Title

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CLINICAL VIGNETTE

Spectrum of IgA Glomerular Disease in Light of the MEST-C Classification: *Why Clinical Presentation Matters as Much as Pathological Findings*

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Introduction

IgA (immunoglobulin-A) nephropathy is the most common primary glomerular disease globally, particularly in East Asia, and is characterized by deposits of IGA in the glomerular mesangium.[1] It was first described in 1968 by the French pathologist Jean Berger at the same time that immunofluorescence was being developed.[2] It has a variable clinical course and though originally a pathologic diagnosis, clinical parameters and not biopsy finding, were the only way to predict prognosis.[3] Development of the Oxford classification represented a major advance to predict renal outcomes based upon histopathology in 2009.[4-7] This pathological grading system describes biopsies with the MEST designation: Mesangial hyper-cellularity=M, Endo-capillary hyper-cellularity=E, Segmental glomerulosclerosis=S, Tubular atrophy/interstitial fibrosis=T.[7] These variables were developed from a cohort of 265 subjects with IGA nephropathy and were both reproducible and independent of each other.[7] Later observations found that proportion of glomeruli with crescents (C) also predicted prognosis, especially in patients with low GFR, leading to the current MEST-C nomenclature.[8]

There is a large clinical spectrum of disease which has created treatment controversy about the role of glucocorticoid and cytotoxic treatment in patients with IgA nephropathy.[2] In most cases, conservative treatment is initiated with RAAS (Renin-Angiotensin-Aldosterone) blockade and treatment of hypertension, though glucocorticoids can benefit some patients.[3]

Systemic and necrotizing IgA nephropathy is often termed crescentic IgA nephropathy or Henloch Schonlein Purpura (HSP) if systemic involvement is suspected.[9] Targeted rituximab therapy has not proven effective,[10] and has risks as well.[9] However, it is recognized that even glucocorticoid therapy carries increased risk of severe infections.[11]

We report two patients with a clinically benign phenotype who had concerning features on biopsy who did well with conservative therapy. Case 1 failed RAAS blockade for almost 2 years before responding well to glucocorticoid therapy despite presence of a crescent and a 3/4 features found from the MEST-C score. Case 2 showed more severe crescentic changes but responded well to RAAS blockade with disappearance of the worrisome crescentic features on re-biopsy. This highlights the importance of considering the clinical phenotype in addition to the pathological phenotype in determining the best treatment course.

***Case 1*:** Clinically mild IgA with one crescent on biopsy

The first patient is a 45 year old Chinese male who presented with proteinuria with an initial level of 3.8 g protein/g creatinine. He had been previously treated with angiotensin receptor blocker for hypertension one year prior to onset of renal pathology. He had only mild microscopic hematuria, 24-85 red blood cells / hpf and a serum creatinine of 0.7-0.8 mg/dL corresponding to an estimated glomerular filtration rate of > 89ml/min. His 24 hour urine protein was 2.262 grams/24 hour. Clinically the patient had hypertension with blood pressure of 130-140 mmHg on several measurements. The diagnosis of IgA nephropathy was suspected with hematuria, proteinuria, and preserved renal function. A full serological workup was negative.

Renal biopsy showed 20 glomeruli with confirmed IgA nephropathy on light microscopy and immunofluorescence. The biopsy showed mild global glomerulosclerosis of 10%, minimal interstitial fibrosis and tubular atrophy of about 5%. According to the MEST-C classification [Mesangial hyper-cellularity=M, Endo-capillary hyper-cellularity=E, Segmental glomerulosclerosis=S, Tubular atrophy/interstitial fibrosis=T, Cellular or fibro-cellular crescents=C] the score was M1, E1, S1, T0, C1.[1] There were four poor prognostic outcomes predicted, and the finding of one fibro-cellular (Chronic) crescent and one acute cellular crescent on pathology was concerning.[2] Given the patient's fairly mild clinical course without control of his proteinuria on renin angiotensin aldosterone (RAAS) blockade, 1 gram/kilogram methylprednisolone was started along with *pneumocystis* prophylaxis with cotrimoxazole. The patient tolerated therapy well and maintained a low salt diet and low carbohydrate intake along with regular exercise to maintain his weight and A1C despite steroid treatment. After initiation of steroids urine protein to creatinine ratio promptly decreased to 1-gram protein/gram creatinine from his prior 2.4-3.8 gram/gram range pre-treatment. The patient's serum creatinine remained within normal range. Please see Figure 1 for trends of urinary rbc, urinary protein, and serum creatinine along with timing of steroid initiation. Please see Figure 2 for biopsy results.

