

# COVID-19 and Sepsis Co-infection: The Impact of Advanced Detection and Diagnosis

Sepsis is characterised as life-threatening and fast-progressing organ dysfunction caused by a dysregulated host response to infection. Sepsis shares several clinical manifestations with COVID-19 including fever, laboured/rapid breathing, and increased heart rate,<sup>1</sup> making diagnosis challenging.

SARS-CoV-2 co-infection, where an individual may be infected with the virus and one or more additional pathogens concomitantly, leads to both innate and adaptive immune responses which, in some cases of severe disease, can become dysfunctional and cause significant lung and systemic pathology.<sup>2</sup> This lung damage and dysregulated immune response in severe COVID-19 pneumonia puts these patients at an increased risk of secondary infection with bacteria, fungi, or other viruses. In addition, individuals with pre-existing conditions could be more susceptible to severe COVID-19 disease if infected.

Rapid diagnosis is critical to identifying and diagnosing such infections and determining the correct course of treatment as quickly as possible. However, as COVID-19 has a variety of clinical manifestations, it may be challenging to distinguish co-infections which share clinical features, such as sepsis. It is vitally important to rapidly detect co-infection in COVID-19 patients and accurately identify causative pathogens to deliver effective treatment.

## Challenges in Patient Diagnosis and Treatment

There are several factors that can complicate patient diagnosis and treatment in the case of co-infection. Secondary infection could be more easily missed and go undiagnosed in the face of SARS-CoV-2 primary infection, especially if symptoms overlap. Diligent testing of COVID-19 patients for other infectious diseases is therefore vital. Importantly, patients with severe COVID-19 disease in intensive care units (ICU) are at increased risk of nosocomial infection and should be carefully monitored. Rapid

treatment decisions are needed, particularly in the case of multi-drug-resistant (MDR) microorganisms.

Although the reported incidence of bacterial, fungal, and viral co-infections in hospitalised COVID-19 patients is relatively low,<sup>3</sup> when present they may cause severe diseases with poorer outcomes. For example, many studies have reported a higher incidence of secondary infections in patients admitted to ICU,<sup>4,5</sup> and those diagnosed with secondary infections had lower discharge rates and higher mortality rates than those without secondary infection.<sup>6</sup> Researchers are still looking to determine whether this outcome is a function of longer ICU stay, concomitantly administered medications (e.g., antibiotics, immunomodulators), the immunocompromising effects of severe COVID-19 itself, or other factors.<sup>7</sup>

## Sepsis

The high prevalence and poor recognition of sepsis make it a considerable burden to public healthcare systems worldwide. The repercussions associated with longer bed stays and prolonged antimicrobial treatment impact both patient wellbeing and the cost to hospitals. Treatment with broad-spectrum antibiotics is the first step in tackling sepsis. Although these drugs can help bring the infection under control, without knowing the identity of the microorganism and providing targeted antimicrobials, the severity of sepsis can rapidly increase.

Bloodstream infections have been reported to represent approximately 20% of ICU-acquired cases of sepsis and septic shock,<sup>8</sup> and a growing body of research demonstrates the increased risk of secondary infection in hospitalised patients with severe COVID-19, particularly ventilated ICU patients.<sup>9</sup> Most SARS-CoV-2-infected patients admitted to ICU show a dysregulated host response characterised by hyperinflammation, alterations in coagulation, and dysregulation in the immune response that contributes to multiple organ failure – common clinical features to sepsis.

There are two mechanisms to consider when evaluating the incidence of sepsis

in COVID-19 ICU patients. Firstly, many patients with severe COVID-19 meet the Third International Consensus Definitions for Sepsis (Sepsis-3), which define sepsis as “a life-threatening condition that arises when the body’s response to infection damages the host’s own tissues”.<sup>10</sup> Therefore, SARS-CoV-2 viral infection is likely the most common cause of sepsis. Secondly and perhaps most easily overlooked, co-infection with bacteria, fungi, or another virus could lead to bloodstream infection and sepsis.

