# INTRODUCTION

Systemic lupus erythematosus or (SLE) is a chronic, relapsing autoimmune disease that can affect various organs, such as the skin, joints, kidneys, and serosal membranes. Lupus disease is of unknown etiology but is thought to be a failure of the regulatory mechanisms of the autoimmune system. Lupus symptoms include swollen joints, extreme fatigue, skin rashes, and sensitivity to sunlight. **(Rahman and Isenberg, 2008).**

Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factor.s **(Rahman and Isenberg, 2008).**

Lupus affects people of all ages, including infants, children and older adults, but it's most often diagnosed in women between the ages of 15 and 40, lupus is more common in blacks, Hispanics and Asians **(Ferri, 2009).**

A patient in whom SLE is diagnosed by age 20 years still has a 1 in 6 chance of dying within 15 years, most often from lupus or infection **(Gladman and Urowitz, 2007).**

Lupus nephritis, one of the most serious manifestations of SLE, usually arises within 5 years of diagnosis. Lupus nephritis

is histologically evident in most patients with SLE, even those without clinical manifestations of renal disease. The symptoms of lupus nephritis are generally related to hypertension, proteinuria, and renal failure. With the advent of more aggressive immunosuppressive and supportive therapy, rates of renal involvement and patient survival are improving. **(Dooley, 2007).**

Autoimmunity plays a major role in the pathogenesis of lupus nephritis. The immunologic mechanisms include production of autoantibodies directed against nuclear elements. These autoantibodies form pathogenic immune complexes. Deposition of these immune deposits in the kidneys initiate an inflammatory response by activating the complement cascade and recruiting inflammatory cells that can subsequently be observed on biopsy specimens **(D'Agati and Appel, 2007).**

Glomerular thrombosis is another mechanism that may play a role in pathogenesis of lupus nephritis, mainly in patients with antiphospholipid antibody syndrome, and is believed to be the result of antibodies directed against negatively charged phospholipid-protein complexes **(D 'Agati and Appel, 2007).**

Renal biopsy should be considered in any patient with SLE who has clinical or laboratory evidence of active nephritis, especially upon the first episode of nephritis. It may be useful in

patients with recurrent episodes of nephritis, depending on the clinical circumstances. By revealing the histological pattern and stage of disease (activity and chronicity), renal biopsy is useful in determining prognosis and treatment **(Dooley, 2007).**

The current international society of nephrology (ISN) pathologic classification divides the glomerular disorders into different patterns or classes. Being the mildest: Minimal mesangial lupus nephritis (class I), mesangial proliferative lupus nephritis (class II), focal proliferative lupus nephritis (class III),diffuse proliferative lupus nephritis (class IV), segmental (IV.s) and global (IV.g), membranous lupus nephritis (class V), advanced sclerosing lupus nephritis (classVl) **(Weening et al, 2004).**

The principal goal of therapy in lupus nephritis is to normalize renal function or, at least, to prevent the progressive loss of renal function. Therapy differs depending on the pathologic lesion **(Dooley., 2007).**

Corticosteroid therapy should be instituted if the patient has clinically significant renal disease. Use of immuno-suppressive agents, particularly cyclophosphamide, azathioprine, or mycophenolate mofetil, if the patient has aggressive proliferative renal lesions, as they improve the renal outcome.

They can also be used if the patient has an inadequate response or excessive sensitivity to corticosteroids **(Houssiau and Ginzler, 2008).**

# AIM OF THE WORK

The aim of this work is to compare the outcome of Lupus Nephritis patients regarding the achievement of complete remission or the achievement of partial remission or failure of therapy after 3 month of induction therapy with two different immunosuppressive regimens in single Egyptian centre.

# SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease that primarily affects young females. The primary pathological findings in patients with SLE are those of inflammation, immune complex deposition and vasculopathy **(Robak, et al., 2009).**

SLE remains a clinical enigma for both patients and physicians due to its unpredictable course. In many cases, this disease may be mild and patients may live a normal life, whereas in many others, it is a devastating dis- ease process. For this reason, a multidisciplinary management approach is often necessary for SLE patients.**(Askanase et al, 2012).**

## Epidemiology of SLE:

The life expectancy of such patients is improved from an approximate 4 year survival rate of 50% in the 1950s to a 15-year survival rate of 80% in 2008 **(Rahman and Isenberg, 2008).**

Even so, a patient in whom lupus is diagnosed at 20 years of age still has a 1 in 6 chance of dying by 35 years of age, most often from lupus or infection **(Gladman and Urowitz, 2007).**

Later, myocardial infarction and stroke become important causes of death **(Gladman and Urowitz, 2007),** this bimodal pattern of mortality in lupus was recognized more than 30 years ago **(Rahman and Isenberg, 2008).**

