Epidemiology of Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an often severe autoimmune rheumatic disease of unclear etiology that affects people worldwide. SLE presents with a wide spectrum of clinical patterns and can affect all ages and ethnicities [1]. Regardless of the age of disease onset, the diagnosis relies upon a combination of clinical and laboratory findings which are addressed in more detail in other sections of the book. In this chapter we aim to critically review the epidemiology of SLE.

2.1 Issues in Epidemiological Studies About SLE

Epidemiological studies about SLE are complicated by many issues such as variable disease presentation, the remitting and relapsing nature of the disease, and the presence of different classification criteria. The American College of Rheumatology (ACR) classification is the most widely accepted, and the only validated instrument for "diagnosing" lupus [2–4]; however, these criteria do not represent the full spectrum of disease and other classification criteria have been proposed [5, 6]. These classification criteria were created to identify SLE patients for clinical studies. Patients fulfilling 4 out of the 11 1982 ACR criteria are classified with SLE with

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approximately 95 % certainty, although many individuals who meet only two or three criteria are "diagnosed" with SLE.

The use of different and more sensitive criteria for the assessment and the inclusion of milder cases may partly explain the differences in incidence and prevalence observed in different periods. A study conducted in Olmsted County, Minnesota, analyzed SLE incidence rates in two periods. The age- and sex-adjusted incidence rate was higher in the latter period (1.5 and 5.6 per 100,000 person-years, respectively, in 1950–1979 and 1980–1992) [7]. Similar increases were seen in an incidence study in 1980–1984, 1985–1989, and 1990–1994 in Denmark [8].

Moreover, the different study designs can affect estimation of the prevalence, incidence, morbidity, and mortality. Studies based on the use of population registries potentially allow to identify a greater number of cases. However, often the used diagnostic criteria are not sufficiently controlled. On the other hand, studies carried out by reference centers allow a more precise definition of the reported cases but suffer from a selection bias. In fact, often, patients treated at referral centers are more complex and serious and do not represent the full spectrum of the disease.

Another issue is the potential contribution of undiagnosed disease to the total burden within a population. This issue was addressed by a community survey in Birmingham (United Kingdom), combined with antinuclear antibody testing and clinical assessment of "positive" respondents and reported a prevalence of diagnosed SLE in women ages 18–65 years of 54 per 100,000. With the addition of the cases found during the screening, this estimate rose to 200 per 100,000 [9]. These results were confirmed by subsequent studies conducted in Israel and in Michigan [10, 11].

2.2 Incidence and Prevalence of SLE

According to the last available revision of the literature, incidence rates of SLE range from approximately 1 to 10 per 100,000 person-years, and prevalence rates generally range from 20 to 70 per 100,000 [12]. After that review many studies about SLE epidemiology were conducted worldwide [11, 13–30]. Even if SLE occurs throughout the world, many variables such as ethnicity, geography, sex, and age affect the epidemiology of SLE. In the following sections, we will analyze each of these variables.

Kidney involvement plays a pivotal role in the prognosis of patients with SLE, as it deeply affects mortality and morbidity. Thus, in this chapter we will address this aspect with a special emphasis.

2.3 Ethnicity, Geography, and Genetics in SLE

In North America, the lowest incidences of SLE were seen among Caucasian Americans, Canadians, and Spaniards with incidences of 1.4, 1.6, and 2.2 cases per 100,000 people, respectively [12]. A higher incidence is observed among Arab and Chaldean Americans (age-adjusted incidence of 7.6 and 62.6 per 100,000,

respectively) [30] and among black people (age-adjusted incidence of 3.2 and 13.4 6 per 100,000 for men and for women, respectively) [19, 31].

Throughout Europe, the highest incidences were found in Sweden (4.7 cases/100,000) [32], in France (3.32 cases/100,000) [22], and in Asian (17.45 cases/100,000) and Afro-Caribbean (31.46 cases/100,000) residents of the United Kingdom [24].

Consistent with data from the United Kingdom, the prevalence of SLE was also high in Puerto Rico, with an overall prevalence of 159 per 100,000 individuals (277 per 100,000 for females and 25 per 100,000 for males) [33].

In Australia some studies focused on the difference in SLE prevalence and clinical and laboratory expression between Aboriginal and non-Aboriginal Australians. Prevalence of SLE was higher in Aboriginal than among non-Aboriginal (52.0–92.8 vs 19.3–39.0 cases per 100,000 population) [25]. Both ethnographic and genetic differences and more complex social factors related to poverty and access to care are likely associated with increased risk of the disease.

A systematic review, published by Osio-Salido and Manapat-Reyes in 2010, identified the epidemiological data for 24 Asian countries. Prevalence falls within 30–50/100,000, with a higher prevalence of 70 in Shanghai and a lower prevalence ranging from 3.2 to 19.3 in India, Japan, and Saudi Arabia. Incidence data were available only for three countries (Japan, Hong Kong, and China) and varied from 0.9 to 3.1 per annum [13].

The influence of genetics is one of the factors implicated in differences in epidemiology and clinical expression of SLE in different populations. The genetic basis of SLE is very complex and recent genome-wide studies have identified more than 50 robust loci associated with SLE susceptibility [34]. One study conducted by Wang and coworkers on 695 Chinese SLE patients estimated that the heritability of SLE should be of 43.6 %. The authors concluded that the genetic model of SLE could be a polygenetic model and major gene mode is the best fitted one [35]. Studies on twin show a concordance rate ranging from 2 to 5 % for dizygotic twins and 24–60 % for monozygotic twins. However, this concordance in twins can be explained by behavior as well as by genetic predisposition [36].

