

# Bundle for pediatric COVID-19 sepsis

Jaime Fernández-Sarmiento<sup>1\*</sup> , Werther Brunow de Carvalho<sup>2</sup> 

## SUMMARY

COVID-19 infection can progress to severe respiratory infection and have high mortality rates. Several pathophysiological factors are observed in fatal cases, with mortality related to multiple organ failure, in addition to the evolution with high levels of serum ferritin, D-dimer, and C-reactive protein. These severe cases often meet the criteria for macrophage activation syndrome with changes in the host's inflammatory response and an inadequate resolution phase. In the present study, the bundle for COVID-19 sepsis is proposed, including early recognition; protection, handwashing and isolation measures; oxygen therapy; early invasive mechanical ventilation; treatment aimed at modifying the clinical course. This strategy may be useful in the control of children with severe COVID-19 cases, as already demonstrated with the implementation of bundles in sepsis and other etiologies.

**KEYWORDS:** COVID-19. Sepsis. Infections. Respiratory Distress Syndrome. Respiratory tract infections.

## INTRODUCTION

Several pathophysiological factors have been found in COVID-19 fatal cases, which may explain its severe behavior<sup>1</sup>. People with greater comorbidities<sup>4,5</sup>, such as heart disease, diabetes, hypertension, or obesity have been noted to present a greater risk of death. Mortality has been related to multiple organ failure as the common final pathway of pneumonia, sepsis, and acute respiratory distress syndrome (ARDS) (Figure 1).

Patients with this outcome have been found to have higher serum ferritin, D-dimer, and C-reactive protein (CRP) levels than those who survive<sup>5</sup>. These findings have been seen in other severe viral infections, especially in children, due to the activation of some signaling pathways by increased interleukin 6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor alpha (TNF- $\alpha$ )<sup>6</sup>. These severe cases often meet the criteria for macrophage activation syndrome (MAS), which is characterized by a disorderly inflammatory response in the host with an inadequate resolution phase. One of the defining criteria for MAS has been ferritin >500 mg/dL, which has also been seen in patients with severe COVID-19 infection<sup>5,7,8</sup>.

This virus, in a septic patient scenario, can release damage-associated molecular patterns (DAMP) and pathogen-associated molecular proteins (PAMPs), which lead to severe inflammation with microcirculation injury, thrombosis, and fibrinogen consumption, coinciding with the increased D-dimer seen in patients who die from COVID-19<sup>5,9</sup>. If this inflammation could be modulated, the microcirculation damage (especially endothelial cell damage) would stabilize, which would stop the apoptotic and pyroptotic cascade, allowing recovery of innate immunity and lung function (the lung being one of the most severely affected organs)<sup>10</sup>.

Accordingly, the implementation of a rapid approach has been a determining factor in many of the outcomes seen in this pandemic<sup>1</sup>, as proposed in the paper by Al-Hajjar and McIntosh<sup>5</sup>, the disease manifestation is less serious than so in the pediatric population than in adults. Thus, a sepsis bundle is proposed for patients with COVID-19 infection, which we believe could be useful in modifying the clinical course of the disease, just as it has proven useful in sepsis from other etiologies<sup>11</sup> (Figure 2).

<sup>1</sup>Universidad de la Sabana, Fundación Cardioinfantil-Instituto de Cardiología, Department of Pediatric Critical Care Medicine – Bogotá, Colombia.

<sup>2</sup>Universidade de São Paulo, Instituto da Criança, Pediatrics Department – São Paulo (SP), Brazil.

\*Corresponding author: [jaimefe@unisabana.edu.co](mailto:jaimefe@unisabana.edu.co)

Conflicts of interest: The authors declare there are no conflicts of interest. Funding: None.

Received on August 20, 2020. Accepted on September 20, 2020.

The bundle components for COVID-19 sepsis should include:

1. **Early recognition:** The recent sepsis guidelines for both adults and children, as well as the recommendations for management of COVID-19 sepsis, indicate that this measure is key in modifying the clinical course. It should be adhered to fulfill the case definition proposed by WHO, adapted to each center<sup>1</sup>. Keep in mind that fever associated with rapidly developing respiratory

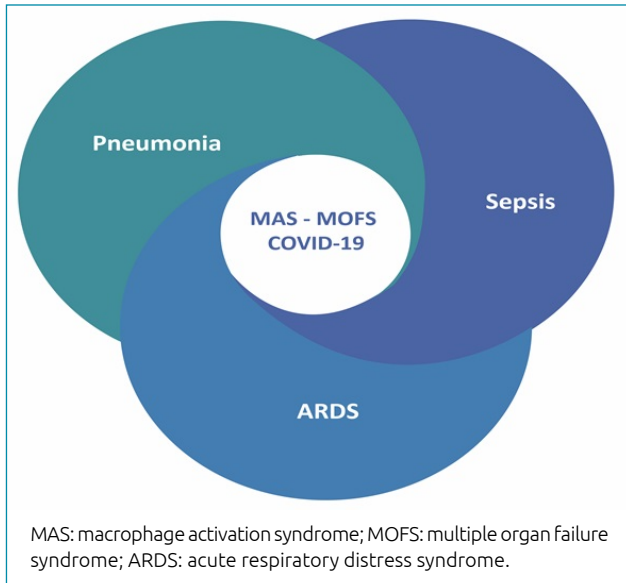


Figure 1. Various pathways leading to MAS and MOFS in COVID-19 infection.

