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RESEARCH ARTICLE

A REVIEW ON LUPUS NEPHRITIS: PATHOGENESIS, CLASSIFICATION, AND MANAGEMENT

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Abstract

Lupus nephritis is an autoimmune disease caused by systemic lupus erythematosus, the prevalence of SLE and the chances of developing lupus nephritis (LN) vary considerably between different regions of the world and different races and ethnicities, a number of factors like genetic, environmental and immunology lead to inflammation of kidneys which is identified by biopsy, it is classified into six types based on the level of tissue damage and it is treated by induction, maintenance, adjuvant therapy and biological therapy. Mostly immunosuppressant's, antimalarials are used.

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Introduction:-

Definition:

Lupus is an autoimmune disease in which one's own immune system attacks its cells and organs; lupus nephritis is inflammation of kidneys caused by systemic lupus erythematosus (SLE).

Epidemiology:

The prevalence of SLE and the chances of developing lupus nephritis (LN) vary considerably between different regions of the world and different races and ethnicities. A study of 208 cases of biopsy-proven lupus nephritis (176 women, 32 men): the overall prevalence was 4.4 per 100,000 population (95% confidence interval [95% CI] 3.8–5.0), 7.1 per 100,000 (95% CI 6.1–8.2) in women, and 1.4 per 100,000 (95% CI 1.0–2.0) in men. The prevalence was significantly higher among women in the ethnic subgroups: 110.3 per 100,000 population (95% CI 55.0–197.3) in Chinese patients 99.2 per 100,000 (95% CI 55.5–163.6) in Afro-Caribbean, 21.4 per 100,000 (95% CI 12.0–35.2) in Indo-Asian (Asians from the Indian subcontinent), and 5.6 per 100,000 (95% CI 4.7–6.7) in white patients. The overall annual incidence rate was 0.40 per 100,000 population per year (95% CI 0.24–0.63), with a rate of 0.68 (95% CI 0.40–1.10) in women and 0.09 (95% CI 0.01–0.32) in men. ⁽¹⁾

Etiology:

There are multiple susceptible etiologies which results in abnormal immune responses, some of the factors are:

Genetic Factors:

Disease susceptibility genes associated with lupus nephritis

Programmed cell death: FAS, DNASE1, RIG1, ATG5, and MTMR3.

Immune complex clearance: FCGR[2A,2B,3A,3B], C1Q(A,B,C), C4(A,B), CRP, MBL2, CR1, ITGAM, IKZF1.

Intra renal pathogenesis: TNFRSF1B, CCL2, CXCL8, CCR5, CXCL12, AGT, APOL1.

Adaptive immunity: HLA-DR, PTPN22, CTLA4.

Innate immunity: IFIH1, RIG1, MAVS, TREX1, MYD88, TRAF6, IRAK1, TNIP1.

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Immunologic factors:

The presence of autoantibodies in patients, including anti-dsDNA, anti-SSA (Ro), anti-SSB (La), anti-Sm and anti-RNPs, autoreactive B-lymphocytes.

Environmental factors:

UV light, Epstein–Barr virus smoking, alcohol, silica dust.

Clinical presentation of lupus nephritis^[8]

