

Disease classification

2.1 Historical development

The term ‘lupus’, Latin for wolf, has been used in medicine for centuries to denote a severe and chronic skin disease leading to scarring. It is now clear that many different pathophysiological entities were included in that term, most importantly infectious ones such as mycobacterial diseases as well as various autoimmune and vascular diseases where the term lupus is still used today. ‘Lupus erythematosus’ (or ‘erythematoses’) was used to narrow this down to more specific inflammatory skin conditions where the classical sign of inflammation, redness, was prominent. The term systemic lupus erythematosus (SLE) was first introduced in the late 19th century when it became clear that some individuals who were affected by these characteristically scarring skin diseases were also suffering from severe disease manifestations in the internal organs, most notably in the kidneys. At that time the concept of autoimmunity was not accepted; notably, the great pioneer of immunology Paul Ehrlich had declared that autoimmunity was not possible, nature had an aversion to this, a ‘horror autotoxicus’. However, in the middle of the 20th century several important discoveries overturned this dogma. Hemagglutinins found in patients with severe anemia were shown to be autologous anti-erythrocyte antibodies [1], rheumatoid factor was found to bind to naturally occurring IgG antibodies [2], and in patients with SLE, anti-nuclear [3] and anti-DNA antibodies [4] were demonstrated, followed by many other autoantibodies. These observations placed SLE firmly in the emerging domain of the systemic autoimmune diseases.

2.2 Classification criteria

For many decades, the distinctions between SLE and other autoimmune diseases remained a matter of the clinician's individually applied diagnostic skills, creating difficulties in the comparability across clinics, specialties, and nations. In order to facilitate such comparisons, the American Rheumatism Association, which later became the American College of Rheumatology (ACR), endorsed the first widely used classification criteria for SLE in 1972 [5]. These first criteria were derived by comparing patients in whom the diagnosis of SLE had been made by an experienced clinician with patients in whom another diagnosis had been made, in most cases rheumatoid arthritis (RA). The resulting criteria were thoroughly revised in 1982 [6] (and underwent a relatively minor modification in 1997 [7]) and they are widely used today. A more recent set of classification criteria was derived by the Systemic Lupus International Collaborative Clinics (SLICC) [8], and a current initiative jointly by ACR and the European League Against Rheumatism (EULAR) is expected to provide yet another set of such criteria in the coming years.

2.3 The American College of Rheumatology classification criteria for systemic lupus erythematosus

The ACR classification of SLE is based on a list of 11 items (or small groups of related items), at least four of which must be documented in a patient for her or him to be classified as having SLE (shown in Table 2.1). These manifestations need not be present at the same time, and for many patients a significant amount of time passes between the first and the fourth manifestation. How to classify patients during this period of time remains somewhat controversial. Conceptually, the problem is that, while in 'real-time' it may be entirely correct to withhold the diagnosis of SLE, in retrospect it is often clear that the patient was already suffering from the disease that was diagnosed later.

Applying the ACR criteria may be challenging in other ways as well. The publications provide some guidance on their interpretation but also leave many matters unresolved. A recurring theme is that the manifestation must not be explained by another disease, a requirement that is

Criterion	Definition
1. Malar rash	Fixed edema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	1. Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria >0.5 grams per day or >than 3+ if quantification not performed OR 2. Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	1. Seizures—in the absence of offending drugs or known metabolic derangements eg, uremia, ketoacidosis, or electrolyte imbalance OR 2. Psychosis—in the absence of offending drugs or known metabolic derangements eg, uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	1. Hemolytic anemia—with reticulocytosis OR 2. Leukopenia—<4,000/mm ³ on ≥2 occasions OR 3. Lymphopenia—<1,500/mm ³ on ≥2 occasions OR 4. Thrombocytopenia—<100,000/mm ³ in the absence of offending drugs
10. Immunologic disorder	1. Anti-DNA: antibody to native DNA in abnormal titer OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen OR 3. Positive finding of antiphospholipid antibodies on: i. an abnormal serum level of IgG or IgM anticardiolipin antibodies ii. a positive test result for lupus anticoagulant using a standard method, or iii. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Table 2.1 1997 update of the 1982 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. IgG/M, immunoglobulin G/M. Reproduced with permission from © John Wiley & Sons, Inc, 1982. All rights reserved. Tan et al [6]. Reproduced with permission from © John Wiley & Sons, Inc, 1997. All rights reserved. Hochberg [7].

