Management of life-threatening acute respiratory syndrome and severe pneumonia secondary to COVID-19 in pregnancy: a case report and literature review

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Case Report

Keywords: COVID-19, maternal, pandemic, perinatal, ECMO, convalescent plasma, pharmacological interventions.

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Abstract

Background

As COVID-19 continues to infect women of all gestational ages; gravida in labor and the acutely ill parturient are particularly at higher risk of infection. No therapeutic agent or vaccine is approved to treat COVID-19 till date. Thus, managing COVID-19 and associated complications during pregnancy is often challenging and requires a multidisciplinary approach to treatment.

Case Presentation

We narrate our perspectives on managing a 32-year-old, critically ill obstetric patient at 32-week gestation, diagnosed with acute respiratory distress syndrome (ARDS) secondary to COVID-19 pneumonia. Upon confirmation of COVID-19, as per the local protocol antivirals, antimalarial, and antibiotics were commenced. Due to rapidly exacerbating maternal respiratory functions, and potential chances of fetal hypoxemia emergency caesarian was performed. Following delivery, the maternal respiratory functions further deteriorated as she required prolonged mechanical ventilation and initiation of extracorporeal membrane oxygenation until she was clinically stable on day 23. The patient also received convalescent plasma and tocilizumab as a part of the treatment protocol. The newborn was shifted to neonatal intensive care for intubation for respiratory distress and was found negative for SARS-CoV-2 and COVID-19 immunoglobulin (Ig). At day 25, the patient was clinically stable and was transferred to step down unit and discharged thereafter.

Conclusion

Through this case, we present the thought process, multidisciplinary team-based strategy and sequel of managing a complex, critically ill obstetric patient with ARDS and COVID-19 pneumonia. We anticipate that this case report will assist other healthcare institutions to manage critically ill patients with COVID-19 pneumonia.

Key words: COVID-19, maternal, pandemic, perinatal, ECMO, convalescent plasma, pharmacological interventions.

Background

The novel coronavirus disease 2019 (COVID–19) has been declared as a ‘pandemic outbreak’ and public health emergency of utmost international concern (1). Over 8.2 million confirmed cases and more than 446,392 deaths (as of 17/06/2020), the pandemic continues to harm significant number of people worldwide. Approximately, 5% of the infected cases are complicated by hypoxia and respiratory failure (2). The reported prevalence of severe pneumonia among Chinese patients was as high as 5% with an estimated mortality rate of 2.3—3.83% (3–5). Partial immune suppression, physiological and anatomical changes and multiple interaction with the healthcare system during pregnancy, presents an unprecedented challenge in managing this vulnerable population (2,6,7).

Previous infectious outbreaks such as, H1N1 influenza virus, Zika virus, severe acute respiratory syndrome corona virus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERSCoV) have had significant adverse impact on maternal as well as perinatal outcomes (6,8). Data collated from these patients demonstrated higher rates of intensive care unit admission, intubation, and death compared with non-pregnant patients (7,9). Anecdotal evidence demonstrates 0.1–0.2% of all pregnancies are complicated by respiratory failure (10,11).

Till date, no pharmacological intervention has been proven effective to treat COVID–19. Despite promising outcomes, no high-quality evidence exists for the safety and efficacy of convalescent plasma in treating SARS-COV2 infection. Inconclusive, limited clinical experience has been reported supporting the use ECMO in the management of COVID–19 (12,13). In the absence of any definitive therapy, the cornerstone of COVID–19 treatment varies from symptomatic ambulatory care management to intensive care treatment (14).

Over the past decade, the healthcare system in Qatar has transformed to a world class public health system providing free or highly subsidized healthcare to all its citizens and residents (15–17). The tiny Arabian Peninsula is also reported to have one of the lowest COVID–19 fatality rates in the world estimating less than 0.07% (18).

