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Crucial aspects of the management of solid organ transplant patient with COVID-19: a narrative review

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Abstract

Many centers worldwide raised the concern that immunocompromised patients for solid organ transplantation may be at high risk of developing a severe respiratory disease by COVID-19. Currently, there are no specific data on the COVID-19 in patients with generalized immunosuppression and transplantation.

In this narrative review, we reported the main data of COVID-19 in patients with solid organ transplantation presented in the literature. The aim is to elaborate a strategy for tailored management, from diagnosis to therapy.

The management of adult patients with solid organ transplantation and COVID-19 is a challenge for the clinicians. There is a lack of data in the literature, but three key-points are crucial: in the “pandemic era,” consider the symptomatic patient as positive for COVID-19 until proven otherwise; adjust/stop immunosuppressive agents; protect graft function with adequate route and dose administration of glucocorticoid and supportive measures. For pediatric patients, data are scarce. It is unclear if immunosuppression in patients with solid organ transplantation alters the predisposition to acquiring COVID-19 or if the disease implications are modified for better or for worse. Further studies are needed.

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Introduction

Immunosuppressive therapy, in patients with solid organ transplantation (SOT), has effects on humoral, cell-mediated immunity, and neutrophil function, increasing the risk of severe infections caused by common viral agents (1). Patients receiving immunosuppressive therapy are at risk for more severe or complicated influenza induced disease (2).

Since December 2019, the world healthcare community faced with Coronavirus Disease 2019 (COVID-19) caused by a novel coronavirus infection. Due to the high viral contagiousness and the possible transmission during the pre-symptomatic phase, COVID-19 progressively spread to several countries. In the general population, the reported case fatality rate is low, about 1-6%. However, most of the fatal cases have occurred in patients with advanced age or underlying medical comorbidities. Therefore, high-risk populations need more careful attention (3).

As the outbreak grew to a pandemic, many centers worldwide raised the concern that immunocompromised patients for SOT may be at high risk of developing a severe respiratory disease by COVID-19.

Currently, there are no specific data on the COVID-19 in patients with generalized immunosuppression and transplantation. In this narrative review, we reported the main data presented in the literature of COVID-19 in patients with SOT. The aim is to elaborate a strategy for tailored management, from diagnosis to therapy.

COVID-19 in Heart transplanted patients

Li et al. (4) reported two heart transplant recipients with COVID-19, one a severe presentation, and another mild. The first was a 51-year-old man and immunosuppression maintenance with tacrolimus 1 mg twice daily plus mycophenolate mofetil 0.5 g twice daily. On January 23rd, 2020, the patient presented with intermittent fever (38.5 °C), chills, fatigue, poor appetite, and diarrhea. Oxygen saturation was 99% on room air, respiratory rate of 20

breaths per minute without distress. Laboratory tests showed a normal white blood cell count (WBC), elevation in C Reactive Protein (CPR), with a positive chest computed tomographic (CT) scan for bilateral ground-glass opacities. Subsequently, his clinical conditions worsened, requiring nasal oxygen supplementation. Oxygen saturation deteriorated (75% without supplemental oxygen after slight activity), and a CT scan revealed worsening of lung lesions. Oxygen was given through a face mask with an improvement in saturation to 95%. Intravenous human gamma globulin (10 g/day) plus methylprednisolone (80 mg/day) initiated for 5 consecutive days, and the clinicians stopped the administration of other immunosuppressive drugs. After treatment, the patient's symptoms improved, and oxygen saturation maintained above 96% with a nasal cannula. Immunosuppressive and antihypertensive drugs were resumed. The patient's temperature normalized for more than 20 days, without cough for 10 days, and preserved oxygen saturation. CT scan showed significant resolution of lung lesions, and subsequently, the patient was discharged at home. The second heart transplant male recipient aged 43-years old and immunosuppression maintenance with tacrolimus (1.5 mg in the morning and 2 mg in the evening) and mycophenolate mofetil (0.5 g twice daily), presented with fever for 2 days on January 25th 2020, exhibited mild lung lesions on CT scan. Then his clinical condition worsened with the development of fatigue and poor appetite. He was hospitalized. Laboratory tests showed a normal WBC count with lymphocytopenia and elevation in CPR. However, his clinical course had no other complication and was discharged at home.

