Connective tissue disease

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NEW ZEALAND PAEDIATRIC RHEUMATOLOGY SERVICE

kidz first
Children's Hospital & Community Health

Overview

- Approach to Connective Tissue Disease
- Systemic Lupus Erythematosus
- Juvenile Dermatomyositis
- Exam application

Approach to CTD's

- Consider infection and malignancy
- End organ involvement?
  - Which systems?
  - Treatment specific and maybe multi systemic
- Specific patterns of disease?
  - Signs and symptoms evolve and maybe modified by previous treatment

Clinical features

- Skin and hair
  - Photosensitivity
  - Hair loss/ alopecia
  - Mucosal ulceration
  - Malar, discoid rash
  - Raynauds
  - Peripheral ulceration, pulp space loss
  - Nail bed capillaries
  - Skin texture, mobility
- Musculoskeletal
  - Myalgia, arthralgia
  - Arthritis
  - Bone pain
- Neurological
  - Mood changes
  - School difficulties
- Respiratory / CVS
  - Serositis
  - Interstitial pneumonitis or fibrosis
  - Myocarditis
- Abdominal / GIT
  - Peritonitis
  - Masses
- UGT
  - Oedema
  - Hypertension
  - Urine microscopy
  - Urine protein:Cr ratio
- Haematological
  - Petechiae, bruising
  - Blood count (cytopenias)
  - Coombs

Investigations?

Full Blood Count	Anaemia, thrombocytopenia, leukopenia (neutropenia, lymphopenia) Coombs, haptoglobins, blood film
Inflammatory markers	ESR, CRP
Chemistry	Urea, Cr, LFT's, CK, LDH
Complement	C3, C4
Urine	Pr:Cr, microscopy
Autoantibodies	ANA, ENA, dsDNA
Antiphospholipid antibodies	LAC, ACL, beta 2 glycoprotein
Respiratory	CXR, lung function, HRCT, 6MWT
Cardiac	ECG, echocardiogram
MRI (EMG, muscle biopsy)	Proximal muscles

Management

- Supportive and adjunctive therapy
  - Review, monitor, anticipate complications
  - Maintain/regain function, PT, OT, psych support
- Organ specific therapy

Induction

Mild		Severe	Refractory
HCQ	Oral – steroids ~ IV	MMF/CYC	Rituximab

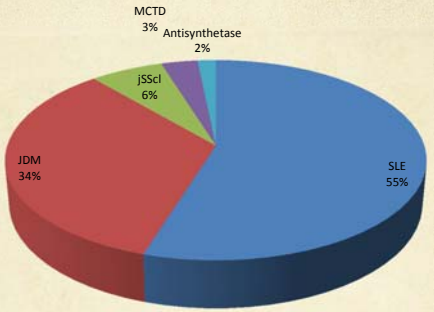
Maintenance

Mild		Severe
HCQ	MTX/AZA	MMF/CYC

Prognosis

- Depends on type and number of end organ involvement
- Time to response
  - 'Remission' vs 'Relapses'
- Medication side-effects
- Psychosocial support

Connective tissue disease: Starship 2000- 2010
(0- 16 years, n= 62)



	CTD	jSLE	JDM	jSScl	MCTD	Antisynthetase
Average age (years)	10.4	12	7.6	9.6	12.3	12.8
Female: (%)	71	77	62	100	100	100
Total	62	34	21	4	2	1

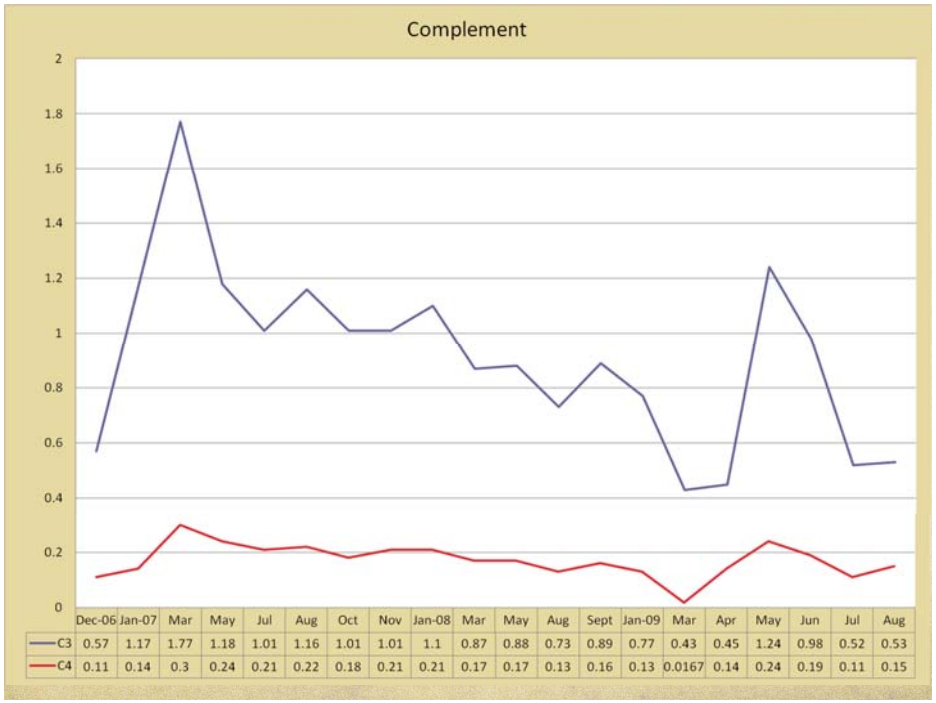
Case 1

- 13 year old Asian girl
- December 2006
  - Facial swelling, ankle swelling +++ proteinuria
  - Hypertension
  - Impaired renal function (Peak 184)
  - Albumin 24
  - 24 total protein 5.42g/day, CrCl 0.71ml/sec
  - Prednisolone 60mg/d
  - Aspirin, penicillin
- USS – single right kidney
  - Left kidney small and 20% of function
- Difficult to control BP
  - Ramipril 5mg, amilidopine 10mg,
  - Prazosin 0.5mg bd
- BP settled and sent home

