

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



Hernán Trimarchi¹, Jonathan Barratt², Daniel C. Catran³, H. Terence Cook⁴, Rosanna Coppo⁵, Mark Haas⁶, Zhi-Hong Liu⁷, Ian S.D. Roberts⁸, Yukio Yuzawa⁹, Hong Zhang¹⁰ and John Feehally² on behalf of the IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society¹; for Conference Participants¹¹

¹Hospital Británico de Buenos Aires, Argentina; ²Department of Infection, Immunity, and Inflammation, University of Leicester, Leicester, United Kingdom; ³Department of Medicine, Toronto General Research Institute, University Health Network, Toronto General Hospital, Toronto, Ontario, Canada; ⁴Centre for Complement and Inflammation Research, Department of Medicine, Imperial College, London, United Kingdom; ⁵Fondazione Ricerca Molinette, Nephrology, Dialysis, and Transplantation, Regina Margherita Hospital, Turin, Italy; ⁶Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA; ⁷Department of Nephrology, National Clinical Center of Kidney Disease, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China; ⁸Department of Cellular Pathology, Oxford University Hospitals, Oxford, United Kingdom; ⁹Department of Nephrology, Fujita Health University School of Medicine, Toyoake Aichi, Japan; and ¹⁰Renal Division, Peking University First Hospital, Beijing, China

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.

Kidney International (2017) **91**, 1014–1021; <http://dx.doi.org/10.1016/j.kint.2017.02.003>

KEYWORDS: chronic kidney disease; glomerulonephritis; IgA nephropathy; proteinuria

Copyright © 2017, International Society of Nephrology. Published by Elsevier Inc. All rights reserved.

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

Correspondence: Hernán Trimarchi, Nephrology Service Hospital Británico de Buenos Aires, Perdriel 74 (1280), Buenos Aires, Argentina. E-mail: htrimarchi@hotmail.com

¹¹See Appendix for other contributing members of the Working Group.

Received 8 December 2016; revised 10 January 2017; accepted 2 February 2017; published online 22 March 2017

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 m² 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.”

Table 1 | Summary of studies correlating Oxford MEST parameters with clinical outcomes in IgA nephropathy (minimum cohort size: 99 patients)

Study	Center	No. of patients	End point	Univariate analysis	Multivariate analysis	IS bias
Cattran <i>et al.</i> ¹ (Oxford), 2009	Multicenter global	265 (206 A, 59 C)	Rate of eGFR decrease, ESRD, or $\geq 50\%$ eGFR decrease	M, S, T M, S, T	S, T M, T	Yes
Katafuchi <i>et al.</i> , ⁶ 2011	Single center, Japan	702 C	ESRD	MET	MET	Yes
Herzenberg <i>et al.</i> , ⁷ 2011	Multicenter, United States and Canada	187 (143 A, 44 C)	Rate of eGFR decrease	Not done	E, S, T	Yes
El Karoui <i>et al.</i> , ⁸ 2012	Single center, France	128 A	ESRD or doubling of Scr; rate of eGFR decrease	None	M, E, S, T	No
Shi <i>et al.</i> , ⁹ 2011	Single center, China	410	ESRD	M, S, T	S, T	Yes
Alamartine <i>et al.</i> , ¹⁰ 2011	Single center, France	183	ESRD or doubling of Scr	E, S, T	None	Yes
Edström Halling <i>et al.</i> , ¹² 2012	Single center, Sweden	99 C	ESRD or $\geq 50\%$ eGFR decrease	M, E, T	None	Yes
Shima <i>et al.</i> , ¹³ 2012	Single center, Japan	161 C	Rate of eGFR decrease	M, E, T	M, T	Yes
Le <i>et al.</i> , ¹⁵ 2012	Multicenter, China	218 C	eGFR decrease (doubling Scr) or ESRD	S, T S, T	T T	Yes
Zeng <i>et al.</i> , ¹⁷ 2012	Multicenter, China	1026 A	Rate of eGFR decrease, ESRD, or $\geq 50\%$ eGFR decrease	M, S, T M, S, T	M, T M, T	Yes
Kang <i>et al.</i> , ¹⁸ 2012	Single center, South Korea	197 A	ESRD or $\geq 50\%$ eGFR decrease	T	T	Yes
Gutierrez <i>et al.</i> , ²⁰ 2012	Single center, Spain	141 A	eGFR decrease (doubling Scr), ESRD	T S	T S	Yes
Nasri <i>et al.</i> , ²² 2012	Multicenter, Iran	102 A	Scr	ST	Not done	Yes
Coppo <i>et al.</i> , ²³ 2014, VALIGA	Multicenter, Europe	1147 (973 A, 174 C)	ESRD or $\geq 50\%$ eGFR decrease, rate of eGFR decrease	M, S, T M, S, T	S, T S, T	Yes
Espinosa <i>et al.</i> , ²⁴ 2014	Multicenter, Spain	283 (A + C)	ESRD	M, S, T	S, T	Yes
Moriyama <i>et al.</i> , ²⁵ 2014	Single center, Japan	1012 A	eGFR decrease or ESRD	T	None	Yes
Park <i>et al.</i> , ²⁶ 2014	Multicenter, South Korea	500 A	ESRD or doubling of Scr	M, T	T	Yes
Chakera <i>et al.</i> , ²⁷ 2016	Multicenter, Australia, United Kingdom	156 A	ESRD or eGFR decrease >5 ml/min per year	E, T	E	No
Hou <i>et al.</i> , ²⁸ [e-pub ahead of print]	Multicenter, China	176 A	Proteinuria	Not done	Not done	Yes