These cases represented the first descriptions of COVID-19 in heart transplant recipients and suggested that presentations appeared to be similar to those observed in non-transplant recipients. The authors concluded that, whether patients with ROT are more susceptible to COVID-19, there is the need for further large-scale epidemiological investigation.

COVID-19 in Kidney transplanted patients

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Guillen et al. (5) presented the case of a COVID-19 infection in a kidney transplant recipient. A 50-years old man, recipient of a 3rd deceased-donor kidney transplant in 2016 with a serum creatinine of 1.3 mg/dL and estimated glomerular filtration rate (eGFR) of 60 mL/min, was admitted on February 28th to the emergency room (ER) with a 24-hour history of fever (38.2 ºC) and vomiting. He reported no other symptoms, nor had a history of travels abroad nor exposure to patients infected or suspected of contagious COVID-19 infection. In this patient, the maintenance therapy provided tacrolimus, everolimus, and prednisone (5 mg four times a day). Laboratory test showed normal values of CRP and WBC count, but a mild kidney function impairment. Five days later, the patient returned to the ER with persistent fever and productive cough but no gastrointestinal symptoms. Physical examination revealed a body temperature of 37.4°C, respiratory rate of 16 breaths per minute, and a blood oxygen saturation of 98% on room air. WBC count on peripheral blood was 10.15×10^9/L (total lymphocyte count 1.8×10^9/L), with a platelet count of 126×10^9/L, a CRP of 13.2 mg/dL, and a procalcitonin of 0.18ng/mL (normal range <0.50ng/mL). Persistent mild kidney function impairment (Cr 1.6 mg/dL) and hyponatremia of 129 mEq/L were also observed. Liver transaminases and coagulation were within normal reference values. There was a medium lobe consolidation on the posteroanterior chest radiograph. The diagnosis of community-acquired pneumonia was assumed but, although the patient didn't have any travel history nor reported known contacts with contagious or infected people, nasopharyngeal and oropharyngeal swab specimens were collected for testing COVID-19, revealing a positive result.

However, despite the adoption of protocol therapy (oral Lopinavir/Ritonavir 400/100 mg, twice a day), the patient presented a worsening in respiratory symptoms, with hypoxia despite the use of high-flux nasal oxygen delivery, and a progression to diffuse bilateral infiltrates on chest X-ray, requiring intubation, with ventilatory supportive care. The authors concluded that, as of today, the patient remains under supportive respiratory therapy in the

ICU, hemodynamically stable, with serum creatinine of 3.0 mg/dL, WBC count of 14.5×10^9/L, lymphocytes 0.9×10^9/L, Haemoglobin 9.3 g/dL, platelet count of 410×10^9/L, D-Dimer of 8900 ng/mL (normal range <500), and procalcitonin of 0.54 ng/mL without further progression of respiratory failure.

The authors stated that immunocompromised patients could present atypical clinical manifestations, like fever, diarrhea, fatigue, without, followed by respiratory symptoms. However, in the endemic zone, when faced with a transplanted patient with an unspecified viral clinical presentation, and without any microbiological isolation, medical personnel must be aware and take COVID-19 into account.