The strongest genetic associations are reported for the human leukocyte antigen (HLA) class II (DR2 and DR3), with relative risks of approximately 2.0, with differing strengths of association in different racial populations, and HLA class III region (MSH5 and SKIV2L) [36, 37]. Other non-HLA genes associated with SLE can be classified by the pathway in which they are involved, such as type I interferon pathway (TLR7, IRF5 and IRF7, IFIH1, STAT4, TYK2, and SLC15A4), nuclear factor kB (TNFAIP3, IRAK1, and possibly MECP2), B- and T-cell signaling (PTPN22, c-Src tyrosine kinase, BANK1, BLK, IL10, and IKZF1), immune complex clearance (FCGR2A,FCGR3A, FCGR3B, ITGAM, a protein involved in forming complement receptor 3, and protein involved in classic pathway of complement, especially C1q), production of oxygen reactive species (NCF2, a protein coding for a NADPH oxidase subunit), cell-cycle regulation (CDKN1B), autophagy (ATG5 and DRAM1), and DNA demethylation (TET3) [34].

2.4 Age, Sex, and SLE

Age at onset defines different subtypes of SLE: neonatal lupus, secondary to passive transfer of antibodies from an affected mother to the child, pediatric lupus (pSLE), adulthood SLE, and late-onset SLE (loSLE) [36].

SLE onset is more common in young adults, between 15 and 40 [36]. Pediatric lupus accounts approximately 10–20 % of cases [38]. The onset of SLE beyond the age of 50 years is reported to occur in 3–18 % of patients [39].

During the child-bearing years, the ratio of women to men with lupus is approximately 9:1. This ratio is less in younger (2:1) and older (3:1) populations, supporting a role for hormonal factors in disease induction and pathogenesis [1, 36]. The higher incidence among women is clearly seen in black people in the United States (crude incidence per 100,000 of 13.6 in women vs 2.6 in men) [19]. A similar pattern is observed in other populations, as seen in a large study from the United Kingdom as well as in smaller studies from the Sweden and Iceland. However, in these populations the highest age-specific incidence rates are generally seen after 40 years of age. Although there are no incident data for Hispanics in the United States or Latin America, some studies suggest they also develop lupus earlier in life [24].

The importance of hormonal and reproductive factor in the highest susceptibility of women to SLE has been proven by few studies that correlate age at menarche with risk to develop SLE (odds 4.6-fold higher for women with menarche at age 10 years versus menarche at age 13 years). Menstrual irregularities were also associated with increased risk of SLE in a Japanese case–control study and in the Carolina Lupus study [36].

Many authors have studied the influence of oral contraceptives on SLE onset but the results are controversial. In addition, the effect of breastfeeding has been analyzed with an apparent protective effect. Finally, early menopausal and postmenopausal hormone therapy seems to be correlated with a higher risk of SLE [36].

2.5 Other Risk Factors for SLE Development

Tobacco smoking has been proposed to be a trigger for the development of SLE. Results of nine studies have been summarized in a meta-analysis by Costenbader and coworkers. The authors revealed a small but significantly increased risk for the development of SLE among current smokers compared with nonsmokers (OR 1.50, 95 % CI 1.09–2.08). They did not observe a similar association for ex-smokers compared with never smokers, concluding that the effect of active smoking on risk appears to be stronger than a past exposure [40]. A subsequent Japanese study showed that the association between smoking and a particular polymorphism of the receptor for TNF, TNFRSF1B, was associated with a greater risk of developing SLE [41]. Moreover, two studies conducted in Japan showed a dose–response relationship between smoking and the risk of SLE [41].

The role of alcohol consumption is more controversial. A meta-analysis conducted by Wang and coworkers showed that moderate alcohol intake has a protective effect on the development of SLE [42]. Heavy alcohol consumption (>4–5 days/week) was shown to be associated with odds of 4.49 (95 % CI, 1.43–14.08) for the occurrence of SLE only in some populations, suggesting that additional genetic or environmental factors can interact with alcohol consumption in SLE development [41].

Some medications, such as procainamide, can induce lupus-like disease, typically without the presence of autoantibodies, in susceptible individuals. To date, the drugs mainly associated with the development of SLE in animal models are estrogen. However, even if some case series described the induction of SLE and disease flares in patients who took combined oral contraceptive pills, a randomized controlled trial found that combined oral contraceptives did not confer a higher risk of disease flares in women with clinically stable SLE. On the other hand, another randomized controlled trial did find a higher risk of mild to moderate lupus flares in postmenopausal women with SLE who used hormone replacement therapy [41].

Other drugs that have been supposed to be associated with SLE induction are anti-TNF used in the treatment of inflammatory arthritis. Even if cases of anti-TNF-induced lupus have been reported, we lack a clear figure of real impact of these agents in SLE induction [43].

The supposed association between LES and vaccines has never been proven [41]. A recent analysis conducted in silico by McGarvey and colleagues suggests that the presence of some genetic variations associated with specific immunological pathways could be associated with a higher risk to develop autoimmune diseases such as SLE as a consequences of vaccination [44]. These preliminary data need confirmation that should necessarily be based on genetic epidemiology studies conducted on large populations.

Many other chemicals, such as crystalline silica, chlorinated compounds, mercury, liquid pesticides, solvents, phthalates (that are also present in lipsticks), and aromatic amines (that are also found in hair dyes), have been associated with SLE onset or flairs [41].

2.6 SLE Mortality, Morbidity, and Clinical Expression

SLE still remains an important cause of morbidity and mortality among young and middle-aged people, but, until the middle of the last century, 5-year survival was <50 % [36].

Owing to improvements in disease management and recognition over the past 20–30 years, patients now live longer, but as a result have increased disease damage.

Such as incidence and prevalence, also the clinical expression, the morbidity, and the mortality of SLE are influenced by ethnicity, geography, sex, and age at the onset.

Few Australian studies investigated the differences in SLE expression between Aboriginal and non-Aboriginal in Australia with heterogeneous results. One study reported that laboratory anomalies and organ involvement were similar in Aboriginal and non-Aboriginal Australians, but another reported differences (not statistically significant) between these populations in clinical manifestations and certain laboratory features, including malar rash, discoid rash, photosensitivity, oral ulcers, pleuritis and anticardiolipin, anti-Smith and anti-ribonucleoprotein antibodies, and lupus anticoagulant. Other analyses investigated SLE features in Asian Australians. Two studies reported that Asian Australians were more affected by SLE than non-Asian Australians in terms of disease severity, renal involvement, photosensitivity, laboratory characteristics, and flares [25].