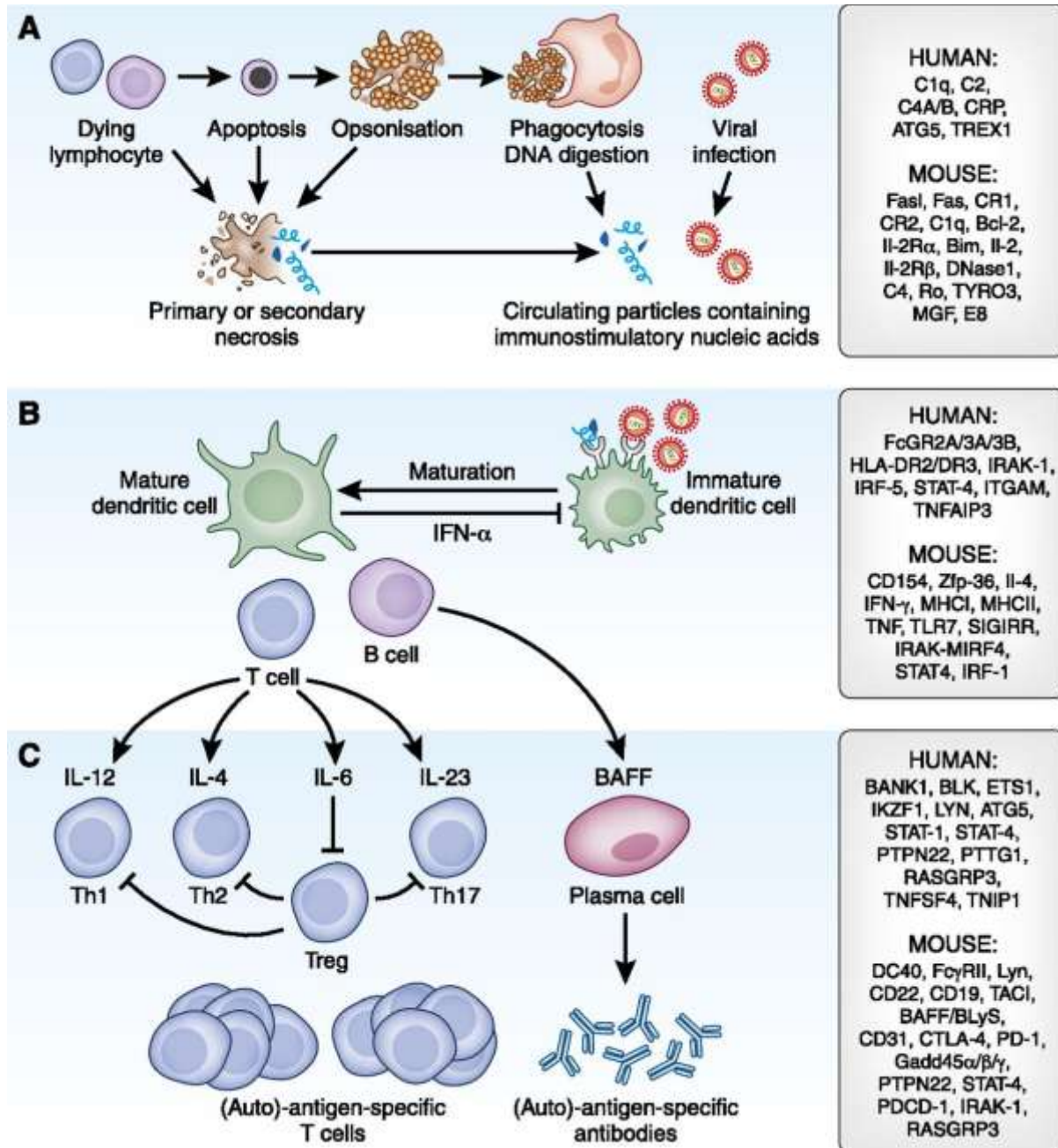
1. proteinuria
2. hematuria
3. hypertension
4. Swelling of the legs, ankles and feet.
5. Less often, there can be swelling in the face or hands^[7]
6. Weight gain
7. Dark urine
8. Frothy urine
9. The need to urinate during the night.

Prevalence of clinical manifestations in patients with lupus nephritis^[12]:

Clinical Manifestation	Approximate Prevalence, %
Proteinuria	100
Nephrotic range proteinuria/ nephrotic syndrome	50
Microscopic hematuria	80
Macroscopic hematuria	<5
Urinary red blood cell casts	30
Other urinary cellular casts	30
Renal insufficiency	60
Rapid decline in kidney function	15
Hypertension	30
Tubular abnormalities	70

Pathogenesis of lupus nephritis:**Extrarenal pathogenic mechanisms of lupus nephritis:**

1. Impaired silent cell death and dead cell removal
2. Nuclear particles mimic viruses at viral recognition receptors of the innate immune system
3. Antiviral immunity
4. Autovaccination leading to persistent antinuclear antibody production
5. Flares triggered by transient autoantigen loads or unspecific immune activation



Intrarenal Pathomechanisms of SLE-Related Nephritis^[4]

Immune Complex (IC) Formation and Classical Complement Pathway Activation:

Circulating polyclonal autoantibodies bind to intrarenal nucleosomes and other autoantigens, which leads to local complement activation, cell injury, and subsequent cytokine and chemokine secretion.

