bpacnz
PRIMARY CARE
UPDATE SERIES

04

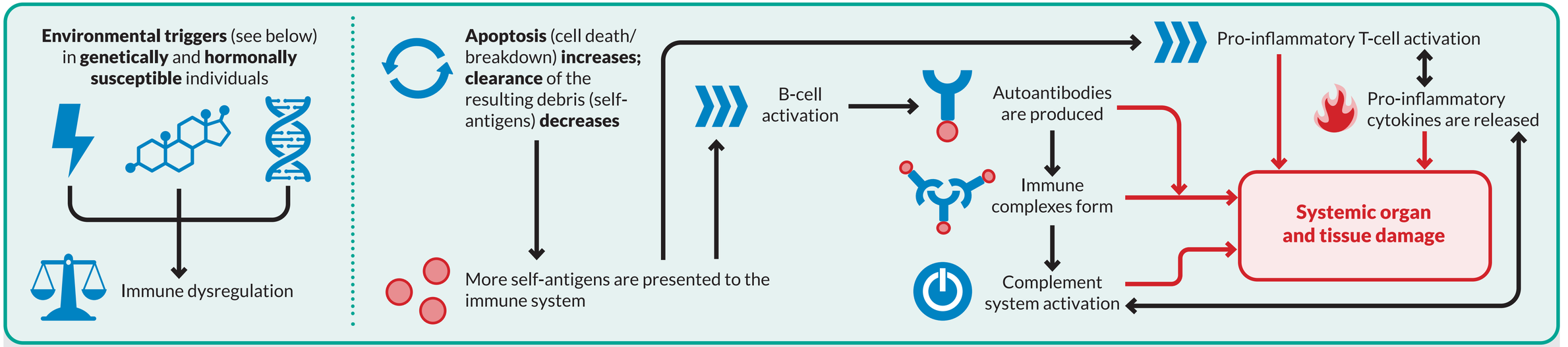
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

WHEN THE IMMUNE SYSTEM MISIDENTIFIES ITS TARGET

JULY 2021
VER 1.1

SLE pathophysiology – an overview

The pathophysiology of SLE is complex – there is no single discernible cause



Possible environmental triggers include:

UV light
Vitamin D deficiency is often present

Viruses
particularly Epstein-Barr virus

Allergens, chemicals and pollution e.g. smoking

SLE is 9–10× more common in females, oestrogen has an important role in disease activity – particularly during pregnancy

Onset: SLE can affect people of all ages, however, it most commonly affects females of reproductive age

Ethnicity: more common in Asian and Pacific peoples (and Māori to a lesser extent) compared with NZ Europeans

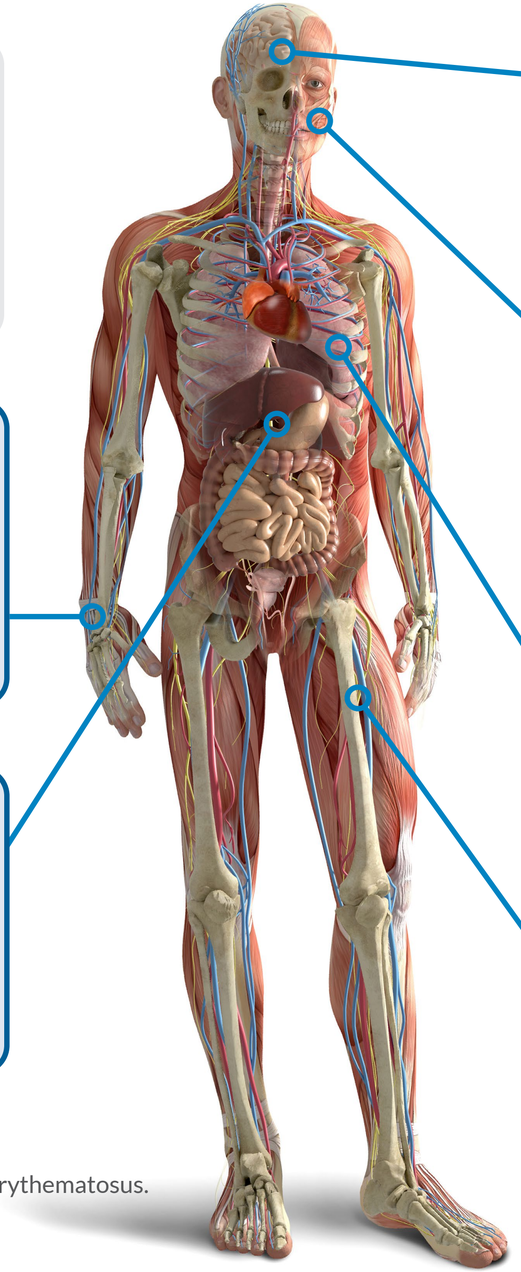
1. Moulton VR, Suarez-Fueyo A, Meidan E, *et al*. Trends Mol Med. 2017; 23: 615–35; 2. Gordon C, Amissah-Arthur M-B, Gayed M, *et al*. Rheumatology (Oxford). 2018;57:e1–45; 3. Systemic lupus erythematosus. DermNet NZ. 2021. Available at: https://dermnetnz.org/topics/systemic-lupus-erythematosus/ (Accessed July, 2021); 4. Concannon A, Rudge S, Yan J, *et al*. Lupus. 2013;22:1156–61.