A recent study from Qian and colleagues explored the correlation between SLE activity and altitudinal variations. The authors performed a retrospective analysis of 1,029 hospitalized patients in China. The study did not found significant correlation between SLE activity (recorded using SLEDAI) and altitudes. However, the authors found a correlation between the age at diseases onset and at hospital admission, the presence of Sm antibodies, and living at high altitudes [45].

Pediatric cases are associated with higher disease severity, more rapid damage accrual (the majority of patients will have developed damage within 5–10 years of disease onset), and atypical presentations than adult-onset SLE. Premature atherosclerosis and osteoporosis have become increasingly prevalent morbidities in pSLE patients. Differential ethnic expression is present in pediatric patients such as in adult with a more severe disease course in patients of African ancestry. The most prevalent manifestations of SLE in pediatric patients are musculoskeletal, ocular, renal, and neuropsychiatric. Furthermore, the presentation of a serious incurable, potentially devastating disease, in a period of important psychosocial development, may result in significant psychosocial stress [38]. The serological pattern of pediatric patients can be characterized by absence of ANA and anti-nDNA antibodies, mostly in SLE secondary to complement deficiencies [46]. Due to the more severe course of disease, patients with pSLE have a higher mortality than patients with adult onset (mortality hazard ratios of 6.29 vs 1.75) [47].

loSLE is usually associated with milder manifestations. The most prevalent manifestations are pulmonary involvement and serositis. Furthermore, late-onset SLE can be associated with Sjogren's syndrome and may present an atypical serological pattern with the presence of rheumatoid factor and of antinuclear antibody and a lower frequency of anti-ribonucleoprotein (anti-RNP) and anti-Sm antibody [39]. Despite the milder presentation, loSLE is associated with poorer survival than early-onset SLE (mortality hazard ratios of 3.44 vs 1.75 in patients with adult onset) [47]. The higher mortality likely reflects the consequences of aging rather than true differences in survival. Importantly, the cause of death in late-onset SLE patients is usually not SLE itself, but rather the more frequent occurrence of infections, cardiovascular disorders, malignancies, or drug-induced complications [39].

Few studies tried to explore the role of socioeconomic factors as risk factors for SLE outcome. Poorer outcomes and higher disease activity have been associated with measures of socioeconomic status (SES) such as insurance, income, and education. It is often difficult to disentangle these from other closely related potential

risk factors associated with disease susceptibility such as environmental and toxic exposure. Non-Caucasian race, lower levels of education, and limited access to medical care appear to be associated with SLE-related organ damage and higher morbidity. Broader measures of lower SES, such as the Hollingshead Index, were associated with patients' perceived health outcomes such that lower SES was associated with higher morbidity [36].

Deficiency of vitamin D was demonstrated to be associated with higher lupus disease activity. In a recent study from Petri and colleagues, 1,006 SLE patients were assessed for serum 25(OH)D levels, 76 % of which had levels of 25(OH)D that were <40 ng/ml (insufficient). This percentage was significantly higher among African-Americans (85 %) and among those ages 30–59 (79 %). Moreover, in patients with insufficient 25(OH)D levels, a 20-ng/ml increase in serum was shown to be associated with a 15 % decrease in the odds of clinically important proteinuria (urine protein-to-creatinine ratio >0.5) [48].

2.7 Lupus Nephritis

Renal involvement is a major complication of SLE and a strong determinant of morbidity and mortality. About 60 % of SLE patients develop kidney involvement [49].

A clear definition of what we are referring to as "lupus nephritis" must be introduced. Traditionally, authors refer to lupus nephritis (LN) as the glomerular involvement in the course of SLE. However, the kidney involvement in the context of the disease may be heterogeneous, also including tubulointerstitial nephropathy, which manifests clinically with electrolyte disorders and/or renal acidosis, and different features of vascular disease.

In the following paragraphs, we will refer to the lupus glomerulonephritis as LN. Similarly to other manifestations of SLE, many factors influence LN incidence estimates: location, ethnicity, gender, and method of diagnosis.

The literature reports a frequency of LN among SLE patients ranging from 40 to 70 % [50]. However, this estimation is probably lower than the real one, because of the bias generated by the method of diagnosis. Patients with less severe forms of lupus glomerulonephritis may not undergo renal biopsy ascertainment, hence resulting in incorrect estimate.

Moreover the incidence of LN may have been modified over the recent years by the use of more aggressive treatments.

Most SLE patients develop nephritis early in the course of their disease. The vast majority is younger than 55 years. Children are more likely to develop severe nephritis than elderly patients [51].

2.8 LN Histological Classification

The 2003 edition of the ISN/RPS classification of the modified WHO histological classification of LN [52] has significantly improved management and prognosis of the disease [49].

According to the ISN/RPS classification [52], lupus glomerulonephritis ranges from less severe to highly severe forms. The most active forms, such as class III, IV, and V, are usually ascertained by biopsy. On the contrary, patients with less severe forms (class I, II, and probably some of class III cases) may not be submitted to renal biopsy, so that these forms may elude the epidemiologic estimates.

At this regard, in one study kidney biopsy was offered to all patients with SLE seen at a Japanese hospital over an 11-year period, whether or not clinical signs of renal disease were present [53]. Of the 195 patients who had adequate biopsies, 86 had no clinical renal involvement. Of these 86 patients without clinical renal disease, 13 (15 %) had either class III or IV lupus nephritis and 9 (10 %) had class V disease.

2.9 Immunosuppression and Renal Replacement Advancements

Despite the ancient history of SLE, the renal manifestations were described for the first time in the early 1900s [54] (Fig. 2.1).

Renal failure soon emerged as an important cause of death among SLE patients. Survival rate was less than 50 % at 5 years for LN patients in the late 1950s [55]. Survival of LN patients with end-stage kidney disease (ESKD) was negatively affected by the absence of renal replacement therapies (RRTs) or by their delayed utilization (Fig. 2.1).

