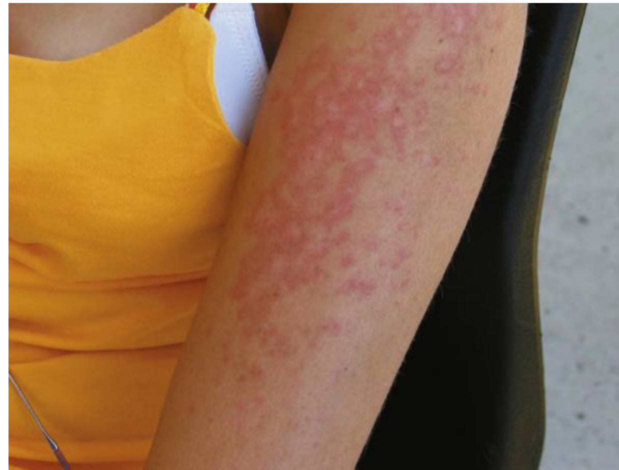


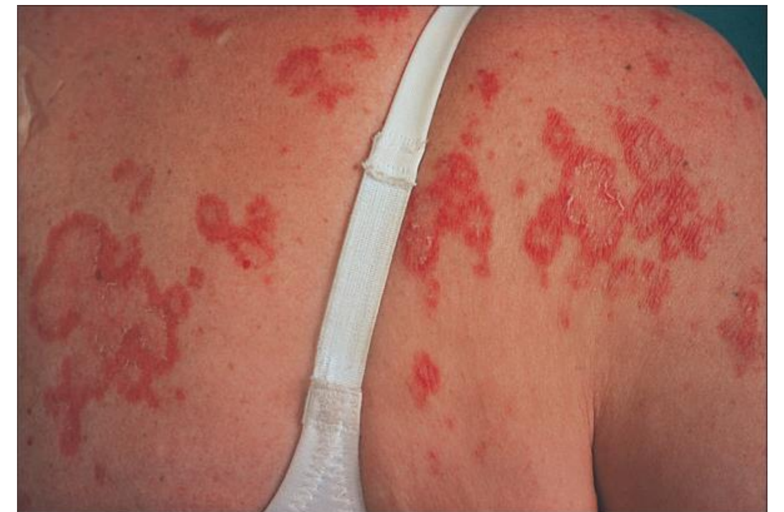
DIAGNOSI DIFFERENZIALE CON ROSACEA

CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

1. **Lupus Subacuto**

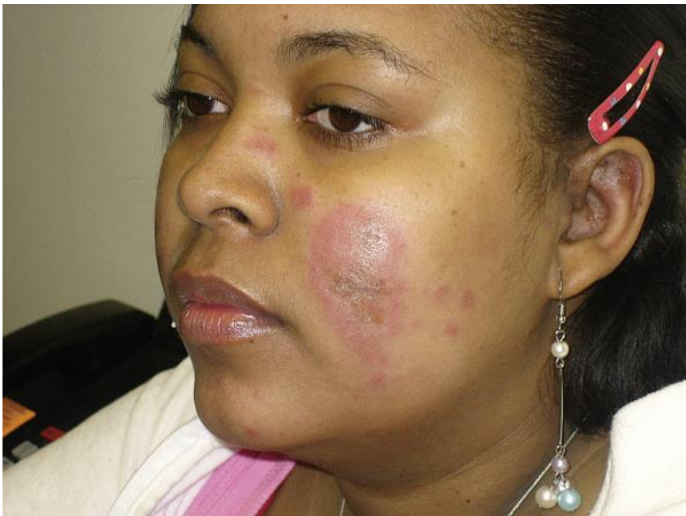
papule eritematose ed eritemato-squamose; evolve in placche eritemato-squamose o in lesioni policicliche

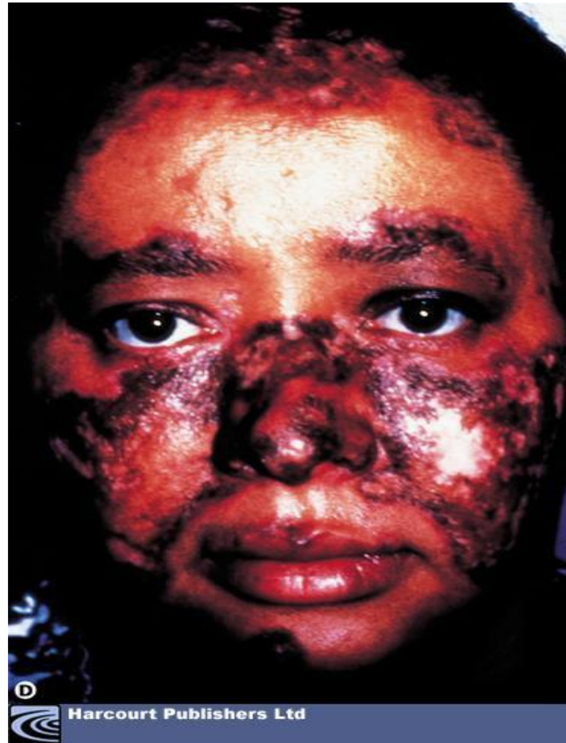


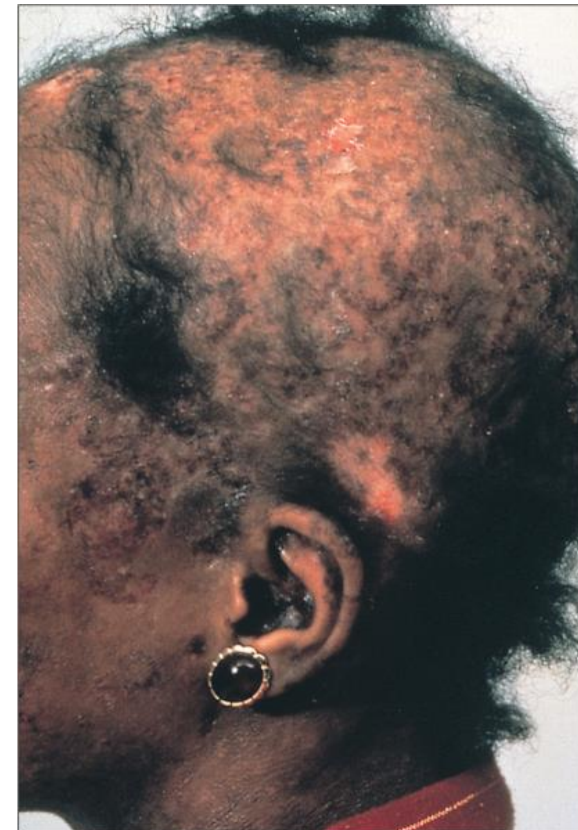


CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

2. Rash discoide (placche eritematose sollevate, con cheratosi aderente ad evoluzione cicatriziale)

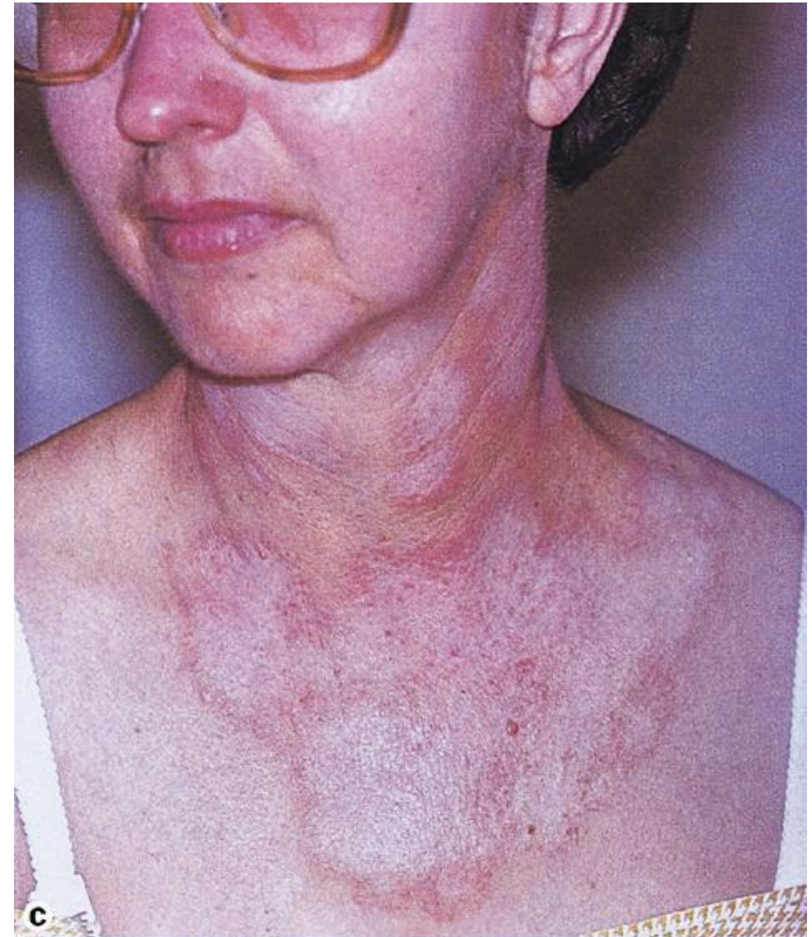






CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

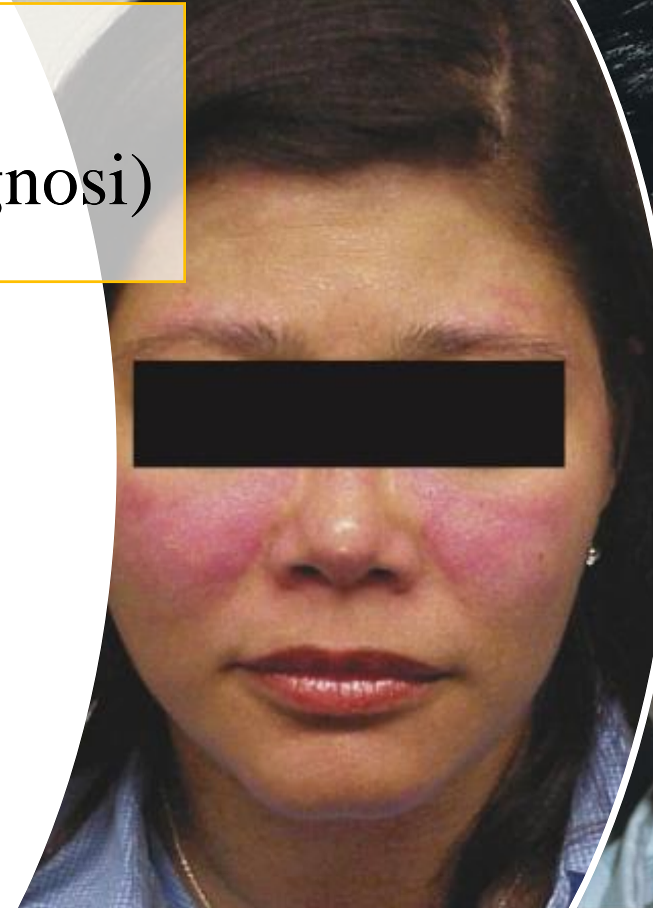
3. **Fotosensibilità**

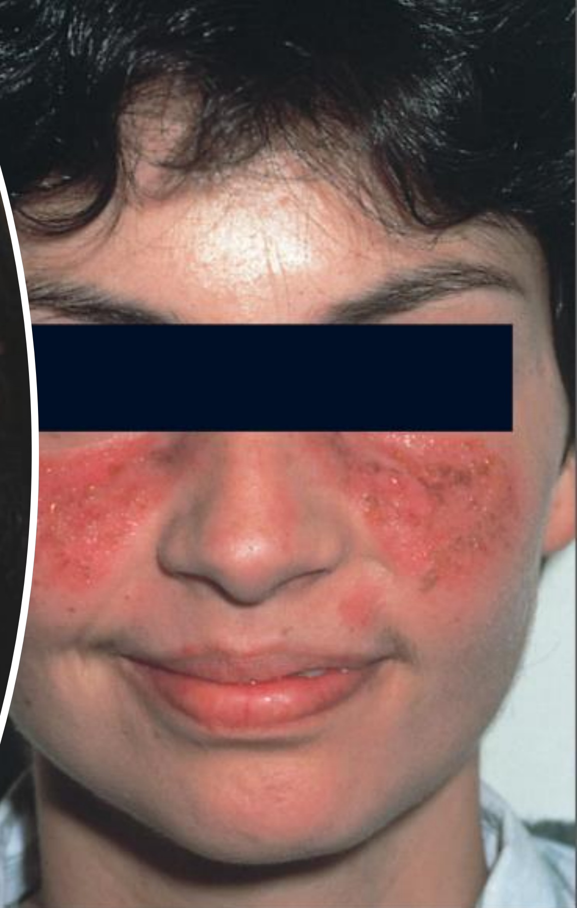


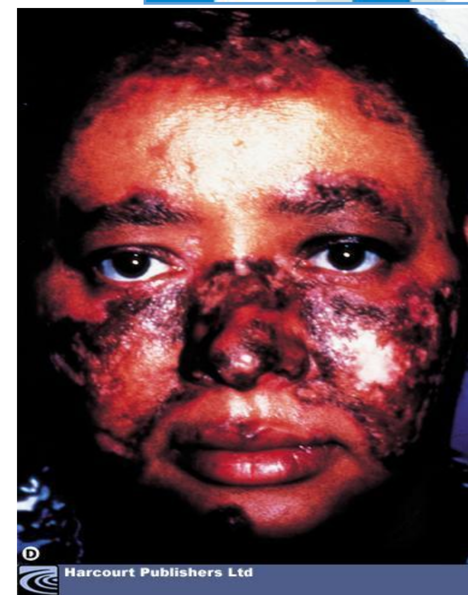
CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

