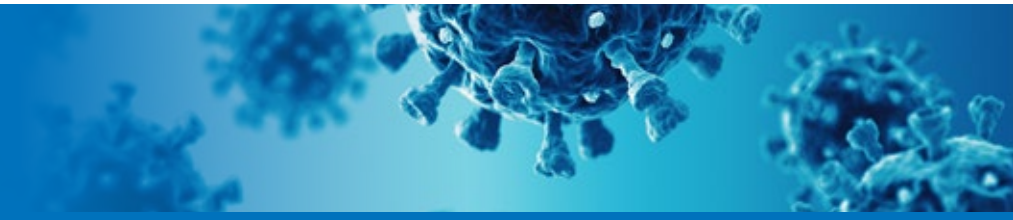
Whitepaper



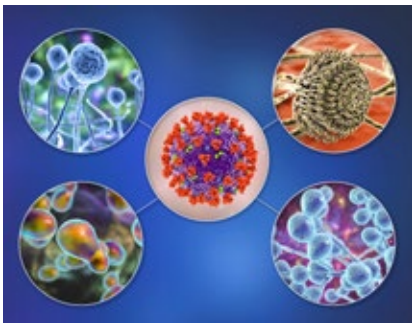
COVID-19 and co-infection: The importance of vigilant and advanced detection and diagnostic capabilities

Abstract

The global effort to contain the novel coronavirus (COVID-19) has seen extraordinary worldwide collaboration from healthcare workers, researchers, industry bodies, and governments. 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. An increasing amount of research is uncovering the true impact of secondary bacterial, fungal, and viral infections in COVID-19 patients. Rapid diagnosis is critical to identifying and diagnosing such infections and determining the correct course of treatment as fast 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 invasive pulmonary aspergillosis (IPA) or tuberculosis (TB). This paper discusses the importance of quickly detecting co-infection in COVID-19 patients and accurately identifying causative pathogens to deliver effective treatment. We review the current literature evaluating a range of parameters relating to co-infection and secondary infection including increased morbidity and mortality, implications for diagnosis and treatment, and recommendations on approaches to antimicrobial stewardship, for four key disease states/pathogens: fungi, mycobacteria, sepsis, and human immunodeficiency virus (HIV).

Introduction

Since the World Health Organization (WHO) officially announced the novel coronavirus (COVID-19) outbreak as a pandemic on 11 March 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has continued to challenge healthcare systems worldwide. A year later, as of 5 May 2021, there have been 153,738,171 confirmed cases of COVID-19 globally, including 3,217,281 deaths, reported to WHO, and a total of 1,047,709,623 vaccine doses administered as of 4 May 2021 [1]. Healthcare systems have come under immense pressure in many regions and some countries are still battling severe waves of the virus.



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. Another important but complex area of research is SARS-CoV-2 co-infection, where an individual may be infected with the virus and one or more additional pathogens concomitantly. SARS-CoV-2 infection 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 [2]. 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.

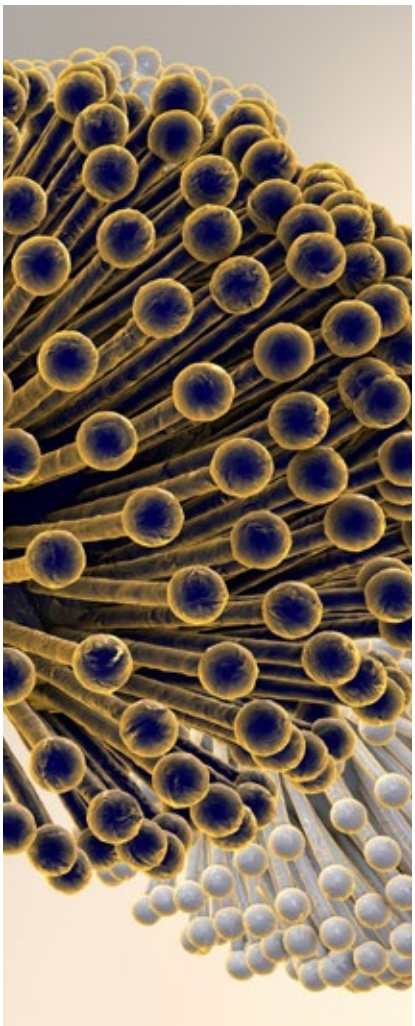
There are several factors that can complicate patient diagnosis and treatment in the case of co-infection. Secondary infection could be more easily missed and go undiagnosed in the face of SARS-CoV-2 primary infection, especially if symptoms overlap. Diligent testing of COVID-19 patients for other infectious 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 as rapid treatment decisions are required, particularly in the case of multi-drug-resistant (MDR) microorganisms.

