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CASE OF COVID-19 PNEUMONIA: LESSONS LEARNT

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ABSTRACT

This is a case of a patient with Coronavirus (COVID-19) Pneumonia, with pneumonitis, complicated by transaminitis. Evidence for non-pharmacological approaches, such as prone positioning, and pharmacological management, such as Hydroxychloroquine and Azithromycin are discussed and evaluated. The sensitivity and specificity of COVID-19 swab tests, the association between COVID-19 infection and specific acute phase laboratory markers and current known evidence versus ongoing controversial debates revolving around the topic of COVID-19 infection have also been briefly explored.

Keywords: Angiotensin-Converting Enzyme; Azithromycin; Coronavirus; COVID-19; Ferritin; Hydroxychloroquine; Lactate Dehydrogenase; Prone positioning; QT interval; Transaminases

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INTRODUCTION

This is a case of a patient with Coronavirus COVID-19 Pneumonia, presenting with pneumonitis, and complicated by transaminitis. Non-pharmacological and pharmacological management were explored and implemented to manage and optimise his care in an acute hospital setting.

CASE PRESENTATION

Mr B, a 58-year-old Chinese Malaysian gentleman, previously well with no past medical problems. He presented to an acute hospital with a one-week history of intermittent fever, associated with throat irritation. Prior to admission, he had visited his private General Practitioner and completed a five-day course of antibiotics, of which he was unsure of the name. He denied any coryzal symptoms, cough or urinary tract infection symptoms. He also denied any recent travel or contact with positive COVID-19 patients. He lives with his sister in Singapore and works as a mechanic with occasional contact with foreign workers. At the Emergency Department (ED), he had a temperature of 38.4 Degree Celsius and was noted to have deranged liver enzymes (Table 1). A Chest X-Ray (CXR) was done, which showed faint ground glass changes in the right middle zone and bilateral lower zones of his lungs (Figure 2). His C-reactive protein (CRP) was elevated at 74.7 mg/L, while the rest of his other inflammatory markers were not raised (Table 1). He was treated for Community-Acquired Pneumonia and was started on Intravenous Augmentin 1.2 g Q8hrly in ED in addition to Paracetamol and Thymol gargle. COVID-19 swabs were also performed.

Examination Findings

On physical examination, he was alert, comfortable, speaking in full sentences without any respiratory distress. No jaundice was noted, and his hydration was fair. He had a Body Mass Index (BMI) of 21.7 kg/m^2. His heart sounds were dual without any additional beats or murmurs heard, lungs were clear to the bases bilaterally, abdomen soft, non-tender, no liver edge palpable, and his calves were supple, without any odema.

His COVID-19 swab done returned positive, detectable for COVID-19 infection, with a cycle threshold (CT) value of 34.17, and he was diagnosed with COVID-19 Pneumonia with pneumonitis, complicated by transaminitis.

Insights

The daily discussions around the management of patients diagnosed with COVID-19 Pneumonia triggered the following insights:

1. Does performing prone positioning result in a faster recovery from COVID-19 infections?
2. When should we start Hydroxychloroquine?
3. When should we decide to add on Azithromycin?
4. Does it matter whether COVID-19 swab samples are obtained from patients' noses or throats?
5. How sensitive and specific are these COVID-19 swab tests?
6. Do ferritin and LDH have any association with COVID-19 infection?

MANAGEMENT

Non-pharmacological approach

1. Does performing prone positioning result in a faster recovery from COVID-19 infections?

The respiratory infection associated with COVID-19 usually involves pneumonitis rather than an exudative consolidation. The patients usually experience a dry, non-productive cough. Thus, respiratory physiotherapy interventions are not indicated.[1] However, it is recommended for adult patients diagnosed with COVID-19 infection and severe acute

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respiratory distress syndrome (ARDS) to perform prone positioning ventilation for 12 to 16 hours daily,[2] to improve systemic oxygenation. Thus, Mr B was attended by the physiotherapist to assist him with prone positioning exercises during his inpatient stay.

Pharmacological approaches

(i) Prednisolone

In view of his CXR showing faint ground-glass changes, which indicated signs of hyper-inflammatory response, Prednisolone 30 mg every morning was started for him for a duration of six days, to suppress lung inflammation.[3]

(ii) Hydroxychloroquine

2. When should we start Hydroxychloroquine?

There are currently no proven Food and Drug Administration (FDA)-approved drugs to treat or prevent COVID-19 infection. Although emergency use authorisation has been issued by the FDA to permit administrating Hydroxychloroquine to adult patients weighing 50 kg or more, and who are hospitalised with COVID-19, the drug has not been approved by FDA for the treatment of COVID-19.[4]

A number of promising repurposed pharmacological agents, including Hydroxychloroquine, potentially together with Azithromycin, are being evaluated in ongoing randomised clinical trials (RCTs).