Case Presentation

We present a case of a 33-year old pregnant women at 32 weeks of gestation, referred to a tertiary care center following 8-day history of malaise, cough, sore throat and shortness of breath. Her past medical history revealed, asthma (>10 years) on inhaled steroids, gestational diabetes (from first pregnancy, 2017). Prior to admission, she was taking vitamins and budesonide and reported no history of allergies to medications. She is non-smoker and no recent travel was reported.

During the current admission, her vital signs were as follows: temperature 37.4°C, heart rate - 98 beats per minute, respiratory rate 25 br/min, blood pressure 98/63 mm Hg, and oxygen saturation (SpO2) 90% room air, 96% with nasal canula. The patient complained of tiredness, lower back ache while breathing, pertinent dry cough and shortness of breath. There were no obstetric concerns, no abdominal pain, contractions, leaking or labor pain. Fetal movements were remarkable, and no other obstetric problems were noted. All relevant blood tests, nasopharyngeal swab/real-time reverse transcriptase polymerase chain reaction (RtPCR), and chest X-ray were performed. Chest X-ray demonstrated patchy ground glass pneumonic infiltrates in both lung fields suggesting clinical correlation for pneumonia. The test results are presented in Table 1. There were no signs of deep vein thrombosis and transthoracic echocardiogram was normal. Nasopharyngeal and throat swabs confirmed positive for SARS-CoV–2 infection.

Following positive Rt-PCR, on day 1 of the hospital stay the patient was commenced on HMC's COVID–19 treatment protocol, chloroquine 400 mg once daily for 10 days, azithromycin 500 mg once daily for 10 days, oseltamivir 150 mg twice orally for 10 days, intravenous ceftriaxone 2gm once daily for 10 days. However, soon after the admission, she developed severe hypoxemia and acute respiratory distress, tachypnea (RR: 35 b/min) as was unable to complete sentences. Considering the maternal acuity and gestational age she was transferred to the intensive care unit of an obstetric specialty care.

The patient was admitted to a negative pressure intensive care room with multi-disciplinary expertise to manage critically ill obstetric patients. On examination, she was afebrile, decreased breath sounds with presence of crackles and wheezes, tachypnea. Additional oxygen support was provided, non-breather mask 15L/mins, with positive end-expiratory pressure (PEEP) at 5 cm H_2O, and fraction of inspired oxygen (FiO_2) at 100%. However, no improvement was observed, methylprednisolone 40mg was administered to decrease the host inflammatory responses in the lungs. On day 2, as the patient was not tolerating the non-invasive ventilation (NIV) as she complained of uneasiness, shortness of breath, pain while breathing and mild abdominal cramps. As a part of the treatment protocol Kaletra® lopinavir/ritonavir (80/20mg) and one dose of Tocilizumab 400mg (for hyper-inflammation caused by cytokine release) were administered. On day 3, considering the deteriorating respiratory functions, a multidisciplinary team including, internists, medical team, obstetric specialty, anesthetist decided to intubate her.

As patient required deep sedation to tolerate lung protective ventilation, continuous sedation/analgesia with propofol: 50mcg/kg/min + fentanyl: 5mcg/kg/hr, was administered aiming the Richmond Agitation and Sedation Scale (RASS) (19) more than –4. However, despite intubation and other medical interventions, the respiratory functions and static compliance worsened remarkably, and positive end-expiratory pressure (PEEP) and Fi02 was kept high. The ventilator flow was adjusted are as follows, peak pressure: 21mbar, plateau pressure: 20mbar, mean pressure: 14mbar, MV: 10.8L/min, minute volume (MV): 0.8L/min, respiratory rate: 22bpm, VT (tidal volume): 393mL, Resistance (R): 7.6mbar/L/s, Compliance: 119.5mL/mbar, PEEP: 14.7mbar. End-tidal carbon dioxide (EtCO2): 29mmHg. The cardiotocography (CTG) demonstrated no fetal heart acceleration and non-reassuring fetal outcomes anticipated mostly due to maternal hypoxemia. Considering persistent deterioration in maternal respiratory function and signs of fetal distress, a multidisciplinary team comprising the obstetrician, anesthetists, and medical internists decided to terminate the pregnancy by cesarean section (C-section). Magnesium sulphate 2gm infusion was commenced for fetal neuroprotection and was monitored for toxicity. The patient underwent an uncomplicated lower segment transverse cesarean section delivering a 1900gms baby boy, with a blood loss of 300ml. As per current recommendations, there was no need for a delayed cord clamping, and the baby was separated from the patient immediately.

