

# The Immunocompromised Transplant Recipient and SARS-CoV-2 Infection

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For the transplant specialist, microbiology represents a series of potential tools with which to probe the human immune system. We assume that, for each pathogen, the immunocompromised host will demonstrate reduced resistance to infection, atypical clinical signs and symptoms, more rapid progression, and greater mortality.<sup>1</sup> There are few data that guide the clinician for modification of immunosuppressive regimens for specific infections. Confronted with novel coronavirus-19 infection (COVID-19), clinicians have strong opinions regarding the best immunosuppressive manipulations on the basis of extensive, but uncontrolled experience with other infections. A major challenge is that *immune modulation in the immunocompromised transplant recipient infected with COVID-19 infection has an undefined role in systemic inflammatory response syndrome and progression to severe lung injury (adult respiratory distress syndrome, ARDS)*.

The initial presentation of COVID-19 infection in transplantation has been only modestly different from that of other hosts, possibly suggesting that whereas viral infection may progress more rapidly, progression to respiratory failure might be blunted. Limitations in viral testing, in medical equipment, and in hospital capacities have adversely affected the entire population. These gaps may be more prominent in immunocompromised hosts, due to: (1) more rapid progression of infection, (2) hindered evaluations for infections *other than or in addition to COVID-19* for patients in respiratory isolation, (3) the need to balance the adverse effects of transplant immunosuppression against potential benefits relative to systemic inflammation, (4) the potential for donor-derived COVID-19 infection, (5) the potential for prolonged shedding by immunocompromised hosts with nosocomial and

community transmission of severe acute respiratory syndrome (SARS)-CoV-2, (6) limited availability of rapid and highly sensitive and specific quantitative assays for SARS-CoV-2 (in multiple specimen types, donors, and recipients), and (7) *the need to identify biomarkers that define the risk for disease progression, appropriate therapeutic interventions, and graft rejection, all of which are lacking*. Various guidelines have been developed on the basis of uncontrolled experience in highly affected regions (China, Italy, and Spain), on *in vitro* data, or on experience with prior epidemics of coronavirus or influenza, the relevance of which are uncertain. The risks to organ transplant recipients are not yet known.

Variability in clinical presentation has been observed. This may reflect viral strain differences between regions (e.g., differences in time from illness onset to first hospital admission in Zhejiang province, China (1.0–4.3 days) and Wuhan, Hubei province (9.1–12.5 days)).<sup>2,3</sup> This may also reflect allelic variation in innate immune function driving the inflammatory cytokine profile. In SARS, similar variability was observed and attributed to mutation and adaptation of the SARS-CoV genome over time; sequence data from SARS-CoV-2 from multiple regions will be informative.

Patients presenting with a “viral syndrome” and ultimately found to be COVID-19 positive may have initially negative viral assays in up to 30%. In normal hosts, patients present with combinations of fever, cough, shortness of breath, myalgia, some gastrointestinal disturbances, and sputum production.<sup>3–6</sup> It is estimated that 20%–51% of patients have other comorbid medical conditions. Dyspnea develops in over one half of patients at a median 8.0 days into symptoms.<sup>5</sup> Many have leukopenia and most have lymphopenia; patients at risk for assisted ventilation, intensive care unit admission, or mortality have lower white cell and lymphocyte counts.<sup>7</sup> Patients may have normal chest radiographs but generally develop abnormal chest computed tomography scans with bilateral patchy infiltrates or ground glass opacities.<sup>7</sup> Progression to ARDS is most common in older individuals (regardless of underlying conditions), those with higher viral loads, and higher levels of systemic inflammatory mediators (Table 1), as observed in epidemic influenza. Viral clearance coincides with seroconversion.

In transplant recipients with COVID-19 infection, clinical variability remains common; fever may be absent in up to one half and cough is more common. Many become infected without obvious exposures. In the study by Mohan in this issue, 33% had normal chest radiographs.<sup>8</sup> Renal injury was common (40%), often at presentation; this is probably multifactorial including the effects of calcineurin inhibitors, hypotension, graft rejection after reduced immunosuppression, viral cytopathic effect, or immune responses to viral antigens in the kidney.<sup>8</sup> A single report found ARF in 27% of *normal*

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**Table 1. Biomarkers of inflammation in SARS-CoV-2 infection**

Biomarker
Hypoxemia
White blood cell count (variable) and differential
Lymphocyte counts (relative lymphopenia)
T-cell subsets and markers (e.g., PD-1)
SARS-CoV-2 viral load (RNA)
IgM/IgG to SARS-CoV-2
Procalcitonin (often normal)
D-dimer (elevated)
Ferritin (elevated)
Lactic dehydrogenase (elevated)
IL-1 $\beta$ , IL-2, IL-6, IL-7
TNF- $\alpha$
Serum creatinine (GFR reduced)
Creatine kinase (elevated)/cardiac troponin I (elevated)
Liver function tests (variable transaminitis)
Erythrocyte sedimentation rate (variable)
C-reactive protein (variable)

