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INTRODUCTION Systemic lupus erythematosus (SLE or lupus) is one of the most common systemic autoimmune connective tissue diseases. It is characterized by a highly variable clinical presentation that may range from mild skin involvement to life-threatening multi-organ failure^{1,2}. Some authorities from the government of a country such as The Japanese Ministry of Health, Labor and Welfare even designated SLE as an intractable disease because there is no established way to cure the existing disease, but with appropriate management³.

Systemic lupus erythematosus is, without a doubt, a debilitating and life-altering illness. Systemic lupus erythematosus may cause severe symptoms such as discomfort, excessive weakness, hair loss, cognitive problems, and physical impairments; many people with SLE develop cardiovascular disease, strokes, disfiguring rashes, and sore joints; and some people with SLE have no apparent symptoms⁴. The etiology of SLE has not yet been elucidated in detail, although genetic factors and environmental factors are thought to play a role in its development⁵. The discrepancies of rates (i.e.,

higher rates in certain ethnic groups) are due to genetic factors and environmental factors such as smoking and dietary habits⁶. The history of SLE goes back even further than the 4th-century. Hippocrates recorded the documented case of lupus in 400 BC⁷. The four main types of lupus are neonatal and pediatric lupus erythematosus (NLE); cutaneous or discoid lupus erythematosus (CLE); drug-induced lupus erythematosus (DILE); and SLE, as presented in Table I. Systemic lupus erythematosus can be divided into three periods: the classical period, the neoclassical period, and the modern period. Each period is marked with important discoveries that have allowed a better understanding of this disease⁸.

This mini-review will discuss several things related to SLE and its clinical approach, including epidemiology, pathogenesis, diagnosis, and treatment, based on a review of the latest related studies. **EPIDEMIOLOGY** The SLE is seen worldwide and occurs in all racial or ethnic groups, although regional variations in frequency and severity have been reported⁹. An estimated 5 million people worldwide have some form of lupus disease. The 70% of lupus cases diagnosed are SLE, 20% of people with lupus will have a parent or sibling who already has lupus or may develop lupus, and about 5% of the children born to individuals with lupus will develop the illness^{10,11}.

Studies have shown that the incidence rate of SLE around the world is about 1 to 10 per 100000 people/years¹², while the prevalence rates range 3.2 cases per 100000 persons, with the highest prevalence reported in India, and it appears to be increasing as the disease is recognized more readily and survival increases^{13,14}. In the US, people of African, Hispanic, or Asian ancestry as compared to those of other racial or ethnic

groups, tend to have an increased prevalence of SLE and greater involvement of vital organs¹⁵⁻¹⁷. Table I.

The four categories of lupus and their descriptions^{18,19}

Lupus types	Descriptions
Neonatal and pediatric lupus erythematosus (NLE)	Neonatal lupus erythematosus is a rare condition that affects infants of women who have lupus and is caused by antibodies (Abs) from the mother acting upon the infant in the uterus. At birth, the infant may have a skin rash, liver problems, or low blood cell counts, but these symptoms disappear completely after several months with no lasting effects ^{20,21} .
Cutaneous or discoid lupus erythematosus (CLE)	This form of lupus is limited to the skin. Although CLE can cause many types of rashes and lesions (sores), the most common discoid rash is raised, scaly, and red, but not itchy.

Areas of rash appear like disks or circles. Another typical e.g., of CLE is a rash over the cheeks and across the bridge of the nose. Hair loss and changes in the pigment, or color, of the skin are also symptoms of CLE²².

Drug-induced lupus erythematosus (DILE) The symptoms of DILE are similar to those of SLE, but it rarely affects major organs. DILE is a lupus-like disease caused by certain prescription drugs like Hydralazine, Procainamide, Isoniazid, and others²³.

Systemic lupus erythematosus (SLE) Systemic lupus erythematosus is the most common form of lupus—it can be mild or severe—some of the more severe complications involving major organ systems.

Inflammation of the kidneys can affect the body's ability to filter waste from the blood. Inflammation of the nervous system and the brain's blood vessels can cause high fevers, seizures, behavioral changes, confusion, headaches, and strokes²⁴.

PATHOGENESIS The etiology of SLE is unknown to date. Many factors contribute to SLE development, including genetic, environmental, hormonal, and immunoregulatory factors²⁵⁻²⁷, as described in Figure 1. Certain risk factors have been identified and shown to contribute to disease susceptibility or activate the immune system causing an inflammatory response, ultimately leading to the development of the disease²⁸.

Genetic factors influence predisposition to SLE. The female predominance in SLE may be explained, in part, by the contribution of certain hormones. Environmental factors, such as smoking, exposure to ultraviolet light, viral infections, and specific medications (e.g., sulfonamide antibiotics) are known to trigger SLE²⁹. The pathogenesis of SLE is complex, with contributions from many components of the immune system.

