Lupus: Knowing and taming the wolf

Dr. Marline Squance

No-one is (EMU)ne to autoimmunity
Discussion Points

- History
- Definitions and classification
- Epidemiology & pathogenesis
- Clinical features
- Diagnosis
- Treatment
  - lifestyle
  - pharmacological
- Impact
- Outlook
- Research directions
- Resources

Quality of life through education, support & research
Autoimmune Disease: More Common Than You Think

• Number 3 cause of illness (after vascular disease and cancer)
• Autoimmune diseases affect 1:20 people
• Organ-specific and systemic

ARRC Mission

To increase awareness of and research on autoimmune diseases, which are a major health problem, affect as many as 4.8 million Australians.

Autoimmune diseases encompass more than 100 interrelated diseases
- lupus, multiple sclerosis, rheumatoid arthritis,
  Sjögren's syndrome, polymyositis, pemphigus, myasthenia gravis,
  Wegener’s granulomatosis, psoriasis, coeliac disease,
  autoimmune platelet disorders, scleroderma, alopecia areata,
  vitiligo, autoimmune thyroid disease, and sarcoidosis etc

No-one is (EMU)ne to autoimmunity  
Quality of life through education, support & research
Lupus (Latin for “wolf”) was a Roman family name, and a St. Lupus lived in central France around 600AD.

It is unclear how this name came to be attached to the disease:

1. thought the rash resembled the pattern of fur on a wolf's face.
2. thought that the rash, which was often more severe in earlier centuries, created lesions that resembled wolf bites or scratches.
Classification

• No single clinical feature or laboratory test is diagnostic of SLE because no two patients present alike.
• Diagnosis requires a careful review of symptoms, detailed physical examination and appropriate investigations.

<table>
<thead>
<tr>
<th>SLICC Classification Criteria for Systemic Lupus Erythematosus</th>
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<tbody>
<tr>
<td>Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)</td>
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<tr>
<td>OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA</td>
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</tbody>
</table>

### Clinical Criteria

1. Acute Cutaneous Lupus (*
2. Chronic Cutaneous Lupus (*
3. Oral or nasal ulcers (*
4. Non-scarring alopecia
5. Arthritis (*
6. Serositis (*
7. Renal (*
8. Neurologic (*
9. Hemolytic anemia
10. Leukopenia (*
11. Thrombocytopenia (<100,000/mm³)

### Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab (*
5. Low complement (C3, C4, CH50)
6. Direct Coombs’ test (do not count in the presence of hemolytic anemia)

• Although the criteria are useful for research studies, they should not be used to diagnose patients because they are designed to be highly specific at the cost of sensitivity.
• There are no definitive diagnostic criteria for SLE, so patients with mild or early SLE may not be diagnosed.
Epidermiology

- 50% systemic (SLE), 40% skin (cutaneous), 10% crossover/overlap/MCTD, < 1% drug-induced
- Higher prevalence in females than men
- Prevalence 1:700-1:1000
  - More common in African-American women (1:250)
  - More common in indigenous population

<table>
<thead>
<tr>
<th>Age</th>
<th>Female</th>
<th>Male</th>
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<tbody>
<tr>
<td>0-4</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>5-9</td>
<td>2.3</td>
<td>1</td>
</tr>
<tr>
<td>10-14</td>
<td>5.8</td>
<td>1</td>
</tr>
<tr>
<td>15-19</td>
<td>5.4</td>
<td>1</td>
</tr>
<tr>
<td>20-29</td>
<td>7.5</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
<td>8.1</td>
<td>1</td>
</tr>
<tr>
<td>40-49</td>
<td>5.2</td>
<td>1</td>
</tr>
<tr>
<td>50-59</td>
<td>3.9</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>2.2</td>
<td>1</td>
</tr>
</tbody>
</table>
Pathogenesis

• Critical “dose” of susceptibility genes

• **Environment**: infection, UV light, drugs, chemicals, hormones, stress

• **Antigens**: altered to become more immunogenic, molecular mimicry

• **B & T cell abnormalities**: activation with less antigen, more reactivity, abnormal receptor engagement, cytokine interactions

• **Apoptotic defects & impaired I-C clearance**

• **T & B cell signalling aberrations**

• Targeted tissues more permissive to antibodies
Pathogenesis (II)

Inflammation is a key factor.