Possible manifestations associated with SLE

Systemic symptoms:
- Fatigue (often severe)*
- Fever*
- Weight loss*
- Myalgia (severe muscle weakness is uncommon)

Arthritis and arthralgias*
- Occurs in >90% of patients with SLE, often early in disease progression
- Commonly occurs as swelling/tenderness in small joints of hands, feet, knees and wrists

Renal manifestations
- Renal involvement (lupus nephritis) occurs in up to half of patients with SLE during disease course
- Patients who have renal dysfunction identified at their initial presentation have worse outcomes (this is rare)



Neuropsychiatric manifestations
- Challenging to identify; can range from headache, through to cognitive dysfunction, delirium, seizures and psychosis

Mucocutaneous manifestations*
- Most patients experience skin and/or mucous membrane lesions at some point – although the type/extent of varies significantly
- The most common lesion is the “butterfly rash”
- Usually triggered by sun exposure

Serosal manifestations
- Pericardial and pleural inflammation often develops in patients with active disease
- May present as chest pain or shortness of breath

Haematological manifestations
- Anaemia can occur due to chronic inflammation
- Leukopenia and thrombocytopenia occur less frequently
- ESR is usually increased (but not CRP)

* Common presenting features in patients with SLE.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus.

Aringer M, Costenbader K, Daikh D, *et al*. Arthritis Rheumatol. 2019;71:1400–12.

Possible manifestations associated with SLE

Cutaneous lupus erythematosus (CLE) in patients with SLE

Acute CLE

- SLE usually presents initially as acute CLE
- **Butterfly rash** is the main variant and involves a red or purple malar rash with well-defined margins
  - Occurs mainly around the nose and cheeks, with nasolabial sparing
  - May come and go, or persist for days or weeks at a time

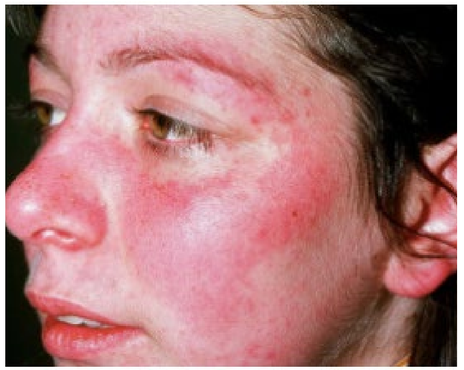
Subacute CLE

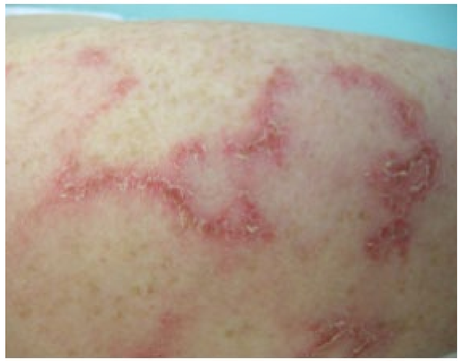
- Flat, scaly patches appearing on the skin in areas exposed to sunlight
- Can resemble psoriasis

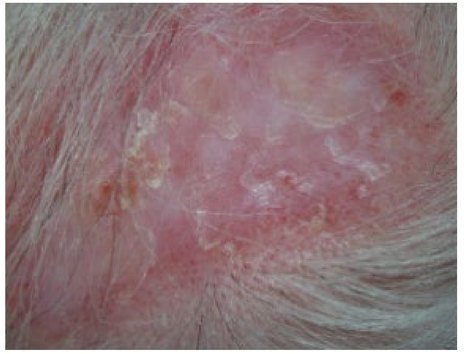
Chronic CLE

- Classic discoid lupus is the most common form – dry red lesions that often begin to scar
- Generally localised above the neck
- Rarely progresses to systemic disease

