CLINICAL
INVESTIGATION

An update on the management of comorbid conditions in lupus nephritis

Patients with lupus nephritis suffer from excessive morbidity and mortality compared with patients without renal involvement and the general population. Over the past few decades, early mortality in lupus nephritis due to uncontrolled renal disease activity and acute renal failure has decreased, whereas cardiovascular, metabolic, infectious comorbidities and malignancies have emerged as important long-term complications. Their pathogenesis involves chronic inflammatory burden, exposure to drugs with high toxicity potential (particularly glucocorticoids), and metabolic abnormalities due to impaired renal function. Although the lupus literature lacks controlled data for the management of most of the aforementioned disorders, there is evidence from other patients with chronic kidney disease to guide therapeutic decisions. Importantly, a multitargeted approach is recommended, which includes adequate control of disease activity with minimization of exposure to glucocorticoids, tight control of cardiovascular risk factors, and prompt identification and management of other chronic kidney disease comorbidities according to existing recommendations.

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The burden of renal involvement in systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease that can affect essentially any organ or tissue. Renal involvement develops in approximately 40–60% of SLE patients, most commonly within 5 years after diagnosis [1]. Age-standardized prevalence of lupus nephritis differs significantly by ethnicity, being $3.5/10^5$ for white, $13/10^5$ for Indo-Asian, and $65–67/10^5$ for Afro-Caribbean and Chinese patients [2]. Despite improvements in the care of SLE patients, nephritis remains one of the most severe manifestations associated with considerable morbidity and mortality [3]. With existing treatments, it is estimated that 30–40% of lupus nephritis patients will develop chronic kidney disease and 10–20% will progress into end-stage renal disease [2–4].

Recent analyses have suggested an overall trend of improvement in survival of patients with lupus nephritis with 10-year rates ranging from 77 to 98% [2,5]. Notably, since the introduction of cytotoxic therapy, early mortality due to uncontrolled lupus activity and acute renal failure has become much less common. Instead, infections remain a significant cause of mortality, and with longer patient survival, cardiovascular complications have emerged as an important source of late morbidity and mortality. These trends were illustrated in a recent single-center report of 230 Chinese lupus nephritis patients followed for an average of 17.7 years: the 10-year

survival rate was 98% and leading causes of death were infections (50%), cardiovascular disease (21%) and malignancy (13%) [5]. In this study, seven of the 21 patients with end-stage renal disease died during follow up; five of them died of infection, one of cardiovascular disease, one due to malignancy and none due to lupus. The increased burden of lupus nephritis also translates into increased direct and indirect health costs. In an economic analysis of data from a US Claims Database, SLE patients with nephritis consumed significantly more health care resources, with >2.5-fold the costs, compared with those without nephritis [6]. This was attributed to an increased number of inpatient hospitalizations, but also to increased outpatient visits to nonrheumatology specialists and increased cost for medications not related to SLE.

In this paper, we discuss the management of common comorbidities in patients with SLE and renal involvement. Since for most conditions there is a paucity of controlled data specifically for SLE, we describe the results of randomized trials that have been conducted in the general population and how they can be applied in lupus nephritis patients.
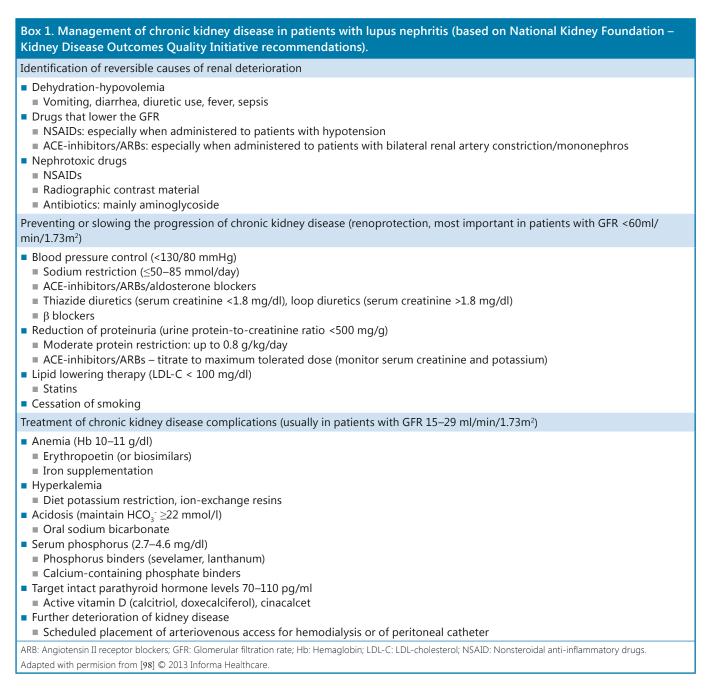
Hypertension

Hypertension is related to a deterioration of renal function in addition to an increased risk for cardiovascular events. There are higher than expected rates of hypertension in SLE patients [7,8], particularly among those with nephritis in whom it plays a significant pathophysiological role even from disease onset. In a study of 44 patients with lupus nephritis, hypertension (diastolic blood pressure >95 mmHg) was diagnosed in 17 patients (38%) and the incidence of renal impairment (serum creatinine >120 µmol/l) was significantly higher in the hypertensive versus normotensive group (47 vs 19%) [9]. Font *et al.* evaluated 70 patients with lupus nephritis and 70 age- and sex-matched SLE patients without nephritis for an average follow up of 10 years [10]. A high prevalence of hypertension was found in the nephritis group (62 vs 32%), associated with the development of renal failure. Indeed, prospective controlled studies have demonstrated that persistent hypertension is an independent risk factor for adverse long-term renal and patient outcomes, thus emphasizing the need for adequate blood pressure control in these patients [11–13].