- A hallmark of lupus is the presence of hyperactive B cells and loss of B-cell tolerance.
- Immune complexes containing nucleic acid autoantigens can engage and activate endosomal TLRs and promote inflammation in SLE.
- Plasma cell expansion & production of autoantibodies are also features,
  - autoantibodies are benign unless generated in an inflammatory milieu.
- Proinflammatory cytokines drive T-cell activation and dendritic cell maturation, that can lead to:
  - expansion innate immune cells, & production of acute-phase proteins.
- Autoantibodies become deposited in tissues such as the glomeruli of the kidney, leading to tissue destruction.

Numerous factors, including genetic make-up, environment, diet, and stress, can modify disease course and severity.
Clinical Features

• 50% present with organ-threat
  – Renal, cardiopulmonary, liver, CNS, cytopenia
  – Haematological & Immunological indicators
  – Readily diagnosed: ≤ 3 months

• 50% present non-specifically – can take > 2 years to diagnose
  – Arthralgia, myalgia, rash, fatigue
Constitutional

- Fatigue ~ 100%
- Fever > 50%
- Can be lupus-related or infection-associated
  - Risk factors for infection (seen in ~1/2): active LE, long-term organ damage, ↓WC/neut, ↓C3/C4, renal dis., neuropsych. manifestations, use of c/s & immune suppressants
- Myalgia – common
- Weight change
  - Loss with initial presentation
  - Gain with fluid/salt retention, steroid effects
Skin

- Photosensitivity
- Raynaud’s
- Mucosal ulcers
- Malar (“butterfly”)
- Alopecia
- Pigmentary changes
- Urticaria (“hives”)
- Telangiectasia
- Vasculitis
- Purpura
- Ulceration / ischaemia
- Calcinosi
- Livedo reticularis

Seen at some stage in most patients
Musculoskeletal

- Arthritis, arthralgia > 90% - often early
- Migratory, polyarticular, symmetrical
- Non-erosive, usually non-deforming
- Fibromyalgia in up to 1/3
- Osteonecrosis
- Osteoporosis
Cardiovascular & Pulmonary

- Pleurisy [60%]
- Myocardial dysfunction [40%]
- Hypertension [25%]
- Pleural effusion [25%]
- Interstitial lung dis [10%]
- PE [7%]
- Lupus pneumonitis [5%]
- PAH [5%]
- Shrinking lung [1%]
- Pulmonary haemorrhage [1%]
- Neonatal CHB [1:200 SSA/B+ mums]
Cardiovascular & Pulmonary

• 5-fold greater risk of atherosclerosis in SLE patients
• critical to address classical risk factors such as smoking, obesity, hypertension, dyslipidaemia and diabetes mellitus

As more targeted therapies are developed and patient survival increases, it is likely that CVD will become the primary health issue in SLE, emphasising the need early cardiovascular risk modification

Neuropsychiatric syndromes in SLE

as defined by ACR Research Committee

Central

– Aseptic meningitis
– Cardiovascular disease
– Demyelinating syndrome
– Headache
– Movement disorder
– Myelopathy
– Seizure disorders
– Acute confusional state
– Anxiety disorder
– Cognitive dysfunction
– Mood disorder
– Psychosis

Peripheral

– Guillain-Barre syndrome
– Autonomic neuropathy
– Mononeuropathy
– Myasthenia gravis
– Cranial neuropathy
– Plexopathy
– Polyneuropathy
Gastrohepatic

- G-I involvement seen in 40%
- Major causes include medication S/E and infection
- Includes oesophagitis, pseudo-obstruction, reflux, IBS
- Any organ can be affected
Haematological

- Can affect all three blood lines
- Anaemia of chronic disease commonest type of anaemia
- Leucopenia is common (~50%)
- Mild thrombocytopenia frequent
- Lymphadenopathy and splenomegaly also common

Sources of anaemia in SLE
1. Anaemia of chronic disease
2. Iron deficiency
3. Folic acid or B12 deficiency
4. Bone marrow suppression
5. Drugs (e.g. NSAIDs, immune suppressives)
6. Sickle-cell anaemia
7. Renal impairment
8. Immune anaemias (e.g. Haemolytic, thrombotic, thrombocytopenic purpura)
9. Heavy menses
Renal

- Seen in ~ 50% of patients
  - Screen with urinalysis & eGFR periodically
- May progress to hypertension, though HT is usually “essential”

