

## INDIAN GUIDELINES ON THE MANAGEMENT OF SLE

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### Introduction

Systemic lupus erythematosus (SLE) is the prototype of systemic autoimmune diseases. The aetiology is not known as yet and the pathogenesis is complex, involving immunological, genetic, hormonal and environmental factors. Damage to tissues and cells results from pathogenic autoantibodies and immune complexes. It affects predominantly women in their reproductive years. The median age of onset in Indian SLE is 24.5 years and the sex ratio (F:M) is 11:1<sup>1</sup>. Remissions and relapses characterize the disease. The clinical manifestations and their severity in individual patients may vary considerably and, therefore, the treatment strategy needs to be tailored accordingly.

### Incidence and prevalence

SLE is rare in India. A prevalence study in India (carried out in a rural population near Delhi) found a point prevalence of 3 per 100,000<sup>2</sup>. This is a much lower figure than reported from the west (varying from 12.5 per 100,000 adults in England<sup>3</sup> to 39 per 100,000 in Finland<sup>4</sup> and 124 per 100,000 in USA<sup>5</sup>). However, a fair number of cases of SLE are encountered in any large hospital in India. Copcord Bhigwan study (an ongoing, prospective population study from Pune) found a crude incidence rate of 1 per 25,000 person years i.e. 4 per 100,000 population per year (personal communication). Despite its rarity, SLE has considerable impact on the patient, her/his family and health services available.

### General outlook of the disease

The prognosis of SLE is quite grim with more than half of the patients developing irreversible organ damage over time. Although the survival has improved in the west with modern treatment to the tune of 80% at 10 years after diagnosis<sup>6</sup>, the Indian figures are not so good (50%-60% survival at 10 years)<sup>7,8</sup>. Possible reasons for poor survival in Indian SLE include delay in diagnosis, referral bias (only the most serious cases are referred by practitioners), suboptimal health care facilities and an inherently more severe disease (genetic factors?) and endemic tuberculosis to which the lupus patients are more susceptible. The major causes of death in the first few years after diagnosis include disease activity and infec-

tions. Late mortality i.e. 10 years after diagnosis, on the other hand, is mainly attributed to atherosclerotic vascular disease<sup>9</sup>. There is a fair amount of iatrogenic morbidity and mortality.

### Indian guidelines on SLE: Why and for whom?

Since SLE is a rare disease, a general physician is not likely to be familiar with the complexities of its presentation and the therapeutic challenges and dilemmas it can pose. It is a disease, which primary care physicians would find difficult to manage without the help of a specialist. Firstly, they should be able to recognize the possibility of this disease among patients in their practice. An early referral to the specialist is desirable for improving the outcome. Once the diagnosis is established and appropriate treatment instituted by a specialist, the patient can follow up with a primary care physician provided the disease is mild and stable. All other patients with SLE require periodic clinical reviews by a specialist. A family physician can certainly collaborate with the specialist in monitoring disease activity and treating patients with moderate or severe disease. These guidelines have been formulated to improve the quality of care for SLE patients. It is hoped that the prognosis of Indian patients with SLE will improve significantly with better awareness of diagnosis and treatment of the disease among doctors.

### Clinical features of SLE in India

Clinical features reported by workers from different parts of India show some interesting regional variations<sup>10-15</sup> and these are brought out in Tables 1-3. It is evident that oral ulcers are seen in about one-half of patients at presentation in those from eastern India as against about 10% from other parts. Raynaud's phenomenon is conspicuous by its absence in patients from southern India where lymphadenopathy tends to be a presenting feature more often. Low frequency of neuropsychiatric manifestations at onset in northern India emerges as another significant difference. When patients are followed up for several years, significant differences can still be made out. These include lower frequency of photosensitivity and neuropsychiatric manifestations in western India, lower frequency of nephritis in central India and the rarity of Raynaud's in southern India in comparison to other parts of the country.

**Table 1 Percentage frequency of presenting clinical features in patients with SLE from different regions in India**

Manifestations	Northern (n = 329) <sup>10</sup>	Southern (n = 330) <sup>11</sup>	Western (n = 315) <sup>12, 13</sup>	Eastern (n =192) <sup>14</sup>	Central (n = 200) <sup>15</sup>	Mean
Arthritis	57	68.5	2 <sup>nd</sup> *	75	50	63
Fever	44	52	1 <sup>st</sup> *	60	50	50.6
Skin lesions	36	48	3 <sup>rd</sup> *	50	50	45
Nephritis	8	7.4	NA	49	NA	17
Raynaud's	6	0	NA	NA	4	3.3
Oral ulcers	4	12.6	4 <sup>th</sup> *	49	10	16
Neuropsychiatric	12	35	NA	30	NA	25
Gastrointestinal	1	2.2	NA	NA	NA	1.5
Lymphadenopathy	NA	21	NA	NA	8	16
Cardiac	1	5.2	NA	NA	NA	3
Thrombocyto-paenic purpura	4	1.5	NA	NA	NA	2.7

NA = not available, \* = the 4 commonest presenting features (exact figures NA)

**Table 2 Cumulative percentage frequency of clinical manifestations in patients with SLE from different regions in India**

Manifestations	Northern (n = 329)	Southern (n = 330)	Western (n = 315)	Eastern (n =192)	Central (n= 200)	Mean
Arthritis	92	90	71	88	NA	85
Fever	NA	74	80	NA	NA	77
Skin rash	85	74	81	90	NA	70
Photosensitivity	67	52	24	NA	NA	48
Alopecia	82	75	53	70	NA	83
Nephritis	73	45	40	62	35	57
Raynaud's	24	2	14	NA	NA	13.3
Oral ulcers	64	51	41	52	NA	55
Neurological	63	42	27	34	37	51
Neuro-psychiatric	38	29	8	NA	NA	25
Seizures	7	12.6	13	3	NA	11
Psychosis	15	7.5	8	NA	NA	10
Focal neurological	13	9	9.5	2	NA	9
Others	12	6	4	NA	NA	10
Hepatomegaly	44	23	6.3	NA	NA	30
Splenomegaly	15	18	2	NA	NA	15
Lymphadeno-pathy	47	39	23	NA	NA	30
Cardiac	29	28	14	NA	15	22
Vascular	28	17	3.2	NA	NA	20
Ocular	10	9	NA	NA	NA	9.5
Muscle	48	20	5.3	NA	NA	30
S/C nodule	5	3	NA	NA	NA	4
Thrombocyto-paenia	11	17.5	9.5	NA	NA	9