Although the reported incidence of bacterial, fungal, and viral co-infections in hospitalized COVID-19 patients is relatively low [3], 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 [4, 5], and those diagnosed with secondary infections had lower discharge rates and higher mortality rates than those without secondary infection [6]. 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 [7].

This paper reviews the current research investigating four key co-infections and disease states – fungal infections, tuberculosis (TB), sepsis, and human immunodeficiency virus (HIV) – and their impact on patient management and clinical outcomes. As more research comes to light, microbiologists and healthcare professionals will be armed with a better understanding of co-infection and the importance of lessening the burden of these diseases in the face of the ongoing COVID-19 pandemic.

Fungal infections

Symptoms of some fungal diseases can be similar to those of COVID-19, including fever, cough, and shortness of breath, which is likely to contribute to the underdiagnosis of fungal co-infections. In addition, clinical mycology remains an often underrepresented field of infectious diseases, where diagnosis requires significant expertise and awareness which is often lacking compared with bacterial and viral pathogens.



The main fungal pathogens for co-infections in severe COVID-19 patients are *Aspergillus* and *Candida*, but other infrequent opportunistic species such as *Mucor* and *Cryptococcus* may cause lung infections [8]. These fungal co-infections are becoming more widely reported and can be associated with severe illness and death. Awareness of the possibility of co-infection and accurate diagnosis of the infecting pathogen is vital to reduce delays in antifungal treatment.

Aspergillosis

COVID-19-associated pulmonary aspergillosis (CAPA) has been the predominant fungal disease reported among COVID-19 patients with acute respiratory distress syndrome (ARDS) [9] and many studies have assessed risk factors, incidence, and mortality rates associated with CAPA:

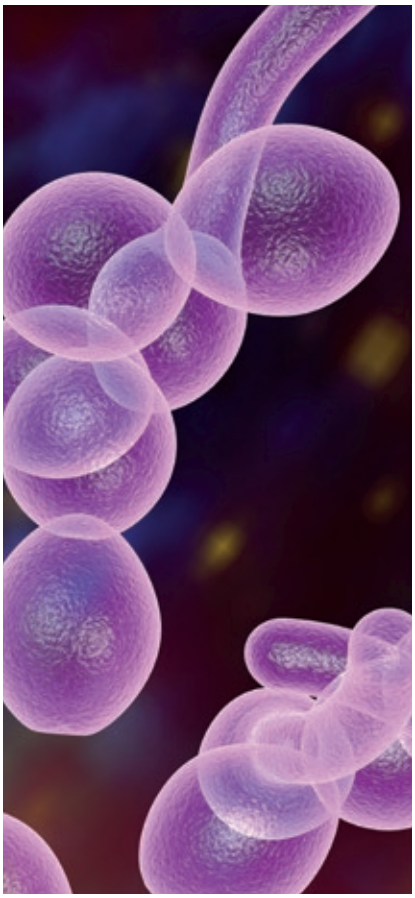
- Risk factors: Patients hospitalized in ICU for COVID-19 share risk factors and underlying diseases reported for invasive fungal infections (IFI), particularly chronic respiratory diseases, corticosteroid therapy, intubation/mechanical ventilation, and severe immune response such as cytokine storm [10].
- Incidence: CAPA incidences vary widely – ranging from 4% [11] to 35% [12] across multiple countries – with differences possibly attributed to the misdiagnosis and underdiagnosis of CAPA, variable access to screening methods, and differences in treatment modalities for severe COVID-19.
- Mortality: Although mortality rates have varied between studies, many have reported high rates between 44% [13, 14] – 67% [15].

