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## EDITORIAL

# Novel Coronavirus-19 (COVID-19) in the immunocompromised transplant recipient: #Flatteningthecurve

*COVID-19 has caused "closure of all schools and universities throughout Italy... cinemas, theaters and discoteques are shut down as well....(among) the few individuals who are out and about, I notice a lot of elbow bumping rather than both-cheek kissing and greater distance between people as they talk....the trains between Florence and Rome ...are largely empty."*

Lori Heatherington, Florence, Italy

Experience with respiratory viruses in organ transplant recipients compared with normal hosts demonstrates greater susceptibility, more rapid progression to pneumonia, greater disease severity and prolonged shedding of potentially infectious virus. These hosts are also more likely to develop bacterial or fungal superinfection. Diagnosis and therapy are aided by the availability of sensitive and specific molecular assays for each virus. These assays aid in clinical management, including avoidance of unnecessary antimicrobial agents and antiviral treatment when available (as for influenza). Equally important, such assays allow description of the epidemiology of infection including determination of the duration of carriage, transmission probability and identification of susceptible hosts.

With the pandemic of novel Coronavirus-19 or COVID-19 associated with the virus SARS-CoV-2, almost 500 000 cases have been identified worldwide with over 22 000 deaths reported. Approximately 14% develop severe disease. Based on experience with prior coronavirus outbreaks, COVID-19 poses a new threat for immunocompromised patients. Limitation in the availability of testing has delayed understanding of the evolution of the epidemic. In the general population, the median incubation period is estimated at 5.1 days, and 97.5% of those who develop symptoms will do so within 11.5 days of infection.<sup>1</sup> Nasopharyngeal swab samples appear to be more sensitive for diagnosis than oropharyngeal and sputum samples; given sensitivity limitations, multiple negative assays are often used for ruleouts.<sup>2</sup> Viral shedding may persist for weeks (~20 days). Nosocomial transmission is common.  $R_0$  (transmission kinetics) is ~2; this means that, without physical separation, 50% of the population must become immune to prevent spread in the community.

Clinical variability is marked among normal hosts.<sup>3</sup> Some early screening for SARS-CoV-2 may be negative, becoming positive subsequently. As for other viral infections, clinical manifestations include fever, cough, shortness of breath, myalgias, and sputum

production.<sup>4-7</sup> Dyspnea develops in over half of patients at a median of 8.0 days from illness onset.<sup>5</sup> 20%-51% of patients have other comorbid medical conditions. The majority (~83%) have leukopenia and lymphopenia; patients admitted to the ICU were more likely to be older and have lower white cell and lymphocyte counts.<sup>8</sup> All patients developed abnormal radiographic findings including bilateral patchy shadows or ground glass opacities on chest CT.<sup>8</sup> Lung injury from infection and progression to adult respiratory distress syndrome or ARDS are most common in those with higher viral loads and heightened systemic inflammation (measured by IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels) as was observed in epidemic influenza. However, the need for viral clearance may mitigate against routine use of systemic steroids and immune modulatory therapies. Viral clearance coincides with seroconversion. Intervention *after* establishment of severe pneumonia does not appear to affect clinical progression and recovery once intubated or on ECMO have been slow. One single-center series reported that 22.4% of confirmed infections (11 of 49) were coinfecting with other respiratory viruses; of 127 with other viruses, 11 (8.66%) had a SARS-CoV-2 co-infection (Nigam Shah, unpublished data, <https://medium.com/@nigam/higher-co-infection-rates-in-covid-19-b24965088333>). The overall case fatality rate for documented pneumonia has been reported variably as 1.4%-2% but may be lower in the absence of comorbidities (eg, 0.5%-1.0% or less).<sup>4,9</sup>

Significant variability seems to exist also in the clinical progression of disease between regions suggesting viral strain differences. For example, in confirmed cases in adults, the time from illness onset to first hospital admission in Zhejiang province, China was reported as 1.0-4.3 days, while a mean interval of 9.1-12.5 days was observed between onset of symptoms and hospitalization in Wuhan, Hubei province, China.<sup>6,9</sup> Patterns of spread and progression for COVID-19 differ from those of Middle Eastern Respiratory Syndrome (MERS-CoV, from 2012) and Severe Acute Respiratory Syndrome (SARS-CoV, 2002-2003). SARS-CoV-2 shares 79% sequence homology with SARS CoV and 50% homology with MERS CoV. Interperson spread of SARS-CoV-2 appears to occur from minimally symptomatic individuals as well as from superspreaders, individuals who transmit infection more often to other persons, as was seen in SARS-CoV and MERS-CoV. However, a Massachusetts, USA coronavirus cluster with at least 82 cases was started by asymptomatic individuals. The error-prone RNA-dependent RNA polymerase of SARS-CoV allowed mutation and adaptation of SARS to human hosts (not observed in

MERS). Sequence data from SARS-COV-2 from multiple regions will be informative in this regard.

