Updated Oxford classification for IgA nephropathy; current status and future prospects

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ABSTRACT

Since the first promulgation of Oxford classification of IgAN in 2009, various investigations have been conducted throughout the world, firstly to validate the findings of the original Oxford classification and secondly, to investigate the significance of other morphologic lesions, which were not included or studied in the original classification due to non-representation of those lesions, in turn due to restrictive inclusion criteria.
PubMed, EBSCO, Embase, Web of Science, directory of open access journals (DOAJ), Scopus, and Google Scholar with keywords of IgA nephropathy, MEST scores, Oxford classification, mesangial proliferation, crescents, MEST classification, endocapillary proliferation, segmental sclerosis, interstitial fibrosis/tubular atrophy, podocytopathy, end-stage renal disease, dialysis, glomerular filtration rate, extra-capillary hypercellularity and chronic kidney disease have been searched to prepare this review.
The updated Oxford classification represents a timely effort on the part of the Oxford classification Working Group for incorporation of additional pathological features not included in the original Oxford classification and it broadens the scope and extent of the pathological classification to cover the expanded spectrum of the disease.
The additive impact of extra-capillary hypercellularity to the MEST scores for improved predictive power remained elusive in the original Oxford study and subsequent validation studies with similar restrictive entry criteria. The updated classification has recommended the incorporation of crescents (C) score to make the MEST classification the MEST-C classification.

Implication for health policy/practice/research/medical education:
The updated Oxford classification represents a timely effort on the part of the Oxford classification working group for incorporation of additional pathological features not included in the original Oxford classification and it broadens the scope and extent of the pathological classification to cover the expanded spectrum of the disease.
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Introduction

A dedicated international Working Group comprising of world-renowned nephrologists and nephropathologists from the International IgA Nephropathy Network and the Renal Pathology Society, with special interest in IgA nephropathy (IgAN) set out in November 2004 to find out the morphologic lesions on renal biopsy which have prognostic and predictive implications and are also reproducible. This was finally achieved after 5 years of concerted and collaborative effort and a novel approach was adopted to develop a pathological classification of IgAN, popularly known as Oxford classification of IgAN (1,2). Since the first promulgation of Oxford classification of IgAN in 2009, various investigations have been conducted throughout the world, firstly to validate the findings of the original Oxford classification and secondly, to investigate the significance of other morphologic lesions, which were not included or studied in the original classification due to non-representation of those lesions, in turn due to restrictive inclusion criteria (3-15).

Materials and Methods

PubMed/Medline, EBSCO, Embase, Web of Science, directory of open access journals (DOAJ), Scopus, and

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Google Scholar with keywords of IgA nephropathy, MEST scores, Oxford classification, mesangial proliferation, crescents, MEST classification, endocapillary proliferation, segmental sclerosis, interstitial fibrosis/tubular atrophy, podocytopathy, end-stage renal disease, dialysis, glomerular filtration rate, extra-capillary hypercellularity and chronic kidney disease have been searched to prepare this review.

Oxford classification for IgA nephropathy

The validated morphologic lesions in the original classification comprised of mesangial proliferation (M score: M0; absence of mesangial proliferation, M1; presence of mesangial proliferation in at least 50% of glomeruli), endocapillary proliferation (E score: E0; absence of endocapillary proliferation, E1; presence of endocapillary proliferation), segmental sclerosis (S score: S0; absence of segmental sclerosis, S1; presence of segmental sclerosis) and interstitial fibrosis/tubular atrophy (IFTA) (T score: T0, T1, and T2 suggest fibrosis/tubular atrophy involving 1%–25%, 26%–50%, or >50% of the cortical area). It was established that these morphologic lesions, popularly known as MEST scores, predicted kidney outcome independently of clinical parameters at the time of kidney biopsy and also during follow-up of treatment both in adults and children (1,3,4,16-22).