A, adults; C, children; E, endocapillary proliferation; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IS, immunosuppression; IS bias, inherent bias due to nonrandomized use of immunosuppressive therapy in study cohort; M, mesangial proliferation; S, glomerulosclerosis; Scr, serum creatinine; T, tubular atrophy.

Additional pathologic features considered for inclusion in the Oxford Classification

Pattern of glomerular IgA deposition. The Oxford Classification was developed using light microscopic findings only. Other reports have suggested that the presence of IgG, in addition to IgA, and also the location of IgA are predictive of outcome, for example, that glomerular capillary wall deposits may carry a worse prognosis than mesangial deposits alone.⁴ However, review of the Oxford Classification cohort has shown that although the presence of glomerular IgG and capillary wall IgA deposits (identified by immunofluorescence or immunohistochemistry) are associated with a worse outcome, they do not add predictive value to MEST scores.⁴

Crescents. In the original Oxford study¹ and several validation studies with similarly restrictive entry criteria,^{7,9,15,16} crescents were not found to be an independent predictor of renal outcomes. However, individuals with severe renal impairment (estimated GFR <30 ml/min per 1.73 m²) were not included in these studies, and Katafuchi *et al.*⁶ found crescents to be predictive of ESRD in 286 IgAN patients not meeting entry criteria for the original Oxford study. Crescents were also found to be predictive of poor renal outcomes in several other studies including patients with an estimated GFR <30 ml/min per 1.73 m².^{12,13} A working subgroup of the IgAN Classification Working Group has addressed crescents

as a potential predictor of renal outcomes in IgAN in a pooled cohort of 3096 patients assembled from 4 retrospective studies,³¹ Oxford^{1,2} and VALIGA,²³ and 2 large Asian databases, 1 from China¹⁷ and another from Japan.⁶ The working subgroup studied relationships between the proportion of glomeruli containing cellular or fibrocellular crescents and the rate of renal function decline and survival of a 50% decline in renal function or ESRD (combined event), while adjusting for covariates used in the original Oxford study.

In this combined cohort (including biopsy specimens with a minimum of 8 glomeruli, as required for a MEST score), the presence of crescents was strongly associated with subsequent use of immunosuppression. Overall, crescents were independently predictive of a higher risk of a combined event (hazard ratio: 1.37, 95% confidence interval 1.07–1.75). This association remained statistically significant only in those patients who did not receive immunosuppression. There was also a proportion-dependent relationship between the fraction of crescents and outcomes: in individuals with crescents in $\geq 1/6$ and $\geq 1/4$ of glomeruli, the hazard ratio of a combined event increased to 1.63 (95% confidence interval 1.10–2.43) and 2.29 (95% confidence interval 1.35–3.91), respectively. Interestingly, the risk of a combined outcome associated with crescents in $>25\%$ of glomeruli remained significant in patients receiving immunosuppression as well as those who were not.

