MANAGEMENT PLAN OF SYSTEMIC LUPUS ERYTHEMATOSUS — A FLOW CHART

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SYNOPSIS

A therapeutic management plan consisting of three steps has been devised for the treatment of systemic lupus erythematosus (SLE). Although the treatment of any single patient should be individualized we believe such a system offers a proper balance between the severity of the disease on one hand and morbidity and mortality associated with treatment on the other. It gives adequate guide-lines on the various modalities of treatment, reduction of drug dosage and monitoring of disease activity for the interested physicians.

Systemic lupus erythematosus (SLE) is not an uncommon disease in Singapore. Although no specific figures are available most medical departments see about 10-20 new cases per year. The high incidence of the disease in certain racial groups has been highlighted in a number of scientific communications. Studies conducted in New York (Siegel and Lee, 1968), San Francisco (Fessel, 1974) and Jefferson City, Alabalma (Siegel et al, 1970) attested to the high incidence of the disease in Blacks and Puerto Ricans compared to Whites. In a study in Hawaii (Serdula and Rhoads, 1979) comparing the prevalence of SLE in Orientals with other ethnic groups, the age-adjusted prevalence rates per 100,000 population were White 5.8, Chinese 24.1, Filipino 19.9, part-Hawaii 20.4 and Japanese 18.2. Cameron (1977) found that 15 of 44 of his patients with lupus nephritis were born abroad although residing in the United Kingdom. This suggests that 1/3 of patients with lupus came from groups forming no more than 3% of the total population in U.K. suggesting an incidence of about 20 times as great in these immigrant groups.

Notwithstanding the substantial progress accomplished in epidemiological and immunopathological studies in our understanding of the disease (Decker et al, 1979) the management of these patients still pose a major challenge for clinicians (Berlyne, 1977). Prior to the availability of steroids a frequent event occurring early in the course of the disease was death (Klemperer et al, 1941). The introduction of corticosteroids in the early 1950s provided effective therapy for the acute fulminant form of the disease and resulted in improved survival (Dubois et al, 1952; Soffer and Bader, 1952). Prolonged use of steroids is unfortunately associated with serious side effects. Immunosuppressants like cyclophosphamide were introduced in the early 1970s (Feng et al, 1973a). Apart from the difficulty of evaluating effects of treatment in a capricious and pleomorphic disease, the principle problem in the management of

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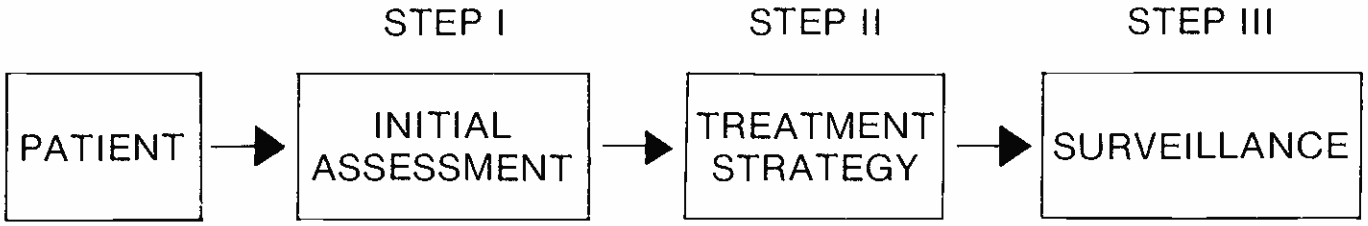
SLE is to balance the apparent benefit of drug therapy against their toxic effects. This is particularly so in patients with mild disease who may not require energetic or prolonged treatment with potentially lethal agents.

Much data and experience have been gained from the past 15 years treating about 300 patients with the disease. A therapeutic management plan involving three simple steps have been devised for these patients.

