Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis

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Background

- A cause for acute meningoencephalitis cases is not identified in approximately 50% of patients.
- Poor patient outcomes, increased patient and family anxiety, high cost burden to the health care system.
- Metagenomic next-generation sequencing is a promising approach to evaluate the comprehensive spectrum of potential causes in a single assay.

**Aim**: to evaluate the real-life clinical performance of the metagenomic NGS assay in comparison with conventional microbiologic testing.
Methods

• 1-year, multicenter, prospective case series

• Target condition: clinical syndrome of meningitis, encephalitis, or myelitis without etiologic diagnosis at time of enrollment

• Index test: metagenomic NGS assay of CSF

• Study enrollment target: 300 patients
Methods

• Results reported in the patient EMR and discussed in the clinical microbial sequencing board

• Final clinical diagnoses were adjudicated by retrospective, in-depth chart review

• Orthogonal confirmation of discrepant results was performed

• Standardized physician surveys before and after reporting of metagenomic NGS results
Results
June 2016 - July 2017

Eight participating sites in USA

214 Patients enrolled → 204 completed the study
Mean laboratory turnaround time: 90 hours
- 11 Serologic testing alone
- 7 Samples other than CSF
- 8 Low titers of pathogens
Clinical microbial sequencing board

• Modeled after the “tumor board” concept in oncology

• Weekly teleconferences for review of metagenomic NGS results in clinical context

• Among the 13 cases diagnosed solely by metagenomic NGS:
   Results favorably affected clinical reasoning in 8 cases
   In 7 cases guided therapy
E  Clinical Effect (13 cases diagnosed by metagenomic NGS only)

- 7 (54%) Enabled appropriate and targeted treatment
- 1 (8%) Helped to rule out coinfections; enabled patient to proceed with chemotherapy (EBV-associated lymphoma)
- 1 (8%) Supported clinical decisions to narrow coverage (neisseria)
- 2 (15%) Had no effect, because patient already discharged from hospital (enterovirus)
- 1 (8%) Had no effect, because clinical significance unclear (MW polyomavirus)
- 1 (8%) Provided reassurance to patient or surrogate (SLEV)

- *N. farcinica* — long-term treatment with oral moxifloxacin and minocycline
- *Candida tropicalis* — treatment with high-dose fluconazole and liposomal amphotericin B (started empirically for elevated 1,3-β-D-glucan level)
- HEV — successful treatment with IV ribavirin after patient was readmitted with liver failure and consideration of liver transplantation
- *E. aerogenes* — narrowing of antibiotic therapy to IV cefepime and oral trimethoprim–sulfamethoxazole
- *Enterococcus faecalis* — narrowing of antibiotic therapy to IV vancomycin; discontinuation of meropenem
- *S. mitis* — narrowing of antibiotic therapy to IV cefepime; continuation of antibiotics for 4 wk to treat CNS infection
- *S. agalactiae* — treatment with an additional 4 wk of therapy with IV ceftriaxone and vancomycin
Hepatitis E virus meningoencephalitis

• 58 y/o woman

• Bilateral lung transplant, multiple sclerosis on chronic immunosuppression

• Fever, headache, nausea, vomiting, neck stiffness, and photophobia

• Transaminitis beginning at the time of her lung transplant. Deterioration of liver function

• CSF profile: lymphocytic pleocytosis, normal glucose and protein levels. All microbiologic studies returned negative

• mNGS testing: Hepatitis E virus infection

• Treatment with IV ribavirin, with resolution of both neurologic symptoms and liver failure

• Lung donor: previously unrecognized HEV infection → first reported case of HEV infection transmitted by lung transplant
**Nocardia farcinica** meningoencephalitis

- 66 y/o man
- Lung transplantation
- Fever, altered mental status, sepsis, and pneumonia following a flu-like illness
- Empirically treated with meropenem, vancomycin, azithromycin, and oseltamivir
- Brain MRI revealed ventriculitis and multiple T2 hyperintense lesions throughout the cerebral hemispheres
- CSF 126 WBCs (78% N, 20% L, 2% M), normal glucose, and elevated protein. Microbiological testing was negative
- mNGS testing: Nocardia farcinica
- Initial treatment with IV imipenem followed by long-term treatment with oral moxifloxacin and minocycline
Discussion

**Advantages**

- Unbiased approach → ability to detect many potential infectious agents in a single assay
- Earlier and more targeted treatments
- Identification of emerging infections
- Earlier workup and treatment for noninfectious causes (e.g. suspected autoimmune encephalitis)
- Concordance with conventional testing: reassurance, immunocompromised patients (ruling out co-infections)
- Clinical microbial sequencing board → precision medicine
Limitations

• Cost, accessibility, and turnaround time

• The preferred timing and patient population for clinical metagenomic NGS testing remain to be defined

• High host background $\rightarrow$ higher risk of false negative results

• Clinical thresholds for reporting a positive test on metagenomic NGS
  ➢ more liberal reporting thresholds for high-priority pathogens?
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Conclusions

• Clinical metagenomic NGS of CSF represents a potential step forward in the diagnosis of meningoencephalitis.

• The highest diagnostic yield resulted from a combination of metagenomic NGS of CSF and conventional testing.