Zhu et al. (6) reported the case of a COVID-19 infection in a 52-year-old man who underwent living-related kidney transplantation. This patient has received triple maintenance immunosuppressive therapy with oral tacrolimus, mycophenolate mofetil, and prednisone. On January 20th, 2020, the patient showed initial symptoms of fatigue, dyspnea, tightness, chest pain, nausea, loss of appetite, intermittent abdominal pain, and occasional dry coughs. Two days later, he developed a fever (37.5°C) and headache. Subsequently, his clinical conditions worsened, with a temperature of 38.9°C. His laboratory exams showed lymphocyte count and lymphocyte percentage significantly lower than baseline values, neutrophil and monocyte count markedly higher, and CRP significantly elevated (30.2 mg/L). CT scan found multiple patchy ground-glass density shadows in the upper lobe of both lungs and the lower lobe of the left lung, as well as a small patchy ground-glass density shadow in the middle lobe of the right lung. These abnormalities suggested the possibility of COVID-19 pneumonia. The clinicians immediately advised the patient to discontinue all immunosuppressive agents and instead to start therapy. The patient's symptoms continued unabated, and, in addition, he lost 10 kg of body weight within one week due to poor eating. Because of his ongoing symptoms, the patient was admitted to an isolation ward in hospital. Physical examination on admission revealed a body temperature of 37.7°C, respiratory rate

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of 20 breaths per minute, and oxygen saturation of 96% while the patient breathed ambient air. Laboratory exams showed a decreased peripheral blood lymphocyte count (0.99 x 10^9/L), raised in CRP (54 mg/L), increased erythrocyte sedimentation rate (35 mmHg), normal value of procalcitonin. Serum levels of some inflammatory cytokines were elevated, including interleukin 2 (IL-2) receptor, IL-6, and tumor necrosis factor-alpha (TNF-α). At this time the patient discontinued all immunosuppressive agents and started the therapy with methylprednisolone (40 mg daily, intravenously), intravenous immunoglobulin (5 g on the first day and 10 g/die for the next 11 days), biapenem (0.3 g iv drip q12h), pantoprazole (60mg iv qd), interferon α (5 million units daily, atomization inhalation). The following days, the patient's body temperature returned to normal, nausea and chest tightness were relieved, and oral tacrolimus was resumed at half its original dosage. The patient's CRP started to decrease (29.8 mg/L). However, a second chest CT showed that the range of lesions in both lungs had enlarged and that new lesions had appeared.

Additionally, the patient had an increased level of serum alanine aminotransferase (ALT). Therefore, glycyrrhizic acid diamine (100 mg po, tid) was administered to protect liver function. The patient's weakness and dry cough had significantly improved, and analysis of a throat swab sample was negative for the presence of COVID-19. CRP levels decreased to nearly normal (3 mg/L), and the lymphocyte count began to rise (1.37 x 10^9/L). A third chest CT showed that the lung lesions were almost entirely resolved, with only a few indistinct shadows remaining. Supplemental oxygen was discontinued, and the patient's oxygen saturation values were at above 96%. Oral tacrolimus and MMF were administered to their full pre-illness dosage levels, and three days later, the patient was discharged from the hospital.

The authors concluded that a single, successfully treated case could not define effective therapy. The patient recovered well but received a variety of novel therapies, which may or not have been helpful. It is difficult to extrapolate from this patient the recommendations for

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the transplant population. More data are necessary to optimize the treatment protocol for patient with SOT and COVID-19 infection.

COVID-19 in Liver transplanted patients

D'Antiga (7) reported the preliminary experience in Bergamo hospital, where approximately 700 children have received a liver transplant, 3 in the last two months. The authors stated that among around two hundred transplant recipients at the center, including ten current inpatients, one hundred with autoimmune liver disease, three under chemotherapy for hepatoblastoma (inpatients), none have developed clinical pulmonary disease, despite three tested positive for COVID-19. Considering the infection is currently endemic in the area, other immunosuppressed children are likely to be carriers of the virus, but none was reported to clinics or daily shared-care phone consultation because of pneumonia.

What can we learn?

Data presented in the literature are lack, and a well-designed management strategy for patients with SOT and COVID-19 is unclear. About liver transplantation, we found only 1 article (7) reporting cases of COVID-19 in pediatric patients.

However, it is possible to elaborate key-words for the management of this particular cluster of patients, especially for adult.