The target blood pressure levels and the optimal selection of antihypertensive agents are important issues in patients with renal involvement. In view of the paucity of controlled data in patients with lupus nephritis, management decisions may be guided by practice recommendations applicable to the general population of patients with chronic kidney disease (CKD) (Box 1).

According to the recommendations issued by the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure [14], the Kidney Disease Outcomes Quality Initiative (KDOQI) [15] and the European Society of Hypertension/European Society of Cardiology [16], the target blood pressure in patients at high risk for cardiovascular disease – including patients with CKD – should be <130/80 mmHg, compared with the conventional target level of 140/90 mmHg in persons without risk factors. In patients with proteinuria >1 g/24 h, achievement of lower blood pressure levels (125/75 mmHg) is beneficial in terms of maintaining lower rate of glomerular filtration rate (GFR) decline, whereas there are no beneficial effects in patients with urine protein excretion <1 g/24 h. Meta-analyses of randomized controlled trials (RCTs) have confirmed these findings but have also drawn caution to possible deleterious effects of very low blood pressure levels (systolic blood pressure <110 mmHg) as these may be associated with kidney disease progression [17].

The cornerstone of therapeutic intervention in patients with hypertension and CKD is blockade of the renin–angiotensin–aldosterone system (RAAS). Apart from its systemic role [18,19], recent studies have focused on the effects of local RAAS activation in the kidney on regulation of blood pressure levels and renal function impairment [20]. Of interest, genetic polymorphisms of the RAAS have been associated with the development of nephritis in SLE patients [21]. To this end, the protective role of ACE inhibitors and angiotensin II receptor blockers (ARBs) on renal function is well established, and is due to both blood pressure-lowering and antiproteinuric effects, but possibly due to extra-renal functions as well, such as antifibrotic effects [22]. Accordingly, these agents are preferred in patients with proteinuric kidney disease [23]. Optimal dose-uptitration should be sought, and their effect is maximized when treatment is started early and independent of the severity of kidney disease. Although dual RAAS blockade with combination of ACE inhibitors and ARBs has been shown to further reduce proteinuria, there is no clear additive effect with regards to renal function [24], and this combination is not recommended for patients with overt vascular disease [25]. In fact, combination therapy carries increased risk for hyperkalemia and GFR reduction. Although the direct renin inhibitor aliskiren could represent a novel approach in combination RAAS-blockade therapies [26], no benefit has been demonstrated to date. Aldosterone receptor antagonists represent another class of RAAS blocking agents with antiproteinuric properties that are recommended for combination therapy with ACE-inhibitors or ARBs in proteinuric kidney disease [27]. Restriction of dietary salt intake to target level of

Box 1. Management of chronic kidney disease in patients with lupus nephritis (based on National Kidney Foundation – Kidney Disease Outcomes Quality Initiative recommendations).

Identification of reversible causes of renal deterioration

- Dehydration-hypovolemia
    - Vomiting, diarrhea, diuretic use, fever, sepsis
- Drugs that lower the GFR
    - NSAIDs: especially when administered to patients with hypotension
    - ACE-inhibitors/ARBs: especially when administered to patients with bilateral renal artery constriction/mononephros
- Nephrotoxic drugs
    - NSAIDs
    - Radiographic contrast material
    - Antibiotics: mainly aminoglycoside

Preventing or slowing the progression of chronic kidney disease (renoprotection, most important in patients with GFR <60ml/min/1.73m^2)

- Blood pressure control (<130/80 mmHg)
    - Sodium restriction (≤50–85 mmol/day)
    - ACE-inhibitors/ARBs/aldosterone blockers
    - Thiazide diuretics (serum creatinine <1.8 mg/dl), loop diuretics (serum creatinine >1.8 mg/dl)
    - β blockers
- Reduction of proteinuria (urine protein-to-creatinine ratio <500 mg/g)
    - Moderate protein restriction: up to 0.8 g/kg/day
    - ACE-inhibitors/ARBs – titrate to maximum tolerated dose (monitor serum creatinine and potassium)
- Lipid lowering therapy (LDL-C < 100 mg/dl)
    - Statins
- Cessation of smoking

Treatment of chronic kidney disease complications (usually in patients with GFR 15–29 ml/min/1.73m^2)

- Anemia (Hb 10–11 g/dl)
    - Erythropoetin (or biosimilars)
    - Iron supplementation
- Hyperkalemia
    - Diet potassium restriction, ion-exchange resins
- Acidosis (maintain HCO_3^- ≥22 mmol/l)
    - Oral sodium bicarbonate
- Serum phosphorus (2.7–4.6 mg/dl)
    - Phosphorus binders (sevelamer, lanthanum)
    - Calcium-containing phosphate binders
- Target intact parathyroid hormone levels 70–110 pg/ml
    - Active vitamin D (calcitriol, doxecalciferol), cinacalcet
- Further deterioration of kidney disease
    - Scheduled placement of arteriovenous access for hemodialysis or of peritoneal catheter

ARB: Angiotensin II receptor blockers; GFR: Glomerular filtration rate; Hb: Hemaglobin; LDL-C: LDL-cholesterol; NSAID: Nonsteroidal anti-inflammatory drugs.