- Treatments based on histopathology grading range from prednisone, immunosuppressants (grade VI no treatment and high risk of dialysis)
- As grading increases so does 10-year dialysis risk.
Diagnostics

Clinical

- ARC and SLICC criteria are for classification but not diagnosis used in research

Serology

- ANA
- DNA, ENA
- Phospholipid antibodies
- C3 / C4

No-one is (EMU)ne to autoimmunity
Homogeneous
- dsDNA, Histones
- SLE, DILE

Coarse Speckled
- Sm, U1-RNP
- SLE, MCTD

Fine Speckled
- SSA, SSB
- Sjögren's, SLE

Nucleolar
- RNAP, Pm-Scl
- Systemic sclerosis

Centromere
- CENP-A, B, C
- CREST
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Specificity and Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sm</strong></td>
<td>95% specific for lupus, but only seen in 15-30% of patients</td>
</tr>
</tbody>
</table>
| **RNP**  | In a range of autoimmune conditions (rheumatoid, lupus, scleroderma, Sjögren's)  
In lupus, it is associated with milder, non-renal disease  
Isolated RNP (without other ENAs) associated with “mixed connective tissue disease” (Raynaud’s, swollen digits, arthropathy, serositis, myopathy & oesophageal dysfunction) |
| **SSA**  | Associated with photosensitive lupus skin disease (“subacute cutaneous lupus”), neonatal lupus syndrome, and Sjögren’s syndrome |
| **SSB**  | More specific for Sjögren’s than SSA |
| **Ribosomal-P** | 95% specific for lupus  
Argument over its association with psychosis & renal disease |
| **Scl-70** | Highly specific for diffuse scleroderma, but only has a sensitivity of 30% for the disease  
Associated with interstitial lung disease as well as severe skin and musculoskeletal involvement in scleroderma |
| **Jo-1** | Highly specific for polymyositis, but only has a sensitivity of 30%  
Associated with development of interstitial lung disease |
Treatment Overview

• General treatments for symptom management
• Lifestyle changes

• Self management activities and strategies
• Medications
  – Anti-inflammatories, Antimalarials, Immunosuppressants
  – Therapeutic agents
Treatment Principles

• Controlling the symptoms
• Preventing or limiting organ involvement and damage
• Improving quality of life

Self management works together to enhance traditional medical care
Treatment Principles

Lifestyle Management

- Education
- Acceptance
- Support
- Energy Conservation
- Sleep & Rest
- Diet
- Accommodation

Regular Specialist Management & Monitoring

- Stress Cognitive Counselling
- Physical & Occupational Therapy
- Bone Density
- BR Lipids
- Blood sugar
- Chest x-ray
- ECG
- Weight control
- Anti phospholipid
- Kidney function
Warning signs of FLARES

Increased fatigue, pain, rash, fever, abdominal discomfort, headache, dizziness

Known triggers of FLARES

UV sunlight
Post infection
Stress – physical & emotional

Suspected triggers of FLARES

Chemicals
Environmental pollutants
Occupational exposures
Gut microbiome
General Treatments

• Sun minimisation
  – Outdoor activities in morning, late afternoon or early evening
  – Sun protective clothing and barriers

• Painful joints respond to moist heat, massage and movement (3Ms)

• Fatigue is managed by pacing, alternating activity with rest
  – Listening to flare signs and avoiding identified triggers
  – Restful sleep is important, addressing poor sleep hygiene
  – Effective pain management

• Physical & occupational therapists can teach about optimising body mechanics and perform evaluation of ADLs
  – promote use of assistive devices living aids

• Stop smoking
  • ↑Raynaud's, ↓aerobic capacity, ↑Cardiovascular risk factors
General Treatments

• Exercise reduces inflammation and steroid-induced muscular atrophy, bony demineralisation and improves pain management.
  – when joints are inflamed choose gentle supported exercise rather than a large program of isotonic exercises, but, ROM activities risks for contractures
  – Tai Chi, Pilates-based stretching, warm water exercise,
  – Isometric based strengthening, walking & low-impact aerobics