Images from DermNet: https://dermnetnz.org/topics/systemic-lupus-erythematosus/





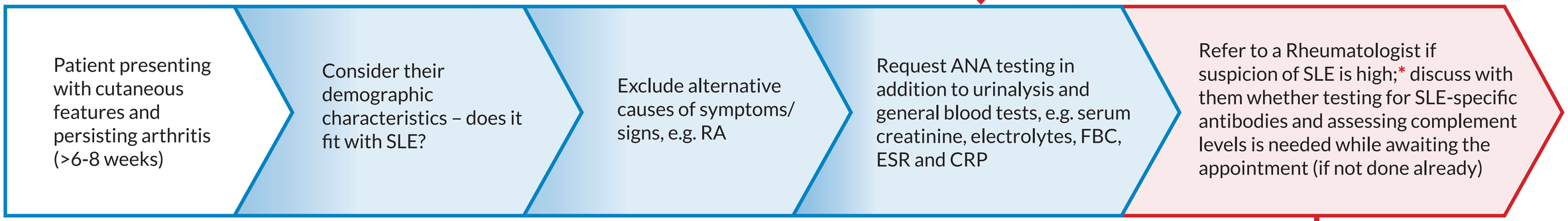


CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus.

Aringer M, Costenbader K, Daikh D, *et al*. Arthritis Rheumatol. 2019;71:1400–12.

Piecing together the puzzle: what's the practical approach to diagnosing SLE in primary care?

If SLE is strongly suspected, then ESR can usually be requested concurrently with CRP (document SLE as the suspected indication on the laboratory request form).



ANA testing is important as a negative predictor; >95% of patients with SLE are positive for ANA antibodies

- However, ANA testing alone is a poor diagnostic marker as it can still be present in patients without SLE
- Additional **SLE-specific antibody testing** is informative and can add to clinical suspicion, e.g. anti-dsDNA antibody or anti-Sm antibody – this can occur either alongside ANA testing or while awaiting rheumatologist appointment
- Low complement levels (C3 and C4) can support a diagnosis and are generally correlated with disease activity
- Rheumatologists sometimes subsequently test for **antiphospholipid antibodies**; these are not-specific for SLE, but are part of the immunological abnormalities that can be associated with pregnancy morbidities and thrombotic complications

* See the next slide for a framework to assess the combination of clinical and immunological parameters

ANA, antinuclear antibody; anti-dsDNA, anti-double stranded deoxyribonucleic acid; anti-Sm, anti-Smith; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

1. Moulton VR, Suarez-Fueyo A, Meidan E, *et al*. Trends Mol Med. 2017 Jul; 23(7): 615–635; 2. Gordon C, Amissah-Arthur M-B, Gayed M, *et al*. Rheumatology (Oxford). 2018;57:e1–45.

Piecing together the puzzle: what's in the guidelines?

2019 EULAR/ACR classification criteria for patients with suspected SLE

Note: these criteria are more suited for identifying patients to include in clinical trials rather than diagnosing patients primary care – if you have a strong suspicion of SLE, then refer the patient to a rheumatologist

Entry criteria: patients must have a positive antinuclear antibody (ANA) test result

* **Note:** specific criteria in guidelines requires a titre of ≥1:80 on HEp-2 cells or an equivalent positive test

Additional criteria:

- Do not count a criterion if there is a more likely explanation than SLE
- The occurrence of a criterion on a single occasion is sufficient
- Criteria do not need to occur simultaneously
- Within each domain, only the highest weighted criterion is counted toward the total score

An SLE classification using this framework requires the presence of at least one clinical criterion and ≥10 total points

For example: a patient presenting with a subacute cutaneous rash on their forearm (4 points) and swelling/tenderness in four joints across their hands (6 points) that cannot be explained by another cause – who subsequently tests positive for ANA (entry criteria) – would be classified as having SLE

	Domain	Criteria*	Weight
Clinical	Systemic	Fever	2
	Haematologic	Leukopaenia	3
		Thrombocytopaenia	4
		Autoimmune haemolysis	4
	Neuropsychiatric	Delirium	2
		Psychosis	3
		Seizure	5
	Mucocutaneous	Non-scarring alopecia	2
		Oral ulcers	2
		Subacute cutaneous or discoid lupus	4
		Acute cutaneous lupus, e.g. malar (butterfly) rash	6
	Serosal	Pleural or pericardial effusion	5
		Acute pericarditis	6
	Musculoskeletal	Joint involvement	6
	Renal	Proteinuria >0.5 g per 24 hours	4
		Renal biopsy Class II or V lupus nephritis	8
		Renal biopsy Class III or IV lupus nephritis	10
Immunological†	Antiphospholipid antibodies	Positive test for anti-cardiolipin antibodies **or** anti-beta-2GP1 antibodies or lupus anticoagulant	2
	Complement	Low C3 **or** low C4 (i.e. below lower limit of normal)	3
		Low C3 **and** low C4 (as above)	4
	SLE-specific antibodies	Positive test for anti-dsDNA antibody or anti-Sm antibody	6
			Total

* For definitions of the criteria listed, see Aringer *et al*, 2019 (below); † These tests would generally usually ordered after a positive ANA result (which is the entry criteria for this scoring system).