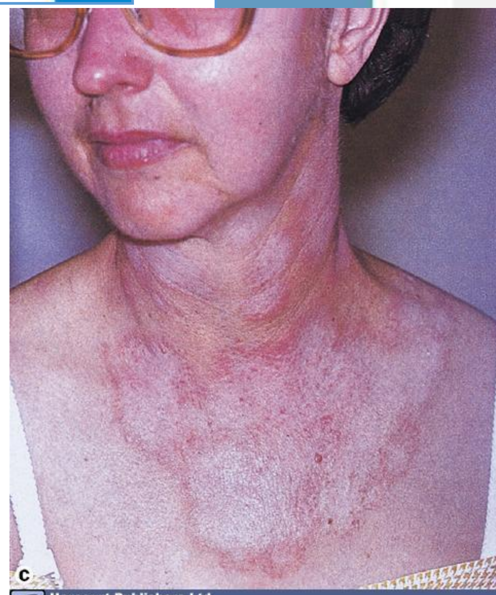
Dermatologo

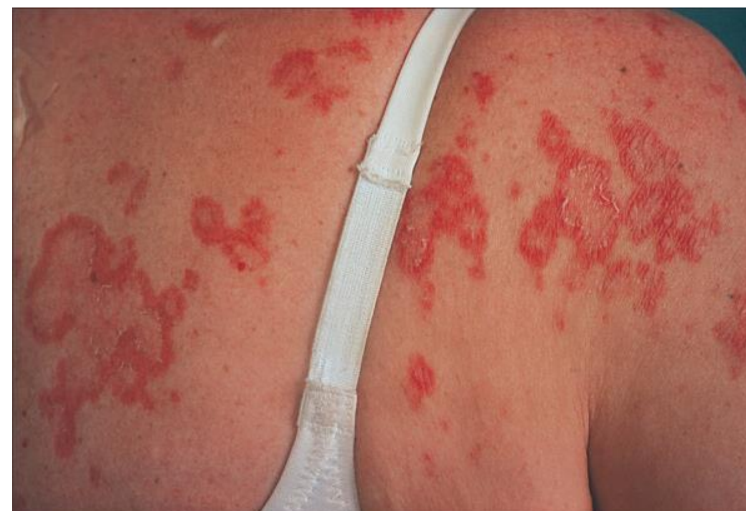
MMG

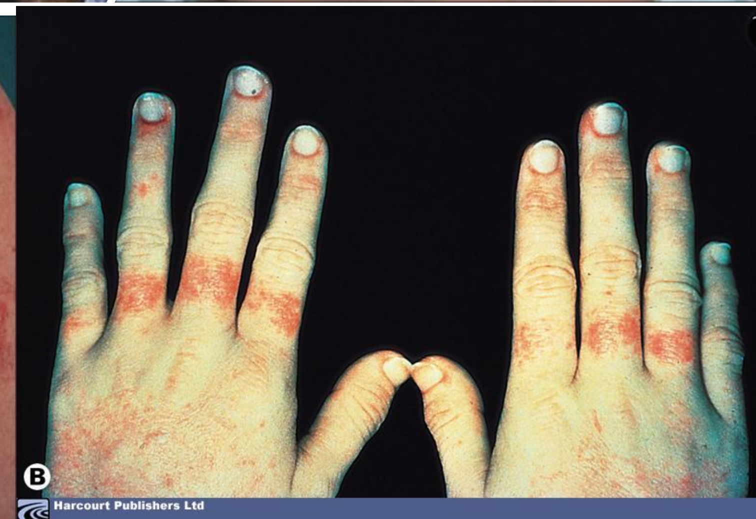






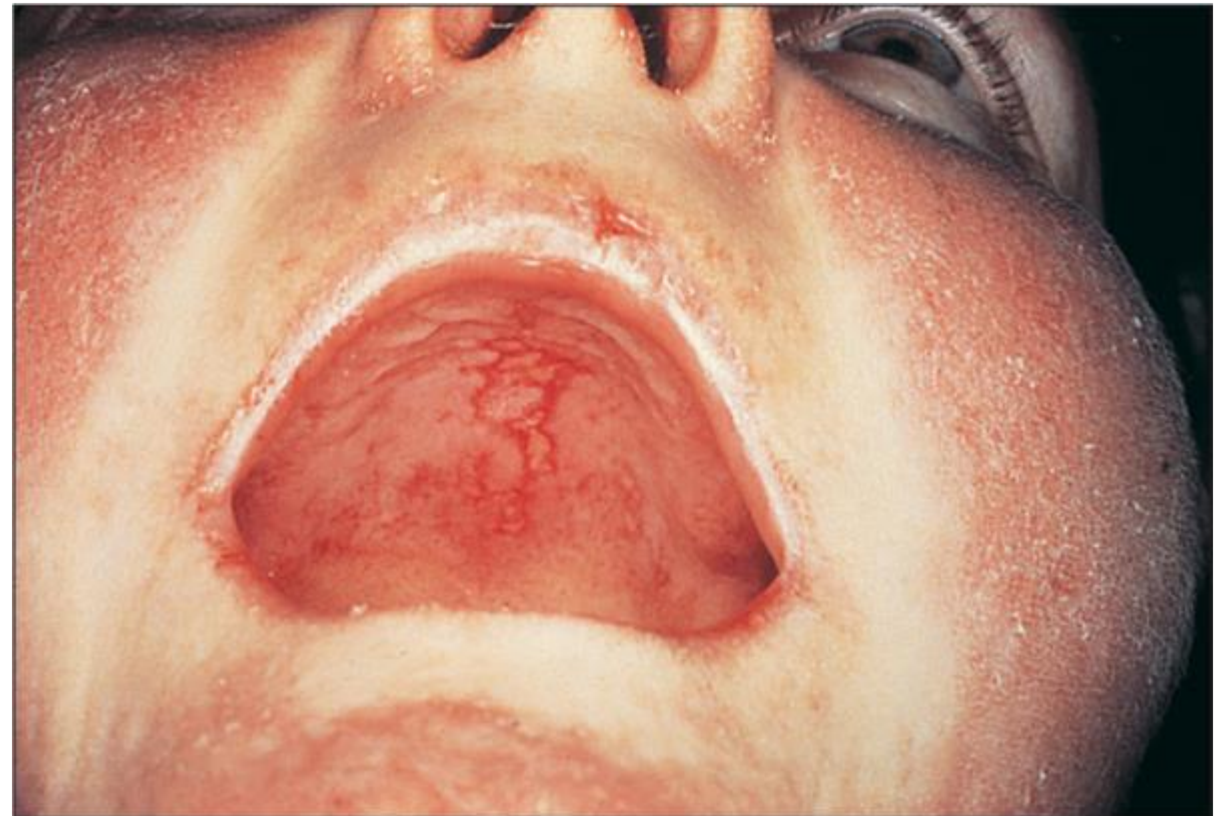






CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

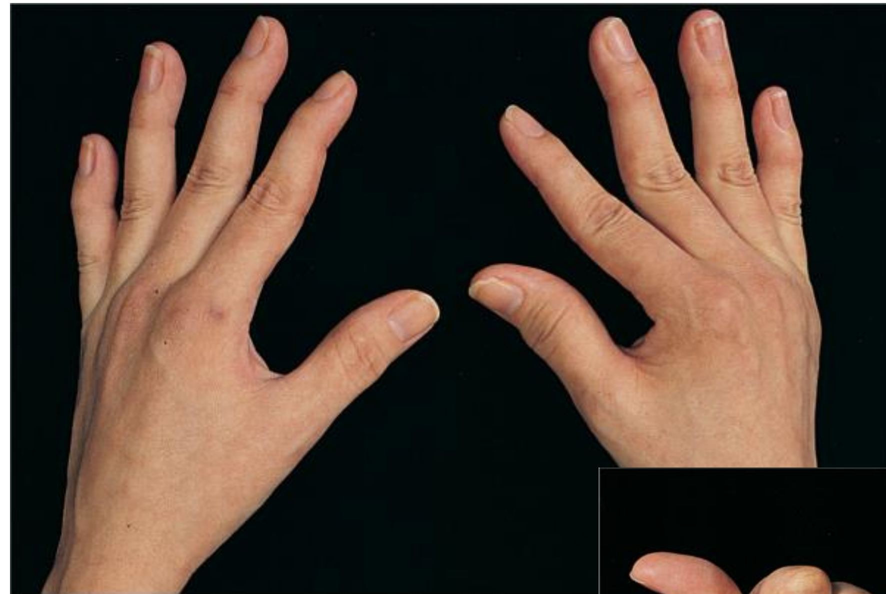
4. Ulcere orali

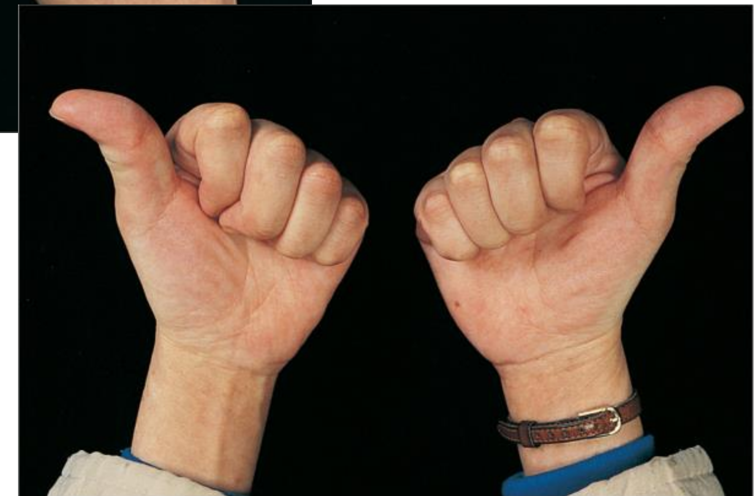


CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

5. Artralgia e/o Artrite

non erosiva coinvolgente 3 o più articolazioni periferiche, caratterizzata da dolenzia e tumefazione)

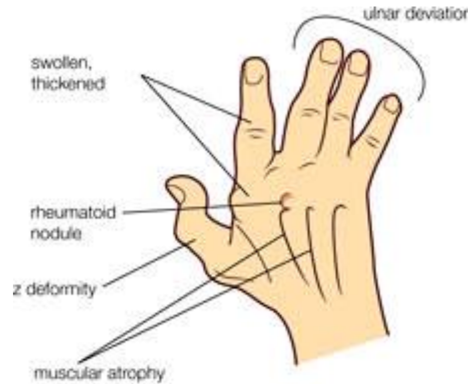


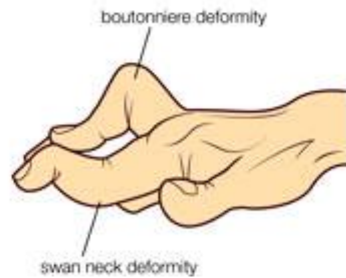


Coinvolgimento articolare nel LES

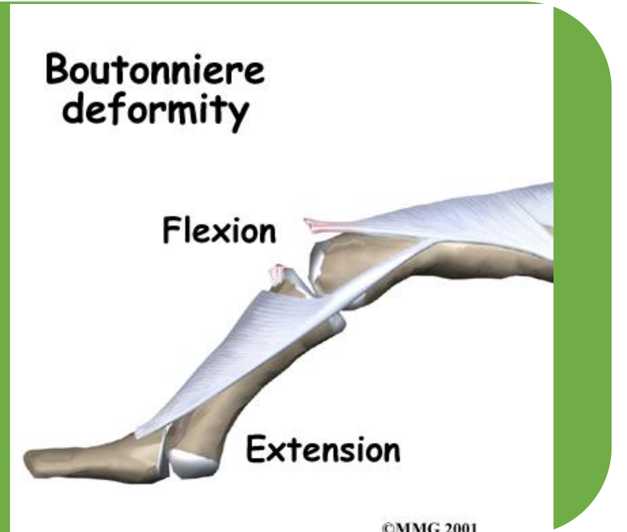
Tumefazioni articolari con deviazione delle metacarpo-falangee, senza erosioni ossee

(cosiddetta artropatia di Jaccoud)





Immunologo/Reumatologo

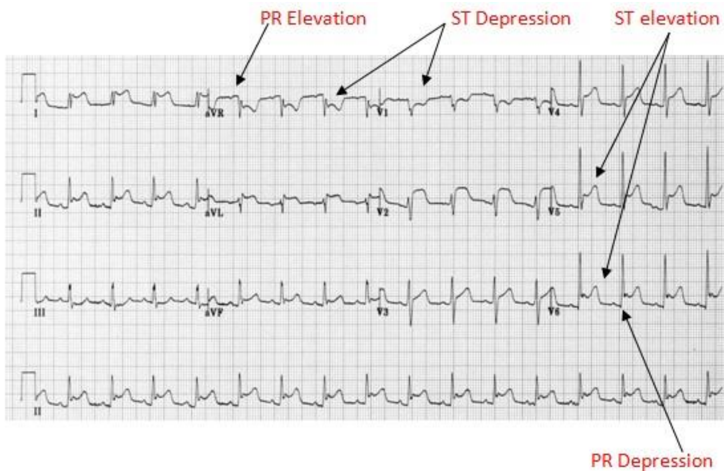


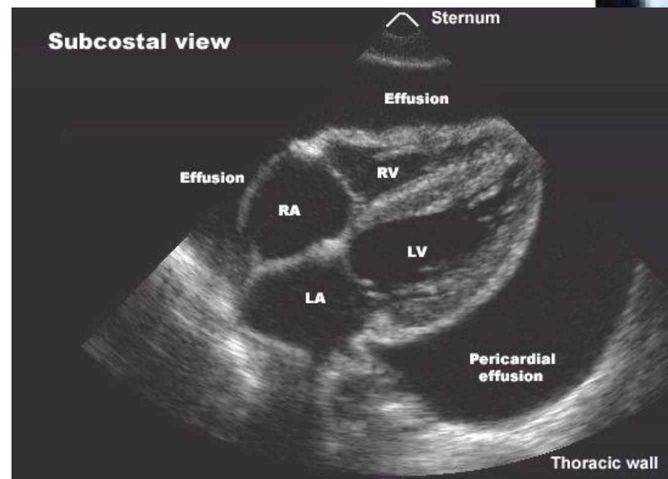
CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

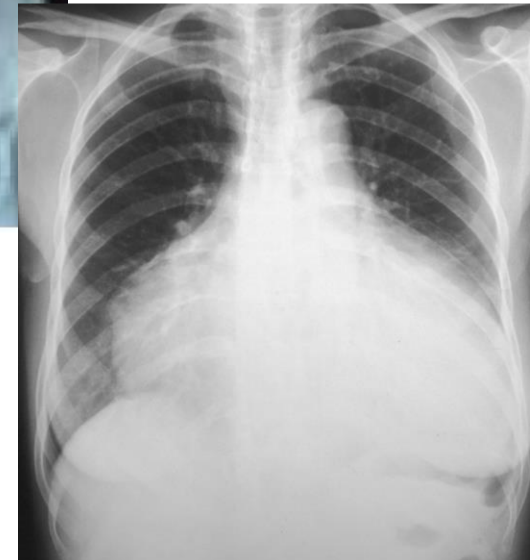
6. Sierosite

(a) pleurite — anamnesi convincente di dolore pleurico o di sfregamento pleurico o evidenza di versamento pleurico

(b) pericardite — documentata da ECG, sfregamento o evidenza di versamento pericardico





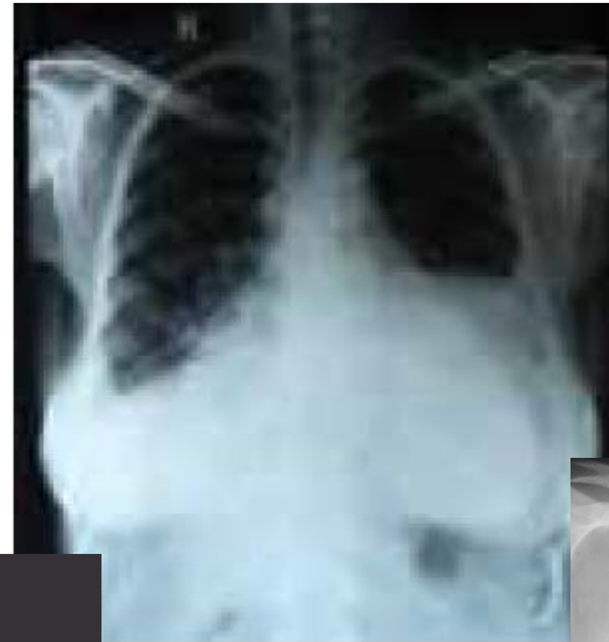


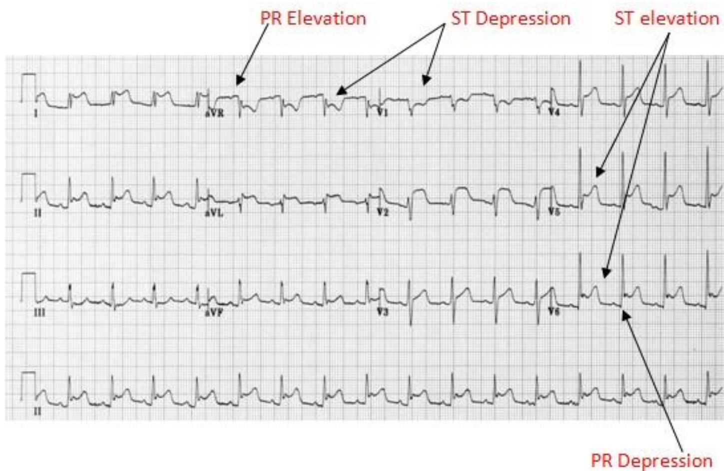
CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

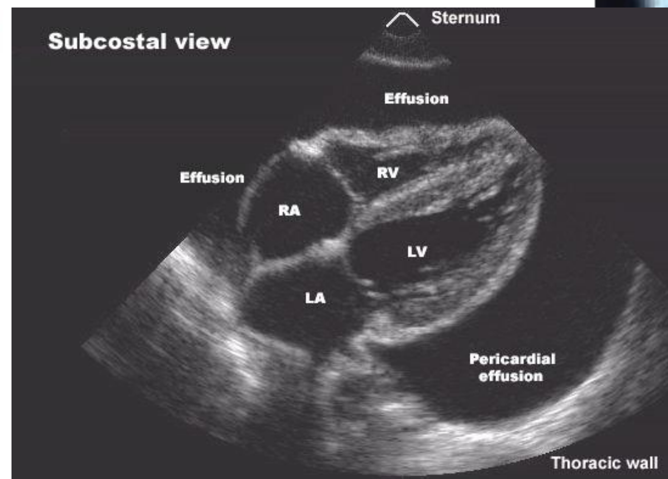
6. Sierosite

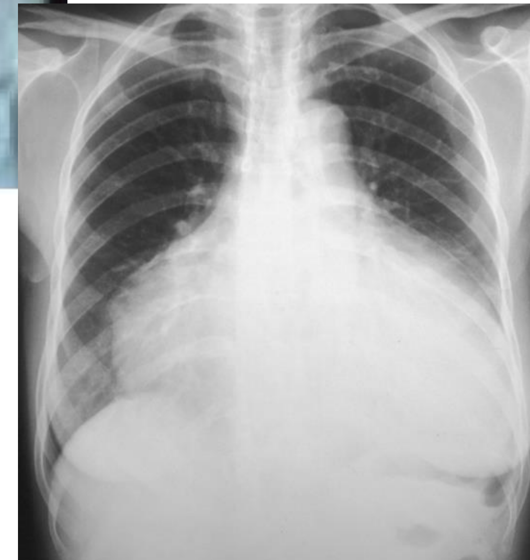
Pneumologo

Cardiologo







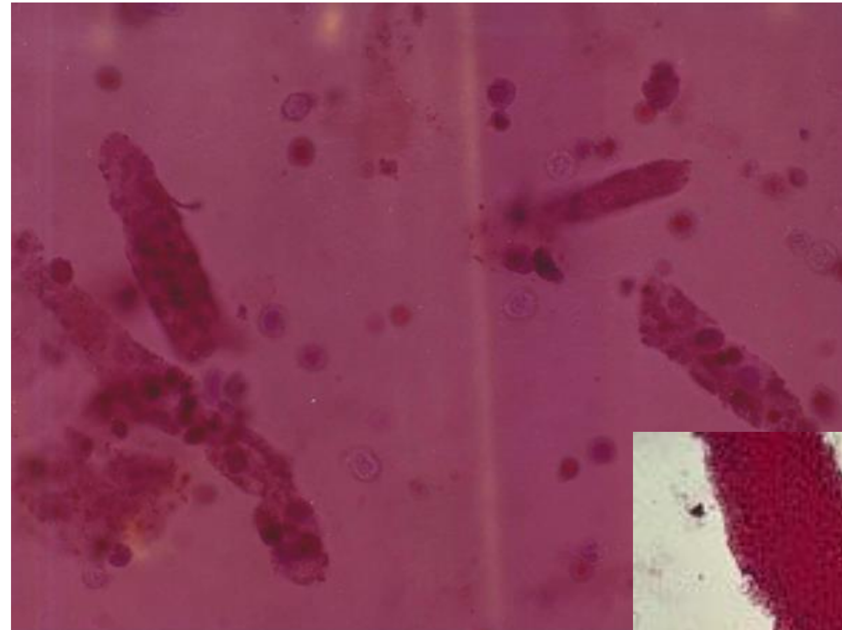


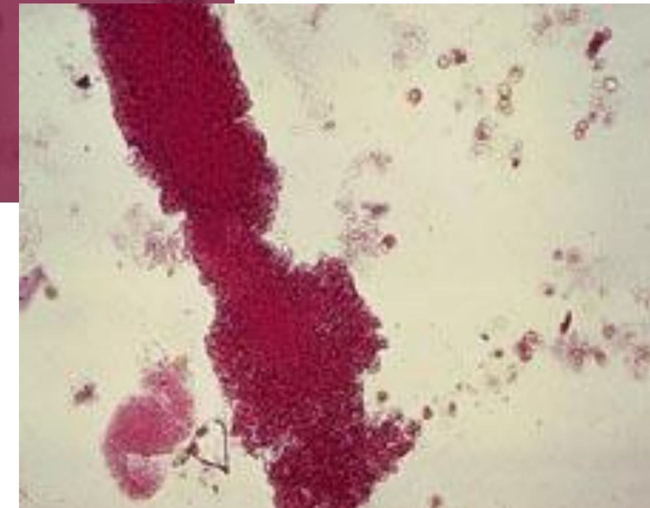
CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

7. **Coinvolgimento renale**

(a) *persistente proteinuria*: > 0.5 gr/24h o 3 + in un campione o

(b) *cilindri cellulari — eritrocitari*, granulari, tubulari o misti



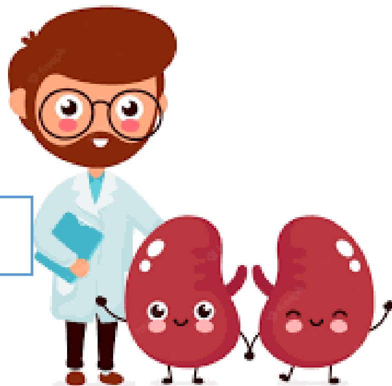


WHO CLASSIFICATION OF LUPUS NEPHRITIS (2004)

- Classe I Nefrite minima mesangiale
- Classe II Nefrite mesangiale proliferativa
- Class III Nefrite focale
- Class IV o Nefrite diffusa segmentaria (IV-S) globale (IV- G)
- Class V Nefrite membranosa
- Class VI Nefrite sclerosante avanzata

BIOPSIA RENALE

CORRETTA DIAGNOSI
=
TERAPIA MIRATA
e
RIDOTTA PROGRESSIONE DI MALATTIA



Nefrologo

CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

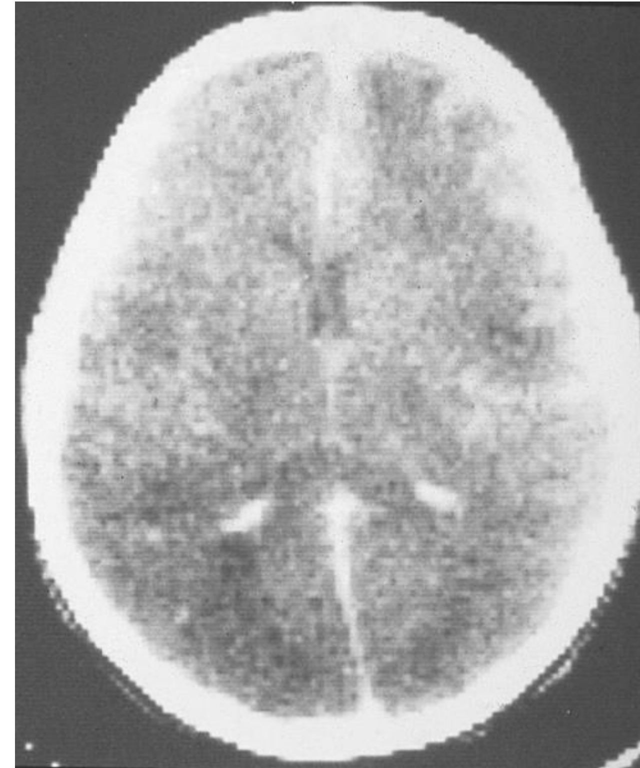
8. Coinvolgimento neurologico

(a) **convulsioni** — in assenza di farmaci epilettogeni o alterazioni metaboliche note (es. uremia, chetoacidosis o iposodiemia)

o

(b) **psicosi** — in assenza di farmaci o alterazioni metaboliche note

Neurologo



CLASSIFICATION OF SLE 1997 ACR REVISED CRITERIA (4 criteri per la diagnosi)