***Case 2*:** Clinically mild IgA with crescentic biopsy

The second patient is a 19-year-old male of mixed white and Filipino ancestry. He had a few episodes of synpharangitic hematuria at age 10 although he denied prior episodes of gross hematuria. At age 18 was referred to nephrology for microhematuria and proteinuria. Physical exam showed a healthy young adult male with blood pressure of 133/93 who was otherwise normal. Serum creatinine was 1.0 and urinalysis showed 2+ blood, trace protein, 33 RBC/uL, no casts, and urine prot/cr ratio of 0.6. Serologic testing was negative. He underwent a kidney biopsy showing IGA nephropathy with 40% (5/13) cellular crescents, segmental sclerosis, and thin glomerular basement membranes. No chronic tubulointerstitial changes were seen. The biopsy had 3 of 4 adverse prognostic features according to the Oxford classification: focal endocapillary proliferation, mesangial proliferation, and segmental sclerosis.

Glucocorticoids were considered but the patient elected to do a trial of RAAS blockade and fish oil. Four months later, urine prot/cr ratio had fallen to 0.2, BP improved to 113/66, creatinine 1.0, and UA had 52 RBC/uL. Repeat biopsy 5 months later (9 months after the initial biopsy) showed IGAN with rare segmental sclerosis, no crescents, no adverse prognostic features, and no chronic change. He continued on angiotensin receptor blocker (ARB) and fish oil.

***Case 3*:** Clinically severe HSP with very heavily inflammatory (Crescentic) biopsy

Our third patient is a 38-year-old Caucasian female who was previously healthy, but developed an increasing serum creatinine from her normal baseline to 2.1 mg/dL. She had no initial symptoms, but developed a small patch of erythema on her left lower thigh. There was no spotted rash across her back and buttocks. Serum creatinine continued to climb to 2.7 and she had gross hematuria on urinalysis and near nephrotic range proteinuria (6.1 grams).

Biopsy revealed active IgA glomerulonephritis. The pathological features showed necrotizing crescentic glomerulonephritis with 20% of glomeruli with active crescents and 25% with global sclerosis. While the percentage of crescents was below 50% the quantity of crescents from the biopsy, the skin findings, and most importantly the progressive clinical course suggested a more HSP like presentation as opposed to the more minor pathology and clinical phenotype of the hitherto presented cases.

She presented to UCLA for a second opinion, and elected treatment with cyclophosphamide in an attempt to prevent ESRD. She was counseled that cyclophosphamide may not work for her HSP like IgA nephropathy, which is often resistant to therapy. Data about rituximab is limited efficacy in crescentic IgA nephropathy was also reviewed.[9] Her serum creatinine continues to rise and she is preparing for peritoneal dialysis and eventual renal transplantation. Please see figure 5 for biopsy findings in case 3: severe crescentic IgA with concern for HSP. The reading pathologist graded her biopsy as histologic grade IIIb HSP nephritis.[10,12]

Discussion

The MEST-C scoring system from the Oxford classification offers some interesting pathological correlates to outcomes and disease course and has been shown (particularly the T component) to improve prognostic ability beyond clinical parameters alone in some cohorts.[13-15] The clinical parameters shown to predict prognosis are proteinuria more than 1g per day, low kidney function, and elevated blood pressure.[1] These perform best ifpersistent over 2 years.[3] The highly variable nature of IGA nephropathy distinguishes this disease from many forms of primary glomerulonephritis. The risk of ESRD is very low among patients with benign clinical parameters regardless of pathology.[16-17] The Oxford classification excluded patients with mild clinical disease,[7] and suffers from selection bias because many patients with clinically mild kidney disease are not biopsied.[18] The three cases presented demonstrate that the clinical course is equally important to prognosis as pathological findings. Determining indications for immunosuppression is a major reason why the estimation of prognosis is critical for patients with IGA nephropathy. Based on several decades of treatment to alter the course of IGA nephropathy, the indications for immunosuppression in IgA nephropathy should be for clearly worsening clinical disease (IE, high grade proteinuria, worsening kidney function but recently good baseline, elevated blood pressure) along with risk factors for disease progression noted on biopsy. The risks of glucocorticoid therapy, particularly severe and occasionally fatal infection, often have outweighed the benefits as has been demonstrated in two large interventions trials STOP IGA Nephropathy trial[19] and the TESTING trial[20] and.[21] The risks of cytotoxic therapy including increased lifetime risk of malignancy should be discussed prior to initiating treatment.[22]

