Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group

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Since the Oxford Classification of IgA nephropathy (IgAN) was published in 2009, MEST scores have been increasingly used in clinical practice. Further retrospective cohort studies have confirmed that in biopsy specimens with a minimum of 8 glomeruli, mesangial hypercellularity (M), segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T) lesions predict clinical outcome. In a larger, more broadly based cohort than in the original Oxford study, crescents (C) are predictive of outcome, and we now recommend that C be added to the MEST score, and biopsy reporting should provide a MEST-C score. Inconsistencies in the reporting of M and endocapillary cellularity (E) lesions have been reported, so a web-based educational tool to assist pathologists has been developed. A large study showed E lesions are predictive of outcome in children and adults, but only in those without immunosuppression. A review of S lesions suggests there may be clinical utility in the subclassification of segmental sclerosis, identifying those cases with evidence of podocyte damage. It has now been shown that combining the MEST score with clinical data at biopsy provides the same predictive power as monitoring clinical data for 2 years; this requires further evaluation to assess earlier effective treatment intervention. The IgAN Classification Working Group has established a well-characterized dataset from a large cohort of adults and children with IgAN that will provide a substrate for further studies to refine risk prediction and clinical utility, including the MEST-C score and other factors.

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The Oxford Classification of IgA nephropathy was first published in 2009 following a 5-year effort by a working group of nephrologists and renal pathologists representing the International IgA Nephropathy Network and the Renal Pathology Society.[1,2] The classification was based on objective evidence developed in a cohort of 265 adults and children of European Caucasian and East Asian ethnicity with IgA nephropathy (IgAN). The classification indicated that there were only 3 reproducible variables seen on the renal biopsy in IgAN that independently predicted outcome and provided prognostic information in addition to prognosis prediction given by clinical features alone. The 3 features were mesangial hypercellularity (M), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T). In addition, among patients with endocapillary hypercellularity (E), the rate of renal functional decline was significantly lower in those receiving immunosuppressive therapy. The Oxford Classification thus includes these 4 parameters, the MEST scores.

Since 2009, the classification has been widely adopted in clinical practice, largely replacing other previously popular classifications that were not fully evidence based. A number of studies have sought to validate the predictive value of MEST score in other more inclusive retrospective cohorts. This has included demonstrating the value of the Oxford Classification predicting long-term outcomes of Henoch-Schönlein

purpura nephritis (IgA vasculitis) as well as IgAN,[3] although data are not yet sufficient to make a recommendation that the MEST score should be used routinely in IgA vasculitis

Other studies have investigated features not predictive of outcome in the original Oxford study, most notably patterns of immunofluorescence staining for IgA and complement components and glomerular crescents.[4] Studies have also sought to develop more precise approaches to the combination of clinical features with the MEST score to improve prognostic accuracy. The original working group, with some changes in membership, continues to be active, has held further meetings including another in Oxford in 2014, and has established subgroups that focus on individual unanswered questions.

In this report, we review the relevant studies published since 2009 as well as report the published and yet unpublished studies of our working subgroups. We make recommendations for changes to the Oxford Classification and also propose additional work that will improve still further the value of the classification in research and in clinical practice.

Published retrospective validation studies

A limitation of the original Oxford study cohort was that it included only 265 adults and children, and only those of white Caucasian (from Europe and North America) and East Asian (from China and Japan) ethnicities. Furthermore, the cohort was selected to be enriched for typical slowly progressive IgAN, excluding patients with very low levels of proteinuria. It also excluded those with an estimated glomerular filtration rate (GFR) <30 ml/min per 1.73 m^2 with the intent of avoiding the selection of very advanced cases in which glomerulosclerosis and interstitial fibrosis would be dominant, but having the effect of also excluding some rapidly progressive cases in which crescents might more likely be predictive of outcome.

Since 2009, numerous studies have been published that apply the Oxford Classification to cohorts of subjects with IgAN. These studies are typically described as validation studies, although none prospectively studied new cohorts; nevertheless, they provide valuable corroborative evidence. Sixteen such studies,[5–20] including cohorts from Europe, North America, and East Asia, were meta-analyzed in a report published in 2013.[21] Recently, more studies have been published that included cohorts from Iran, Europe, Japan, and South Korea.[22–28] All these studies are summarized in Supplementary Table S1.

Review of current classification parameters (M, E, S, and T)

The published cohorts provide robust and consistent evidence that M, S, and T lesions each reliably provide prognostic information by univariate analysis, although only T lesions were a consistent, independent predictor of renal outcomes, with more variable results for M and S lesions (Table 1). This is likely to be a consequence of the end point (end-stage renal disease [ESRD]) chosen in most studies. The T score largely reflects the stage of the disease at the time of biopsy; those patients with more advanced chronic damage have a shorter time to ESRD. Those studies that included the rate of loss of renal function as an end point more consistently reported that active cellular lesions (M and E scores) were associated with this outcome.

E (endocapillary hypercellularity). The E lesion was not predictive of outcomes in the original Oxford Classification cohort, and this was also true in most of the subsequent studies (Table 1). However, the original Oxford Classification cohort and all but 2 of the published validation studies show treatment bias, with nonrandom immunosuppression. Patients whose biopsy specimens were scored E1 were more likely to receive immunosuppressive therapy, most frequently corticosteroids, and patients with E lesions had an improved outcome if treated with corticosteroids. The 2 studies in which no patients received corticosteroid/cytotoxic therapy both reported that E1 was independently associated with more rapid loss of renal function and worse renal survival.[8,27] This is consistent with the reversibility of E lesion following immunosuppression in a study reporting repeat renal biopsies after treatment.[29] These studies suggest that the use of immunosuppression may mask the predictive value of E in renal outcomes. Although these findings do not in themselves support the routine use of immunosuppression when the E lesion is present, they do justify a prospective trial of immunosuppression in IgAN with the E lesion.

S (segmental sclerosis). Segmental sclerosis might develop as a consequence of distinct processes. It might result from the organization of segmental necrotizing or endocapillary inflammatory lesions. Alternatively, it may reflect a response to podocyte injury (podocytopathy) analogous to primary focal segmental glomerulosclerosis. The underlying cause of the sclerosis might be associated with different histologic features within the segmental sclerosing lesions. A recent publication reviewed segmental sclerosing lesions in the Oxford Classification patient cohort and correlated histology with clinical presentation and outcome.[30] This showed that podocyte hypertrophy or sclerosis at the tubular pole (tip lesion), features typically associated with podocytopathies, were associated with more proteinuria at presentation and a more rapid decline in renal function. In addition, in individuals with podocyte hypertrophy or tip lesions, immunosuppressive therapy was associated with a better renal survival. The identification of these podocytopathic features was found to be reproducible between the pathologists in the study, but it remains to be determined whether this is also the case for pathologists in different units around the world. If the associations between histologic subclassification of segmental sclerosis and outcome are confirmed, then a refinement of the definition of the S lesion may be appropriate, using S1 only for sclerotic lesions with podocytopathic features. Pending such studies, we recommend no change in the definition of S1, but reporting all S1 lesions with the additional descriptive text "segmental sclerosis with/without podocyte hypertrophy/tip lesions."