NA = not available

**Table 3 Frequency of laboratory abnormalities in Indian SLE**

Abnormality	Northern <sup>10</sup> (n = 329)	Southern <sup>11</sup> (n = 330)	Mean
Anaemia	38	52	45
Thrombocytopenia	10	7.5	9
Leucopenia	16	12.6	14
Lymphopenia	20	7.5	14
Haemolytic anaemia	7	1	4
Non-nephrotic	45	40	43
Nephrotic	8	5	6.5
Haematuria	23	20	22
Casturia	36	12.6	24
ANA	98	96	97
Anti-dSDNA	55	60.5	58
Anti-Sm	21	35	28
Anti-RNP	31	NA	31
Anti-Ro	34.5	40	37
Anti-La	18	14	16
Low C3	66	60	63
RF	21	6	13.5
STS (false positive)	5	12.5	9
ACL	28	41	34.5

### Diagnosis of SLE

The American College of Rheumatology has a criteria for the classification of patients as having SLE<sup>16</sup> (Table 4). If a patient has, at any time in his or her medical history, 4 of the 11 criteria documented, the diagnosis of SLE can be made with about 95% specificity and 85% sensitivity. These criteria are actually meant for epidemiological purposes (to ensure that SLE patients reported in the literature do in fact have the disease) and not for bedside diagnosis of an individual patient. The diagnosis of SLE is based on clinical judgement. SLE can be suspected whenever 2 or more organ systems listed in Table 4 are involved. Thus, a lady with nephritis and presence of ANA and anti-dSDNA meets only 3 criteria but almost certainly has SLE.

### Serology in SLE

Since SLE is associated with a number of autoantibodies, it is important to understand their relevance in clinical practice. Some of these are useful as diagnostic markers, others help in quantifying disease activity and still others are primarily of research interest, making no contribution to patient care. A brief discussion follows:

#### 1. Antinuclear antibody (ANA):

ANA is a good screening test for SLE because 95% of cases show a high titre (1:80 or more) of this autoantibody. A negative test result makes the diagnosis highly improbable. ANA may be positive in other rheumatic disorders such as systemic sclerosis, Sjogren's syndrome, overlap syndrome, antiphospholipid syndrome, polymyositis and rheumatoid ar-

**Table 4 Revised ACR classification criteria for SLE (1997 update)<sup>16</sup>**

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing nasolabial folds
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight by history or on physical exam.
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Non-erosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
Pleuritis/pericarditis	a. Pleuritis- convincing h/o pleuritic pain or rub or pleural effusion on physical examination OR b. Pericarditis- documented by ECG, rub or e/o effusion
Renal disorder	a. Persistent proteinuria > 0.5 gm/day or > +++ , OR b. Cellular casts- may be red cell, Hb, granular, tubular or mixed
Neurological disorder	a. Seizures- in the absence of offending drugs, or known metabolic derangement, e.g. uraemia, ketoacidosis or electrolyte imbalance, OR b. Psychosis- in the absence of offending drugs, or known metabolic derangement, e.g. uraemia, ketoacidosis or electrolyte imbalance
Haematological disorder	a. Haemolytic anaemia with reticulocytosis, OR b. Leukopaenia < 4000/cu mm on 2 or more occasions, OR c. Lymphocytopenia < 1500 on 2 or more occasions, OR d. Thrombocytopenia < 100,000/cu mm in the absence of offending drugs
Immunological disorder	a. Anti-DNA: antibody to native DNA in abnormal titre, OR b. Anti-Sm: presence of antibody to Sm nuclear antigen, OR c. Positive finding of aPL antibodies based on: 1) ↑ serum level of IgG or IgM aCL or 2) a positive test result for lupus anticoagulant, using a standard method, or 3) a false-positive test for syphilis for at least 6 months and confirmed by TPI or FTA-abs test
Positive ANA	An abnormal titre of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of drug

thritis. Like the rheumatoid factor test, ANA may also be positive in chronic infections, malignancies and in normal individuals. Thus, the specificity of ANA for diagnosis of SLE is quite low (app. 40% only).

Although many laboratories use ELISA technique for the sake of convenience and economy, the gold standard method for testing and reporting ANA is the indirect immunofluorescence method. The preferred substrate is a dividing cell line such as 'HEp-2', with rat liver sections as the next choice. Different types of staining patterns can be identified by this method such as homogeneous (diffuse), speckled (fine, coarse), rim (peripheral) and nucleolar. The staining patterns have been associated with different sub-types of clinical manifestations of lupus, though validated data are not published as yet.

It is important to stress that the diagnosis of SLE must be strongly suspected at the clinical evaluation before requesting for ANA test. A positive result supports the diagnosis of

SLE. Also, performing serial titres of ANA in a diagnosed case of SLE is of no clinical value because it does not correlate well with disease activity. It can remain positive for long periods in the absence of any disease activity. What we treat is disease and not ANA.

ANAs are actually a family of autoantibodies, which may be directed against any one of the following nuclear antigens:

1. Double stranded-DNA
2. Extractable nuclear antigens (ENA)
3. Histones
4. Nuclear RNA

Antibodies to the above subspecificities are also useful in some situations and are discussed below:

**Anti-double stranded DNA antibody (anti-dsDNA):** This test has high specificity for SLE. However, the technique must ensure absence of any contamination with single stranded DNA in the antigen used. Farr assay (radioimmunoassay) and

Crithidia lucilae method are very good in this regard but they are cumbersome and hence not very popular with most laboratories. Newer methods such as ELISA and haemagglutination have become available and are reasonable alternatives. The positivity of anti-dsDNA in SLE at the time of presentation is in the range of 60% (although the cumulative positivity during the course of disease may approach 90%). Hence, anti-dsDNA can not be a good screening test for SLE. When positive, the test establishes the diagnosis of SLE. The anti-dsDNA titres most often correlate with disease activity.

**Antibodies to extractable nuclear antigens (anti-ENA):**

These include anti-Sm, anti-U1RNP, anti-Ro and anti-La antibodies. Anti-ENA are found only in about 50% of sera which are positive for ANA. High titres of anti-U1RNP are associated with mixed connective tissue disease (MCTD) which is a subset of SLE with prominent Raynaud's phenomenon, sclerodactyly, proximal myopathy and mild or no renal involvement. Anti-Sm antibody is quite specific for SLE but it is found only in 10-30% of patients. Anti-Ro is associated with ANA negative SLE, Sjogren's syndrome, congenital heart block, neonatal SLE and subacute cutaneous lupus erythematosus. Anti-La is associated with SLE and Sjogren's syndrome. Anti-histone antibodies are associated with drug-induced SLE.

**Anticardiolipin antibodies (aCL) and lupus anticoagulant:**

This is discussed under 'Antiphospholipid syndrome' (please see appendix)

**Complement levels (C3 and C4):** These two complement components are useful in the diagnosis and follow up of SLE. Their levels drop because of consumption. C3 and C4 levels are negatively correlated with lupus activity.