The findings of this working group support the addition of crescent scores (C0, C1, and C2) to the Oxford MEST scores. A score of C1 (crescents in <25% of glomeruli) versus C0 (no crescents) identifies a group of patients having a significantly higher risk of a poor renal outcome than patients whose biopsy specimens had no crescents (C0 score) if not treated with immunosuppression, but not if treated with immunosuppressive therapy. The findings with C1 are similar to those found in the original Oxford¹ and validation⁷ cohorts for E1; however, as with the latter, these observational data are not sufficient to extrapolate to a recommendation that those with C1 lesions should be treated with immunosuppression. A score of C2 (with crescents in >25% of glomeruli) further identifies patients at risk of a poor renal outcome even if treated with immunosuppression.³¹ Therefore, we propose that the Oxford classification should now involve 5 components, MEST-C rather than MEST. Cases of Henoch-Schönlein purpura nephritis were not included in this cohort, so it is not yet possible to confirm whether crescents have similar significance in that condition.

Quantification of glomerular macrophages. It has been proposed that E1 in IgAN is a reflection of glomerular inflammation and that use of immunohistochemistry for CD68 to identify glomerular macrophages might assist in the recognition of E1 lesions and be potentially superior to evaluation of periodic acid-Schiff-stained sections in prognostication. There are provisional data from the study of biopsy specimens in a cohort of patients who received no immunosuppression and in whom E1 was an independent predictor of the rate of loss of renal function and renal survival.²⁷ In these biopsy specimens, quantitative analysis of CD68-stained sections has demonstrated that the number of glomerular macrophages correlates strongly with the extent of endocapillary hypercellularity and E1 score, assessed on periodic acid-Schiff-stained sections, but not M, S, or T scores. Using a cutoff of a maximum glomerular macrophage count of 6 correctly identifies an E score in 80% of biopsy specimens (M. F. Soares *et al.*, unpublished data). It remains to be determined whether glomerular macrophage counts have superior clinical value to E scoring.

Children. The validation studies in children younger than 18 years of age from Japan,¹³ China,¹⁶ and Sweden¹² and the VALIGA study,²³ confirmed the value of the MEST scores using univariate analysis. However, by multivariate analysis, no individual feature maintained an independent predictive value, apart from T lesions in pediatric Chinese patients. This was likely due to the limited number of patients reaching end points. In subjects 23 years of age or younger enrolled in the VALIGA study, the MEST variables were predictive by multivariate analysis for survival from a combined end point of a 50% decline in renal function or ESRD.³² In other cohorts, significant predictive values for some scores (mostly M, E, and T) were found in models including clinical data at renal biopsy. The most powerful predictive factor in children and young subjects, using Cox models as

well as tree analysis, is M1. In the Japanese cohort, the presence of crescents in >30% glomeruli was also significant in multivariate models considering proteinuria at biopsy.¹³ These analyses stress the need for a collaborative effort to generate a large database for children with IgAN in order to solve the problem of inadequate statistical power due to small numbers of progressive cases, especially with relatively short periods of follow-up.

Combined clinicopathologic information. The major aims of our work in developing and refining a classification of IgAN are to improve the prognostic information for individual patients and recruitment criteria for clinical trials. Earlier prediction algorithms sought to integrate clinical findings at presentation and over time with renal pathology using the histologic classifications for IgAN available at the time.³³ On univariate analysis, many clinical and pathologic elements were relevant to outcomes, but on multivariate analysis, the only factors that maintained their independent value were mean arterial pressure and urine protein excretion over time.³³ The maximum predictive power to explain variabilities in outcome in any patient was only available when mean arterial pressure and proteinuria were followed for a 2-year period. Recently, this was explored further using a combined cohort of 901 adults from the original Oxford cohort, the North American validation study, and the VALIGA study. The previous prediction algorithm, using clinical data (including proteinuria, mean arterial function, and GFR) over the first 2 years was repeated using the hard end points of a 50% decrease in estimated GFR or ESRD and with current prediction model statistical approaches. The predictive power of that original algorithm was then compared with the predictive power of the MEST scores alone and to the addition of MEST scores to the initial clinical data at time of biopsy. There was significant improvement in prediction by adding MEST scores to clinical data at biopsy and in predicted outcome and the 2-year clinical data alone, with comparable calibration curves. This effect did not change with further analyses of those who were and were not treated with renin-angiotensin system blockade or immunosuppression. The impact on outcome of individual elements of the MEST score was analyzed. Mesangial hypercellularity decreased the likelihood of renal survival from 90% (M0) to <80% (M1) at 5 years in patients with the same clinical parameters.³⁴ Further prospective studies are needed to establish whether this combination of clinical and pathologic information at the time of biopsy would allow earlier introduction of therapy with better long-term preservation of renal function.