Invasive aspergillosis (IA) is notoriously challenging to diagnose, requiring microbiologic and/or histopathologic evidence, and definitions of CAPA are yet to be widely standardized in a clinical setting. It is also important to consider the distinction between *Aspergillus* colonization and invasive infection, and the subsequent classification.

A review of 38 published CAPA cases highlights the diagnostic and therapeutic challenges posed by this novel fungal co-infection and suggested that, for patients with severe COVID-19 pneumonia in critical care, a combination of two or more mycological criteria could aid in the early initiation of antifungal therapy [16]:

- Galactomannan (GM) detection from serum, bronchoalveolar lavage fluid (BALF), or endotracheal aspirates (ETA)
- Isolation of *Aspergillus* sp. from BALF/ETA/sputa
- Serum 1-3 β-d-glucan (BDG) detection
- Detection of *Aspergillus* DNA by real-time polymerase chain reaction (PCR) in blood or respiratory samples.

This approach may aid in establishing early antifungal therapy, which has shown to reduce the mortality rate of COVID-19 patients with *Aspergillus* co-infection [17]. Including rapid and reliable molecular testing such as PCR alongside other biomarkers and culture can reduce the time to diagnosis and support physicians in optimizing patient management.



Fungal infections resistant to antifungal treatment have been described in patients with severe COVID-19, including Azole-resistant *Aspergillus* [18, 19], demonstrating the importance of early diagnosis and the need for resistance surveillance.

Candidiasis

Candida auris is an emerging fungus that can cause outbreaks of severe infections in healthcare facilities. Since the start of the COVID-19 pandemic, outbreaks of *C. auris* have been reported in COVID-19 units of acute care hospitals globally. Patients hospitalized for COVID-19 are at risk of nosocomial infections including candidemia, or bloodstream infections caused by *Candida* [20]. Considering the increase of healthcare-associated *C. auris* outbreaks in the region of the Americas and in the context of the COVID-19 pandemic, the Pan American Health Organization/World Health Organization (PAHO/WHO) recommends that member states build capacity for early detection and effective reporting, with the goal of implementing public health measures to prevent and control its spread in health services [21].

Commercial methods available in standard clinical laboratories often incorrectly identify *C. auris* and as a result, the incidence or prevalence of infections may be underestimated and its management could be inappropriate. Protein analysis, using Matrix-Assisted Laser Desorption/ Ionization Time-Of-Flight (MALDI-TOF) mass spectrometry (MS), with an up-to-date reference library, as well as molecular biology techniques (PCR) have shown to be the most reliable methods for correctly identifying *C. auris* [22, 23].

A multiplex real-time PCR test

Bruker's culture-free real-time PCR kits are designed to improve rapid, targeted results in clinical areas that suffer from poor culture sensitivity or where organism growth rate has an impact on clinical care and health economic outcomes, such as fungal infection.

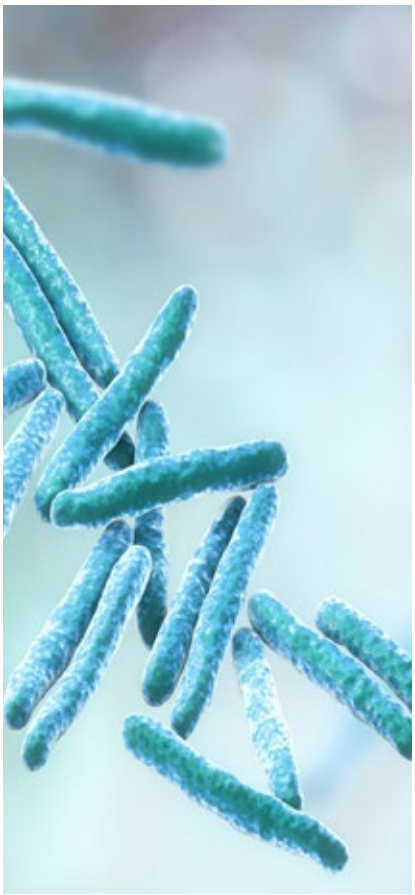
The Fungiplex® Aspergillus IVD Real-Time PCR Kit is designed to detect the primary species associated with invasive aspergillosis. It delivers results in **less than two hours** when performed on DNA extracted from serum, plasma and bronchoalveolar lavage, to support critical clinical decisions on targeted therapy for *Aspergillus* in ventilated patients.