A Chinese RCT in 62 patients showed that treatment with Hydroxychloroquine was associated with a shorter clinical recovery time than placebo in patients with mild COVID-19 infection.[5] However, the sample size was small and results from this RCT could not be extrapolated to critically ill COVID-19 patients. Another RCT done by Chen et al. reported a decrease in duration of hospitalisation, and a reduction in median time required for body temperature normalisation in COVID-19 patients treated with Hydroxychloroquine, as compared to those treated with conventional treatment.[6] However, results from this RCT were insignificant and sample sizes were small. In contrast, results from another open-label RCT by Tang et al. did not support the use of Hydroxychloroquine in patients with persistent mild to moderate COVID-19 infection, failing to provide evidence to support that Hydroxychloroquine increases the negative conversion probability of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[7]

Experimental data from studies have assessed the anti-SARS-CoV-2 properties of Hydroxychloroquine in vitro and clinically, and have suggested that Hydroxychloroquine is superior to control in inhibiting COVID-19 Pneumonia exacerbations[8], through its immunomodulatory capacity, preventing inflammation flares.[9] Additionally, administration of a loading dose of Hydroxychloroquine may be necessary to optimise treatment of COVID-19, prior to commencing a maintenance dose.[10]

Hydroxychloroquine was started for Mr B, at a loading dose of 400 mg twice a day followed by a dose of 200 mg three times a day for another six days. Intravenous Augmentin was concurrently stopped. His blood culture reported no bacterial growth, and his CRP down trended three days following commencement of Hydroxychloroquine (Table 1).

(iii) Azithromycin

3. When should we decide to add on Azithromycin?

A French open-label non-randomised trial conducted showed a significant decrease in viral load and viral carriage duration in patients with COVID-19 infection who received Hydroxychloroquine, at a dose of 600 mg per day for ten days, with enhanced effects of virus elimination when Azithromycin was administered in addition to Hydroxychloroquine.[11] On the other hand, other studies had reported an increased risk of 30-day cardiovascular mortality, heart failure, angina, when Azithromycin was added to Hydroxychloroquine, potentially due to synergistic effects that Azithromycin has on QT corrected (QTc) intervals.[12] The use of Azithromycin in combination with Hydroxychloroquine could also theoretically increase the risk of a patient developing Torsades de Pointes[13], an abnormal heart rhythm that has the potential to lead to sudden cardiac death. A baseline electrocardiogram (ECG) done on admission revealed a mildly prolonged QTc interval at 456 ms. Thus, the decision was made not to commence Mr B on Azithromycin.

4. Does it matter whether COVID-19 swab samples are obtained from patients' noses or throats?

Respiratory shedding of the COVID-19 virus peaks after a week from the onset of symptoms of the infection, and this shedding may be intermittent. Therefore, a single negative swab result may be misleading and repeated swabs will need to be conducted.[14]

Mr B's COVID-19 swabs were done consecutively for five days in order to achieve two consecutive negative swabs (Figure 1).

COVID-19 swab test results are best taken on the first onset of symptoms and are more sensitive when samples are obtained from the nasopharyngeal region as compared to the oropharyngeal region.[15] Swabs from both these sites were obtained from Mr B to increase testing sensitivity.

5. How sensitive and specific are these COVID-19 swab tests?

There are no specific clinical features or laboratory findings that have been found to reliably distinguish COVID-19 infection from other viral respiratory infections.[16]

False-negative polymerase chain reaction (PCR) assay results on nasopharyngeal and oral swabs have been reported, and literature on the sensitivity of nasopharyngeal swab PCR for COVID-19 is scarce. Current available data indicate the sensitivity of nasopharyngeal and oral swabs PCR assays for COVID-19 range between 56-83 percent. However, the

quality of methodology of these studies is low.[17] Although a negative COVID-19 PCR swab test can exclude COVID-19 infection in the majority of cases, the negative predictive value of the test decreases with increasing prevalence.[18] Another study by Zayet et al. supports this, concluding that the COVID-19 PCR swab test is specific for detecting COVID-19 infection, but lacks in sensitivity.[19] Thus, it is highly possible that patients who have tested negative for the COVID-19 PCR swab test may actually be infected with the COVID-19 virus. Late presentations to medical facilities, with a decreased viral load, below the detection limit of COVID-19 PCR assays, could explain the false-negative rate of the PCR swab test.[20] On the other hand, Chest CT findings have been reported to have a greater sensitivity of 97 percent, compared to PCR assays, but lack specificity.[21]

