- Describe the options for the treatment of patients in these scenarios
- Discuss new trends in research on new markers for the diagnosis of the antiphospholipid syndrome

29 CARDIOVASCULAR DISEASE BURDEN IN SLE: RISK ASSESSMENT AND MANAGEMENT

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Background: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in systemic lupus erythematosus (SLE).[1] Patients with SLE have a 2- to 10-fold higher risk of ischemic heart disease and stroke compared with the general population. An interrelationship between immunological, disease-related, and traditional cardiovascular risk factors contributes to CVD pathogenesis.

CVD Risk Assessment: Early recognition and management of CVD risk factors is important for the prevention of CVD events. For the assessment of CVD risk, generic clinical prediction scores have been used. Evidence has shown that Framingham score underestimates CVD risk in SLE, while limited data are available about the performance of the Systematic COronary Risk Evaluation (SCORE). The modified Framingham,[2] and the modified SCORE, multiplied by 2 and 1.5, respectively have been developed, and the most recent version of the QRISK prediction score (QRISK3) included weights for SLE. The SLE Cardiovascular Risk Equation[3] was recently developed including both traditional and disease-related CVD risk factors (SLEDAI, lupus anticoagulant, C3) and was found to have higher estimated risks than the ACS/AHA risk equation.

Several vascular imaging markers (e.g. intima-media thickness, carotid and femoral atherosclerotic plaques) and circulating biomarkers have been evaluated for CVD risk stratification. Vascular ultrasound studies showed a 2- to 3-fold increased risk for asymptomatic plaque presence in patients with SLE compared to healthy controls, and a comparable risk to other high-cardiovascular risk disorders such as rheumatoid arthritis and diabetes mellitus.[4] Markers of arterial stiffness or endothelial dysfunction such as the pulse wave velocity and flow-mediated dilation, respectively, have been also more impaired in SLE than in the general population in some studies.

CVD Risk Management: According to the recent 'EULAR recommendations for cardiovascular risk management in Rheumatic and Musculoskeletal Diseases including Systemic Lupus Erythematosus and Antiphospholipid Syndrome',[5] a blood pressure target of <130/80 mm Hg should be considered in patients with SLE. Use of ACE inhibitors or angiotensin receptor blockers is recommended for patients with lupus nephritis with urine protein-to-creatinine ratio >500 mg/g or arterial hypertension. Patients with SLE may be candidates for preventative strategies as in the general population, including low-dose aspirin, based on their individual cardiovascular risk profile. Regarding lipid control, recommendations used in the general population should be followed.

Evidence from several observational studies has shown a lower risk of CVD events in patients treated with hydroxychloroquine versus those not treated. EULAR recommendations stated that treatment with hydroxychloroquine (which is recommended for all SLE patients) should be considered to also reduce the risk of cardiovascular events.[5] Accordingly, the lowest possible glucocorticoid dose is recommended to minimise any potential cardiovascular harm. No specific immunosuppressives can be recommended for lowering the risk of cardiovascular events.

In conclusion, CVD burden in SLE is high. Increasing of awareness of CVD risk in patients with SLE, regular screening and control of modifiable CVD risk factors, as well as patient education and lifestyle modifications, are crucial for CVD prevention and management in these patients.

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Learning Objectives

- Describe the need for regular screening and control of modifiable CVD risk factors in patients with SLE
- Explain the importance of increasing awareness of CVD risk in patients with SLE, for improving patient outcomes
- Discuss the potential impact of paient education and lifestyle modification for the prevention of CVD in patients with SLE