On day 4, the patient encountered prolonged QTC intervals anticipated mostly due to hydroxychloroquine /+ Kaletra® lopinavir/ritonavir. Following intervention of the clinical pharmacist, the hydroxychloroquine was withheld, and timely monitoring was recommended. ECMO team was consulted and were involved in case the condition deteriorates. The patient encountered life-threatening hypoxia and severe acute respiratory failure post operatively. Veno-venous ECMO, bi-femoral cannulation was initiated after consent was obtained from the husband. All supportive medications including, noradrenaline 0.07 mcg, fentanyl 3 mcg, Propofol 15mcg/kg/min continued, the patient was also commenced onCisatracurium 1mc/kg/min. After placement on VV-ECMO her oxygenation significantly improved.

On day 5, during infectious disease consultation ribavirin was added and 2 units of convalescent plasma was administered to improve her respiratory mechanisms. On day 6, the ECMO team decided to stop Cisatracurium and noradrenaline and to wean off sweep gas aiming for oxygen saturation >88% and PH >7.25. Cabergoline 1mg, potent dopamine receptor agonist (to inhibit milk production) was administered to avoid breast engorgement and pain.

On day 14, on ECMO, the liver enzymes remained high, anticipated mostly due to antiviral medications, following which the ribavirin was withheld. The inflammatory markers drastically reduced following administration of methylprednisolone 20mg. On day 18, the patient developed hematuria and hematoma at the C-section wound antibiotics were started, low dose of fibrinogen was replaced. On day 19, the patient developed subcutaneous emphysema due to gram positive galenium bacteria, which was treated with antibiotics including cefipime, which was later changed to piperacillin tazobactum sodium 4500mg. On day 23, following an improved clinical and respiratory functions, ECMO decannulation was performed and was well tolerated. After 24 hrs, the patient was extubated on high flow nasal oxygen (2L), echocardiogram revealed no evidence of infective endocarditis. On day 25, following improved clinical findings, the patient was shifted from the intensive care unit to a step-down unit with continuous monitoring. The patient was clinically stable and was discharged two weeks later.

Neonatal summary

Following a preterm delivery, the neonatal APGAR scores documented at 1,5 and 10 minutes were 2, 3, and 7 respectively. However, an hour after delivery, the newborn encountered severe asphyxia and was transferred to neonatal intensive care unit for resuscitation and intubation. The baby received one dose of surfactant and was extubated after 16 hours to nasal continuous positive airway pressure. The newborn was tested twice (14 days

interval) for COVID–19 IgG and IgM and was found negative in both the occasions. The baby was discharged on day 14.

Discussion

We report a multidisciplinary approach to treating and complete recovery of acute respiratory failure and severe pneumonia secondary to SARS-COV2 infection during pregnancy. A plethora of studies have demonstrated the management of mild—moderate cases of SARS-COV2 infection in pregnancy with positive outcomes (2,10,20). However, very few studies have reported the management of critically ill patients, particularly in pregnancy. Pneumonia during pregnancy is often accompanied by hospitalization and critical care management including ventilatory support (20). Although the treatment of pneumonia during pregnancy mirrors that of non-pregnant state, the use of convalescent plasma and ECMO in pregnancy is rare (9,11,21).

The clinical presentations, symptoms and the radiological findings in our case were consistent to previous case reports (3,22,23), of SARS-COV2 infection. A nationwide population-based cohort (n = 1942) reported, pregnant women with viral pneumonia (other than COVID–19) demonstrated higher risk of preterm birth, intrauterine growth retardation low birthweight and poor Apgar scores when compared to those without pneumonia (24). Hence, as demonstrated in this case, an early delivery is considered as an alternative for critically ill pregnant women with ARDS.