6. Do ferritin and LDH have any association with COVID-19 infection?

Recent studies have reported that patients with severe COVID-19 infection develop liver injury, detected as increased aminotransferase levels, more frequently than those with mild symptoms.[22] In addition to Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), other typical acute phase laboratory findings such as Lactate Dehydrogenase (LDH), ferritin, and CRP have also often been found to be elevated in patients with COVID-19 infection.[23] During the COVID-19 disease course, trending of LDH and CRP assist in identifying patients with poorer prognosis; higher risk of acute respiratory distress syndrome (ARDS)[24], high risk of requiring Intensive Care Unit (ICU) admissions and even death, thus prompting intervention to improve clinical outcomes, while high levels of ferritin have been studied to be poor prognostic factors.[25]

Mr B's liver enzymes were repeated and trended (Table 1), and his Hepatitis and Dengue Screen came back negative (Table 1). His ferritin levels were also trended and noted to be elevated at 981 ng/mL and mildly down trended to 874 ng/mL when repeated (Table 1).

Follow up care

Mr B recovered well from his symptoms and was subsequently discharged to a community isolation facility to be monitored and for further clearance swabs to be conducted, until two consecutive negative COVID-19 swabs are obtained. Mr B was given an outpatient appointment to visit the Polyclinic doctor in six weeks from his discharge date, to follow up on his liver function tests, to consider further abdominal hepatobiliary system imaging if his liver enzymes continue to worsen, and to repeat a CXR to document resolution of bilateral lower zone opacities.

LITERATURE REVIEW ON LATEST EVIDENCE

The outbreak of COVID-19, an emerging disease due to a novel coronavirus, started in Wuhan, China in December 2019. The epidemic of COVID-19 was declared as a pandemic by the World Health Organisation (WHO) on 12th March 2020. As of mid-May 2020, more than four million people have already been infected with COVID-19 infection across the world, resulting in more than 300,000 deaths[26], making the need for both safe and effective treatments to prevent COVID-19 related deaths and respiratory failure urgent.[27]

COVID-19 infection is caused by the virus binding to the human angiotensin-converting enzyme 2 (ACE-2) receptor, which is usually expressed in the lung, heart, kidneys, intestinal and vascular epithelium, thus serving as a possible portal for infection.[28] However, there have been conflicting data from studies reporting the concerns of increasing expression of ACE-2 with use of ACE-inhibitors (ACE-I) and Angiotensin receptor blockers (ARB), versus weak evidence demonstrating the effects of ACE-I and ARB in decreasing severity of COVID-19 related pulmonary injury.[28] No clear evidence has yet been reported to suggest that ACE-I or ARB increases susceptibility to, or severity of COVID-19 infection. Therefore, it is recommended for patients to continue their ACE-Is and ARBs as prescribed, and any changes in medication in the setting of COVID-19 infection should be carefully reviewed.[29]

Amongst many various drugs tested to treat COVID-19, Hydroxychloroquine and Azithromycin have been the most studied. While many studies have suggested Hydroxychloroquine, with or without Azithromycin, to have an association with reduced viral load in COVID-19 patients and in vitro[11], other studies have reported no evidence of clinical benefit with this combination of drugs in treating severe COVID-19 infection.[30] The clinical efficacy of Hydroxychloroquine alone, and in combination with Azithromycin, is still under evaluation with controversial results.[31] Both Hydroxychloroquine and Azithromycin are known to have effects of prolonged QT intervals, especially when used in combination. Therefore, their uses pose concerns regarding the potential risk of patients developing Torsades de Pointes and cardiac arrhythmias leading to death.[13] However, there is still limited data evaluating the effects of this combination therapy on ECG readings, especially in relation to patients with COVID-19 infection.[32]

LESSONS LEARNT AND CLINICAL POINTERS

1. It is recommended for adult patients diagnosed with COVID-19 infection ARDS to perform prone positioning ventilation for 12 to 16 hours daily, to improve systemic oxygenation.

2. The clinical efficacy of Hydroxychloroquine alone, and in combination with Azithromycin, is still under evaluation with controversial results.

3. Hydroxychloroquine and Azithromycin are known to have effects of prolonged QT intervals, especially when used in combination. Therefore, it is crucial to obtain a baseline electrocardiogram and to monitor QTc and cardiac functioning while on these drugs to prevent Torsades de Pointes, cardiac arrhythmias, and death.

4. Acute phrase laboratory markers such as ferritin, LDH, CRP, and transaminases have found to be elevated in patients with COVID-19, however larger clinical trials and studies are needed to provide clearer evidence of the

association between these biomarkers and prognosis of COVID-19 infection.

5. No clear evidence has yet been reported to suggest that ACE-I or ARB increases susceptibility to or severity of COVID-19. Therefore, it is recommended for patients to continue their ACE-Is and ARBs as prescribed.

