Brief Communication

Glomerular Diseases with Reference to COVID-19

Abstract

COVID pandemic affected every individual across the world. Patients with primary glomerular disease and glomerular disease secondary to systemic diseases who are on moderate to high doses of immunosuppression are at an increased risk of COVID because of their immunosuppressed state. The data to quantify the degree of risk in relation to the amount of immunosuppression or their duration of use is not robust. The patients on immunosuppression need to modify the drugs balancing the risk relapse and flare of the disease, simultaneously minimizing the risk of developing COVID. We tried to develop a guideline about the modification of the treatment regimen in such conditions.

Keywords: *Immunosuppression, primary glomerular disease, secondary glomerular diseases*

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Introduction

Patients with a glomerular disease in reference to COVID-19 have two broad issues. First, in view of reports of proteinuria and hematuria in patients with COVID-19, there is a possibility of glomerular disease secondary to COVID-19; and second, patients with the glomerular disease may develop COVID-19. At present, there is insufficient evidence to suggest that COVID-19 itself can produce secondary glomerular disease, though being a viral infection, potentially it is possible. Therefore, the main issue is COVID-19 infection in patients with the preexisting glomerular disease and handling their immunosuppression. Patients with primary glomerular disease and glomerular disease secondary to systemic diseases like systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), who are on moderate to high doses of immunosuppression are at an increased risk of COVID because of their immunosuppressed state.[1] However, as of now, there is a paucity of data to quantify the degree of risk in relation to the amount of immunosuppression or their duration of use. Therefore, what is being suggested is based on the extrapolation of evidence from otherinfections.

A simple way to evaluate these patients is to classify them into newly diagnosed patients, and those on follow-up on immunosuppressant medications, separately.[2]

A. For newly diagnosed patients:
   a. We suggest that newly diagnosed patients with primary and secondary glomerular disease should be managed on their merit if they do not come under category of "suspected" COVID or have a positive test for COVID-19. However, these patients should receive the Pneumococcal vaccine to reduce the chances of secondary Pneumococcal pneumonia
   b. If a patient is suspected or positive COVID and needs immunosuppressive medication, we suggest using immunosuppression, after explaining the risk-benefit ratio to the patient.

B. For follow-up patients:
   Follow-up patients on immunosuppressants may be in the induction phase or the maintenance phase of the treatment.
   a. Induction phase:
      As there is currently no policy that non-suspected patients should be tested for COVID-19 before each dose of induction therapy, we suggest that patients of the induction phase should get standard induction medication unless directed otherwise by their attending renal team. All patients coming to the

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hospital for induction therapy should be triaged on arrival before any infusion to exclude symptoms of active COVID-19 infection and to check for raised temperature. Those who are considered to have a "suspected" COVID-19 infection can then be seen in a separate area away from other patients and appropriate treatment plans made. If the patient is not able to come to the hospital due to lock-down for getting an intravenous (iv) injection of induction immunosuppression (Cyclophosphamide), we suggest the following options:

1. In patients of vasculitis, we suggest switching over to oral cyclophosphamide temporarily under monitoring another option is using oral mycophenolate mofetil (MMF) especially in patients with low risk of relapse[3]
2. In patients with SLE, if the patient is on iv cyclophosphamide, he/she can be easily changed to oral MMF, a well-established alternative to iv cyclophosphamide as induction therapy.[4]

As there is no experience that how COVID-19 infection could behave during rituximab therapy, it will be wise to avoid using rituximab in such uncertain situation. In general, to reduce infection risk, we suggest minimizing steroids promptly.

We recommend a risk stratification approach to help manage these patients. *Some patients, particularly* those on steroids, iv cyclophosphamide, and biologics, will be significantly immunosuppressed and should, therefore, be considered "high risk". This is particularly true in the induction phase of their treatment. Others on steroid monotherapy will be at intermediate risk.

b. Maintenance Phase

Patients of glomerular disease on maintenance immunosuppression, if doing well, and are not in COVID-19 "suspect" or "positive" group, should continue to take their maintenance medication unless directed otherwise by their treating team. Immunosuppressive therapy needs to be reviewed on a case by case basis, balancing the risk of inadequately treated disease, or acute relapse, against the risk of the effect of COVID-19 infection in the individual patient. Patients on long term glucocorticoids SHOULD NOT stop these abruptly. Patients receiving hydroxychloroquine should continue this as it may afford some protection against COVID-19. All patients with glomerular disease if fall in the category of "suspected" COVID-19 should be tested as per standard guidelines. Inpatients who are COVID-19 positive, the nephrologist may consider modifying maintenance immunosuppression regimens on a case by case basis. In the case of long-acting rituximab maintenance regimens, delaying intervals between rituximab infusions could be considered for patients where the risk of disease progression or flare is deemed low. Lower doses of rituximab may be considered as given evidence from the Mainritsan study suggesting equivalent efficacy.[5] Children with idiopathic nephrotic syndrome who are on alternate day prednisone and develop symptoms of upper respiratory tract infection (URTI) should not be switched to daily prednisone as per usual practice.

Where standard immunosuppression protocols are modified on a balance of risk, we recommend to optimize surveillance for relapse with increased clinical assessment, autoantibody screening, and lymphocyte subset analysis where possible, though one must realize that in the situation of COVID-19 pandemic, such close monitoring and repeated test may not be logistically possible.

Policy on Isolation for Patients with Glomerular Diseases

We suggest that patients of glomerular disease on immunosuppression should be risk-stratified into the following three groups:

a. Group A (High Risk):
   - Those patients of glomerular disease who are Currently on induction immunosuppressive medications, whether steroid or cytotoxic medication, are at a high risk because of the degree of higher immunosuppressive agents. They should all be advised to follow strict social distancing, hand hygiene, and face mask. If they reside in the hot spot area in reference to COVID-19, it will be a better idea to self-isolate for few weeks
   - Are currently on stable maintenance IS but whose additional comorbidities make them susceptible to a severe course in COVID-19—(a) age >70 years (b). Those with any non-autoimmune underlying co-morbidity of COAD, CVD, hypertension, or diabetes mellitus.

b. Group B (Moderate risk):

   Those patients of glomerular disease who are currently on stable maintenance immunosuppression (single drug) but whose additional comorbidities make them susceptible to a severe course in COVID-19— (a) age >70 years (b). Those with any non-autoimmune underlying comorbidity of `COAD, CVD, hypertension, or diabetes mellitus; will fall in this group. These patients should follow strict social distancing, hand hygiene, and face mask. We recommend not to stop medications as this can lead to the relapse of the disease or nephrotic syndrome.

C. Group C (Low Risk)

We suggest that these patients may not require self-isolation in the first instance but should follow all hygiene measures listed below. These include:

(1) Children with idiopathic nephrotic syndrome who are on levamisole or low dose alternate-day prednisone
(2) Children with idiopathic nephrotic syndrome who are infrequent relapsers
(3) Patients <60 years who are generally well and whose disease (SLE, AAV, MCD, FSGS, membranous nephropathy, or IgA nephropathy) have been stable for >6 months and off immunosuppression
(4) SLE patients who are on hydroxychloroquine alone.

These recommendations are and will remain dynamic and might change as new data emerge.

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Conflicts of interest

There are no conflicts of interest.

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