**Differential diagnosis of SLE:** The following conditions need to be considered in differential diagnosis of SLE-

- Undifferentiated connective tissue disease
- Primary Sjogren's syndrome
- Primary antiphospholipid syndrome
- Fibromyalgia with positive ANA

Idiopathic thrombocytopenic purpura

Drug-induced lupus

Early RA

Systemic vasculitis

**Laboratory investigations to be requested:**

Although investigation plan for a case of SLE will depend on the clinical picture, the minimum laboratory work-up should include:

1. Haemoglobin, WBC, Differential count, ESR
2. Urine routine (preferably a fresh sample examined) and microscopy, and 24 hour protein and creatinine estimation if necessary
3. Serum chemistry (urea, creatinine, liver function tests, lipid profile)
4. Chest x-ray
5. ANA, anti-dsDNA, C3, C4

Additional investigations can be obtained depending on the clinical indications and these are mentioned at appropriate places in this document.

**Referral to Rheumatologist/Specialist:**

Referral to a rheumatologist is indicated for the following purposes:

1. Confirmation of diagnosis
2. Periodic evaluation of disease activity and severity
3. Management: general plan of treatment, patient education, management of uncontrolled/serious, life threatening disease, prevention and treatment of drug-toxicities
4. Special situations such as pregnancy, antiphospholipid syndrome, concomitant infection and surgery

**Evaluation of disease activity and severity**

A number of validated indices are available for quantifying disease activity. The more popular indices include-BILAG<sup>17</sup>, SLEDAI<sup>18</sup>, SLAM<sup>19</sup> and LAI.<sup>20</sup> These help in formulating the overall treatment plan and assessment of prognosis. Table 5 shows the details of scoring used in SLEDAI. A valid measure of damage in patients with lupus is the SLICC/ACR Damage Index (DI).<sup>21</sup>

**Table 5 SLE Disease Activity Index (SLEDAI)**

Descriptor	Definition	Score
Seizure	Recent onset, exclude metabolic, infectious or drug causes	8
Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, markedly loose associations, impoverished thought content, markedly illogical thinking, bizarre, disorganised or catatonic behaviour. Exclude uraemia and drug causes	
‘Organic brain syndrome’ or Acute confusional state	Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, drug or infectious causes	8
Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal haemorrhages, serous exudates/haemorrhages in choroid or optic neuritis. Exclude hypertension, infection or drug causes	8
Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves	8
Lupus headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.	8
CVA	New onset of CVA. Exclude atherosclerosis.	8
Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram evidence of vasculitis	8
Arthritis	≥ 2 joints with pain and signs of inflammation (tenderness, swelling or effusion)	4
Myositis	Proximal muscle aching/weakness, associated with elevated CPK/aldolase or EMG changes or biopsy evidence of myositis	4
Urinary casts	Haemoglobin, granular or RBC casts	4
Haematuria	> 5 RBC/HPF. Exclude stone, infection or other causes	4
Proteinuria	> 0.5 grams/24 hrs	4
Pyuria	> 5 WBCs/HPF. Exclude infection	4
Rash	Inflammatory type rash	2
Alopecia	Abnormal, patchy or diffuse loss of hair	2
Mucosal ulcers	Oral or nasal ulcerations	2
Pleurisy	Pleuritic chest pain with pleural rub/effusion/pleural thickening	2
Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion or ECG or Echo confirmation	2
Low complement	Decrease in CH50, C3 or C4 below the normal limit of Lab	2
Increased DNA binding	Increased DNA binding using Farr assay	2
Fever	> 38 Deg C. Exclude infection	1
Thrombocytopenia	< 100,000/cu mm, exclude drug causes	1
Leukopenia	< 3000/cu mm, exclude drug causes	1

## Management

### Patient Education

In order to obtain optimal results from drug therapy, patient education plays a vital role and must be paid due attention. This is discussed below:

#### *How to educate the patient about the disease?*

Every newly diagnosed patient needs to be educated about the disease. In this regard, pamphlets especially written for patients can be very helpful. For illiterate patients, the treating physician or a specialist nurse will have to spend the necessary time on education. It is often useful to offer a new patient the opportunity to interact with other previously diagnosed lupus patients who are identified by the specialist as having a positive outlook of the disease and the enthusiasm to function as a counsellors. In many advanced centres (outside India), community-based lupus support groups exist and they perform this vital function. The biological behaviour of the disease, in particular, the long remitting and relapsing course of the disease must be explained to the patient. The need for long-term treatment and careful monitoring of various parameters must be emphasized. Some useful web-sites for lupus patients include [www.lupus.org/lupus](http://www.lupus.org/lupus), [www.livingwithlupus.com](http://www.livingwithlupus.com) and [www.patient.co.uk/illness/lupus.htm](http://www.patient.co.uk/illness/lupus.htm) Patients also need advice regarding marriage, contraception, pregnancy and breast-feeding. As regards marriage, the physician should discuss the risks involved openly with the patient. Participation of the fiancée is crucial. The patient must be encouraged to take other important participants also into confidence; otherwise marriage is not likely to succeed. The relapsing and remitting nature of the disease must be explained clearly. However, it should be emphasized that fertility in lupus is not impaired though abortions and foetal wastage occur frequently. Normal outcome of pregnancy is possible with appropriate care. Contraception is essential during phases of active disease. Oral contraceptives with relatively small amounts of oestrogens (< 35 µg) or pure progesterone preparations are preferred. Alternatives include condom and diaphragm with spermicidal jelly. Intrauterine devices should be avoided because of the increased risk of infections in lupus. Pregnancy and breast feeding are discussed under 'Pregnancy in SLE'.

#### *Educating the family*

Family support is vital in the management of SLE, and the spouse or parents must be taken into confidence and explained in detail about the disease. Explaining the disease requires skill and maturity on the part of the physician and should focus on a positive weighted overview and a realistic expectation of treatment that essentially is disease activity

control with safe and established medications. Most married women in India are housewives, and with active systemic lupus erythematosus their emotional stress worsens if the husband's moral support is inadequate or the in-laws have unrealistic expectations from the patient whose functional status may be significantly compromised due to the symptoms, dominantly fatigue and polyarthralgias. The physician can play a vital role in counselling the family members thereby facilitating the process of obtaining the much needed support from them. It has to be emphasized that the disease is eminently controllable with appropriate treatment and patients can enjoy long periods of remission and have happy and successful family lives.

#### *Avoidance of sun-exposure*

Sunlight is generally detrimental to the health of lupus patients and frequently responsible for exacerbations of lupus activity. Photosensitive patients must be advised to wear protective clothing with long sleeves etc, use sunscreens (creams/lotions) with sun-protection factor (spf) of more than 15 and to avoid going outdoors during daytime when sunlight is intense (if absolutely necessary, they must use an umbrella to screen off sun). Sun rays reflected from sea water around sunrise and sunset are also harmful. Office-workers should avoid sunlight from windows and even exposure to overhead fluorescent lights. The ultraviolet rays, in particular, have to be avoided, and hence the unprotected exposure to low pollution areas such as seashores and hill stations frequently precipitate relapse of lupus activity. Computer screens can also be a source of ultraviolet rays. Even photosensitizing drugs (e.g. demeclocycline, sparfloxacin, dapsone, amiodarone etc.) are harmful.