The Immune Complex Formation Site Determines Lupus Nephritis Outcomes:

The polyclonal lupus autoantibody isotopes can localize to different compartments within the glomerulus, which affects the type of histopathological lesion as well as the alterations of glomerular function. Immune complex formation in the mesangium induces mesangioproliferative glomerulonephritis (lupus nephritis classes I and II), which is often mild and rarely progresses to end-stage kidney disease. Subendothelial immune complex formation (lupus nephritis classes III and IV) causes vascular obstruction by endothelial cell swelling and clotting, which promotes a decline of glomerular filtration rate. Vascular necrosis and glomerular basement membrane ruptures

promote hematuria, crescent formation, and subsequently glomerulosclerosis. Subepithelial immune complex formation (membranous lupus nephritis class V) injures podocytes, which promotes massive proteinuria and podocyte loss-related glomerulosclerosis.

Induction of Cytokines, Chemokines, and Adhesion Molecules Recruits Leukocytes:

Leukocyte recruitment amplifies intrarenal inflammation and promotes secondary tissue injury related to tissue inflammation and drives a vicious cycle of inflammation-induced tissue injury and injury-related inflammation.

Tertiary Lymphoid Organ Formation inside the Kidney:

Local expression of lymphotoxin and homeostatic chemokines drives tertiary lymphoid organ formation at sites of chronic inflammation to promote the (auto-) immune response, e.g. by local autoantibody production.

Insufficient Regeneration and Tissue Scarring:

Attempts to heal tissue injury often create new lesions. Lesions of hyperactive repair include hyperproliferation of mesangial cells (mesangioproliferative lupus nephritis), endothelial cells (endocapillary lupus nephritis), and parietal epithelial cells (crescentic lupus nephritis). Lesions of insufficient repair include podocyte loss-related scarring (glomerulosclerosis).

Environmental Triggers of SLE Activity^[5] :

Viral infections induce IFN- α release, which triggers antiviral immunity as well as lupus disease activity. Bacterial infections have a nonspecific immunostimulatory effect, which involves a transient expansion of autoreactive lymphocyte clones. Furthermore, bacterial products stimulate intra renal immune cells and renal cells, which can trigger a transient aggravation of proteinuria and kidney damage.

Drug-induced SLE involves inhibition of methyl-transferases, a process that enhances the unmasking of endogenous nucleic acids and the activation of TLR7 and TLR9. Progesterone and estrogens stimulate the sex hormone-dependent immune regulatory pathways. Together, SLE develops from a peculiar combination of genetic variants that impair those mechanisms that normally prevent the exposure of nuclear particles to the immune system and their capacity to activate viral recognition nucleic acid receptors. The auto adjuvant activity of endogenous nucleic acids promotes an adaptive immune response against the components of the nuclear particle, a process identical to vaccination. This implies the expansion of T and B cell clones with specificities for predominantly nuclear autoantigens that account for the production of anti-nuclear antibodies, immune complex disease, and T cell-dependent tissue damage. Hormonal and environmental stimuli can enhance these processes at different levels.

Diagnosis:^[9]

X-rays of the kidneys

Blood tests^[10]:

If there is a loss of protein in the urine, a blood test can show if there is a lower level of protein in the blood. Blood tests can also show if there are imbalances of salt and water in the blood. Finally, blood tests can show the presence of antibodies-anti nuclear antibody, Antiphospholipid Antibodies, Anti-Sm, Anti-dsDNA, Anti-Ro(SSA) and Anti-La(SSB), that are typically high in persons who have lupus nephritis. Anti-C1q antibody (Ab) titers have been elevated in patients with lupus with renal involvement^[6]