Hemodialysis (HD) for LN was first reported only in the mid-1970s and only in the European literature. Initial reports indicated that the outcomes of LN patients with ESKD who underwent RRT seemed to be worse than those of the general

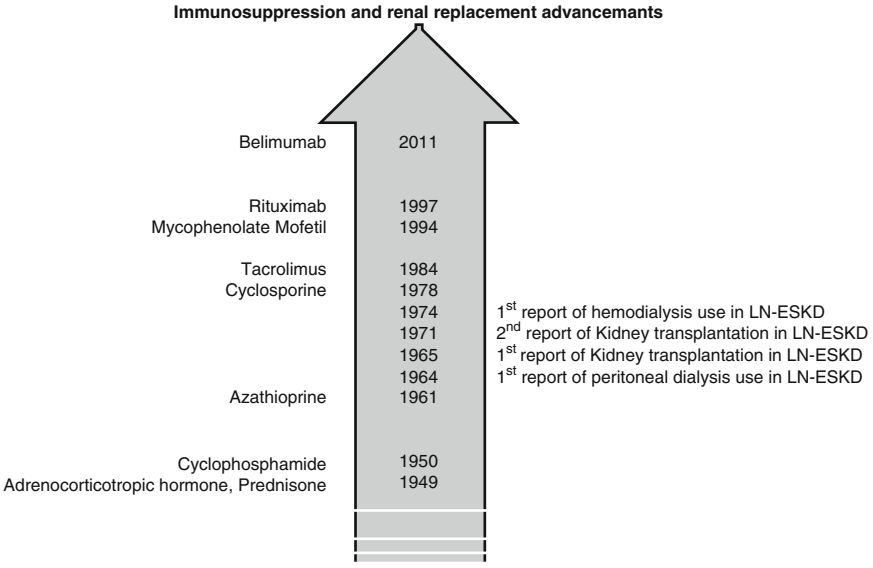

Fig. 2.1 Timeline of immunosuppressions and renal replacement advancements

ESKD population [56]. Morbidity in the SLE group was primarily associated with infection and vascular access problems, but no deaths were directly attributable to SLE activity.

The 5-year survival rate in the early 1980s was reported to be significantly lower in HD-dependent SLE patients than in non-SLE HD patients (58.6 % versus 88.5 %).

With advances in lupus treatment, outcome improved dramatically. Studies from the 1990s reported that more than 93 % of LN patients survived for 5 years and 85 % survived for 10 years [57] and the 5-year survival rate for patients on dialysis increased to 73 % [56, 58]. As the need for a dialytic treatment may be only temporary, dialysis now represents the opportunity for renal recovery.

Hence the almost free availability of dialysis also affects epidemiologic data: the incidence of LN-associated ESKD has increased from 1.16 cases per million in 1982 to 4.9 cases per million in 2004 in the United States [59, 60].

2.10 General Data on Lupus Nephritis

Several data are reported about prevalence and incidence of LN.

The overall annual incidence rate has been rated 0.40 per 100,000 subjects per year (95 % CI 0.24–0.63) [61] and the prevalence ranging from 4.4 per 100,000 inhabitants (95 % CI 3.8–5.0) (in northwest England in 2001-Patel-) to 6.85/100,000 person-years [62].

Prevalence and incidence are increasing over the years. Iseki et al. [63] analyzed 566 SLE patients in Japan over a 20-year period. They found that the annual incidence and prevalence of LN in women had increased from 16.0 per million and 66.0 per million, respectively, in 1972 to 46.7 and 683.3, respectively, in 1991 and that the annual incidence and prevalence in men had increased from 4.2 and 8.3, respectively, in 1972 to 8.3 and 70.0, respectively, in 1991.

It is unclear why the prevalence of end-stage LN increased by nearly tenfold in 20 years. One possible explanation is an improvement in therapeutic option, resulting in a lower patient mortality and a possible longer life span, compatible with a potential development of renal failure.

In a recent retrospective study, male sex, young age (<33 years), and non-European ancestry were found to be determinants of earlier renal disease in patients with SLE [49].

2.11 Gender

The striking prevalence of women affected with SLE is less evident as regards LN.

More severe renal disease, skin lesions, serositis, thrombotic events, and seizures have been reported in males by several authors [64].

Whereas the incidence of SLE among the male population is low when androgen levels are high, the incidence approaches the same of the female population during childhood and old age when androgen levels are low.

In the study of Patel [61], the annual incidence rate was higher in women, at 0.68 per 100,000 per year (95 % CI 0.40–1.10), than in men, at 0.09 per 100,000 per year (95 % CI 0.01–0.32).

The prevalence rates were also higher in women than in men (7.1 per 100,000 [95 % CI 6.1–8.2] versus 1.4 per 100,000 [95 % CI 1.0–2.0], respectively) [61], and this was true for all ethnic groups.

In Saxena study [49], the median age at diagnosis was 35 years (IQR 65.1–65.9) in men.

Male gender was found to be a poor prognostic factor for the clinical course of LN, progression to ESKD, and morbidity [59, 65].

2.12 Ethnicity

It is well known that frequency and severity of LN differ among ethnicities.

Besides a higher SLE incidence, African-American ethnicities may present with more severe presentation and earlier renal disease, as shown in a retrospective study [50].

In the Saxena study [49], a higher proportion of Indo-Asian patients with SLE (27 %) and an even higher proportion of Afro-Caribbean patients with SLE (58 %) were estimated to have LN when compared to the white population, in which the estimated proportion of SLE patients with LN was 10 %. The prevalence estimates were significantly higher in women, in particular, in the Chinese and Afro-Caribbean populations when compared with the white population. Indeed, there was a marked ethnic gradient, with the prevalence estimates increasing from the white population to the Indo-Asian, Afro-Caribbean, and the Chinese populations.

2.13 Socioeconomic Status

A number of studies suggest that LN is both more common and more severe in some ethnic minorities and progression to end-stage renal disease is higher in uninsured and low SES groups [66, 67].

An interesting study based on the Medicaid Analytic eXtract (MAX) administrative data system analyzes LN patients searched on the basis on ≥2 ICD-9 hospital discharge diagnoses of LN from January 1, 2000, to December 31, 2004.

The study was conducted utilizing combined categories: white, black or African-American, Hispanic or Latino, Asian (including Pacific Islander), Native American, and others. Seven SES indicators were taken into account: median household income, proportion with income below 200 % of the federal poverty level, median home value, median monthly rent, mean education level, proportion of people age >25 who were college graduates, and proportion of employed persons with a professional occupation.