9. Coinvolgimento ematologico (1 o +)

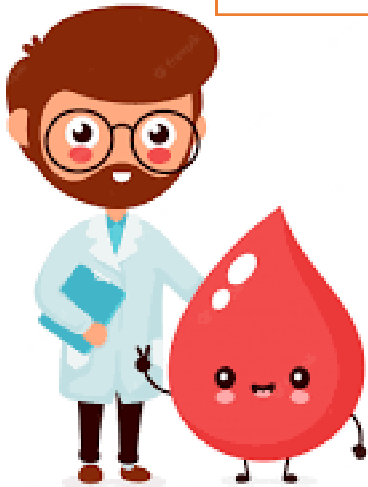
(a) anemia emolitica — con reticolocitosi

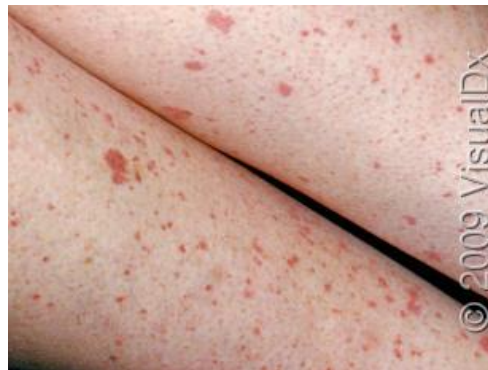
(b) leucopenia <4000/mm3 in 2 o più occasioni

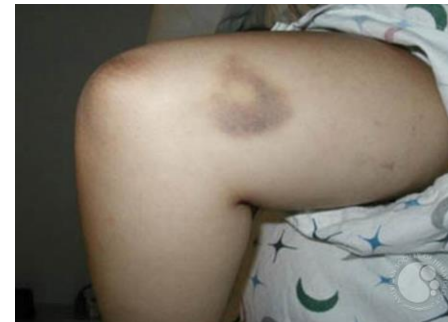
(c) linfopenia <1500/mm3 in 2 o più occasioni

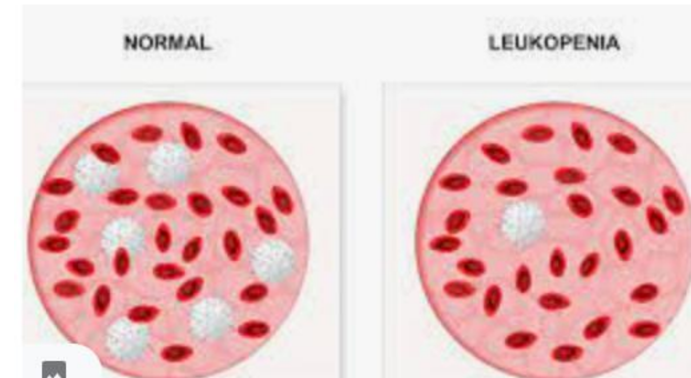
(d) trombocitopenia <100,000/mm3 in assenza di farmaci

Ematologo









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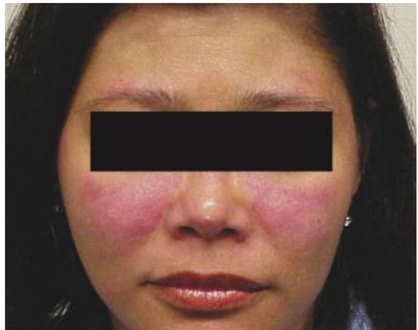
Unmet needs: diagnosi precoce

LES

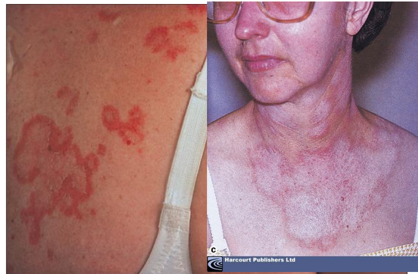
LES: Red Flags diagnostiche

Cute e Mucose

Eritema malare-rosacea

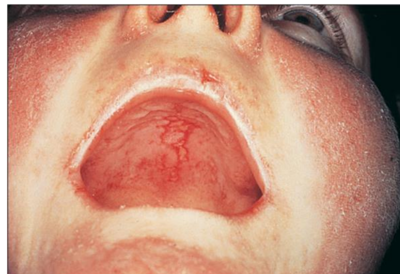


Lupus Subacuto



Lupus cutaneo acuto-dorso mani

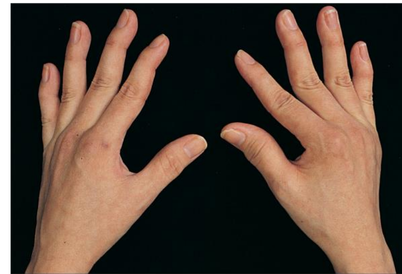
Aftosi Orale



Fotosensibilità

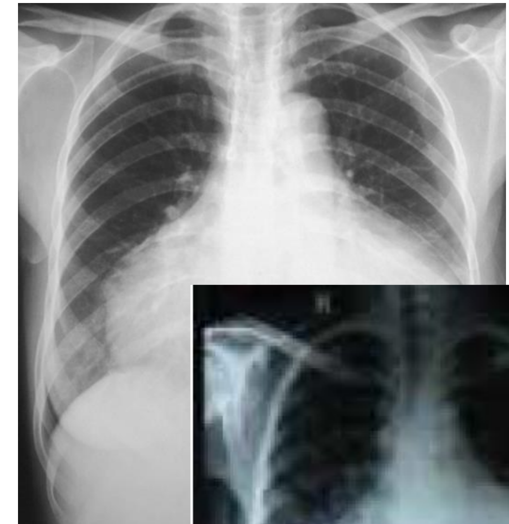
Articolazioni

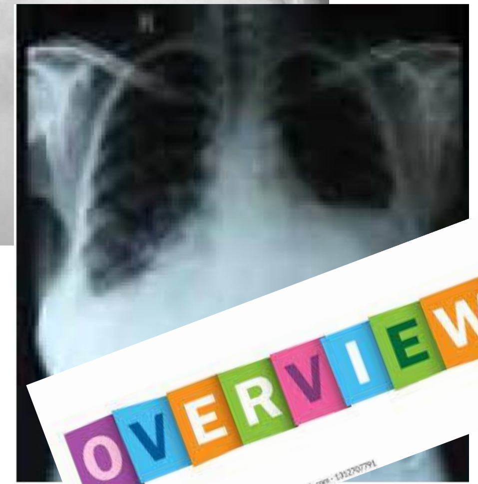
Poliartralgia



Artrite non erosiva

Sierose



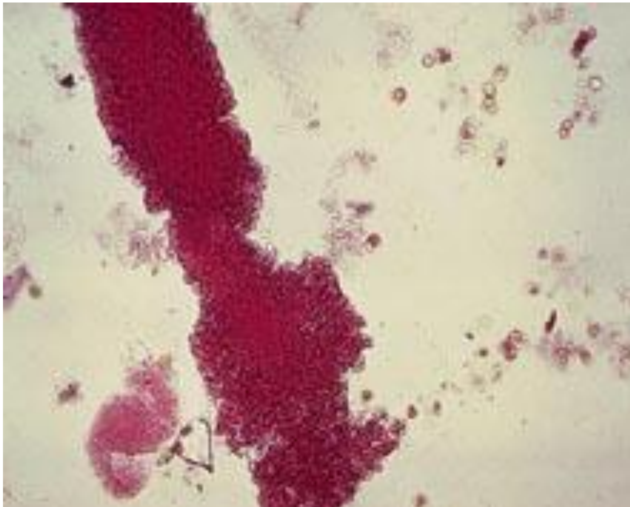


LES: Red Flags diagnostiche

RENE

(a) *persistente proteinuria:* > 0.5 gr/24h

(b) *cilindri cellulari — eritrocitari*, granulari, tubulari o misti

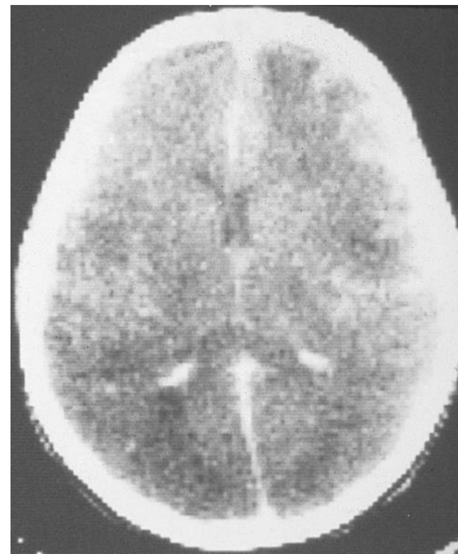


SNC

(a) convulsioni —

o

(b) **psicosi** —



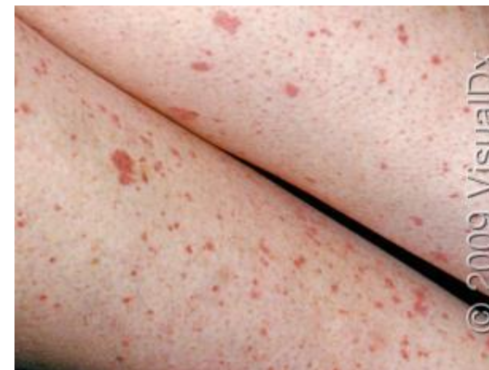
Coinvolgimento ematologico

(a) anemia emolitica —

(b) leucopenia

(c) linfopenia

(c) trombocitopenia



OVERVIEW

Clinical Rheumatology

LES: Diagnosi Precoce

20%

4-6 anni

Sintomi clinici	**Segni laboratristici**
• Febbre	Proteinuria/casts
• Artralgia	Anti-DNA
• Rash cutaneo	Ipo-C3
• Fotosensibilità	Anti-PL
• Aftosi	IgG autoreattive

M. Gatto et al. / Best Practice & Research Clinical Rheumatology 33 (2019) 101422

Agenda

LA GESTIONE MULTIDISCIPLINARE

LES

- Perchè parlarne?
- LES-Imitatore
- Manifestazioni cliniche
- Diagnosi precoce: un unmet need
- **Danno d'organo**
- Trattamento

ASMA ed EGPA

- Una paziente con asma grave
- Il patient Journey
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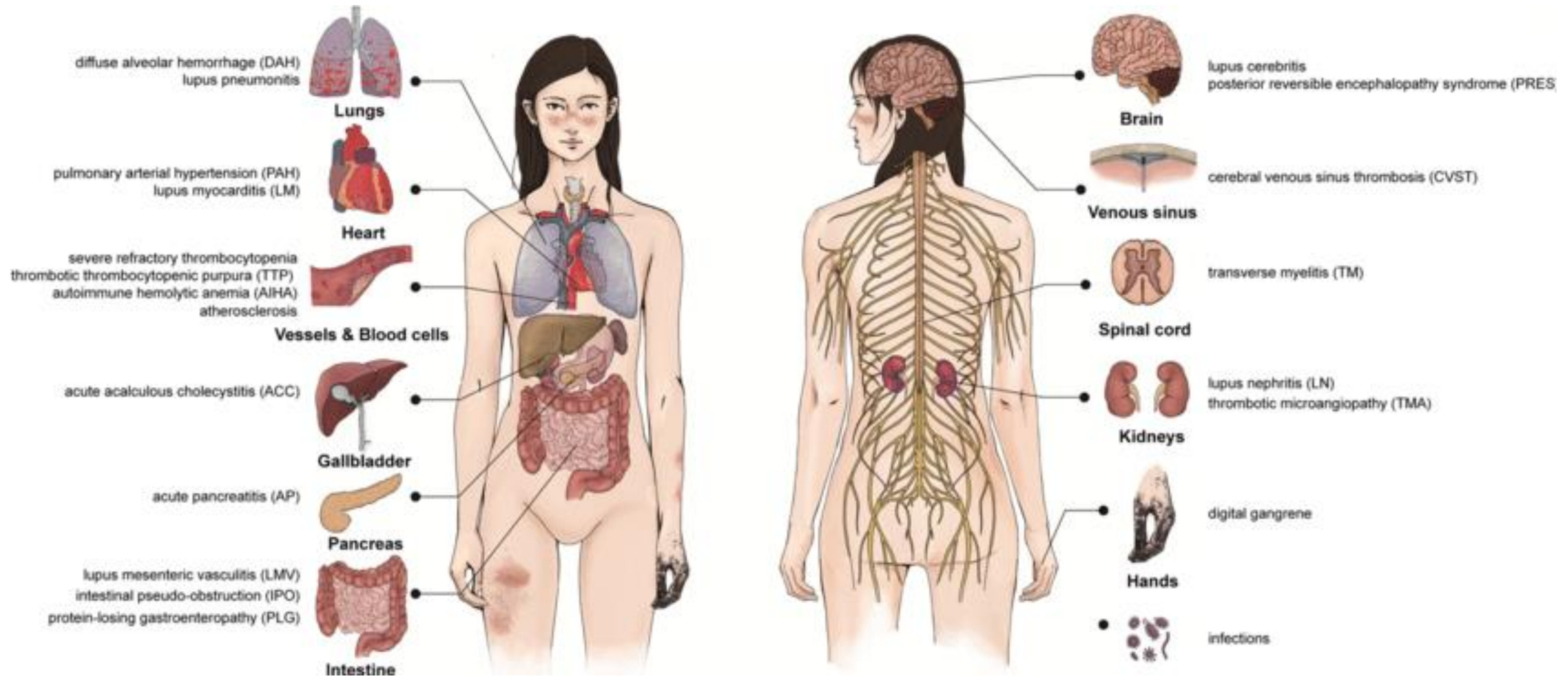
- Diagnosi
- Potevamo pensarci prima?
- Trattamento

Danno d'organo



Yang, H et al. Clinical Reviews in Allergy & Immunology, 2021

Definizione

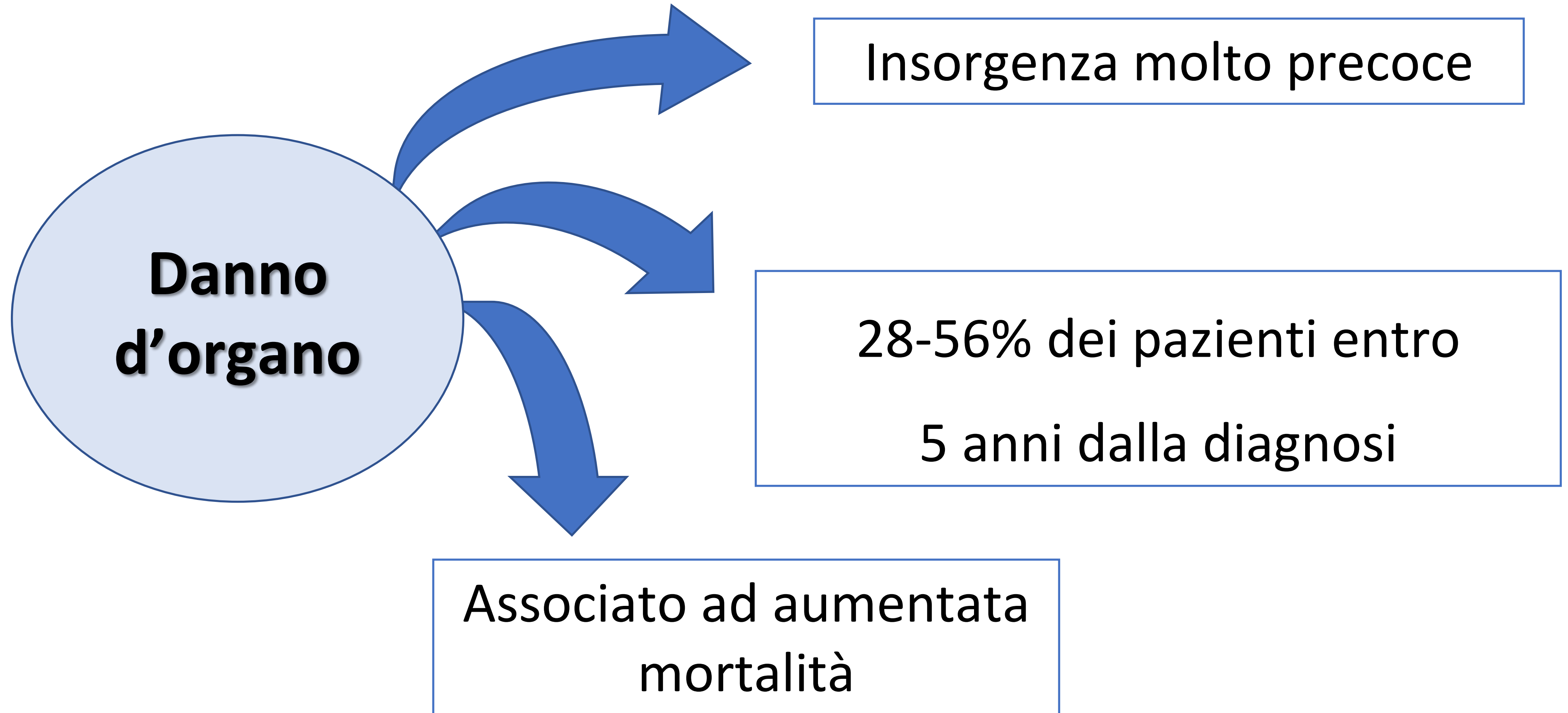
Insieme di alterazioni irreversibili legate a:

- **Patologia** di base (LES)
- **Terapie** utilizzate
- **Comorbidità** associate al LES

  (Es. cardiovascolari o neoplasie)

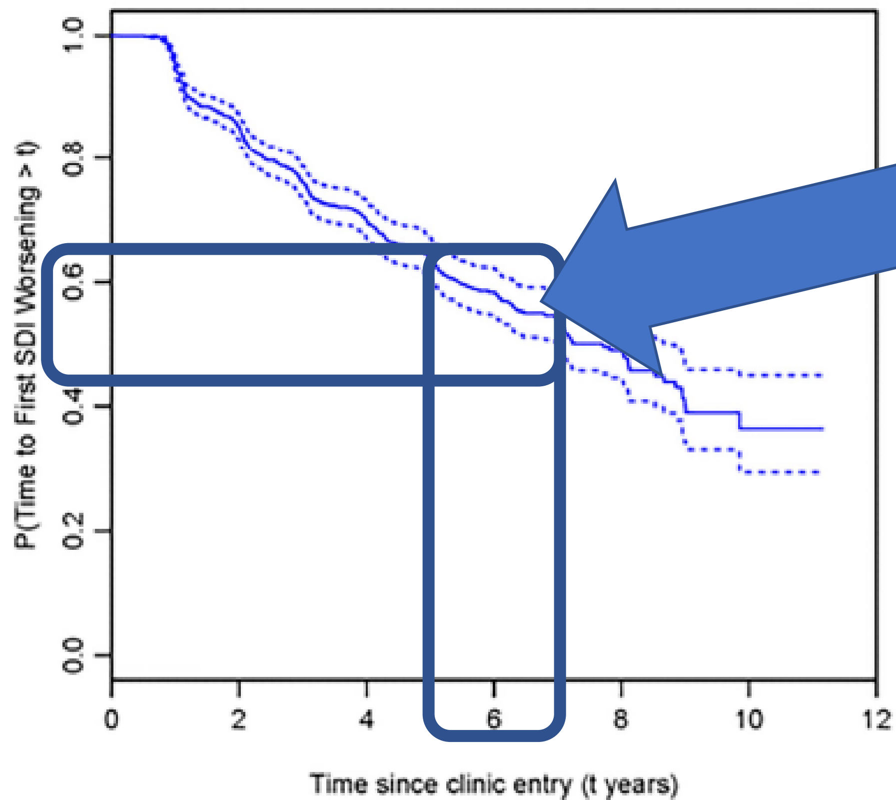
González,LA et al. Revista Colombiana de Reumatología, 2021