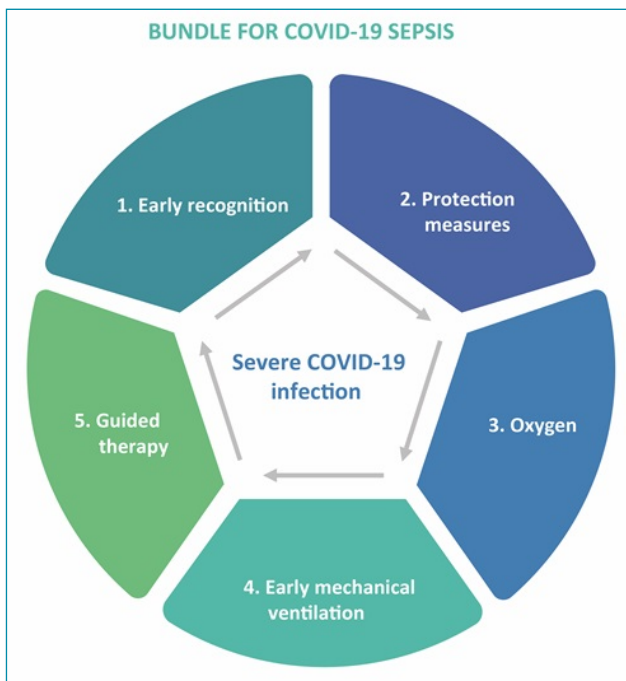


Figure 2. Bundle for COVID-19 sepsis

symptoms and deterioration have been the most important characteristic of this pandemic.

2. **Protection, handwashing, and isolation measures:** These measures are what have helped lower the pandemic's peak. Personal protection for health care personnel who care for these patients is essential. Countries like Spain have described up to 12% contagion of the health care team<sup>1</sup>. Universal isolation measures will avoid nosocomial contagion and dissemination of the virus (SARS-CoV-2).
3. **Oxygen therapy:** Given that the lung is the main organ affected, oxygen delivery systems should be offered quickly, according to the patient's needs. Consider using non-rebreather masks with high-efficiency face masks (N95 or FFP) over them<sup>1</sup>. This technique has also been described with the use of high-flow nasal cannulas (HFNCs) to avoid aerosol dissemination<sup>2,10</sup>. The non-invasive ventilation (NIV) should be limited and recommended only if adequate levels of staff protective equipment is available.
4. **Early invasive mechanical ventilation:** In the experience of the most severely affected countries (China, Italy, and Spain, given their greater number of cases), rapid initiation of mechanical ventilation has been essential for those who have survived<sup>1,2</sup>. Delaying intubation and ventilatory support has been associated with greater mortality<sup>5</sup>. Adequate preparation for intubation, pre-oxygenation without positive pressure ventilation, and rapid sequence of intubation using videolaryngoscope should be considered<sup>1,2</sup>. The presenting pathophysiological pattern will guide the ventilatory support which will cause the least alveolar damage. It may be useful to establish an "optimal" PEEP graphically, numerically or using an esophageal balloon with monitoring with volumetric capnography<sup>12</sup>. The hypoxic pulmonary vasoconstriction phenomenon may be leading to severe pulmonary hypertension, right heart failure, and death. Therefore, reports have indicated that the early use of nitric oxide could be useful. The prone position should be considered when  $PaO_2/FiO_2$  is  $<150$ <sup>12</sup>.
5. **Treatment aimed at modifying the clinical course:** The studies published to date have not described a specific treatment which could be universally recommended. The use of hydroxychloroquine, azithromycin, and ritonavir, among others, has been reported with inconsistent results<sup>13</sup>. In this respect, the presenting immunophenotype in the disease's severe phase could help guide treatment. If we posit that the scenario meets the MAS criteria with immunoparalysis

related to MOF (TNF-alpha <200pg / ml), immunoglobulins or colony stimulating factor could be useful<sup>8,9</sup>. Likewise, in patients with TAMOF (<57% ADAMTS-13 activity), plasmapheresis, or eculizumab could be considered<sup>9</sup>.

## CONCLUSION

The bundle for COVID-19 sepsis can be a useful strategy for the control of the disease, as it has been demonstrated in sepsis of another etiology. Studies are needed to confirm its utility and its potential to modify the clinical course in this disease.

## TO EDITOR

In December 2019, for the first time in history, a new viral infection was reported, causing severe respiratory infection and extremely high mortality rates<sup>1</sup>. The virus, which based

on its genetic sequence belongs to the *Betacoronavirus* genus, has been found to be highly related to the SARS virus and is known as SARS-CoV-2 (COVID 19)<sup>2</sup>. We have observed its epidemiological behavior with concern, noting that its main characteristic has been its high transmissibility, severity, and lethality, particularly in people over the age of 60<sup>3,4</sup>. We have read with great interest the article published in your magazine entitled: “*Pediatric COVID-19: An Update on the Expanding Pandemic*” by Al-Hajjar and McIntosh<sup>5</sup>. It is with great interest we see that this pandemic is progressing rapidly, and these papers updates are necessary in pathophysiological, diagnostic, and treatment aspects.

## AUTHORS' CONTRIBUTION

**JFS:** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **WBC:** Conceptualization, Writing – Original Draft, Writing – Review & Editing

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