From 2000 to 2004, the prevalence of LN was 30.9 per 100,000 (7,388 individuals) or 21.5 % of SLE cases, with higher rates among all non-Caucasian racial/ethnic groups compared to whites.

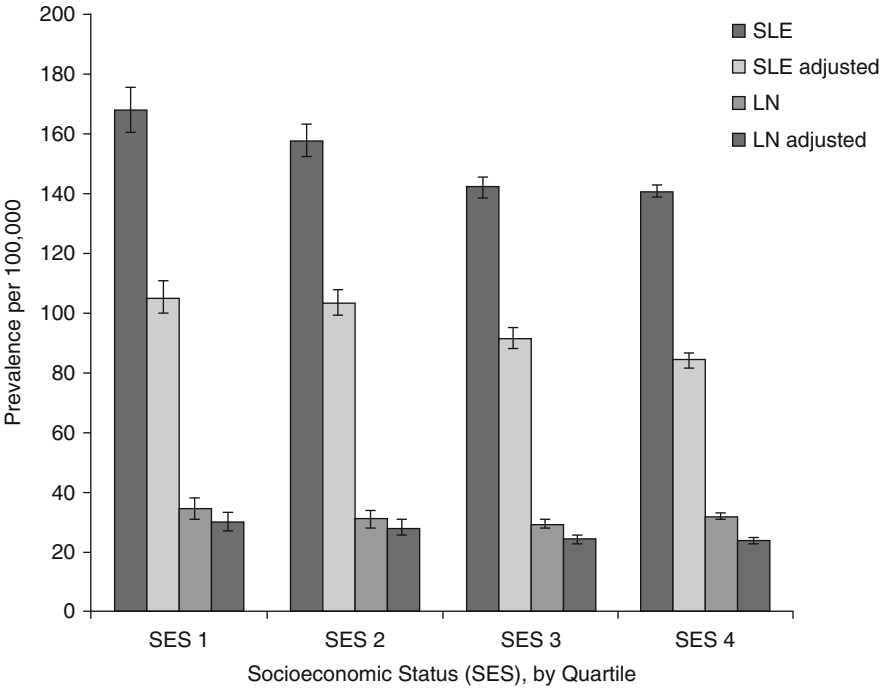

Fig. 2.2 Prevalence of systemic lupus erythematosus (*SLE*) and lupus nephritis (*LN*) per 100,000 US Medicaid enrollees ages 18–65 years, stratified by socioeconomic status (*SES*) quartile (SES 1 [lowest] = –1.62 or below, SES 2 = above –1.62 through –0.74, SES 3 = above –0.74 through 0.26, SES 4 [highest] = above 0.26). Results of crude analyses and analyses adjusted for age group, sex, and race/ethnicity are shown. Bars represent 95 % confidence intervals. (Modified from Feldman et al. [62])

By dividing the population into quartiles of county level SES, statistically significant differences were found between the lowest SES group, which had the highest SLE prevalence (167.9 per 100,000, 95 % CI 160.4–175.7) and the two highest SES quartiles, which had the lowest SLE prevalence. A similar pattern was found after adjusting for age, sex, and race/ethnicity.

On the opposite, the trend of LN prevalence did not differ significantly across SES quartiles. This suggests that genetics may be a more important determinant in the development of LN compared to SLE. It is also possible that once individuals enter into care for their SLE, SES contributes less to disease complications (Fig. 2.2).

2.14 Lupus Nephritis and Progression Toward End Stage Kidney Disease

Overall prognosis of SLE patients has improved in recent decades [59]. However, approximately 10–30 % of patients with proliferative LN progress to ESKD.

The incidence of LN-associated ESKD has increased from 1.16 cases per million in 1982 to 4.9 cases per million in 2004 in the United States (Fig. 2.3) [59, 60].

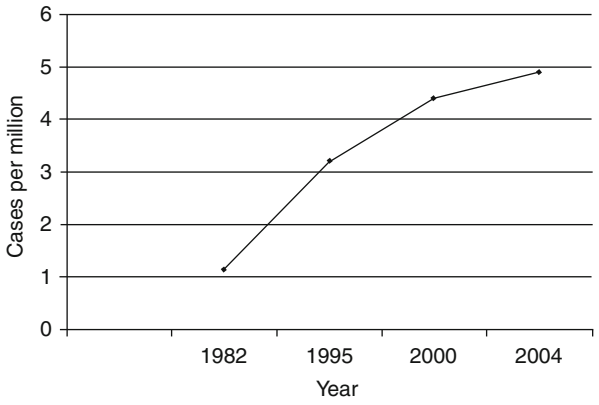

Fig. 2.3 Incidence of end-stage kidney disease from lupus nephritis in the United States, 1982–2004 (Modified from [59, 60])

Analysis of the US Renal Data System from 1996 to 2004 showed that there were 9,199 new cases of ESKD attributable to LN with most patients being of African-American descent and of female sex (49 % and 82 % of cases, respectively) [59, 68]. This increase in the incidence of ESKD due to LN is a cause for concern. Recent epidemiological studies have pointed to several risk factors associated with the progression of LN to ESKD that could affect these estimations.

Young age is one of the primary risk factors for progression to ESKD. It was reported that up to 75 % of children with SLE eventually develop nephritis and 18–50 % show progression to ESKD [69, 70]. The lack of standardized protocols for treating LN in pediatric populations is a challenge in managing treatment.

Delayed renal biopsy [71, 72] and delay in treatment of LN are other important risk factors associated with poor outcomes and progression to ESKD. Specifically, an elapsed time of more than 6 months between urinary evidence of nephropathy and biopsy has been associated with progression to ESKD.

While ESKD in LN appears to have stopped increasing in the last decade, ethnical disparities in outcomes persist: the African-Americans are still more likely to die prematurely [73].

Tubulointerstitial involvement with or without immune deposits along the tubular basement membrane is a common finding in LN, almost always being seen with concurrent glomerular disease [74, 75].