In transplant recipients described in this issue and by colleagues in China, Italy, and the United States, initial presentations have been heterogeneous as for other hosts. Many patients had no known epidemiological contacts. Common symptoms have been fever, fatigue, and dry cough at the onset of illness. Few patients manifest upper airway symptoms such as congestion or rhinorrhea. Multiple patchy shadows and ground-glass opacities are observed on all chest radiographs, often at presentation. Leukopenia and marked lymphopenia are observed in most patients. Many patients have a significant increase in serum LDH levels with inconsistent elevations of inflammatory markers. Renal function is impaired to varying degrees in all kidney transplant recipients. This may reflect rejection following reduction in immunosuppression or with interferon therapies, or from the inability to monitor calcineurin inhibitor levels in the face of drug interactions with lopinavir/ritonavir therapy – each intervention specified in the “Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 5th Edition from China's National Health Commission).<sup>10</sup> Overall, the progression of disease has varied but appears to be more rapid in immunocompromised hosts with greater rates of ICU admission and death (a fatality rate of ~21.4%). Some recipients have viral or bacterial superinfection at the time of presentation with COVID-19. Other viral respiratory infections remain common. Reductions in immunosuppression are strongly advocated by many clinicians; this approach risks immune reconstitution and rejection but may improve viral clearance. Many transplant recipients have recovered with or without such manipulations. Potential antiviral effects of immunosuppressants are untested.<sup>11,12</sup> An unblinded study of respiratory viral loads with azithromycin and hydroxychloroquine provides a basis for trials which include data on inflammatory markers, viral loads, and diagnostic techniques.<sup>13</sup> Given the apparent role of inflammatory cytokines in COVID-19 infection, the benefits of more modest, individualized, reductions coupled with addition of immune modulation (eg, statins, modest dose corticosteroids or IL-6 inhibition therapies) might be considered when confronted with progressive disease. Suppression of inflammatory responses in the absence of effective antiviral therapy risks uncontrolled infection. Case fatality rates remain to be determined in immunocompromised hosts.

This new epidemic is overwhelming healthcare resources in some regions and forcing rationing of care, including ICU beds and ventilatory supports. In some countries with resources stretched by epidemic infection, transplant patients may be excluded from assisted ventilation. Life-saving transplantation allows our patients to lead productive lives in the face of organ failure. We should not allow infections disproportionately affecting transplant recipients to limit their access to clinical interventions offered to individuals with other, potentially less reversible, clinical comorbidities.

As was noted by Michaels and by Gori, the management of organ donation is critical.<sup>14,15</sup> Life-saving transplantation is generally continuing in screened recipients; decisions must be individualized. Many centers have cancelled live donor transplants

to avoid exposure of healthy donors to the hospital and of potentially infected recipients to immunosuppression. Procurement teams must use respiratory precautions. Approximately 15% of infected individuals demonstrate RNA-emia,<sup>5</sup> some with viral loads in excess of 10 million copies per mL (unpubl. data, Hans Hirsch, Basel). Transmission from infected donors to immunosuppressed recipients is not yet described; the viral receptor is ubiquitous. Ideally, both donors and recipients should be screened in affected regions. Sensitive assays exist using either bronchoalveolar lavage or nasopharyngeal swab specimens; testing in some areas remains limited. Some false negative assays have been identified in early infections which may impair any strategy developed. Blood samples should be obtained and banked for subsequent analysis. Empiric antiviral therapies may be considered if donor or recipient screens are positive but all should be considered experimental. Agents include boosted lopinavir or darunavir which carry significant interactions with calcineurin inhibitors and may only provide benefit if used early<sup>16</sup>; remdesivir with or without other agents; chloroquine and hydroxychloroquine which have both antiviral effects by blocking egress of SARS-CoV-2 from endocytic vesicles and anti-inflammatory effects (with caution regarding dosing, significant side effects and drug interactions); and interferon-1 $\beta$  and inhaled  $\alpha$ -interferon. Achievement of effective antiviral levels with these agents is uncertain. Anti-inflammatory therapies (eg, anti-IL-6 or corticosteroids) are generally reserved for those with progressive pneumonia.

Reduction of the spread of infection will require the determination of the extent of community spread, viral mutation rates, and whether various viral strains have differing transmission kinetics. We do not yet know the incidence of asymptomatic infection and how long infectious virus persists during convalescence, notably among immunocompromised hosts. There is an urgent need to define viral pathogenesis, correlates of immunity, and biomarkers for the risk for progression. Cell entry is via the ACE2 receptor (on the X-chromosome) which is secreted in women and may reduce cellular entry – possibly accounting for gender differences in severe illness. The cytokine storm with infection appears greater in the elderly. Excess immunity may, therefore, *increase* the severity of disease and may mitigate against a rapid reduction in immunosuppression. Various antiviral therapies are under study; current data are often difficult to assess in the face of polypharmacy of antivirals (lopinavir/ritonavir, RNA polymerase inhibitor remdesivir, umifenovir/oseltamivir, chloroquine, angiotensin receptor blockers) and immune modulators (IL-6 inhibitors, corticosteroids, immunoglobulins, interferon- $\alpha$  or 1 $\beta$ ). A vaccine is urgently needed but an effective clinical vaccine development is likely to take at least a year. In the meantime, public health measures include “social distancing” (reducing public contacts), school closings, working remotely and adequate paid sick leave (stay home when sick!).

Clinical trials are essential to study the pathophysiology of COVID-19 infection and to develop effective therapies – for this and subsequent coronavirus outbreaks. We must avoid “cognitive bias by anecdote” and maintain clinical equipoise while striving to help our


patients. In the meantime, sharing of experiences worldwide provides a foundation for clinical care.

## KEYWORDS

antibiotic: antiviral, clinical decision-making, complication: infectious, cytokines/cytokine receptors, editorial/personal viewpoint, immunosuppression/immune modulation, infection and infectious agents – viral, infectious disease, organ transplantation in general

## DISCLOSURE

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