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## Case report

## Methylprednisolone pulse therapy: An alternative management of severe COVID-19

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## ABSTRACT

We present two cases of severe COVID-19 that were rejected by medical institutions. The management of the disease was done at home with methylprednisolone (MP) pulse therapy for three days. This resulted in a favorable evolution and resolution of most symptoms. COVID-19 infection presents as asymptomatic disease, non-severe symptomatic disease, and severe respiratory inflammatory disease. The first two forms are dependent on viral response and a “cytokine storm” is responsible for the progression into severe disease. Glucocorticoids (GC) reduce inflammation by different mechanism depending of their concentration. Pulses lead to overall apoptosis of immune cells. Studies using pulse MP as treatment for SARS-CoV-1 showed clinical improvement and decreased incidence of ARDS compared with patients who received low dose steroid treatment. Inhibition of excessive inflammation through timely administration of GC in the early stage of inflammatory cytokine storm effectively prevents the occurrence of ARDS.

## 1. Introduction

As the world faces the new COVID-19 pandemic, Peru struggles to provide health infrastructure and resources to infected patients. Health establishments, continuously reject probable cases of infection due to limited space and resources in hospitalization wards and the Intensive Care Unit (ICU). Peru now faces increased COVID-19 mortality of patients who fail to acquire basic care and who are forced to weather their illness outside the health system.

## 2. Cases

Two 52 and 48-year-old males from Lima, Peru present increasing symptoms compatible with SARS-CoV-2 infection (Table 1). Both have a history of social smoking and drinking alcohol. Patient 1 has a family

history of diabetes mellitus type II from his father and arterial hypertension from his mother, and refers contact with a coworker that tested positive for a SARS-CoV-2 molecular test. Patient 2 reports a laparoscopic cholecystectomy for gallstones and a family history of arterial hypertension and stroke from both of his parents.

Patient 1 attempted twice to receive medical care at a hospital, but was dismissed because he tested negative for the SARS-CoV-2 serologic or immunological test. He begun treatment at home on day 10 (Table 1) and the physical examination highlighted a compromised general aspect, decreased muscle strength, and wheezing located in his mid-lower right lung. His BMI was 25.3 and he referred to have lost approximately 5 kg in the last couple of weeks.

Patient 2 unsuccessfully attempted twice to test for SARS-CoV-2. On the second attempt, he attended a private hospital where he had a chest X-ray performed that showed bilateral lung inflammatory infiltrates but was not hospitalized due to lack of space. Therefore on day 17, he begun

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**Abbreviations**

- Acute Respiratory Distress Syndrome (ARDS)
- Body Mass Index (BMI)
- Glucocorticoids (GC)
- Intensive Care Unit (ICU)
- Methylprednisolone (MP)
- Middle East Respiratory Syndrome (MERS)
- Latin America (LATAM)
- Oral Rehydration Units/Unidades de Rehidratación Oral (UROS)
- Secondary Hemophagocytic Lymphohistiocytosis (sHLH)
- Severe Acute Respiratory Syndrome (SARS)

treatment at home (Table 1) and the physical examination highlighted a compromised general aspect, skin pallor that predominated in his limbs, decreased muscle strength, and diffuse wheezing in his lungs. His BMI was 32.7 and he referred unquantifiable weight loss in the last couple of weeks. Both patients lived in the same street block where two of their neighbors diagnosed with COVID-19 did not receive medical attention in the overcrowded health service and unfortunately, passed away.

**3. Discussion**

Nowadays it is no surprise that the COVID-19 pandemic has oversaturated even the most established health systems. In a low-to-middle income country such as Peru, the pandemic ruthlessly affects the already ill-equipped health system that lacks enough mechanical ventilators, hospital beds and oxygen supplies for all those infected. Both of our patients repeatedly attempted to obtain medical attention, but were turned away by health institutions. In Patient 1, the negative result from a SARS-CoV-2 rapid test overruled clinical evidence in favor of hospitalization and treatment; Patient 2 did not even get access to prompt testing. The grim reality that many Peruvians are facing today pushes us to seek alternatives within our limited possibilities, a situation that is not strange to our history in epidemic management.

