## Methylprednisolone/mycophenolate-mofetil/tacrolimus

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### COVID-19, *Klebsiella oxytoca* and *Klebsiella pneumoniae* infections: 2 case reports

In a case report, two patients (a man aged 59-years and a woman aged 56-years) were described, who developed COVID-19 infection, *Klebsiella oxytoca* or *Klebsiella pneumoniae* infections while receiving immunosuppressant therapy with methylprednisolone, mycophenolate-mofetil and tacrolimus following heart transplant [*not all dosages stated; routes and durations of treatments to reactions onsets not stated*].

Patient 1: A 59-year-old man with end-stage ischaemic heart disease, was hospitalised on 17 March 2020 for heart transplant. Due to the ongoing COVID-19 pandemic, he and the donor were screened for the COVID-19 and showed negative result. He then underwent the transplant in orthotopic position. After that he was transferred to the ICU on mild inotropic support. In the ICU, he became haemodynamically unstable requiring an escalation of inotropic and vasopressor support. He was again shifted to the operation theatre and underwent surgical revision due to stenosis of the superior vena cava anastomosis. After that, his haemodynamic condition stabilised, and he was again transferred to the ICU. He received induction immunosuppressive therapy with a standard triple regimen including decreasing doses of methylprednisolone, tacrolimus (trough levels between 8 and 10 µg/L) and mycophenolate mofetil 1000mg twice daily. He also received cotrimoxazole [sulfamethoxazole/trimethoprim] and valganciclovir [valganciclovir-hydrochloride] as anti-infectious prophylaxis. On post-operative day 2 (POD-2), RT-PCR showed positive result for COVID-19 infection. Hence, he received off-label treatment with hydroxychloroquine 400mg twice daily as loading dose followed by 200mg twice daily from POD-2 to POD-7. Examinations showed right ventricular dysfunction and low cardiac output syndrome that required a further increase in the doses of dobutamine and norepinephrine along with inhalation nitric-oxide for refractory hypoxia. Further, he developed acute renal failure requiring renal replacement therapy. After a gradual improvement by POD-14, the respiratory exchanges started to worsen, and chest CT scan showed bilateral ground-glass opacities compatible with COVID-19 infection. On the same day, a right cardiac catheterisation demonstrated mild post-capillary pulmonary hypertension with a slightly reduced cardiac index. Blood cultures of bronchoalveolar lavage showed positive result for *Klebsiella oxytoca* infection. He received treatment with cefepime for 10 days, and his mycophenolate-mofetil was discontinued. The dose of methylprednisolone was also reduced to 16mg daily. However, his respiratory exchanges continued to worsen. He died on POD-27 due to refractory hypoxia and multiorgan failure. Development of COVID-19 and *Klebsiella oxytoca* infection was attributed to his immunosuppressed state due to methylprednisolone, mycophenolate-mofetil and tacrolimus. It was later identified that, he was living in an area of high number of COVID-19 infection cases, and he was an unknown asymptomatic carrier of the COVID-19 infection before the transplant.

Patient 2: A 56-year-old woman ad a history of decompensated hypertrophic heart disease, and was on the waiting list for heart transplant for more than 12 months. She was hospitalised three times in the past three months due to recurrent episodes of heart failure. In March 2020, she was again hospitalised due to another episode of heart failure. She was admitted to the cardiology unit and placed on inotropic support while waiting for the transplant procedure. Due to the ongoing COVID-19 pandemic, she and the donor were screened for the COVID-19 and showed negative result. She then underwent the transplant procedure uneventfully. She received induction immunosuppressive therapy with a standard triple regimen including decreasing doses of methylprednisolone, tacrolimus (trough levels between 8 and 10 µg/L) and mycophenolate mofetil 1000mg twice daily. She also received cotrimoxazole [sulfamethoxazole/trimethoprim] and valganciclovir [valganciclovir-hydrochloride] as anti-infectious prophylaxis. However, the operation theatre used for the transplant procedure was previously used for another patient who later tested positive for COVID-19 (patient 1; the man aged 59 years). Hence, due to the indirect contact RT-PCR was again performed on POD-2, which showed a weak positive result. Hence, she received off-label treatment with hydroxychloroquine 400mg twice daily as loading dose followed by 200mg twice daily from POD-2 to POD-7. As no post-operative complications were noted, she was transferred from ICU to an isolation ward on POD-4. However, on POD-19, she developed fever and breathing difficulties with a slow decrease in her oxygen saturation requiring nasal oxygen supplementation. Chest-CT scan showed ground-glass opacities. Another RT-PCR performed with BAL fluid showed strongly positive result. She received off-label azithromycin for 7 days. On POD-20, due to progressive worsening of her respiratory status, she was shifted to the ICU. She required prompt invasive ventilation along with prone positioning. Her, mycophenolate-mofetil was stopped. Her clinical status continued to deteriorate. On POD-34, PCR on bronchial aspirate showed positive result for *Klebsiella pneumoniae,* but standard Gram staining and cultures were negative. She received treatment with meropenem. She died on POD-35 due to refractory hypoxemic respiratory failure. Development of the COVID-19 infection and *Klebsiella pneumoniae* infection was attributed to was attributed to her immunosuppressed state due to methylprednisolone, mycophenolate-mofetil and tacrolimus.

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