Perspective

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How COVID-19 Has Changed the Management of Glomerular Diseases

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A 26-year-old woman contacted our office asking for an urgent call back. She had a history of steroid-dependent and frequently relapsing minimal change disease, and calls like this usually meant her home dipsticks had turned positive. Instead, she reported that she had just tested positive for the 2019 novel coronavirus (SARS-CoV-2 or COVID-19). She had a low-grade fever, myalgias, and a reduced sense of smell, but fortunately no cough or shortness of breath. She was worried about her dipsticks, however, which were still negative. What was usually a reassuring do-it-yourself test now frightened her. "Does that mean the rituximab is still in my system?" she asked, referring to the infusion she had done about 4 months earlier.

As COVID-19 infections spread across the world, nephrologists and their patients face difficult decisions regarding management of glomerular diseases. Our Center for Glomerular Diseases has fielded countless questions in the last few weeks, not just from patients but from other nephrologists about the most appropriate way to handle immunosuppression in the current climate. Should lupus nephritis patients reduce their mycophenolate mofetil doses or stop the drug altogether? Should membranous nephropathy patients with rising titers of antibodies to the phospholipase A_2 receptor (PLA_2R) proceed with their scheduled rituximab infusions? Should severe ANCA-associated GN patients in the midst of an intravenous course of cyclophosphamide switch over to oral cyclophosphamide to avoid trips into the infusion center? Of course, there are no perfect, or even evidence-based, answers to these and other inquiries. Here, we offer some insight as to how our center in New York City, currently the world's hottest spot for COVID-19 infections, has adapted the management of our glomerular disease patients to reduce complications of potential COVID-19 disease (Table 1). We also speculate on how our practice will be altered in the future, even at a time when, hopefully, COVID-19 infections are a thing of the past.

While considering the impact of immunosuppression on COVID-19 outcomes, nephrologists must simultaneously account for the potential impact on kidney outcomes from withholding immunosuppression. Therefore, we are still advising that patients who are at high risk of progression to ESKD without immediate therapy begin standard of care immunosuppression regimens. These patients are principally those with rapidly progressive glomerulonephritides due to lupus, ANCA, and anti–glomerular basement membrane-associated disease. In addition, patients with severe forms of nephrotic syndrome that are already manifesting reductions in kidney function, or complications related to proteinuria and hypoalbuminemia (*e.g.*, deep venous thrombosis and anasarca), fit this criterion. In contrast, we have advised many of our patients who otherwise would be treated with immunosuppression to postpone treatment until their local transmission rates of COVID-19 are low enough that social distancing measures are no longer recommended. These include the following: (*1*) membranous nephropathy patients with nephrotic syndrome and/or rising anti-PLA_2R antibody titers, but without complications and with preserved eGFR, (*2*) minimal change disease or FSGS patients with preserved eGFR, and (*3*) IgA nephropathy patients with endocapillary hypercellularity and/or low crescentic burden on kidney biopsy with preserved eGFR. In addition, for diseases without a validated standard of care regimen, such as immune complex or complement-mediated forms of membranoproliferative GN, we are not advocating immunosuppressive therapy at this time regardless of clinical parameters.

Glomerular disease patients who started immunosuppressive therapy prior to the COVID-19 pandemic require a risk-benefit assessment regarding continuation of immunosuppression, which should account for the potential impact of modifying or stopping treatment, as well as patient access to therapies. Patients in the midst of an intravenous induction regimen (*e.g.*, EuroLupus dosing of intravenous cyclophosphamide for lupus nephritis) can be changed to an equivalent oral induction regimen if one exists (*e.g.*, use of oral cyclophosphamide or high-dose mycophenolate mofetil for lupus nephritis) to potentiate stay-at-home adherence and avoid exposure to health care settings. Likewise, many patients who would receive pulse methylprednisolone intravenous treatments can be treated with high-dose oral prednisone or oral methylprednisolone. We have leveraged home infusion services to maintain necessary infusions while minimizing (without eliminating) social contact. Alterations to maintenance immunosuppression regimens should be individualized according to disease status and drug class. For example, stable patients on chronic

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Table 1. Concise guidelines for management of glomerular disease patients during the COVID-19 pandemic (opinion-based)