#### *Infections*

Infections are common in SLE and therefore, patients must get any unexplained fever evaluated promptly. This is particularly necessary when patient is on long-term steroid/cytotoxic therapy. Other situations such as renal failure, cardiac valvular vegetations and ulcerative mucocutaneous lesions also predispose SLE patients to infections. When lupus patients present with fever of unknown origin the cause could be an infection or lupus activity itself. A diagnostic dilemma may present when work-up for infection is negative and there are no obvious leads. In this situation, elevated C-reactive protein levels in blood favour a diagnosis of infection. Lupus activity is generally not accompanied by rise in CRP. Patients undergoing splenectomy, must receive pneumococcal vaccine preferably before surgery. It is a good policy to give influenza vaccine yearly and to institute antibiotic prophylaxis for all dental, genitourinary and other invasive procedures.

### General approach to the drug therapy of SLE:

Since there is a range of severity of disease manifestations, proper categorization based on clinical and laboratory features is the first therapeutic step. The following scheme is recommended:

#### Category I (Mild SLE)

Characterised by arthritis, arthralgia, myalgia, fatigue, mild mucocutaneous involvement, low-grade fever, mild serositis, lupus headache

Musculoskeletal complaints are the commonest features of SLE. For mild symptoms, NSAIDs and analgesics may suffice. NSAIDs can occasionally cause adverse effects which may resemble those produced by the disease itself such as proteinuria, edema, renal failure and aseptic meningitis.

In some patients, the above symptoms may not be alleviated with NSAIDs alone, and they should be prescribed antimalarials (chloroquine, hydroxychloroquine). These drugs are particularly useful for cutaneous manifestations of SLE. These agents have multiple properties: immunosuppressive anti-inflammatory and sun-blocking. They are also reported to possess anti-platelet and cholesterol lowering effects. The drug of choice is hydroxychloroquine (200 mg BD for 3 months and then 200 mg daily). The maintenance dose must not exceed 6 mg/kg/day. Although the incidence of retinal toxicity is very low, annual monitoring of vision with perimetry using a red object is recommended (for chloroquine, 6-monthly monitoring is desirable). The drug must be discontinued if a central scotoma is detected at any stage. Other significant side effects include nausea, pruritus, hyperpigmentation, myopathy and rarely psychosis. Use of hydroxychloroquine during pregnancy is controversial. When antimalarials are withdrawn after prolonged administration, some patients may develop a relapse of lupus activity. In refractory cases, quinacrine may be combined with hydroxychloroquine. Alternatives include dapsone and thalidomide. Quinacrine and thalidomide are, however, not available in India.

Patients not responding to the above measures may be treated with low-dose steroid therapy (Prednisolone 0.3-0.5 mg/kg/day) for 4-6 weeks followed by slow tapering. For lupus dermatitis, there is also a role of local steroids, including topical creams and ointments and injections into unresponsive skin lesions. However, the steroid cream application for facial rash is not recommended. Adequate protection against sun is essential (vide supra).

#### Category II (Moderate SLE)

Characterised by high-grade fever, toxemia, severe mucocutaneous manifestations, marked photosensitivity, moderate to severe serositis, lupus pneumonitis, mild to moderate

myocarditis, mesangioproliferative or minimal change lupus nephritis, haemolytic anaemia and thrombocytopenia

For moderate and severe manifestations, prednisolone 1 mg/kg orally per day is the drug of choice. Antimalarials may be administered concomitantly. High dose of steroid must be continued till disease activity is well controlled that usually takes up to 6 weeks when it should be tapered off slowly over 6 to 12 months. In a toxic appearing patient, the administration of intravenous pulse methylprednisolone (15 mg/kg, max. 1 g) over an hour for 3 or 5 consecutive days may achieve rapid control of lupus activity. Dexamethasone 100 mg is a good, cheap and equally effective alternative steroid for pulse therapy. Although rare, arrhythmias, accelerated hypertension, psychosis, seizures and sudden death have been reported with pulse therapy. The pulses should be followed by oral prednisolone.

Calcium supplements (1 gm/day) and vitamin D (800 units/day) prescribed along with steroids retard osteoporosis. Alendronate 10 mg daily or 70 mg once a week is a good antiresorptive drug for prevention of osteoporosis in patients starting on long-term steroid therapy.

A maintenance dose of oral steroid (beyond 6 months) is not necessary in the majority of these patients and most often it is possible to maintain the remission with antimalarials and intermittent use of NSAIDs. INH prophylaxis in Indian patients has been a point of debate because of fear of promoting INH resistance. However, this risk is very low because of the small bacillary load present in this setting. One Indian study on patients with SLE starting on steroids showed 82% protection from tuberculosis with INH prophylaxis in one year.<sup>22</sup> In the Indian context, it may be better to use 2-drug prophylaxis (Rifampicin + INH or INH + Ethambutol) for a period of one year.

#### Category III (Severe SLE)

Characterised by organ/life-threatening features such as focal/diffuse proliferative glomerulonephritis with or without azotaemia/hypertension, lupus cerebritis with recurrent seizures, acute confusional state, coma; systemic necrotizing vasculitis such as one causing peripheral gangrene, GI bleeding or mononeuritis multiplex.

A combination therapy consisting of high-dose daily oral prednisolone (40-60 mg/day) and intravenous cyclophosphamide pulses (0.75 gm/m<sup>2</sup>, maximum of 1 g, over 1 hour) is recommended. The cyclophosphamide pulses are given once a month for 6 months by which time usually remission is achieved and then a maintenance pulse is administered every 3 months for a total of 2 years of cytotoxic therapy. Prednisolone

lone is tapered off or reduced to a very low dose i.e. 5-7.5 mg per day by 6 months. At least two-thirds of patients maintain a long-term remission after this treatment regimen. Haemorrhagic cystitis is rare if attention is paid to adequate hydration after the pulse and prompt voiding of bladder and co-administration of MESNA. The overall risk of irreversible ovarian failure was noted to be 39% in one study. It was much higher for women aged more than 30. Infertility is common in men as well and sperm banking is recommended, if facilities are available. Bone marrow suppression and secondary infections (Herpes zoster, tuberculosis, pneumocystis carinii, staphylococcus, pseudomonas etc.), sclerosing cystitis and bladder carcinoma, are the other adverse outcomes.

Some authorities recommend the above regimen for induction of remission (the first 6 months), which is then maintained with azathioprine 2-2.5 mg/kg/day for about 2 years. Alternatives include intravenous pulses of steroids on 3 consecutive days each month, daily oral administration of cyclophosphamide (2 mg/kg/day) or azathioprine from the beginning or a combination of these two agents along with oral prednisolone. The latter is believed to be the most potent (and the most toxic) regimen. Cyclophosphamide based regimens have been shown to be superior in achieving renal preservation. Plasmapheresis, methotrexate, cyclosporine and mycophenolate mofetil are other options.