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50–85 mmol/day has also been shown to reduce blood pressure levels and improve protein excretion in patients with CKD [28,29]. Adequate blood pressure control often requires the addition of other classes of antihypertensive agents such as diuretics and calcium-channel blockers, which exert modest antiproteinuric effect.

Atherosclerosis & dyslipidemia

Coronary heart disease accounts for approximately 21% of overall mortality in SLE [5,30]. Patients with lupus nephritis are at an even higher risk and demonstrate a 2.8–10-fold increased rate of acute myocardial infarction [31]. In addition to conventional risk factors such as hypertension, diabetes mellitus and dyslipidemia, attributed both to increased inflammatory burden and the concomitant use of glucocorticoids, other metabolic abnormalities such as premature menopause, kidney failure, dysfunctional HDL, oxidized LDL particles, and higher plasma homocysteine levels are also more prevalent in SLE [32,33]. In a prospective study of 78 SLE patients with no clinically overt atherosclerosis and a follow up of 5 years, thickened intima was found in 28% and plaque formation in 17% [34]. Risk factors that have been correlated with a progression of

subclinical atherosclerosis in SLE include age, hypertension, hypercholesterolemia, low complement, hyperhomocysteinemia, and cumulative prednisone dose [34,35]. Dyslipidemia occurs in 34–51% of SLE patients and it is more prevalent in patients with renal involvement [36]. In a controlled study, dyslipidemia was found in 44% of lupus nephritis patients compared with 2% of the patients without nephritis [10]. Importantly, persistent proteinuria and dyslipidemia are major factors for CKD progression in lupus patients with renal involvement similar to other glomerular diseases [37].

Since lupus nephritis patients, particularly those with chronic renal insufficiency are considered to be at a high risk for developing cardiovascular disease, it has been proposed that target blood lipid levels are the same as those for other high risk populations [7]. Based on recommendations by the National Cholesterol Education Program Adult Treatment Panel III [38], the KDOQI [39] and the European Society of Cardiology/European Atherosclerosis Society [40], target LDL-cholesterol (LDL-C) levels should be <100 mg/dl (<70 mg/dl in cases of acute coronary syndrome). In patients with mixed hypercholesterolemia and hypertriglyceridemia, non-HDL-cholesterol (HDL-C) is considered a second treatment target and should be 30 mg/dl below the target level of LDL-C.

Statins are considered the drug of choice for treating dyslipidemia based on their potent hypolipidemic effect and their impact on primary and secondary prevention of cardiovascular disease. The Pravastatin Pooling Project demonstrated reduced risk for cardiovascular disease (hazard ratio 0.77) in patients with moderate kidney disease (GFR <60 ml/min/1.73m^2) treated with pravastatin 40 mg/day [41]. Five-year follow-up studies have shown that pravastatin treatment is well tolerated with no excess in serious adverse events on liver function or muscle enzymes [42]. Unexpectedly, RCTs have failed to demonstrate definite clinical benefit in hemodialysis patients despite significant improvement in serum lipids (reviewed in [43]). The most likely explanation for these discordant results is that the pathogenic processes for adverse cardiovascular outcomes among patients with end-stage renal disease differ from those with either mild to moderate renal dysfunction or normal kidney function.

In SLE, a number of controlled trials have failed to demonstrate beneficial effect of statin therapy on progression of atherosclerosis assessed by coronary calcification or carotid intima-media thickness [44–46]. However, these studies had relatively short follow up (up to 3 years) and included SLE patients without kidney involvement and with variable degrees of dyslipidemia and atherosclerosis. A single placebo-controlled RCT has assessed the effects of fluvastatin (40–80 mg/day)

in 33 patients who had received a renal transplant due to end-stage renal disease [47]. At the time of trial initiation, all patients had dyslipidemia and they were on triple immunosuppressive treatment with calcineurin inhibitor, azathioprine and prednisone. The controlled phase of the trial lasted 5–6 years, followed by a 2-year open-label extension phase (average follow up 7.3 years). Fluvastatin treatment was associated with significant reduction in LDL-C (by 29%) and total cholesterol (by 20%), whereas there were no significant alterations in HDL-C or triglycerides. There was a trend for increased major cardiac events in the placebo versus the fluvastatin arm (relative risk 26.6; p = 0.064) [47]. To this end, additional data will be required to define the indications and targets of lipid-lowering therapies in SLE patients. In the meantime, the management of dyslipidemia in these patients should be similar to that in the general population with CKD [48].

Anemia

Anemia is defined by the WHO as a hemoglobin concentration below 13 g/dl for adult males and postmenopausal women, and hemoglobin below 12 g/dl for premenopausal women. Based on these criteria, nearly 90% of patients with a GFR less than 30 ml/min have anemia, many with hemoglobin below 10 g/dl [49]. Anemia in SLE is multifactorial and includes anemia of chronic inflammatory disease, iron deficiency anemia, autoimmune hemolytic anemia or anemia due to immune-mediated bone marrow damage, anemia of CKD and treatment-related anemia (mainly due to cyclophosphamide-induced myelotoxicity) [50]. In patients with lupus nephritis, anemia is often present even at disease onset and correlates with histological findings and the degree of disease severity [13,51]. Hemoglobin levels <9 g/dl have been shown to predict adverse renal and patient outcomes, suggesting that anemia is a surrogate of underlying inflammatory disease activity and kidney damage. In addition to organ damage due to decreased blood flow, affecting primarily the cardiovascular and kidney function, anemia contributes to fatigue, loss of normal physical activity, and reduced quality of life.

