ICU
MANAGEMENT & PRACTICE

New protocol for respiratory infectious disease diagnosis in ICU

Lower respiratory tract infections (LRTIs) are the leading cause of infectious disease-related deaths worldwide yet remain challenging to diagnose because of limitations in existing microbiologic tests. In critically ill patients, noninfectious respiratory syndromes that resemble LRTIs further complicate diagnosis and confound targeted treatment. New research suggests that a single streamlined protocol offering an integrated genomic portrait of pathogen, microbiome, and host transcriptome may hold promise as a tool for LRTI diagnosis.

Early and accurate determination of acute respiratory disease etiology is crucial for implementing effective pathogen-targeted therapies but is often not possible due to the limitations of current microbiologic tests in terms of sensitivity, speed, and spectrum of available assay targets. In the absence of a definitive microbiologic diagnosis, clinicians may presume symptoms are due to a noninfectious inflammatory condition and initiate empiric corticosteroids, which can exacerbate an occult infection.

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Furthermore, even with negative microbiologic testing, providers often continue empiric antibiotics due to concerns of falsely negative results, a practice that drives emergence of antibiotic resistance and increases risk of *Clostridium difficile* infection.

To address the need for improved LRTI diagnostics, a team of researchers, mostly from University of California - San Francisco, performed metagenomic next-generation sequencing (mNGS) on tracheal aspirates from 92 adults with acute respiratory failure and simultaneously assessed pathogens, the airway microbiome, and the host transcriptome. To differentiate pathogens from respiratory commensals, the researchers developed a rules-based model (RBM) and logistic regression model (LRM) in a derivation cohort of 20 patients with LRTIs or noninfectious acute respiratory illnesses. When tested in an independent validation cohort of 24 patients, both models achieved accuracies of 95.5%.

The next step involved the development of pathogen, microbiome diversity, and host gene expression metrics to identify LRTI-positive patients and differentiate them from critically ill controls with noninfectious acute respiratory illnesses. When tested in the validation cohort, the pathogen metric performed with an area under the receiver-operating curve (AUC) of 0.96 (95% CI, 0.86–1.00), the diversity metric with an AUC of 0.80 (95% CI, 0.63–0.98), and the host transcriptional classifier with an AUC of 0.88 (95% CI, 0.75–1.00). Combining these achieved a negative predictive value of 100%, according to the research team.

"Host transcriptional profiling has gained attention as a promising approach to LRTI diagnosis but is understudied in critically ill and immunocompromised patients, who may be the most likely to benefit from this technology," study authors write. "We addressed this gap by interrogating airway gene expression in a critically ill cohort with 45 percent immunocompromised patients to develop an accurate host transcriptional classifier."

Unlike existing classifiers, host–microbe mNGS offers the advantage of simultaneous species-level microbial identification. This study, however, found some limitations of host–microbe mNGS, including false-positive detection of pathobionts such as H. influenzae and S. pneumoniae in the no-LRTI group.

The relatively small sample size of our derivation and validation cohorts, the authors note, increased the potential for data overfitting and was a limitation of this study. Learning curve estimates, however, indicated that the sample size was optimal for pathogen versus commensal prediction, and adequate for the host classifier, consistent with the estimate from an established sample size prediction tool for high-dimensional classifiers, the authors add.

"Nonetheless, a larger cohort will be necessary to improve the robustness of model performance estimates and better assess synergy resulting from combining host and microbial metrics," the authors conclude.

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