Progressive organ damage may still occur over several years despite achieving good short-term remissions in these patients. Although the overall incidence of end stage renal disease (ESRD) is reduced, there is no firm evidence that patient survival is improved by double or triple drug regimens compared with steroid alone. This is because the outlook of ESRD is so much better now with the availability of dialysis and renal transplantation services. However, in India where more than 90% of eligible ESRD candidates do not have access to maintenance dialysis or renal transplantation, combination therapy offers definite survival advantage.

There are no definite protocols for lupus cerebritis but cyclophosphamide pulses have been used in combination with oral high-dose steroids, as in the case of lupus nephritis.

#### **Category IV (SLE with miscellaneous features)**

Characterised by antiphospholipid syndrome (recurrent DVT, CVAs, recurrent foetal loss etc.), pure membra-

nous lupus nephritis, chronic sclerosing lupus nephritis, seizures without other evidence of lupus activity, behavioural disorders without other serious manifestations, resistant thrombocytopenia or haemolytic anaemia

Immunosuppressive therapy does not play any significant role in these conditions. Treatment of antiphospholipid syndrome is described in appendix.

If seizures or psychosis occur as isolated events with no evidence of lupus activity elsewhere in the body, only symptomatic treatment is recommended. Steroids are not indicated.

Pure membranous glomerulonephritis (WHO Class V) may be treated initially with prednisolone 1 mg/kg/day. If there is no response after 6 weeks (85-90% of cases), steroids may be quickly tapered off because they are not likely to help. There is no proven role of cytotoxic drugs in the treatment of this condition in SLE. Renal failure occurs but is less frequent as compared with proliferative glomerulonephritis. However, transformation of pure membranous nephropathy to proliferative nephropathy is well documented and can occur in about one-third of patients in follow up.<sup>23</sup> There must be awareness of this fact and repeated urine examination should be done so that the transformation, when it occurs, is picked up and treated adequately.

Chronic sclerosing glomerulonephritis is best treated with conservative therapy, dialysis and transplantation. Immunosuppressive therapy is not beneficial. At least, 3 months of dialysis is recommended before considering renal transplant as the outcome of the transplant is better in patients whose lupus disease activity remains clinically stable on dialysis for at least 3 months.

For refractory thrombocytopenia, danazol may be useful. Colchicine and vincristine are sometimes useful to improve the platelet count. Splenectomy may be indicated in some cases where platelet count tends to be less than 50,000/cu mm and maintenance requirement for steroids is high. Such patients should receive pneumococcal vaccine.

Plasmapheresis may be employed in refractory cases where steroid and cyclophosphamide pulses do not produce satisfactory results. Intravenous immunoglobulin has also been used in similar situations. A few instances of successful remission of refractory lupus following stem cell transplant are reported.

## SPECIFIC ISSUES IN THE MANAGEMENT OF SLE

### NEUROPSYCHIATRIC LUPUS

Neuropsychiatric manifestations in SLE are an important cause of morbidity and even mortality. These can be the initial presenting symptoms or may come up subsequently during the course of illness. The following entities have been recognized as features of nervous system manifestations of lupus:

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| <p>I. Central nervous system</p> <p>a. Aseptic meningitis.</p> <p>b. Cerebrovascular diseases</p> <p>c. Demyelinating syndrome</p> <p>d. Headaches</p> <p>e. Movement disorders (e.g. chorea)</p> <p>f. Myelopathy</p> <p>g. Seizure</p> <p>h. Acute confusional state</p> <p>i. Cognitive dysfunction</p> <p>j. Anxiety and mood disorder</p> <p>k. Psychosis</p> | <p>II. Peripheral nervous system</p> <p>a. Cranial neuropathy</p> <p>b. Polyneuropathy</p> <p>c. Plexopathy</p> <p>d. Mononeuropathy, single/multiplex</p> <p>e. Guillaine Barre syndrome (AIDP)</p> <p>f. Autonomic disorder</p> <p>g. Myasthenia gravis</p> |
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**a. Aseptic meningitis** – Features of meningeal irritation are present in up to 5% of patients. It is necessary to exclude pyogenic, fungal and tuberculous infection. The CSF shows an increased protein, lymphocytosis and a reduced glucose content. All of these findings are encountered with fungal and tuberculous meningitis and the differentiation is frequently difficult.

**b. Cerebrovascular disease** – Stroke is seen in up to 15 % of cases. The causes of stroke include large and small vessel thrombosis, intracerebral haemorrhage and subarachnoid haemorrhage. Ischemic stroke is partly attributable to the presence of circulating antiphospholipid antibodies and premature atherosclerosis. Large haemorrhage is less common and is due to aneurysmal rupture and active vasculitis. The occurrence of a cerebrovascular disease in patient with SLE adversely affects survival.

**c. Demyelinating syndrome** – It refers to relapsing myelopathy and optic neuropathy in patients with lupus. These were earlier referred to as ‘lupoid sclerosis’ and reflect that multiple sclerosis and SLE share several clinical features.

**d. Headaches**- The frequency of headache in lupus is not particularly increased. However, intractable headache or headache of recent origin could be due to stroke, encephalopathy, subdural haematoma, cerebral sinus thrombosis and aseptic meningitis. The earlier description of lupus headache as migrainous has been refuted by recent studies.

**e. Movement disorders** – Chorea is characteristic and is present in in up to 1% of patients. Hemiballismus and parkinsonian like features are reported in fewer numbers.

**f. Myelopathy**- Transverse myelitis, is an acute illness with symptoms of back pain, weakness or paralysis, bilateral sensory deficits and loss of sphincter control which may progress over hours to days. It occurs in approximately 1% of cases. Diagnosis is made clinically and supported by CSF pleocytosis, elevated protein or reduced glucose level, and magnetic resonance studies showing focal cord edema. Antiphospholipid antibodies have been associated with this entity. Up to 25% of cases may have optic neuropathy.

**g. Seizures** are amongst the commonest neurological manifestations (17-37%) and one of the features listed in ACR classification criteria for SLE. Generalised, simple partial and partial complex seizures have been reported. The aetiology is multifactorial and secondary causes include metabolic derangement due to uraemia, hypertensive crisis and antiphospholipid antibodies. The presence of status epilepticus is a grave prognostic sign.

**h. Acute confusional state** –The ACR nomenclature and case definitions for neuropsychiatric lupus syndromes suggest using the term ‘acute confusional state’ for the entire spectrum of delirium to coma. Old term ‘organic brain syndrome’ has been dropped. It is present in 2-40% of cases and has a serious prognostic significance. The two most frequent causes of coma in SLE are stroke and acute confusional state.

**i. Cognitive dysfunction** has been reported in 21-35% of cases. This consists of difficulty in recall, calculation, concentration and word finding. The use of instruments like Mini Mental State and the Neurobehavioural Cognitive Status Examination is required to bring out this abnormality. It may affect performance status at work.