Other prediction models for outcome in IgAN have been published³⁴ using a variety of pathologic and clinical features. Our working group will continue to refine these prediction models using the MEST-C score and will seek international consensus so that 1 prediction model enters common use. This will not only benefit individual patient care but will also facilitate collaborative research and enable comparison and interpretation of different studies.

The revised MEST-C score

Criteria for adequacy of renal biopsy; for scoring of M, E, and T lesions; and for overall reporting of IgAN biopsy specimens are unchanged from our original recommendations^{1,2} (Tables 2 and 3). In light of the recent data summarized here, we recommend the addition of a C (crescent score) to the MEST score. All adequate biopsy specimens with a diagnosis of IgAN should be scored as C0 (no crescents), C1 (crescents in a least 1 but <25% of glomeruli), or C2 (crescents in at least 25% of glomeruli) (Tables 2 and 3). We also recommend refining the S score, noting the presence or absence of podocytopathic features (podocyte hypertrophy/tip lesions) in biopsy specimens scored as S1.

Therefore, we propose that the renal biopsy specimen in IgAN should be reported using a 5-component MEST-C score. Because cases of Henoch-Schönlein purpura nephritis were excluded from the recent study of crescents in IgAN,³¹ we recommend the MEST-C score not be applied to cases of Henoch-Schönlein purpura nephritis yet.

Reproducible identification of MEST: need for an educational tool

The definitions for each component in the Oxford Classification were the result of an iterative process involving the renal pathologists in the original working group.² Definitions were written to be straightforward and to maximize the likelihood that pathologists would be able to consistently identify the lesions in clinical practice. However, a subsequent analysis using the VALIGA cohort showed significant inconsistencies in identification of M and E lesions.³² Local pathologists diagnosed M1 twice as often as the central review pathologist and E1 3 times as often. The M score given by the central but not the local pathologists was an independent predictor of renal outcome. To help overcome this issue, a Web-based tool has been developed to provide examples of each lesion and assist pathologists to overcome the commonly

Table 2 | Recommendations for updating the Oxford Classification of IgAN

- We recommend no changes to the published criteria for biopsy adequacy in cases of IgAN. A minimum of 8 glomeruli is required.
- We recommend that MEST criteria continue to be applied to cases of IgAN.
- We confirm the predictive value of M, S, and T.
- We confirm the predictive value of E in patients not treated with immunosuppression.
- We recommend that a C score be added to the MEST score in all cases of IgAN to indicate the frequency of cellular and/or fibrocellular crescents.
 - C0 (no crescents) or
 - C1 (crescent in a least 1 glomerulus) or
 - C2 (crescents in at least 25% of glomeruli)
- We recommend no change in the definition of S1, but adding text to indicate whether there are podocytopathic features.
- We recommend that MEST criteria are not yet applied to cases of Henoch-Schönlein purpura nephritis (IgA vasculitis).

C, crescent; E, endocapillary cellularity; IgAN, IgA nephropathy; M, mesangial hypercellularity; S, segmental sclerosis; T, interstitial fibrosis/tubular atrophy.

