Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/clinicians-roundtable/improved-pathogen-id-in-sepsis-with-clinical-metagenomic-sequencing/32854/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Improved Pathogen ID in Sepsis with Clinical Metagenomic Sequencing

Ryan Quigley:
You're listening to *Clinician's Roundtable* on ReachMD, and this is an *AudioAbstract*. I'm Ryan Quigley, and today, I'll be reviewing the Next GeneSiS trial, a large, multicenter study that asked a critical question: can clinical metagenomic sequencing of microbial cell-free DNA help us identify the pathogens behind sepsis faster *and* more often than traditional blood cultures? This matters because in sepsis, if you miss the bug, you're flying blind on antimicrobials—and *that* can cost lives.

But to fully understand the trial's impact, it helps to look at where things stand now. Blood cultures remain the standard test in sepsis, but they're slow, often negative even when infection is real, and prone to contamination. As a result, clinicians are left to start broad-spectrum therapy and hope they guessed right. But the good news is that metagenomic next-generation sequencing, which scans plasma for microbial DNA without needing to preselect targets, offers a broader, faster, and potentially more precise approach.

So what did this study do? The Next GeneSiS trial was a prospective, observational study conducted across 17 intensive care units in Germany between 2019 and 2020. It enrolled 491 adults with sepsis or septic shock. Each patient had blood drawn for both blood culture and plasma metagenomic sequencing at the time of diagnosis and again at 72 hours. An independent panel of infectious disease experts then reviewed the sequencing results to determine whether they were clinically plausible and whether they might change antimicrobial therapy.

And so here's what the investigators found. At the initial sampling, next-generation sequencing identified a likely pathogen in 76.2 percent of patients, compared with just 28.4 percent by blood culture. At seventy-two hours, sequencing remained positive in 63.8 percent of patients, while cultures were positive in only 8.6 percent. Overall, metagenomic sequencing detected a likely pathogen in about 70 percent of patients, which is more than triple the amount of standard blood cultures. It's also important to note that over 98 percent of all sequencing results were judged to be clinically plausible by the expert panel.

Now, in terms of the organisms that showed up, E. coli topped both methods, but next-generation sequencing detected more species per patient, revealing frequent polymicrobial infections. It also picked up anaerobes and fungi that standard cultures often missed.

So given these results, could they change our management approach? According to independent reviewers, the answer is yes. In about one-third of patients, the sequencing data would have prompted an antimicrobial adjustment. Most of those changes were de-escalations, but some called for escalation to cover newly identified pathogens.

These findings are important because faster and broader pathogen detection could help clinicians tailor therapy sooner, avoid unnecessary antifungal or antiviral coverage, and reduce toxic or redundant combinations. For instance, among patients who were sequencing-positive but culture-negative, those who may have been inadequately treated had longer ICU stays and more days requiring organ support.

But of course, there are caveats to note here. This was an observational study, so it can't prove causality. And all sequencing was performed after the study period, so turnaround time and real-time clinical impact weren't measured. Lastly, despite rigorous controls, trace contamination remains a possibility, and expert recommendations could have been influenced by stewardship principles. Given

these limitations, the authors note that a randomized trial testing real-time sequencing-guided management is already underway.

So with all this being said, the clinical takeaway is that in adults with sepsis or septic shock, plasma metagenomic sequencing identified plausible pathogens far more often than blood cultures, and experts would have changed antimicrobial therapy in roughly one in three patients based on those results. But until real-time trials are complete, sequencing may be a valuable complementary tool, especially when cultures are negative or the clinical picture suggests a complex, polymicrobial infection.

This has been an *AudioAbstract* for *Clinician's Roundtable*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference

Brenner T, Decker SO, Vainshtein Y, et al. Improved pathogen identification in sepsis or septic shock by clinical metagenomic sequencing. *J Infect*. 2025;91(3):106565. doi:10.1016/j.jinf.2025.106565