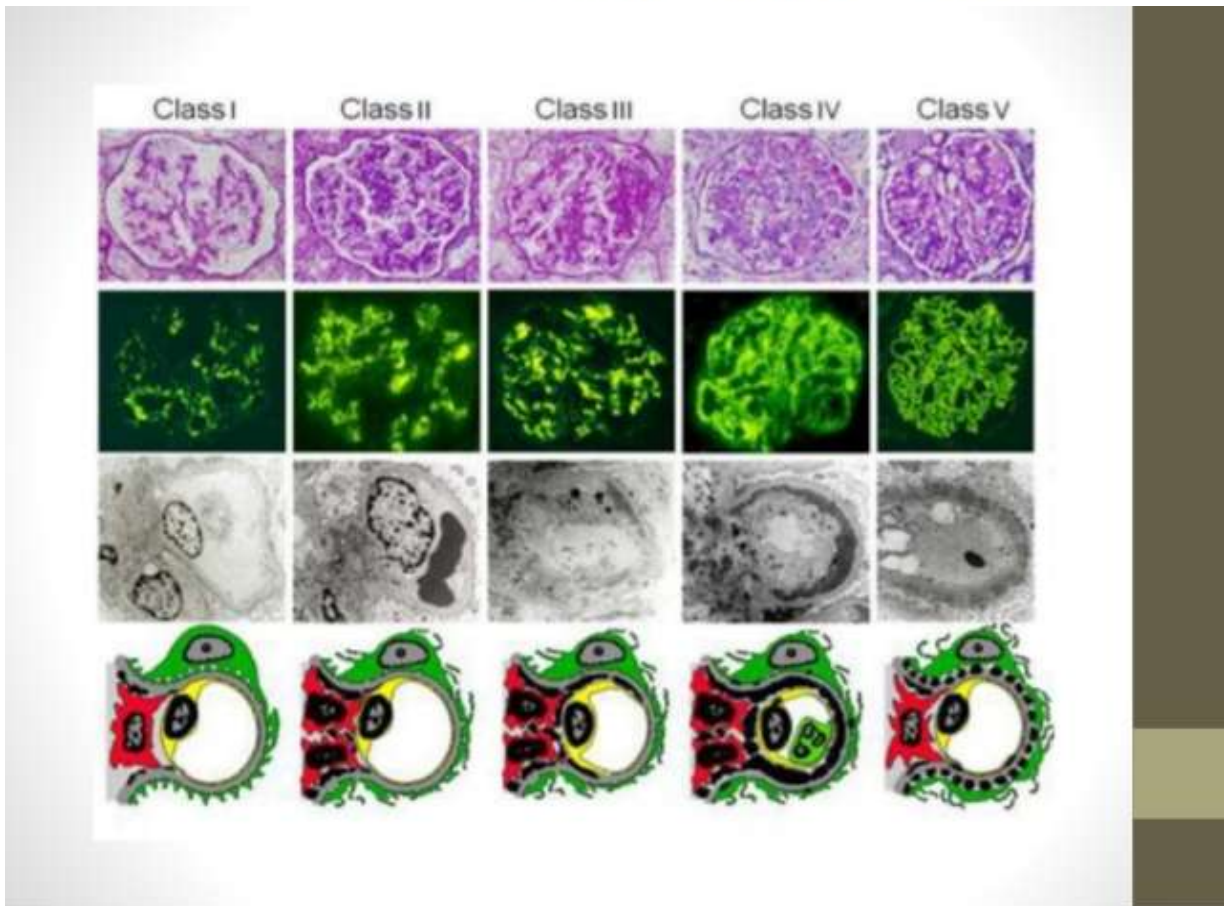
Urine tests: A urinalysis will check for the presence of red and white blood cells in the urine or high levels of Urine Protein/Microalbuminuria and Creatinine Clearance

Imaging studies: Two of these types of studies - an intravenous pyelogram and a sonogram - are usually done before a kidney biopsy. In an intravenous pyelogram, the dye is injected into the body and collects in the kidneys. An X-ray is taken that shows the outline of the kidneys with the dye. A sonogram uses soundwaves transmitted through the body and their echoes to show the shape and size of the surfaces of the kidney.

A biopsy of the kidney. This test involves taking a sample of kidney tissue to examine under a microscope. If blood and urine studies suggest lupus nephritis, a biopsy is done to confirm the diagnosis. A biopsy can also help find out how widespread and severe the kidney disease is, A biopsy is most often done by inserting a narrow needle through the skin of the back and removing a small piece of kidney.