Danno d'organo - Epidemiologia



Wan Syamimee Wan Ghazali,, Medicine (Baltimore). 2018 Oct; 97(42): e12787. - Íñigo Rua-Figueroa Fernández de Larrinoa et al. Expert Opinion on Biological Therapy, 2022

Danno d’organo - Epidemiologia



Dopo 6 anni:

51,1% dei pazienti

con danno d’organo

Bruce IN, et al. Ann Rheum Dis 2015

Danno d'organo - Epidemiologia

Danno d'organo

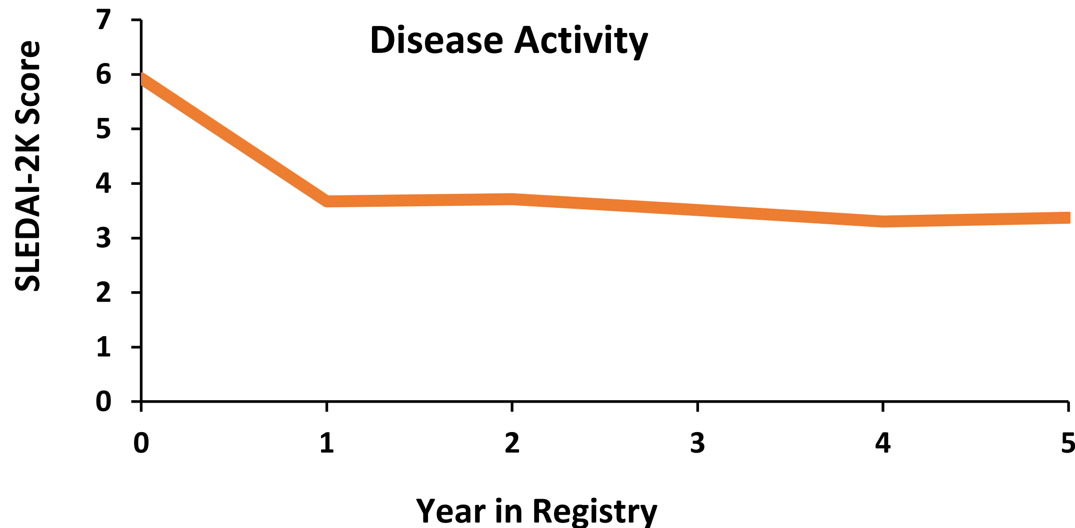
Presente alla diagnosi:
25% mortalità a 10 anni

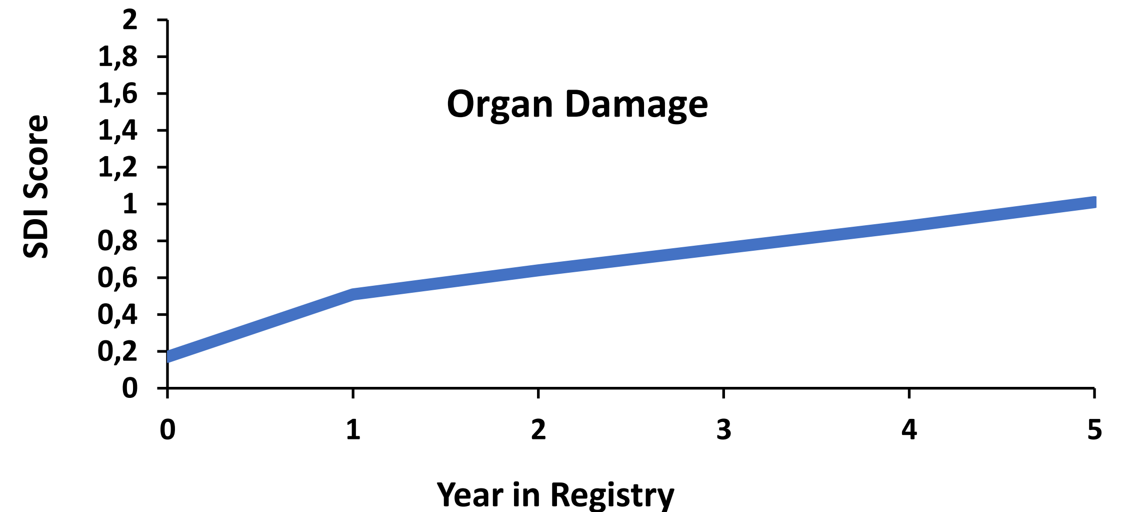
Assente alla diagnosi:
7.3% mortalità a 10 anni

Wan Syamimee Wan Ghazali,, Medicine (Baltimore). 2018 Oct; 97(42): e12787.

Organ Damage - Reduced Disease Activity

Disease activity and organ damage in newly diagnosed patients with SLE followed over 5 years (n=298; SLICC Inception Cohort, 2000-2009)[1]





SLEDAI-2K was used to measure global SLE disease activity[1]

SDI was used to assess accumulated organ damage since the onset of SLE, stemming from the disease and/or sequelae[1,2]

1. Urowitz MB et al. *Arthritis Care Res (Hoboken)*. 2012;64(1):132-137. 2. Rahman P et al. *Lupus*. 2001;10(2):93-96.

Agenda

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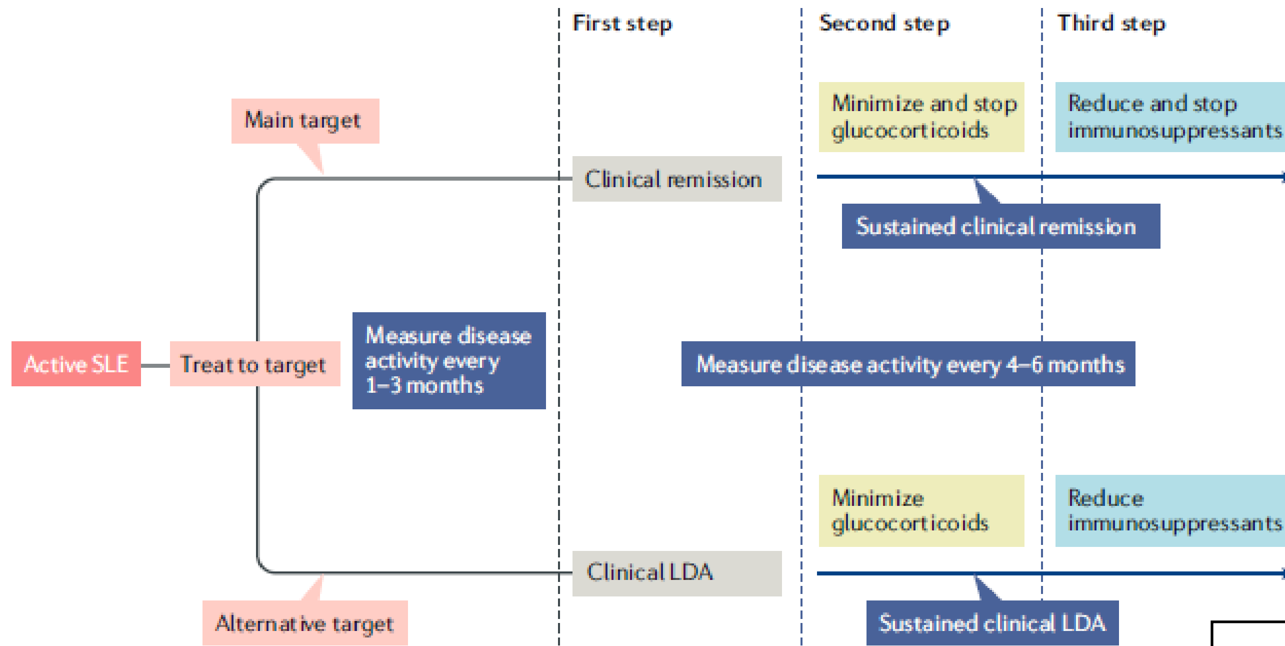
- Diagnosi
- Potevamo pensarci prima?
- Trattamento

Proposed approach treat-to-target in SLE



Gatto M, et al Nat Rev Rheumatol 2019

TERAPIA *treat to target:*

- Farmaci anti malarici
- Corticosteroidi
- **Immunosoppressori**
- Farmaci biologici (Belimumab – Rituximab)

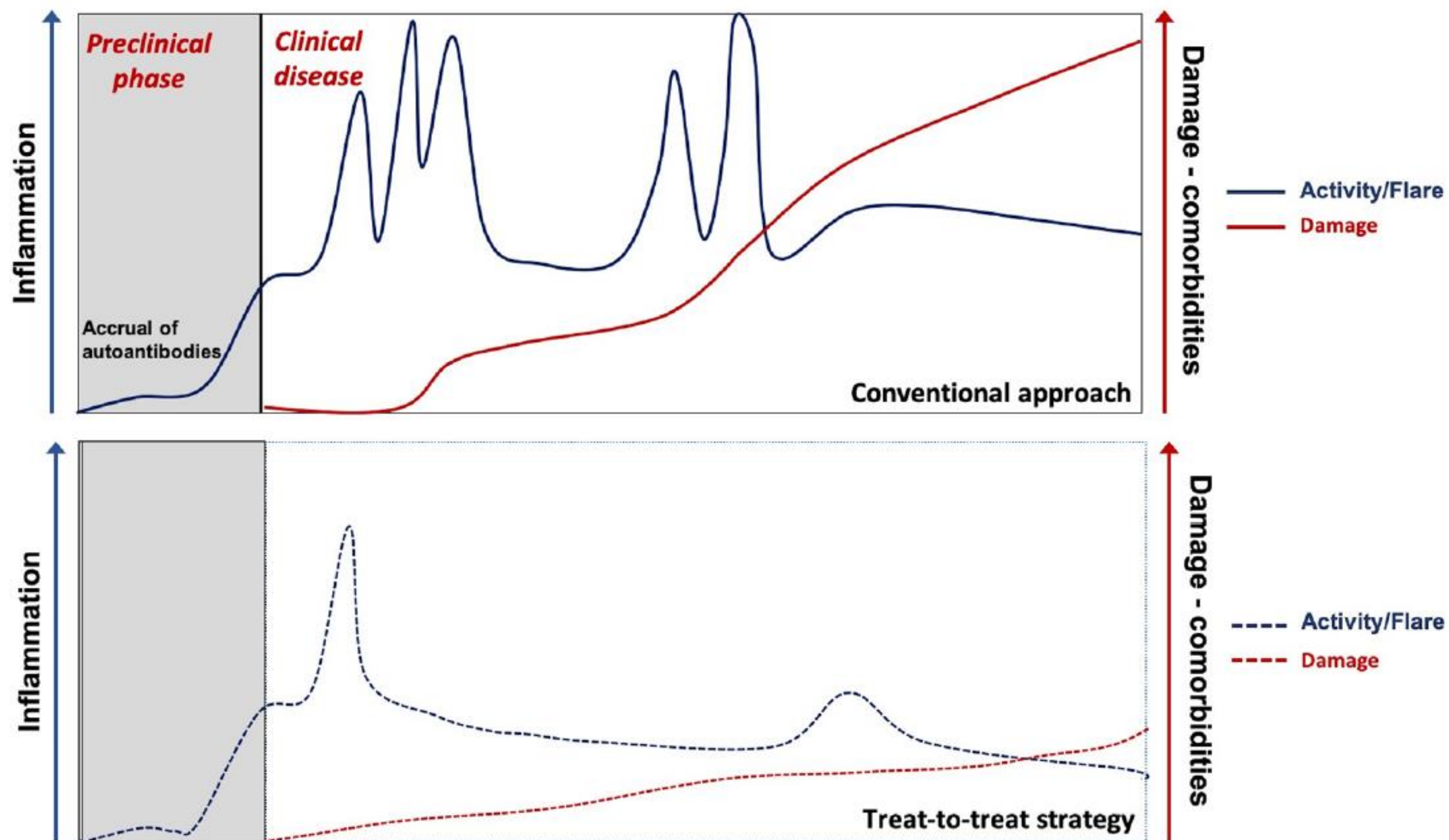
TARGET:

a. Ridurre attività di malattia

b. Evitare danno d'organo permanente

Fanouriakis A et al. *Ann Rheum Dis.* 2019

LES: storia naturale e potenziale della treat to target



Clinical course of SLE:
70% Relapsing Remitting
15%persistently active
15% prolonged remission

Fanouriakis A, *et al*. *Ann Rheum Dis* 2021;**80**:14–25.

REMISSIONE CLINICA

MEDICO

Associata a:
- **Attività di malattia,** ad esempio tramite SLEDAI-2K, PhGA
- **Trattamento farmacologico**

- **Clinical remission on corticosteroids**: cSLEDAI=0, immunosopressori e/o antimalarici a dosi stabili, corticosteroidi ≤ 5 mg/die.
- **Clinical remission off corticosteroids**: cSLEDAI=0, immunosopressori e/o antimalarici a dosi stabili
- **Complete remission**: SLEDAI-2K=0, ammessi solo antimalarici

PAZIENTE

Per il **paziente** la remissione clinica è correlata alla **qualità di vita**

La **qualità di vita** è influenzata da:
- Dolore cronico
  - Coinvolgimento articolare
  - Fibromialgia
- Astenia
- Ansia e depressione
- Trattamento farmacologico

Zen et al. Annals of the Rheumatic Diseases, 74, 2117–2122 (2015); Kiani et al. Rheumatology, 52, 1651–1657 (2013) ; Zhu et al. Journal of Rheumatology, 37, 568–573 (2010); Piga et al. Lupus, 27, 190–198 (2018); Elefante et al. Arthritis Research and Therapy, 22, 1–8 (2020); Doria et al. Rheumatology, 43, 1580–1586 (2004)

Terapia immunosoppressiva calibrata sulla gravità

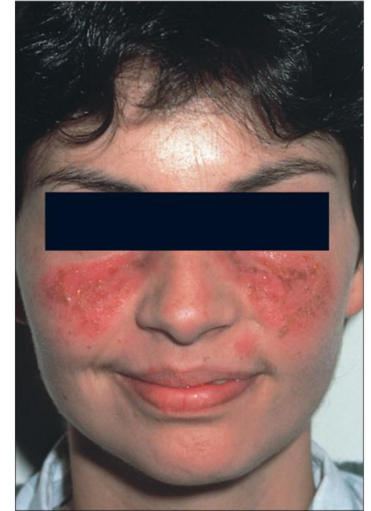
MALATTIA LIEVE

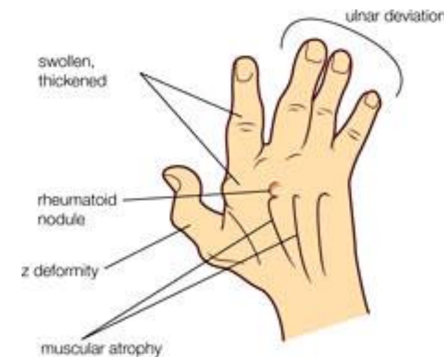
- **Idrossiclorochina:** manifestazioni cutanee e articolari. *Sembra utile per prevenire le esacerbazioni*

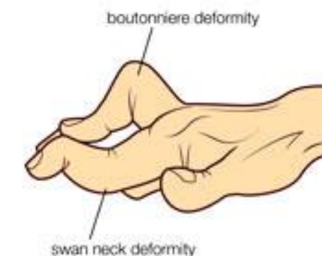
- **Metotrexate:** manifestazioni articolari e cute

OFF-LABEL

- **Micofenolato:** inibisce la sintesi de novo delle purine (manifestazioni renali)







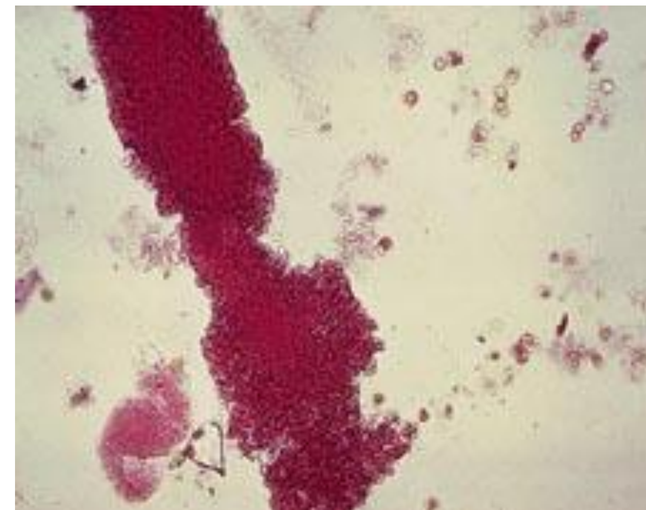
Terapia immunosoppressiva calibrata sulla gravità

MALATTIA MODERATA

- Micofenolato (2 g/die) o azatioprina associato a prednisone come sopra. Se non risposta dopo 6-12 mesi passare a

OFF-LABEL

- Ciclofosfamide pulse dose (0.75 g /mq) ogni 3-4 settimane per 7 dosi + pulse steroidi (15 mg/Kg) associato a prednisone come sopra.