None of the 3 cases presented fit the “mild” IgA or severe necrotizing crescentic IgA paradigm, rather two cases with concerning pathological findings responded to conservative treatment, and one case with pathological changes failed to respond to conservative therapy and was started on cytotoxic therapy. The more clinically severe and progressive features in case 3 included inexorably rising serum creatinine and nephrotic range proteinuria.

These cases are a good reminder that patient selection is a critical part of treating IGA nephropathy. We advocate conservative treatment with RAAS blockade in IgA
nephropathy with a benign course, and glucocorticoid therapy in patients with clinically and pathologically concerning features if RAAS blockade fails. We would advocate reserving cytotoxic therapy only for rapidly progressive, crescentic, necrotizing disease where both the pathological findings are concerning and the clinical course is progressive.

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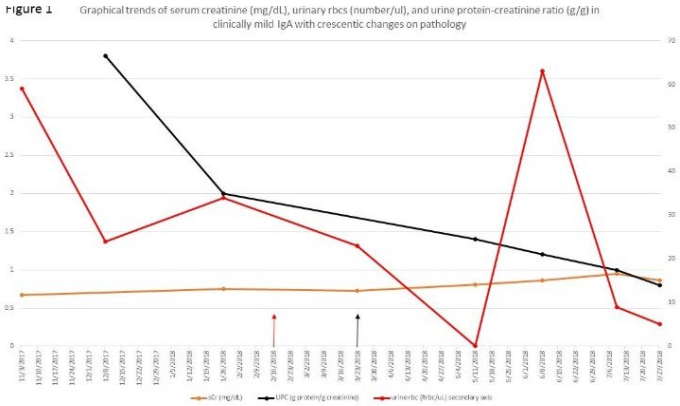

Figure 1: Graphical trends of urinary red blood cells/microliter (rbc/ul), urine protein/creatinine ratio (gram protein/gram creatinine), and serum creatinine (mg/dL) in patient showing crescentic changes present pathologically, but clinically mild IgA nephropathy in case 1. Red arrow renal biopsy, black arrow starting steroids.

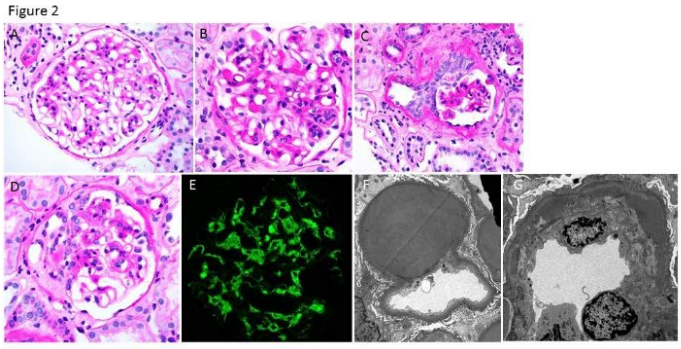

Figure 2: Renal biopsy micrographs showing crescentic pathological changes in clinically mild IgA nephropathy in case 1.
A) H&E stain 40x, mesangial hyper-cellularity
B) H&E stain 40x, endo-capillary hyper-cellularity and prominent mesangial deposits
C) H&E stain 40x, small segmental cellular crescent
D) H&E stain 40x, segmental glomerular scar/fibrous crescent
E) Immunofluorescence, IgA predominant flouresence
F) Electron micrograph showing large mesangial deposits
G) Electron micrograph showing large endothelial deposits