• Psychosocial Support
  • Emotional stress flares autoimmune disease
  • Coping is often difficult due to fears, anxiety, anger, pain, fatigue, or depression; patients may not look sick, so empathy is reduced
  • patient-physician relationships may be suboptimal – communication improvement and a positive relationship is vital
  • Patients should develop concrete goals and positive attitudes, optimise their family/social environment, and seek counselling when appropriate
  • CBT, biofeedback, and stress-reduction strategies improve coping mechanisms
Autoimmune, Anti-inflammatory Diet

- Science is not solid, a scientifically proven and validated autoimmune anti-inflammatory diet has not yet occurred
- Variety of approaches with anecdotal support – calorie restriction, sugar free, ketogenic, gluten free, paleo, etc.
- Probably best is close to *Mediterranean* diet (lots of fruits, vegetables, legumes, nuts, healthy grains, fish, olive oil, small amounts of meat and dairy, red wine, dietary fibre)
- Minimise saturated and trans fats
- Omega3 (fish, walnuts)
- Watch the refined carbs (pasta, white rice)
- Lots of whole grains (brown rice, bulgur wheat)
- Lean protein (chicken; watch red meat and full fat dairy foods)
- Avoid refined and processed foods
- Whole foods that are “real” foods
### Complementary Therapies

Herbs studied for lupus, fibromyalgia, and other rheumatic disorders using evidence-based principles.

<table>
<thead>
<tr>
<th>Herb</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfalfa</td>
<td>L-canavanine in alfalfa sprouts may flare lupus</td>
</tr>
<tr>
<td>Capsicum</td>
<td>Capsaicin is a proven topical analgesic in osteoarthritis</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Reports of lupus flares from immune stimulation</td>
</tr>
<tr>
<td>Gingko biloba</td>
<td>May help cognitive impairment</td>
</tr>
<tr>
<td>Green tea extract</td>
<td>Reports of improvement in collagen-induced arthritis models</td>
</tr>
<tr>
<td>L-tryptophan</td>
<td>Sleep aid: contaminants can cause a scleroderma-like illness</td>
</tr>
</tbody>
</table>
Pharmacotherapy Overview

1. NSAIDs - Used for fever, headache, serositis, arthralgia/arthritis, myalgia fever
   • Naproxen has the best efficacy/safety profile in doses of 500mg BID
   • Gastroprotective measures may be advisable with chronic use.

   • Has disease-modifying properties and is steroid sparing.
   • Useful in patients with antiphospholipid syndrome, Sjögren's
   • ↓ cholesterol levels, glucose, fatigue, dryness, rash, risk of clots.
   • Indicated in 90% of lupus patients in doses of 5mg/kg/day. Not tolerated in 10%; retinal examinations should be performed annually.
   • Quinacrine or chloroquine can be used for resistant skin lesions.
   • Good side effect profile, can continue use in preg

3. Corticosteroids – FDA approved (SLE)
   • Induction therapy for organ-threatening disease followed by tapering.
   • Can be reintroduced in times of flare
   • Steroid-sparing alternatives (immunosuppressants) should be introduced with chronic use.
Pharmacotherapy Overview (ii)

4. Immunosuppressive medications (often steroid sparing)
   • Cyclophosphamide
     – Mainstay of treatment in severe renal and CNS involvement in SLE.
     – The Euro-Lupus regimen - fixed low dose of cyclophosphamide for a short period, followed by maintenance therapy with azathioprine or mycophenolate mofetil, is now widely used and effective
   • Azathioprine
     – Frequently used in moderate to severe SLE: Check FBC, LFTs
     – Can continue in pregnancy / lactation
   • Mycophenolate
     – One of the most frequently used immunosuppressive agents in SLE
     – Less likely than cyclophosphamide to cause toxicity
   • Methotrexate
     – esp. good for synovitis, musculocutaneous disease
     – Give weekly with folate: monitor FBC, LFT
5. Biological Agents (Blockers)
Blockers of various chemicals produced by B and T cells, or interactions between cells

- Anti-TNF blockers: FDA approved RA can be used in selected lupus patients. Issues - can exacerbate rashes, autoantibody production and infection
- Rituximab - dramatic improvements in refractory disease, reduces B cells. Clinical trials in non-renal SLE have not met primary endpoints.
- Tocilizumab – lupus trials underway
- Baricitinib an inhibitor of janus kinase (JAK), blocking the subtypes JAK1 and JAK2
- Abatacept – lupus nephritis trials underway
- Belimumab – approved for active autoantibody +ve SLE
  - Limited real world benefit
  - Not necessarily superior to other treatments
Just another tool, not a cure all
Pharmacotherapy Overview (iii)

Biological Agents

Blockers of various chemicals produced by B and T cells, or interactions between cells

Figure 1. Potential targets and relevant drugs in connection with B and T-cells in the management of SLE.

