27th ECCMID Vienna, Austria 22 – 25 April 2017
The congress of ESCMID

Session: OS156 Time is crucial - direct detection

Category: 4b. Diagnostic bacteriology – non-culture based, including molecular and MALDI-TOF

24 April 2017, 17:00 - 17:10
OS0782

Liquid biopsy for infectious diseases: a novel next-generation sequencing assay to detect cell-free pathogen DNA in plasma from individuals with deep infections

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Background: The diagnosis of life-threatening deep infections frequently requires invasive sampling of infected tissue to provide a microbiologic diagnosis. These procedures can lead to increased morbidity in patients and add significant cost to a hospitalization. The ability to reliably diagnose these infections using a non-invasive test would allow targeting of anti-infective therapy more effectively while significantly reducing the number of unnecessary procedure-associated complications. We have developed a next-generation sequencing (NGS) assay capable of detecting cell-free pathogen DNA in plasma. Here we describe the application of this non-invasive assay in identifying pathogens at deep infection sites.

Material/methods: Patients with biopsy-proven infections were identified in the microbiology laboratory. These included patients who had diagnostic procedures performed on brain, lung, heart, lymph node, or other deep body tissue types. Residual plasma obtained from prior to the biopsy was used for NGS analysis. Cell-free DNA was extracted from plasma, libraries prepared, and NGS applied. After the removal of sequences associated with human DNA, remaining reads were aligned against a pathogen reference-sequence database. Relative abundance of each individual microorganism was estimated and pathogens present at high statistical significance were identified.

Results: A total of 60 patients were identified, having both a microbiologically-confirmed infection from an invasive procedure and pre-procedure plasma available for NGS testing. For these cases, parallel non-invasive testing such as blood and urine cultures, PCRs, and serology were unable to provide a definitive diagnosis. Our assay successfully detected pathogen DNA matching the invasive

microbiologic diagnosis in 27/60 cases (45%). The results included the correct identification of fungi including Candida, Aspergillus, and Rhizopus sp in 8/20 cases (40%), as well as *Mycobacterium tuberculosis* and non-tuberculous Mycobacterium in 4/9 cases (44.4%).

Conclusions: We have developed a novel NGS plasma-based assay capable of detecting cell-free pathogen DNA that originated from deep infection. Our open-ended assay can detect pathogens over a broad range of viruses, bacteria, and fungi, including both yeasts and molds. As demonstrated by our results, the non-invasive plasma assay can aid in the identification of a causal pathogen in cases of deep infections. This test would be particularly useful when an invasive diagnostic procedure is delayed, or impractical due the patient's clinical status.