Immunisation in AIIRD

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&

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Declarations

- I have accepted travel assistance to national and international conferences from UCB, BMS and Abbvie.

- Research grants from Pfizer, Arthritis UK, Arthritis QLD.

Learning Outcomes

- When is the best time?
- Which vaccines are indicated?
- Which vaccines are safe?
- Which vaccines should be avoided?

When is the best time?

- Treating specialist should initiate - however given by GP.
  - (*quoted by patients as reason why not had vaccines*)

- **No** evidence for flare of disease.
  - *Common question from patients.*
  - *Efficacy is also reasonable (exception reduced titres with RTX)*

- Ideally before immunosuppression
  - *but often in a rush to start treatment.*
  - *should consider getting up to date when diagnosis is made.*

What Qualifies as **Immunosuppression?**

- Which drugs are the issue?
  - Prednisolone
    - >20mg for 2 weeks or >60mg for 1 week
  - bDMARD and tsDMARD
    - *emerging data can be safe if wait until due dose then skip two weeks.* **Seek advice from Rheumatologist and discuss with patient.**
  - NOT the issue:
    - csDMARD
      - MTX <0.4mg/kg/week
      - AZA <3mg/kg/day

Mechanism of action	Agent
Targeted synthetic DMARDs	
Janus kinase inhibitor	Tofacitinib
Phosphodiesterase-4 inhibition	Apremilast
Biologic DMARDs	
Tumour necrosis factor inhibition	Etanercept
	Adalimumab
	Infliximab
	Certolizumab pegol
	Golimumab
T-cell co-stimulation blockade	Abatacept
B-cell depletion	Rituximab
Interleukin 12/23 inhibitor	Ustekinumab

DMARDs, disease-modifying anti-rheumatic drugs.

Useful to have handy reliable resources

INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

REVIEW

A practical approach to vaccination of patients with autoimmune inflammatory rheumatic diseases in Australia

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Influenza and Pneumococcal

Vaccine	Recommendations	Dosing	Frequency	Cost covered by NIP	Approx. cost if not covered by NIP	Reference
Influenza	Annually	Two doses 4 weeks apart for 1st year and then one dose annually	Annually	Yes	NA ***only first funded**	5
Pneumococcus-vaccine-naïve	13vPCV, 23vPPV vaccines	13vPCV first, then 23vPPV after ≥8 weeks	Rpt in 5 years, then 3rd dose at age 65	For adults ≥65 years	Standard co-payment $37.70 or $6.10 for concession card holders ***only first funded**	5
Pneumococcus-previously vaccinated	23vPPV at age 18 or at diagnosis of AIIRD, or 5 years after last dose	23vPPV at diagnosis of AIIRD, or 5 years after last dose	<2 More doses, 5 years apart	For adults ≥65 years	Standard co-payment $37.70 or $6.10 for concession card holders	5

- No adjustment needed with medication (exception: best as far away from RTX as possible)

- FIRST dose may need two. (“prime and boost”) ideally before MTX

Influenza

- Quadrivalent influenza (inactivated virus) vaccines are recommended for people aged from 6 months to less than 65 years of age.

- Trivalent (inactivated virus) +/- adjuvant vaccines are recommended for people aged 65 years or older

- lower titres of Abs may be seen in the presence of DMARDs
  - BUT most patients have an adequate level of protective antibody after influenza vaccination, with no worsening of AIIRD symptoms.

- Exception - Rituximab has been shown to decrease response to vaccine

- *Watch this space… ?hold methotrexate for two weeks in everyone - no increased risk of flare and better titres, not yet in guidelines.*

Herpes Zoster

Vaccine	Recommendations	Dosing	Frequency	Cost covered by NIP	Approx. cost if not covered by NIP	Reference
Herpes zoster	Consider in those aged ≥50 years with AIIRD Note: live vaccine	One dose	Once, re-vaccination interval unclear	Yes, 70–79 years from November 2016	$220 for each dose	Consensus

- In Australia - Licensed >50, *funded >70.*
    - However risk of HZ in those aged 50-59 with AIIRD approximate those of healthy people aged 70-79.
    - Therefore **recommended for our patients >50.**
- Need to check baseline immunity in immunocompromised patients.
    - (case reports of severe reactivation when no baseline immunity)
    - If negative can consider varicella vaccine two doses 4 weeks apart.