*individuals* with COVID-19 infection in China; in six post-mortem specimens, SARS-CoV-2 nucleoprotein antigens were found in renal tubules with CD68+ macrophage infiltration and complement deposition (B. Diao, C.H. Wang, R.S. Wang, Z.Q. Feng, Y.J. Tan, H.M. Wang, *et al.*: Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection [preprint posted online April 10, 2020]. *medRxiv* doi:10.1101/2020.03.04.20031120). Angiotensin-converting enzyme 2 (ACE2) serves as the receptor for SARS-CoV-2 and is found on renal epithelial cells; lung alveolar epithelial cells; oral, nasal, and bladder mucosal epithelia; endothelia; and other sites<sup>9</sup> (W. Lin, L. Hu, Y. Zhang, J.D. Ooi, T. Meng, P. Jin, *et al.*: Single-cell analysis of ACE2 expression in human kidneys and bladders reveals a potential route of 2019-nCoV Infection [preprint posted online February 18, 2020]. *bioRxiv* doi: 10.1101/2020.02.08.939892). SARS-CoV-2 may therefore bind and injure renal cells directly. Normally, upregulation of the renin-angiotensin-aldosterone system (RAAS) is balanced by ACE2. Concern for increased ACE2 expression (as viral receptor) in patients on RAAS inhibitors with COVID-19 infection have led to routine discontinuation at many sites, risking cardiovascular compromise; current data do not necessarily support this general approach and individualization is recommended. Of interest, a different approach might be suggested by a small study of COVID-19 patients with elevated levels of plasma angiotensin II that was correlated with the viral load and the degree of lung injury.<sup>10</sup> Studies of modulators of RAAS, including recombinant ACE2 and angiotensin receptor blockers, are underway for viral-associated myocarditis and ARDS, and might be considered in renal failure.

Systemic inflammation as measured by diverse biomarkers has been observed in individuals progressing to ARDS (Table 1). The variability in inflammatory markers in transplant

recipients does not yet allow their routine use as a basis for therapeutic intervention. The variability is substantiated in C-reactive protein data in the Monhan study.<sup>8</sup> Between groups who either cleared infection or required intubation for ARDS, C-reactive protein levels overlapped and varied widely. Thus, we do not yet understand the pathogenesis of COVID-19 infection nor the role of the immune response in pathogenesis. In the meantime, individualization may be possible *via* serial monitoring of inflammatory markers with early intervention *before progression to severe lung injury*. The utility of agents targeting inflammatory pathways is under study.

Management of immunosuppression in transplantation remains uncertain. Cancer patients with neutropenia do less well than normal individuals with COVID-19 infection, consistent with the importance of the innate immune system in viral infection.<sup>11</sup> Coinfection of COVID-19 with Pneumocystis, other viruses or bacteria is more common than was initially appreciated. Thus, intensive steroid therapy may be disadvantageous. However, cessation of immunosuppression may augment systemic inflammation and risk graft rejection. More modest, individualized manipulations seem warranted. Some patients may benefit from switch of mammalian target of rapamycin inhibitors to other agents. Hydroxychloroquine (HCQ) and chloroquine may have antiviral effects (blocking egress of SARS-CoV-2 from endocytic vesicles) and anti-inflammatory activity but these have been modest in clinical practice; significant caution is required regarding HCQ dosing, drug interactions, and side effects, notably on QTc interval in combination with azithromycin. Some uncontrolled data suggest efficacy in COVID-19 infection with or without azithromycin.<sup>12</sup> Further data are essential given diverse side effects and drug interactions.

Transmission from infected donors to immunosuppressed recipients is not yet described; SARS-CoV-2 RNAemia (uncommon), and renal, cardiac, and pulmonary involvement suggest that transmission might occur. Ideally, both donors and recipients should be screened. Sensitive assays exist using either bronchoalveolar lavage or nasopharyngeal swab specimens; testing in some areas remains limited. Empirical antiviral therapies may be considered if donor or recipient screens are positive, but all should be considered experimental. It is essential that data be collected to define the pathogenesis of infection including adaptive and innate immune responses. These must be coupled to genetic (polymorphisms of immune system, RAAS, HLA, and ABO) and demographic data to develop meaningful insights. Similarly, because this epidemic overwhelms healthcare resources, and despite the urgency posed by critically ill patients, it remains essential to develop therapies on the basis of data from clinical trials.

Medicine will forever be altered by this experience. Biomarkers developed in this pandemic will allow improved individualization of care. The real opportunity presented by this pandemic is one of worldwide collaboration in clinical care and biomedical research, if we have the will.

Be safe out there.

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See related article, "Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York," on pages 1150–1156.