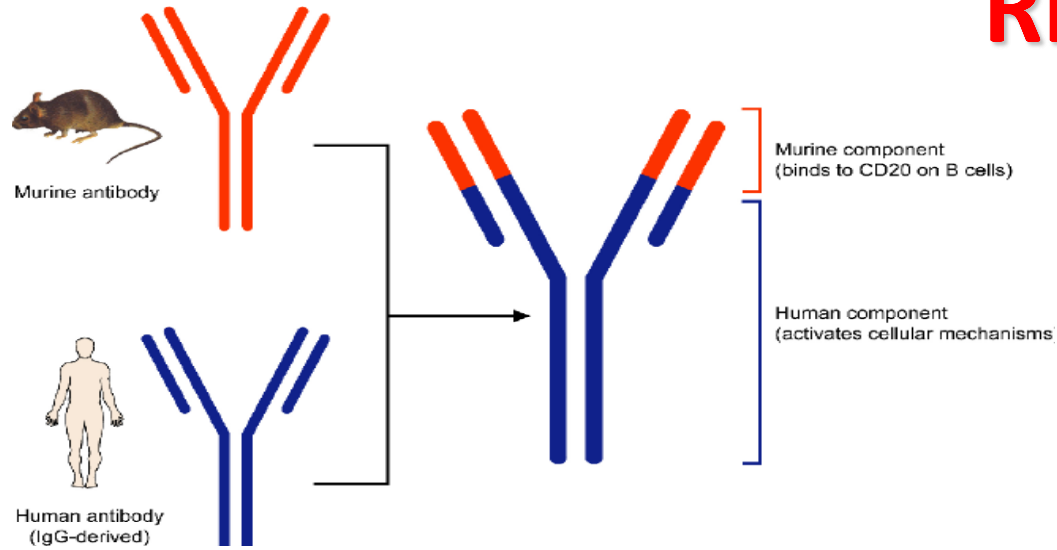
Terapia immunosoppressiva calibrata sulla gravità

MALATTIA GRAVE

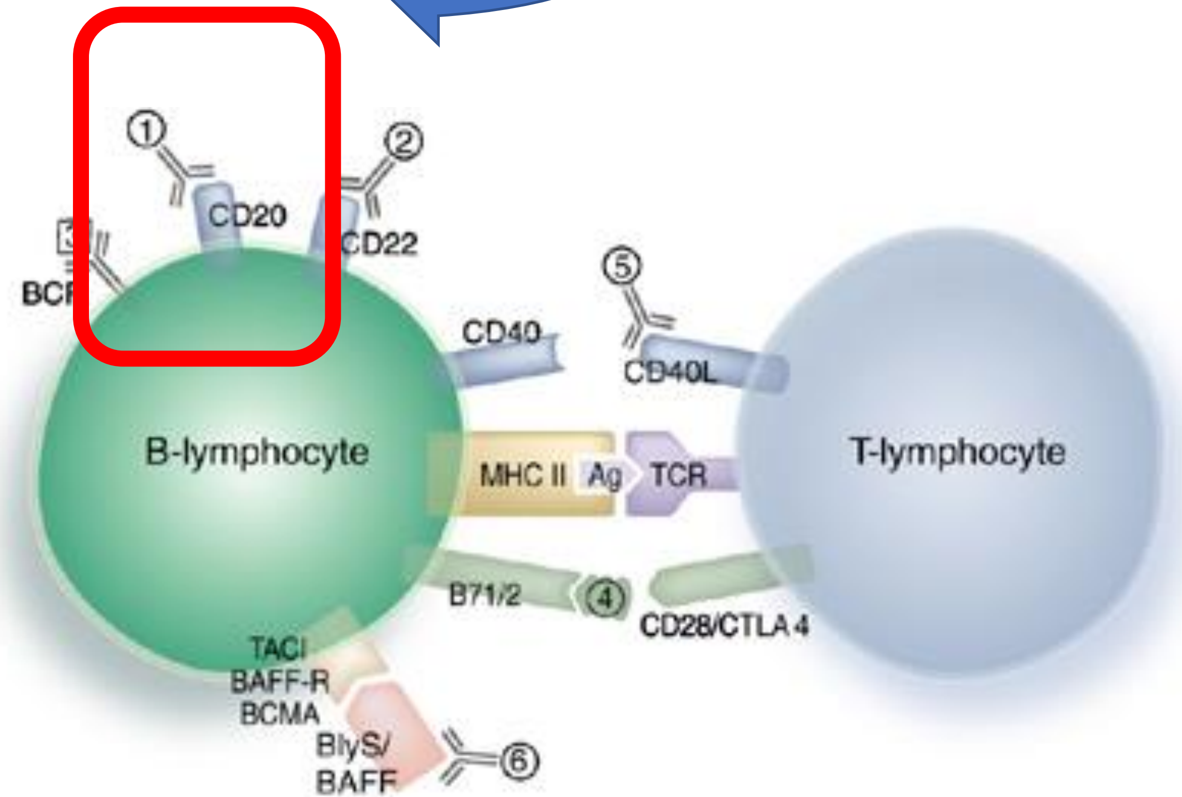
- ciclofosfamide a boli 0.75-1 g / mq per 4-6 mesi
- metilprednisolone a boli (15 mg/Kg) per 3 gg seguito da 1 mg/Kg
- Se non risposta micofenolato o rituximab

OFF-LABEL

Rituximab:

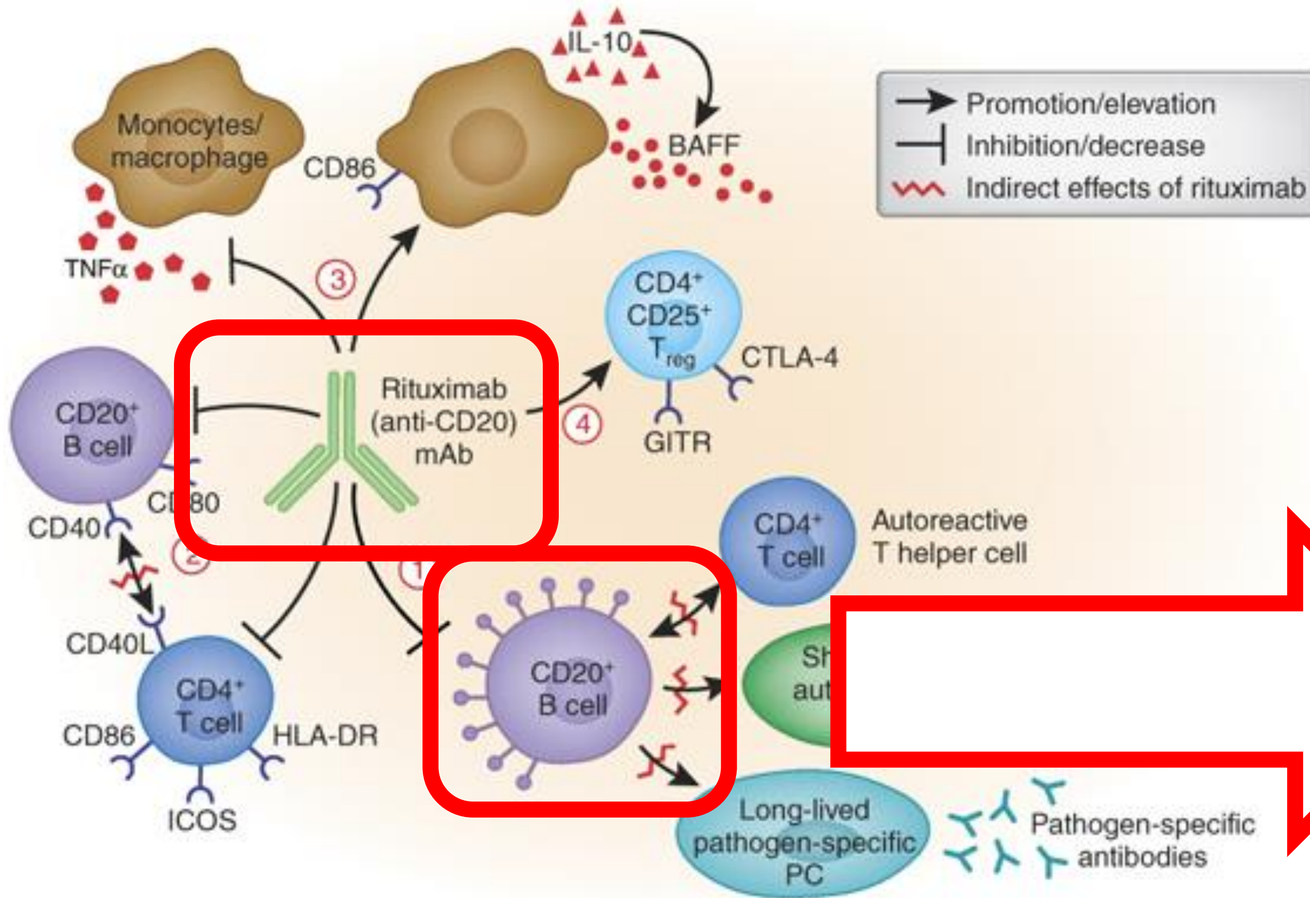


Lega il CD20



Anticorpo monoclonale umanizzato

Rituximab:



Apoptosi celllule B

Rituximab - indicazioni

Granulomatosi con poliangite (**GPA**)

e poliangite microscopica (**MPA**)

Pemfigo volgare

Artrite Reumatoide

Linfoma non-Hodgkin (**LNH**)

LLC

Disease	Level I	Level IIa	Level IIb	Level IIIa	Level IIIb	Level IV	Too little information
ANCA-associated vasculitis	Achieved						
Antiphospholipid syndrome							Failed
Autoimmune hemolytic anemia			Achieved				
Autoimmune hepatitis							Failed
Behçet's disease		Mixed result					
Bullous pemphigoid						Achieved	
C1-INH-AAE*						Achieved	
Castleman's disease						Achieved	
Cryoglobulinemia						Achieved	
Goodpasture's disease				Mixed result		Achieved	
Graves' disease				Failed			
IgA nephropathy							
IgG4-related disease						Achieved	
Immune thrombocytopenia			Achieved				
Inflammatory myositis			Failed				
Juvenile idiopathic arthritis						Achieved	
Membraneous nephropathy				Mixed result			
Multiple sclerosis – PPMS			Mixed result				
Multiple sclerosis – RRMS			Achieved				
Myasthenia gravis						Achieved	
Nephrotic syndrome				Achieved			
Neuromyelitis optica						Achieved	
Pemphigus	Achieved						
Rheumathoid arthritis	Achieved						
Sjörgen's syndrome			Mixed result				
Spondyloarthropathy						Achieved	
Systemic lupus erythematosus			Failed				
Systemic sclerosis				Achieved			
Ulcerative colitis					Failed		

Legend

Level	Description
Level I	Approved by FDA/EMA
Level IIa	Multicentric double-blind RCTs proving a significant superiority over standard-of-care treatment
Level IIb	Multicentric double-blind RCTs proving a significant superiority over placebo
Level IIIa	Clinical study, not fulfilling the above-mentioned criteria, but proving a superiority over standard-of-care treatment
Level IIIb	Clinical study, not fulfilling the above mentioned-criteria, but proving a superiority over placebo
Level IV	Case series or open-label trials without control group with positive results
Achieved	
Failed	
Mixed result	

Rituximab – Uso off-label

Off-Label

In **organ-threatening disease** refractory or with intolerance/contraindications to standard immunosuppressive agents

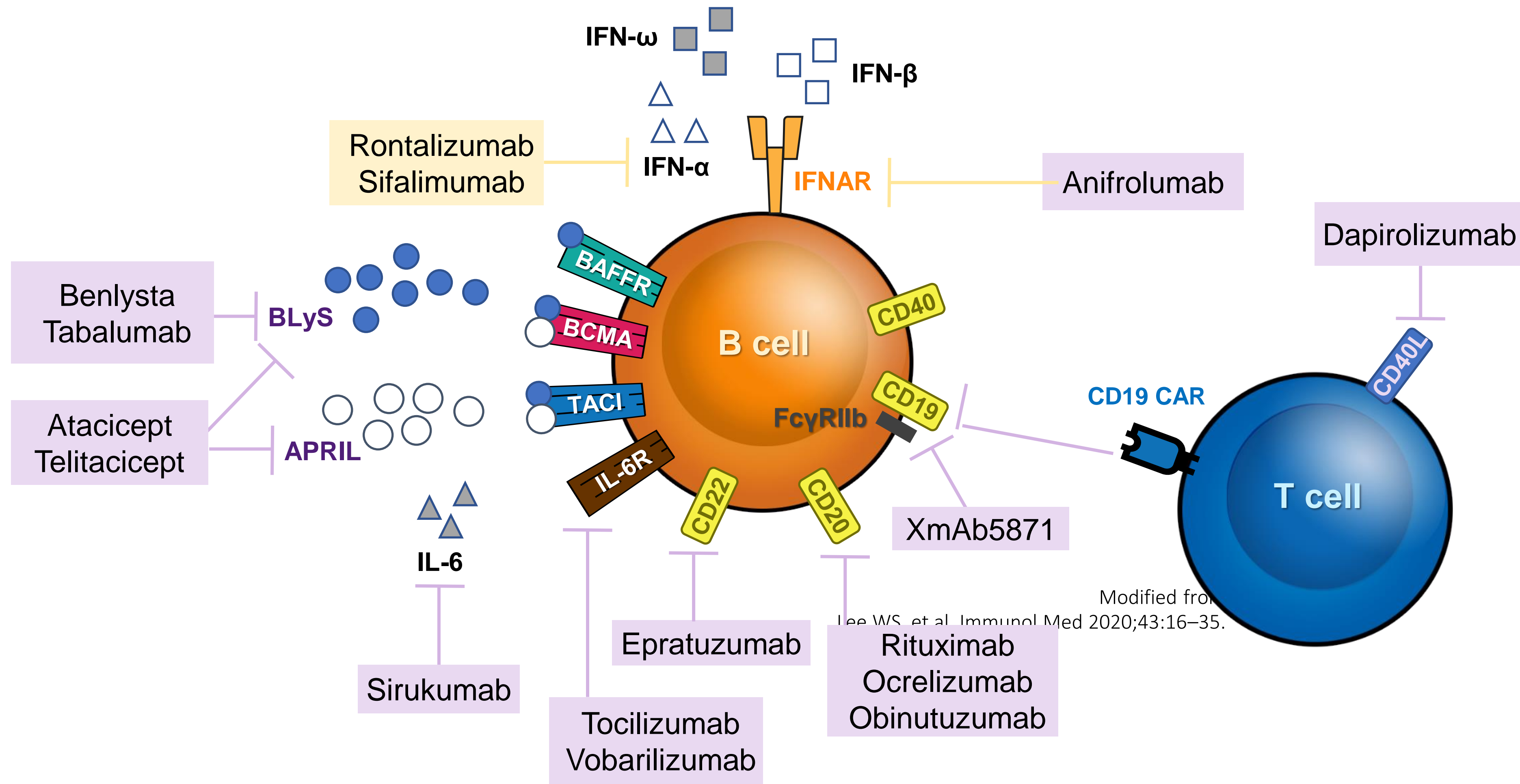
More than one IS drug need to have failed prior to RTX administration (except for severe autoimmune thrombocytopenia and haemolytic anaemia)

Recommendation

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus

To cite: Fanouriakis A, Kostopoulou M, Alunno A, *et al. Ann Rheum Dis* 2019;**78**:736–745.

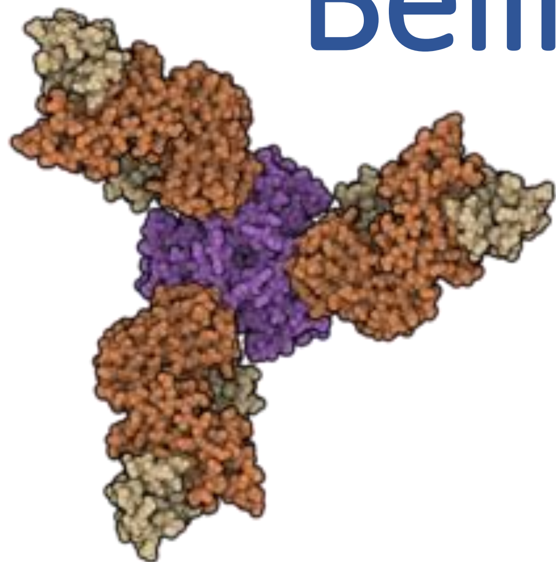
Therapies have been developed to target a variety of SLE pathogenic pathways



Modified from Lee WS, et al. Immunol Med 2020;43:16–35.

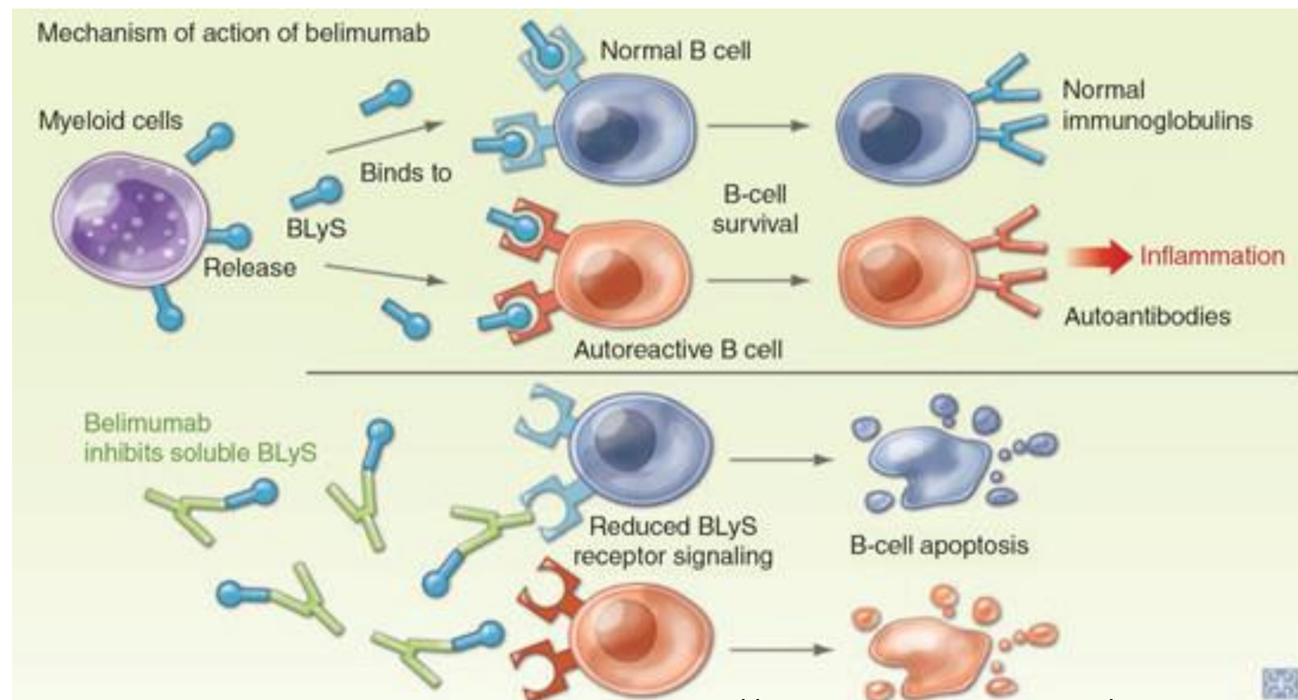
APRIL = a proliferation-inducing ligand; BAFFR = B-cell-activating factor receptor; BCMA = B-cell maturation antigen; BLyS = B-lymphocyte stimulator; CAR = chimeric antigen receptor; CD = member of the tumour necrosis factor receptor family on the surface of B cells; CD40L = cluster of differentiation 40 ligand; IFN = interferon; IFNAR = interferon-α/β receptor; IL-6 = interleukin-6; IL-6R = interleukin-6 receptor; TACI = transmembrane activator and cyclophilin ligand interactor.