Table 3 | Recommendations for the renal biopsy report in IgA nephropathy (updated from refs. 1, 2, and 32)

Detailed description of the features present on:
Light microscopy
Immunohistochemistry or immunofluorescence
Electron microscopy
Summary of 5 key pathologic features
Mesangial score <0.5 (M0) or >0.5 (M1)
Endocapillary hypercellularity absent (E0) or present (E1)
Segmental glomerulosclerosis absent (S0) or present (S1); presence or absence of podocyte hypertrophy/tip lesions in biopsy specimens with S1
Tubular atrophy/interstitial fibrosis ≤25% (T0), 26%–50% (T1), or >50% (T2)
Cellular/fibrocellular crescents absent (C0), present in at least 1 glomerulus (C1), in >25% of glomeruli (C2)
Quantitative data
Total number of glomeruli
Number of glomeruli with endocapillary hypercellularity, necrosis, extracapillary hypercellularity (cellular/fibrocellular crescents), global glomerulosclerosis, and segmental glomerulosclerosis

identified reporting errors. The link to training slides will soon be available on the Renal Pathology Society Website (www.renalpathsoc.org).

Next steps

Development of international cohorts for further studies. A key achievement of the original Oxford Classification working group was the assembly of a study cohort of sufficient size with detailed clinical and pathologic data that allowed us to address the questions posed. The international collaborative effort that led to the original Oxford Classification continues, and we are currently assembling a cohort from multiple centers across Europe, China, Japan, and North and South America. The objective is to develop a cohort representing the full spectrum of disease severity in IgAN with no limitations on proteinuria or renal function. This cohort will be representative of a wide range of ancestries, countries, patterns of practice, and age and is characterized by deep patient-level clinical phenotyping, consistent data collection, and detailed histologic long-term follow-up analysis to enable addressing novel questions that are not possible using smaller local datasets. Approximately 5000 such patient datasets that include children and adults have been collected, and a preliminary analysis has been published.³⁵ This cohort will be a powerful substrate for further studies in IgAN to improve outcome prediction for individual patients and refine recruitment and outcome criteria for clinical trials. The primary purpose will be to validate a prediction model in IgAN applicable worldwide across the range of disease severity and ethnic groups and to be easy to use in clinical practice (analogous to the Framingham prediction rule for cardiovascular disease). In addition, we expect that this cohort will be a data source for further studies including the potential for virtual assessment of novel biomarkers.

Biomarkers. An important research focus in IgAN is the identification of novel biomarkers that can add to the

available information through clinical and pathologic features, improving diagnosis, risk stratification, therapy selection, prediction of response to therapy, and risk of transplantation recurrence. With the continued evolution of “omics” platforms, it is now possible to measure a very wide range of potential “biomarkers” in the serum, plasma, urine, and kidney. However, in IgAN, there are few such biomarker studies and those lack rigorous prospective validation in diverse populations.³⁶ Variable collection and storage of biological samples for biomarker analysis can be a significant confounder in such analyses. Undergalactosylated serum IgA1 and circulating autoantibodies to that IgA1 have been studied and may be of value for predicting progression risk and transplantation recurrence.³⁷ Biomarkers have the potential to improve prediction of ESRD, to assist the clinician in managing individual patients, and to define surrogate end points for the evaluation of clinical trials. To maximize the opportunity being created by the described large international IgAN cohort, recommendations will be agreed on and published that cover the collection, storage, and transport of biological specimens for biomarker analysis.

DISCUSSION

The active study of the Oxford Classification of IgAN since its original publication has led to the compilation of substantial data to endorse its validity in increasingly large and diverse cohorts of patients. This progress provides further assurance that it was correct to develop the Oxford Classification using a rigorous evidence-based approach, which sets it apart from other, largely opinion-based, classifications currently used in renal pathology.

The Oxford Classification has now become the accepted norm used by the majority of clinicians and investigators worldwide. Nevertheless, there are challenges in its use. Although intended to be straightforward for use in everyday clinical practice because it provided simple and reproducible descriptions of each of its elements, evidence indicates that there is inconsistent reporting of the M lesion and particularly the E lesion. To improve the accuracy of MEST reporting, an online educational program has been developed (www.renalpathsoc.org).

Another approach to improving the accuracy of E-lesion reporting is to develop an additional cellular marker for endocapillary hypercellularity. Identification of tissue macrophages by CD68 staining is a promising approach that improved accurate identification of the E1 lesion in 1 study,³⁸ but corroboration is needed before recommendation for inclusion in the Oxford Classification.

Recent data have clarified the prognostic significance of the E lesion. E1 is predictive of outcome only in patients who have not received immunosuppression. This strongly suggests the E lesion is responsive to immunosuppression, an interpretation supported by evidence from a repeat-biopsy study showing resolution of E lesions after immunosuppression.²⁹ However, there are very few supporting data for this proposition from randomized clinical trials. Further histologic data

from controlled trials are required to determine the role of the MEST score and selection of therapy.