The combined maximal numerical score of the original MEST (Oxford) classification (M1+E1+S1+T2) is 5, and biopsy morphologic lesions with a sum score of 2 or higher are judged as independent risk factors for the development of end-stage renal disease (ESRD) (dialysis or estimated glomerular filtration rate [eGFR] below 15 mL/min/1.73 m^2). Furthermore, each morphologic lesion of MEST classification was found to be an independent significant predictive factor for poor renal outcomes. The MEST scores were also individually correlated with long-term kidney outcome. It was also shown that addition of MEST scores to baseline eGFR, proteinuria and blood pressure (at the time of biopsy), considerably augmented prediction of the patient risk of developing 50% drop in kidney function or end-stage kidney failure (1,2). However, the original classification did not address some morphological lesions because of rarity of the lesions or deliberate exclusion of such lesions due to relatively stringent inclusion criteria. In particular, the significance of crescents (C score) was not addressed (15-24). It is well known that crescents on renal biopsy, irrespective of the underlying cause, do have significant prognostic impact. During the ensuing years, several investigators examined such morphologic lesions that were not analyzed in the original Oxford study. The original classification did not include extra-capillary cellular proliferation/hyper-cellularity (glomerular crescents) or immunofluorescence staining data. In addition, the original study was limited to 265 patients of East Asian (from China and Japan) and Caucasian (from Europe and North America) ethnicities, and did not include patients from other parts of the world. In fact, IgAN is one of the most common glomerulopathies throughout the world including Asian region, and is also a leading cause of ESRD in many parts of the world. In most cases of IgAN, the disease is mild and has a good long-term outcome. Very mild forms of IgAN also exist with proteinuria less than 0.5 g/d (25,26). These patients were not included in the original Oxford classification, because of generally excellent long-term prognosis in such patients. However, around 30% of IgAN patients develop end-stage kidney failure within 10–20 years. It is critical to identify these patients or their clinical or pathological features which foretell the risk of progression of the disease. There are also regional differences in the evolution of disease. In some patients, the disease progresses to end-stage kidney failure more rapidly (for example, within 10 years of diagnosis) than in others. The range of clinical presentations of IgAN is also broad, from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis. Since chronic kidney disease (CKD) is a global public health problem that involves millions of people from all racial and ethnic groups, and IgAN is one of the common causes of CKD, it is imperative to identify factors that lead to progression of disease in IgAN (25,26).

Crescentic IgAN is diagnosed when more than 50% of glomeruli are involved by extra-capillary hypercellularity on kidney biopsy, and it presents clinically as rapidly progressive kidney function deterioration with poor outcome. Thus, it is reasonable to assume that, crescents may have prognostic implications. However, the prognosis of IgAN with extra-capillary hypercellularity involving less than 50% of glomeruli differs significantly (23,24).

The additive impact of extra-capillary hypercellularity to the MEST scores for improved predictive power remained elusive in the original Oxford study and the subsequent validation studies with similar restrictive entry criteria. However, Katafuchi et al studied the significance of extra-capillary proliferation as a potential prognosticator in a cohort of 286 patients (out of a total of 702 IgAN patients) not meeting the entry criteria of the original Oxford study that included rapidly progressing forms of IgAN (21). They concluded that extra-capillary proliferation is an independent predictor of poor outcome and should be included in the revised Oxford classification to be published in future. Similarly, crescents were also found to be predictive of poor renal survival by many other studies which included patients with eGFR of less than 30 mL/min/ 1.73 m^2. A working subgroup of the IgAN classification Working Group addressed this unmet issue of value of crescents as potential independent predictors of poor renal outcomes in a large cohort of 3096 patients with IgAN collected from four large retrospective cohorts (22). This group studied the relationship between the

proportion of glomeruli with cellular or fibrocellular crescents and survival from either a ≥50% decline in eGFR or ESRD (combined event) adjusting for covariates used in the original Oxford study (22). It is well established that when cellular crescents are not treated, they will evolve to fibrocellular and eventually fibrous crescents. This condition will lead to glomerular obsolescence and accompanying interstitial inflammation, fibrosis and tubular atrophy and a loss of renal function. In other renal diseases such as lupus nephritis, the presence of crescents is noted as a part of classification and is reported in the pathology reports and classified in the category of activity (cellular crescents) or chronicity (fibrous crescents) of classification. Although extra-capillary hypercellularity is a usual finding in IgAN biopsies, the presence of more than 30% of glomeruli with crescents may portend a negative kidney prognosis. We previously conducted an investigation on 102 IgAN biopsies, in which crescents were found in 21.9% of the cases (23). We found a significant correlation between serum creatinine and the proportion of glomeruli with extra-capillary hypercellularity ($P < 0.001$). There was also a significant positive association between the number of crescents and the proportion of globally sclerotic glomeruli. In this study, we suggested broadening the scope of Oxford classification to include crescents as independent factors having prognostic implication (23,24). Some earlier investigations have also reported that IgAN patients with crescents involving >50% of glomeruli are at high risk of progression, with 75% reaching end-stage kidney failure within 10 years (25,26).