In terms of therapeutic management, no specific pharmacological agent or vaccine to treat COVID–19 is available (12). Once COVID–19 was confirmed, hydroxychloroquine, azithromycin, oseltamivir, intravenous ceftriaxone and methylprednisolone were administered. Hydroxychloroquine and methylprednisolone are considered safe in pregnancy and have been used extensively to treat COVID–19 (25). However, there is a paucity of evidence regarding the use of antimalarial and antiviral therapy in treating SARS-COV2 infections (26), even in this case, it is unclear if the empirical use of these medications had any role in the recovery of our patient. Tocilizumab (monoclonal antibody IL–6 receptor antagonist) was administered post operatively, due to the deteriorating respiratory functions, hemodynamic instability and persistently elevated inflammatory markers. Several COVID–19 studies have demonstrated improved respiratory functions, and successful recovery in patients receiving one dose, (27–30).

Anecdotal evidence from previous viral infections including Ebola, SARS-CoV, H5N1 avian influenza, and H1N1 influenza suggests the use of convalescent plasma containing neutralizing antibody is effective (31–34). Food and Drug Administration (FDA) has recently approved the use of convalescent plasma to treat critically ill COVID–19 patients (35). A meta-analysis investigating effectiveness of convalescent plasma in SARS coronavirus infection and severe influenza, reported significant reduction in viral loads and mortality (36). In this case the transfusion of convalescent plasma demonstrated improved clinical outcomes, and COVID–19 specific inflammatory markers were significantly improved.

There is a scarcity of evidence behind the use of lung-protective ventilation and ECMO in COVID–19 infection during pregnancy (10). The use of ECMO in pregnancy and postpartum is rare. An estimated 40% of pregnant or postpartum women admitted to ICU are complicated by ARDS or cardiac arrest (37,38). Like previous reports demonstrating improved maternal survival (39,40), the use of VV-ECMO in this patient is expected to have potentially resulted in positive respiratory outcomes and successful recovery. Furthermore, providing adequate rest to lungs using VV-ECMO was necessary to avoid ventilator-associated and oxygen-induced lung injury.

Conclusions

Whilst, COVID–19 pandemic continues to harm pregnant women of all gestational age, obstetric patients, particularly gravida in labor and the acutely ill parturient are at higher risk of SARS-COV–2 infection. Through this case, we present the thought process, team-based strategy and sequel of managing a complex, critically ill pregnant women with ARDS and COVID–19 pneumonia. Furthermore, we demonstrate the importance of involving multidisciplinary team in decision making, as managing maternal complications as well as reassuring fetal being during such critical period is imperative. We have thus confirmed the feasibility of using convalescent plasma and ECMO during early postnatal period in critically ill obstetric patients with respiratory failure. Our perspectives in managing this complex case identifies several factors including, aggressive treatment, use of tocilizumab, convalescent plasma, followed by intensive care management with intubation and ECMO might have potentially contributed to the complete recovery of the mother and the newborn. Whether antimalarials-hydroxychloroquine (in particular), and/or antivirals are effective in treating COVID–19 - remains unknown. Further well-defined studies are necessary to study the effectiveness and safety of plasma transfusion in COVID–19 patients.

Declarations

Acknowledgement

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Conflicting interests

The authors declare that there is no conflict of interest

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Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article and shall be presented on request.

Ethical approval

Ethical approval to report this case was obtained from the institutional review board at Hamad Medical Corporation.