**j. Anxiety and mood disorder** – This is commonly seen in SLE but the cause is not clear. Reaction to the presence of a chronic illness or SLE primarily could be responsible.

**k. Psychosis** - Occurs in up to 23% of cases. Presents as paranoia and hallucinations (visual or auditory). Recovery is complete but relapses are common. Distinction from corticosteroid psychosis can be difficult.

Some of the above manifestations are known to be associated with antiphospholipid antibodies, e.g. strokes, chorea, some myelopathies and seizures. However, others such as cognitive dysfunction, seizure, acute confusional state, psychosis, anxiety and depression, myelopathy, peripheral neuropathies and headache are non-thrombotic disorders and could be due to antineuronal antibodies, antiribosomal P antibodies, immune-complexes and vasculitis. Other important considerations are as follows:

1. Side effects of medications for the treatment of SLE – Corticosteroid in particular can cause psychosis, euphoria and altered moods. Antimalarials can induce hyperirritability and seizures. NSAIDs are known to be associated with aseptic meningitis.
2. CNS infections - Tuberculosis, bacterial endocarditis, herpes simplex encephalitis, meningitis have been mistaken for CNS lupus. A lumbar puncture for CSF fluid analysis is a must to exclude infections.
3. Fluid and electrolyte imbalance: Hypokalemia, hyponatremia, water intoxication and syndrome of inappropriate antidiuretic hormone can induce psychosis.

**Clinical and Laboratory evaluation:**

- a. Thorough history and detailed physical examination including neurological and mental status evaluation.
- b. Baseline haematology, chemistry and immunological studies. The serology should include lupus anticoagulant, anticardiolipin antibodies. If facilities are available anti ribosomal P antibody levels and antineuronal antibodies may be done.
- c. CT and MRI are indicated in cases of stroke, stupor/coma and psychosis. MRI is more sensitive than CT in picking up haemorrhages, infarcts and oedema. CT is better for detecting cortical atrophy.
- d. CSF IgG index (CSF IgG / CSF albumin divided by serum IgG / serum albumin) is often a useful test to differentiate between cerebritis and vascular stroke as the cause of mental disequilibrium or confusional state or loss of consciousness. However, the normal index (usually around 0.5) must be established for the laboratory and if it is higher than the normal, then cerebritis or vasculitis is the more likely cause necessitating aggressive immunosuppression whereas a lower index

value suggest vascular insufficiency and in absence of haemorrhage proved by an imaging study, anticoagulation is indicated.

**Treatment**

In diffuse disease, such as acute confusional state, evidence of active inflammation in the brain, such as increased cells and protein in the CSF, brain swelling on MRI or CT, or psychosis is generally managed with prednisolone 1-2 mg/kg/day administered orally. Those who are unresponsive to this dose of prednisolone may be administered IV methylprednisolone 1000mg/day for 3 consecutive days. Pulse administration of IV cyclophosphamide in a dose of 750 mg/m<sup>2</sup> every 3-4 weeks may be tried in refractory cases. Focal disease such as cerebral thrombosis, chorea and some cases of transverse myelitis where anticardiolipin antibodies may be associated, is treated on the lines of APS (vide infra). Steroids are not useful in this condition.

**Other specific entities**

**Transverse myelitis** : Requires aggressive treatment with prednisolone orally 1.5 mg/kg/day and IV cyclophosphamide bolus. If there is no improvement, plasmapheresis should be considered.

**Seizures**: For generalized seizure, phenytoin and barbiturates are used and for focal, carbamazepine, valproate or gabapentin is used.

**Headaches**: Most patients respond to NSAIDs. In intractable cases steroid may be used.

**Chorea**: No specific therapy is required.

**Cranial/autonomic and peripheral neuropathy**: Oral Prednisolone in a dose of 1mg/kg/day is useful.

**Cognitive dysfunction**: Consider reducing the dose of prednisolone. If associated with APS, anticoagulate.

## LUPUS NEPHRITIS

Lupus nephritis is currently defined as the presence of more than +++ or 0.5 gram/24 hr proteinuria or presence of cellular casts of any type (Table 4). Using this definition, lupus nephritis occurs in about half of SLE patients (range: 35%-73%) in India (Table 2). It is rare for lupus nephritis to present with progressive renal insufficiency with repeatedly normal urinalysis. Also, nephrotic range proteinuria is uncommon (app. 10%) in Indian lupus (Table 3). Thus, reliable urine examination is the single most important investigation for early diagnosis of lupus nephritis; clinical examination is generally unhelpful. Renal tubular acidosis is known to occur more frequently in SLE.

Renal histology can be studied by light microscopy, immunofluorescence and electron microscopy. The WHO classification scheme combines all 3 modalities (Table 6). Activity and Chronicity indices can be derived by the pathologist from the renal histology picture.

**Table 6 : WHO Classification of lupus nephritis**

Patterns	Immunofluorescence		Electron Microscopy		
	Mesangial	Peripheral	Mesangial	Subendothelial	Subepithelial
I. Normal	0	0	0	0	0
IIA. Mesangial deposits	+	0	+	0	0
IIB. Mes. hypercellularity	+	0	+	0	0
III. Focal-segmental GN	++	+	++	+	+
IV. Diffuse GN	++	++	++	++	+
V. Membranous GN	+	++	+	+	++

### Indications for kidney biopsy in SLE

1. A patient with glomerular disease in whom the diagnosis of lupus is not certain
2. Mild proteinuria and haematuria
3. Nephrotic syndrome with a bland sediment
4. A repeat biopsy may be performed for late progression of the disease to distinguish between active lupus (which may require immunosuppressive therapy) and scarring of previous inflammatory injury

In the first 3 situations, the histology may be focal or diffuse proliferative disease, membranous lupus, or, less often, thrombi associated with antiphospholipid antibodies. Each of these disorders may require a different form of therapy. Patients with acute renal insufficiency, active lupus serology, and an active sediment (red cells and red and white cell casts) almost always have diffuse proliferative disease; these patients do not need histologic confirmation if there is clear clinical and serologic evidence for SLE.

### Principles of treatment of lupus nephritis

**General measures:** It is advisable to restrict salt if hypertension is present, fat if hyperlipidemia or nephrotic syndrome is present, protein should be restricted if azotaemia is present and calcium should be supplemented with steroid therapy. Meticulous control of hypertension is desirable. Pregnancy should be avoided during active lupus nephritis with suitable contraception (vide infra). NSAIDs should be avoided in the presence of impaired renal function.