It has always been intended that the Oxford Classification would be subject to review and development, not least because of the rather narrow inclusion criteria used to assemble the original Oxford cohort of only 265 subjects. The original cohort was enriched with slowly progressive IgAN cases, thus maximizing the chance of identifying significant associations of pathologic features and outcome in such a small cohort. Further data from the many validation studies summarized here and elsewhere^{21–26} endorse the continued use of the MEST score. These data also provide evidence of the predictive value of a C score. A C1 score (crescents in <25% of glomeruli) identifies those at risk of a poor renal outcome if not treated with immunosuppression; a C2 score (crescents in >25% of glomeruli) further identifies patients at risk of a poor renal outcome even if treated with immunosuppression.³¹ Immunosuppressive therapy is often used when crescents are identified in IgAN, although the evidence to support this approach is only anecdotal. Although it is still premature to regard our observations as justifying the use of immunosuppression when C1 lesions are found, this should be investigated further in randomized clinical trials to determine whether specific treatment recommendations should be made.

Another valuable role for the MEST-C score could be in interpreting repeat renal biopsies in IgAN. There are currently very few data on MEST scores in repeat biopsies, so no recommendations can currently be made, although in the study of Shen *et al.*,²⁹ the number of patients with biopsy specimens showing E1 lesions and crescents (but not M1 and S1 lesions) before immunosuppressive treatment decreased significantly on posttreatment biopsies.

A significant additional benefit of the development of the Oxford Classification for IgAN has been the building of an international network of investigators willing to work together, to share data and biosamples, and to deliver collaborative projects not attainable by each investigator working with smaller cohorts. This network has now assembled a cohort of >5000 subjects with detailed, consistently held data on demographic characteristics, clinical phenotyping, and outcome, expecting to provide the substrate for future studies including analysis of novel biomarkers. Limited numbers provide a challenge to the study of IgAN in children; this cohort addresses this issue by including >1000 children.

In summary, we propose an extension of the MEST score in the Oxford Classification of IgAN to become a MEST-C score for use in routine clinical practice and research. In addition to providing the evidence base to endorse this recommendation, the continuing efforts of our group have built a network to facilitate the assembly of a large unique cohort of well-characterized subjects with IgAN, providing fertile ground for further collaborative international studies addressing the pathogenesis, epidemiology, and clinical care of IgAN patients.

DISCLOSURE

HT received honoraria from Genzyme-Sanofi and Alexion. DCC received honoraria from Mallinkrodt Pharmaceuticals, Omerus, and Bristol-Myers Squibb. RC received honoraria from Alexion and Novartis. MH received honoraria from Shire-Viropharma and AstraZeneca. All the other authors declared no competing interests.

AUTHOR CONTRIBUTIONS

HT drafted the manuscript; interacted with all authors, and integrated opinions in the manuscript; provided data; revised the manuscript; and approved the final version. JB provided data and discussed results, revised the manuscript, and approved the final version. DDC conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results; drafted or revised the manuscript; and approved the final version. HTC provided pathology data, revised the manuscript, and approved the final version. RC provided data and/or played an important role in interpreting the results, drafted or revised the manuscript, and approved the final version. MH acquired pathology data, interpreted clinicopathologic correlations, revised the manuscript, and approved the final version. Z-HL provided and approved the final data. ISDR designed the work, acquired pathology data, interpreted clinicopathologic correlations, revised the manuscript, and approved the final version. YY provided and approved the final data. HZ provided and approved the final data. JF conceived the work that led to this report, drafted and revised the manuscript, and approved the final version.

SUPPLEMENTARY MATERIAL

Table S1. Summary of studies correlating Oxford MEST parameters with clinical outcomes in IgA nephropathy (minimum cohort size, 99 patients).