Herpes zoster

- 50-55% efficacy rate
- Protection wanes
  - In first year after vaccination about 50% effective, but about year 5 no significant protection left
  - Probably need to boost about year 4
  - Recombinant vaccine theoretically safe.
    - Nov 2018 PBS declined due to cost.

Which to avoid?

- Live - **MMR, Yellow Fever.**
- And in Infants of mothers on bDMARD - avoid live for 6m (inc **rotavirus**)

Other vaccines to consider

Hepatitis B	Those at increased risk of contracting infection (see text)	3 doses in 6/12. Engerix-B day 0 – 1st dose, 2nd dose 1 month post-1st injection and 3rd dose, 6/12 after 1st injection	3 Doses over 6/12	Yes	$25 Each vaccine × 3 = $75

- Hep B
  - Give anytime
  - Indication: if the patient is at higher risk of severe disease, for example, on immunosuppression;
  - the risk of contracting HBV is increased, e.g. travel to, or residence in countries endemic for HBV;
  - there is increased risk of exposure or proven exposure to HBV, for example, healthcare professionals, infected family member or contacts
  - when protective HBV antibodies are absent.

- HPV
  - Give anytime
  - should consider the likelihood of previous exposure to HPV
  - the future risk of HPV exposure
  - extent/duration of immunosuppression

Human papilloma virus	Case-by-case basis (see text)	injection Three doses, second at least 1 month after the 1st, and 3rd at least 3 months after the 2nd	Once	No	$450 for course

Summary

- When is the best time? Depends on vaccine but ideally before biologics.
- Which vaccines are indicated? Influenza, Pneumococcal, Zoster, Hep B
- Which vaccines are safe?
- Which vaccines should be avoided? Live - MMR, Yellow Fever. inc rotavirus.