Author contribution

All authors have made substantial contribution to the case report. **SY** (Consultant obstetrician) and **MH** (Pharmacy Executive Director) has contributed to the conceptualization of the case report and were responsible for supervision, planning and execution. **SH** is a senior consultant and head of obstetric emergency who was involved in the initial assessment of the case. **ZM** is the primary obstetrician (senior consultant) who was involved in treating the case along with **TR & IB** (obstetric consultant) and **MJ** (specialist obstetrician). **AA** is a senior research fellow and ECMO consultant who managed the case in intensive care unit. **AM** is a senior consultant at the emergency department, involved in the initial management of the case. **MM** is infectious disease consultant and provided valuable input to the manuscript and managing the COVID-19 and related complications. **AT** and **FM** have contributed by interpreting the laboratory and radiological findings. **HS** is consultant neonatologist who managed the newborn in the NICU. **PR** and

WK are pharmacy administrative, involved in the acquisition of the financial support, scientific review and verification for the validity of content. **BT** is a clinical pharmacy specialist and doctoral researcher who took the lead in writing the manuscript in consultation with **SY, MH, AM, PR, FM**. All authors discussed, reviewed and edited the case report. All authors agreed to the final version prior to its submission.

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Table

Table 1: Laboratory values (maternal) for the first 10 days of admission

Lab Values	Reference range	D1	D2	D3	D3	D5	D6	D7	D8	D9	D10
Hemoglobin (g/dL)	12-15	11.6	11.2	12.8	10.6	11.5	8.1	8	9.1	9.1	8.9
WBC (10^3/uL)	4 - 10	5.08	6.2	8.1	19.2	11.9	11.0	9.3	9.5	8.8	8.6
Lymphocyte (10^3/uL)	1-3	0.6	0.4	0.5	0.4	0.5	0.6	0.5	0.3	0.4	0.1
Platelets (10^3/Ul)	150-400	126	153	189	257	291	258	308	348	379	329
C-reactive protein(mg/L)	0 - 5	168	149	170	66	103.9	90.5	NA	22.2	NA	7.8
Procalcitonin (micrograms/L)	<0.5	NA	1	0.42	0.29	0.18	0.16	0.11	0.06	0.06	0.05
Creatinine (mg/dL)	44-80	35	25	29	32	60	67	53	49	39	40
Aspartate transaminase (units/L)	0-32	36	39	43	32	68	124	163	204	232	216
Alanine transaminase (units/L)	0 - 33	16	17	19	16	35	76	136	205	332	424
Alkaline phosp	35-104	132	158	192	155	158	97	90	85	86	80

hatase (units/L)											
Prothrombin time (sec)	9.7 – 11.8	9.9		NA	9.2	9.6	10.1	9.9	10.9	11.4	11.9
Glucose mmol/L	3.3 – 5.5	7.8	5.9	6.7	6.9	11.8	9.5	7.5	4.4	7.2	7.9
Ferritin (micrograms/L)	12-160	236	253	NA	355	NA	NA	1039	1110	1431	1530
Lactate dehydrogenase (units/L)	135 - 214	NA	NA	NA	386	NA	NA	NA	868	NA	848
Fibrin D-dimers (ng/mL)	0 - 0.44	2.01	NA	NA	1.01	3.8	NA	2.7	2.1	NA	3.1