The severity of the tubulointerstitial involvement is an important prognostic sign. In a Chinese study of 313 patients with LN, for example, the presence of tubulointerstitial nephritis was significantly associated with a twofold higher risk of developing end-stage renal disease [76].

In a few cases, tubulointerstitial involvement is the only manifestation of LN. This possibility should be suspected when a patient with SLE presents with a rising plasma creatinine concentration and a urinalysis that is relatively normal or shows only a few red cells and/or white cells. These changes may be accompanied by signs of tubular dysfunction such as metabolic acidosis due to type 1 (distal) renal tubular acidosis, hyperkalemia, or hypokalemia [77, 78].

Involvement of the renal vasculature is not uncommon in LN, and its presence can adversely affect the prognosis of the renal disease [79]. The most frequent manifestations are immune complex deposition, immunoglobulin microvascular "thrombi" [78], a thrombotic microangiopathy [80, 81], vasculitis [82], or atheroembolic disease and atherosclerosis.

Rarely, patients with LN develop renal vein thrombosis [83].

Conclusions

According to the most recent revision of the literature, incidence rates of SLE range from approximately 1 to 10 per 100,000 person-years, and prevalence rates generally range from 20 to 70 per 100,000. Even if SLE occurs throughout the world, many variables such as ethnicity, geography, sex, and age affect the epidemiology of SLE.

Kidney involvement plays a pivotal role in the prognosis of patients with SLE, as still approximately 10–30 % of patients with proliferative LN progress to ESKD.

Prevalence and incidence are increasing over the years. A "big data" approach in perspective studies will enable hitherto unseen connections in SLE epidemiology to emerge.

References

1. Tsokos GC (2011) Systemic lupus erythematosus. N Engl J Med 365(22):2110–2121. doi:10.1056/NEJMra1100359
2. Tan EM, Cohen AS, Fries JF et al (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25(11):1271–1277, http://www.ncbi.nlm.nih.gov/pubmed/7138600. Accessed 13 May 2015
3. Levin RE, Weinstein A, Peterson M et al (1984) A comparison of the sensitivity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 27(5):530–538, http://www.ncbi.nlm.nih.gov/pubmed/6721885. Accessed 13 May 2015
4. Passas CM, Wong RL, Peterson M et al (1985) A comparison of the specificity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 28(6):620–623, http://www.ncbi.nlm.nih.gov/pubmed/4004972. Accessed 13 May 2015
5. Petri M (2005) Review of classification criteria for systemic lupus erythematosus. Rheum Dis Clin N Am 31(2):245–254, vi. doi:10.1016/j.rdc.2005.01.009
6. Petri M, Orbai A-M, Alarcón GS et al (2012) Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 64(8):2677–2686. doi:10.1002/art.34473
7. Uramoto KM, Michet CJ, Thumboo J et al (1999) Trends in the incidence and mortality of systemic lupus erythematosus, 1950–1992. Arthritis Rheum 42(1):46–50. doi:10.1002/1529-0131(199901)42:1<46::AID-ANR6>3.0.CO;2-2
8. Voss A, Green A, Junker P (1998) Systemic lupus erythematosus in Denmark: clinical and epidemiological characterization of a county-based cohort. Scand J Rheumatol 27(2):98–105, http://www.ncbi.nlm.nih.gov/pubmed/9572634. Accessed 23 May 2015

9. Johnson AE, Gordon C, Hobbs FD et al (1996) Undiagnosed systemic lupus erythematosus in the community. Lancet 347(8998):367–369, http://www.ncbi.nlm.nih.gov/pubmed/8598703. Accessed 23 May 2015
10. Geva E, Lerner-Geva L, Burke M et al (2004) Undiagnosed systemic lupus erythematosus in a cohort of infertile women. Am J Reprod Immunol 51(5):336–340. doi:10.1111/j.1600-0897.2004.00165.x
11. Somers EC, Marder W, Cagnoli P et al (2014) Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol (Hoboken NJ) 66(2):369–378. doi:10.1002/art.38238
12. Pons-Estel GJ, Alarcon GS, Scofield L et al (2010) Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum 39(4):257–268. doi:10.1016/j.semarthrit.2008.10.007
13. Osio-Salido E, Manapat-Reyes H (2010) Epidemiology of systemic lupus erythematosus in Asia. Lupus 19(12):1365–1373. doi:10.1177/0961203310374305
14. Mok CC (2011) Epidemiology and survival of systemic lupus erythematosus in Hong Kong Chinese. Lupus 20(7):767–771. doi:10.1177/0961203310388447
15. Barnabe C, Joseph L, Belisle P et al (2012) Prevalence of systemic lupus erythematosus and systemic sclerosis in the First Nations population of Alberta, Canada. Arthritis Care Res (Hoboken) 64(1):138–143. doi:10.1002/acr.20656
16. Furst DE, Clarke AE, Fernandes AW et al (2013) Incidence and prevalence of adult systemic lupus erythematosus in a large US managed-care population. Lupus 22(1):99–105. doi:10.1177/0961203312463110
17. Ng R, Bernatsky S, Rahme E (2013) Observation period effects on estimation of systemic lupus erythematosus incidence and prevalence in Quebec. J Rheumatol 40(8):1334–1336. doi:10.3899/jrheum.121215
18. Shim J-S, Sung Y-K, Joo YB et al (2014) Prevalence and incidence of systemic lupus erythematosus in South Korea. Rheumatol Int 34(7):909–917
19. Lim SS, Bayakly AR, Helmick CG et al (2014) The incidence and prevalence of systemic lupus erythematosus, 2002–2004: the Georgia Lupus Registry. Arthritis Rheumatol (Hoboken NJ) 66(2):357–368. doi:10.1002/art.38239
20. Zou Y-F, Feng C-C, Zhu J-M et al (2014) Prevalence of systemic lupus erythematosus and risk factors in rural areas of Anhui Province. Rheumatol Int 34(3):347–356. doi:10.1007/s00296-013-2902-1
21. Simard JF, Sjowall C, Ronnblom L et al (2014) Systemic lupus erythematosus prevalence in Sweden in 2010: what do national registers say? Arthritis Care Res (Hoboken) 66(11):1710–1717. doi:10.1002/acr.22355
22. Arnaud L, Fagot J-P, Mathian A et al (2014) Prevalence and incidence of systemic lupus erythematosus in France: a 2010 nation-wide population-based study. Autoimmun Rev 13(11):1082–1089. doi:10.1016/j.autrev.2014.08.034
23. Ferucci ED, Johnston JM, Gaddy JR et al (2014) Prevalence and incidence of systemic lupus erythematosus in a population-based registry of American Indian and Alaska Native people, 2007–2009. Arthritis Rheumatol (Hoboken NJ) 66(9):2494–2502. doi:10.1002/art.38720
24. Rees F, Doherty M, Grainge M et al (2014) The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012. Ann Rheum Dis. doi:10.1136/annrheumdis-2014-206334
25. Nikpour M, Bridge JA, Richter S (2014) A systematic review of prevalence, disease characteristics and management of systemic lupus erythematosus in Australia: identifying areas of unmet need. Intern Med J 44(12a):1170–1179. doi:10.1111/imj.12568
26. Ju JH, Yoon S-H, Kang KY et al (2014) Prevalence of systemic lupus erythematosus in South Korea: an administrative database study. J Epidemiol 24(4):295–303
27. Nasonov E, Soloviev S, Davidson JE et al (2014) The prevalence and incidence of systemic lupus erythematosus (SLE) in selected cities from three Commonwealth of Independent States countries (the Russian Federation, Ukraine and Kazakhstan). Lupus 23(2):213–219. doi:10.1177/0961203313512881