**Immunosuppressive therapy:** This is generally guided by the WHO Class of lupus nephritis.

1. Class I: Immunosuppressive therapy is not indicated.
2. Class IIa: -do-
3. Class IIb: If proteinuria is > 1 gram/24 hours, anti-dsDNA is high and C3 is low, prednisolone should be administered at a dose of 20 mg daily for 6-12 weeks, followed by tapering over next 3 months.
4. Class III & IV: Protocol for this group is already described above (See Category III under management).
5. Class V: Described under management above (Category IV)

A high chronicity index correlates with poor renal outcome with progression to end stage renal disease despite treatment. High activity Index is also associated with poor outcome if not treated aggressively with appropriate immunosuppressive therapy. Patients with high chronicity index and serum creatinine more than 3 mg/dL should not be treated aggressively unless activity index is also high. If serum creatinine is chronically high and more than 5 mg/dL, aggressive immunosuppressive therapy is harmful. Such patients will be better managed with dialysis and transplantation in due course.

## ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) or Hughes syndrome can present as a subset of SLE. More often, however, it occurs as a primary condition. The hallmark of APS is thrombosis (venous and/or arterial). The disease is characterised by the presence of antiphospholipid antibodies (aPL) in the blood. Cross-sectional studies reveal 30% frequency of thrombosis in patients with aPL.

### Clinical and laboratory features

Both arterial and venous thrombosis can occur in APS. This contrasts with other prothrombotic conditions such as protein C, S or antithrombin III deficiency where only venous thrombosis is seen. The common clinical manifestations of APS comprise recurrent pregnancy loss, recurrent deep venous thrombosis and cerebrovascular accidents. Some patients develop the catastrophic APS in which thrombosis affects the blood vessels supplying vital organs simultaneously or in quick succession leading to a picture, which may mimic TTP or DIC. The prognosis of catastrophic APS is poor.

Antiphospholipid antibodies can be detected by 2 methods: an anticardiolipin ELISA and a haematological test called lupus anticoagulant assay. Anticardiolipin antibody is usually of IgG class and this may exist alone or in combination with IgM aCL. However, as many as 12% of patients may have only IgM aCL antibody. It is recommended that both IgG and IgM aCL should be tested in a suspected case of APS. Lupus anticoagulant is a less sensitive test but it is associated with the clinical syndrome of thrombosis more often than is aCL. A patient with APS may test positive for either or both LAC and aCL. Both tests should be carried out when investigating APS.

### Diagnosis (Consensus Classification Criteria)

#### A. CLINICAL CRITERIA

1. Vascular thrombosis: One or more episodes of arterial, venous or small-vessel thrombosis, occurring within any tissue or organ
2. Complications of pregnancy: One or more unexplained deaths of morphologically normal foetuses at > 10 weeks of gestation, or One or more premature births of morphologically normal neonates at < 34 weeks of gestation, or Three or more unexplained consecutive spontaneous abortions at < 10 weeks of gestation

#### B. LABORATORY CRITERIA

1. aCL: Anticardiolipin IgG or IgM antibodies present at moderate or high titres on 2 or more occasions at least 6 weeks apart
2. LAC: Lupus anticoagulant antibodies detected on 2 or more occasions at least 6 weeks apart

A diagnosis of definite APS requires the presence of one clinical + one laboratory criterion

### Treatment of APS

This can be considered under the following heads:

1. Deep venous thrombosis: The main purpose of treatment here is to prevent pulmonary embolism. Standard measures include bed-rest, elevation of the affected limb to allow the oedema and tenderness to subside and anticoagulant therapy. Heparin and warfarin should be started simultaneously so as to allow an overlap of about 5 days. INR should be adjusted between 3 and 4 on long-term warfarin therapy. The duration of warfarin therapy is life-long in patients with recurrent venous thrombosis. Thrombolytics such as streptokinase, urokinase and tPA can be used but they are not more effective in preventing pulmonary embolism. Thromboendarterectomy and percutaneous insertion of IVC filter may be considered in special circumstances.
2. Acute arterial thrombosis: In a patient with APS this usually means a TIA or stroke, with MI and digital gangrene being less common. In some patients with acute stroke (< 3 hours duration), thrombolytics can be used but the standard of care is usually heparin followed by warfarin. Low-dose aspirin is strongly recommended in patients who continue having thrombotic events despite full anticoagulation. APS patients with acute MI can be treated with thrombolytics, angioplasty or coronary stents. Peripheral arterial thrombosis can be treated with thrombolytics or heparin or angioplasty.
3. Catastrophic APS: These patients develop thrombosis in multiple organs and the features mimic DIC and TTP. Oral contraceptives and other drugs, pregnancy, infection and surgical procedures have been identified as predisposing factors. Besides standard treatment, IVIG or plasmapheresis is recommended in such patients. Still, prognosis remains poor.
4. Pregnancy (see next section)
5. Thrombocytopenia: This is usually mild and does not require treatment. If the count tends to drop below 50,000/cu mm, treatment on the lines of ITP may be started.

## PREGNANCY IN SLE

SLE does not impair the woman's fertility except during periods of severe disease activity. However, there is increased risk of abortions (2-3 times), intrauterine growth retardation and stillbirth. Pregnancy increases the risk of disease flare (40%-50% probability). The risk of flare is doubled in women who have active disease at the time of conception. About 10% patients develop severe flares and therefore, lupus pregnancy is rightly labeled 'high-risk' pregnancy. With better understanding of lupus pregnancy, the outcome has improved considerably in the last 2 decades. Published data on lupus pregnancy from India are scant.<sup>24,25</sup> Both studies reported poor foetal outcome in lupus pregnancy (40% and 58% respectively). Active disease at the time of conception correlated with adverse foetal outcome. Laboratory monitoring during pregnancy

1. Initial evaluation: Hb, WBC, DLC, platelets, urinalysis with microscopy, 24-hour urinary estimation of protein and creatinine, blood urea, glucose and serum creatinine, serum lipids if patient is nephrotic or on steroids, Coombs' test, aPL (IgG and IgM aCL, LAC), VDRL, anti-dsDNA, C3. Anti-Ro and anti-La should be done if there is a past history of giving birth to a baby with neonatal lupus.

2. Monthly laboratory assessment includes: Hb, WBC, DLC, platelets, urinalysis (with 24-hr analysis if nephritis), chemistry panel as above, anti-dsDNA and C3. Elevated anti-dsDNA and low C3 indicate active SLE or impending flare in over 80% of patients.

3. In case anaemia develops, peripheral smear should be reviewed and Coombs' test repeated.

### General principles of treatment of lupus pregnancy

It is strongly recommended that the disease should be in clinical remission for at least 6 months before the patient plans pregnancy. At the onset of pregnancy, a complete assessment of disease activity and severity should be made. The spouse and other family members should be counselled. If disease is in remission, patient should be seen once every month in the first half of pregnancy and more frequently, later on. Laboratory evaluation should be performed as mentioned above. Blood pressure should be measured at every visit and more frequently in patients with nephritis. The prime focus of the entire exercise of follow up should be early detection and prompt treatment of lupus flare during pregnancy and the postpartum period. Presence of nephritis with or without hypertension is an indication for low-dose daily aspirin from 10<sup>th</sup> week till 36<sup>th</sup> week for prevention of pre-eclampsia. Patients on long-term steroid therapy (> 2 years) are administered

'stress doses' of steroids during delivery. Indications for Caesarian section include maternal reasons (avascular necrosis of the hips with inadequate hip abduction) or foetal reasons (foetal distress, abnormal nonstress test, cephalo-pelvic disproportion and transverse presentation etc.).