Positive ANA & SLE essentials

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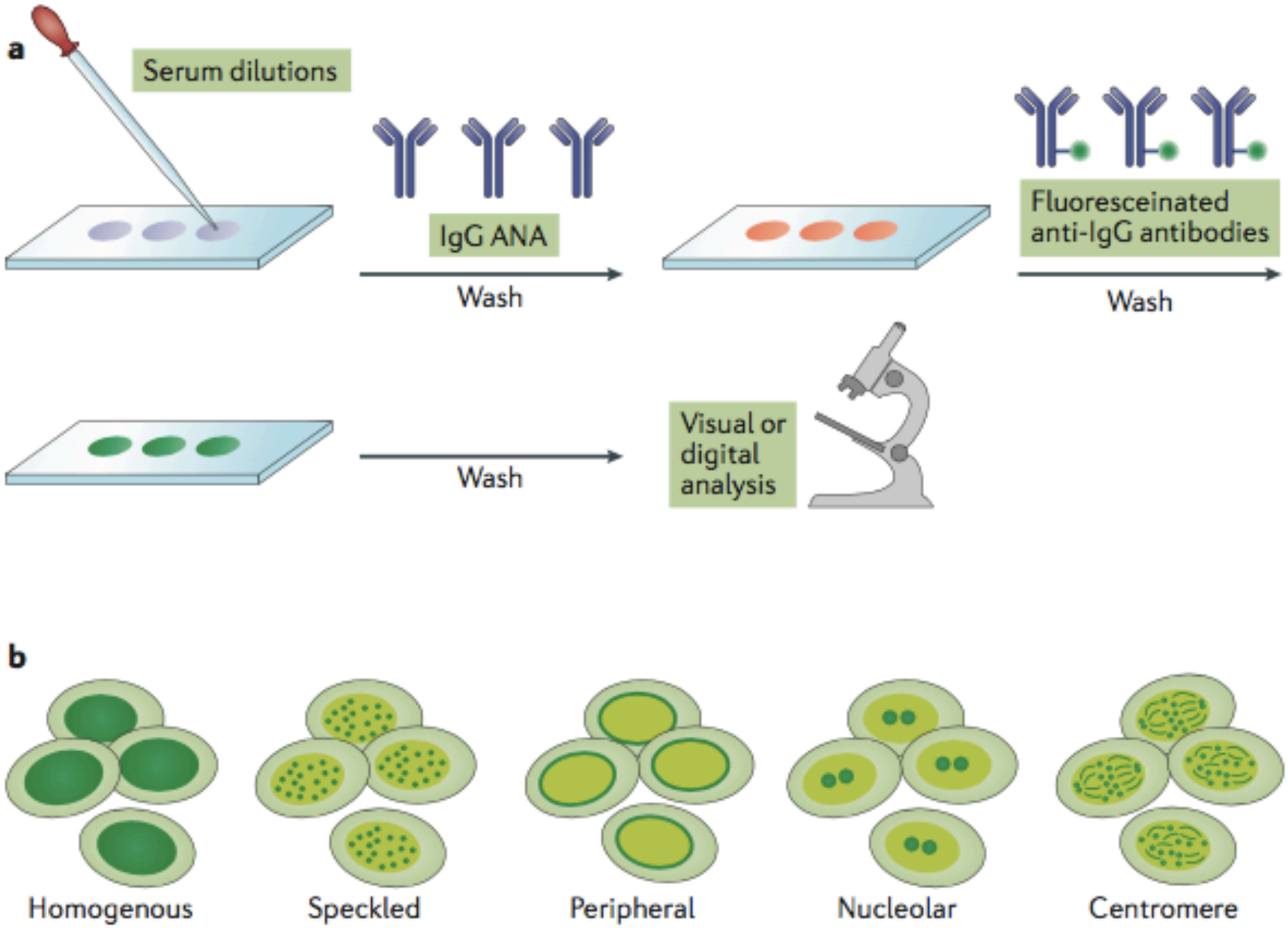
Learning Outcomes

- When is an ANA indicated?
- What to do when positive?
- Does the pattern matter?
- Management of SLE in a nutshell

ANA - How is it done?



Nature Reviews Rheumatology **13**, 495–502 (2017)

ANA - Importance of the Titre

- Reported as the highest titre that the immunofluorescent pattern is still visible.

- 1:40 /80 /160 /320 /640 /2560

- Change in titre is rarely clinically useful.
- Repeating ANA is rarely clinically useful.

When to Consider ordering an ANA?

Table 2. Conditions other than SLE associated with positive ANA[23,24]

Systemic autoimmune diseases	Organ-specific autoimmune diseases	Non-autoimmune associations
Scleroderma	Autoimmune hepatitis	Viral infections (Infectious mononucleosis, parvovirus, hepatitis C, HIV)
Sjögren's syndrome	Primary biliary cirrhosis	Bacterial infections (infective endocarditis, TB)
Polymyositis or dermatomyositis	Grave's disease	Parasitic infections
Rheumatoid arthritis	Hashimoto's thyroiditis	Malignancy
Mixed connective tissue disease	Idiopathic pulmonary fibrosis	Normal population 1:40 (25–30%) 1:80 (10–15%) 1:160 (5%)

so… when to order?

Signs and Symptoms

- Inflammatory joint pain (generally small joints)
- Photosensitive or discoid rash
- Dry eyes or mouth
- Serositis (pericarditis or pleuritis)
- Sclerodactyly
- Raynaud's phenomenon
- Muscle weakness
- Alopecia
- Seizures
- Dilated nail fold capillary loops

Adapted from “EVOLVE” Draft

When to order?

Pathology Results

- Haemolytic anaemia
- Thrombocytopaenia
- Leucopaenia –lymphopaenia
  +/- neutropaenia
- Hypergammaglobulinaemia
- Haematuria
- Proteinuria

ANA positive, now what?