Classification of lupus nephritis^[1]:

Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN (<50% of glomeruli) ^a
Class IV	Diffuse LN (\geq 50% of glomeruli) ^{a,b}
Class V	Membranous LN
Class VI	Advanced sclerotic LN (90% of glomeruli globally sclerosed without residual activity)

**Class I (minimal mesangial LN) and Class II (mesangial proliferative LN)^[3]:**

The high regenerative capacity of mesangial cells, mesangial expansion does not progress and usually does not cause proliferative or sclerosing glomerular injury. Disease class I includes early glomerular involvement with minimal mesangial tissue injury mediated by IC. In LN class II, injury mediated by IC is accompanied by hypercellularity and mesangial expansion. These classes are associated with a good prognosis. Treatment with immunosuppressants is generally recommended to manage extrarenal manifestations.

Class III (focal proliferative LN) and Class IV (diffuse proliferative LN) :

Proliferative LN (classes III and IV) is caused by the deposition of IC in the subendothelial space of the glomerular capillaries, either alone or in combination with the deposition of IC in the mesangial region. Sub endothelial deposition triggers the production of IFN-gamma by endothelial cells and, consequently, local inflammation and endocapillary hypercellularity. Reticular aggregates – ultrastructural findings characteristically seen in scenarios of elevated IFN-gamma secretion - may also form. Severe modes of the disease have been associated with crescentic formations stemmed from the rupture of glomerular capillary loops and leakage of mitogenic proteins (mainly

fibrinogen) into the urinary space, with subsequent involvement of the parietal epithelium. Proliferative LN presents lesions that characterize activity and chronicity.

The criteria for **activity** are endocapillary hypercellularity; glomerular neutrophils/karyorrhexis; fibrinoid necrosis; wire loop lesions and/or hyaline thrombi in the glomeruli; cellular and/or fibro cellular crescents; and interstitial inflammation.

The criteria for **chronicity** include: total score of segmental or global glomerulosclerosis; fibrous crescents; tubular atrophy and interstitial fibrosis

Involvement with active (A) and/or chronic (C) lesions in less than 50% of the glomeruli is seen in LN class III. Involvement of more than 50% of the glomeruli indicates LN class IV, which is subdivided into "S" - segmental glomerular injury^[13], i.e., injuries affecting less than half of the glomerular tufts - and "G" - global glomerular injury, i.e., injuries affecting more than half of the glomerular tufts.

Although other injuries may occur with LN, they are not used for classification purposes. Nevertheless, they may affect the choice of treatment.

Tubulointerstitial injury:

clonal expansion of B cells and plasma cells may trigger local production of antibodies and consequent increases in inflammatory response and formation of tertiary lymphoid tissue. The Deposition of IC along the tubular basement membrane also occurs. These injuries may help identify patients responsive to therapies targeting B cells, such as treatment with rituximab.

Vascular injuries are common and may affect patient prognosis. They originate from the deposition of IC in vascular smooth muscle cells and endothelial cells or by local complement activation. Five types of vascular injuries are often observed: vascular IC deposits, arterio nephrosclerosis, thrombotic microangiopathy, noninflammatory necrotizing vasculopathy, and vasculitis. Other possible events include endothelial edema, transmural vasculitis with fibrinoid necrosis, mesangiolysis or fibrin thrombi and, enlargement of the lamina rara interna of the glomerular basement membrane seen with the aid of electron microscopy. Some of these injuries may be related to manifestations of LN, including systemic hypertension, dyslipidemia, and thromboembolism. Vascular injuries may help identify patients potentially responsive to eculizumab and thrombomodulin.

Podocyte injuries are common and stem from the loss of expression of the proteins present in the slit diaphragm (nephrin and podocin) and the disorganization of the podocyte cytoskeleton, culminating with the flattening, effacement, and microvillus transformation of the foot processes. Affected patients develop marked proteinuria. Podocyte injuries may be used to identify patients potentially responsive to calcineurin inhibitors.