With the underlying genetic predisposition and in response to various triggers, the balance of the immune system shifts towards reacting against it rather than self-tolerance³⁰. The T and B cells become activated, leading to antibody production

and eventual immune complex formation. These complexes circulate and deposit in critical tissues causing organ injury³¹. / Figure 1. Factors involved in the pathogenesis of SLE³² DIAGNOSIS According to the American College of Rheumatology, the diagnosis of SLE is based on the clinical and laboratory criteria³³, as summarized in Table II.

The diagnosis of SLE requires four or more of the following eleven criteria during the observation³⁴. Since the early signs and symptoms of SLE are non-specific and can mimic those of other diseases, for example, rheumatoid arthritis, glomerulonephritis, anemia, or dermatitis, it can be challenging to diagnose. The accuracy of diagnosis and early recognition of SLE is essential^{35,36}. An algorithm for the diagnosis of the SLE shows in Figure 2. Table II.

Diagnosis of SLE based on clinical and laboratory criteria

Problems	Descriptions
_ Malar rash	_ Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
_ Discoid rash	_ Erythematous, raised patches with adherent keratotic scaling and follicular plugging; possibly atrophic scarring in older lesions.
_ Photosensitivity	_ Skin rash as a result of unusual reaction to sunlight, as determined by patient history or physician observation.

_ Oral ulcers	_ Oral or nasopharyngeal ulceration, usually painless, observed by the physician
_ Arthritis	_ Non-erosive arthritis involving two or more peripheral joints, characterized by swelling, tenderness, or effusion.
_ Serositis	_ Pleuritis, by the convincing history of pleuritic pain, rub heard by a physician, or evidence of pleural effusion; or pericarditis documented by electrocardiography, rub heard by a physician, or evidence of pericardial effusion.
_ Renal disorder	_ Persistent proteinuria, 0.5 g/day or >3+ if quantitation is not performed; or cellular casts (maybe red blood cell, hemoglobin, granular, tubular, or mixed cellular casts).

_ Neurologic disorder	_ Seizures or psychosis occur in the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance).
_ Hematologic disorder	_ Hemolytic anemia with reticulocytosis; or leukopenia, $4.0 \times 10^9/L$ on two or more occasions; or lymphopenia, $1.5 \times 10^9/L$ on two or more occasions; or thrombocytopenia, $100 \times 10^9/L$ in the absence of offending drugs.
_ Immunologic disorder	_ Antibody to a double-stranded deoxyribonucleic acid antigen (anti-dsDNA) in abnormal titer; or presence of antibody to Smith nuclear antigen (anti-Sm); or positive finding of antiphospholipid Abs based on an abnormal serum level of Immunoglobulin (Ig) G or Ig M anticardiolipin Abs, a positive test result for lupus anticoagulant using a standard method, or a false positive serologic test for syphilis that is known to be positive for at least six months and is confirmed by negative Treponema pallidum immobilization or fluorescent treponemal antibody absorption test.

__Antinuclear antibodies __An abnormal antinuclear antibodies (ANA) titer by immunofluorescence or an equivalent assay at any time and in the absence of drugs known to be associated with DILE. __

/ Figure 2. Factors involved in the pathogenesis of SLE37

TREATMENT There is no cure for SLE at present, but the condition is most often very treatable and usually responds well to some different types of drugs-especially when treatment is started in the early stages of the disease³⁸. Most of the drugs described in Table III were initially developed for other diseases but were later found to be helpful in SLE³⁹. There are many levels of severity and complications of SLE that require management.

Treatment is dependent on presentation, and options include antimalarials, glucocorticoids, immunosuppressants, and biologics. NSAIDs may also be used to treat inflammation and pain⁴⁰. In addition to these therapies, the current development of treatments for SLE has primarily led to the development of monoclonal antibodies⁴¹, as presented in Table IV. Two newer drugs (rituximab and belimumab) are now sometimes used for the treatment of severe SLE⁴². Also, several small-molecule inhibitors have shown promising progress in the treatment of SLE.

Research is continuing to find out which patients respond best to these drugs⁴³⁻⁴⁵.
Table III. Common medications to control SLE Agents _ Descriptions _
_ NSAIDs
_ Over-the-counter NSAIDs, such as naproxen sodium and ibuprofen may be used to treat pain, swelling, and fever associated with SLE. Stronger NSAIDs are available by prescription.
_ Anti-malarial _ Drugs commonly used to treat malaria, such as hydroxychloroquine, affect the immune system, and decrease the risk of SLE flares. _
_ Cortico-steroids _ Prednisone and other types of corticosteroids can counter the inflammation of SLE.