## Pathogenesis:

The imbalance of T-helper 1 (Th1)/Th2 cells is critical in the pathogenesis of SLE. The T-cell immunoglobulin mucin (TIM) proteins comprise a family of cell surface molecules expressed on T cells that regulate Th1- and Th2-cell-mediated immunity. Recent work has found increased expression of TIM-1 and TIM-3 ligand (galactin-9) mRNA in SLE patients and implied that TIM proteins might be involved in the pathogenesis of SLE **(Li, Chen et al. 2011).**

Cytokine patterns might also be important in the pathogenesis of lupus. Investigations have drawn attention to the over expression of the type I interferon pathway in patients the so called interferon signature **(Hau et al., 2006).**

## Predisposing factors:

### *1. Gender& Race:*

SLE seems to affect people of all races, genders, and ages, with a higher peak of incidence/prevalence among African Americans and African Caribbeans, with a predilection for women in their third to fourth decades of life. **(Laustrup, 2009).**

Few data from Asia are available: the prevalence from 24 different Asian countries usually ranges from 30 to 50 per 100, 000 population, whereas incidence rates, as re- ported from only 3 countries, varied from 0.9 to 3.1 per 100, 000.**( Osio-Salido , 2010).**

The role of sex hormones on autoimmunity has been most extensively evaluated in SLE patients: as the female gender represents a strong risk factor linked to both the cause and pathology of the disease. The tendency for lupus flares during pregnancy and remissions after menopause or cyclophosphamide induced ovarian fai1ure; suggest that female sex hormones are crucial regulators of lupus activity **(Peeva, et al., 2005).**

## *2. Genetic susceptibility:*

The concordance rate for lupus is 25% among monozygotic twins and approximately 2% among dizygotic twins **(Sullivan, 2000);** these rates indicate that a genetic contribution is important. But it is not sufficient to cause the disease. Many genes that probably contribute to lupus have been identified by means of whole-genome scans from families in which multiple members have lupus **(Namjou, et al., 2007).**

Some single-nucleotide polymorphisms seem to predispose to particular clinical subsets of SLE; for instance, a single-nucleotide polymorphism in the STAT4 gene seems to predispose to high titer of anti-DNA autoantibodies, nephritis, and antiphospholipid syndrome. **(Svenungsson, 2010).**

## *3. Environmental factors:*

The possible explanations for differences of susceptible genetic factors between populations could be different genetic backgrounds, contribution of gene-gene or gene-environment

interaction, and the relation between marker and causal variants **(Lee and Bae, 2010).**

***(a) Ultra violet light:***

Photosensitivity shows a strong association with manifestation of all CLE subtypes, and abnormal reactivity to UVL is an important factor in the pathogenesis of this disease **(Kuhn and Beissert, 2005).**

The usefulness of photosensitivity as a criterion for the classification of SLE by the American College of Rheumatology has been questioned **(Albrecht et al., 2004).**

In several reports, a potentially crucial role in the initiation of the autoimmune reaction cascade has been attributed to UV-induced keratinocyte apoptosis **(Kuhn and Beissert., 2005).**

***(b) Drugs:***

Drugs that induce lupus also induce auto-antibodies in a much higher frequency. By far the highest risk drugs are procainamide and hydralazine, with approximately 20% incidence for procainamide and 5-8% for hydralazine during 1 year of therapy at currently used doses. The risk for developing lupus-like disease for the remainder of the drugs is much lower, considerably less than 1% of treated patients. Quinidine can be

considered moderate risk while sulfasalazine, clorpromazine, penicillamine, methyldopa, carbamazepine, acebutalol, isoniazid, captopril, propylthiouracil and minocycline are relatively low risk **(Rubin et al, 2004).**

Drugs associated with sub acute cutanous lupus erythromatosus include particularly calcium channel blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, terbinafine and the recently reported tumour necrosis factor (TNF)-alpha antagonists. Drug-induced CCLE is very rarely described in the literature and usually refers to fluorouracile agents or TNF-alpha antagonists **(Marzano et al., 2009)**

***Infection:***

It is believed that SLE occurs when an environmental trigger acts on a genetically predisposed individual, leading to a loss of tolerance towards native proteins. Viruses such as cytomegalovirus (CMV), Epstein-Barr (EBV) and parvovirus B19 are frequently involved as environmental triggers in SLE autoimmunity ***(*Zandman-Goddard and Shoenfeld, 2005*).***