- At low titters 5-10% population positive. May not be significant.
- To assess for extent of disease:
  - ELFT's, FBC, Urine dipstick,
  - (optional) CK, CXR etc
- Management of all AIRD is based on extent of organ involvement and severity of symptoms.

If suspect SLE:

ENA and dsDNA
C3/4
Coombs
Urine MCS and PCR
IgG,A,M, EPP
APLS Abs (Lupus A/C, anti C/L and Anti B2)
ESR
CRP

+/- CXR, CK

Does the pattern matter?

- 120 patterns have been described but relatively few have clinical significance

- Two do:
- Centromere (Scleroderma/ Sjogrens)
- Dense Fine Speckled

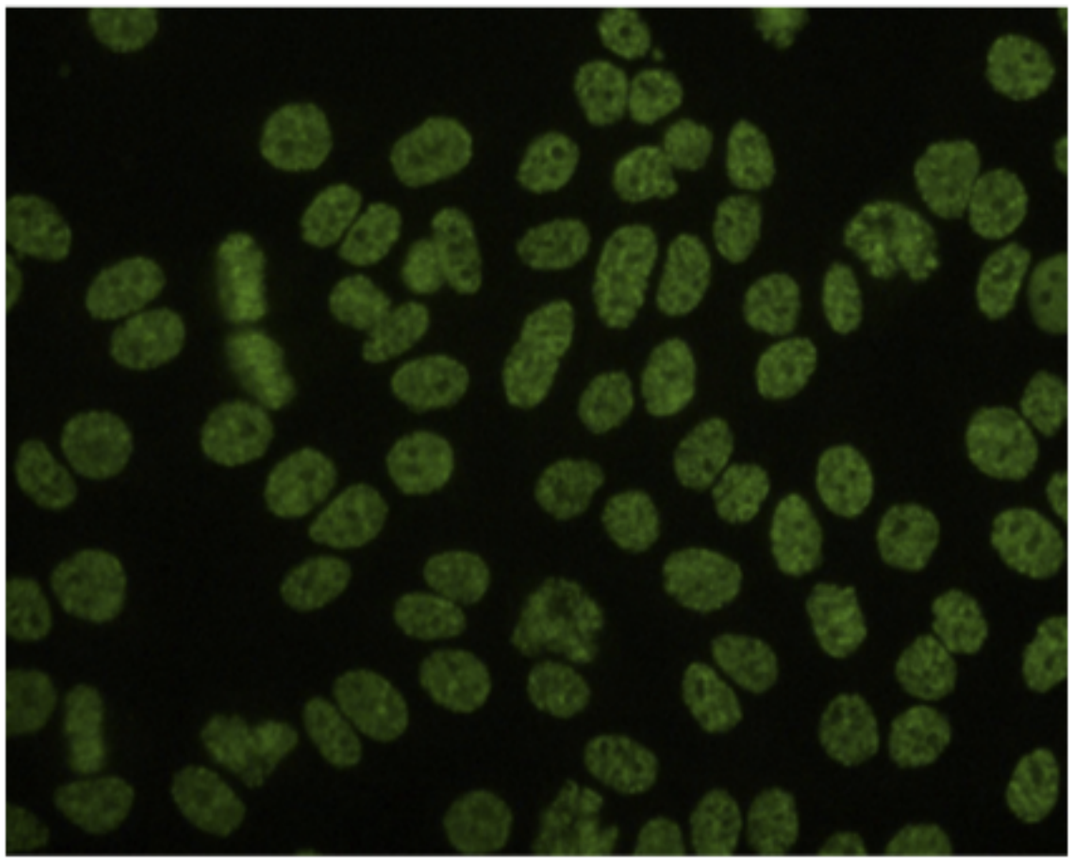


Fig. 1 The DFS pattern on IIF HEp 2000 Slides. Serum dilution 1:80.

