Clinical Utility of Metagenomic Next-Generation Sequencing in Fever of Unclear Etiology: a Single Center Retrospective Cohort Study

Marilyne Daher[1], Roumen Iordanov[2], Ahmed M. Hamdi[2]

[1]Department of Internal Medicine, Baylor College of Medicine; [2]Department of Internal Medicine, Division of Infectious Diseases, Baylor College of Medicine

Background

- Metagenomic next-generation sequencing (mNGS) utilizes untargeted genetic sequencing to identify a large number of pathogens.
- Advantages include comprehensive sequencing analysis, identification of organisms that are difficult to isolate via conventional methods, high taxonomic resolution, and fast turnaround time.
- Our objective was to evaluate clinical utility of mNGS in hospitalized patients with fever of unclear etiology.

Methods

- We retrospectively reviewed charts of hospitalized patients with 'fever of unclear etiology' (defined as ≥2 fevers [>38.3℃], 4 hours apart without apparent source) and mNGS testing between June 2017 and July 2021.
- Immunocompromised patients were excluded.
- Clinical utility was defined using Hogan et al.'s standardized criteria(1), shown in Figure 1.

Positive Clinical Impact

- New diagnosis based on mNGS
- Earlier diagnosis based on mNGS vs conventional methods
- Avoidance of invasive interventions
- Initiation of appropriate therapy
- Appropriate escalation of therapy
- Appropriate de-escalation of therapy
- mNGS confirmed clinical diagnosis

Neutral Clinical Impact

- mNGS showed new organism but not acted upon
- mNGS confirmed conventional method's diagnosis
- mNGS negative and not acted upon
- Patient died prior to mNGS results

Negative Clinical Impact

- mNGS led to unnecessary treatment
- mNGS led to unnecessary diagnostic evaluation
- mNGS led to longer length of stay

Figure 1: Hogan et al. Standardized Criteria for Clinical Impact of mNGS

Results

- Our study consisted of 72 patients, median age 56 (19-84), 62.5% of whom were male.
- The most common chief complaints were cough (26.4%), abdominal pain (16.7%), and shortness of breath (15.3%). All patients had a fever at time of evaluation.

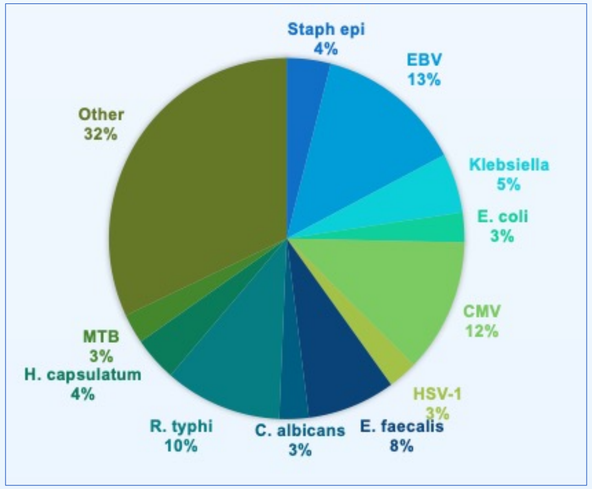

Figure 2: Organisms Identified on mNGS

- Median turnaround time of mNGS was 26 hours.
- ≥1 organism was reported in 65.3% of cases.
- Organisms identified on mNGS are shown in Figure 2. Most commonly identified organisms were EBV (N=10; 13.3%), CMV (9; 12.0%), and Rickettsia typhi (8; 10.7%).
- mNGS had a positive clinical impact in 40.3% of cases, negative impact in 2.8%, and no impact in 56.9% of cases (Figure 3).

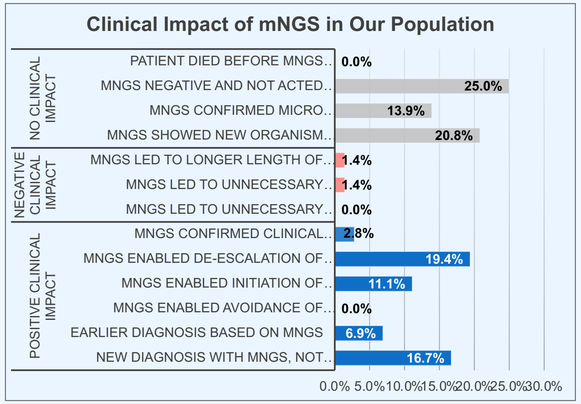

Figure 3: Clinical Impact of mNGS based on Hogan et al.'s Standardized Criteria

- Of those with an infectious etiology of fever (N=38), 86.8% had ≥1 organism identified on mNGS.
- Of those with a non-infectoius etiology (N=16), only 43.8% had an organism identified on mNGS.
- Concordance between the organism(s) identified on mNGS and the etiology of fever was 81.8%.
- On logistic regression analysis: older age was the only factor associated with a higher odd of positive clinical impact (OR 1.37; p=0.049).

Discussion

- Our rate of positive clinical impact is consistent with other studies that have ranges from 7.3%(3) to 43%(4).
- A comparison of our outcomes to those in the literature is shown in Figure 4.
- In our study, a positive impact was mainly driven by the ability to de-escalate antimicrobial therapy, highlighting the importance of careful evaluation of mNGS results, with potential for antimicrobial stewardship.

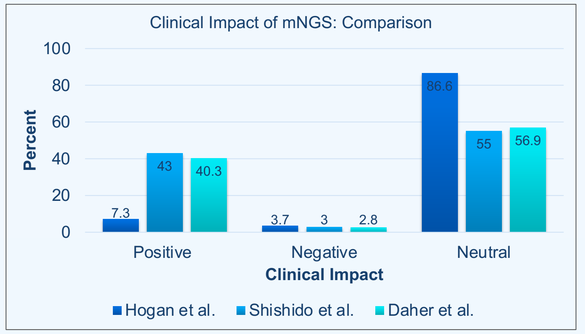

Figure 4: Comparison of Clinical Impact of mNGS in our study vs literature

Conclusion

- mNGS is a valuable tool that will likely play a larger role in the ID physician's toolbox in the future.
- One of the challenges of this tool is its appropriate use in the clinical setting given its high degree of sensitivity.
- To maximize benefits and avoid negative clinical impacts, ordering and interpretation of such diagnostic tools should be guided by infectious disease specialists.
- Further studies are warranted to identify patient and disease characteristics that maximize the effectiveness of mNGS testing.

References

1. Hogan CA et al. Clinical Impact of Metagenomic Next-Generation Sequencing of Plasma Cell-Free DNA for the Diagnosis of Infectious Diseases: A Multicenter Retrospective Cohort Study. Clin Infect Dis. 2021 Jan 27;72(2):239-245.
2. Morales M. The Next Big Thing? Next-Generation Sequencing of Microbial Cell-Free DNA Using the Karius Test. Clinical Microbiology Newsletter. 2021;43(9):69-79.
3. Hogan CA, Yang S, Garner OB, Green DA, Gomez CA, Dien Bard J, et al. Clinical Impact of Metagenomic Next-Generation Sequencing of Plasma Cell-Free DNA for the Diagnosis of Infectious Diseases: A Multicenter Retrospective Cohort Study. Clin Infect Dis. 2021;72(2):239-45.
4. Shishido AA, Noe M, Saharia K, Luethy P. Clinical impact of a metagenomic microbial plasma cell-free DNA next-generation sequencing assay on treatment decisions: a single-center retrospective study. BMC Infect Dis. 2022;22(1):372.