Box 2 | Biologics studied since 2005

Drugs no longer in development for SLE
- Abetimus, ocrelizumab, rontiluzumab, tabalumab, sirukumab

Drugs currently under study from a registrational standpoint
- Abatacept, epratuzumab, lupuzor, sifilumumab, edratide, abatacept, blisbmlob, several iterations of anti-IL-6 agents

Drugs currently under study from a nonregistrational standpoint
- Etanercept, infliximab, rituximab
Social and economic Impacts

- Relapsing remitting pattern which can be unpredictable
- Disease burden can be high
- Quality of life reduced
- Financial burden is high
- Work loss is common

- 1/3 stopped work by 4-yr
  - Musculoskeletal [1/3]
    - Arthralgia, arthritis
    - myalgia
  - Neuropsychiatric [1/3]
    - Depression, anxiety
  - Thrombotic [½]
Outlook

- In 1955, 5 yr survival was 50%; by 2000+, it had risen to 95%
- Between 1970 and 2010, 10 yr survival has risen from 60% to 90%
- 95% have normal life expectancy, esp. in setting of drug-induced LE, chronic cutaneous, and non-organ-threatening LE without antiphospholipid antibodies
- Critical to target CV risk factors

- Quality of life factors
  - Education
    - Learning about illness
    - Learning about triggers
    - Learning about management
  - Lifestyle management
  - Symptom self-management
  - Maintenance of networks

Research Approaches

Basic Science Innovations

• T cell vaccination
• Chemokine modulators
• Peptide tolerogens (HLA, Sm, Ig)
• Promote T regulators
• Gene therapies
• Upregulate TGFbeta
• Target FcRs
• Gene transcription regulators
• Induce anergy in Th cells
• Mesenchymal stem cells
• Inhibit adhesion molecules
• Inhibit costimulation (anti-CD80)
• Target urinary cytokines
• Epigenetics (inhibit histone deacetylase; promote methylation)
Research Approaches

**Lifestyle based**
- Fatigue management
- Targeted exercise
- Stress minimisation & mental health
- Mindfulness and meditation benefits
- Better breathing
- Photosensitivity mechanism
- Microbiomes
  1. skin
  2. oral
  3. Gut
     - classification, quantification of microbes
     - microbe interactions with inflammation, pain transmission, mood etc
     - targeted dietary improvements & advice (soluble fibre, supplements)
Summary

- Standardised criteria useful for research, but insensitive for everyday practice
- LE affects 1:700 – 1:1000 people, up to 8:1 female predominance
- LE results from immune confusion - transformation of “benign” to damaging autoimmunity
- Can present with organ-threatening or nonspecific features
- Diagnosis can be challenging and protracted
- Significant personal & social impact
- Prognosis is being positively transformed by evolving therapies and understanding of mechanisms
- Good outcomes with ongoing management and monitoring of signs of organ stress.

Better outcomes are found when self-management is applied along with medical and social supports
Goal is for the individual to find their right balance to Live well with illness “Living a life, not an illness”
Lupus Resources

- Autoimmune Resource and Research Centre [www.autoimmune.org.au](http://www.autoimmune.org.au)
- Lupus Association of Tasmania [www.lupustasmania.org.au](http://www.lupustasmania.org.au)
- Lupus UK [www.lupusuk.org.uk](http://www.lupusuk.org.uk)
- American Autoimmune Related Diseases Association (AARDA) [www.aarda.org](http://www.aarda.org)
- Arthritis Foundation [www.arthritis.org](http://www.arthritis.org)
- Lupus Foundation of America [www.lupus.org](http://www.lupus.org)
- ACR [www.rheumatology.org](http://www.rheumatology.org)
- National Institute of Arthritis and Musculoskeletal and Skin diseases (NIAMS) [www.niams.nih.gov](http://www.niams.nih.gov)
- Alliance for lupus research [www.lupusresearch.org](http://www.lupusresearch.org)
- Lupus research institute [www.lupusresearchinstitute.org](http://www.lupusresearchinstitute.org)
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