Culture Independent Diagnostics for Immunocompromised Patients with Covid-19 at Risk for Sepsis

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Background

The global pandemic caused by the emergence of the SARS-CoV-2 virus (COVID-19) has led to a burden on healthcare systems worldwide, most notably in patient outcomes and hospital resources.[1]

Critically ill patients and those patients with co-morbidities are more likely to develop COVID-19. These patients are also at a higher likelihood of developing acute respiratory distress and septic shock.[1] Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection[3], can be caused by bacteria, fungus, viruses, or parasites.[4]

Severely ill hospitalized COVID-19 patients are more likely to develop secondary infections that could lead to sepsis and are often initiated on antimicrobial agents[5]. Because of the high likelihood that a severely ill COVID-19 patient will develop a secondary infection, there is a clinical, unmet need for culture-independent laboratory diagnostics that identify pathogens direct from a whole blood sample. Culture-independent tests can reduce the time to detection and identification of causative pathogens without a positive blood culture result. A reduction in the time to species identification may aid in antimicrobial stewardship by reducing the use of unnecessary antimicrobials through more rapid targeted therapy for patients with co-infections.

Figure 1. T2DX Instrument Laboratory Workflow

Figure 2. T2 Biosystems FDA-cleared Assays

T2Candida Panel	T2Bacteria Panel
Sensitivity: 91%[6] Specificity: 99%[6]	Sensitivity: 90%[7] Specificity: 98%[7]
C. albicans *C. tropicalis* *C. parapsilosis* *C. krusei* *C. glabrata*	*E. faecium* *S. aureus* *K. pneumoniae* *P. aeruginosa* *E. coli*
FDA-Cleared CE-marked 1-3 CFU/mL LoD	FDA-Cleared CE-marked 2-11 CFU/mL LoD

T2Candida and T2Bacteria Panel Pathogens

- T2Candida Panel pathogens cover 90% of all *Candida* blood stream infections[6,8]
- T2Bacteria Panel pathogens cover 50%-70% of all bacterial blood stream infections[8,10] and ~90% of ESKAPE pathogens.[7,9,10]
- ESKAPE pathogens are concerning due to their ability to "escape" and survive antibiotic therapy leading to increased morbidity and mortality.[12]

Method

A literature review and analysis of COVID-19 patients was done for suspected pathogens that may cause sepsis[11] as well as the potential benefits of utilizing culture-independent rapid diagnostics in COVID-19 or immunocompromised patients. We examined patients who may have had different variants including Alpha, Delta and Omicron variants of SARS-CoV-2. The review was focused on patients that presented with COVID-19 and those patients who were immunocompromised with possible sequelae of SIRS or sepsis-causing pathogens to determine if there is a need for appropriate therapy to prevent antibiotic resistance, increase intensive care unit bed turnover and improve time to detection/species identification.

Literature Summaries

Puzniak, et al., 2021[11]

Study Design	Multicenter, retrospective cohort analysis of data from 241 US medical facilities. This analysis focused on pathogens, antimicrobial use, and healthcare utilization in hospitalized US patients with and without severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).
Outcomes	• *Staphylococcus aureus* and *Enterococcus spp.* were the most common pathogens detected • The proportion of patients with specimens positive for *Candida spp.* was almost twice as high in SARS-CoV-2 positive patients compared with SARS-CoV-2 negative and untested patients • SARS-CoV-2-positive patients had higher rates of hospital-onset pathogens, greater antimicrobial usage, and extended hospital and ICU length of stay compared with SARS-CoV-2-negative or –untested patients. • A positive pathogen specimen was associated with a longer LOS in all groups. LOS was further increased by the presence of multiple pathogens for SARS-CoV-2-positive patients.

Clancy, Nguyen, 2020[12]

Study Design	Review of published data on bacterial and fungal infections among COVID-19 patients.
Outcomes	• The most common type of infection in ICU patients was bacterial or fungal pneumonia, bloodstream and urinary tract infections (UTI) were also noted. • Median times to ICU admission and onset of secondary infection among patients at 2 hospitals were 10-12 days and 17 days after first COVID-19 symptoms, respectively. Median time to death was 19 days, suggesting that superinfections were often terminal events. • Empiric antimicrobial usage was likely widespread because 25%-70% of severely ill COVID-19 patients manifested evidence of sepsis, and it was very difficult to exclude bacterial or fungal superinfections based on signs and symptoms, physical findings, radiographic abnormalities and laboratory results • Hospitalized patients, especially those who are undergoing mechanical ventilation or otherwise critically ill, are at increased risk for infections, independent of SARS-CoV-2 infection

Giannella et al., 2021[13]

Study Design	Independent meta-analysis including 14 studies comparing antimicrobial and resource utilization with T2 Magnetic Resonance (T2MR) versus blood culture (BC) in patients with suspected bloodstream infection.
Outcomes	• Time to Detection with T2MR: 81 hours faster (p <0.001) • Time to Species ID with T2MR: 77 hours faster (p <0.001) • Patients testing positive on T2MR: received targeted antimicrobial therapy 42 hours faster (p <0.001) • Patients testing negative on T2MR: de-escalated from empirical therapy 7 hours faster (p =0.02 • Length of Stay: intensive care stay was 5 days shorter (p=0.03), and length of hospital stay was 4.8 days shorter (p=0.04)

Conclusion

Utilizing culture-independent diagnostic tests, like the T2Bacteria and T2Candida Panels, and magnetic resonance technology (T2MR) have the potential to impact patient outcomes and management for COVID-19 patients who are at high risk of infection by reducing the time to pathogen detection and identification. Earlier identification of causative pathogens can lead to faster initiation of targeted therapy or de-escalation, thereby reducing the overuse of inappropriate antibiotic therapy, which adds to the global burden of antimicrobial resistance (AMR). The length of ICU and overall hospital stay can also be reduced with culture-independent diagnostics. T2MR may not only save hospital resources but may also reduce hospital costs associated with antimicrobial usage and extended length of stays.

Disclosures

SS and AA are former employees of T2 Biosystems, Inc and MB is an employee of T2 Biosystems, Inc.

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