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES

- Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Cattran DC, Coppo R, Cook HT, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int.* 2009;76:534–545.
- Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Coppo R, Troyanov S, Camilla R, et al. The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults. *Kidney Int.* 2010;77:921–927.
- Kim CH, Lim BJ, Bae YS, et al. Using the Oxford classification of IgA nephropathy to predict long-term outcomes of Henoch-Schönlein purpura nephritis in adults. *Mod Pathol.* 2014;27:972–982.
- Bellur SS, Troyanov S, Cook HT, et al., Working Group of International IgA Nephropathy Network and Renal Pathology Society. Immunostaining findings in IgA nephropathy: correlation with histology and clinical outcome in the Oxford classification patient cohort. *Nephrol Dial Transplant.* 2011;26:2533–2536.
- Joh K, Hashiguchi A, Okonogi H, et al. Histological evaluation on IgA nephropathy in 233 Japanese adult patients: retrospective analysis (abstract; poster no. 12). Oral and poster presented at: the World Congress of Nephrology 2009 Satellite Symposium on IgA Nephropathy. May 22–26, 2009; Milan Italy.
- Katafuchi R, Ninomiya T, Nagata M, et al. Validation study of oxford classification of IgA nephropathy: The significance of extracapillary proliferation. *Clin J Am Soc Nephrol.* 2011;6:2806–2813.
- Herzenberg AM, Fogo AB, Reich HN, et al. Validation of the Oxford classification of IgA nephropathy. *Kidney Int.* 2011;80:310–317.
- El Karoui K, Hill GS, Karras A, et al. A clinicopathologic study of thrombotic microangiopathy in IgA nephropathy. *J Am Soc Nephrol.* 2012;23:137–148.
- Shi SF, Wang SX, Jiang L, et al. Pathologic predictors of renal outcome and therapeutic efficacy in IgA nephropathy: validation of the oxford classification. *Clin J Am Soc Nephrol.* 2011;6:2175–2184.
- Alamartine E, Sauron C, Laurent B, et al. The use of the Oxford classification of IgA nephropathy to predict renal survival. *Clin J Am Soc Nephrol.* 2011;6:2384–2388.
- Yau T, Korbet SM, Schwartz MM, et al. The Oxford Classification of IgA Nephropathy: a retrospective analysis. *Am J Nephrol.* 2011;34:435–444.
- Edström Halling S, Söderberg MP, Berg UB. Predictors of outcome in paediatric IgA nephropathy with regard to clinical and histopathological variables (Oxford classification). *Nephrol Dial Transplant.* 2012;27:715–722.
- Shima Y, Nakanishi K, Hama T, et al. Validity of the Oxford classification of IgA nephropathy in children. *Pediatr Nephrol.* 2012;27:783–792.
- Kataoka H, Ohara M, Shibui K, et al. Overweight and obesity accelerate the progression of IgA nephropathy: prognostic utility of a combination of BMI and histopathological parameters. *Clin Exp Nephrol.* 2012;16:706–712.
- Le W, Zeng CH, Liu Z, et al. Validation of the Oxford Classification of IgA Nephropathy for pediatric patients from China. *BMC Nephrol.* 2012;13:158.
- Lee H, Yi SH, Seo MS, et al. Validation of the Oxford Classification of IgA Nephropathy: a single-center study in Korean adults. *Korean J Intern Med.* 2012;27:293–300.
- Zeng CH, Le W, Ni Z, et al. A multicenter application and evaluation of the Oxford Classification of IgA Nephropathy in adult Chinese patients. *Am J Kidney Dis.* 2012;60:812–820.
- Kang SH, Choi SR, Park HS, et al. The Oxford Classification as a predictor of prognosis in patients with IgA nephropathy. *Nephrol Dial Transplant.* 2012;27:252–258.
- Moriyama T, Nakayama K, Iwasaki C, et al. Severity of nephrotic IgA nephropathy according to the Oxford Classification. *Int Urol Nephrol.* 2012;44:1177–1184.
- Gutierrez E, Zamora I, Ballarin JA, et al. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. *J Am Soc Nephrol.* 2012;23:1753–1760.
- Lv J, Shi S, Xu D, et al. Evaluation of the Oxford Classification of IgA nephropathy: a systematic review and meta-analysis. *Am J Kidney Dis.* 2013;62:891–899.
- Nasri H, Mortazavi M, Ghorbani A, et al. Oxford-MEST classification in IgA nephropathy patients: a report from Iran. *J Nephropathol.* 2012;1:31–42.
- Coppo R, Troyanov S, Bellur SS, et al., VALIGA study of the ERA-EDTA Immunonephrology Working Group. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int.* 2014;86:828–836.
- Espinosa M, Ortega R, Sánchez M, et al., Spanish Group for Study of Glomerular Diseases (GLOSEN). Association of C4d deposition with clinical outcomes in IgA nephropathy. *Clin J Am Soc Nephrol.* 2014;9:897–904.
- Moriyama T, Tanaka K, Iwasaki C, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. *PLoS One.* 2014;9:e91756.
- Park KS, Han SH, Kie JH, et al. Comparison of the Haas and the Oxford classifications for prediction of renal outcome in patients with IgA nephropathy. *Hum Pathol.* 2014;45:236–243.
- Chakera A, MacEwen C, Bellur SS, et al. Prognostic value of endocapillary hypercellularity in IgA nephropathy patients with no immunosuppression. *J Nephrol.* 2016;29:367–375.
- Hou JH, Le WB, Chen N, et al. Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial [e-pub ahead of print]. *Am J Kidney Dis.* <http://dx.doi.org/10.1053/j.ajkd.2016.11.02>. Accessed March 15, 2017.
- Shen XH, Liang SS, Chen HM, et al. Reversal of active glomerular lesions after immunosuppressive therapy in patients with IgA nephropathy: a repeat-biopsy based observation. *J Nephrol.* 2015;28:441–449.
- Bellur SS, Lepeyre F, Vorobyeva O, et al. Evidence from the Oxford Classification cohort supports the clinical value of subclassification of focal segmental glomerulosclerosis in IgA nephropathy. *Kidney Int.* 2017;91:235–241.
- Haas M, Verhave JC, Liu ZH, et al. A Multicenter study of the predictive value of crescents in IgA nephropathy. *J Am Soc Nephrol.*, in press.
- Coppo R, Lofaro D, Camilla RR, et al. Risk factors for progression in children and young adults with IgA nephropathy: an analysis of 261 cases from the VALIGA European cohort. *Pediatr Nephrol.* 2017;32:139–150.