Lupus flares should be treated with the appropriate steroid dose. Cytotoxic drugs such as cyclophosphamide and methotrexate should be avoided during first trimester except in rare circumstances such as pulmonary alveolar haemorrhage due to SLE. Azathioprine and cyclosporine can be used in pregnancy with active SLE. More safety data are needed for mycophenolate mofetil.

If antiphospholipid syndrome is present, there is greatly increased risk of thrombosis and foetal loss. Warfarin must be omitted as early as possible after conception (preferably the next day her first menses are missed and pregnancy confirmed) and daily subcutaneous injections of low molecular weight heparin (either enoxaparin 40 mg/day or dalteparin 5000 units per day) or low dose of heparin sodium along with low dose aspirin must be continued until delivery. The heparin is omitted 12 hours before delivery or cesarean section whereas low dose aspirin may continued. After post partum bleeding stops, usually within a week after delivery, warfarin is restarted. Corticosteroids are not recommended for APS alone because they increase maternal morbidity. In refractory cases, IVIG can be tried.

Foetal health should be monitored with repeated ultrasound examinations, foetal heart monitoring and nonstress test. It is needless to emphasize that a neonatologist should be available at the time of delivery. During the postpartum period, the mother should be watched for infection and disease exacerbation; both require aggressive treatment, when detected.

Breast-feeding is an important issue to be addressed after successful pregnancy outcome. Majority of drugs are excreted in human milk in variable amounts. From neonatal perspective, maternal intake of prednisolone upto 30 mg/day, warfarin, cyclosporine in standard doses and weekly chloroquine for malaria prophylaxis are considered safe. If the dose of prednisolone is greater than 30 mg/day, feeding should be avoided for 4 hours after ingestion of the morning dose of steroid. By this time the blood levels are quite low and very limited amounts are secreted into the milk. However, breast-feeding is contraindicated if mother is on cyclophosphamide, azathioprine, hydroxychloroquine for SLE, salicylates, indomethacin and sulindac.

## **DRUG-INDUCED LUPUS (DIL)**

Drugs can sometimes induce lupus-like disease and associated autoantibodies. The incidence of DIL is estimated at about 10% of idiopathic SLE. Numerous drugs have been incriminated or suspected. Those associated with moderate to high risk include procainamide, hydralazine and quinidine. Others such as INH, minocycline, d-penicillamine, methyl-dopa, captopril, chlorpromazine, carbamazepine and phenytoin are associated with a low risk.

DIL typically develops several months to 3 years after continuous intake of the drug. Patients present with arthralgias, myalgias, malaise, fever, serositis and polyarthri-

tis. Rash and renal involvement are rare. Laboratory profile consists of ANA (antihistone type, usually IgG anti-H2A and H2B), leucopenia, thrombocytopenia, mild anaemia and raised ESR. Serological markers which are conspicuous by their absence include anti-DSDNA, anti-Sm, anti-RNP, anti-Ro/La and hypocomplementaemia. Patients frequently do not satisfy ACR criteria for classification of SLE. After withdrawal of the suspected agent, clinical improvement follows within days to weeks. However, autoantibodies may take several months to disappear. Sometimes, NSAIDs and corticosteroids may be required for a short period to obtain symptomatic relief

## CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS

### Salient features

Childhood SLE is an autoimmune multisystem connective tissue disorder occurring in children below 16 years of age. It is the second commonest paediatric rheumatic disorder next to Juvenile Idiopathic Arthritis. Childhood SLE usually occurs in the age group of 5-16 years (Mean age - 12 years) with female predominance (5:1). It is said that female preponderance is lower in childhood but Indian experience does not support this observation. The mean duration of illness before diagnosis is about 1 year. Table 7 and 8 give the clinical and laboratory features noted in 2 different series on Indian children.<sup>26,27</sup> Clinical features in children are generally similar to those described in adults but the disease tends to be more severe. Renal involvement is more common. Lymphadenopathy is also seen more commonly in children.

**Table 7 Clinical features of Indian children with SLE**

Parameter	Northern India (n = 83) <sup>26</sup>	Southern India (n = 59) <sup>27</sup>
Female to male ratio	9.3 : 1	4.9 : 1
Age range	5 yrs-16 yrs	5 yrs-16 yrs
Fever	89%	80%
Rash	83%	69%
Photosensitivity	73%	20%
Arthralgia/arthritis	90%	87%
Lymphadenopathy	54%	61%
Hepatosplenomegaly	55%	40%
Renal involvement	79%	49%
Pulmonary involvement	29%	22%
CNS symptoms	21%	27%
Cardiac involvement	29%	10%
Raynaud's	29%	0%

Children are extremely vulnerable to the psychological impact of both lupus as chronic illness and the medications that dramatically change their appearance. The peer-group pressures may exert overwhelming effects on a child's mind. The complex interaction of these unique challenges with the usual medical problems of SLE poses difficult dilemmas before the treating physician. Patient and family education as well as support play a crucial role. The basic principles of treatment of childhood SLE, however, are similar to those employed in adult SLE.

Neonatal lupus usually occurs in babies of mothers with anti-Ro (SSA) and anti-La (SSB) antibodies (presence of both is more specifically correlates with CHB). Mothers may be asymptomatic. It may present as a transient syndrome with cutaneous lesions like annular lesions, malar erythema and discoid lesions either immediately after birth or within

the first few months of life. The cutaneous lesions may clear with the disappearance of maternal antibodies. Treatment is usually not required. Thrombocytopenia, haemolytic anaemia and leucopenia also can occur. Complete heart block can also occur which needs early delivery and pacing in 50% of cases. Nephritis does not seem to occur.

The risk of a second baby with CHB being born to a mother with neonatal lupus is only about 10%. It is not worthwhile to treat the pregnant mother with plasmapheresis and dexamethasone in an attempt to prevent the recurrence. When foetal monitoring does reveal presence of CHB and hydrops in foetus, dexamethasone and plasmapheresis may succeed in controlling CHF but not CHB.

The revised ACR classification criteria (1997) for SLE can be used for children, too.

**Table 8 Laboratory features Indian children with SLE**

Parameter	Northern India (n = 83) <sup>26</sup>	Southern India (n = 59) <sup>27</sup>
Anaemia	NA	51%
Leucopenia	26%	18%
Thrombocytopenia	14%	12%
Haemolytic anaemia	13%	0%
Proteinuria	79%	49%
ANA	100%	100%
Anti-DSDNA	65%	92%
Low C3	80%	58%

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