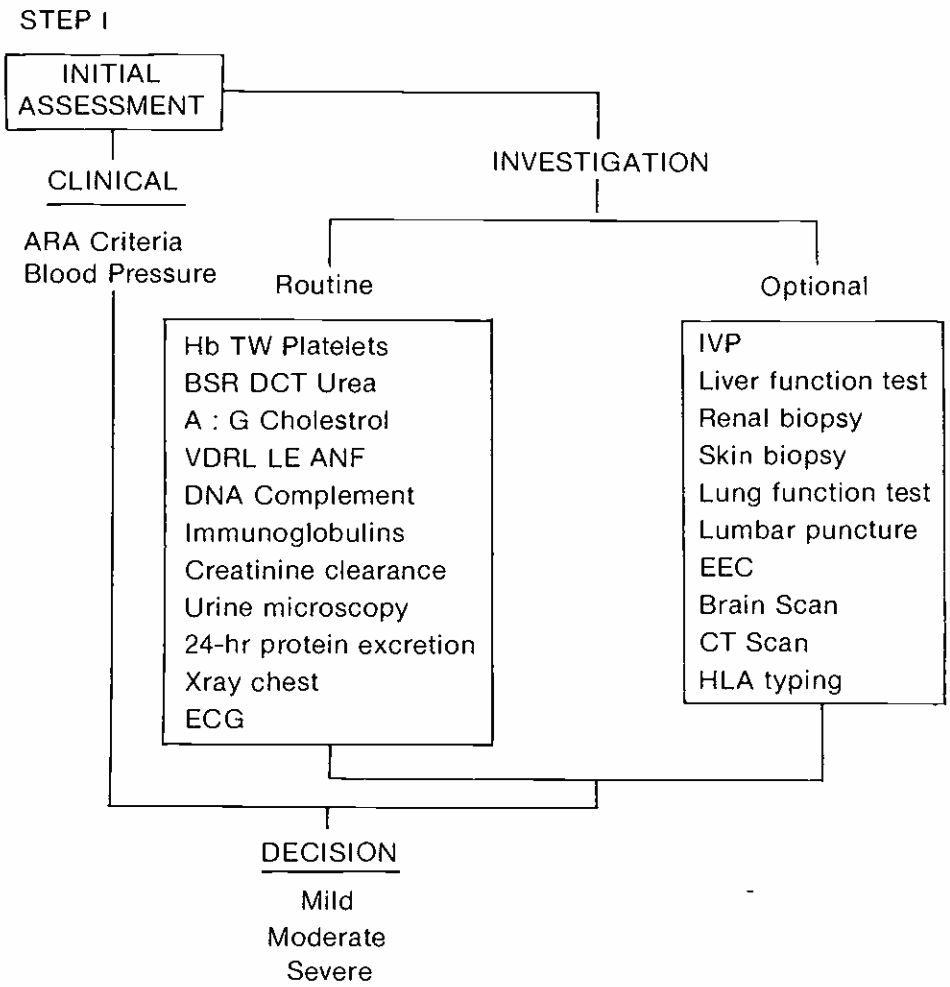
SLE MANAGEMENT PLAN — FLOW CHART



STEP ONE — Initial assessment

The first and most important step in management strategy is to categorise patients into mild, moderate and severe disease groups. This can be achieved by means of history, physical examination and investigations. Such a step can have a direct bearing both on drug therapy and prognosis. Patients with skin and musculo-skeletal involvements alone are categorized into the mild or moderate groups. Those with renal, cardiac, CNS and other major organ involvements are classified into the severe group.

Another method is to classify patients by means of renal histological changes as diffuse and membrano-proliferative changes have a worse prognosis (Baldwin et al, 1970). It is possible for patients to pass from one disease group into another or from one renal histological type into another (Ginzler et al, 1974 ; Mahajan and Ordonez, 1978).



STEP TWO — Treatment strategy.