Crescentic injuries arise from immune deposits or direct attack by inflammatory cells. Between 30-100% of the patients with diffuse crescentic injury are positive for ANCA and/or anti-myeloperoxidase antibodies, showing overlapping SLE and ANCA-positive vasculitis. This group of injuries may help identify patients potentially responsive to plasmapheresis and monoclonal anti-C5aR antibody.

Class V (membranous LN):

LN class V originates from the subepithelial IC deposition of either immune complexes transiting through the glomerular basement membrane of immune complexes formed locally to deal with podocyte antigens. The complement system is then activated locally, usually with the formation of membrane attack complex (C5b-9), thickening of the glomerular basement membrane, and destabilization of the podocyte cytoskeleton. LN class V is often associated with nephrotic-range proteinuria with or without hematuria. This class of the disease may occur in association with proliferative LN (Class III or IV). As class V evolves to chronicity, there is typically the development of segmental or global glomerulosclerosis, without the super-imposition of proliferative lupus nephritis^[14].

Class VI (advanced sclerosing LN):

LN class VI results from the progression of lupus nephritis. In this disease class, glomerular, vascular, and tubule interstitial injuries from glomerulosclerosis are seen in more than 90% of the analyzed glomeruli.

Therapies used in the treatment of lupus nephritis^[15]

Patients who present with class I or class II mesangial disease generally have good long-term outcomes, and treatment with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is recommended for any patient with proteinuria ≥ 0.5 g/day, with the primary goal being the prevention of the progression of nephritis.

Focal or diffuse lupus nephritis (classes III-IV) confers a much greater risk of progression, potentially to ESRD, and requires more aggressive treatment with immunosuppressive medications. Treatment regimens generally include an aggressive induction phase in which the goal is to induce complete or partial disease remission over the course of a few months. This is followed by a maintenance phase in which lower doses of immunosuppressive agents are used to maintain remission and prevent flare-ups. antimalarials may reduce the risk of renal flares, improve maintenance of remission, and reduce the risk of progression to ESRD in addition to reducing the risk of thrombosis. The current ACR guidelines recommend the addition of hydroxychloroquine to the regimens of all SLE patients with nephritis

Table 2. Medications Used for the Treatment of Lupus Nephritis	
Medication	Dosing
INDUCTION THERAPY	
MMF	2-3 g IV/po daily \times 6 mo
Cyclophosphamide	"Euro-Lupus": 500 mg IV every 2 wk \times 6 doses High dose: 500-1,000 mg/m ² IV monthly \times 6 doses
Methylprednisolone	Pulse: 500-1,000 mg IV daily \times 3 doses, followed by 0.5-1 mg/kg/day of oral glucocorticoid tapered to minimal effective dose
MAINTENANCE THERAPY	
MMF	1-2 g po daily \times 3 y
Azathioprine	2 mg/kg po daily \times 3 y ^a
ADJUNCTIVE TREATMENT	
Hydroxychloroquine	200-400 mg po daily
<i>^a Length of treatment extrapolated from the American College of Rheumatology's recommendation for maintenance treatment with MMF. MMF: mycophenolate mofetil. Source: Reference 2.</i>	

Cyclophosphamide Induction Therapy:

Cyclophosphamide, a synthetic antineoplastic drug chemically related to the nitrogen mustards, It exerts its antineoplastic and immunosuppressant effects by cross-linking DNA preferentially in quickly dividing cells, such as cancerous cells and leukocytes.

The combination of cyclophosphamide and methylprednisolone as induction therapy has been effective than corticosteroids alone. Daily oral cyclophosphamide may also be used for induction therapy; however, IV pulse therapy is preferred due to the decreased cumulative exposure to cyclophosphamide reduces the incidence of cytopenia. Amenorrhoea, infertility, and opportunistic infections such as herpes zoster While this combination is effective, patients treated with cyclophosphamide and methylprednisolone for induction therapy in lupus nephritis are at an increased risk of adverse drug events as compared to those treated with methylprednisolone monotherapy. Adverse events include amenorrhea cervical dysplasia, herpes zoster, and infection.

Lower-dose cyclophosphamide for induction therapy: traditional high-dose therapy, dosed monthly for 6 months followed by quarterly dosing (0.5 g/m² initially, then adjusted based on white blood cell count nadir), with low-dose

therapy (500 mg every 2 weeks × 6 doses followed by azathioprine maintenance therapy of 2 mg/kg/day) has reduced adverse effects.