often not as easy to apply as it may seem. Most manifestations among the eleven, for example photosensitivity, oral ulcers, or seizures do sometimes occur in isolation in otherwise healthy individuals, and are then usually referred to as ‘idiopathic’ or ‘non-specific’. Other manifestations are seen in isolation and often attributed to viral infection, for example pleurisy, and the anti-nuclear antibody test is known to have a relatively high false-positive rate.

Some details of each of the 11 criteria are important to keep in mind:

- The malar rash, often referred to as the classical butterfly rash of SLE, must be an indurated inflammatory lesion, and not a simple erythema of the malar eminences.
- The discoid lesion is correctly listed as a possible manifestation of SLE but may very well exist in isolation as the main form of chronic cutaneous lupus.
- Photosensitivity can be understood in different ways. Some individuals react with a strong inflammatory skin reaction to ultraviolet light exposure, and this reaction is highlighted in the criteria. However, others may develop systemic illness following such exposure, in the form of fever and generalized symptoms, and both reactions can occur at the same time; some clinicians feel that the latter reaction should also be considered as photosensitivity for the purpose of classification.
- Oral (and to a lesser extent nasal) ulcers are of course very common in the general population as incidental findings and must therefore be used for classification only when clearly in excess of the ‘normal’ background occurrence. The typical ulcer of SLE is said to be painless, but in practice both painless and painful ulcers are encountered. It does not appear that this aspect contributes to the accuracy of classification.
- The arthritis of SLE is generally said to be non-erosive, posing a clear distinction with RA. Nevertheless, erosions have been reported in SLE, and a non-erosive but strongly deforming type of arthritis, Jaccoud’s arthropathy, can also be seen in SLE.
- Sometimes pleurisy and pericarditis are clearly demonstrated, yet it may be very hard to rule out that they are caused by viral

infection, especially Coxsackie virus (Bornholm disease). In other cases the diagnosis of pleurisy is made purely on clinical grounds, because of typical pain or a friction rub. It remains somewhat controversial what level of evidence is needed to make these diagnoses, and how far one needs go to rule out other causes. An autoimmune inflammation of the peritoneum ('abdominal serositis') is sometimes seen in patients with SLE and most experts feel this should also be included in this category.

- Two distinct neuropsychiatric manifestations are included in the ACR classification criteria for SLE: psychosis and seizures. This is remarkable for several reasons. The occurrence of psychosis as an SLE manifestation is very rare. Seizures as a manifestation of SLE tend to have an unusual course in that they are not rarely seen many years before any other SLE manifestations; and developing seizures later in the course of SLE is unusual. Perhaps most remarkably, none of the many other genuine SLE-related neuropsychiatric manifestations of SLE are included in this set of classification criteria: aseptic meningitis, transverse myelitis, and stroke syndrome are uncommon but well-defined whereas mild cognitive impairment, white substance abnormalities, organic brain syndrome, affective disorders, and cranial and/or peripheral neuropathies are all seen frequently in patients with SLE, but are not part of the classification criteria, either.
- Renal manifestations that are included in the classification criteria are proteinuria and urinary casts. It is again noteworthy that some well-established SLE-related renal findings, such as erythrocyturia or progressively worsening renal function, are not included. Perhaps most odd is that a clear histopathological diagnosis of lupus nephritis is not counted towards the classification criteria.
- The hematological manifestations include hemolytic anemia, leukocytopenia, lymphopenia, and thrombocytopenia. While all of these can be genuine SLE manifestations, modest lymphopenia is commonly seen without clear underlying disease, and is very often present in patients treated with glucocorticoids.

- The ‘immunological manifestations’ in the ACR classification criteria have undergone some modification since the original version, mostly driven by changes in laboratory technologies and the increasing awareness of the anti-phospholipid syndrome as a distinct disease entity. In the most recent version of the criteria, the presence of anti-DNA, anti-Sm, and/or anti-phospholipid antibodies is considered as one criterion. Some of the tests included in older versions of the criteria, such as the ‘LE cell phenomenon’ have fallen into disuse.
- The positive antinuclear antibodies (ANA) are very commonly found in SLE but also seen in many other diseases and at a relatively high rate in healthy individuals.