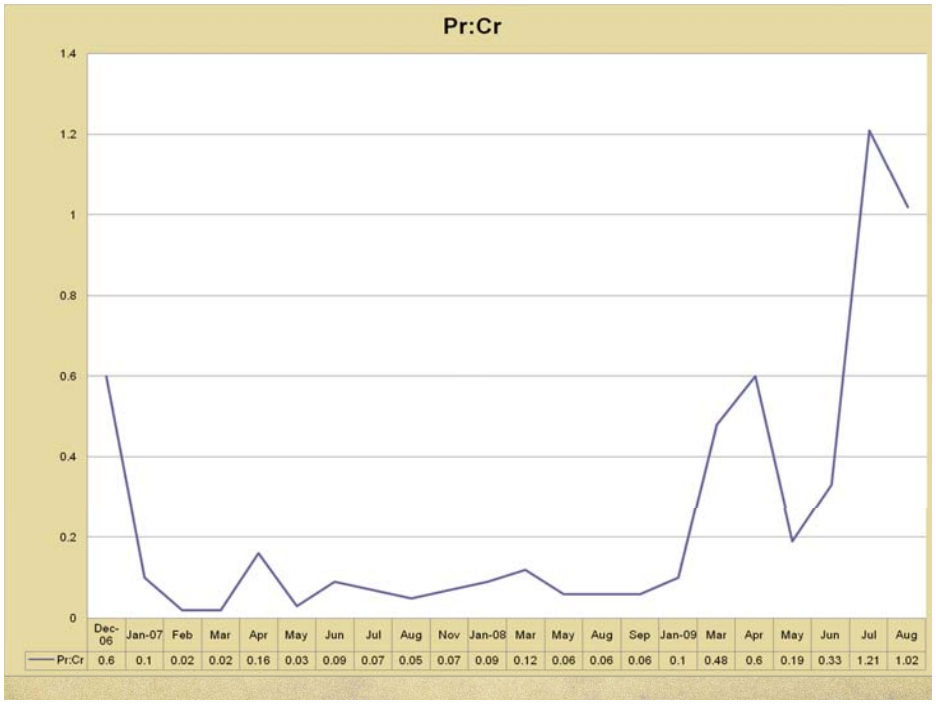
FBC and LFT's	Normal
UEC	Cr 148
Complement	C3 and C4 LOW
Immunology	ANA positive >1280
	ENA: Anti La and Ro positive
	Farr assay >105
	ACA positive
Renal Biopsy	Class 2 LN Focal glomerulonephritis