30 FATIGUE IN SLE

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Fatigue is one of the most common symptoms in those with systemic lupus erythematosus (SLE), and may impair daily activities, decrease health-related quality of life and lead to employment disability. In SLE, significant fatigue is reported by two-third of patients and rated as severe by one-third. Due to the highly multifactorial nature of fatigue, its assessment and treatment remains a major challenge in SLE. A careful assessment of its determinants is therefore key for an efficient and individualised management in SLE. First, common causes of fatigue unrelated to SLE such as sideropenic anemia, sleep apnea or adrenal failure should be ruled out based on a thorough medical history as well as targeted clinical and laboratory examinations. Then, disease activity and organ damage due to SLE should be assessed. The relationship between fatigue and disease activity remains very controversial in SLE. In those with active disease, remission is the most appropriate therapeutic target and may improve fatigue. Significant damage such as renal or cardiac failure is also associated with high levels of fatigue in SLE, and symptomatic treatment may also improve fatigue levels. In patients with inactive disease and no significant damage, anxiety and depression are common and

independent predictors of fatigue. This requires dedicated assessment and care, including psychological counseling and pharmacological intervention if needed. Besides psychological support, lifestyle changes including physical activity should be incorporated in the management of fatigue in SLE.

Learning Objectives

- Explain why fatigue is one of the most common symptoms in SLE and highlight the importance of facing this challenging unmet need in SLE
- Describe why the common causes of fatigue unrelated to SLE (e.g. sideropenic anemia, sleep apnoea, etc…) should systematically be ruled out
- Discuss the controversial relationship between fatigue and disease activity, and explain the importance of minimising the significant damage commonly associated with high levels of fatigue in SLE
- Explain why anxiety and depression are common in SLE and act as independent predictors of fatigue
- Explain why lifestyle changes including physical activity should be incorporated in the management of fatigue in SLE

31 INFECTIONS IN SLE

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Infectious agents especially viruses e.g. Epstein Barr virus contribute to systemic lupus erythematosus (SLE) pathogenesis and can trigger lupus disease activity by driving autoimmunity through molecular mimicry, bystander activation and epitope spreading.[1] This intricate relationship between viruses and autoimmunity is further substantiated by contemporary observations on the effects of dysregulated host immune response in severe COVID-19 infection resulting in development of autoantibodies and clinical manifestations simulating a lupus flare, albeit with distinguishing features.[2]

Infections are a significant cause of morbidity and mortality in SLE, with infections and active lupus as the most frequent causes of death across various cohorts. Compared with the general population, SLE patients have a median 3-fold increased risk of severe infection and are more likely to die of an infection with standardised mortality ratio (SMR) of 5 specifically due to infections alone.[3] The most common infections in SLE are pneumonia and bacterial sepsis, with *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Escherichia coli* as the most common causative agents. There is also a 2.5-fold higher risk of herpes zoster in SLE, and a 6-fold risk of tuberculosis especially in endemic countries. There is a higher incidence of Hepatitis B infection especially in Asia usually triggered by B-cell depleting agents, as well as *Pneumocystis jirovecii* pneumonia and other opportunistic infections.

The susceptibility to infections among lupus patients may be explained by several intrinsic and acquired defects in the immune system. Established risk factors for infection in SLE patients are disease activity including high anti-double-stranded DNA titres, low complement levels, active nephritis, leucopenia, and medications including prednisone or prednisone-equivalent dose greater than 7.5 mg/day, corticosteroid pulse therapy, and high-dose cyclophosphamide.[4] Conversely, antimalarials particularly hydroxychloroquine not only control disease activity and prevent flares, but also prevent serious infections in SLE.[5 6]

Although vaccination is essential in the prevention of infections, concerns regarding efficacy (lower immunogenicity and seroprotection), and safety (adverse events or disease flares), among physicians and patients are major deterrents for vaccination. In general, vaccinations against influenza, *Streptococcus Pneumonia*, Hepatitis A and B, and *Human Papilloma Virus* are recommended for SLE patients with clear benefit-risk/side-effect profile. Vaccinations should be administered during stable disease and before B cell depletion therapy. Conversely, live vaccines should be avoided in patients on immunosuppressive therapy.

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Learning Objectives

- Explain the role of infections in SLE pathogenesis
- Describe the spectrum of infections in SLE
- Discuss the risk factors for infections
- Discuss strategies for prevention of infections in SLE