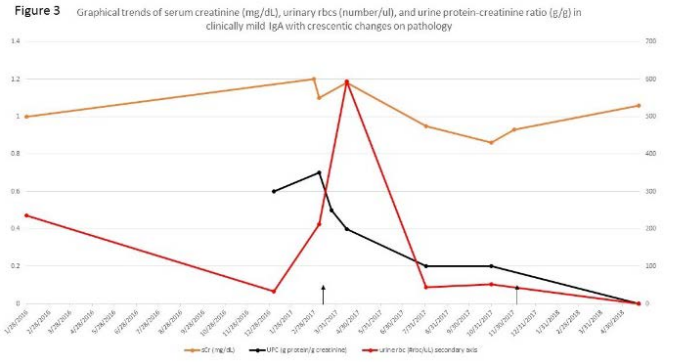

Figure 3: Graphical trends of urinary red blood cells/microliter (rbc/ul), urine protein/creatinine ratio (gram protein/gram creatinine), and serum creatinine (mg/dL) in patient showing crescentic changes present pathologically, but clinically mild IgA nephropathy in case 2. Black arrows = dates of two biopsies, which showed marked improvement in pathology with only angiotensin receptor blocker therapy.

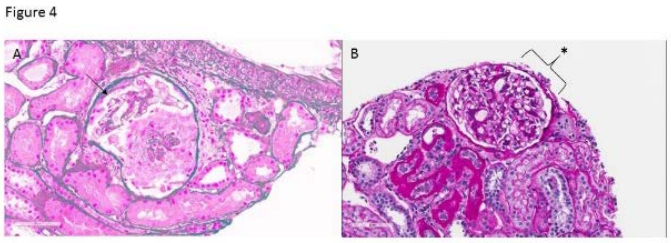

Figure 4: Sequential renal biopsy micrographs showing crescentic pathological changes in clinically mild IgA nephropathy in case 2.
A) Initial biopsy showing an example of a glomerulus with a cellular crescent (40% crescents on this biopsy). The black arrow demonstrates the location of crescent on biopsy slide. B) Follow up biopsy obtained nine months later: shows merely changes of the glomerular mesangium consistent with mild IGA nephropathy without any crescents after only RAAS blockade.

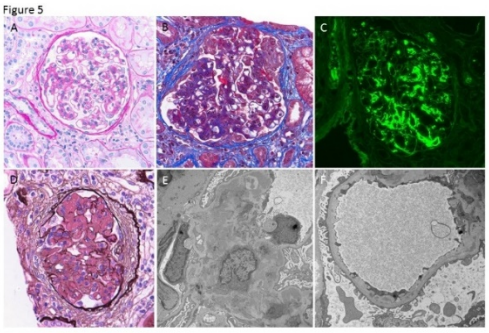

Figure 5: Renal biopsy micrographs showing crescentic pathology in clinically severe crescentic IgA nephropathy/suspected Henloch Schonlein Purpura (HSP) in case 3.
A) H&E stain 40 x, segmental necrotizing lesion
B) Masson stain, 40 x, cellular crescent
C) Immunofluorescence showing IgA deposits
D) Methenamine silver stain 40x-showing extensive glomerular deposits
E) Electron micrography showing mesangial deposits
F) Electron micrography showing sub-endothelial deposits

REFERENCES

1. **Rodrigues JC, Haas M, Reich HN.** IgA Nephropathy. *Clin J Am Soc Nephrol.* 2017 Apr 3;12(4):677-686. doi: 10.2215/CJN.07420716. Epub 2017 Feb 3. Review. Pub Med PMID: 28159829; PubMed Central PMCID: PMC 5383386.
2. **Feehally J, Cameron JS.** IgA nephropathy: progress before and since Berger. *Am J Kidney Dis.* 2011 Aug;58 (2):310-9. doi: 10.1053/j.ajkd.2011.03.024. Epub 2011 Jun 25. PubMed PMID: 21705126.
3. **Bartosik LP, Lajoie G, Sugar L, Cattran DC.** Predicting progression in IgA nephropathy. *Am J Kidney Dis.* 2001 Oct;38(4):728-35. PubMed PMID: 11576875.
4. **Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, Roberts IS, Morando L, Camilla R, Tesar V, Lunberg S, Gesualdo L, Emma F, Rollino C, Amore A, Praga M, Feriozzi S, Segoloni G, Pani A, Cancarini G, Durlik M, Moggia E, Mazzucco G, Giannakakis C,**