Anemia of CKD is normocytic hypochromic with reduced plasma iron and transferrin concentrations while ferritin levels are normal or even elevated. Several pathogenic mechanisms are implicated including decreased production of erythropoietin (EPO) from the kidney, nonresponsiveness of hematopoietic progenitors to EPO, or autoantibodies against EPO [52]. Iron availability is also reduced. Therapy with erythropoiesis-stimulating agents (ESAs) or biosimilar erythropoietins [53], which do not promote the development of anti-EPO antibodies, is indicated to achieve the target hemoglobin

level of 10–11 g/dl [54]. Hemoglobin levels should be monitored every 2–4 weeks after initiation of ESA therapy until hemoglobin levels and the ESA dose are stable; thereafter, hemoglobin levels should be checked every 4–6 weeks. An adequate response to ESAs requires the maintenance of sufficient iron stores, and ESAs should not be initiated until iron status has been evaluated. Supplemental iron should be administered, as needed, to maintain a transferrin saturation of ≥20% and a serum ferritin level of ≥100 ng/ml [54]. Since increased hepcidin production in anemia of chronic disease may limit the ability to achieve these levels with oral iron preparations alone, parenteral iron (monthly intravenous sucrose iron) may be required in some patients.

The use of ESAs has been related to increased rates of hypertension, seizures, vascular access thrombosis and cardiovascular events. These adverse events have been mostly associated with hemoglobin levels >11–12 g/dl and to a lesser extent, with the cumulative dose of ESAs. Titration of antihypertensive treatment will often be required along with tight control of other vascular risk factors. A slow rate of increase in hemoglobin levels (not more than 1 g/dl per month) is recommended to minimize treatment-related adverse events [55]. Despite reports for enhanced tumor proliferation and angiogenesis in patients with certain types of malignancies who received ESAs to target hemoglobin of ≥12 g/dl [56], there is no evidence for increased risk of *de novo* carcinogenesis in patients with CKD who are treated to achieve a target hemoglobin of <12 g/dl.

Bone metabolism & osteoporosis

Bone mineral imbalances and osteoporosis may occur in lupus nephritis as a consequence of the development of CKD, but also due to the underlying disease and its treatment. In patients with moderate-to-severe renal insufficiency, disturbances in mineral and bone metabolism become prevalent and are associated with increased morbidity and mortality. Results from the Study of Osteoporotic Fractures showed that women with GFR 45–59 ml/min had a 1.5-fold increased risk for trochanteric hip fracture; the risk increased to sevenfold in women with GFR <45 ml/min [57].

The management of bone loss and fractures in patients with renal insufficiency represents a clinical challenge, due to the diagnostic dilemma in differentiating a dynamic bone disease, which is a low bone turnover state, from other forms of metabolic bone disease, especially osteomalacia and hyperparathyroid bone disease. Establishing a certain diagnosis may require bone biopsy in certain cases, and there is no consensus how to diagnose osteoporosis in patients with advanced stages of kidney disease. To this end, the KDOQI has issued clinical practice guidelines for the diagnosis, evaluation,

prevention, and treatment of metabolic bone disease in CKD [58]. Treatment strategy includes reducing the risk for falls, normalizing serum 25-OH-vitamin D levels, controlling parathyroid hormone levels, and administration of anti-osteoporotic agents [59]. Patients with osteoporosis or high risk for fracture who have stage 1–3 CKD (GFR >30 ml/min/1.73m²) and no laboratory abnormalities suggestive for bone mineral disease, may be treated with oral bisphosphonates without dose adjustment. In the absence of published data on the impact of bisphosphonates on adynamic bone, it is recommended that in patients with GFR <30 ml/min/1.73m² with biochemical abnormalities of bone mineral disease, and low bone mineral density (BMD) and/or fragility fractures, bone biopsy is performed prior to therapy with antiresorptive agents. Fracturing patients with stage 4 CKD (GFR 15–29 ml/min/1.73m²) or, exceptionally, stage 5/5D CKD (GFR <15 ml/min/1.73m² or permanent renal replacement therapy), may be treated according to clinical expert consensus for no longer than 3 years, in the case of biopsy-proven high-turnover osteoporosis. In patients with severe hyperparathyroidism and bone mineral disease, parathyroidectomy may be an option after vitamin D replacement therapy and use of calcimimetics.

Increased prevalence of low BMD and fragility fractures has been demonstrated in SLE patients with reported rates of osteopenia and osteoporosis ranging 25–74% and 1.4–68%, respectively [60]. Modifiable factors that contribute to lupus-related bone loss include traditional risk factors for osteopenia, such as sedentariness due to fatigue, premature gonadal failure due to cytotoxic treatment, and vitamin D insufficiency [61]. Metabolic and hormonal abnormalities associated with lower BMD such as hyperhomocysteinemia and reduced dehydroepiandrosterone levels, are also more common in SLE [62,63]. In addition, chronic systemic inflammation may stimulate bone resorption by enhancing osteoclastic activity and decrease bone formation by diminishing osteoblastic function. To this end, higher levels of disease activity and damage in SLE, such as lower serum complement concentration and presence of renal impairment, have been associated with a lower BMD [64,65].