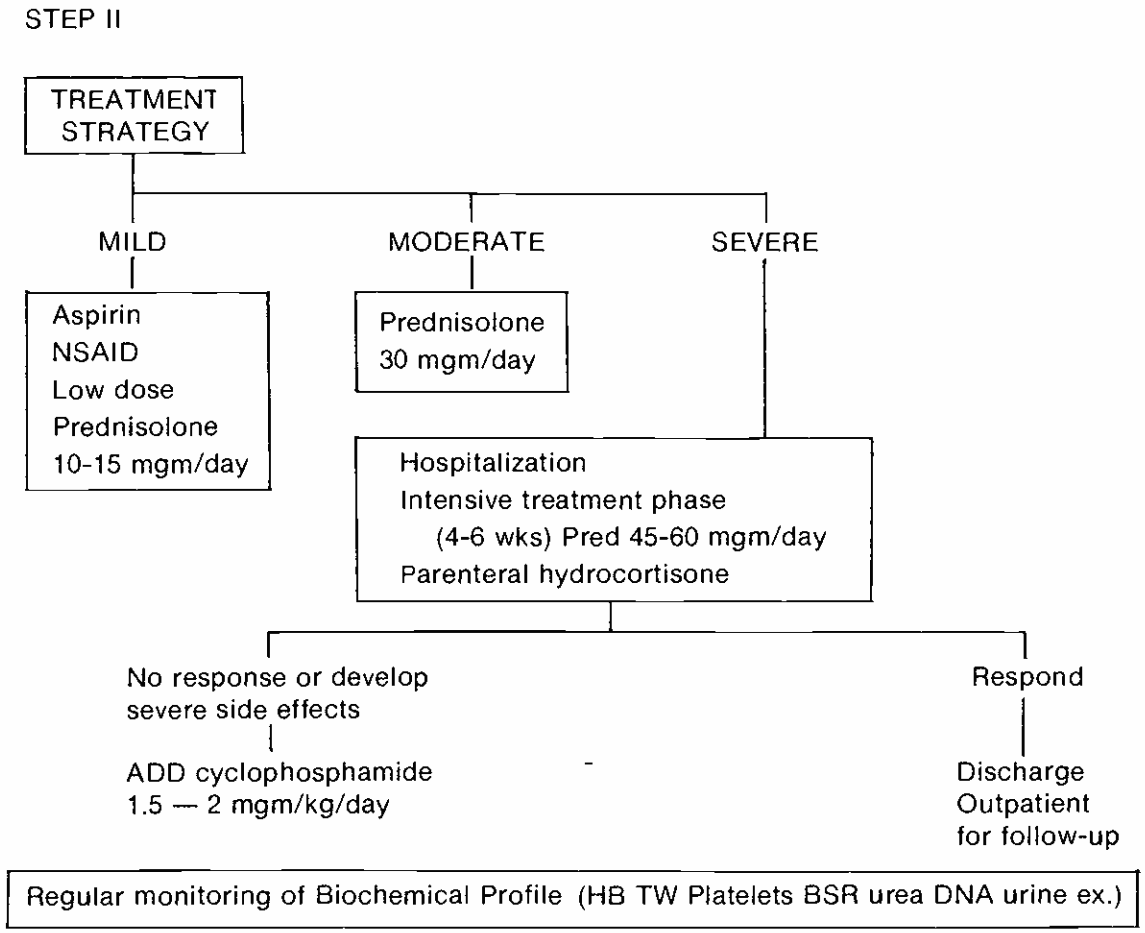
In a disease that is so protean in its manifestations and variable in its course, treatment strategy must be individualized. Many patients with mild disease can be treated symptomatically with aspirin and non-steroidal anti-inflammatory drugs. However adverse reactions have been reported with these drugs in LE patients (Sonnenblick and Abraham, 1978; Travers and Hughes, 1978). If steroids are required dosage of 10-15 mgm per day are sufficient. Once symptoms are controlled the drugs can be reduced. Our method of drug reduction is 5 mgm (one tablet) per month. This is more for the convenience of patients rather than any hard reason. Too rapid a reduction will result in exacerbation of the disease. In some patients it may be possible to stop drug therapy altogether but these patients require prolong follow-up in case of relapse.

For patients with moderate disease an initial dose of Prednisolone 30 mgm per day are required. The dose reduction regime is very much similar to above.

Patients with severe disease require special attention since mortality in this group is high. These patients are usually admitted to the hospital for an initial phase of intensive treatment. This consists of Prednisolone 45-60 mgm per day depending on body weight. In patients with severe systemic manifestations like fever, skin rash and arthritis intravenous hydrocortisone 100-200 mgm 6 hourly for 48-72 hours in addition are extremely useful. Other measures like diuretics, hypotensives, fluid balance and diet are equally important. This intensive in-hospital treatment phase usually lasts 6 weeks by which time some response should be noticeable. If patient's condition deteriorates during this period or severe side effects like hypertension, diabetes or steroid psychosis develope, cyclophosphamide 1.5-2 mgm/day is added. Careful monitoring of total white and platelets are important. This intensive treatment phase is maintained for a further period of six weeks as an outpatient. Steroids can then be reduced according to the previous regime. Immunosuppression is maintained for a period of one year. A common mistake is to reduce the drugs too rapidly over too short a period of time. Maintenance steroid dosage in this group varies from 15-5 mgm per day and majority of patients should achieve this level in about one year. Unfortunately a fair number of patients with severe disease will require relatively large doses of drugs to achieve suppression of symptoms. This group is at risk of developing infections, bone problems, vascular episodes and marrow suppression which all contribute to the high mortality in this group. Other immunosuppressive agents like azathioprine (Sztejnbok et al, 1971) and chlorambucil (Snaith et al, 1973) have also been used.

MONITORING OF DISEASE ACTIVITY.

This should form an integral aspect of treatment strategy. The single most important marker of disease activity is the anti-DNA level since it can ante-date a clinical relapse by months. Complement levels are also useful. However simple tests like haemoglobin levels, serum albumen, blood urea, urine microscopy are adequate for most cases. Majority of patients with active disease have a haemoglobin of less than 10 gms and a serum albumen of less than 3 gm even in those with no renal loss of proteins (Fries and Holman, 1975). As disease regresses these two parameters rise. BSR as a marker of disease activity is too non-specific to be of any significant weightage since it can be affected by a large number of unrelated factors like infection.