Honsova E, Sundelin BB, Di Palma AM, Ferrario F, Gutierrez E, Asunis AM, Barratt J, Tardanico R, Perkowska-Ptasinska A; 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 Oct;86(4):828-36. doi: 10.1038/ki.2014.63. Epub 2014 Apr 2. PubMed PMID: 24694989; PubMed Central PMC ID: PMC4184028.

5. **Das U, Dakshinamurty KV, Prayaga A, Uppin M.** Spectrum of IgA nephropathy in a single center. *Saudi J Kidney Dis Transpl.* 2015 Sep;26(5):1057-63. doi: 10.4103 /1319-2442.164612. PubMed PMID: 26354591.
6. **Roberts IS.** Pathology of IgA nephropathy. *Nat Rev Nephrol.* 2014 Aug;10(8):445-54. doi: 10.1038/nrneph. 2014.92 Epub 2014 May 27. Review. PubMed PMID: 24861083.
7. **Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, Alpers CE, Amore A, Barratt J, Berthoux F, Bonsib S, Bruijn JA, D'Agati V, D'Amico G, Emancipator S, Emma F, Ferrario F, Fervenza FC, Florquin S, Fogo A, Geddes CC, Groene HJ, Haas M, Herzenberg AM, Hill PA, Hogg RJ, Hsu SI, Jennette JC, Joh K, Julian BA, Kawamura T, Lai FM, Leung CB, Li LS, Li PK, Liu ZH, Mackinnon B, Mezzano S, Schena FP, Tomino Y, Walker PD, Wang H, Weening JJ, Yoshikawa N, Zhang H.** The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int.* 2009 Sep;76(5):534-45. doi: 10.1038/ki.2009. 243. Epub 2009 Jul 1. PubMed PMID: 19571791.
8. **Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, Liu ZH, Roberts IS, Yuzawa Y, Zhang H, Feehally J; IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society; Conference Participants.** Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int.* 2017 May;91(5):1014-1021. doi: 10.1016/j.kint. 2017.02.003. Epub 2017 Mar 22. Review. PubMed PMID: 28341274.
9. **Floege J, Eitner F.** Current therapy for IgA nephropathy. *J Am Soc Nephrol.* 2011 Oct;22(10):1785-94. doi: 10.1681/ ASN.2011030221. Epub 2011 Sep 8. Review. PubMed PMID: 21903997.
10. **Koskela M, Ylinen E, Ukonmaanaho EM, Autio-Harmainen H, Heikkilä P, Lohi J, Jauhola O, Ronk-ainen J, Jahnukainen T, Nuutinen M.** The ISKDC classification and a new semiquantitative classification for predicting outcomes of Henoch-Schönlein purpura nephritis. *Pediatr Nephrol.* 2017 Jul;32(7):1201-1209. doi:10.1007/ s00467-017-3608-5. Epub 2017 Feb 14. PubMed PMID: 28197887.
11. **Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, Sethi S, Tumlin JA, Mehta K, Hogan M, Erickson S, Julian BA, Leung N, Enders FT, Brown R, Knoppova B, Hall S, Fervenza FC.** A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction. *J Am Soc Nephrol.* 2017 Apr;28(4):1306-1313. doi: 10.1681/ASN. 2016060640. Epub 2016 Nov 7. PubMed PMID: 27821627; PubMed Central PMCID: PMC 5373458.
12. **Counahan R, Winterborn MH, White RH, Heaton JM, Meadow SR, Bluett NH, Swetschin H, Cameron JS, Chantler C.** Prognosis of Henoch-Schönlein nephritis in children. *Br Med J.* 1977 Jul 2;2(6078):11-4. PubMed PMID: 871734; PubMed Central PMCID: PMC1631306.
13. **Tanaka S, Ninomiya T, Katafuchi R, Masutani K, Tsuchimoto A, Noguchi H, Hirakata H, Tsuruya K, Kitazono T.** Development and validation of a prediction rule using the Oxford classification in IgA nephropathy. *Clin J Am Soc Nephrol.* 2013 Dec;8(12):2082-90. doi: 10.2215/CJN.03480413. Epub 2013 Oct 31. PubMed PMID: 24178970; PubMed Central PMCID: PMC 3848397.
14. **Barbour SJ, Espino-Hernandez G, Reich HN, Coppo R, Roberts IS, Feehally J, Herzenberg AM, Cattran DC; Oxford Derivation, North American Validation and VALIGA Consortia; Oxford Derivation North American Validation and VALIGA Consortia.** The MEST score provides earlier risk prediction in lgA nephropathy. *Kidney Int.* 2016 Jan;89(1):167-75. doi:10.1038/ki.2015. 322. PubMed PMID:26759049.
15. **Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, Itabashi M, Takei T, Uchida K, Nitta K.** Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. *PLoS One.* 2014 Mar 21;9(3):e91756. doi: 10.1371/journal.pone.0091756. eCollection 2014. PubMed PMID: 24658533; PubMed Central PMCID: PMC3962373.
16. **Gutiérrez E, Zamora I, Ballarín JA, Arce Y, Jiménez S, Quereda C, Olea T, Martínez-Ara J, Segarra A, Bernis C, García A, Goicoechea M, García de Vinuesa S, Rojas-Rivera J, Praga M; Grupo de Estudio de Enfermedades Glomerulares de la Sociedad Española de Nefrología (GLOSEN).** Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. *J Am Soc Nephrol.* 2012 Oct;23(10):1753-60. Epub 2012 Sep 6. PubMed PMID: 22956820; PubMed Central PMCID:PMC3458461.
17. **Imai N, Shirai S, Yasuda T, Shibagaki Y, Kimura K.** Long-term prognosis of IgA nephropathy presenting with minimal or no proteinuria: A single center experience. *Indian J Nephrol.* 2016 Mar-Apr;26(2):107-12. doi:10. 4103/ 0971-4065.157010. PubMed PMID: 27051134; PubMed Central PMCID: PMC4795425.
18. **Fuiano G, Mazza G, Comi N, Caglioti A, De Nicola L, Iodice C, Andreucci M, Andreucci VE.** Current indications for renal biopsy: a questionnaire-based survey. *Am J Kidney Dis.* 2000 Mar;35(3):448-57. PubMed PMID: 10692270.
19. **Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, Panzer U, Peters H, Benck U, Mertens PR, Kuhlmann U, Witzke O, Gross O, Vielhauer V, Mann JF, Hilgers RD, Floege J; STOP-IgAN Investigators.** Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med.* 2015 Dec 3;373(23):2225-36. doi: 10.1056/NEJMoa1415463. PubMed PMID:26630142.