The original derivation of the ACR classification criteria used expert opinion as the gold standard against which to measure its accuracy, and similar approaches were used for some of the updates. In each of these instances, the sensitivity and specificity of the criteria were 80–90%, underscoring on the one hand their robustness, but on the other hand the risk of ‘blindly’ applying the criteria for diagnostic purposes, as up to one in five patients could be misclassified in either direction.

2.4 Limitations of the American College of Rheumatology classification criteria for systemic lupus erythematosus

The ACR classification criteria for SLE have served the global community of physicians and academicians who deal with SLE rather well. It has been possible to compare studies of various types across centers, countries, and continents. They have also been very useful in education and training. It is also clear that these criteria have increasingly been used as diagnostic criteria, for better or worse. However, some distinct disadvantages of these criteria have also emerged. For example, four mucocutaneous manifestations are included among the 11, lending disproportionate weight to this particular organ system involvement in SLE. The specific definitions of some of the criteria seem too restrictive, as indicated above. The criteria allow the classification of patients as having SLE without any evidence for autoimmunity per se, which seems to go against the generally held conception of SLE as a prototypic autoimmune disease.

Additionally, it was noted in the clinical trial setting that ambiguities in the criteria could result in the incorrect inclusion of individuals with mild undifferentiated connective tissue disease.

2.5 The Systemic Lupus International Collaborative Clinics classification criteria for systemic lupus erythematosus

Partly in response to the limitations of the ACR classification criteria for SLE, the SLICC group, a consortium of 35 SLE experts from 30 centers in Northern and Central America, Europe, and Korea set out in 2002 to redefine classification criteria for SLE [8]. The group recognized that it would not be possible to do so without first defining which patient would be considered truly to have SLE, in other words, the gold standard had to be made explicit. It was decided by consensus to use a two-step approach for this: each member would submit vignettes describing real patients from their own practice or cohort, in whom they as experts had made the diagnosis of either SLE or one of the eight control diseases (other connective tissue diseases, such as dermatomyositis or vasculitis, fibromyalgia, and others). These vignettes would then be studied by the other members of the group and they would indicate whether this was, in their opinion, SLE or not-SLE. If a clear majority concurred, the cases were considered for the further derivation or confirmation steps. Some further adjudication was done for cases where assessments diverged. In the end, around 700 cases where a clear diagnosis by expert opinion was established were used to derive the best possible set of individual items for classification. Most of this was done in an ‘unsupervised’ manner, but some steps were ‘supervised’ to ensure face validity. In the end, a set of 16 items was generated, divided into clinical and immunological ones, and applied in the following manner: classification of SLE was to be based on the presence, sequentially or simultaneously, of at least four items, of which at least one must be clinical and at least one must be immunological. Furthermore, a patient with histologically proven membranoproliferative glomerulonephritis in the presence of ANA or anti-DNA could also be classified as having SLE. The SLICC classification criteria for SLE are shown in Table 2.2.

Clinical criteria**1. Acute cutaneous lupus** including:

- lupus malar rash (do not count if malar discoid)
 - bullous lupus
 - toxic epidermal necrolysis variant of systemic lupus erythematosus (SLE)
 - maculopapular lupus rash
 - photosensitive lupus rash
in the absence of dermatomyositis
- or subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)

2. Chronic cutaneous lupus including:

- classical discoid rash
 - localized (above the neck)
 - generalized (above and below the neck)
- hypertrophic (verrucous) lupus
- lupus panniculitis (profundus)
- mucosal lupus
- lupus erythematosus tumidus
- chilblains lupus
- discoid lupus/lichen planus overlap

3. Oral ulcers:

- palate
- buccal
- tongue
- or nasal ulcers
in the absence of other causes, such as vasculitis, Behcets, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods

4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)

in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia

5. Synovitis involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness.

6. Serositis:

- typical pleurisy for more than 1 day
 - or pleural effusions
 - or pleural rub
- typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
 - or pericardial effusion
 - or pericardial rub
 - or pericarditis by EKG

in the absence of other causes, such as infection, uremia, and Dressler's pericarditis

Table 2.2 1997 update of the 1982 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (continues overleaf). EKG, electrocardiogram.