Belimumab



Inibisce sopravvivenza

delle cellule B

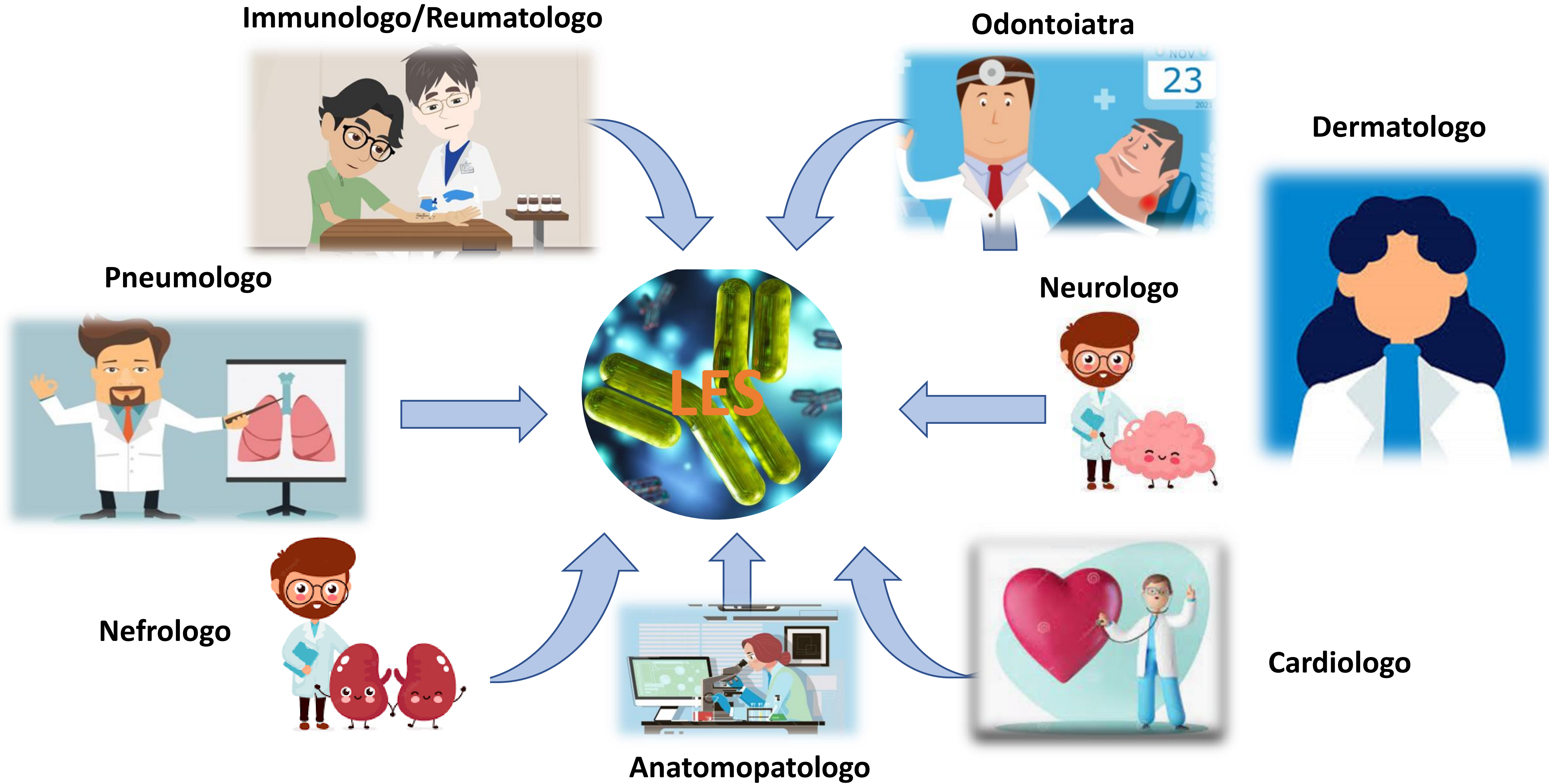


mAb IgG1λ umano

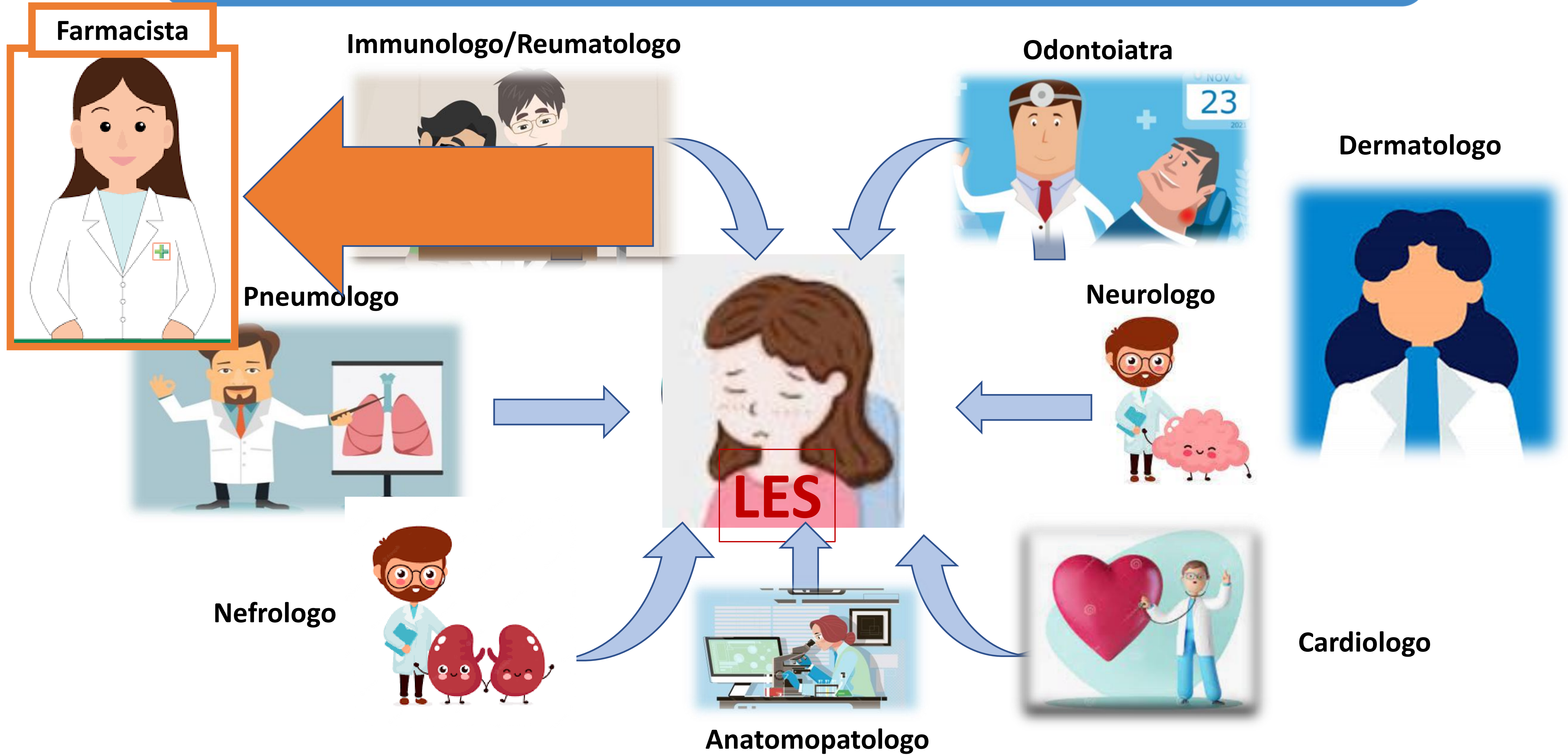
Lega BAFF solubile

https://www.ema.europa.eu/en/documents/product-information/benlysta-epar-product-information_it.pdf - Img from: https://www.medimagazine.it/lupus-sistemico-eritematoso-belimumab-efficace-nella-sperimentazione-clinica/

L'organizzazione della gestione multidisciplinare nel LES: quali figure andrebbero coinvolte?



L'organizzazione della gestione multidisciplinare nel LES: quali figure andrebbero coinvolte?



Sifact
SOCIETÀ ITALIANA DI FARMACIA CLINICA E TERAPIA

Agenda

LA GESTIONE MULTIDISCIPLINARE

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CASO CLINICO

THE TRICKY

PATIENT JOURNEY

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

1) MMG

CASO CLINICO

MMG

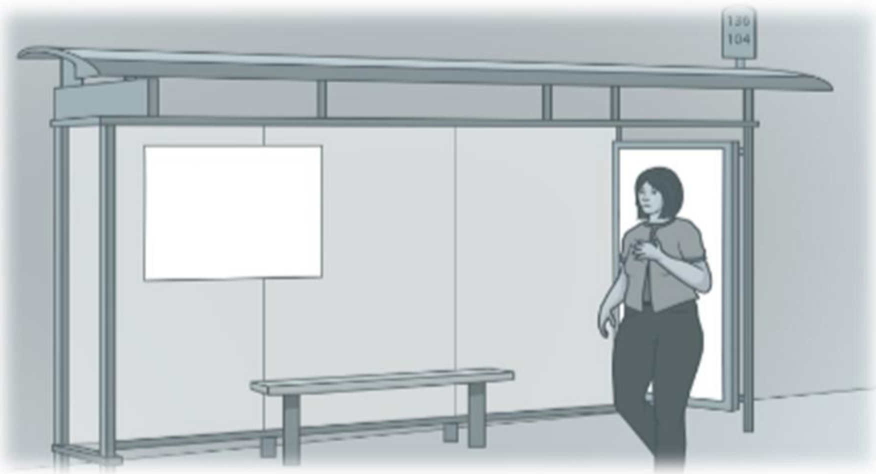
APP:

Tosse, dispnea e sibilo da 6w, in peggioramento.

Dispnea per sforzi lievi (camminata in piano)

Beneficio parziale da salbutamolo

Recente insorgenza di instabilità e zoppia



Nega febbre, brividi, escreato, cefalea, artromialgie, pirosi gastrica, nausea, vomito o necessità di schiarire la voce.

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

MMG

Anamnesi:

Rinite allergica stagionale (estate)

Sensibilizzazione ad acari

Cefalea

Sovrappeso: BMI 26.3

Asma nota da 10 anni

Non fumatrice

Non abitudini voluttuarie

Terapia domiciliare:

Fluticasone nasale

ICS/LABA

Loratadina 10 mg

Paracodina ab

Precedente trattamento con omalizumab INFRUTTUOSO

Donna, 40 anni

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

MMG

Anamnesi personale:

Nata in Repubblica Dominicana

Lavora in una scuola dell'infanzia

Ha un cane, nega esposizione a muffe o insetti

Anamnesi familiare:

Madre con rinite allergica

Sorella con asma bronchiale

Familiarità per neoplasia ematologica

(due zii materni con linfoma)

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

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Recente insorgenza di instabilità e zoppia

EOP: diffusi sibili espiratori, espirazione prolungata. Normale obiettività cavo orale e nasale.

Sat.O2: 96% in AA

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

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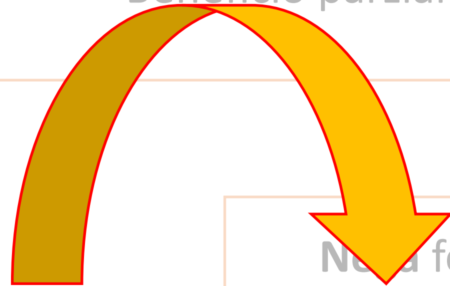


Ne[...] febbre, brividi, escreato,

cefalea, artromialgie, pirosi gastrica,

[...]ità di

EOP: diffusi sibili espiratori, espirazione prolungata. Normale obiettività cavo orale e nasale.

Sat.O2: 96% in AA

Diagnosi di Riacutizzazione di Asma

Visita Pneumologica

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

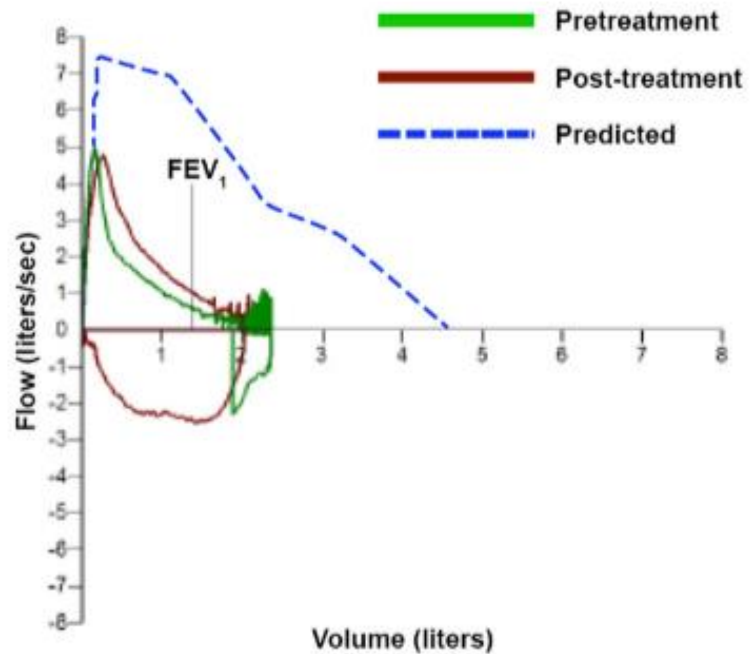
CASO CLINICO

1)MMG

2)Pneumologo

CASO CLINICO

Pneumologo



FEV1: 1,37L (35% predetto)

IT: 58%

FEV1 PB: 1,67L (+300 ml, +22%)

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

Pneumologo

FEV1: 1,37L (35% predetto)

IT: 58%

FEV1 PB: 1,67L (+300 ml, +22%)

Confermata la riacutizzazione di Asma

↑ICS/LABA (salmeterolo/fluticasone 50/500 BID) + SABA

Ciclo di prednisone 25 mg per 5 giorni

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

Pneumologo

Aderenza verificata.
Nessun beneficio da ICS/LABA dopo 3 mesi

ICS/LABA 50/500
+ LTRA
(Tiotropio)

Persistenza di tosse, dispnea per sforzi lievi, sibilo toracico

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

Dopo 4 mesi…

1) MMG

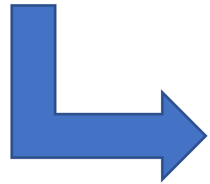
2) Pneumologo

3) PS

CASO CLINICO

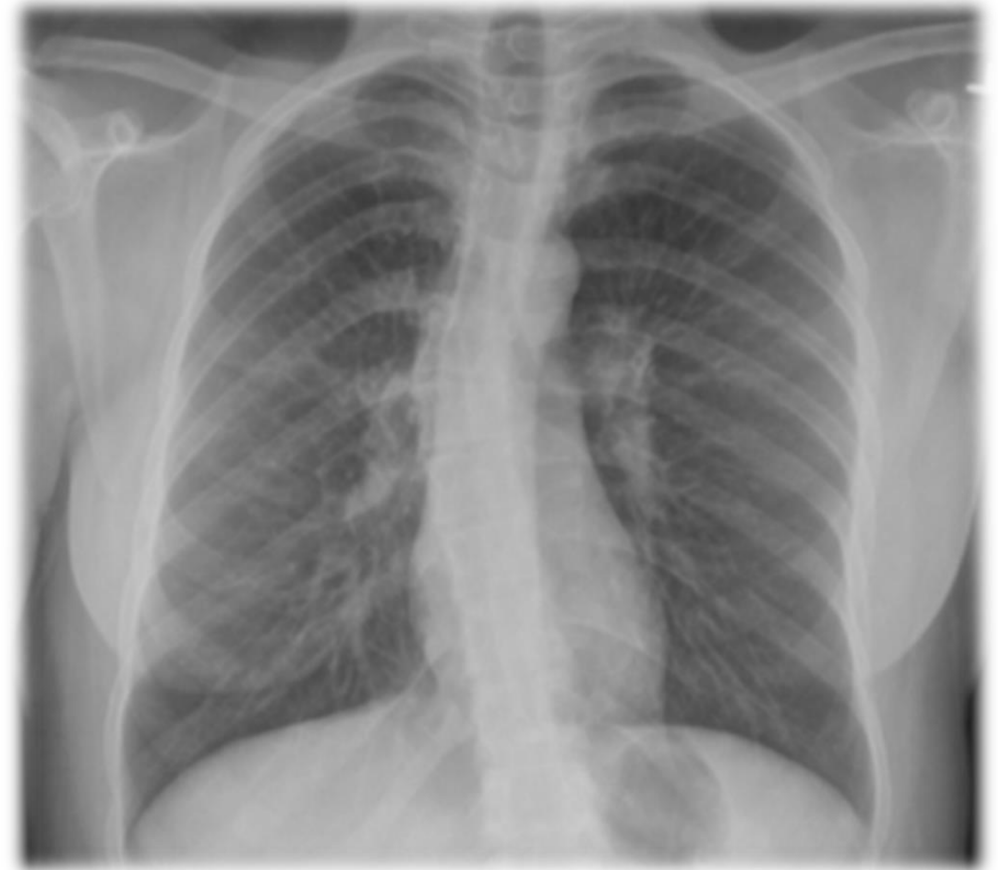
Dopo 4 mesi…PS

Accesso in PS per broncospasmo serrato, nausea e iporessia.



Rx torace 2P

Emocromo
GB: 10500
N: 5000
L: 1700
E: 2100



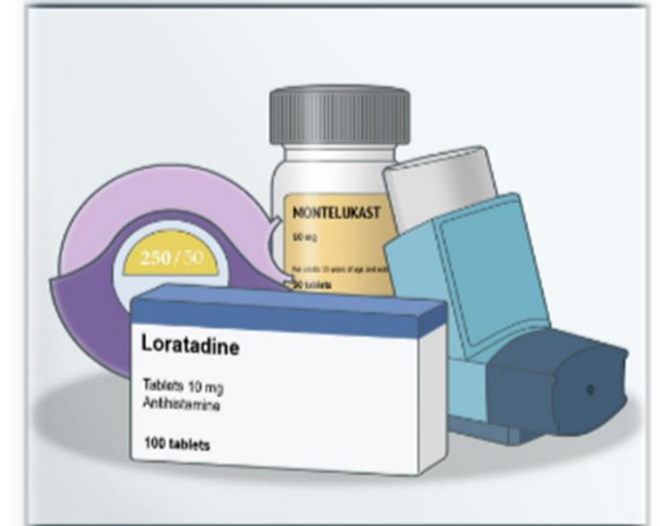
Diagnosi di

Bronchite in paziente asmatica

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

PS



Azitromicina 500 x 6 gg

Prednisone 40 mg/die per 10 gg

Storia di rinite:
Visita allergologica

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

4) Allergo-immunologo

1) MMG

3) PS

2) Pneumologo

CASO CLINICO

Allergo-Immunologo

Physical Examination

Vital Signs and General Appearance

T: 37.0° C
FC: 69 bpm
PAO: 110/60 mmHg
FR: 18/min
Sat.O2: 97% in AA
No distress respiratorio

- Head, eyes, ears, nose, and throat
- Lungs
- Heart
- Abdomen
- Extremities
- Nervous system
- Skin
- Hide All

Head, eyes, ears, nose, and throat

Congiuntiva ndr
Oro-faringe ndr
No dolorabilità trigger points sinusali
No adenopatia
No noduli tiroidei

Abdomen

Piano, non dolente né dolorabile

Extremities

No clubbing, cianosi, edema

Skin

Non rash, eritema, orticaria

Nervous system

Normali NC, no deficit forza
Sensibilità TA-DO ndr
Instabilità per deficit SPE

Heart

Non turgore giugulare
FR nn
Non rumori di galoppo

Lungs

Espirazione prolungata
Sibili espiratori
FVT nn
Non crepitii

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

Visita allergologica

Allergo-Immunologo

Prick test

Dermatophagoides farinae +++

Graminacee +++

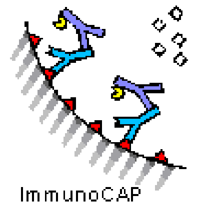
Cereali mix +++

Gatto +++

Aspergillus: -

Penicillum: -

Component-resolved diagnostics



- Der p1: 10,2 kUA/l.
- Der p2: 4,5 kUA/l
- Der p 23: 8,2 kUA/l
- Phl p1: 18,7 KUA/l
- IgE Asp: < 0.35 kU/l

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

Allergo-Immunologo

Esami laboratorio

Mepolizumab 100 mg?