The Fungiplex® Aspergillus Azole-R IVD Real-Time PCR Kit identifies the most common mutations of the Cyp51 gene associated with resistance to the azole class of antifungal drugs.

The Fungiplex® Candida IVD Real-Time PCR Kit rapidly detects the main causative species associated with Invasive Candidiasis, and Fungiplex® Candida Auris RUO Real-Time PCR Kit is a research use only (RUO) PCR assay for the rapid detection of *Candida auris* in hospital hygiene applications.

Designed to run on existing laboratory equipment, Bruker's real-time PCR kits are compatible with most PCR systems and are therefore easily implemented alongside SARS-CoV-2 workflows.

For antifungal susceptibility testing (AFST) of yeast, the MICRONAUT-AM minimum inhibitory concentration (MIC) plates from Bruker enable testing of up to nine antimycotics, making it the ideal solution for testing the resistance of organisms originating from hospital acquired infections, such as *Candida auris*.



Candida auris is a multidrug-resistant (MDR) microorganism, and data is showing rapid development of resistance to the antifungal family echinocandins – the first line of treatment. Local resistance surveillance is imperative to guide treatment recommendations and reducing death from COVID-19 in patients with severe fungal co-infections.

Tuberculosis

Tuberculosis (TB), a chronic disease caused by *Mycobacterium tuberculosis*, is one of the top ten causes of mortality and causes high burdens in developing countries. TB shares many clinical presentations with COVID-19, including cough and fever, which could impact the speed and accuracy of diagnosis and prognosis of either disease. Co-infections of TB with past coronavirus epidemics like SARS and Middle East respiratory syndrome (MERS)-CoV posed a major threat in spread of the disease [24], highlighting the importance of a better understanding of the interactions between *M. tuberculosis* and SARS-CoV-2, for the development of therapeutic strategies against co-infection.

TB co-infection with COVID-19 is also of particular concern because COVID-19 itself or use of immunomodulators in moderate-severe COVID-19 may lead to reactivation of latent TB. In addition, pre-existing TB disease and underlying lung condition will affect the clinical categorization (for severity) of COVID-19. Co-existing active TB disease may predispose individuals to severe COVID-19, and there is also a risk of drug-drug interactions as well as additive hepatotoxicity due to simultaneous use of anti-tubercular drugs and available COVID-19 therapeutic options [25].
A study of 86 suspected COVID-19 cases from participating primary-care hospitals in Shenyang, China, suggests that individuals with latent or active TB may be more susceptible to SARS-CoV-2 infection, and that COVID-19 disease progression may be more rapid and severe [26]. The study recommends that *M. tuberculosis* infection status of COVID-19 patients should be checked routinely at hospital admission.

A review of 6 studies indicated that TB increases susceptibility to COVID-19, as well as contributing to the worsening of its symptom's subset [27]. Individuals in a situation of social vulnerability or presenting comorbidities were found to have a worse prognosis. On the other hand, there are still no data regarding the influence of SARS-CoV-2 on the TB progression.

Drug resistant TB is becoming increasingly prevalent, and is categorized into:

- Multidrug-resistant TB (MDR TB), caused by TB bacteria that are resistant to at least isoniazid and rifampicin, the two most potent TB drugs.
- Extensively drug-resistant TB (XDR TB), which is rarer, is resistant to isoniazid and rifampicin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e. amikacin, kanamycin, or capreomycin).