REFLECTIONS ON THE CASE

When my roster allocation indicated that I would be caring for patients with COVID-19 infection, I was initially overwhelmed with mixed emotions of anxiety, fear, and worry. These feelings were present both at work; while being exposed to patients who were tested positive for COVID-19 infection, and at home; when I thought about the possibility of me being a carrier and bringing home a trace of the virus. I struggled with the dilemma of wanting and needing to care for my patients daily while worrying that I was putting my family at possible risk. Over time, I found ways to alleviate these fears and worries, through support from colleagues and seniors and through learning to trust my personal protective equipment (PPE), ensuring I always put on proper PPE adequately and appropriately.

This case has illustrated the importance of having a high index of suspicion when attending to similar clinical presentations of acute respiratory tract infection in future, whether in an acute hospital setting or in an outpatient polyclinic setting.

Moreover, caring for COVID-19 patients has made me realise that these patients are isolated, in their single room, away from their loved ones and families, and not being able to see or spend time with them, especially with the current visitation restrictions in the hospital during this pandemic period. It makes a significant difference to these patients if we act as an important bearer of messages and the communication link between patients and their families. Even the simplest act of assisting them with a video phone call to their loved ones, or just reminding them that their families have been asking about their clinical progress every day, makes a great difference to these patients, and thus, supporting and encouraging their endurance and their resilience to recovery.

Figure 1. Timeline of COVID-19 Swabs Done for Mr B and the Respective Results

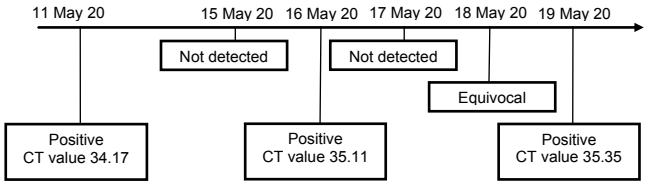

Figure 2. Mr B's Chest X-Ray

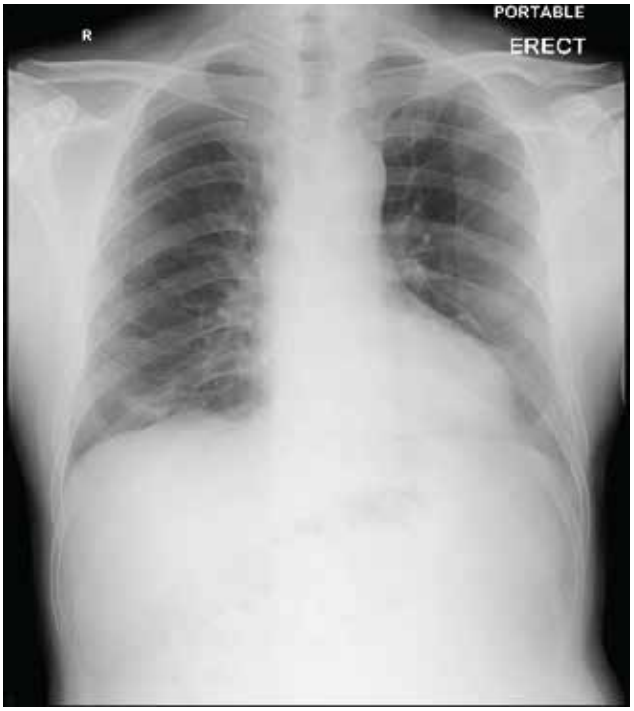

Table 1. Investigations

	11th April 2020	12th April 2020	14th April 2020
Blood Counts (units)			
White blood cell (x10^9/L)	5.47		9.42
Neutrophils (%)	60.0		81.3
Haemoglobin g/Dl	15.5		14.3
Haematocrit %	45.6		42.0
Platelets (x10^9/L)	243		335
Renal Function			
Sodium (mmol/L)	133		
Potassium (mmol/L)	3.5		
Choride (mmol/L)	94		
Bicarbonate (mmol/L)	22		
Creatinine (umol/L)	70		
Urea (mmol/L)	2.4		
Liver Function			
Alanine Aminotransferase (U/L)	54	57	
Aspartate Aminotransferase (U/L)	38	44	
Gamma Glutamyl Transpeptidase (U/L)	184	203	
Lactate Dehydrogenase (U/L)		382	
Total Protein, Serum (g/L)	82	75	
Albumin (g/L)	41	42	
Globulin (g/L)	41	33	
Total Bilirubin (umol/L)	9	12	
Alkaline Phosphatase (U/L)	140	126	
Sepsis Monitoring			
C-Reactive Protein (mg/L)	74.7		26.2
Procalcitonin (ng/mL)	0.13		
Others			
Ferritin (ng/mL)		981	874
Glucose (mmol/L)	7.2		
Dengue Ag/IgM and IgG	Negative		
Hepatitis B Surface Ag	Non-reactive		
Hepatitis B Surface Ab (IU/L)	550		
Hepatitis C Ab	Non-reactive		

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