20. **Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, Monaghan H, Zhao M, Barbour S, Reich H, Cattran D, Glassock R, Levin A, Wheeler D, Woodward M, Billot L, Chan TM, Liu ZH, Johnson DW, Cass A, Feehally J, Floege J, Remuzzi G, Wu Y, Agarwal R, Wang HY, Perkovic V; TESTING Study Group.** Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA.* 2017 Aug 1;318 (5): 432-442. doi:10.1001/jama.2017.9362. PubMed PMID: 28763548; PubMed Central PMCID: PMC 5817603.
21. **Lv J, Xu D, Perkovic V, Ma X, Johnson DW, Woodward M, Levin A, Zhang H, Wang H; TESTING Study Group.** Corticosteroid therapy in IgA nephropathy. *J Am Soc Nephrol.* 2012 Jun;23(6):1108-16. doi: 10.1681/ASN. 2011111112. Epub 2012 Apr 26. Review. PubMed PMID: 22539830; PubMed Central PMCID: PMC 3358763.
22. **Jefferson JA.** Complications of Immunosuppression in Glomerular Disease. *Clin J Am Soc Nephrol*. 2018 Aug 7;13(8):1264-1275. doi: 10.2215/CJN.01920218. Epub 2018 Jul 24. PubMed PMID: 30042223.

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