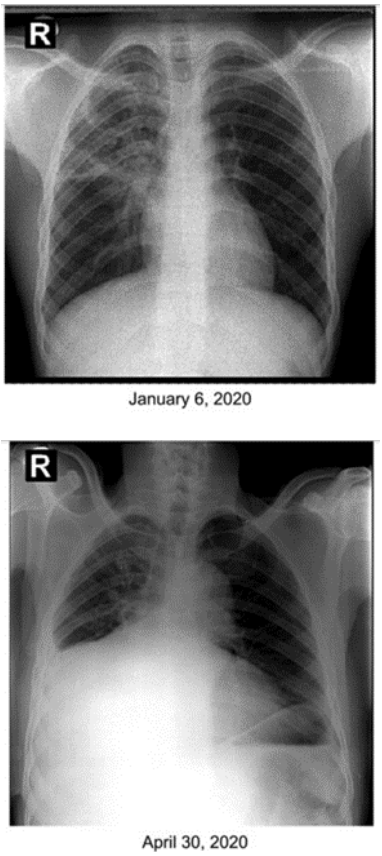


Figure 1: Chest radiograph at patient's first presentation with multidrug-resistant tuberculosis (MDR TB) (top) and when co-infected with SARS-CoV-2 (bottom). Reproduced from [28] in accordance with Creative Commons Attribution 4.0 International (CC BY 4.0).

Reports of MDR TB in COVID-19 patients are emerging, which outline COVID-19 as a threat to successful anti-MDR-TB drug therapy and describe the importance of dedicated screening protocols [28]. Co-infection also leads to a potential increased risk of drug interactions, where MDR TB treatment regimens include therapies that carry potential side effects that could be exacerbated by symptoms associated with COVID-19.

Early and reliable diagnostics are fundamental for successful TB treatment. Culture methods are time-consuming and laborious, whereas nucleic acid amplification tests (NAAT), which enable fast screening, have proven themselves in practice. These molecular genetic assays allow detection of the *M. tuberculosis* complex (MTB) directly from patient specimens with fast turnaround times, allowing clinicians to rapidly screen for TB and improve patient outcomes. Dedicated PCR tests are also capable of detecting MDR TB and XDR TB, which helps to prevent the further spread of resistant TB and offer the most appropriate therapy.

Rapid TB screening and susceptibility testing

Bruker's FluoroType® MTB test uses PCR and an innovative fluorescent-based technology for the detection of *M. tuberculosis* complex directly from pulmonary and extrapulmonary clinical specimens. The results are available within only three hours – making FluoroType® MTB the ideal TB screening test.

FluoroType® MTBDR is based on LiquidArray® technology, which enables reliable MDR-TB diagnostics in just 2.5 hours. This single-tube multiplex PCR can detect the *M. tuberculosis* complex and identify mutations within the *rpoB*, *inhA* and *katG* genes.

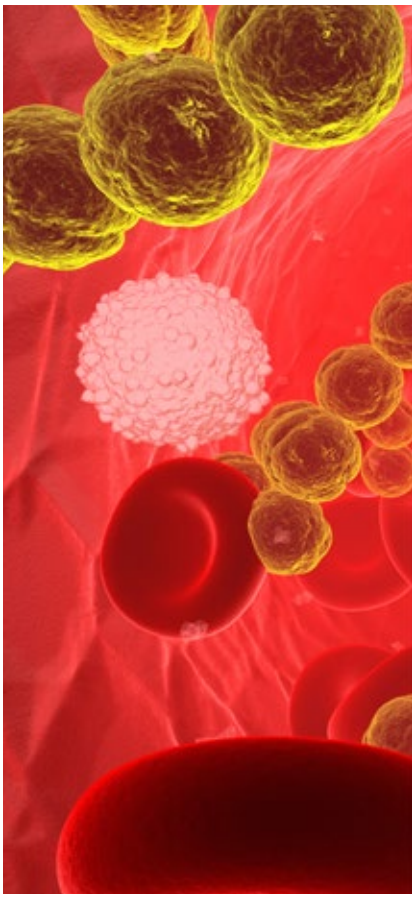
The GenoType MTBDR*plus* molecular genetic assay, based on PCR technology, allows the simultaneous detection of *M. tuberculosis* complex and its resistance against rifampicin and isoniazid directly from clinical specimens.

The GenoType MTBDR*sl* molecular genetic assay detects *M. tuberculosis* complex and its resistances to fluoroquinolones and aminoglycosides/cyclic peptides (and ethambutol).