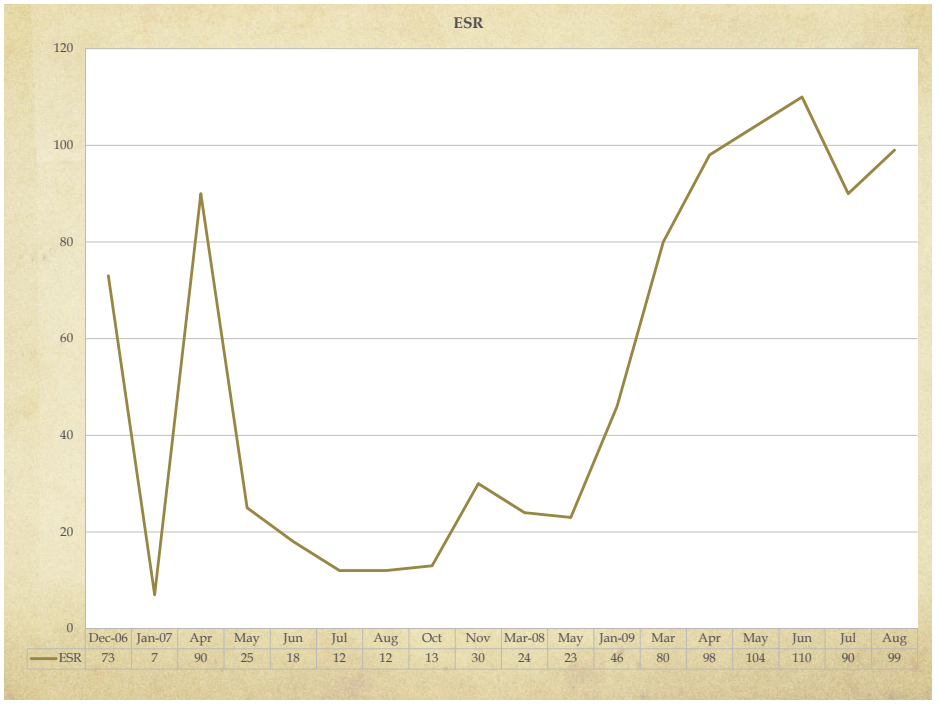
Progress…

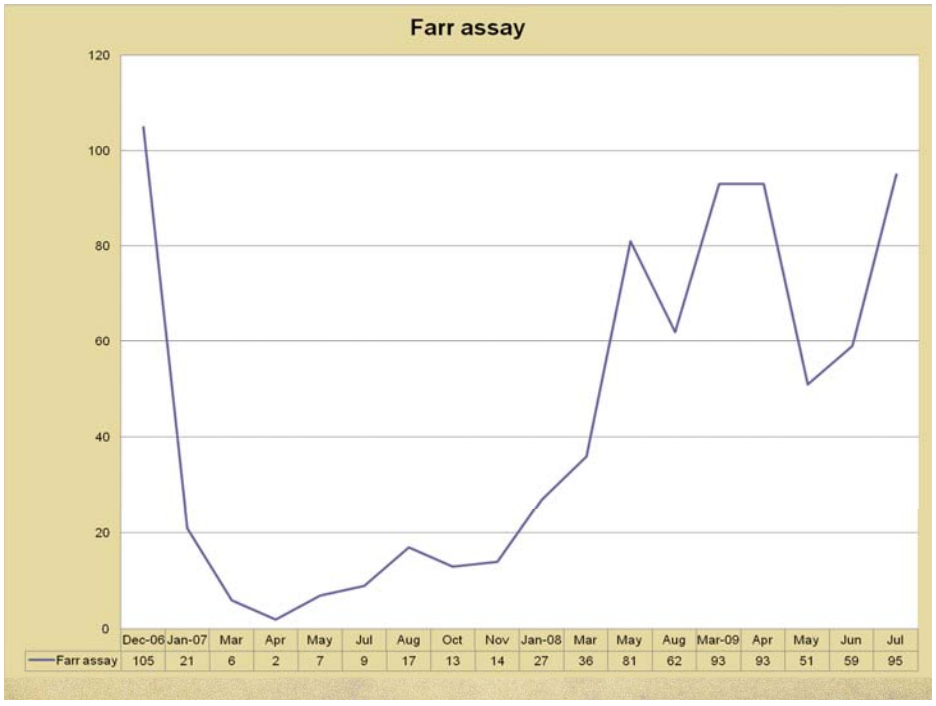
Feb 2007	Developed 200cc peri nephric haematoma BP low and Hb drop RBC transfusion and haematoma resolving Started MMF 500mg bd and weaning prednisone
March 2007	Cushingoid (striae, weight gain)
April 2007	Surgical drainage and IV antibiotics for infected perinephric collection Mycophenolate reduced and stopped (secondary to neutropenia)
October 2007	Prednisone ceased
2008	Stable and ramipril weaned
March 2009	Proteinuria and raised inflammatory markers Restarted prednisone (20mg), plaquenil and Mycophenolate (500mg bd) Arthritis – bilateral wrists, MTP's and MCP's
April 2009	Creatinine elevated (165), hyperkalemia, weight gain, proteinuria Resonium, IV methylprednisolone and albumin Mycophenolate increased to 1gm bd Creatinine rise (215) with fever monitored and settled
July 2009	Prednisone weaning, creatinine rise (190), hyperkalemia (resonium) Cyclophosphamide (6 cycles) and methylprednisolone



	Dec-06	Jan-07	Mar	May	Jul	Aug	Oct	Nov	Jan-08	Mar	May	Aug	Sept	Jan-09	Mar	Apr	May	Jun	Jul	Aug
C3	0.57	1.17	1.77	1.18	1.01	1.16	1.01	1.01	1.1	0.87	0.88	0.73	0.89	0.77	0.43	0.45	1.24	0.98	0.52	0.53
C4	0.11	0.14	0.3	0.24	0.21	0.22	0.18	0.21	0.21	0.17	0.17	0.13	0.16	0.13	0.0167	0.14	0.24	0.19	0.11	0.15







IP Summary

- 16 year old female with proliferative lupus nephritis with prolonged renal flare
  - Presented as atypical nephrotic presentation
  - Initial response to prednisone
  - Then lupus flare and failed to respond to prednisone and MMF
  - IV Cyclophosphamide pulse therapy.....

Worldwide incidence of jSLE

			No. of years	Type of study	No. with jSLE	Age range (yrs)	No./100,000/yr
North America							
Baltimore	Hochburg et al	1970-77	8 years		10	0-14	0.53
New England	Denardo et al	1984 1992	5 years	Prospective, multicentre	6.4 per yr	0-18	0.4
Wiscounsin	Naleway et al	1991-2001	10 years	Retrospective	2	0-19	0.9
Georgia	Lim et al	2002-04		Population registry	31	0-19	2.5
Canada	Malleson et al	1991-93	2 years		52	0-16	0.36
Europe							
Finland	Pelkonen et al	1983-86	4 years	Nationwide prospective	15	0-15	0.37
United Kingdom	Nightingale et al	1992 1998	7 years	GP research database	20	0-18	0.73
Austria	Huemer et al	1997-98	2 years	Population registry	6	< 16	0.48
Asia							
Japan	Fujikawa and Okuni	1984-94	10 years	Survey study	906	< 16	0.47
Oceania							
New Zealand		2000-2010	10 years	Retrospective	31	0-14	0.52
Maori					8		0.60
European					10		0.31
Pacific					6		0.80
Asian					7		1.17

* No paediatric data available for Africa, Australia or South America

Worldwide incidence and prevalence of pediatric onset systemic lupus erythematosus. Pineles, D., A. Valente, et al. Lupus 20(11): 1187-92.
The incidence, diagnostic clinical manifestations and severity of juvenile systemic lupus erythematosus in New Zealand Maori and Pacific Island children: The Starship experience (2000 −2010). A Concannon, S Rudge, J Yan and P Reed. Lupus (2013) 22, 1156–1161.