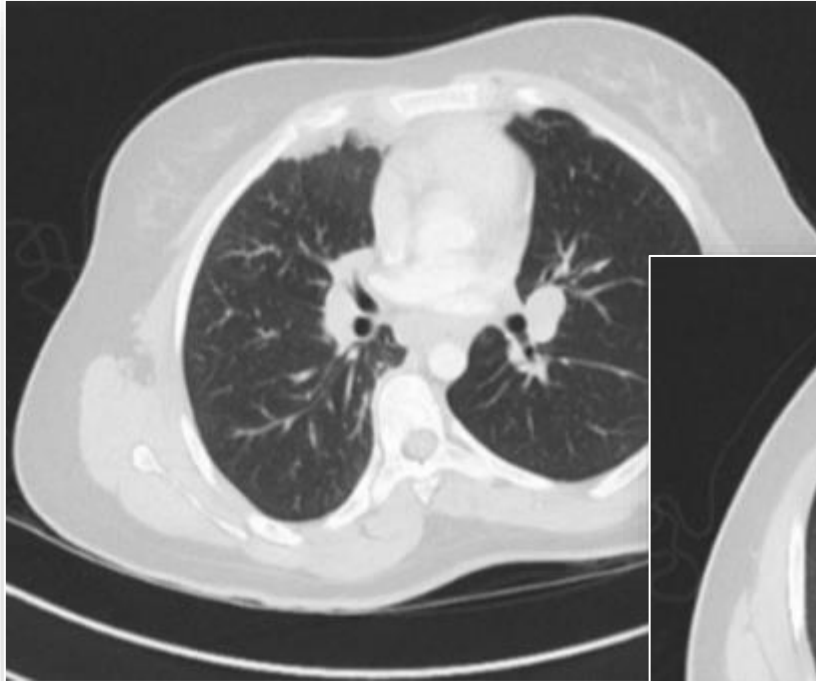
Hb	13.8 g/dl	VES	51 mm/h
Hct	39.9%	PCR	41 mg/l
MCV	86 fl	Elettroliti	ndr
WBC	20.740 cell/mcl	Es. urine	ndr
	L 2.200 N 7.260 E 10.990 M 210	IgE totali	1100 KUA/L
Plts	118.000	ANCA	neg

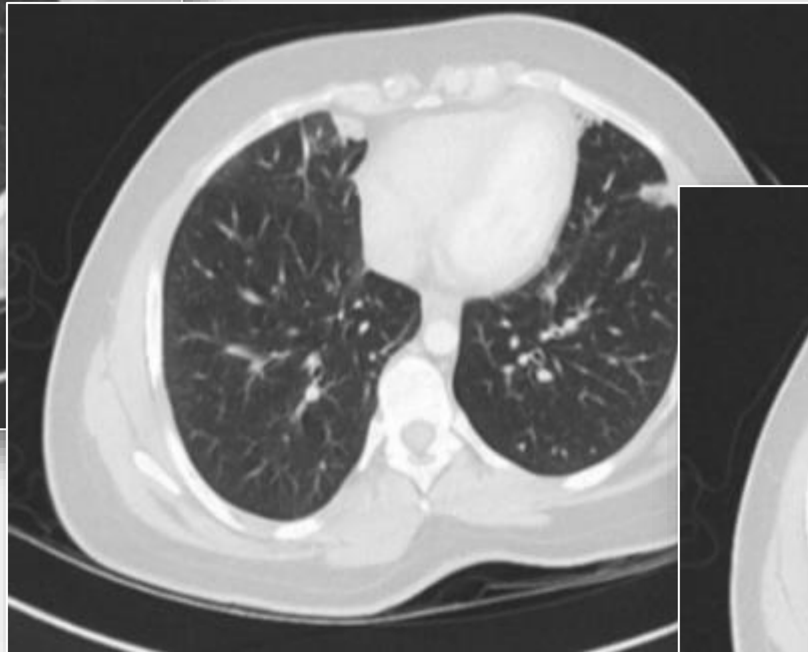
Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

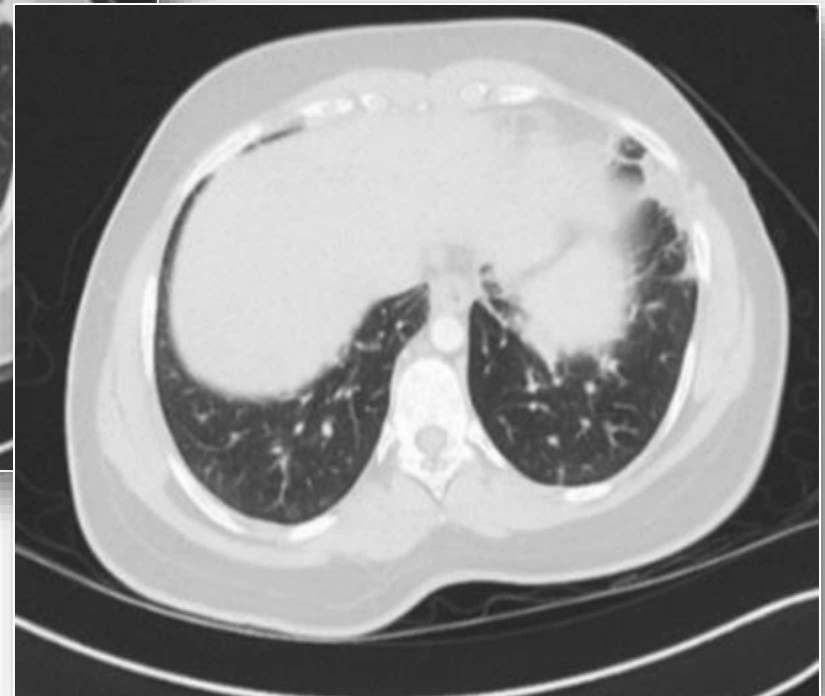
CASO CLINICO

Allergo-Immunologo e Pneumologo

HRTC







Riscontro di opacità subpleuriche

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

Agenda

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CASO CLINICO

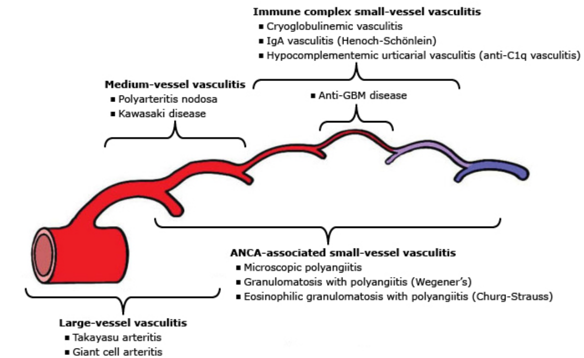
Quali sono i segni clinici che potrebbero indurci al sospetto di una

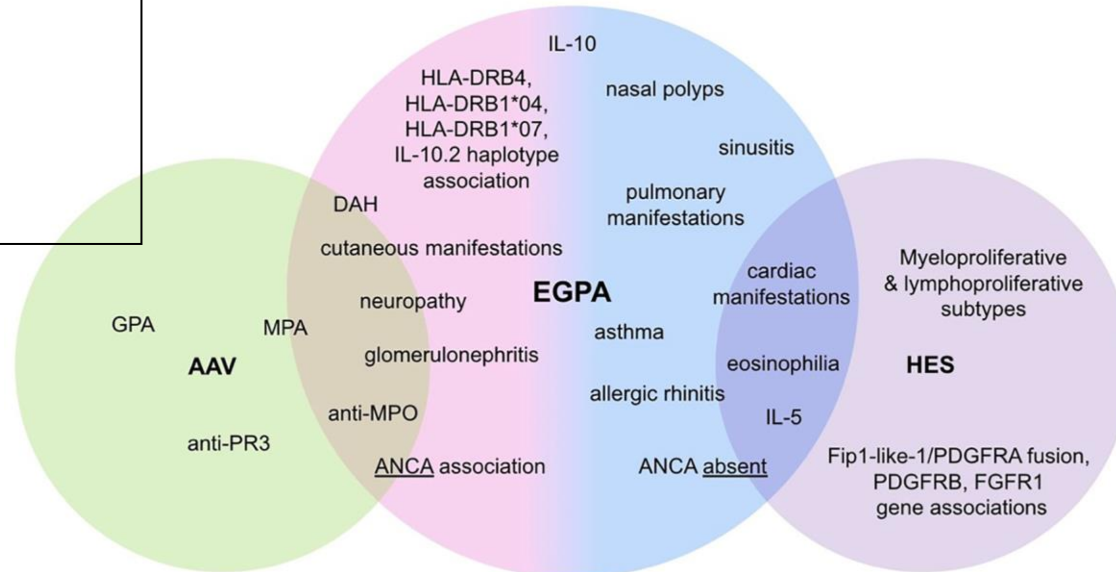
EGPA (*Granulomatosi eosinofila con poliangite***)**

Granulomatosi eosinofila con poliangite (EGPA) già denominata sindrome di Churg-Strauss

- Vasi di medio-piccolo calibro: *infiltrazione eosinofila*
- **Vasculite ANCA associata**: pANCA/MPO, 4*0% dei casi*
- Interessa ***esclusivamente pazienti asmatici***
- **Incidenza 0.3 x 10^5**

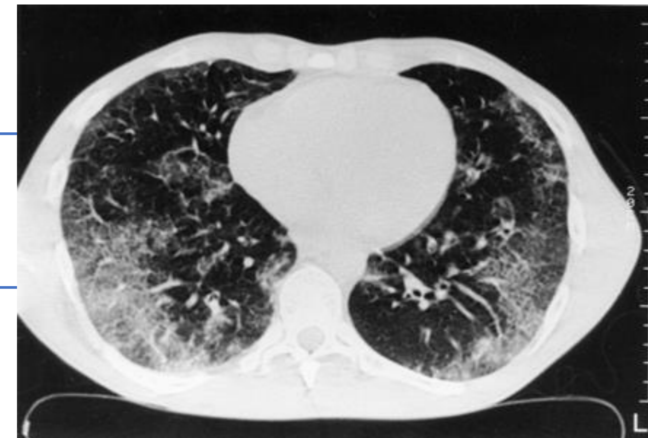
Malattia Rara

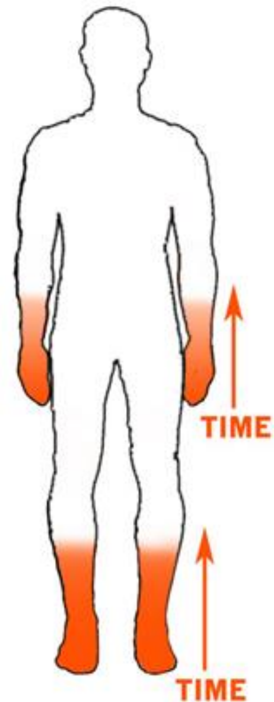




Granulomatosi eosinofila con poliangite (Sindrome di Churg-Strauss) (criteri di classificazione American College Rheumatology 1990)

Asma
Eosinofilia > 10 %
Mononeurite multipla o polineuropatia (distribuzione a calzini o a guanti)
Infiltrati polmonari migranti
Sinusite
Eosinofilia tessutale (biopsia)





La presenza di almeno 4 sui 6 criteri ha una sensibilità del 85% e una specificità del 99%

CASO CLINICO

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR **EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

CLINICAL CRITERIA

Criterion	Score
Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

Criterion	Score
Blood eosinophil count ≥ 1 x10^9/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Sum the scores for 7 items, if present. A score of ≥ 6 is needed for classification of EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS.

Grayson PC et al. Arthritis & Rheumatology Vol. 74, No. 3, 2022

CASO CLINICO

Allergo-Immunologo
Pneumologo
Reumatologo

Asma in peggioramento

Opacità subpleuriche

Ipereosinofilia periferica

EGPA: Probabile

Asma, Eosinofili,

Alterazioni HRTC, Zoppia.

HES:

Possibile

Polmonite Eosinofila Cronica:

Possibile

DD

Granulomatosi Eosinofila con PoliAngioite

Polmonite eosinofila cronica

HES con interessamento di singolo organo?

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

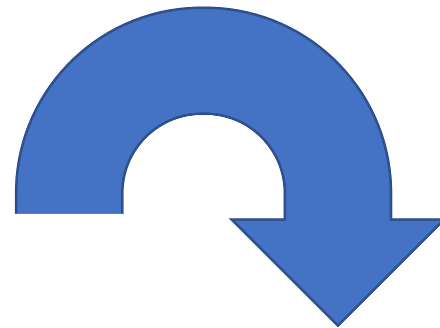
CASO CLINICO

Allergo-Immunologo
Pneumologo
Reumatologo

Asma in peggioramento

Opacità subpleuriche

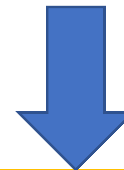
Eosinofilia periferica



EGPA: Probabile

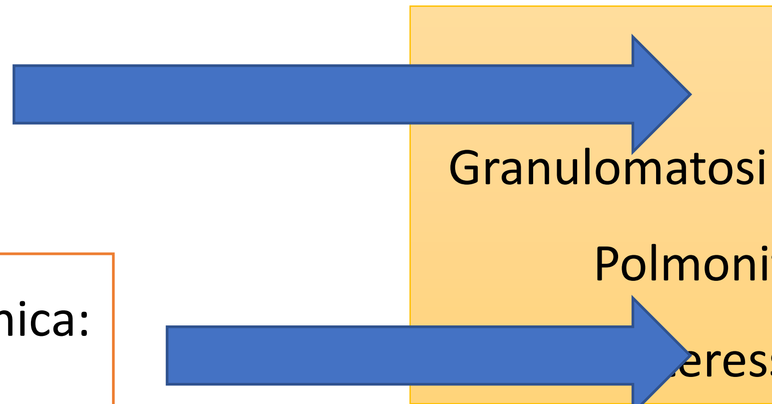
Asma, Eosinofili,

Alterazioni HRTC, Zoppia.



HES:

Possibile



Polmonite Eosinofila Cronica:

Possibile

Biopsia opacità polmonari

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

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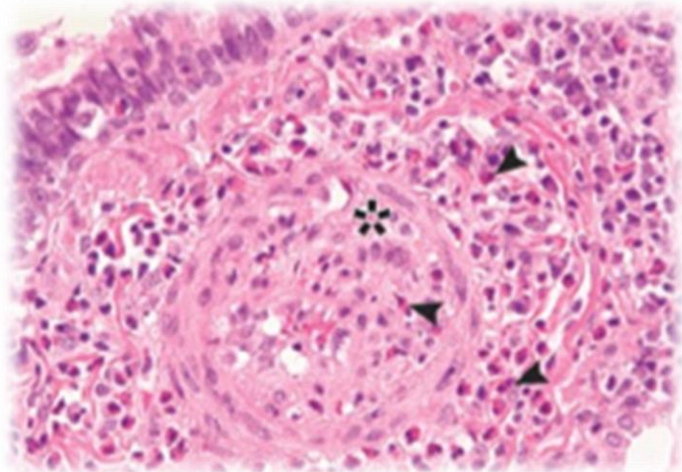
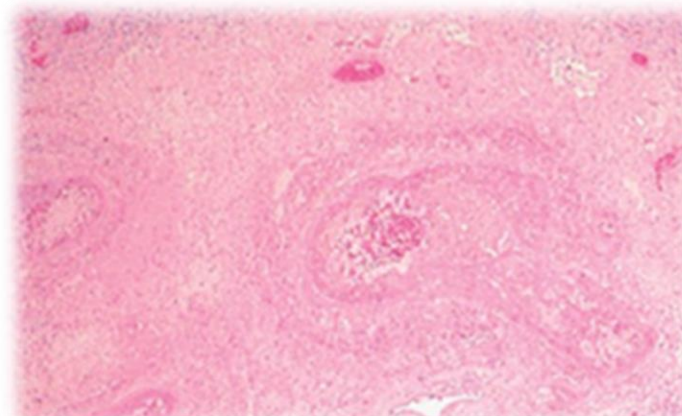
CASO CLINICO

Allergo-Immunologo
Pneumologo
Reumatologo
Anatomo-patologo



Biopsia TC guidata

Vasculite eosinofila
Aree di necrosi

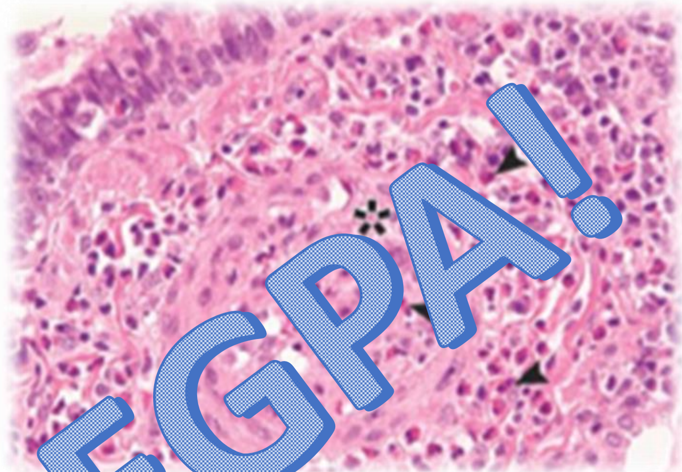


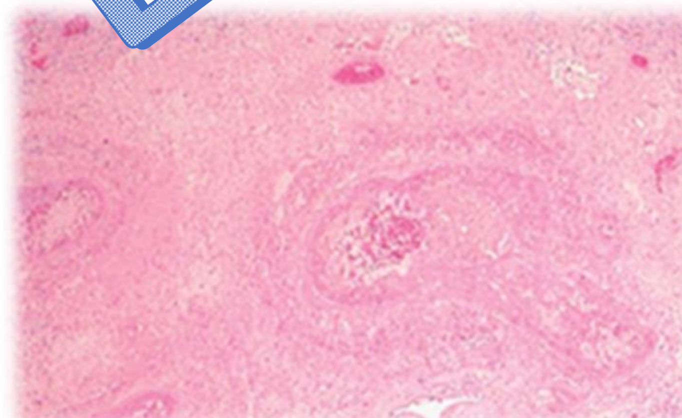
Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

CASO CLINICO

Allergo-Immunologo
Pneumologo
Reumatologo
Anatomo-patologo

Biopsia TC guidata

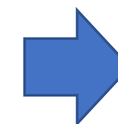




EGPA!

Vasculite eosinofila
Aree di necrosi

Polmonite eosinofila cronica
HES singolo organo



Eosinofili e linfociti negli alveoli e nell'interstizio
No vasculite.

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

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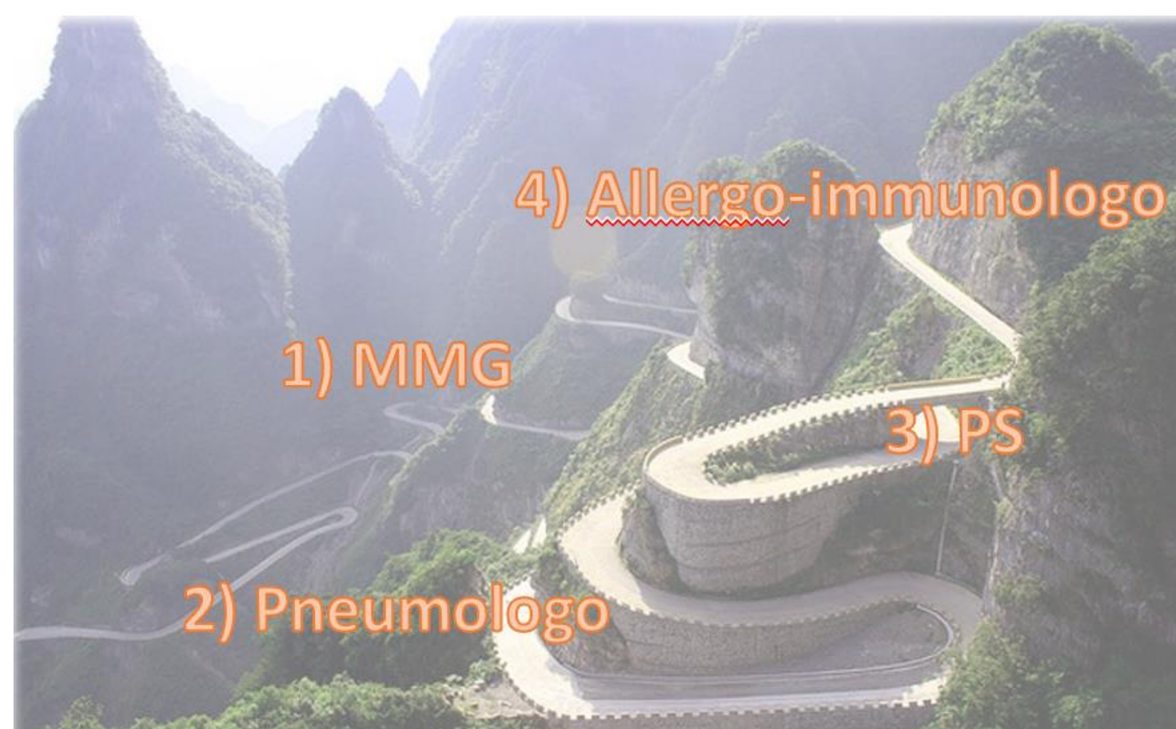
CASO CLINICO

ASMA GRAVE (?)
Instabilità/zoppia
Ipereosinofilia
Infiltrati polmonari

..Cefalea

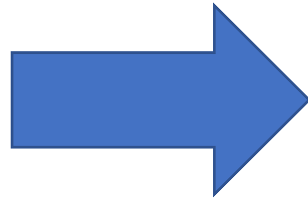


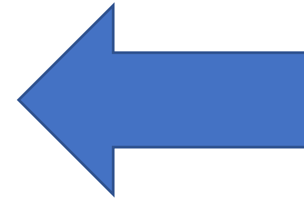
Potevamo pensarci prima?