Pathology (April 2016) 48(3), pp. 247–250

Dense Fine Speckled

- Negative correlation with AIIRD
- ONLY if confirmed with ENA to DFS-70 and no other ENA recognised
- Then very reassuring The likelihood ratio (LR+) for the absence of AIRD 10.9 (if only this ENA positive)
- Can be seen with interstitial nephritis, autoimmune thyroid disease and atopic eczema

Clin Lab. 2016;62(4):499-517.
Ann Rheum Dis 2019;78:879–889.

ANA positive, but no symptoms?

- I would monitor (NOT with repeat ANA) if:
  - low c3/4
  - ENA positive (not DFS-70)
  - dsDNA positive (Farr)
  - high titre >1280
  - positive RF
  - High IgG/polyglonal gammopathy

ENA
you get what you ask for.

Standard Panel:
Ro/SSA
La/SSB
Sm
RNP
SCL70
PM/SCL
JO-1
DFS-70
(CENP-B)

Anti-histone
&
Anti-RNA polymerase
III
Ordered separately.

Myositis Panel:
HMG-Co (requested separately)

Mi-2a
Mi-2b
TIF1 gamma
MDA5
NXP2
SAE1
Ku
PMSCL100
PMSCL75
Jo-1
SRP
PL-7
PL-12
EJ

Scleroderma panel:
SCL-70
CENP A
CENP B
RP11
RP155
Fibrillarin
NOR90
Th/To
PMSCL100
PMSCL75
Ku
PDGFR
Ro-52

When to repeat the test?

Generally don't.

- Remember ANA is NOT a marker of disease activity.
- Could consider if there is a change/new in symptoms. eg/ development of sicca symptoms in a patient with RA.

- New drug and new symptoms- esp: minocycline, TNF inhibitor, Chlorpromazine, Hydralazine, Isoniazid, Methyldopa, Procainamide, Quinidine.
- Can be misleading - e.g.:
  - A phase II clinical trial in SLE for belimumab (monoclonal antibody against BAFF) during the trial measured all patients ANA - with 20-30% negative despite 99% having historical ANA positivity and active disease as entry requirement of study.

SLE Pearls

- C3/4 low, dsDNA high with active disease
- ESR high with active disease (high CRP think infection!)
- 50% can remain undifferentiated at 12months
- Fatigue - whilst common does not correlate with disease activity or improve with immunosuppression
- Steroid related side effects cause burden of morbidity and mortality currently.
- Cardiovascular disease 2-10x higher in SLE