Figures

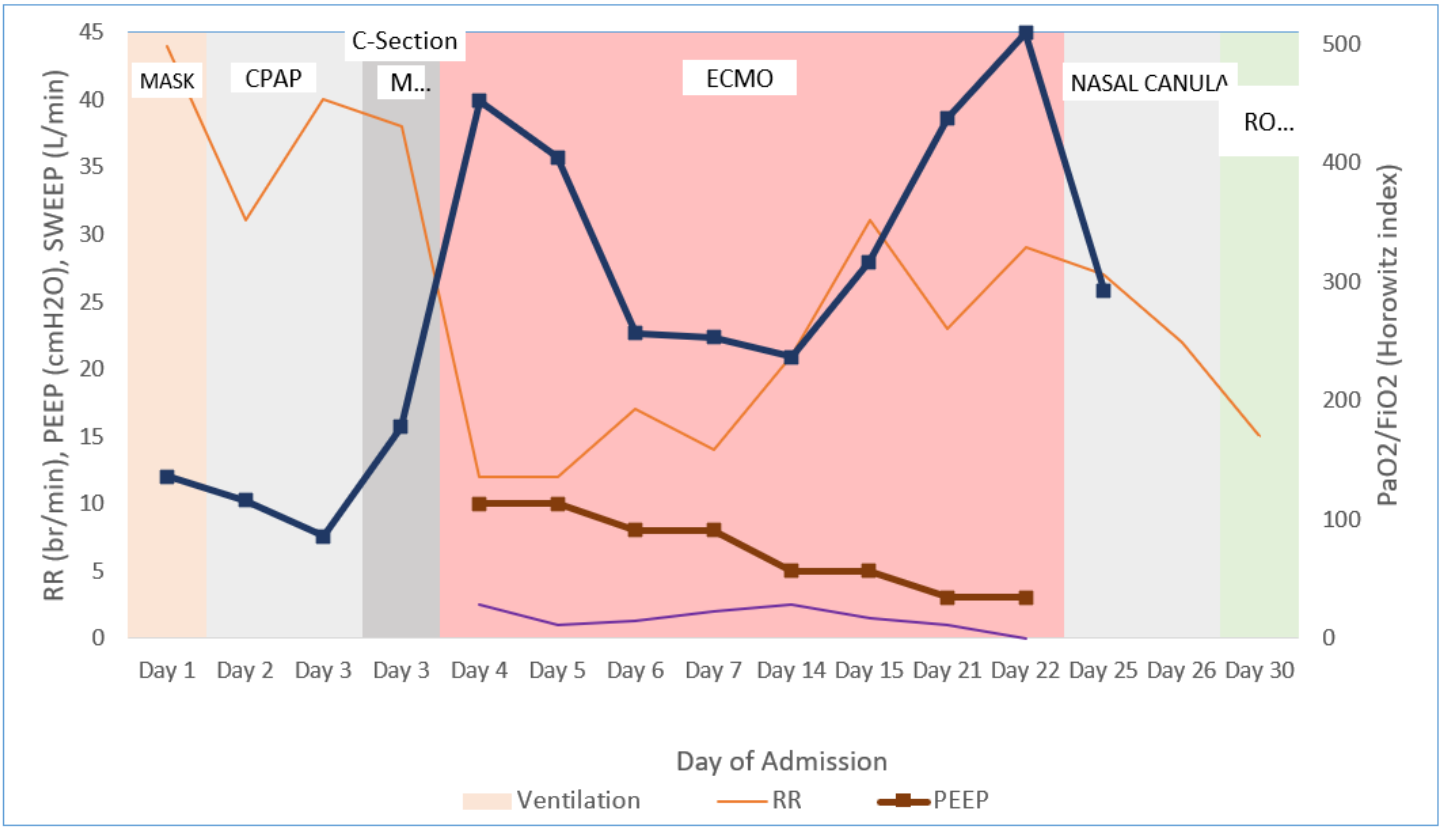
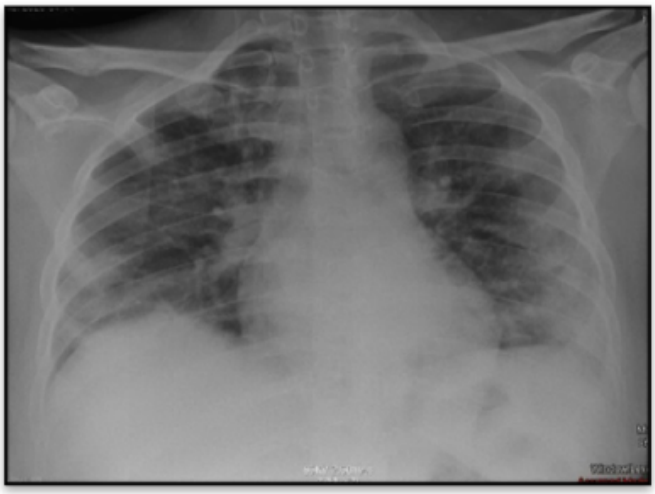
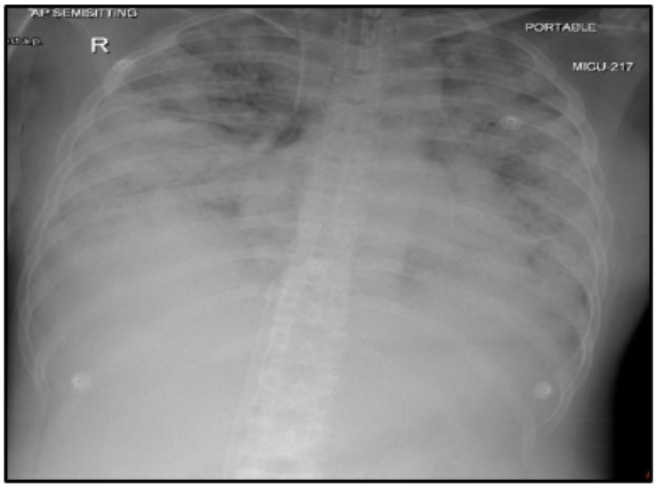


