Multiple drugs

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Bleeding, off-label use and lack of efficacy: 2 case reports

In a report, 31-year-old woman and a 72-year-old man were described, who received off-label treatment with gammaglobulin, lopinavir/ritonavir, ribavirin, thymalfasin or convalescent anti-SARS-CoV-2 plasma for COVID-19 pneumonia, and they exhibited lack of efficacy during treatment with norepinephrine, imipenem/cilastatin, levofloxacin, methylprednisolone, vancomycin or off-label therapies, such as gammaglobulin, lopinavir/ritonavir, ribavirin or thymalfasin for septic shock or COVID-19 pneumonia. Additionally, the woman developed bleeding during anticoagulant treatment with heparin [*time to reaction onset not stated; not all routes stated*].

Case 1: The 31-year-old woman received off-label treatment with gammaglobulin, lopinavir/ritonavir, ribavirin, thymalfasin and convalescent anti-SARS-CoV-2 plasma for COVID-19 pneumonia, and she exhibited lack of efficacy during treatment with norepinephrine, imipenem/cilastatin, levofloxacin, methylprednisolone, vancomycin and off-label therapies, such as gammaglobulin, lopinavir/ritonavir, ribavirin and thymalfasin for septic shock or COVID-19 pneumonia. Additionally, she developed bleeding during anticoagulant treatment with heparin: On 1 February 2020, the pregnant woman (at 35 weeks of gestation) presented to a hospital in China with complaints of throat pain and fever, and she reported that she developed the symptoms 4d previously that coincided with a travel from another city on 25 January 2020. She was hospitalised, and she developed severe hypoxia and septic shock within 6h of admission. Therefore, she was intubated and sedated (drugs unspecified) for mechanical ventilation (MV). On 1 February 2020, she underwent an emergency caesarean delivery at bedside, and she delivered a live male neonate, who was noted to have severe acidosis, hypoxemia and potential cardiac damage. The neonate died on the same day [*definitive cause of death not stated*]. She was moved to another hospital in China on the day after delivery (2 February 2020) in the early morning because she was extremely unstable. On admission, she was placed on assisted MV under mild sedation (unspecified). She received IV norepinephrine 0.8 µg/kg/min. She underwent multiple investigations and lab tests, and she was diagnosed with COVID-19 pneumonia, acute respiratory distress syndrome (ARDS), septic cardiomyopathy, septic shock, multiple organ dysfunction syndrome and post-caesarean condition. She started receiving continuous renal replacement therapy (CRRT) in order to improve oxygenation, remove excessive inflammatory factors and achieve better fluid balance. Also, she started receiving antiviral therapy, antibiotic therapy, steroid therapy and other standard therapies. Medications included off-label antiviral drugs, such as lopinavir/ritonavir 5 m/12h on days 1–4 and ribavirin 400 mg/d on days 1–4 for COVID-19 pneumonia, anti-infective drugs including imipenem/cilastatin [Imipenem/cilastatin sodium] 1 g/8h on days 1–14, vancomycin 100 U/12h on days 1–17 and 500 mg/6h on days 24–33, levofloxacin 500 mg/d on days 1–7 for septic shock and off-label immunotherapy with thymalfasin 1.6 mg/12h on days 1–17 and 1.6 mg/d on days 17–33, gammaglobulin 10–30 g/d on days 1–17 for COVID-19 pneumonia. Also, she received anticoagulation with heparin-coated circuits and standard-level heparin [unfractionated heparin] infusion. Concomitantly, she received steroid therapy with methylprednisolone 20–40 mg/d on days 1–24. Supportive treatments included MV on days 1–33 and CRRT on days 1–24. However, the condition rapidly deteriorated over the subsequent few hours. Arterial blood gas analysis showed respiratory acidosis. Therefore, she was placed on controlled MV with deep sedation with combination of morphine, midazolam and propofol. She received various anti-infective and supportive treatments, despite which her condition continued to deteriorate. She exhibited a lack of efficacy during treatment with norepinephrine, imipenem/cilastatin, levofloxacin, methylprednisolone, vancomycin and off-label therapies, such as gammaglobulin, lopinavir/ritonavir, ribavirin and thymalfasin. Also, she developed mild jaundice. Blood tests showed leucocytosis, neutrophilia, thrombocytopenia, high-level lactate dehydrogenase (LDH), hyperbilirubinaemia, high total bile acid, low prealbumin and high inflammatory biomarkers. Severe hypoxemia and respiratory aci dosis were noted on arterial blood gas analysis. Due to worsening hypoxemia despite maximum conventional support, VV-extracorporeal membrane oxygenation (ECMO) support was started from day 4 (5 February 2020). Also, she received voriconazole and caspofungin. Subsequently, her respiratory status improved during the first 10d. Based on the need of prolonged MV after ECMO, she underwent a tracheostomy on the day 10 of ECMO support. However, on 15 February 2020, she developed surgical bleeding during the operation. Therefore, heparin was temporarily held, and she underwent debridement, which successfully controlled the bleeding. Between days 10–16 of the ECMO support, she again experienced worsening of condition.She underwent multiple tests, which indicated damage of the heart, liver and kidney. An echocardiography showed enlargement of the right ventricle, which suggested development of right ventricular dysfunction (RVD). Therefore, the fluid management, ECMO perfusion, and positive end-expiratory pressure settings were optimised to support the right ventricle function. Imipenem/cilastatin sodium switched to piperacillin/tazobactam. Vancomycin and voriconazole were stopped. She received off-label convalescent-anti-SARS-CoV-2-plasma [Convalescent plasma] on days 18–23. Over the following week, the condition gradually improved, and she showed sufficient oxygenation and improvement in the chest radiography findings. Blood tests revealed that the levels of organ damage biomarkers had reduced remarkably. On 26 February 2020, the VV-ECMO was discontinued after a total of 21 days. Chest X-ray had much improved, which prompted weaning from MV after a total of 36 days on 7 March 2020. A chest CT scan on day 40 revealed absorption of inflammatory lesions compared to that on day 30. She tested negative for SARS-CoV-2 nucleic acid test after 40d of hospitalisation. On 18 March 2020, she was discharged home, with normal vital signs and laboratory tests, after a total of 46 days of hospitalisation.