Childhood lupus manifestations

	At diagnosis		At any time	
	Toronto	pSLE literature	Toronto	pSLE literature
Constitutional				
Fever	55%	60-90%	86%	80-100%
Lymphadeopathy	34%	13-45%	34%	13-45%
Hepatosplenomegaly	30%	16-42%	30%	9-43%
Organ Disease				
Arthritis	78%	60-88%	80%	60-90%
Skin rash	79%	60-78%	86%	60-90%
Malar rash	36%	22-60%	38%	30-80%
Nephritis	51%	20-80%	69%	48-100%
Neuropsychiatric	25%	5-30%	34%	26-95%
Cardiovascular	14%	5-30%	17%	25-60%
Pulmonary	18%	18-40%	18%	18-81%
Gastrointestinal	19%	14-30%	24%	24-40%

Systemic lupus erythematosus. Benseler, S. M. and E. D. Silverman (2005). Pediatr Clin North Am **52(2): 443-67, vi.**

Approach to Suspected Systemic Lupus Erythematosus (SLE) in children

Suspicious clinical features on history
Multiple would be expected

- Fever, Fatigue, weight loss (Constitutional symptoms)
- Arthralgia/Arthritis
- Photosensitivity
- Raynaud phenomenon
- Myalgias
- Headache
- Seizures

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Investigations:

- ANA, dsDNA, ENA (if ANA positive),
- Complement (C3, C4), ESR, CRP, FBC, UEC, Albumin, LFTs, Coombs
- Antiphospholipid antibodies: (Anticardiolipin antibodies, lupus anticoagulant, anti β2 glycoprotein)
- Urine – Pr:Cr ratio, microscopy

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Suspicious clinical signs
Multiple would be expected

- Malar rash
- Proteinuria
- Active urine sediment
- Oral ulcers
- Encephalopathy
- Pleuritis
- Pericarditis
- Localised or disseminated discoid rash
- Chilblains
- Psychosis

→

ACR Criteria

1.Malar Rash
2.Discoid Rash
3.Photosensitivity
4.Oral or nasal Ulceration
5.Non erosive arthritis
6.Nephritis – proteinuria > 0.5g/day (>+3), cellular casts
7.Encephalopathy
8.Serositis
9.Cytopenia
10.Positive Immunoserology – dsDNA, Sm, Antiphospholipid antibodies
11. Positive ANA

↓

Diagnosis:

- Consider discussion with Paediatric Rheumatologist
- Definite if >= 4 Criteria
- Possible if 3 Criteria

Table 2 The demographics and diagnostic clinical manifestations of jSLE

	Total (n = 32)	*Asian (n = 7)*	*Maori (n = 8)*	*Pacific (n = 7)*	*European (n = 10)*	*Maori or Pacific (n = 15)*	*[Maori or Pacific] vs [European] p value*
Demographics: n (%)							
Average age at diagnosis (yrs)	11.9	12.6	11.6	10.4	13	11	
Female	24 (75)	4 (57)	6 (75)	5 (71)	9 (90)	11 (73)	
ACR diagnostic criteria: n (%)							
Mucocutaneous	21 (66)	4 (57)	6 (75)	4 (57)	7 (70)	10 (67)	1.00
Malar rash	12 (38)	3 (43)	3 (38)	2 (29)	4 (40)	5 (33)	1.00
Photosensitive	10 (31)	2 (29)	1 (13)	2 (29)	5 (50)	3 (20)	0.19
Oral ulceration	5 (16)	2 (29)	2 (25)	1 (14)	1 (10)	3 (20)	0.62
Discoid rash	0	0	0	0	0	0	1.00
Arthritis	11 (34)	1 (14)	3 (38)	1 (14)	6 (60)	4 (27)	0.12
Serositis	7 (22)	1 (14)	4 (50)	1 (14)	1* (10)	5 (33)	0.34
Lupus nephritis	20 (63)	4 (57)	6 (75)	6 (86)	4 (40)	12 (80)	0.09
Neuropsychiatric	0	0	0	0	0	0	1.00
Haematological	25 (78)	6 (83)	5 (63)	5 (71)	9 (90)	10 (67)	0.34
Immunological	29 (91)	6 (86)	7 (88)	6 (86)	10 (100)	13 (87)	0.50
ANA	29 (91)	6 (86)	7 (88)	6 (86)	10 (100)	13 (87)	0.50
dsDNA	29 (91)	6 (86)	7 (88)	6 (86)	8 (80)	13 (87)	1.00
APL antibodies	10 (31)	4 (57)	2 (25)	2 (29)	2 (20)	4 (27)	1.00
anti-Sm	13 (41)	1 (14)	4 (50)	3 (43)	5 (50)	7 (47)	1.00

The incidence, diagnostic clinical manifestations and severity of juvenile systemic lupus erythematosus in New Zealand Maori and Pacific Island children: The Starship experience (2000 −2010). A Concannon, S Rudge, J Yan and P Reed. Lupus (2013) 22, 1156–1161.