Induction Therapy With Mycophenolate mofetil (MMF):

MMF is metabolized to mycophenolic acid, which inhibits inosine monophosphate dehydrogenase and in turn inhibits the de novo pathway for guanine nucleotide synthesis. As the proliferation of B and T cells is highly dependent on this pathway, MMF has a potent cytostatic effect on lymphocytes.

oral MMF (2 g daily for 6 months followed by 1 g daily for 6 months) or oral cyclophosphamide (2.5 mg/kg/day for 6 months) followed by oral azathioprine (1.5 mg/kg/day for 6 months). oral prednisolone daily. Infections were significantly less common in the MMF

MMF is an alternative to cyclophosphamide induction therapy, and may confer less risk of toxicity^[18]. 2 to 3 g/day of MMF as part of an induction regimen with pulsed corticosteroids. The 3 g/day dosage is favored in patients with proteinuria and significant rises in serum creatinine.

Maintenance Therapy:

Once remission has been induced, long-term maintenance therapy should be initiated to reduce the risk of recurrence and long-term complications of the disease. MMF-1-2g/po for 3 years. Azathioprine (AZA) is a purine analog which inhibits DNA synthesis and acts most strongly on rapidly proliferating cells. A dose of 2 mg/kg/day for 3 years is preferred. AZA is preferred as maintenance therapy, in pregnant patients and in patients intolerant to other first-line induction agents. however; doses should be tapered over time to reduce the risk of adverse reactions.

Adjuvant therapy:

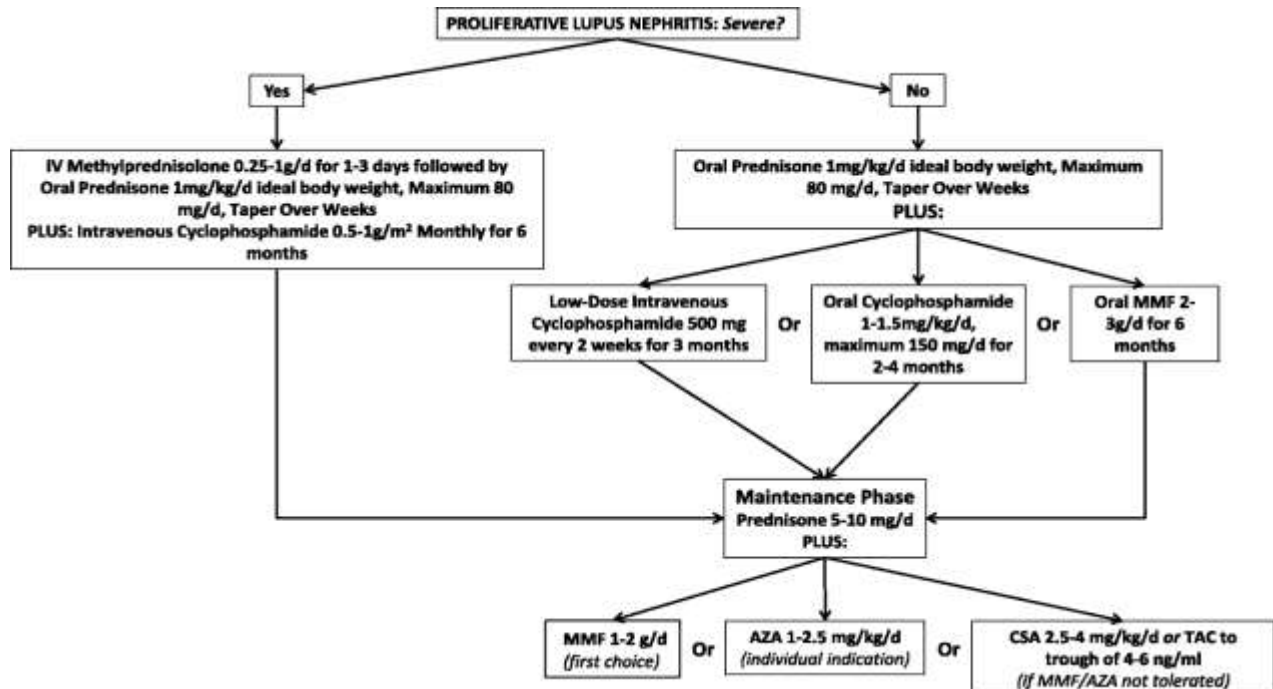
Hydroxychloroquine (HCQ) is an antimalarial drug with anti-inflammatory, antithrombotic and immunomodulatory properties. The use of HCQ has been associated with decreased probability of LN when used before the onset of LN in SLE^[57] and also retards the onset of renal damage in patients with LN^[58] The use of HCQ has also been associated with increased probability of remission, reduced frequency of flares and improved survival.