In the early nineties, Peru was suffering hyperinflation and terrorism when it was hit by the deadly cholera epidemic. Peru was the most severely affected country amongst its Latin American (LATAM) peers, with 82% of all cases reported to the Pan American Health Organization. Nevertheless, the Peruvian case fatality rate (0.9%) has been the lowest of all cholera epidemics due to the national distribution of Oral Rehydration Units (UROS, for “Unidades de Rehidratación Oral” in Spanish). Peru understood that in order to assure patient survival, treatment needed to reach all patients [1]. Similarly, it is important to highlight the value of treatment with methylprednisolone (MP) pulse therapy for

**Table 1**

Showing case development of symptoms, vital signs and management. Quantifiable values shown in numbers. Arrows represent intensity of symptoms variation. Addition sign denotes presence of symptom or treatment administered.

Patient 1																									
Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18						
Symptoms	Myalgia	↑	↑	↑	↑	↑	↑	↑↑	↑↑	↑↑↑	↑↑↑	↑↑	↑	↓											
	Cephalaea								↑	↑	↑	↑	↑	↓											
	Anosmia	+	+	+	+	+	+	+	+	+	+	+	+	+											
	Ageusia	+	+	+	+	+	+	+	+	+	+	+	+	+											
	Chills					+	+	+	+	+	+	+	+	+											
	Fever (axillar temperature °C)			38.2	+					38.5		38.0		38.2											
	Night sweats					+	+	+	+	+	+	+	+	+											
	Cough									+	+	+	+	+	+	+	+	↓	↓						
	Dyspnea									↑	↑	↑	↑	↑	↑	↑	↓								
	Constipation				+	+	+	+	+	+	+	+	+	+											
	Hyporexia	+	+	+	+	+	+	+	+	+	+	+	+	+											
	Insomnia				+	+	+	+	+	+	+	+	+	+											
	Vital signs	Respiratory rate (bpm)										22	30	30	28	23	23	23	18	17					
Heart rate (bpm)											85	110	99	84	81	72	66	64	74						
Oxygen saturation (%)											97	97	97	96	96	96	97	97	97						
Management	Ivermectin (oral 2drops/kg)										+	+													
	Enoxaparin (SC 60mg)										+	+	+	+	+	+	+								
	MP (pulses of 500mg in 250ml of NaCl for 1h)													+	+	+									
Patient 2																									
Day		1-9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24								
Symptoms	Light-headedness				↑	↑↑	↑	↑↑	↑↑	↑↑	↑	↑	↓	+		+	+								
	Cephalaea				↑	↑↑	↑	↑↑	↑↑	↑↑	↑	↑	↓												
	Anosmia	+	+	+	+	+	+	+	+	+	+	+	+	+											
	Ageusia	+	+	+	+	+	+	+	+	+	+	+	+												
	Fever (axillar temperature °C)				+	+			39.0	39.0	39.4														
	Cough	+	+	+	+										+										
	Dyspnea	↑	↑	↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑↑	↑	↓											
	Hoarseness	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
	Pallor					↑	↑	↑	↑	↑	↑	↑	↓												
	Hyporexia								+	+	+	+	+												
	Insomnia	+	+	+	+	+	+	+	+	+	+	+	+												
	Anxiety								+	+	+	+	+												
	Vital signs	Respiratory rate (bpm)										30	27	24	24	23	19	19	20						
Heart rate (bpm)											118	115	96	62	72			87							
Oxygen saturation (%)											89	85	92	96	97			95							
Management	Ivermectin (oral 2drops/kg)										+	+													
	Enoxaparin (SC 60mg)										+	+	+	+	+	+	+								
	MP (pulses of 500mg in 500ml of NaCl for 1h)											+	+	+											

COVID-19 patients in cytokine storm, at primary facilities by trained personnel, when it is impossible to obtain hospital assistance.