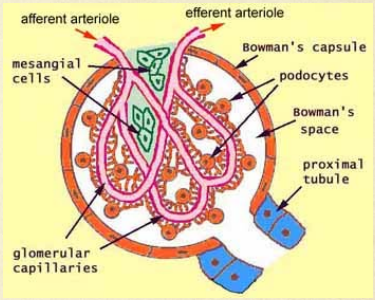
O. Hersh A, von Scheven E, Yazdany J et al. Differences in long- term disease activity and treatment of adult patients with childhood and adult- onset systemic lupus erythematosus. Arthitis and Rheumatism. 2009; 61: 13- 20.

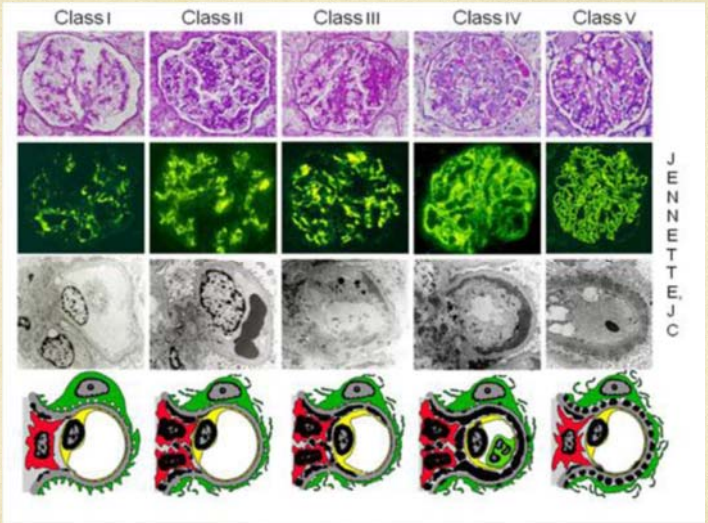
Organ	cSLE	aSLE	P-value
Kidneys	56.2%	37.1%	<0.001
Renal Biopsy	48.2%	18.8%	<0.001
Dialysis	19.1%	5.7%	<0.001
Renal Transplant	12.4%	4%	<0.001

Medication	cSLE	aSLE	P-value
Prednisone	100%	89.3%	
MMF	28.1%	13%	<0.001
IV CYCLO	30.7%	14.1%	<0.001
AZA	33.7%	28.4%	
Cyclosporin	18.6%	9.9%	

Classification – 2003 International Society of Nephrology/Renal Pathology Society

Classification	
1	*Minimal mesangial LN*
2	*Mesangial proliferative LN*
3	*Focal lupus nephritis*
3A	*Active lesions, focal proliferative LN*
3AC	*Active and chronic lesions, focal proliferative and sclerosing LN*
3C	*Chronic inactive lesion, glomerular scars: focal sclerosing LN*
4	*Diffuse LN*
4-S (A)	*Active lesions, diffuse segmental LN*
4-G(A)	*Active lesions, diffuse global segmental proliferative LN*
4-S (A/C)	*Active and chronic lesions, diffuse segmental and sclerosing LN*
4-G (A/C)	*Active and chronic lesions, diffuse global proliferative and sclerosing LN*
4-S (C)	*Chronic inactive lesions with glomerular scars:diffuse global sclerosing LN*
4-G(C)	*Chronic inactive lesions withglomerular scars: diffuse global sclerosing LN*
5	*Membranous lupus nephritis*
6	*Advanced sclerosing lupus nephritis*





Traditional treatment of lupus nephritis

Class of nephritis	Treatment
Class 2	Short course, low dose steroids (0.1-0.5mg/kg/day)
Class 3	Historically steroid alone BUT within proliferative nephritis spectrum therefore treated as class 4
Class 4	High dose steroids (2mg/kg/day, max 60-80mg/day) Second agent – CYC, AZA, MMF
Class 5	Most low dose short course steroids Occasional immunosuppressant – CYC, AZA or MMF ACE inhibitors as adjunct for proteinuria

Clinical features

	Incidence	Proteinuria	Microscopic haematuria	Nephrotic syndrome	Renal insufficency	
Grade 2 (mesangial)	15-25%	No	No	No	20%	Grade 3-4 mo/yrs
Grade 3 (focal)	12-24%	Minimal	Minimal	20%	20%	ESRF rare
Grade 4 (diffuse)	44-64%	Yes	Frequent	60%	60%	88-93% 5yr survival
Grade 5 (membranous)	8-20%	Yes		Yes	Majority	Renal survival 10yr 80% (47-90%)

General Management of jSLE

Maximise disease control

1. Hydroxychloroquine
2. Corticosteroids
3. Organ specific immunosuppressives

Adolescent issues

- Monitor growth, puberty and development
- Sun protection (All)
- Oral contraceptive (thrombosis risk screen)
- HEADSS assessment

Maximise bone density

1. Paediatric DEXA scan
2. Minimise corticosteroids
3. Monitor Vitamin D and Ca
4. Encourage exercise and sunlight exposure

Premature atherosclerosis

Lifestyle modification:

1. Hypertension
2. Hyperlipidaemia
3. Weight management (diet and exercise) and smoking cessation

Monitor steroid side effects:

1. Growth
2. Bone density
3. Blood pressure
4. Ensure adherence
5. Consider body image

Medication	Indication	Side effects/monitoring
Hydroxychloroquine (6.5mg/kg/day)	Fare reduction, corticosteroids effects, skin and joint, APLS and renal disease	Nausea and vomiting (<10%) Baseline ophthamology
NSAIDS (+/- omeprazole)	Arthritis, myalgia, arthralgia	Renal and GI effects
IV methyprednisolone x3 (30mg/kg, max 1 gram) Oral prednisolone (1-2mg/kg) Topical or intra articular steroid	End organ involvement: Lupus nephritis, haematological, CNS, serositis, arthritis and skin	Annual lipids, fasting glucose, DEXA scan Blood pressure
Cyclophosphamide (+MESNA) (500mg/m2) x 6 cycles	Class 3,4,5 lupus nephritis induction, CNS lupus Life or organ threatening	Dose adjust with nadir FBC (10 days) and cotrimoxazole Infection, GI toxicity, marrow suppression (and infertility)
Mycophenolate (600mg/m2 twice daily induction)	Class 3,4,5 lupus nephritis induction and maintainance	GI toxicity, marrow suppression, infection. FBC 1-3 monthly
Methotrexate (with folic acid) (15mg/m2 once weekly)	Arthritis (and skin)	Nausea, infection, teratogenic, marrow suppression, hepatitis 3 monthly liver function and FBC
Azathioprine (0.5-2.5mg/kg/day, max	Class 3,4,5 lupus nephritis maintenance therapy	GI toxicity, marrow suppression Thiopurine methyltransferase 1-3 monthly FBC, LFT's, UEC
Rituximab (CD 20 monoclonal ab) 375-500mg/m2 x2 (0,14 days)	Treatment resistant end organ Lupus nephritis, cytopenia	B cells pre and 1 month post 3 monthly immunoglobulins Infection and infusion reaction
Cyclosporin(3-5mg/kg/day)	Membranous lupus nephritis	Monthly FBC, UEC, LFT's, BP

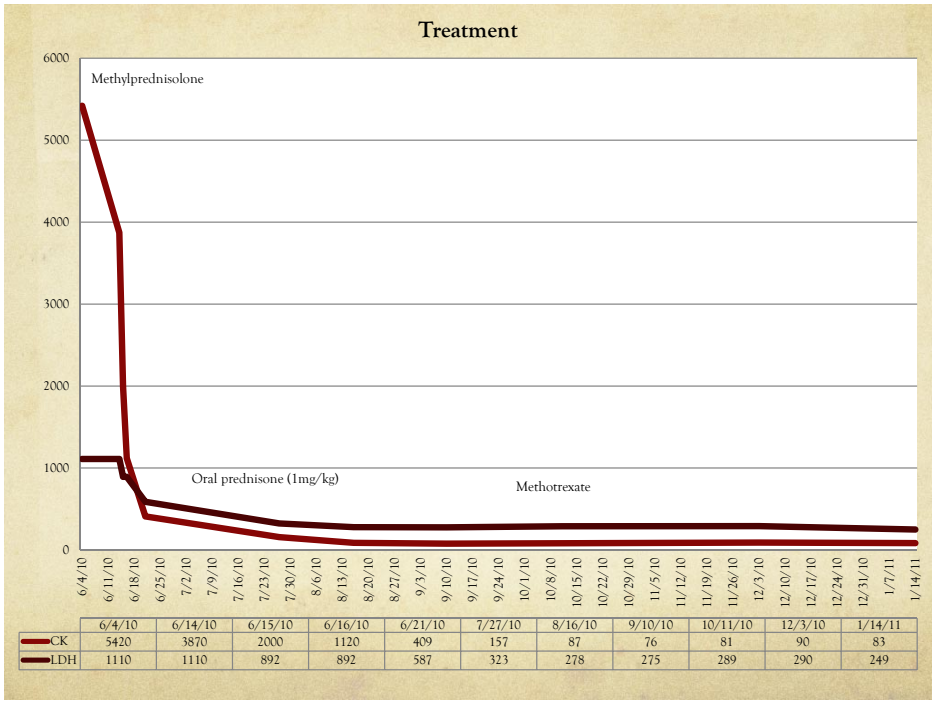
http://www.rheumatology.org.au/community/PatientMedicineInformation.asp

Case 1

- 2 year old European South African boy
- Referred by GP to EC with 2-3 weeks of facial rash
- On review: URTI 3-4 weeks prior, otherwise well
- Leg pains with walking and climbing stairs
- Afebrile, BP 109/62
- Malar rash
- Right cervical adenopathy
- CK 4429
- ?viral myositis

- Hoarse voice, no dysphagia
- Malar rash, gottrons papules (knees, hands), nailbed changes
- Unable to lift head, difficulty sitting from lying and standing from sitting, unable to lift hands above head
- Normal neurology

CK	4429
LDH	1110
ALT	117
AST	211
FBC	Normal
ESR, CRP	9, <1
ANA	negative
CXR	Normal
SLT	Normal swallow
ECG	Normal
CMAS	29/53