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7. Renal:

- Urine protein/creatinine (or 24 hr urine protein) representing 500 mg of protein/24 hr or
- Red blood cell casts

8. Neurologic

- seizures
- psychosis
- mononeuritis multiplex
in the absence of other known causes such as primary vasculitis
- myelitis
- peripheral or cranial neuropathy
in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
- acute confusional state
in the absence of other causes, including toxic-metabolic, uremia, drugs

9. Hemolytic anemia**10. Leukopenia** ($<4000/\text{mm}^3$ at least once)

in the absence of other known causes such as Felty's, drugs, and portal hypertension

or lymphopenia ($<1000/\text{mm}^3$ at least once)

in the absence of other known causes such as corticosteroids, drugs and infection

11. Thrombocytopenia ($<100,000/\text{mm}^3$) at least once

in the absence of other known causes such as drugs, portal hypertension, and TTP

Immunological criteria

1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range, except ELISA: twice above laboratory reference range
3. Anti-Sm
4. Antiphospholipid antibody: any of the following
 - lupus anticoagulant
 - false-positive RPR
 - medium or high titer anticardiolipin (IgA, IgG or IgM)
 - anti- β_2 glycoprotein I (IgA, IgG or IgM)
5. Low complement
 - low C3
 - low C4
 - low CH50
6. Direct Coombs test *in the absence of hemolytic anemia*

Table 2.2 1997 update of the 1982 American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (continued). ANA, antinuclear antibodies; Ig, immunoglobulin; RPR, rapid plasma reagin; TTP, thrombotic thrombocytopenic purpura; Reproduced with permission from © John Wiley & Sons, Inc, 1982. All rights reserved. Tan et al [6]. Reproduced with permission from © John Wiley & Sons, Inc, 1997. All rights reserved. Hochberg [7].

This set of criteria was shown, in the derivation sample of 702 patients, to have excellent sensitivity and specificity, and when compared to the gold standard defined above: the sensitivity was 94% and the specificity 92%, which were both clearly better than the ACR criteria. However, when the same criteria were tested in a similarly large confirmation sample of 690 additional patients, the metric properties were somewhat less – although still very good – and not clearly superior to the ACR criteria (sensitivity 97%, specificity 84%) [8].

The SLICC classification criteria have been widely lauded as an important step forward in the definition of SLE [9,10]. Specifically, it was noted that these criteria seem to ‘fit’ better with our general understanding of SLE, that is, they have better face validity. For instance, the requirement to have both clinical and immunological features is close to the approach that many would take to the patient with possible SLE. It was also seen as a strength that a clear histological demonstration of class IV lupus nephritis, in the presence of ANA or anti-DNA, is sufficient to make a diagnosis of SLE, again matching well with the approach that many clinicians would take. The SLICC criteria publication also provides detailed instructions on each item to aid the clinician in determining whether the criterion is met [8].

On the other hand, the SLICC criteria also have some disadvantages. Having a larger number of items, they are somewhat harder to memorize. They are not clearly superior to the ACR criteria in terms of their metric properties, and still misclassify about one in 10 patients, in either direction. As such, they should not be used blindly in making or rejecting the diagnosis of SLE.

Overall, it can be said that the SLICC criteria for SLE represent a useful new set for clinical studies of SLE, including clinical trials. Indeed, the European Medicines Agency (EMA) in a recent guidance document for the development of medications for the treatment of SLE explicitly endorsed the SLICC criteria as an alternative to the ACR criteria.

2.6 Sub-classification of systemic lupus erythematosus

Some of the specific manifestations of SLE can be classified further according to criteria that in some instances have been developed within the medical discipline most closely involved in its management, and in other instances by multispecialty task-forces. Lupus nephritis is histologically classified into six subtypes [11,12]. For the precise use of terms in neuropsychiatric SLE a glossary of 23 items was defined, indicating the specific description of each item and what other causes should be considered or ruled out before attributing it to SLE [13].

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