The course of SARS-CoV-2 infection is divided into three stages: asymptomatic disease, non-severe symptomatic disease, and severe respiratory inflammatory disease. While the first two forms are dependent on viral response, a cytokine storm/secondary hemophagocytic lymphohistiocytosis (sHLH)/macrophage activation syndrome, is most likely responsible for the progression into severe forms of COVID-19 that presents with progressive pneumonitis and respiratory failure [2].

Furthermore, viral infection is the most common cause of sHLH and the correct treatment for it is not glucocorticoids (GC) at genomic doses; but instead, MP pulse therapy. Ignorance about the correct GC dosage and the reasons behind it has sprung confusion regarding the use of this treatment for COVID-19 patients with cytokine storm. Low concentrations of GC ( $\leq 7.5$  mg/day) mediate effects via genomic events that regulate, in the nucleus, transcription of pro-inflammatory molecules such as IL-1, IL-6, and TNF- $\alpha$ . Medium concentrations (7.5–30 mg/day) activate genomic and non-genomic events [3]. Finally, very high concentrations ( $> 100$  mg/day) intercalate into cellular membranes, disturb cation transport through the plasma membrane and leak protons from the mitochondria. As GC dose increases and the receptors become saturated, non-genomic effects come to play [4] and, with the administration of pulses (500–1000 mg/d), a GC-induced apoptotic effect occurs [5] and explains the very rapid immunosuppressive and anti-inflammatory effects [4]. In the early stage of the inflammatory cytokine storm, MP pulses change the outcome of COVID-19 for a complete recovery [6] like it happened with our patients.

For instance, we believe that if we would biopsy our patients' lungs, we would observe diffuse alveolar damage (DAD) since these findings are present in many patients with cytokine storm [2]. Hospitalized COVID-19 patients with severe disease have more interleukins and pro-inflammatory markers than those with mild forms [7]. SARS-CoV-2 Acute Respiratory Distress Syndrome (ARDS) patients could have high viral RNA loads [8], but there are others with increasing respiratory deterioration without nasopharyngeal RNA viral load [9]. Therefore, a hyper-inflammatory response would be the juncture between these two types of patients.

As with other epidemic respiratory virus infections, GC routine doses of up to 2 mg/kg daily are harmful and not indicated [10]. Their use has been associated with delayed viral clearance in SARS-CoV-1 [11] and MERS [12]. Therefore, a systematic review and meta-analysis on patients with coronavirus infection (SARS-CoV-1, MERS, and SARS-CoV-2) showed that GC treatment was associated with higher mortality rate, longer length of stay, higher rate of bacterial infection, and hypokalemia [13]. For COVID-19 patients, GC should be reserved for those in cytokine storm and when used, they should be as MP pulses as with our two patients. Treatment for SARS-CoV-1 with three MP pulses showed an 88.8% recovery from the progressive lung disease [14] and decreased incidence of ARDS, mechanical ventilation, and mortality compared with patients who received low dose GC treatment [15].

#### 4. Conclusion

We treated two Peruvians male adults with COVID-19 at home because they could not be hospitalized due to the unavailability of beds. They did not recover with traditional COVID-19 medicines and both had symptoms and signs of severe disease. After three MP pulses, both patients recovered which evidences that this management not only prevented the need for their admission to an ICU but also saved their lives. Inhibition of excessive inflammation through pulse GC treatment, rather than antiviral treatment, is essential to the outcome of COVID-19 patients suffering from an inflammatory cytokine storm.

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#### Credit author statement

- Roberto Alfonso Accinelli edited the article and contributed to discussion. He is also the corresponding author who is responsible for ensuring that the descriptions are accurate and agreed by all authors.
- Mayte Bryce-Alberti and Arianna Sibila Portmann-Baracco wrote the article.
- Patricia Merab Saúne collected the data.
- All authors reviewed the article. All authors take responsibility for the integrity of the data and the accuracy of the data presentation.
- CRediT in no way changes the journal's criteria to qualify for authorship.

#### Declaration of competing interest

All authors declare no conflict of interest.

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