Glucocorticoids (GC) represent a major risk factor for accelerated bone loss, and patients with lupus nephritis are often treated with moderate-to-high doses of GC, especially during the initial stages of induction treatment and for the management of disease flares. During the first 6 months of GC therapy, 10–20% of trabecular bone loss occurs, and another 2% per year is lost in the subsequent years. Approximately 26% of patients on long-term (>6 months) GC therapy will develop osteoporosis [66], and the relative risk for vertebral fracture increases from 1.6 at a prednisone dose 2.5 mg/day to

5.2 at doses greater than 7.5 mg/day [67]. To date, there is no consensus on the prevention and management of GC-induced osteoporosis, and this is further complicated by the fact that GC can be administered in various forms (oral, parenteral, pulse), dosages and treatment schedules. Nonetheless, most authorities recommend lifestyle changes and bone protection treatment (primary prevention) with oral calcium (1200–1500 mg/day), vitamin D (800–1000 IU/day), and bisphosphonates for patients who will receive at least 5 mg/day prednisone or equivalent with an estimated duration of at least 3 months [68].

For patients who are already receiving GC, antiresorptive treatment is also indicated (secondary prevention). In premenopausal SLE patients, a RCT reported maintenance of lumbar spine BMD with calcium carbonate (500 mg/day) and calcitriol (0.25 µg/day) after 2.5 years of therapy [69]. In a meta-analysis of trials, calcium and vitamin D and were shown to significantly improve BMD at the lumbar spine (weighted mean change 2.5) and at the radius in 33% of the patient on GC, but not the BMD at the femur or fracture incidence [70]. Evidence for efficacy of bisphosphonates in GC-induced osteoporosis has been reported for alendronate, risedronate, ibandronate and zoledronic acid. Alendronate (5 or 10 mg/day) increases BMD, benefitting one in every three individuals treated for 48 weeks, but no reduction in the incidence of vertebral fracture is observed [69,71]. Risedronate (5 mg/day) may reduce vertebral fractures in up to 70% of patients, benefitting one in every nine individuals treated for 48 weeks [72]. Zoledronic acid is also beneficial and has a convenient dosage scheme (5 mg/single dose) that increases adherence to treatment. Caution is warranted in women desiring a pregnancy, since these agents should not be prescribed during pregnancy and lactation. Also, a significant concern with regard to bisphosphonate use is in patients with GFR <30 ml/min/1.73m^2, in whom slower infusion rates and lower doses than those of standard osteoporosis management are generally used [73].

Teriparatide has emerged as a novel agent for the treatment of GC-induced osteoporosis, due to its anabolic effect on bone formation. When used at a dose of 20 µg/day subcutaneously, it significantly reduces the risk for vertebral fractures. In addition, its pharmacokinetics are not significantly altered at low GFR. However, in view of the absence of data on comparative efficacy with bisphosphonates and due to its relatively higher cost, teriparatide should be considered as a second-line therapy or when bisphosphonates are contraindicated [74]. Furthermore, its use should be restricted to postmenopausal women or men aged ≤50 years, due to insufficient data for other populations. Estrogen-containing agents, and the estrogen receptor modulator raloxifene, have been shown to maintain BMD in SLE patients receiving GC, but their use is limited due to concerns for thrombotic events particularly in antiphospholipid positive individuals [75]. Cessation of anti-osteoporotic therapy is recommended after GC is stopped, unless the patient is at an increased risk for fracture.

Other metabolic complications

Patients with lupus nephritis may develop metabolic disturbances related to the stage of CKD. The diagnostic work-up and management should be similar to that in the general population with CKD. Sodium retention with signs of volume overload usually occurs when GFR is <10–15 ml/min/1.73m^2, and may aggravate hypertension, edema and congestive heart failure. A sodium-restricted diet (< 2 g/day) and/or loop diuretics are often required. Serum potassium levels are elevated when oliguria develops or in case of metabolic acidosis. Hyperkalemia can also arise as a result of antihypertensive agents such as RAAS blockers or potassium sparing diuretics. Dietary restriction and ion resins administered for short time periods are the mainstay of management. Chronic metabolic acidosis may present with advanced CKD (stage 3 or beyond). Acidosis (serum sodium bicarbonate concentrations <22 mEq/l) may contribute to osteopenia and muscle catabolism, and alkali therapy is indicated to maintain serum bicarbonate level >22 mEq/l. In fact, recent clinical trials have suggested that the correction or prevention of metabolic acidosis by alkali administration is able to attenuate kidney damage and to slow progression of CKD, and may hence offer an effective, safe and affordable renoprotective strategy [76,77]. Increases in serum phosphate and decreases in 1,25-$(OH)_2$-vitamin D occur even at stage 1–2 of CKD, whereas hypocalcaemia develops in more advanced stages. Together, these abnormalities contribute to secondary hyperparathyroidism and should be managed accordingly [58]. Dietary phosphorus restriction is recommended (900–1000 mg/day) for cases of hyperphosphatemia and secondary hyperparathyroidism. Administration of the 1,25-$(OH)_2$-vitamin D3 calcitriol or an active vitamin D analogs is also a therapeutic tool for secondary hyperparathyroidism. The active vitamin D analogs lead to less elevation of calcium and phosphorus with a greater suppression of parathyroid hormone levels. Calcimetics (Cinacalcet) are an alternative treatment of secondary hyperparathyroidism. In patients whose levels of parathyroid hormone levels are >800 pg/ml despite other interventions, parathyroidectomy should be considered. High levels of parathyroid hormone are related to renal osteodystrophy, a group of disorders that can be classified as osteitis fibrosa, osteomalacia, mixed uremic osteodystrophy and adynamic

bone disease. Hyperuricemia is particularly common in patients with kidney disease, including Lesch–Nyhan, recent epidemiological studies suggest an independent association between asymptomatic hyperuricemia and increased risk of arterial hypertension, progression of CKD, cardiovascular events, and mortality [78,79]. Although short-term clinical studies support the beneficial effect of pharmaceutical reduction of serum uric acid on cardiovascular risk and renal disease progression, further randomized evidence will be required.