Figure 1

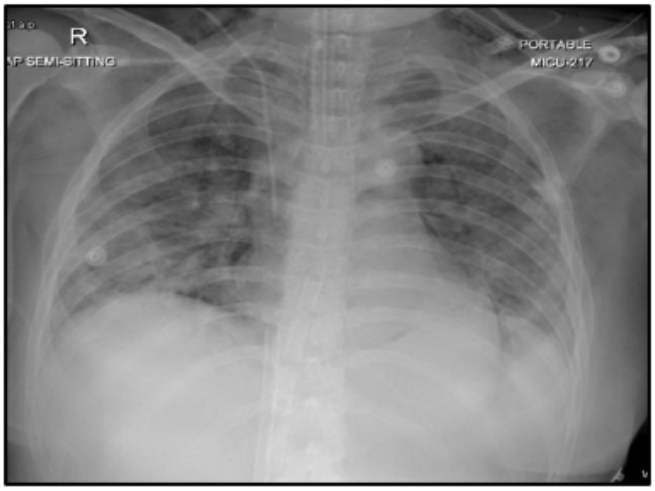
Ventilation flowsheet during hospitalization. RR: Respiratory rate (breaths/min), PEEP- Positive end expiratory pressure (centimeters of water), SWEEP- ECMO gas flow (Liters/min), PaO2/FiO2- Horowitz index – Partial pressure of oxygen arterial/ Fraction of inspired oxygen, ECMO- Extra corporeal membrane oxygenation, MV- Mechanical ventilation



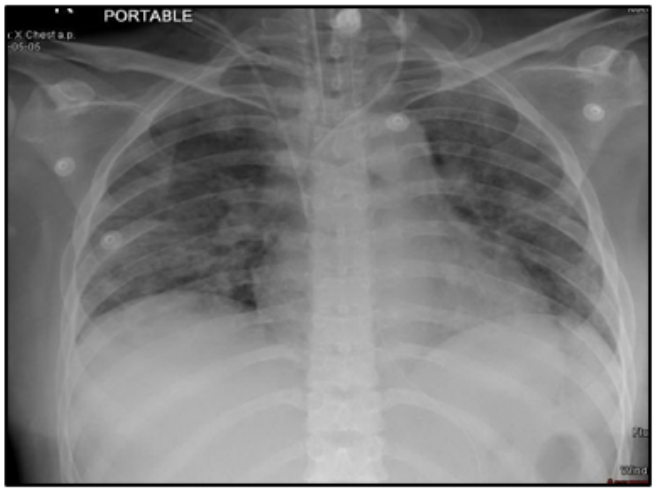
Day of Admission



Day 4 - ECMO



Day 11



Day 23- post extubation

Figure 2

Picture 1: Chest X-ray demonstrating ARDS