Others:

Angiotensin inhibitors/blockers [angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB)] are effective in reducing proteinuria in diabetic nephropathy and other proteinuric glomerular diseases. use of ACEI/ARB was found to be effective in reducing proteinuria and improving serum albumin^[59,60]. Their use was also associated with retarding the occurrence of renal involvement and reducing overall disease activity in SLE^[61].

Membranous Lupus Nephritis Treatment:

The treatment of membranous lupus nephritis, ISN/RPS class V, differs from that of proliferative nephritis. Milder disease with stable kidney function, subnephrotic proteinuria, and the absence of proliferative lesions may only require treatment with an ACE inhibitor or an ARB in order to suppress the renin-angiotensin-aldosterone system (RAAS). For a disease that is more severe or includes proliferative lesions, studies have demonstrated that treatment with a corticosteroid in combination with either cyclosporine, MMF, or cyclophosphamide is an effective regimen^[34,33] The first-line treatment with MMF and prednisone followed by maintenance therapy with MMF or azathioprine.



Calcineurin inhibitors (CNIs) ^[16]:

Calcineurin inhibitors are a class of immunosuppressant drugs that decrease lymphocytic proliferation through the inhibition of a phosphatase calcineurin, CNIs have got a dual mode of action viz., immunosuppression and stabilization of podocyte cytoskeleton^[62] Tacrolimus (TAC) has been found to be effective in proliferative, membranous as well as resistant LN and may have a role in pregnant patients^[63] Although effective in LN, CNI has been invariably associated with the risk of relapse and always carries risk of nephrotoxicity with long-term use. Lower CNI levels may be effective in LN.

Biological agents in lupus nephritis:

The various biological agents consisted of anti-B-cell therapies targeting either B-cell surface antigens (anti-CD20 and anti-CD22) or B-cell survival factors [anti-B lymphocyte stimulator/A proliferation-inducing ligand (anti-BLyS/APRIL) monoclonal antibodies], anti-cytokines antibodies (anti-interleukin-6) and novel drugs intervening in B-T cell co-stimulation [cytotoxic T-lymphocyte-associated protein 4 (CTLA4-Ig) The anti-B-cell-targeted therapies that have been investigated are rituximab (RTX)^[64] [chimeric anti-CD20 monoclonal antibody (MAB)], ocrelizumab^[65] (humanized anti-CD20 MAB), epratuzumab^[66] (anti-CD 22 humanized MAB) and belimumab^[67] [Fully human anti-BlyS (B lymphocyte stimulator) MAB]. Other targeted therapies investigated included abatacept^[68] [(CTLA4-Ig) fusion protein] and atacicept^[69] (soluble fully human recombinant anti-APRIL fusion protein).

Non-pharmacological therapy^[17]:

1. Drink enough fluids to stay well hydrated.
2. Eat a low-sodium diet, especially if hypertension is an issue.
3. Avoid smoking and drinking alcohol.
4. Exercise regularly.
5. Maintain healthy blood pressure.
6. Limit cholesterol.
7. Avoid medications that can affect the kidneys, such as nonsteroidal anti-inflammatory drugs (NSAIDs).
8. avoid over-exposure to sunlight with the use of adequate sunscreen protection
9. avoiding "live" vaccination if on immunosuppressive agents
10. adherence to a diet low in saturated fat and high in fish oil
11. stress avoidance

Conclusion:-

There is more uncertainty about how to treat lupus nephritis.

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