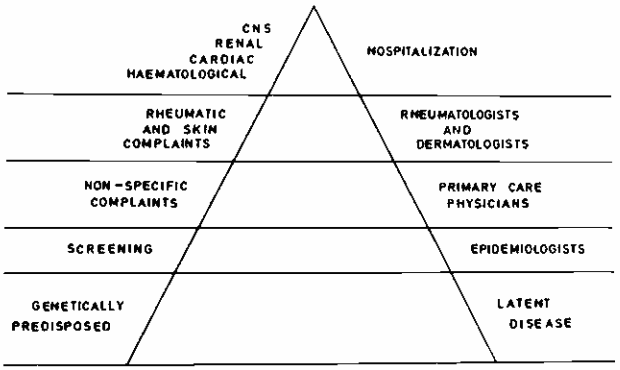
STEP THREE — Surveillance.

Intelligent and prolong medical surveillance is the "sine qua non" of adequate treatment. High risk patients like those in the severe group or pregnant patients should be seen monthly or more frequent. Those patients with mild disease could be seen once in three months. Patients should be allowed free access to her doctors any time since exacerbation and complications like infection can occur and these may prove fatal rapidly. Patient education should form an important aspect of the management plan and counselling concerning work, leisure, marriage and pregnancy are particularly important. To facilitate patient — patient and patient — doctor communication self-help groups like Lupus Clubs have been established in the United Kingdom (Lupus Society, 1979). As the disease is a chronic one characterized by remissions and exacerbations patient compliance is another important aspect. A review of our latest mortality statistics reveals that patient non-compliance such as dropping out from follow-up clinics or stopping therapy on their own contribute up to 15% of the mortality rate (unpublished data).

COMMENTS

Just as syphilis was a hundred years ago, SLE has been called the great imitator of disease. In our cohort of 300 patients about 10% presented with such diverse clinical features as repeated attacks of intestinal obstruction, congestive heart failure of unknown aetiology, unresolved pneumonia, abnormal movements and recurrent epilepsy. Five patients were referred by their doctors to the psychiatric hospital with a diagnosis of schiozophrenia. Other initial diagnosis include typhoid, tuberculosis, lymphoma, aleukaemic leukaemia, fever of unknown origin, meningitis, subacute bacterial endocarditis and hysteria. Hence diagnosis of SLE as characterized by the classical triad of fever, rash and joint pains can be simple on the one hand or notoriously difficult on the other.

The other interesting aspect of the disease is the mortality rate. Reports in the literature especially from the United States suggest a significant reduction through the last decade (Dubois et al, 1974). Yet local mortality and those from the U.K. (Cameron, 1977) is still considerable. A survey of 42 patients followed up for 9 years locally gave a five year survival rate of 67% (unpublished data). This could best be explained by the "Lupus Iceberg" phenonmenon — Figure 1. Patients seen in institutions consist essentially of the upper two strata of the iceberg — namely those with renal, skin and musculo-skeletal manifestations. A large reservoir of patients are not seen in hospital practice. Because of mass screening procedures and greater use of laboratory investigations we believe majority of LE patients in the United States come from the lower strata of the iceberg. The inclusion of patients with mild disease must dilute the mortality statistics.



THE "LUPUS" ICEBERG

STEP III

SURVEILLANCE

Mild and Moderate
Symptoms subside reduce Pred 5 mgm (1 tablet) every month to maintain dose of 5 mgm daily or e.o.d.

Severe group — Continue intensive treatment phase for further 6 weeks as outpatient.
Then reduce Prednisolone as above
Continue immunosuppression for 1 year
Maintenance dose of Prednisolone varies from 5 mgm daily to 15 mgm a day

AIMS
1. Titrate drug dosage
2. Minimize side effects
3. Monitor disease activity
4. Effective therapeutic intervention
5. Patient education

The other cause of the relatively high mortality locally is we believe ethnic. Cobb's summary of the National Centre for Health Statistic in the U.S. (1971) and Kaslow and Masi (1978) reported that SLE was particularly virulent in Black women. This racial bias is further borne out in the review of mortality statistics of the disease in different ethnic groups in the United States and Hawaii. Age-adjusted SLE mortality rates per million population is as follows:— U.S. White 3.04, U.S. non-White 8.82, Hawaii White 1.89, Hawaii non-White 14.5 (Serdula and Rhoads, 1979).

CONCLUSION

SLE is the commonest rheumatic disease requiring hospitalization in Singapore.

Despite advances made in the therapy of the disease mortality is still substantial especially in the severe form. The three commonest causes of death are renal failure, central nervous system involvement and infection (Feng et al, 1973 b).

This relatively high mortality could be explained by the fact that we see a more severe subset of patients. Racial and hence genetic factors are probably important.

SLE is a chronic disease characterized by remissions and exacerbations. Patient education and compliance play an integral part in the total management plan. For doctors patience, perseverance and attention to detail are important. Some features of the disease like renal failure do not show response until 6-12 weeks of continuous therapy.

We believe a systemic approach to the problem can help in some way reduce the overall mortality of the disease.

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