High doses of steroids such as methylprednisolone often used to control serious disease that involves the kidneys and brain. _
_ Immuno-suppressants _ Drugs that suppress the immune system may be helpful in serious cases of SLE e.g. azathioprine and methotrexate. _
_ Biologics _ Biological agents used in the treatment of SLE include rituximab and belimumab, both monoclonal antibodies. Rituximab targets B cells and is used to treat renal and CNS presentations of SLE. This agent is recognized as an II- or III-line agent for active disease. Belimumab targets the B cell-activating factor B-lymphocyte stimulator.

Belimumab is approved for use in active disease in conjunction with standard therapies including glucocorticoids, antimalarials, NSAIDs, mycophenolate mofetil, and azathioprine. Other biologics, such as tumor necrosis factor inhibitors, abatacept, and tocilizumab, are also considered. _
_ Other agents _ Besides the agents listed above, there are other agents used off-label to treat SLE. These include disease-modifying antirheumatic drugs such as methotrexate, leflunomide, and calcineurin inhibitors (tacrolimus and cyclosporine). _
_ Table IV.

Summary of new and emerging therapies or clinical trials **in the treatment of SLE** Target
_Treatment _Status _B cells _BAFF/ APRIL _Belimumab _Approved for non-renal SLE;
Ongoing phase-IV for efficacy, safety, and tolerability; Ongoing phase-III in combination
with Rituximab. _ _ _Tabalumab _Phase-III without significant effect (terminated). _ _
_Blisibimod _Phase-III did not meet the SRI-6 primary endpoint. _ _ _Atacicept
_APRIL-SLE study terminated due to increased infection rate; ADDRESS-II study has an
acceptable safety profile. _ _CD20 _Rituximab _Phase-III failed (nephritis and
non-nephritis). _ _ _Ocrelizumab _Phase-III trial completed.

_ _CD22 _Epratuzumab _Phase-III failed. _ _CD19 _XmAb5871 _Phase-II trial. _
_Proteasome inhibitors _Bortezomib _Phase-II trial. _ _Intracellular signaling _ _Btk
_M2951 _Ongoing phase-II trial. _ _ _Fenebrutinib _Ongoing phase-II trial. _ _mTOR
_N-acetylcysteine _A small study showed a decrease in SLEDAI, with no further
development. _ _ _Rapamycin _An open-label study showed an effect on BILAG. The
larger study was planned. _ _JAK/STAT _GSK2586184 _Ineffective interferon signature in
phase-II, safety data **do not support further** study. _ _JAK 2 _Baricitinib _Phase-II positive
data; Phase-III trial ongoing. _ _JAK3 _Tofacitinib _Ongoing Phase-I/II trial.

_ _ROCK _Fasudil _Effective in preclinical studies in a patient with Raynaud's
phenomenon, Phase-III completed with un-interpretable data. _ _Co-stimulation _
_CD40:CD154 _Dapirolizumab _Ongoing phase-II trial. _ _ _BI 655064 _Ongoing phase-II
trial. _ _CD28: B7 _Abatacept _Ineffective in Phase-III in nephritis and general SLE. _ _
_Lulizumab _Phase-II trial terminated-failed to meet protocol objectives. _ _Cytokines _
_IFN- α _Sifalimumab _The limited effect in phase-II and III. No further development. _ _
_Rontalizumab _Phase-II without significant results. _ _ _Anifrolumab _Phase-II positive
data; 2 Phase-III trials ongoing (one reported negative). _ _ _IAGS-009 _Completed
phase-I, no data released. _ _ _JNJ-55920839 _In recruiting phase.

_ _ _IFN α -k _Successful phase-I; ongoing phase-II trial. _ _Interleukin (IL)-2 _Aldesleukin
_Ongoing open-label phase-II trial. _ _ _AMG 592 _Ongoing phase-Ib and IIa trial. _ _
_ILT-101 _Ongoing phase-II trial. _ _IL-12/23 _Ustekinumab _Met primary end-point in a
phase-II trial; ongoing phase-III trial. _ _IL-6 _PF-04236921 _Failed phase-II trial; safety
compromised. _ _ _Sirukumab _Failed phase-II trial. _ _ _MRA003US _Ongoing phase-II
trial. _ _ _Vobarilizumab _Ongoing phase-I trial. _ _IL-10 _BT063 _Ongoing phase-II trial. _
_Other _ _ _Lupuzor _Phase-III trial failed to meet the primary endpoint.

_ _ CONCLUSION **Systemic lupus erythematosus is a chronic autoimmune** inflammatory
disorder that causes **significant morbidity and mortality**. The disease is a scientifically
challenging, problematic, inspiring, and seminal, clinical syndrome. Systemic lupus

erythematosus treatment has made significant progress over the past decade; however, the management of SLE is complex, with a multitude of complications and various treatment options. Patients require a comprehensive plan for care and management of complications from both the disease and therapy.

Over the past few years, scientific studies and ongoing clinical trials have shifted the paradigm with rapid advances in developing biologics and small molecules.

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