Case 2: The 72-year-old man received off-label treatment with gammaglobulin, lopinavir/ritonavir, thymalfasin and convalescent anti-SARS-CoV-2 plasma for COVID-19 pneumonia and exhibited lack of efficacy during off-label treatment with gammaglobulin, lopinavir/ritonavir and thymalfasin: On 9 February 2020, the man presented to a hospital in China with complaints of subjective fever, cough and fatigue that he developed since 2 February 2020 (1 week before presentation). His medical history included hypertension (20 years) and percutaneous coronary intervention (PCI) for the left main and three-vessel coronary artery disease 5 years previously. He underwent multiple investigations, and he was diagnosed to have COVID-19 pneumonia, hypertension and post-PCI condition. On admission, he stared receiving treatments such as supportive therapy and antiviral treatment. Medicines included off-label lopinavir/ritonavir 0.5 g/12h on days 4–6 for COVID-19 pneumonia, imipenem/cilastatin, ceftriaxone/tazobactam and piperacillin/tazobactam, off-label immunotherapy with thymalfasin 1.6 mg/d–1.6 mg/24h on days 4–51 and gammaglobulin 20 g/d on days 4–8 and days 28–32 and 10–20 g/d on days 36–49 for COVID-19 pneumonia. Also, he received anticoagulation with heparin-coated circuits and standard-level unfractionated heparin infusion. Concomitantly, he received steroid therapy with methylprednisolone. However, after 11 days (20 February 2020), his condition worsened and became severely hypotensive, for which he required vasoactive support with norepinephrine 0.15 mg/kg/min. Severe hypoxemia and respiratory alkalosis were noted on arterial blood gas analysis. On the following day, intermittent non-invasive ventilation was started; however, he complained of a sense of suffocation. His respiratory status did not improve and he was intolerant of the intermittent non-invasive ventilation; therefore, mechanical ventilation (MV) was started. On 22 February 2020, his condition deteriorated again, with worsening of arterial blood gas parameters. Due to failure with conventional therapies, including off-label treatments with gammaglobulin,

lopinavir/ritonavir and thymalfasin, to improve his condition, VV-extracorporeal membrane oxygenation (ECMO) support was started. He was also treated with meropenem, cefoperazone/sulbactam, teicoplanin, caspofungin, polymixin-B [Polymyxin B], tigecycline, vancomycin, avibactam/ceftazidime [Ceftazidime/avibactam], cotrimoxazole [trimethoprim/sulfamethoxazole] and micafungin. During the first 2 days of ECMO support, the haemodynamics were stable and oxygenation was noted to have improved. However, over the following 10 days, he developed thrombosis and bleeding (ECMO-related complications). The posterior pharyngeal wall was injured accidentally during sputum suctioning, which led to repeated bleeding. He underwent insertion of a chest drain to address right-sided pleural effusion and yielded a total drainage volume of 1500mL blood on the subsequent day. Thrombi were observed in the ECMO canula; therefore, the ECMO circuit was replaced. He developed a combination of thrombosis and bleeding (in the ECMO tube system), which were alleviated by adjustments of the unfractionated heparin level, plasma transfusion, cryoprecipitate therapy and replacement of the ECMO circuit. He received off-label convalescent-anti-SARS-CoV-2-plasma [Convalescent plasma] 300mL on day 23 and 200mL on day 31 for COVID-19 pneumonia. Between 8 April 2020–29 April 2020, his condition stabilised, with pulmonary compliance and gradually improvement of circulatory status. He tested negative for SARS-CoV-2 nucleic acid; however, he had developed pulmonary fibrosis and a wide area of mucoid impaction in the small airways in addition to inspiratory muscle weakness. At the time of rep ort, he continued to be on ventilatory support, and there was a possibility of requirement of a lung transplantation.

Wen J-L, et al. Extracorporeal membrane oxygenation for Coronavirus disease 2019-associated acute respiratory distress syndrome: Report of two cases and review of the literature. World Journal of Clinical Cases 9: 1953-1967, No. 8, 16 Mar 2021. Available from: URL: http://doi.org/10.12998/wjcc.v9.i8.1953 803567530