Component	Recommendations
Immunosuppression	Discontinue antimetabolites for patients with confirmed or suspected infection
	Consider discontinuation of antimetabolites for patients in sustained remission >12 mo
	Favor short-acting, reversible agents over long-acting infusions
	Avoid therapy initiation for marginal criteria or nonstandard indications
	Avoid therapy initiation for minimally symptomatic patients with stable eGFR
	Convert intravenous infusions to oral formulation when possible (*e.g.*, cyclophosphamide) and utilize home infusion services in lieu of hospital- or clinic-based infusion suites
	For patients in clinical trials with potential patient benefit, continue study drug by sending medication to their home if an oral or subcutaneous agent, or dosing in a COVID-19–compliant infusion center if an intravenous agent
Diagnosis and monitoring	Reserve biopsies for critical decision-making needs
	Consider empirical treatment, without biopsy, for conditions with high pretest probability diagnoses (*e.g.*, RPGN with positive ANCA serologies)
	Limit blood draws to safety laboratories performed at commercial (*i.e.*, non–hospital-based) laboratories
	Utilize home urine dipsticks for proteinuria monitoring
	Utilize commercially shipped collection kits for 24-h urine collections that can be done at home and shipped back
	Postpone protocol biopsies
Supportive care	Continue ACE inhibitors or ARBs in the absence of clear contraindications at this point
	Continue prophylactic antibiotics (*e.g.*, TMP-SMX)
	Encourage social distancing
	Encourage use of masks while outside of the house
	Complete recommended vaccinations for influenza and pneumococcus (PCV13 and PPSV23) to prevent secondary or coinfection
Office management	Change all appointments to telemedicine video visits
	Allow office staff to manage phones and patient messages from home
	Develop a standard script of recommendations for patients calling with questions about possible COVID-19 exposure based on CDC guidelines
	Use telemedicine video visits rather than telephone calls for patients concerned about COVID-19 infectious symptoms to best triage respiratory status

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; TMP-SMX, trimethoprim-sulfamethoxazole; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; RPGN, rapidly progressive glomerulonephritis; CDC, Centers for Disease Control and Prevention.

immunosuppression should lower their doses to the safest level that will maintain remission; for many of our patients, this translates to a 50% drop in cumulative dose. If disease remission already extends >12 months, we consider immediate cessation of antimetabolites like mycophenolate mofetil or azathioprine, and we are not dosing maintenance rituximab infusions. Patients in sustained remission on maintenance steroids can, if on a low and alternate-day dose, discontinue these agents; otherwise, we begin a taper with dose adjustments every 2 weeks. We do not adjust the dose of calcineurin inhibitors in line with recommendations from our kidney transplant colleagues, who have recently reported that COVID-19–infected allograft recipients maintained on calcineurin inhibitors alone, with the antimetabolite held, have similar hospital-based outcomes compared with non–immune suppressed COVID-19–infected patients (1).

As many glomerular disease patients are young without significant comorbidities, suspected or confirmed cases of COVID-19 infection can often be managed at home without the need for hospitalization. For such patients, we recommend discontinuation of antimetabolites as part of their management and ask for continued communication on their clinical course with our office. Patients with glomerular diseases who require hospitalization for COVID-19 respiratory illnesses should, in addition to holding their antimetabolites, be started on stress doses of corticosteroids if on a long-term steroid regimen. If hydroxychloroquine and azithromycin are started on patients with nephrotic-range proteinuria, close monitoring of calcium levels is required, and it is mandatory to confirm that a baseline electrocardiogram has a normal QTc interval.

Our Center for Glomerular Diseases averages about 3000 annual office visits for glomerular disease care. Since mid-March 2020, we have moved the entirety of our clinic to telemedicine encounters using video visits. Telemedicine video visits with our physicians and support staff have been helpful to answer patients' questions, allay their concerns, and maintain contact with them during home sequestration. Patients can monitor their BPs, daily weights, and symptoms of glomerular disease and relate these in real time to our staff. For example, peripheral edema can be easily visualized with cell phone and tablet cameras. Laboratory surveillance is a critical component of managing glomerular disease patients. We have limited this surveillance to primarily focus on safety laboratories that can be drawn at a commercial laboratory (*i.e.*, not a hospital-based laboratory) that is enforcing social distancing among its clients. As an alternative, for some patients we have been able to use laboratory services that provide home testing visits. We have always relied on the use of urine dipsticks for home monitoring of disease status and include a review of dipstick results in our telemedicine visits. Importantly, if a patient contacts our office with symptoms suggestive of COVID-19 infection, such as cough, fever, and/or myalgias, a video visit potentiates better assessment of dyspnea and respiratory effort than a phone call for

triaging whether the patient should be seen at an emergency room for oxygen therapy and potential hospital admission.