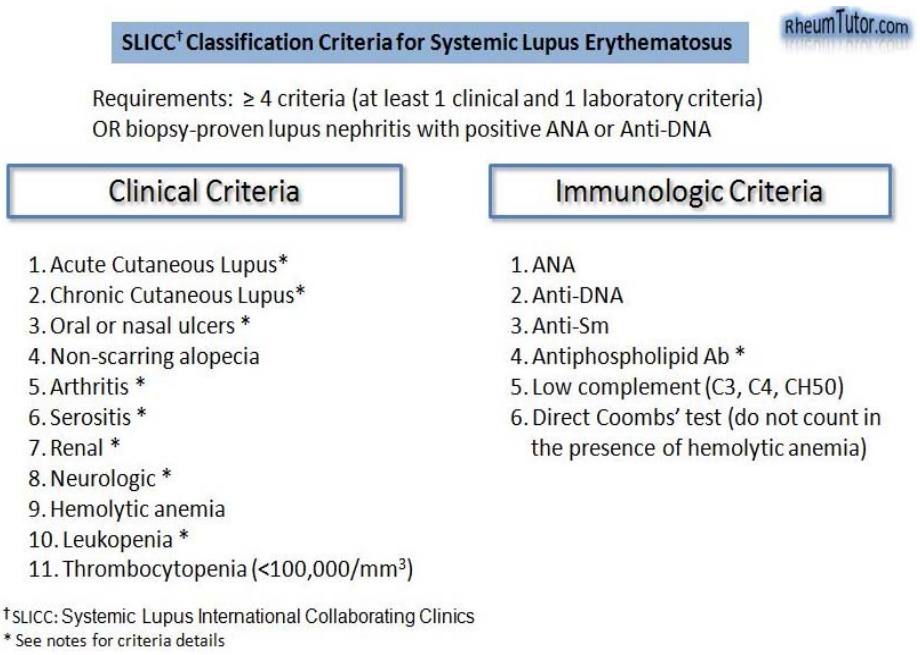
There is a temporal relation between hepatitis B vaccination and the appearance of systemic lupus erythematosus. Systemic lupus erythematosus related to vaccine may differ from idiopathic systemic lupus erythematosus in its clinical presentation and may resemble drug-induced systemic lupus

erythematosus. Thus, physicians should be alerted to this potential association, its possible long latency period and unique presentations ***(*Agmon-Levin et al., 2009*).***

***Hormonal:***

In women, dehy- droepiandrosterone (DHEA), testosterone, and progesterone were found significantly lower in SLE patients compared with controls, whereas estradiol and prolactin were higher. Conversely, in men, DHEA may be low, progesterone un- known, and testosterone and estradiol normal, whereas prolactin was high. Further studies have also highlighted, for instance, that in breastfeeding women the incidence of SLE decreased, 84 whereas nulliparous women seemed to run a higher risk of developing SLE **(Ulff-Moller CJ, 2009).**

## Diagnosis:




## Clinical Presentation of SLE:

### *Constitutional symptoms:*

Malaise, arthralgia, myalgia, fever (usually low grade), and weight loss are common manifestations of active SLE. Some patients will have high temperatures (>40°C [104°F]). Even with very high fever, shaking chills are unusual; when present, they suggest infection. Like the organ- specific manifestations of lupus, the systemic symptoms vary considerably during the day and over weeks.

In approximately one third of lupus patients, sun exposure, usually intense, will induce systemic flare. Sun

exposure that is mild or of short duration does not harm most patients **(Lockshin, 2008).**

***Musculoskeletal involvement:***

Musculoskeletal signs/symptoms usually include arthralgia, arthritis, osteonecrosis avascular necrosis of bone, and myopathy. The arthritis and arthralgias of SLE tend to be migratory, usually involving symmetrically small joints, such as knees, carpal joints, and fingers, especially the proximal interphalangeal joint. All joints, however, may be affected by SLE. Also, periarticular structures can be inflamed, leading to tendonitis, tenosynovitis, and tendon rupture. Avascular necrosis can also occur, causing joint pain and disability, mostly in larger joints, such as hip and knee **(Grossman, 2009).**

Joint symptoms occur in over 90 percent of patients at some time during the illness and are often the earliest manifestation **(Greco et al., 2003).**

Joint pain (arthralgia) is present in most SLE patients. It is symmetrical, flitting and polyarticular, with little morning stiffness **(Greco et al., 2003).**

***Skin and mucosal involvement:***

The skin is one of the most affected organs in SLE patients (85%) and can be the only organ involved, as in

cutaneous LE. Clinically, the mucocutaneous manifestation in SLE patients may be divided in 3 major groups: (1) chronic cutaneous LE (CCLE), (2) subacute cutaneous LE (SCLE), and (3) acute cutaneous LE (ACLE). The associated disease severity is usually evaluated by the cutaneous LE disease area and severity index.

Diagnosis of mucocutaneous SLE needs to be made via histopathologic and immunohistological examinations. Cutaneous manifestations include a wide broad spectrum of different clinical features, which are considered important for diagnosis (discussed later). The main cutaneous manifestations are as follows:

- Malar rash consists of an erythematous rash over the cheeks and nasal bridge, with a butterfly shape and which sometimes can be painful or pruritic

- Discoid lesions (localized and generalized) are disc-shaped lesions with erythematous plaques of different size with follicular hyperkeratosis. These lesions spread centrifugally, may merge, and are sometimes painful and pruritic.

-Some lesions may become hypertrophic. Rarely they may transform into skin cancer. These lesions represent the most common form of cutaneous LE, called discoid LE.