	6/4/10	6/14/10	6/15/10	6/16/10	6/21/10	7/27/10	8/16/10	9/10/10	10/11/10	12/3/10	1/14/11
CK	5420	3870	2000	1120	409	157	87	76	81	90	83
LDH	1110	1110	892	892	587	323	278	275	289	290	249

Progress

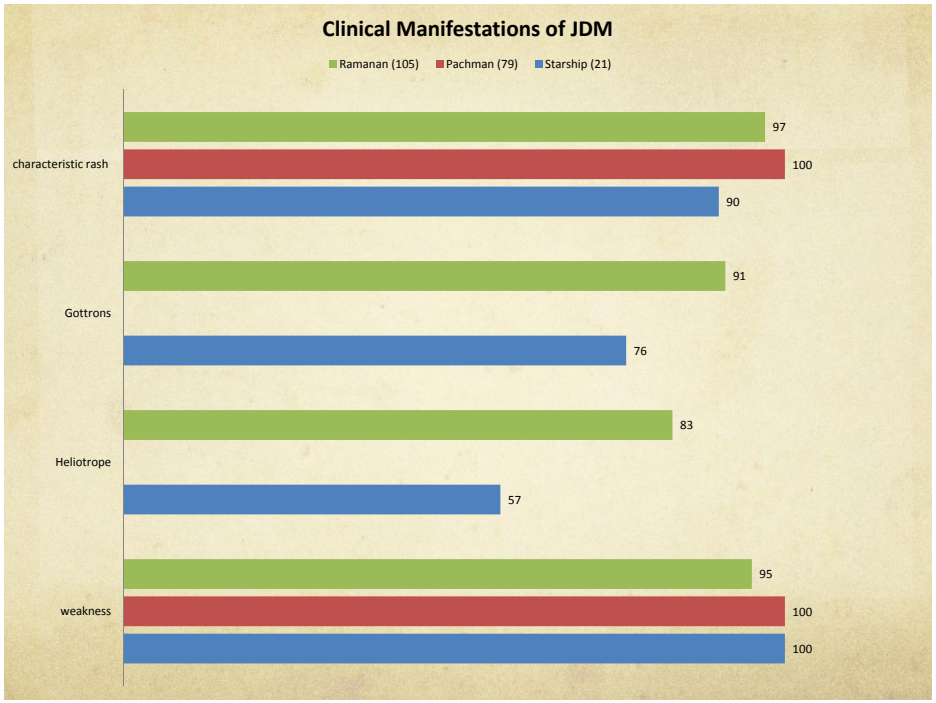
- Muscle strength normalised and steroid weaned completely over 2 years
- Developed calcinosis 5th PIP and knee after weaning steroid (monitored)
- Methotrexate currently being weaned

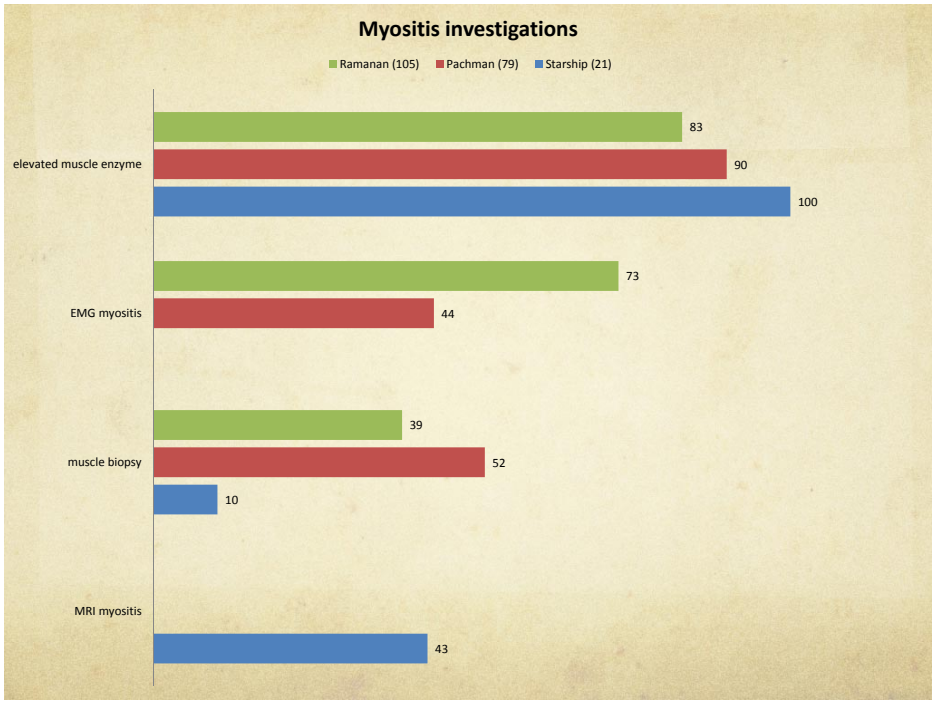
Summary

- 2 year old male diagnosed with JDM on a background of weakness, rashes (malar and gottrons) and elevated CK and LDH
- Responded well to a combination of steroid and methotrexate