In the "pandemic era" consider symptomatic patient with SOT as positive for COVID-19 until proven otherwise

In patients with SOT, the chronic administration of immunodepression therapy alters the immune response. Particularly the T-cell immune response is significantly suppressed by the long-term use of immunosuppressive agents. Tacrolimus and cyclosporine, the most commonly used drugs for maintenance immunosuppression in SOT patients, reduce the

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production of IL-2, a regulator of proliferation, survival, and maturation for all T cells (8). It is unclear if immunosuppression in patients with SOT alters the predisposition to acquiring COVID-19 infection or if the disease implications are modified for better or for worse.

Frequently signs and symptoms of patients admitted to the hospital were fever (77–98%), cough (46%–82%), myalgia or fatigue (11–52%), and shortness of breath (3-31%) at illness onset (9-12). Fever was present in 44% at hospital admission and developed in 89% during hospitalization (13). Other less commonly reported respiratory symptoms include sore throat, headache, cough with sputum production and/or hemoptysis. Some patients have experienced gastrointestinal symptoms such as diarrhea and nausea before developing fever and lower respiratory tract signs and symptoms.

In case reports mentioned above (4-6), the clinical manifestations of COVID-19 infection in this population may be distinctive, with atypical symptoms as asthenia, diarrhea, fatigue, poor appetite (9). Laboratory tests showed an increase in WBC count, with an associated low count of lymphocytes, high CPR, and CT scans showed bilateral ground-glass opacities, the hallmark for lung injury in COVID-19. With the worsening of infection, the patient develops the clinical findings of respiratory distress. In the first evaluation, the level of procalcitonin is useful to detect an opportunistic bacterial infection and, so, start empirical antibiotic therapy (6), but the worsening in symptoms and patient clinical condition should alert the clinicians for suspect COVID-19 infection. The clinical progression in the worst cases is the respiratory failure needed oxygen administration or mechanical ventilation in ICU (5).

In the "pandemic era", despite patients with SOT are prone to develop severe infections caused by common bacterial or viral agents, the clinician must always be alert on COVID-19 infection. Although the patient may not have any travel history or reported known contacts with contagious or infected people, nasopharyngeal and oropharyngeal swab specimens must be collected for testing COVID-19. A delay in diagnosis could translate into an

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unfavorable clinical outcome for patients. The prompt diagnosis of COVID-19 infections could allow the clinician to start the isolation measure and adopt adequate medical therapy.

Adjust/Stop immunosuppressive agents and….

In case of suspected and/or confirmed COVID-19, the clinician must consider to adjust/stop immunosuppressive agents, and, at the same time, protect graft function. The rationale for the modification of immunosuppressive therapy is dual. First, when treating pneumonia due to opportunistic virus infection, a reduction or even temporary discontinuation of immunosuppressants is a common strategy and allows recipients the opportunity to reacquire anti-infection immunity within a short period, which is conducive to eliminating the virus (14, 15).

Second, when COVID-19 was confirmed, clinicians adopted a protocol to treat the viral infection, that provides the administration of oral Lopinavir/Ritonavir, 400/100 mg, twice a day. It has been suggested that cyclosporine, tacrolimus, everolimus, and sirolimus can be discontinued during the therapy with the protease inhibitors Lopinavir/Ritonavir. This drug has been proposed as supportive, off-label therapy in patients with COVID-19 patients but cannot be taken in combination with immunosuppressants due to strong drug interactions. However, the therapeutic efficacy of Lopinavir/Ritonavir has never been confirmed, and its therapeutic potential is still under investigation (16).

The clinician, previous evaluation of risk/benefit ratio, could adjust/discontinue all immunosuppressants to minimize the severity of symptom progression associated with COVID-19, then considers the progression of patient's illness and subsequent improvement for the pre-illness standard regime.