ACR, American College of Rheumatology; anti-dsDNA, anti-double stranded deoxyribonucleic acid; anti-Sm, anti-Smith; EULAR, European League Against Rheumatism; SLE, systemic lupus erythematosus.

Aringer M, Costenbader K, Daikh D, *et al*. Arthritis Rheumatol. 2019;71:1400–12.

Treatment options for patients with SLE

Treatment selection depends on disease severity, co-morbidities, and patient preference

This will be **generally guided by a rheumatologist**

The **aim of treatment** is to achieve the lowest possible level of disease activity, prevent organ damage, improve quality of life and long-term prognosis

Flares are managed by increasing the dose of existing medicines or adding new ones

Mild SLE

E.g. Patients with fatigue, mild skin, joint, and mucosal involvement

Moderate SLE

E.g. patients with significant but non-organ-threatening disease (incl. systemic, cutaneous, musculoskeletal, or haematologic features)

Severe SLE

E.g. Patients with severe or life-threatening manifestations secondary to major organ involvement (incl. renal and central nervous system)

Possible treatments

- Hydroxychloroquine
- NSAIDs
- Corticosteroids (topical/oral/IM/IV – depending on severity)
- Immunosuppressive medicines, e.g. methotrexate, azathioprine, cyclophosphamide
- Biologics, e.g. rituximab

Adjunctive treatment

- Sun protection
- Vitamin D supplementation
- Aim to administer any required vaccines before initiating immunosuppressive treatment*
- Exercise/rest when needed
- Smoking cessation
- Weight loss
- Blood pressure management
- Lipid-lowering medicines

* However, influenza and pneumococcal vaccines can usually be administered while the patient receives immunosuppressive treatment.

IM, intramuscular; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

1. Gordon C, Amissah-Arthur M-B, Gayed M, *et al*. Rheumatology (Oxford). 2018;57:e1–45; 2. Fanouriakis A, Kostopoulou M, Alunno A, *et al*. Ann Rheum Dis. 2019;78:736–45

Long-term monitoring for patients with SLE

Patients with stable SLE can be monitored predominantly in primary care, e.g. three-monthly

Clinical monitoring to consider	**Laboratory monitoring** to consider
Blood pressure (as part of an overall cardiovascular risk assessment)	• Urine dipstick test (for proteinuria) • Serum creatinine • Lipids • FBC • Double-stranded DNA antibody titres* • ESR (if it was raised initially) • Complement levels (particularly C3 and C4)
Rash (and other features indicative of organ involvement, e.g. shortness of breath)	
Medicine-specific adverse effects, e.g. from corticosteroids	

Warn patients with SLE to immediately seek medical attention if they experience deterioration of previously controlled symptoms (or if new SLE symptoms emerge)

* Request these tests immediately if a flare occurs.

ESR, erythrocyte sedimentation rate; FBC, full blood count; SLE, systemic lupus erythematosus.

1. Gordon C, Amissah-Arthur M-B, Gayed M, *et al*. Rheumatology (Oxford). 2018;57:e1–45.

Discussing the clinical course and prognosis of patients with SLE

The initial presentation usually indicates how the patient will progress

E.g.

Good prognosis: presenting with mild and localised cutaneous SLE without organ involvement

Poorer prognosis: presenting with cerebral or kidney involvement*

SLE is generally characterised by remissions and flares

- **The prognosis is worse in patients who are male, of Asian or Pacific ethnicity,** or who are **either very young or very old**
- **Early response to treatment is associated with a better prognosis**

Females with SLE have higher risk pregnancies – all females with SLE planning pregnancy should have a rheumatology review pre-conception (or immediately once they find out they are pregnant)

- SLE increases the risk of **adverse fetal outcomes**, and also **increases the mother's risk of pre-eclampsia, worsening lupus nephritis** (if present), and there is an **increased risk of SLE flares**
- **Some medicines are contraindicated in pregnancy**, e.g. cyclophosphamide, methotrexate, leflunomide

* People with SLE who present without organ involvement may still ultimately progress to have additional complications such as kidney or cerebral damage; however, their prognosis is usually better as early treatment may limit this progression.

SLE, systemic lupus erythematosus.

1. Tselios K, Gladman Z, Touma Z, *et al*. Lupus. 2019;28:114–22; 2. Saavedra MA, Cruz;Reyes C, Vera-Lastra O, *et al*. 2012;31:813–9. 3. Smyth A, Oliveira GHM, Lahr BD, *et al*. CJASN. 2010;5:2060–8.