One multi-centre study reported the increased risk of ICU bloodstream infection for COVID-19 over non-COVID-19 critically ill patients after 7 days of ICU stay, which was associated with the use of IL-1 or IL-6 receptor antagonists in critically ill COVID-19 patients.<sup>11</sup> Coagulase-negative Staphylococci were the most prevalent microorganisms identified in COVID-19 patients with ICU bloodstream infections. While the source of infection in the majority of cases was unknown, catheter and pulmonary routes were the most frequently reported known sources.

There is a clinical need to better understand the relationship of molecular mechanisms dysregulated or mediated by SARS-CoV-2 that can lead to sepsis, the risk factors for co-infection in COVID-19 patients that can lead to hospital-acquired bacterial or fungal sepsis, and how COVID-19-related sepsis impacts morbidity and mortality.

The mortality rate of patients with septic shock who receive inappropriate antimicrobials has been reported at approximately 90%, whereas those who received appropriate antibiotics had a fivefold mortality rate reduction.<sup>12</sup> If this is translated into the current COVID-19 setting, clinicians stand to drastically improve outcomes by rapidly providing targeted antimicrobial treatment to COVID-19 patients with sepsis.

The threat of MDR among gram-negative and gram-positive pathogens has increased worldwide over recent years, impacting both hospital and community acquired infections. The COVID-19 pandemic presents a risk to

antimicrobial stewardship as many patients hospitalised with severe disease are given antibiotics as empiric treatment, despite no bacterial infection being identified. This, plus the greater risk of ICU patients developing serious secondary infections and sepsis, accelerates the emergence of AMR pathogens.

### Identifying and Diagnosing Co-infections

Appropriate and timely clinical decisions depend on rapid and accurate identification of the causative pathogen in sepsis cases. Although culture-based methods remain the 'gold standard', molecular assays are increasingly used as faster alternatives.<sup>8</sup> Multiplex PCR tests applied on positive blood culture (PBC) have been shown to decrease the time to an optimised antibiotic regimen (spectrum narrowing or broadening or even cessation when a contaminant was identified) but neither the mortality nor the length of stay.<sup>13</sup>

However, such methods are limited by the number of PCR probes and require expertise and strong collaboration between microbiologists and clinicians. Matrix assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS) is a user-friendly and reliable solution that can be used to identify microorganisms directly from PBC and is capable of rapid phenotypic resistance detection.

### Looking Ahead

Sepsis is the result of the body's immune response damaging tissues and organs when attempting to fight an infection, with potentially devastating consequences. When appropriate treatment is given quickly, patients can make a full recovery, but poor recognition of symptoms and delays in identifying the causative pathogen can lead to life-changing morbidity and often mortality. Studies have shown that for every hour appropriate treatment is delayed, the chance of survival decreases by 7.6%.<sup>14</sup>

The scientific community is responding to the ongoing threat of COVID-19 by learning as much as possible about how the disease spreads, how it affects people and communities, the long-term impact on the body after infection, and the incidence of concomitant infection with other pathogens. Microbiologists, epidemiologists, virologists, and pathologists have generated vast bodies of research investigating the structure of SARS-CoV-2, its mechanism of infection, the COVID-19 disease pathway and how it affects individuals differently, studying the long-



term effects of COVID-19 and, more recently, studying and tracking mutations that could lead to new viral variants. In addition, more research is unfolding to better understand the challenges of diagnosing and managing co-infections like sepsis.

However, research remains in the early stages and there is not yet a clear picture of how co-infection impacts clinical outcomes or if existing infections predispose individuals to poorer COVID-19 resilience. Rapidly identifying secondary pathogens and diagnosing such co-infections is vital to determining the correct course of treatment and improving patient outcomes. Microbial detection and identification tools, are not only contributing to research discoveries, but allow clinical microbiologists to make fast and well-informed treatment decisions that, for critically ill COVID-19 patients, can make the difference between life or death.

For more information visit <https://www.bruker.com/en/products-and-solutions/microbiology-and-diagnostics/customer-information-covid-19.html>

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