28. Jarukitsopa S, Hoganson DD, Crowson CS et al (2014) Epidemiology of systemic lupus erythematosus and cutaneous lupus in a predominantly white population in the United States. Arthritis Care Res (Hoboken). doi:10.1002/acr.22502
29. Brinks R, Fischer-Betz R, Sander O et al (2014) Age-specific prevalence of diagnosed systemic lupus erythematosus in Germany 2002 and projection to 2030. Lupus 23(13):1407–1411. doi:10.1177/0961203314540352
30. Housey M, DeGuire P, Lyon-Callo S et al (2015) Incidence and prevalence of systemic lupus erythematosus among Arab and Chaldean Americans in southeastern Michigan: the Michigan Lupus Epidemiology and Surveillance Program. Am J Public Health 105(5):e74–e79. doi:10.2105/AJPH.2014.302423
31. Urowitz MB, Gladman DD, Tom BDM et al (2008) Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol 35(11):2152–2158
32. Ståhl-Hallengren C, Jönsen A, Nived O et al (2000) Incidence studies of systemic lupus erythematosus in Southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. J Rheumatol 27(3):685–691, http://www.ncbi.nlm.nih.gov/pubmed/10743809. Accessed 23 May 2015
33. Molina MJ, Mayor AM, Franco AE et al (2007) Prevalence of systemic lupus erythematosus and associated comorbidities in Puerto Rico. J Clin Rheumatol 13(4):202–204. doi:10.1097/RHU.0b013e318124a8af
34. Deng Y, Tsao BP (2014) Advances in lupus genetics and epigenetics. Curr Opin Rheumatol 26(5):1–11. doi:10.1097/BOR.0000000000000086
35. Wang J, Yang S, Chen JJ et al (2007) Systemic lupus erythematosus: a genetic epidemiology study of 695 patients from China. Arch Dermatol Res 298(10):485–491. doi:10.1007/s00403-006-0719-4
36. Simard JF, Costenbader KH (2007) What can epidemiology tell us about systemic lupus erythematosus? Int J Clin Pract 61(7):1170–1180. doi:10.1111/j.1742-1241.2007.01434.x
37. Deng Y, Tsao BP (2011) Genetic susceptibility to systemic lupus erythematosus in the genomic era. Nat Rev Rheumatol 6(12):683–692. doi:10.1038/nrrheum.2010.176.Genetic
38. Kamphuis S, Silverman ED (2010) Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol 6(9):538–546. doi:10.1038/nrrheum.2010.121
39. Arnaud L, Mathian A, Boddaert J et al (2012) Late-onset systemic lupus erythematosus: epidemiology, diagnosis and treatment. Drugs Aging 29(3):181–189. doi:10.2165/11598550-000000000-00000
40. Costenbader KH, Kim DJ, Peerzada J et al (2004) Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. Arthritis Rheum 50(3):849–857. doi:10.1002/art.20049
41. Mak A, Tay S (2014) Environmental factors, toxicants and systemic lupus erythematosus. Int J Mol Sci 15(9):16043–16056. doi:10.3390/ijms150916043
42. Wang J, Pan H-F, Ye D-Q et al (2008) Moderate alcohol drinking might be protective for systemic lupus erythematosus: a systematic review and meta-analysis. Clin Rheumatol 27(12):1557–1563. doi:10.1007/s10067-008-1004-z
43. Postal M, Appenzeller S (2011) The role of Tumor Necrosis Factor-alpha (TNF-α) in the pathogenesis of systemic lupus erythematosus. Cytokine 56(3):537–543. doi:10.1016/j.cyto.2011.08.026
44. McGarvey PB, Suzek BE, Baraniuk JN et al (2014) In silico analysis of autoimmune diseases and genetic relationships to vaccination against infectious diseases. BMC Immunol 15(1):1–12. doi:10.1186/s12865-014-0061-0
45. Qian G, Ran X, Zhou CX et al (2014) Systemic lupus erythematosus patients in the low-latitude plateau of China: altitudinal influences. Lupus 23(14):1537–1545. doi:10.1177/0961203314544186
46. Leffler J, Bengtsson AA, Blom AM (2014) The complement system in systemic lupus erythematosus: an update. Ann Rheum Dis 73(9):1601–1606. doi:10.1136/annrheumdis-2014-205287
47. Chen Y-M, Lin C-HC-H, Chen H-H et al (2013) Onset age affects mortality and renal outcome of female systemic lupus erythematosus patients: a nationwide population-based study in Taiwan. Rheumatology 53(1):180–185. doi:10.1093/rheumatology/ket330