Thrombotic diathesis & renal vasculopathy

Nephrotic syndrome is associated with increased synthesis of clotting factors and loss of fibrinolytic proteins in the urine, such as proteins S and C, and together with antiphospholipid antibodies are important factors for the thrombophilic diathesis in lupus nephritis. Patients with nephrotic syndrome, particularly those with membranous nephropathy, should be informed about the possibility for thrombosis, which can manifest as deep vein thrombosis, pulmonary embolism or renal vein thrombosis.

Renal vein thrombosis, although it may be asymptomatic, usually presents with flank pain, hematuria and new-onset or worsening proteinuria. It has been described in patients with antiphospholipid antibodies, and may be the presenting manifestation of antiphospholipid syndrome (APS) [80]. The risk for thrombosis is further enhanced by the presence of severe nephrotic syndrome with hypoalbuminemia and CKD. Doppler ultrasound studies of the renal vasculature should be performed in any SLE patient with nephrotic syndrome and/or antiphospholipid antibodies who develops worsening of proteinuria and/or GFR, in order to rule out renal vein thrombosis. Alternatively, contrast-enhanced computer tomography and magnetic resonance angiography can be used to establish the diagnosis. Management includes antithrombotic therapy, whereas thrombolysis can be considered in cases of bilateral renal vein thrombosis and acute renal failure.

The role of antiphospholipid antibodies in microvascular renal injury has also been addressed. Microthrombi in glomerular capillaries may contribute independently to progression of renal disease, and several groups have reported on APS-associated nephropathy (APSN), characterized by acute lesions (thrombotic microangiopathy) and chronic vaso-occlusive lesions (fibrous intimal hyperplasia, organized thrombi, fibrous occlusions and focal cortical atrophy) in the absence of inflammatory cells and immune deposits [80]. APSN lesions are present in 67% of patients with SLE and secondary APS, compared with 32% of SLE with positive antiphospholipid antibodies but no APS, and only 4% of SLE patients without antiphospholipid antibodies [81,82].

APSN is associated with poor prognostic indicators at presentation, such as hypertension and lower GFR, although renal outcome is not significantly affected [83]. However, considering that capillary thrombosis in antiphospholipid antibody-positive patients with lupus nephritis may contribute to glomerular sclerosis, anti-platelet/anticoagulation treatment should be considered. No controlled studies evaluating the management of APSN have been published to date. Anticoagulation may be considered in patients fulfilling criteria for APS, and in patients with nephrotic syndrome and serum albumin <20 g/l, especially if persistent, or in the presence of antiphospholipid antibodies [80,81]. For patients with APSN not fulfilling the APS criteria, treatment may include hydroxychloroquine, antiplatelet or anticoagulative agents based on evidence from uncontrolled studies [81,84]. Thrombotic thrombocytopenic purpura in absence of lupus activity or a thrombotic thrombocytopenic purpura-like syndrome with thrombotic microangiopathic hemolytic anaemia in patients with systemic activity may develop in rare cases; because of their poor prognosis they have to be recognized and treated early.

Infections

Infections account for 30–55% of all deaths in lupus nephritis patients [5]. Risk factors for infections include high SLE activity, major organ disease (especially nephritis), persistent leukopenia (neutrophil count <500/mm^3 or lymphocyte count <500/mm^3), low serum albumin levels, use of moderate-to-high doses of GC (each increase of 10 mg/day prednisone is associated with an 11-fold increased risk for serious infection), and recent (within the last 6 months) use of cytotoxic drugs [85,86]. Infections are also a major cause of mortality in lupus nephritis patients who are on renal replacement treatment, particularly if they are receiving high-dose GC or immunosuppressive treatment at the time of initiation of dialysis [87].

Preventive measures include:

- Minimization of exposure to moderate-high doses of GC;

- Adherence to hygiene measures by both patients and health professionals;

- Antimicrobial prophylaxis in selected high-risk patients, such as those who receive heavy immunosuppression or undergo invasive procedures associated with transient bacteremia [88];

- Adherence to the recommended immunizations schedule [89].