New ACR and EULAR criteria for classification of SLE

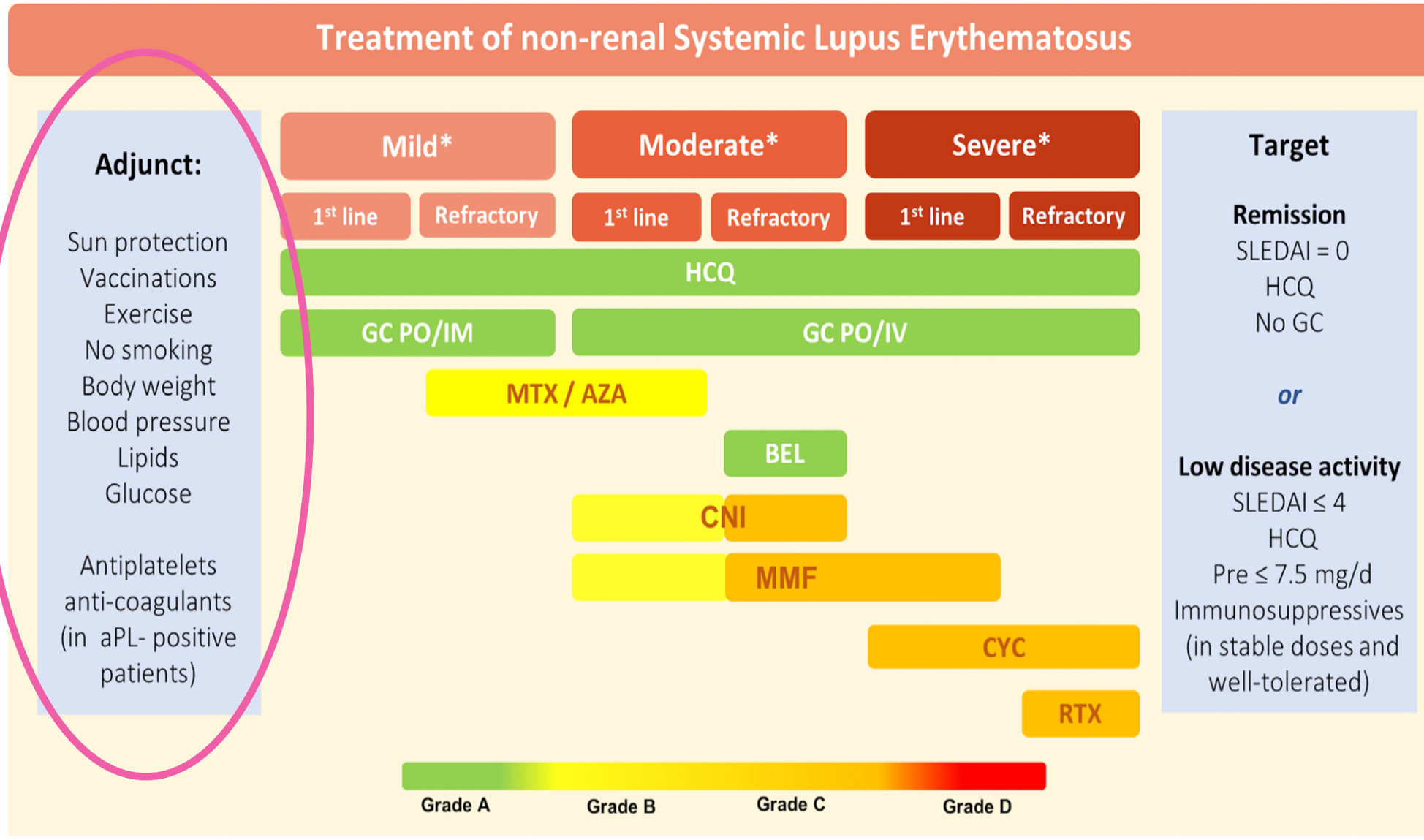
All patients classified as having systemic lupus erythematosus must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2–positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely explanation than SLE. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain only the criterion with the highest point value counts:

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria >0.5g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant	2
Complement proteins domain	
Low C3 or low C4	3
Low C3 and low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Smith antibody	6

Source: Dr. Johnson

MDedge News



Mild: constitutional symptoms/ mild arthritis/ rash ≤9% BSA/PLTs 50-100 x 10^3/mm^3; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation
Moderate: RA-like arthritis/ rash 9-18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20-50x103/mm3/serositis; SLEDAI 7-12; ≥2 BILAG B manifestations
Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20x103/mm3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI>12; ≥1 BILAG A manifestations

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

Antonis Fanouriakis,[1] Myrto Kostopoulou,[2] Alessia Alunno,[3] Martin Aringer,[4] Ingeborg Bajema,[5] John N Boletis,[6] Ricard Cervera,[7] Andrea Doria,[8] Caroline Gordon,[9] Marcello Govoni,[10] Frédéric Houssiau,[11] David Jayne,[12] Marios Kouloumas,[13] Annegret Kuhn,[14] Janni L Larsen,[15] Kirsten Lerstrøm,[16] Gabriella Moroni,[17] Marta Mosca,[18] Matthias Schneider,[19] Josef S Smolen,[20] Elisabet Svenungsson,[21] Vladimir Tesar,[22] Angela Tincani,[23] Anne Troldborg,[24] Ronald van Vollenhoven,[25] Jörg Wenzel,[26] George Bertsias,[27] Dimitrios T Boumpas[1,28,29]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