Crescents were also found to be prognostic of poor outcomes in numerous other investigations containing patients with an eGFR below 30 mL/min/1.73 m². Thus, there was a clear need for revisiting and updating the original Oxford classification, particularly with regard to the inclusion of crescents in the scheme (19,21,22,24).

Recently, the same Working Group of Oxford classification of IgAN, albeit with some change in membership, has published updated Oxford classification for IgAN (27). The Working Group has recommended to include C score (C0, C1, and C2) to the Oxford MEST scores. A score of C0 refers to an absence of crescents, C1 to crescents in less than 25% of glomeruli, while C2 refers to crescents involving equal to or more than 25% of glomeruli. The distinction between C1 and C2 was based on the evidence that prognosis of patients with C1 improved on immunosuppressive treatment, whereas the prognosis did not change in C2 category even with immunosuppression. In addition, the group has also recommended subdividing, when possible, the S lesion into podocytopathic or non-podocytopathic types, to enhance its predictive power (27,28). Regarding immunofluorescence findings, it was concluded that, that as yet there is no sufficient evidence that inclusion of

these data will enhance the predictive power beyond that achieved by the use of light microscopic features alone; hence it was decided not to include immunofluorescence findings at the present time. Thus, in effect, the revised Oxford classification of IgAN now includes a 5-component score, i.e., MEST-C score and the maximal numerical score now equals 7 instead of 5, as in the original classification (27).

The international collaborative and research activities of the Working Group are still continuing and specific subgroups have been developed to address specific problematic areas of the classification. The group has developed an online educational tool for educating the practicing nephropathologists from around the world to improve the reproducibility of diagnosing some of the lesions, particularly the M and E lesions (27). A significant inconsistency was noted between the local and central pathologists in the reporting of these lesions in one study and it was observed that the lesions scored by central or review pathologists and not the local pathologists were independently predictive of outcome (29). This educational material will be made available on Renal Pathology Society website. It should be made freely available to all interested in this tool. The group has also assembled a huge, well collected, international database comprising of more than 5000 patients with IgAN. This database will serve as a useful substrate for future studies on IgAN. Another area of huge research potential in IgAN disease is the identification of biomarkers in body fluids for non-invasive diagnosis, monitoring and prognostication in individual patients. Active research is going on in this field and it is hoped that this will reach fruition in near future (30).

Conclusion
In conclusion, the updated Oxford classification represents a timely effort on the part of the Oxford classification Working Group for incorporation of additional pathological features not included in the original Oxford classification and it broadens the scope and extent of the pathological classification to cover the expanded spectrum of the disease. The Working Group has done a commendable job and it is hoped that their endeavors will continue in the future for the ultimate benefit of individual patients with this common glomerular disease.

Author's contribution
MM and HN contributed equally to prepare the paper.

Conflicts of interest
The authors declare no conflict of interest.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by

the authors.