Vaccines should not be given to patients with active disease. Patients taking immunosuppressive drugs

and/or prednisone at a dose >20 mg/day should not be vaccinated with live vaccines [90]. Influenza vaccine is safe and effective, although seroprotection and seroconversion rates are lower than those in healthy controls [91]; booster vaccination does not increase antibody titers in annually vaccinated patients. Pneumococcal vaccine is safe but serological responses may be dampened in SLE. Protective immune response can be achieved safely in SLE patients with both tetanus toxoid and *Haemophilus influenzae* type B, in addition to pneumococcus. According to the European League Against Rheumatism (EULAR) guidelines, individuals aged >60 years who are not receiving immunosuppressive treatment should be vaccinated with a single dose of varicella-zoster vaccine [90]. Vaccination against varicella-zoster virus should be performed at least 14 days before initiation, or should be deferred for at least 1 month after discontinuation of high-dose GC or immunosuppressive therapy. Prophylaxis against *Pneumocystis pneumonia* with trimethoprim-sulfamethoxasole or other recommended agents should be considered for patients receiving glucocorticoids dose equivalent to ≥20 mg of prednisone daily for at least 4 weeks in combination with a second immunosuppressive agent, particularly cytotoxics [88].

The differential diagnosis between infection and lupus flare is often challenging, particularly in patients with major organ involvement who receive immunosuppressive therapy. Presence of shaking chills, localizing symptoms and signs, increased peripheral blood white blood cell count and/or neutrophilia (especially with increased numbers of band forms or metamyelocytes on peripheral blood smear), and concomitant use of immunosuppression favor the diagnosis of infection. Conversely, lupus exacerbation should be suspected if leukopenia (not explained by cytotoxic therapy), normal C-reactive protein, low C3/C4, and elevated anti-DNA antibody titers are present. If fever fails to resolve in a patient receiving prednisone 20–40 mg daily, it is likely that that fever is due to infection, not SLE. Elevated serum procalcitonin has been reported to be predictive of bacterial or mycotic infections, although their diagnostic utility in patients with systemic autoimmune diseases has been questioned [92]. Pending microbiology results, adequate antimicrobial therapy (including broad-spectrum antibiotics in suspected nosocomial infection) is recommended to reduce adverse outcomes.

Malignancies

Hematological malignancies, cervical and lung cancer occur more commonly in SLE compared with the general population, followed by rare forms of malignancy affecting the hepatobiliary tract and the vulva/vagina. Both immunosuppressive therapy (with the potential for mutagenesis and impairment of antitumor immunity) and intrinsic lupus-related mechanisms (chronic antigenic stimulation, impaired surveillance) may account for this risk. Both Hodgkin's and non-Hodgkin's lymphoma are more frequent in SLE with a standardized incidence ratio of 3.2 and 3.6, respectively [93]. The risk may increase after exposure to immunosuppressive agents, particularly after a period of 5 years following treatment cessation. Indeed, in a multisite international SLE cohort, the adjusted hazard-risk estimate for development of hematological cancers was 3.6 (95% CI: 0.9–13.4) for cyclophosphamide exposure, although this could represent the effect of severe underlying lupus [94]. Respective risks were 1.0 (95% CI: 0.3–3.0) for azathioprine and 2.6 (95% CI: 0.8–8.3) for methotrexate use. Long-term safety data are not yet available for mycophenolate. Manifestations such as fever, lymphadenopathy, splenomegaly, cytopenias and monoclonal B-cell expansion, may occur both in SLE and in hematological malignancies; therefore, a high index of suspicion is necessary for early detection of the latter. A marginally increased risk for urinary bladder malignancy among SLE patients who are using cyclophosphamide has been observed (standardized incidence rate: 1.2; 95% CI: 0.7–2.1) [94], highlighting the importance of preventive measures associated with this agent such as good hydration, co-administration of the drug with with 2-mercaptoethane sodium sulfonate, and by limiting cumulative exposures.

Cervical dysplasia is increased in women with lupus as a result of impaired clearance of human papillomavirus (HPV) due to exposure to cytotoxic agents [95]. SLE, particularly lupus nephritis under cyclophosphamide, should be regarded as a risk factor for cervical malignancy and high-risk HPV infection. Therefore, cervical cytology in combination with HPV DNA testing is recommended [96]. To this end, the EULAR recommends HPV vaccination for women with SLE until the age of 25 years, similarly to the general population [90]. With regard to other types of cancer, there is no evidence to support increased surveillance in SLE and, thus, no particular recommendation should be applied beyond screening guidelines used in the general population.

Strategy for the management of comorbidities in lupus nephritis & EULAR recommendations

As discussed previously, evidence from observational cohort studies and therapeutic trials indicates the high prevalence of comorbidities in patients with lupus nephritis as a result of high disease activity, progressive renal damage and cumulative exposure to drugs with high toxicity potential. Accordingly, and although not formerly tested in the context of a controlled trial, a strategy aiming at early, tight control of renal disease activity

and at minimization of the dose of GC, should lead to a reduction of the inflammatory disease burden and of associated risks for comorbid conditions. To this end, the EULAR together with the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) have recently issued recommendations for the diagnosis and treatment of lupus nephritis based on systematic review of the literature and expert opinion [97]. The management of comorbidities and APSN with adjunctive therapies is emphasized in the manuscript and an outline of these statements together with the level of supporting evidence is presented in Table 1.

Conclusion

Although the risk of death from renal disease has decreased substantially over the last few decades, mortality remains significantly higher among patients with lupus nephritis compared with patients with SLE overall. Consequent to the advent of effective immunosuppressive treatment and the prolongation of patient survival, comorbidities such as hypertension, atherosclerosis, anemia and osteoporosis, have emerged as important long-term complications in patients with lupus nephritis. These complications are the result of chronic ongoing inflammation and exposure to GC and cytotoxic drugs, and may be further accelerated in patients with renal insufficiency due to accompanying metabolic disturbances.