…protect allograft function

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After the adjustment/suspension of immunosuppression therapy is necessary to avoid the allograft deterioration induced by the reactivation of the immune system. If the clinical condition of the patient improves, the immunosuppressive agents can be gradually reinstated. However, if patients cannot take oral tablets or his clinical condition is worsening, the clinician must be considered the use of appropriate doses of intravenous corticosteroids. The immunosuppressive effect of corticosteroids might protect the allograft from acute rejection and avoid imminent Addison crisis in the period of the discontinuation of oral steroid; moreover, the anti-inflammatory effect of corticosteroids may also reduce alveolar exudation and relieve systemic symptoms (such as fever or fatigue) caused by the storm of inflammatory factors (11).

It is crucial to pay attention to the dosage and duration of steroid administration. Long duration and excessive doses of steroids may adversely affect recovery due to the inhibition of antiviral immunity, and may also result in other side effects related to steroids (17). The data presented in the literature reported a wide range of daily doses of methylprednisolone (40-80 mg) (4, 6). Guillen et al. (5) withdrew tacrolimus, for the interaction of ritonavir with calcineurin inhibitors, and everolimus, due to its reported risk for mTOR-inhibitor induced pneumonitis (18), but there is no mention about corticosteroid administration. Strangely, the authors wrote that at the moment, the patient needed respiratory support in ICU.

Further studies are needed to demonstrate the role of corticosteroid administration in patients with SOT and respiratory symptoms caused by COVID-19 infection, and eventually, dosage and time of treatment.

In addition to corticosteroid therapy, it is also necessary to support organ function, avoiding injury induced by other factors. For example, patients with kidney transplants diagnosed with COVID-19 and in-home quarantine, therapy with levofloxacin, rather than azithromycin, is recommended after careful evaluation by the physician. In this case, empirical reduction of cyclosporine should be performed. Adequate hydration and the use of paracetamol are

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suggested in case of fever. Available epidemiological data have confirmed that acute kidney injury is one of the main risk factors in the prognosis of COVID-19.

It is useful to remember that COVID-19 infection can cause a pleiotropic injury with elevation in specific-organ markers, making a challenge the differential diagnosis with allograft rejection caused by discontinuation of immunosuppressive drugs. In fact, about 37% of patients present with elevated alanine aminotransferase and aspartate aminotransferase levels and myocardial injury, manifested as an increase in high-sensitivity cardiac troponin I, occurred in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan (10).

SOT in pediatric patients with COVID-19

Few data are available about the clinical presentation and outcomes for COVID-19 in children, and the only article on this topic stated that, despite three tested positive patients for COVID-19, no one developed clinical pulmonary disease (7).

From data presented in the literature, only 2.1% of confirmed COVID-19 patients were aged <20 years, and no deaths were reported among those <10 years (19). Clinical manifestations of children infected by COVID-19 may be milder than adults, with most pediatric patients presenting with fever, cough, congestion, and rhinorrhea, and primarily gastrointestinal symptoms (vomiting and diarrhea) (20-22). Prolonged detection of coronavirus has been reported in respiratory and stool specimens (20, 23). A report in a 13-month old with COVID-19 described severe complications of acute respiratory distress syndrome and septic shock (22).

For this particular cluster of patients, the data presented in the literature are scarce.

Conclusion

The management of adult patients with SOT and COVID-19 infection is a challenge for the clinicians. There is a lack of data in the literature, but three key-points are crucial:

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1. In the “pandemic era” consider the symptomatic patient as positive for COVID-19 infection until proven otherwise;
2. Adjust/Stop immunosuppressive agents;
3. Protect graft function with adequate route and dose administration of glucocorticoid and supportive measures.

For pediatric patients, data are scarce.

It is unclear if immunosuppression in patients with SOT alters the predisposition to acquiring COVID-19 or if the disease implications are modified for better or for worse. Further studies are needed.

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Author Contributions

Romanelli A. and Mascolo S. wrote the article.

Conflict of interest

The authors declare no conflict of interest.

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