Adapted from-S. Divakaran et al. N Engl J Med 2017; 377:e6

PATIENT JOURNEY

Possibili cambiamenti per migliore presa in carico?





PATIENT JOURNEY

Gestite il paziente in un team multidisciplinare?

E’ veramente utile?

L’organizzazione della gestione multidisciplinare nella EGPA: quali figure andrebbero coinvolte?

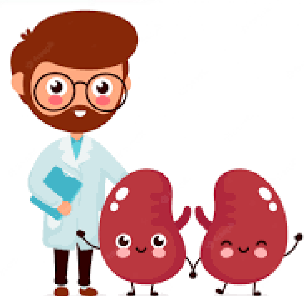
Allergologo/Immunologo/Reumatologo

Otorinolaringoiatra

Pneumologo

Neurologo

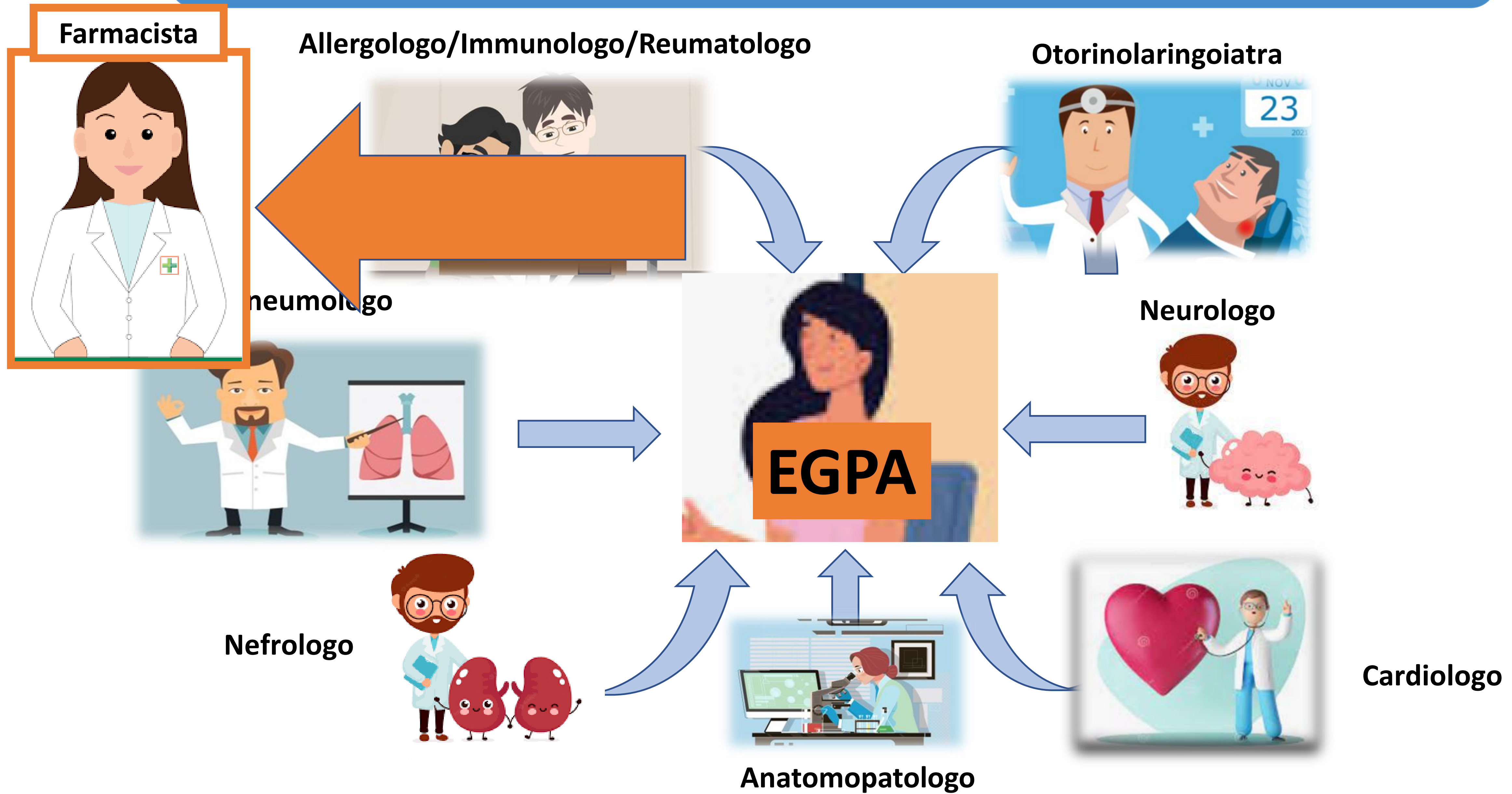
Nefrologo



Anatomopatologo

Cardiologo

L’organizzazione della gestione multidisciplinare nella EGPA: quali figure andrebbero coinvolte?



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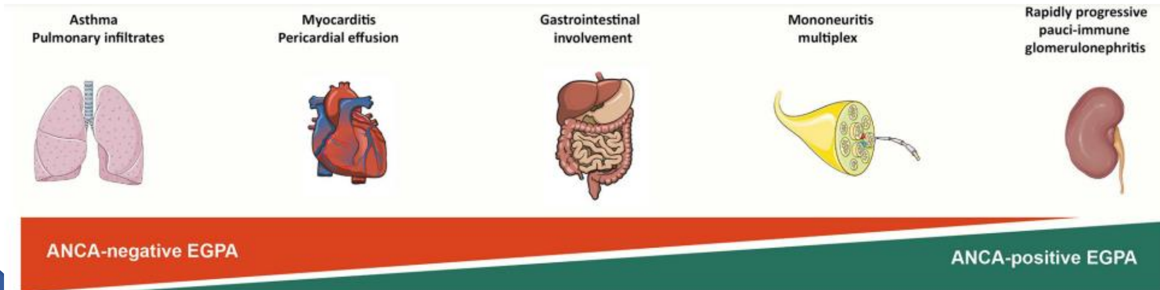
- **Trattamento**

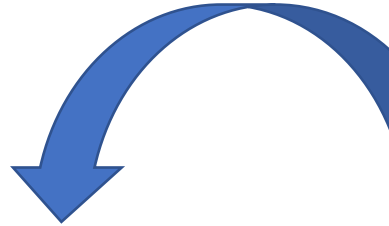
CASO CLINICO

Obiettivi terapeutici in asma grave ed EGPA:

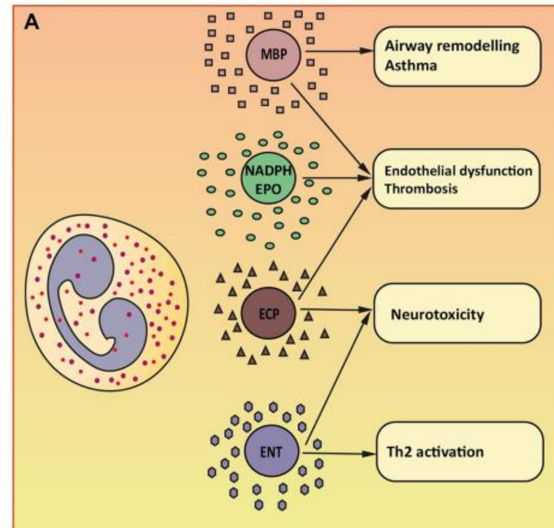
Biologico come OCS sparing?

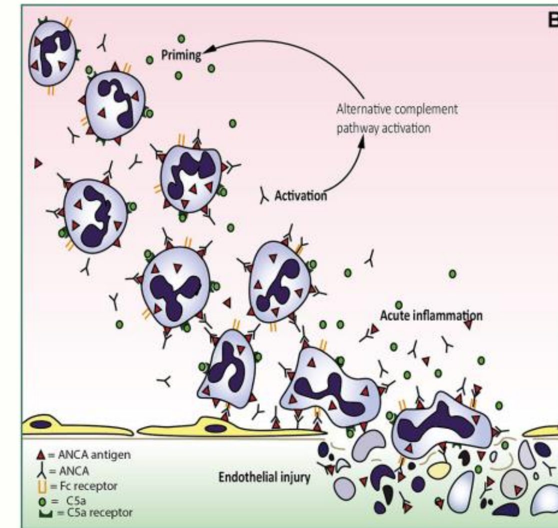
Fenotipi di EGPA

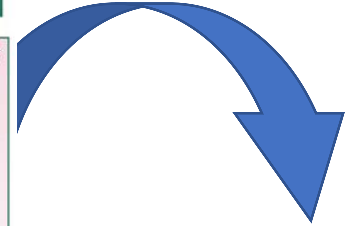




Omalizumab 300 mg
Benralizumab







Ciclofosfamide
Rituximab

Fagni F et al. *Front Med (Lausanne)* 2021

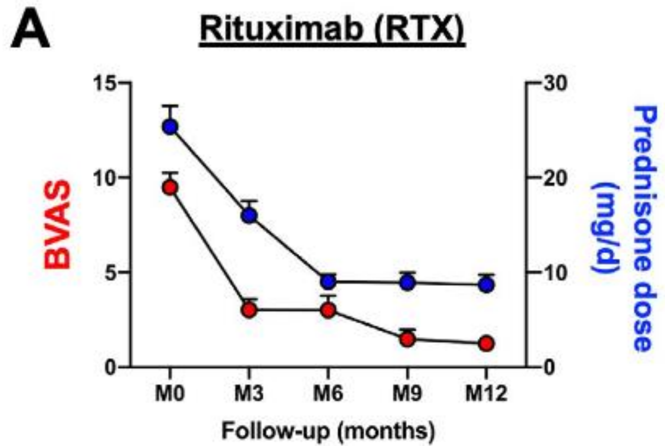
OCS sparing in EGPA

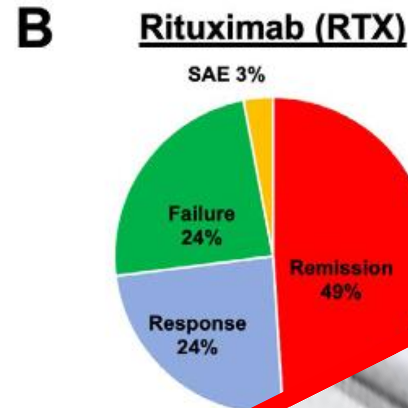
Review

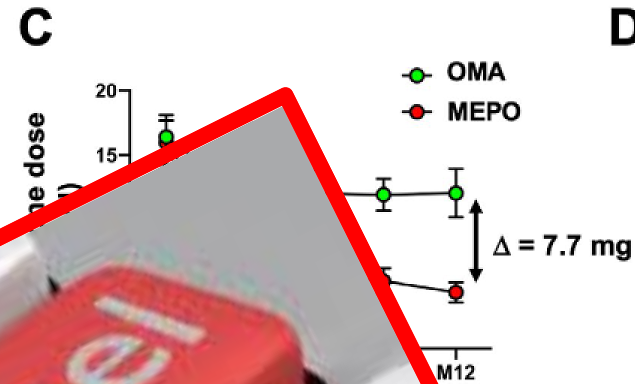
Drug	Pathogenetic basis	Evidence in EGPA	Dose	Clinical use
Rituximab (36–56)	*Anti-CD20—B cell differentiation and B-T cell stimulation* ■ ANCA pathogenetic antibodies ■ Eosinophils maturation and survival promoted by IL-5 (B-T cell interaction) ■ IgG4 (a surrogate of B-lymphocyte activation) infiltration of the organs involved	■ Case reports and open label studies ■ Previous AAV studies (not involving EGPA) ■ Two phase 3 RCT ongoing in EGPA: - *REOVAS* (RTX as induction therapy) (NCT02807103) - *MAINRITSEG* (RTX as maintenance therapy) (NCT03164473)	■ Induction: 375 mg/m^2/week for 4 weeks or 1 g every 2 weeks (AAV treatment) ■ Maintenance: 500 mg every 6 months for almost 18 months	*RCTs ongoing:* ■ New diagnosis or refractory/ remitting disease ■ GC sparing agent
Mepolizumab (57–68)	*Anti-IL-5—eosinophils activation and survival* ■ Eosinophils products: massive tissue toxicity ■ EGPA eosinophils: lower expression of pro-apoptotic genes and defective apoptosis	■ *FDA approval in 2017 as the first specific drug for EGPA* (RTC involving 136 patients with uncontrolled non-severe disease) ■ Long term efficacy: ongoing RCT (NCT03298061)	■ 300 mg/month (FDA approved) ■ 100 mg/month (severe eosinophilic asthma, under evaluation in EGPA)	■ Non-severe relapsing/refractory disease
Omalizumab (71–79)	*Anti-free circulating IgE* ■ Lower mast cells activation and interaction with eosinophils ■ Inhibition of Th2 and IgE mediated antigen presenting processes	*Evidence contradictory and scarce:* ■ Positive results in EGPA with asthma resistant to GC ■ Scarce information about vasculitic involvement ■ Possible trigger factor for EGPA	■ Subcutaneously every 2–4 weeks	■ Maintenance therapy in patients with uncontrolled and severe asthma/ENT symptoms but with a complete control of non-allergic symptoms

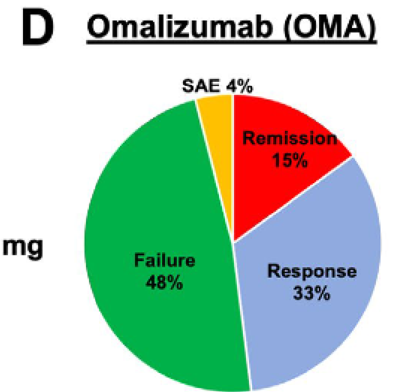
M. Uzzo et al. Front. Med. 2021

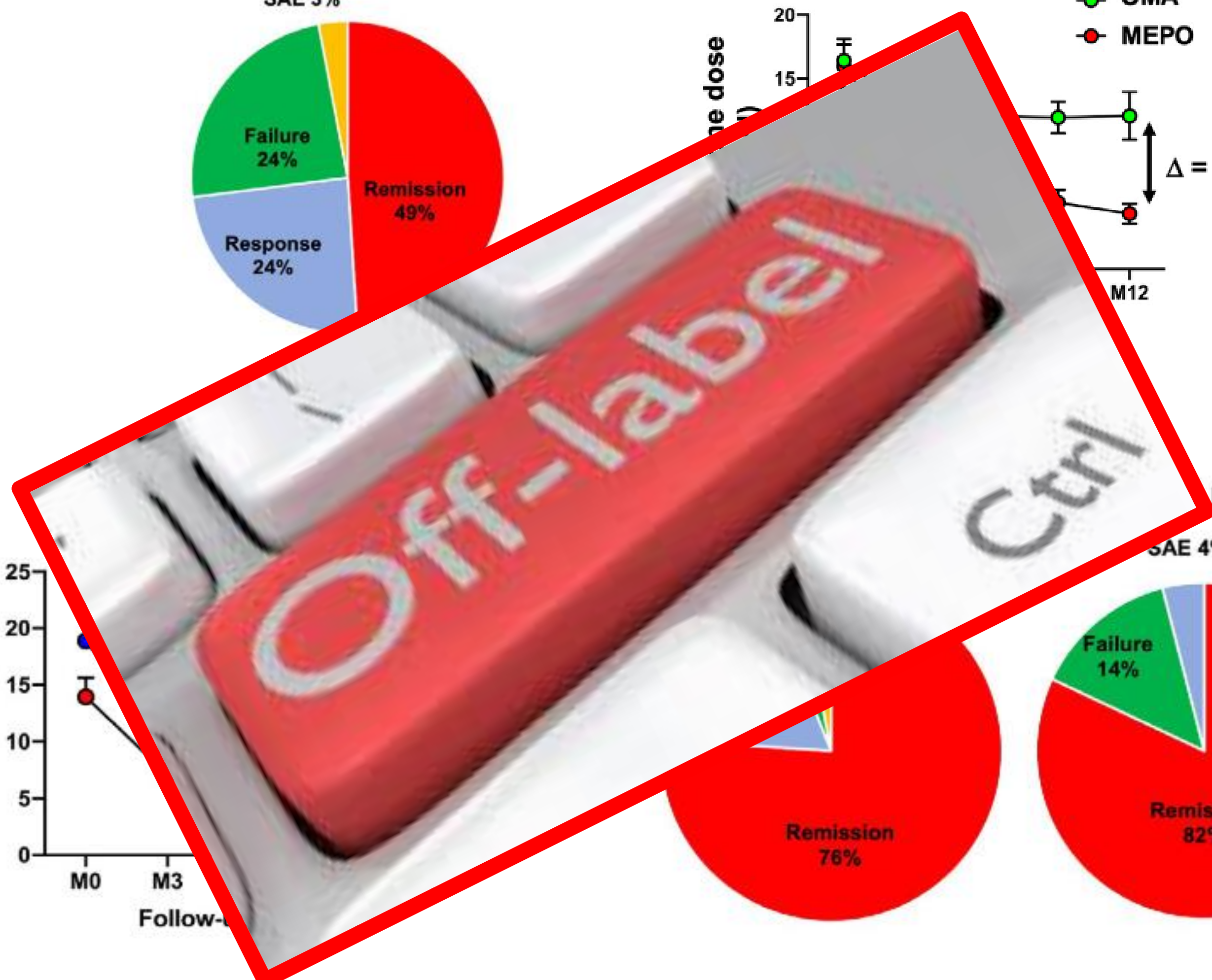
OCS sparing in EGPA







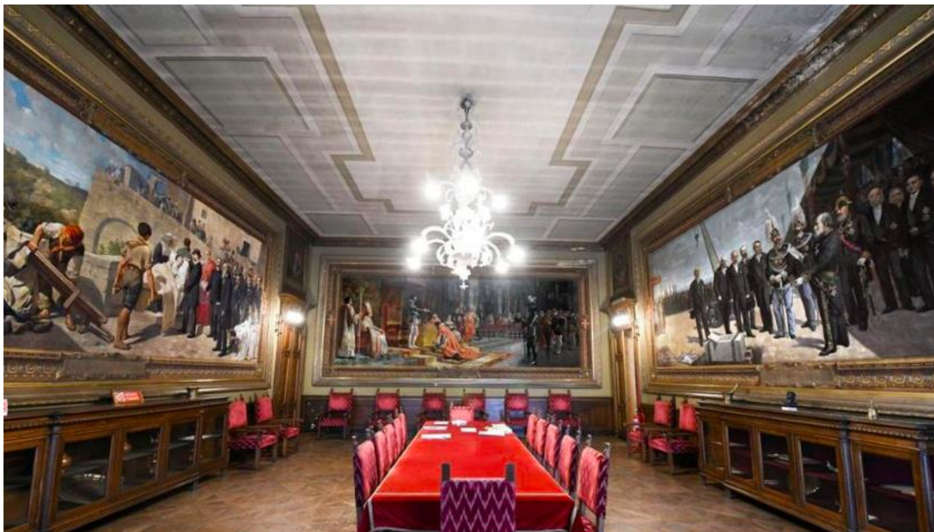




147 pazienti:
63 RTX
51 MEPO
33 OMA

MA. Canzian et al. Arthritis & Rheumatology 2021

Università degli Studi di Torino



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GRAZIE

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