Optimal care of patients with lupus nephritis requires a multidisciplinary approach with involvement of different subspecialties, also acknowledged in the EULAR/ERA-EDTA recommendations [97]. Despite the lack of controlled data in SLE patients, there is sufficient evidence from the other patient populations with chronic kidney disease to guide therapeutic decisions for comorbid conditions such as hypertension, dyslipidemia, anemia and metabolic disorders. To this end, and based on extrapolation from both epidemiological studies and RCTs in lupus nephritis, the authors propose a 'multitarget' approach that includes:

- Adequate control of renal and extra-renal lupus activity;
- Minimization of exposure to GC;
- Tight control of cardiovascular disease risk factors;
- Management of other CKD comorbidities according to existing recommendations;
- Adherence to primary prevention measures for osteoporosis, infections and malignancies;
- Diligent follow up of patients and prompt identification and management of any complications.

Future perspective

Novel therapeutic agents are currently being tested in SLE and lupus nephritis, which could enable the minimization of residual disease activity and of the cumulative dose of glucocorticoids. At the same time, evidence from controlled trials in SLE and non-SLE patients will enhance personalized clinical decisions with regard to the management of cardiovascular disease and other comorbidities. Finally, research in the field of biomarkers will provide useful noninvasive tools for the assessment of the inflammatory and atherosclerotic burden in these patients.

Table 1. The European League Against Rheumatism/European Renal Association – European Dialysis and Transplant Association recommendations for monitoring and the use of adjunctive treatments in patients with lupus nephritis.		
Treatment	Indication(s)	Evidence†
ACE-inhibitors or angiotensin receptor blockers	Proteinuria (urine protein:creatinine ratio >50 mg/mmol) or hypertension	2/B‡
Statin	Persistent dyslipidemia (target LDL-C 2.58 mmol/l [100 mg/dl])	−/C§
Hydroxychloroquine	Reduced risk for renal flares; reduction in accrual of renal and cardiovascular damage	3/C¶
Acetyl-salicylic acid	Positive antiphospholipid antibodies	−/C
Calcium and vitamin D	Bone protection	−/C
Immunizations (nonlive vaccines)	High-dose glucocorticoids or immunosuppressive treatment	−/C
Anticoagulant treatment	Nephrotic syndrome with serum albumin <20 g/l, especially if persistent or in the presence of antiphospholipid antibodies	−/C
†Evidence levels and strengths of statements can be found in Perysinaki G *et al.* (Supplementary Table 1) [97].		
‡Evidence base from randomized controlled trials but with concerns for validity of data due to inclusion of small number of patients with lupus nephritis, inadequate follow up and flaws in the study design.		
§Expert opinion or extrapolation from non-systemic lupus erythematosus literature.		
¶Evidence base from nonrandomized controlled studies.		
LDL-C: LDL-Cholesterol.		
Modified with permission from [97].		

Executive summary

The burden of renal involvement in systemic lupus erythematosus
- Early mortality in lupus nephritis due to uncontrolled renal disease activity and acute renal failure has decreased, whereas cardiovascular, metabolic, infectious comorbidities and malignancies have emerged as important long-term complications.
- The pathogenesis of these comorbidities involves chronic inflammatory burden, exposure to drugs with high toxicity potential (particularly glucocorticoids), and metabolic abnormalities due to impaired renal function.

Hypertension
- ACE-inhibitors/angiotensin II receptor blockers are preferred as first-line agents for patients with hypertension or persistent proteinuria >500 mg/24 h. The target blood pressure should be <130/80 mmHg, and in patients with proteinuria >1 g/24 h, achievement of lower blood pressure levels (125/75 mmHg) is beneficial.

Atherosclerosis & dyslipidemia
- Lupus nephritis patients, particularly those with chronic renal insufficiency, are considered to be at high risk for developing cardiovascular disease. Statins should be used to treat dyslipidemia with target LDL-cholesterol <100 mg/dl.

Anemia
- Anemia in lupus nephritis can be a surrogate of ongoing renal disease activity. The management of anemia due to chronic kidney disease includes the use of erythropoiesis-stimulating factors and maintenance of sufficient iron stores.

Bone metabolism & osteoporosis
- Glucocorticoids represent a major risk factor for accelerated bone loss. Lifestyle changes and administration of oral calcium (1200–1500 mg/day), vitamin D (800–1000 IU/day), and bisphosphonates are recommended for patients who will receive at least 5 mg/day prednisone or equivalent with an estimated duration of at least 3 months. Teriparatide should be considered as a second-line therapy or when bisphosphonates are contraindicated.

Thrombotic diathesis & renal vasculopathy
- In patients with histological features of antiphospholipid syndrome-associated nephropathy, treatment with antiplatelet and/or anticoagulative agents should be considered.

Infections
- Judicious use of glucocorticoids may decrease the frequency of infections in lupus nephritis patients. Other strategies include: simple hygiene measures and education; antimicrobial prophylaxis in certain cohorts of patients, and immunizations as recommended.

Malignancies
- Cervical dysplasia is increased in women with lupus as a result of impaired clearance of human papillomavirus due to exposure to cytotoxic agents. Cervical cytology is recommended once or twice in the first year and then annually, adding human papillomavirus testing to the first year obtained cervical smears, and then modifying subsequent screening based on these results.

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■■   **Recommendations for the diagnosis, management and monitoring of patients with lupus nephritis, based on systematic review of the literature and expert opinion.**

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