Sepsis

Sepsis is characterized 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, labored/rapid breathing, and increased heart rate [29], making diagnosis challenging.

Bloodstream infections have been reported to represent approximately 20% of ICU-acquired cases of sepsis and septic shock [30], and a growing body of research demonstrates the increased risk of secondary infection in hospitalized patients with severe COVID-19, particularly ventilated ICU patients [31].



Most SARS-CoV-2–infected patients admitted to ICU show a dysregulated host response characterized 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" [32]. 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.

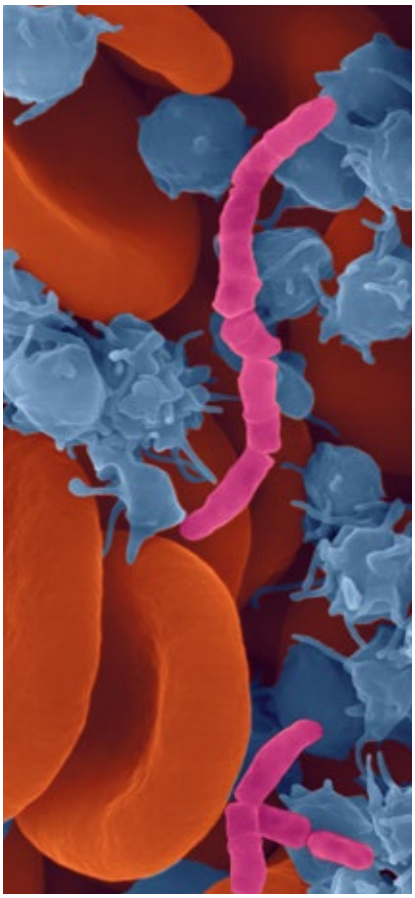
One multi-center study reported the increased risk of ICU bloodstream infection for COVID-19 over non-COVID-19 critically ill patients after 7 days of ICU stay, which was associated with the use of IL-1 or IL-6 receptor antagonists in critically ill COVID-19 patients [33]. Coagulase-negative Staphylococci were the most prevalent microorganisms identified in COVID-19 patients with ICU bloodstream infections, and in the majority of cases, the source of infection was unknown, but 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 [34]. 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 multi-drug resistance 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 hospitalized 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.

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 [30]. Multiplex PCR tests applied on positive blood culture (PBC) have been shown to decrease the time to an optimized antibiotic regimen (spectrum narrowing or broadening or even cessation when a contaminant was identified) but neither the mortality nor the length of stay [35].



However, such methods are limited by the number of PCR probes and require expertise and strong collaboration between microbiologists and clinicians. 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.

Rapid pathogen ID

As a fast and cost-effective tool for unbiased identification of micro-organisms, Bruker's MALDI Biotyper® (MBT) can be integrated into almost any clinical laboratory environment, allowing microbiologists to obtain an identification from culture in minutes, based on proteomic fingerprinting.

Bruker's MBT Sepsityper® IVD Kit, used in conjunction with the IVD-CE MALDI Biotyper®, can identify pathogens from positive blood cultures within 15-20 minutes, in a cost-effective, efficient workflow that allows clinicians to improve patient care.

Antimicrobial resistance testing (AST)

Detecting resistance to key antimicrobials is enabled by combining MBT Sepsityper® workflow with MBT STAR®-BL IVD Assays.
The bacterial cells isolated from positively flagged blood cultures can be used in the MBT STAR®-BL IVD assays for beta-lactamase activity detection.

Based on the broth microdilution procedure, MICRONAUT phenotypic antimicrobial susceptibility testing (AST) plates from Bruker deliver minimum inhibitory concentration (MIC) for a broad range of antimicrobials and enable the detection of important resistance mechanisms, such as:

- ESBL (extended spectrum ß-lactamases)
- AMP-C (Aminopenicillin inactivating cephalosporinase)
- OXA-48-like type D carbapenemases
- MBL (metallo-ß-lactamases)
- KPC (*Klebsiella pneumoniae carbapenemase*)