New enrollment into clinical trials has been paused during the COVID-19 crisis, but glomerular disease patients enrolled in therapeutic clinical trials that offer the prospect of direct benefit to participants should continue on the study drug. Many single-arm but also randomized clinical trials, particularly in phases 2 and 3, allow participants access to novel or unapproved therapies and thus have the prospect of benefit. The Food and Drug Administration has provided guidance (2) on conducting clinical trials during the pandemic, which includes sending study drugs to participants if oral or subcutaneous agents, or dosing study drugs in an outpatient infusion center with appropriate protocols for safe infusion therapy if an intravenous agent. The American College of Rheumatology has provided recommendations (3) for facilities providing infusion therapy during the COVID-19 crisis (Table 2). Visits that do not require study drug administration can be converted to telemedicine encounters. Study laboratories that are required for safety monitoring can be performed at commercial laboratories, at which time outcome-associated laboratories that are standard (*e.g.*, creatinine and proteinuria) can also be collected. Some clinical trials have provided subjects with mailing kits for biosamples procured at local laboratories, so that these specimens can still be processed at a central study laboratory.

Kidney biopsies fit the definition of "elective procedures," which have been cancelled in many institutions at this time. We still are performing kidney biopsies in settings where we expect that findings are crucial for the immediate management of patients (*e.g.*, rapidly progressive GN). Patients with apparent primary nephrotic syndrome and preserved eGFR should not undergo biopsies at this time; they can be managed empirically with calcineurin inhibitors with a biopsy to follow at a safer date. The use of anti-PLA_2R antibody testing to diagnose primary membranous nephropathy can be helpful in this situation (4). Protocol biopsies to assess the efficacy of immunosuppression and activity versus chronicity of disease, as well as research biopsies for clinical trials or observational studies, should be cancelled.

As we reduce our glomerular disease patients' exposure to immunosuppression, we often need to adjust our conservative therapies, particularly renin-angiotensin-aldosterone system blocking agents and diuretics. Despite recent controversies regarding the possible impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 transmission, we adhere to the recommendations made by experts across various disciplines (cardiology, nephrology, and hypertension) not to discontinue these drugs (5–7). Therefore, we keep our patients on these agents and, if proteinuria is heavy in patients being weaned off immunosuppression, consider either increasing the dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers or, alternatively, keeping the dose unchanged but adding a mineralocorticoid receptor blocker (*e.g.*, eplerenone). For patients already on chronic hydroxychloroquine therapy, we are continuing the drug but not altering the dose; in the event of a drug shortage, we will need to consider dose reductions for these patients. We are not starting any patients on this drug prophylactically and are seeing cases of COVID-19 infection in lupus patients on maintenance hydroxychloroquine.

We anticipate that our management of glomerular disease patients will be altered by our current COVID-19–influenced practices even when the current pandemic has resolved. We have seen significantly lower rates of rapidly progressive GN in our hospitalized patients and disease relapses in our clinic patients since widespread adoption of social distancing. We have heard similar reports from our colleagues in other disciplines (*e.g.*, fewer myocardial infarctions seen by cardiologists). This seemingly quiescent disease state supports the hypothesis that environmental exposures, including but not limited to infections, may be a major trigger of glomerular disease onset and relapse. While we do not foresee advocating formal social distancing for immunosuppressed patients outside of a pandemic window, we will repeatedly reinforce patient education on measures to reduce infectious exposures such as strict avoidance of sick contacts, frequent handwashing, avoiding touching of the face, and, whenever possible, staying at least 2 m away from other individuals. We also foresee wide adoption of telemedicine encounters to reduce time in healthcare settings for many of our glomerular disease patients, especially in follow-up visits when these patients are often on their highest doses of immunosuppressants.