Juvenile Dermatomyositis

- Bohan and Peter criteria (1975)
  - Characteristic rash PLUS 3/4 (definite) OR 2/4 (probable)
    - symmetrical muscle weakness
    - elevated muscle enzymes
    - EMG evidence myopathy and denervation
    - Muscle histopathology of necrosis, fibre size variation and mononuclear inflammatory infiltrate
- Incidence
  - Estimated 0.32/100,000
  - 2.3:1 (F:M) with peak age 6 and 11 years (girls) and < 10 years (boys)
    - Pachman et al (n=79, 6.9 years), Kobayashi et al (n=102, 7.1years), Starship (n=21, 7.6 years)





Differential diagnosis

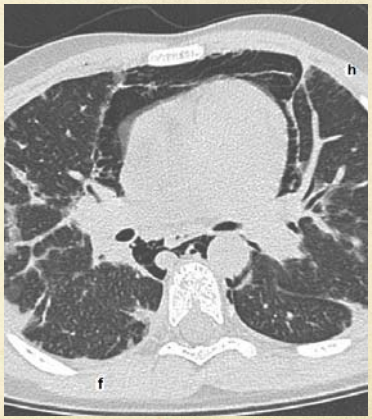
Post infectious myositis	Influenza A and B, Coxsackie B
Neuromuscular diseases	Muscular dystrophy Congenital myopathies Myotonic disorders Neurogenic atrophies
Endocrine myopathies	hyper/hypothyroidism Hyper/hypoparathyroidism Cushings syndrome
Metabolic myopathies	Glycogen storage disease

Screening and complications

- Proximal muscle weakness
- Pharyngeal, hypopharyngeal and palatal muscle weakness
- Interstitial lung disease
- Calcinosis (12-43%)
- Visceral (GI) and cutaneous vasculopathy
- CMAS baseline and monitoring
- SLE assessment and video fluroscopy
- Lung function, CXR, HRCT

Interstitial lung disease

- Rare
- Starship: 3/21 (14%)
- Complicated by air leak
- Death in 2/3



Natural History

Phases	**Duration**
Prodromal nonspecific symptoms	Weeks to months
Progressive muscle weakness, rash	Days to weeks
Persistent weakness, rash, active myositis	Up to 2 years
Recovery with or without residual muscle atrophy, contractures and calcinosis	

Treatment

Pharmacotherapy	
Standard therapy	Prednisone (2mg/kg/day) for 1mo OR IV methylprednisolone THEN Prednisone (1mg/kg/day) AND Taper over 2 years
Standard therapy	Methotrexate (15mg/m2)
Gastrointestinal Interstitial lung Skin ulcerations	Cyclophosphamide
Steroid dependence Failure to obtain remission	IVIG Cyclosporine
Physiotherapy and occupational therapy	Range of motion exercises and splinting Muscle strengthening (recovery)

Intervention	Indication	Side effects/monitoring
Prednisone (2mg/kg/day) for 1mo OR IV methylprednisolone THEN Prednisone (1mg/kg/day) AND Taper over 2 years	First line therapy	Annual lipids, fasting glucose, DEXA scan Blood pressure
Methotrexate (with folic acid) (15mg/m2 once weekly)	First line therapy (when AST and ALT normalise)	Nausea, infection, teratogenic, marrow suppression, hepatitis 3 monthly liver function and FBC
Hydroxychloroquine (6.5mg/kg/day)	Dermatitis	Nausea and vomiting (<10%) Baseline ophthamology
Cyclosporin (3-5mg/kg/day)	First choice second line therapy Steroid dependent or resistant	Monthly FBC, UEC, LFT's, BP
IVIG	Second line with steroid resistant or dependent	Monthly infusions (1gm/kg/day)
Azathioprine (0.5-2.5mg/kg/day, max	Second line therapy	GI toxicity, marrow suppression Thiopurine methyltransferase 1-3 monthly FBC, LFT's, UEC
Cyclophosphamide (+MESNA) (500mg/m2) x 6 cycles	Third line therapy with chronic ulcerative course resistant to steroid or interstitial lung disease	Dose adjust with nadir FBC (10 days) and cotrimoxazole Infection, GI toxicity, marrow suppression (and infertility)
Mycophenolate (600mg/m2 twice daily)	Third line therapy severe treatment resistant	GI toxicity, marrow suppression, infection. FBC 1-3 monthly
Rituximab (CD 20 monoclonal ab) 375-500mg/m2 x2 (0,14 days)	Third line therapy	B cells pre and 1 month post 3 monthly immunoglobulins Infection and infusion reaction

Exam application

- End organ screening and monitoring
  - Skin – vasculitis, rashes, Raynauds phenomenon
  - Joints – arthritis, arthralgia (myalgia)
  - Brain – cognition, headaches, neurology
  - Kidneys – nephritis, renal failure/proteuinuria
  - Lungs – interstitial lung disease, pneumonitis, pleuritis
  - Cardiac – pericarditis
  - Constitutional symptoms - weight loss, lymphadenopathy, fevers

- Medications
  - Immunosuppression – infection, varicella, stress steroid
  - Side effects and monitoring – blood, urine
- Consult Liason - chronic disease, medications
- Allied health – SLT, OT, Physiotherapy
- Subspecialty teams – renal, neurology, dermatology

Summary

- Connective tissue diseases complex but rare conditions with jSLE the most common
- Management requires systemic evaluation, a multidisciplinary approach (OT, PT, subspecialist) and adjunctive and specific pharmacotherapy
- Pharmacotherapy should be tailored to the most significant end organ involvement
- Aim of treatment if to maximise quality of life and minimise morbity and mortality