33. Bartosik LP, Lajoie G, Sugar L, et al. Predicting progression in IgA nephropathy. *Am J Kidney Dis*. 2001;38:728–735.
34. Barbour SJ, Espino-Hernandez G, Reich HN, et al. Oxford Derivation, North American Validation and VALIGA Consortia; Oxford Derivation North American Validation and VALIGA Consortia. The MEST score provides earlier risk prediction in IgA nephropathy. *Kidney Int*. 2016;89:167–175.
35. Barbour SJ, Reich H, Suzuki Y, et al. A global platform for prediction modelling in 4915 patients with IgA nephropathy from Asia, Europe and the Americas (Abstract P0626). Presented at: ASN Annual Meeting, 2016, Chicago, IL.
36. Coppo R. Biomarkers and targeted new therapies for IgA nephropathy [e-pub ahead of print]. *Pediatr Nephrol*. <http://dx.doi.org/10.1007/s00467-016-3390-9>. Accessed March 15, 2017.
37. Berthoux F, Suzuki H, Thibaudin L, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. *J Am Soc Nephrol*. 2012;23:1579–1587.
38. Wu Q, Tanaka H, Hirukawa T, et al. Characterization and quantification of proliferating cell patterns in endocapillary proliferation. *Nephrol Dial Transplant*. 2012;27:3234–3241.

APPENDIX

Other contributing members of the Working Group

Charles E. Alpers, Ana María Asunis, Sean Barbour, Jan U. Becker, Jie Ding, Gabriella Espino, Franco Ferrario, Agnes Fogo, Michelle Hladunewich, Kensuke Joh, Ritsuko Katafuchi, Jicheng Lv, Keiichi Matsuzaki, Koichi Nakanishi, Antonello Pani, Ran Perera, Agnieszka Perkowska-Ptasinska, Heather Reich, Yuko Shima, Maria Fernanda Soares, Yusuke Suzuki, Katsuo Takahashi, Stéphan Troyanov, Jacobien C. Verhave, Suxia Wang, Jan Weening, Robert Wyatt, Nori Yoshikawa, and Caihong Zeng.