Most importantly, given forecasts of a possible second wave of COVID-19 infections after the current pandemic has abated, as well as broader speculation that we are now firmly entrenched in an era of viral pandemics, we will need to consider the degree to which we are immunosuppressing all of our glomerular disease patients regardless of current infection rates. Fortunately, the field of glomerular diseases has been moving in this direction well before the emergence of COVID-19. For example, the Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil

Table 2. Infusion suite strategies to reduce risk of COVID-19 infection (adapted from American College of Rheumatology guidance document)

Strategy
Postpone all nonessential infusions
Adjust schedule so that waiting rooms and infusion suites allow for social distancing with chairs at least 2 m apart
Provide face masks for all patients and staff to wear within the facility
Frequently clean and decontaminate all equipment and surfaces in patient areas with appropriate contact time for disinfectant
Verbally inform patients and post signs about appropriate social distancing and hygiene procedures
Recommend remote check-in (*e.g.*, over the phone from outside the facility) to minimize waiting time
Screen staff with temperature checks at beginning and end of shift
Screen patients by phone prior to their visit about infectious symptoms and exposure to individuals with known COVID-19 infection

Cytoplasm Antibody-Associated Vasculitis study showed noninferior outcomes in Anti-Neutrophil Cytoplasm Antibody-associated GN with a reduced dose of corticosteroids compared with a standard dose of corticosteroids (8), the Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy and Therapeutic Evaluation of Steroids in IgA Nephropathy Global trials argued against use of high dose corticosteroids for IgA nephropathy (9,10), and the Membranous Nephropathy Trial of Rituximab study found better long-term outcomes with just one or two dosing intervals of rituximab compared with year-long therapy with cyclosporine (11). But we likely will need to go even further than these trials and begin to question, for each glomerular disease, how much immunosuppression is needed to induce a remission and whether long-term maintenance therapy is required to sustain this remission. In other words, the debates on risks versus benefits of immunosuppression that we are forced to have now in the face of widespread COVID-19 infections should continue past this year, when our world, and our patients, will be very different because of what we are experiencing now.

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References

1. The Columbia University Kidney Transplant Program: Early description of coronavirus 2019 disease in kidney transplant recipients in New York. *J Am Soc Nephrol* 31: XXX–XXX, 2020
2. U.S. Food & Drug Administration: FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic. Available at: www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic. Accessed April 11, 2020
3. American College of Rheumatology: ACR infusion guidance during COVID-19 crisis. Available at: www.rheumatology.org/Portals/0/Files/ACR-Infusion-Guidance-COVID-19.pdf. Accessed April 11, 2020
4. Bobart SA, De Vriese AS, Pawar AS, Zand L, Sethi S, Giesen C, Lieske JC, Fervenza FC: Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies. *Kidney Int* 95: 429–438, 2019
5. Danser AHJ, Epstein M, Batlle D: Renin-angiotensin system blockers and the COVID-19 pandemic: At present there is no evidence to abandon renin-angiotensin system blockers [published online ahead of print Mar 25, 2020]. *Hypertension* doi:10.1161/HYPERTENSIONAHA.120.15082
6. Sparks MA, South A, Welling P, Luther JM, Cohen J, Byrd JB, Burrell LM, Batlle D, Tomlinson L, Bhalla V, Rheault MN, Soler MJ, Swaminathan S, Hiremath S: Sound science before quick judgement regarding RAS blockade in COVID-19 [published online ahead of print Mar 27, 2020]. *Clin J Am Soc Nephrol* doi: 10.2215/CJN.03530320
7. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD: Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19 [published online ahead of print Mar 30, 2020]. *N Engl J Med* doi:10.1056/NEJMsr2005760
8. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, Hawley CM, Khalidi N, Floßmann O, Wald R, Girard LP, Levin A, Gregorini G, Harper L, Clark WF, Pagnoux C, Specks U, Smyth L, Tesar V, Ito-Ihara T, de Zoysa JR, Szczeklik W, Flores-Suárez LF, Carette S, Guillevin L, Pusey CD, Casian AL, Brezina B, Mazzetti A, McAlear CA, Broadhurst E, Reidlinger D, Mehta S, Ives N, Jayne DRW; PEXIVAS Investigators: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 382: 622–631, 2020
9. 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* 373: 2225–2236, 2015
10. 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* 318: 432–442, 2017
11. Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, Jefferson JA, Gipson PE, Rizk DV, Sedor JR, Simon JF, McCarthy ET, Brenchley P, Sethi S, Avila-Casado C, Beanlands H, Lieske JC, Philibert D, Li T, Thomas LF, Green DF, Juncos LA, Beara-Lasic L, Blumenthal SS, Sussman AN, Erickson SB, Hladunewich M, Canetta PA, Hebert LA, Leung N, Radhakrishnan J, Reich HN, Parikh SV, Gipson DS, Lee DK, da Costa BR, Jüni P, Cattran DC; MENTOR Investigators: Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med* 381: 36–46, 2019

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