References
1. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int. 2009;76:534-45. doi: 10.1038/ki.2009.243.
2. Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009;76:546-56.
3. Kim CH, Lim BJ, Bae YS, Kwon YE, Kim YL, Nam KH, et al. Using the Oxford classification of IgA nephropathy to predict long-term outcomes of Henoch-Schönlein purpura nephritis in adults. Mod Pathol. 2014;27:972-82. doi: 10.1038/modpathol.2013.222.
4. Herzenberg AM, Fogo AB, Reich HN, et al. Validation of the Oxford classification of IgA nephropathy. Kidney Int. 2011;80:310-7.
5. 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;6:2175-84.
6. 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;6:2384-8.
7. Shima Y, Nakanishi K, Hama T, et al. Validity of the Oxford classification of IgA nephropathy in children. Pediatr Nephrol. 2012;27:783-92.
8. Le W, Zeng CH, Liu Z, Liu D, Yang Q, Lin RX, et al. Validation of the Oxford Classification of IgA Nephropathy for pediatric patients from China. BMC Nephrol. 2012;13:158.
9. 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.
10. Zeng CH, Le W, Ni Z, Zhang M, Miao L, Luo P, et al. A multicenter application and evaluation of the Oxford Classification of IgA Nephropathy in adult Chinese patients. Am J Kidney Dis. 2012;60:812-20.
11. Kang SH, Choi SR, Park HS, Lee JY, Sun IO, Hwang HS, et al. The Oxford Classification as a predictor of prognosis in patients with IgA nephropathy. Nephrol Dial Transplant. 2012;27:252–258.
12. Gutiérrez E, Zamora I, Ballarín JA, Arce Y, Jiménez S, Quereda C, et al. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. J Am Soc Nephrol. 2012;23:1753-60.
13. Lv J, Shi S, Xu D, Zhang H, Troyanov S, Cattran DC, et al. Evaluation of the Oxford Classification of IgA nephropathy: a systematic review and meta-analysis. Am J Kidney Dis. 2013;62:891-9.
14. Nasri H, Mortazavi M, Ghorbani A, Shahbazian H, Kheiri S, Baradaran A, et al. Oxford-MEST classification in IgA nephropathy patients: a report from Iran. J Nephropathol. 2012;1:31-42. doi: 10.5812/jnp.7.
15. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int. 2014 Oct;86:828-36. doi: 10.1038/ki.2014.63.
16. Chakera A, MacEwen C, Bellur SS, Chompuk LO, Lunn D, Roberts ISD. Prognostic value of endocapillary hypercellularity in IgA nephropathy patients with no immunosuppression. J Nephrol. 2016;29:367-75. doi: 10.1007/s40620-015-0227-8.
17. Bellur SS, Lepeytre 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;91:235-41. doi: 10.1016/j.kint.2016.09.029.
18. 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.
19. Zhang W, Zhou Q, Hong L, Chen W, Yang S, Yang Q, Chen W, Yu X. Clinical outcomes of IgA nephropathy patients with different proportions of crescents. Medicine (Baltimore). 2017; 96:e6190. doi: 10.1097/MD.0000000000006190.
20. Bellur SS, Troyanov S, Cook HT, Roberts IS; 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;26:2533-6. doi: 10.1093/ndt/gfq812
21. Katafuchi R, Ninomiya T, Nagata M, Mitsuiki K, Hirakata H. Validation study of oxford classification of IgA nephropathy: The significance of extracapillary proliferation. Clin J Am Soc Nephrol. 2011;6:2806-13.
22. Haas M, Verhave JC, Liu ZH, Alpers CE, Barratt J, Becker JU, et al. A multicenter study of the predictive value of crescents in IgA nephropathy. J Am Soc Nephrol. 2017;28:691-701. doi: 10.1681/ASN.2016040433.
23. Rafieian-Kopaei M, Baradaran A, Nasri H. Significance of extracapillary proliferation in IgA-nephropathy patients with regard to clinical and histopathological variables. Hippokratia. 2013;17:258-61
24. Nasri H, Mubarak M. Extracapillary proliferation in IgA nephropathy; recent findings and new ideas. J Nephropathol. 2015;4:1-5. doi: 10.12860/jnp.2015.01.
25. Salvadori M, Rosso G. Update on immunoglobulin A nephropathy, Part I: Pathophysiology. World J Nephrol. 2015;4:455-67. doi: 10.5527/wjn.v4.i4.455.
26. Salvadori M, Rosso G. Update on immunoglobulin a nephropathy. Part II: Clinical, diagnostic and therapeutic aspects. World J Nephrol. 2016;5:6-19.
27. Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, et al. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int. 2017;91:1014-21. doi:

10.1016/j.kint.2017.02.003.

28. Nasri H, Mubarak M. Focal segmental glomerulosclerosis in IgA nephropathy with regard to Oxford classification: Does it matter? Port J Nephrol Hypert 2014;28:210-8.

29. Coppo R, Lofaro D, Camilla RR, Bellur S, Cattran D, Cook HT, 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;32:139-50.

30. Coppo R. Biomarkers and targeted new therapies for IgA nephropathy. Pediatr Nephrol. 2017;32:725-31.