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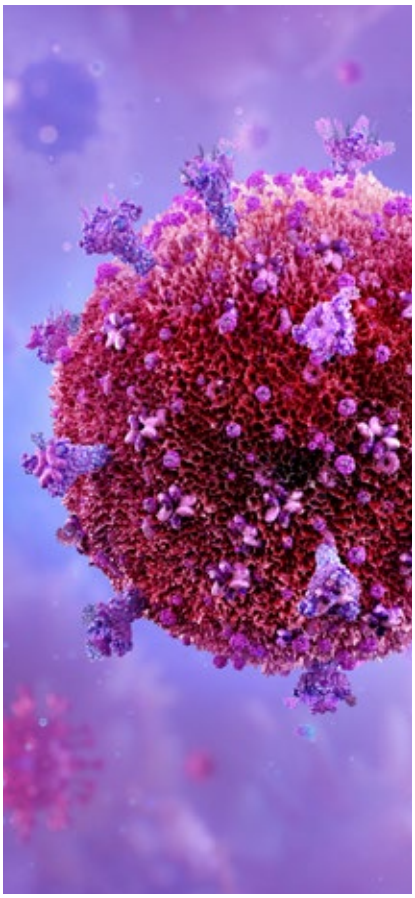

HIV

People living with HIV (PLHIV) who have a compromised immune system, including those with a low CD4 count or high viral load, may be less able to cope with infectious diseases such as COVID-19 and any bacterial or fungal co-infections. However, the rate of COVID-19/HIV co-infection and impact on patient outcomes is not clear, and reports differ over morbidity and mortality rates. Studies are often limited by small patient groups – many including a single case report of HIV co-infection – and results depend heavily on HIV epidemiology in specific geographies.

For example, one study of a cohort of patients from Western Cape Province, South Africa, reported that HIV was associated with a doubling of COVID-19 mortality risk [36], whereas a systemic literature review found that PLHIV are largely affected by similar features of disease risk and progression as those without HIV [37], and studies from the UK [38], Germany [39] and the United States [40] report no excess morbidity or mortality in HIV patients.

A key factor determining whether HIV increases risk from COVID-19 infection is whether the patient is receiving antiretroviral therapy (ART). ART is widely used for treating PLHIV and anti-HIV drugs have even been proposed as possible treatments for COVID-19 [41] [42]. Therefore, HIV-infected patients receiving standard ART may be at increased risk from COVID-19, and such risk may be skewed in regions where ART is less well distributed.

Researchers are also working to understand the impact of TB/HIV co-infected patients on COVID-19 pathogenesis. The interaction between TB and HIV has been extensively studied: without ART, the risk of latent TB infection progressing to active TB disease in PLHIV is greater than in immunocompetent individuals [43]. In addition, management of MDR TB in people living with HIV is complicated by higher rates of drug toxicities that may be exacerbated in the setting of COVID-19 co-infection [28].

HIV drug resistance (HIVDR) is a growing concern that, if not addressed, could jeopardize the successful scale up of ART that has been seen in recent years. An increased incidence of HIVDR could limit the possible protection that antiretroviral drugs afford HIV patients infected with COVID-19.

Viral load testing

Fast and simple HIV viral load testing is needed to appropriately monitor HIV patients and ensure antiretroviral therapy (ART) programs are followed to minimize comorbidity with COVID-19.

Bruker's next-generation PCR thermal cycler and reader, together with the easy-to-use GENERIC® HIV Charge Virale assay enables fast HIV viral load testing to facilitate successful ART. By using the same automated extraction protocol as COVID-19 assays, labs can quickly implement the GENERIC® HIV Charge Virale assay with minimal training.

Future considerations

The volume of literature surrounding COVID-19 research continues to grow at a significant pace. Around 4% of the world's research output was devoted to the coronavirus in 2020, according to one database, as the scientific community endeavors to deepen its knowledge of the virus' epidemiology, understand public health and mental health impacts, gather data on hospital mortality, and develop better diagnostics and therapies. In addition, more research is unfolding to better understand the challenges of diagnosing and managing co-infections, such as with fungal pathogens and mycobacteria (TB), and the impact of concomitant disease states such as sepsis and HIV/AIDS.

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, such as those provided by Bruker, 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 all the difference.

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

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