48. Petri M, Bello KJ, Fang H et al (2013) Vitamin D in systemic lupus erythematosus: modest association with disease activity and the urine protein-to-creatinine ratio. Arthritis Rheum 65(7):1865–1871. doi:10.1002/art.37953
49. Saxena R, Mahajan T, Mohan C (2011) Lupus nephritis: current update. Arthritis Res Ther 13:240–252
50. Seligman VA, Lum RF, Olson JL, et al (2002) Demographic differences in the development of lupus nephritis: a retrospective analysis. Am J Med 112:726–729
51. Mak A, Mok CC, Chu WP et al (2007) Renal damage in systemic lupus erythematosus: a comparative analysis of different age groups. Lupus 16:28–34
52. Weening JJ, D'Agati VD, Schwartz MM et al (2004) The classification of glomerulonephritis in systemic lupus erythematosus revisited. Am J Kidney Dis 15:241–250
53. Wakasugi D, Gono T, Kawaguchi Y et al (2012) Frequency of class III and IV nephritis in systemic lupus erythematosus without clinical renal involvement: an analysis of predictive measures. J Rheumatol 39:79
54. Osler W (1904) On the visceral manifestations of the erythema group of skin diseases. Am J Med Sci 127:1–23
55. Maroz N, Segal MS (2013) Lupus nephritis and end-stage kidney disease. Am J Med Sci 346:319–323
56. Jarrett M, Santhanam S, Del Greco F (1983) The clinical course of endstage renal disease in systemic lupus erythematosus. Arch Intern Med 143:1353–1356
57. Cervera R, Khamashta M, Hughes G (2009) The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. Lupus 18:869–874
58. Mojcik C, Klippel J (1996) End-stage renal disease and systemic lupus erythematosus. Am J Med 101:100–107
59. Ward MM (2009) Changes in the incidence of endstage renal disease due to lupus nephritis in the United States, 1996–2004. J Rheumatol 36:63–67
60. Ward MM (2000) Changes in the incidence of end-stage renal disease due to lupus nephritis, 1982–1995. Arch Intern Med 160:3136–3140
61. Patel M, Clarke AM, Bruce IN et al (2006) The prevalence and incidence of biopsy-proven lupus nephritis in the UK: evidence of an ethnic gradient. Arthritis Rheum 54:2963–2969
62. Feldman CH, Hiraki LT, Liu J et al (2013) Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among U.S. adults with Medicaid coverage, 2000–2004. Arthritis Rheum 65:753–763
63. Iseki K, Miyasato F, Oura T et al (1994) An epidemiologic analysis of end-stage lupus nephritis. Am J Kidney Dis 23:547–554
64. Andrade RM, Alarcon GS, Fernandez S et al LUMINA Study Group (2007) Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. Arthritis Rheum 56:622–630
65. Chen HA, Wang JJ, Chou CT et al (2011) Predictors of long term mortality in patients with and without systemic lupus erythematosus on maintenance dialysis: a comparative study. J Rheumatol 38:2390–2394
66. McCarty DJ, Manzi S, Medsger TA Jr et al (1995) Incidence of systemic lupus erythematosus: race and gender differences. Arthritis Rheum 38:1260–1270
67. Bastian HM, Roseman JM, McGwin G Jr et al (2002) Systemic lupus erythematosus in three ethnic groups. XII. Risk factors for lupus nephritis after diagnosis. Lupus 11:152–160
68. Costenbader K, Desai A, Alarcon G et al (2011) Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupusnephritis in the US from 1995 to 2006. Arthritis Rheum 63:1681–1688
69. Hiraki L, Lu B, Alexander S et al (2011) End-stage renal disease due to lupus nephritis among children in the US, 1995–2006. Arthritis Rheum 63:1988–1997
70. Bartosh SM, Fine RN, Sullivan EK (2001) Outcome after transplantation of young patients with systemic lupus erythematosus: a report of the North American pediatric renal transplant cooperative study. Transplantation 72:973–978

71. Fiehn C, Hajjar Y, Mueller K et al (2003) Improved clinical outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment. Ann Rheum Dis 62:435–439
72. Esdaile J, Levinton C, Federgreen W et al (1989) The clinical and renal biopsy predictors of long-term outcome in lupus nephritis: a study of 87 patients and review of the literature. Q J Med 72:779–833
73. Sexton DJ, Reule S, Solid C et al (2015) ESKD from lupus nephritis in the United States, 1995–2010. Clin J Am Soc Nephrol 10:251–259
74. Brentjens JR, Sepulveda M, Baliah T et al (1975) Interstitial immune complex nephritis in patients with systemic lupus erythematosus. Kidney Int 7:342
75. Park MH, D'Agati V, Appel GB et al (1986) Tubulointerstitial disease in lupus nephritis: relationship to immune deposits, interstitial inflammation, glomerular changes, renal function, and prognosis. Nephron 44:309
76. Yu F, Wu LH, Tan Y et al (2010) Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. Kidney Int 77:820
77. Kozeny GA, Barr W, Bansal VK et al (1987) Occurrence of renal tubular dysfunction in lupus nephritis. Arch Intern Med 147:891
78. DeFronzo RA, Cooke CR, Goldberg M et al (1977) Impaired renal tubular potassium secretion in systemic lupus erythematosus. Ann Intern Med 86:268
79. Wu LH, Yu F, Tan Y et al (2013) Inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis improves renal outcome predictions. Kidney Int 83:715
80. Kwok SK, Ju JH, Cho CS et al (2009) Thrombotic thrombocytopenic purpura in systemic lupus erythematosus: risk factors and clinical outcome: a single centre study. Lupus 18:16
81. Song D, Wu LH, Wang FM et al (2013) The spectrum of renal thrombotic microangiopathy in lupus nephritis. Arthritis Res Ther 15:R12
82. Abdellatif AA, Waris S, Lakhani A et al (2010) True vasculitis in lupus nephritis. Clin Nephrol 74:106
83. Gelfand J, Truong L, Stern L et al (1985) Thrombotic thrombocytopenic purpura syndrome in systemic lupus erythematosus: treatment with plasma infusion. Am J Kidney Dis 6:154