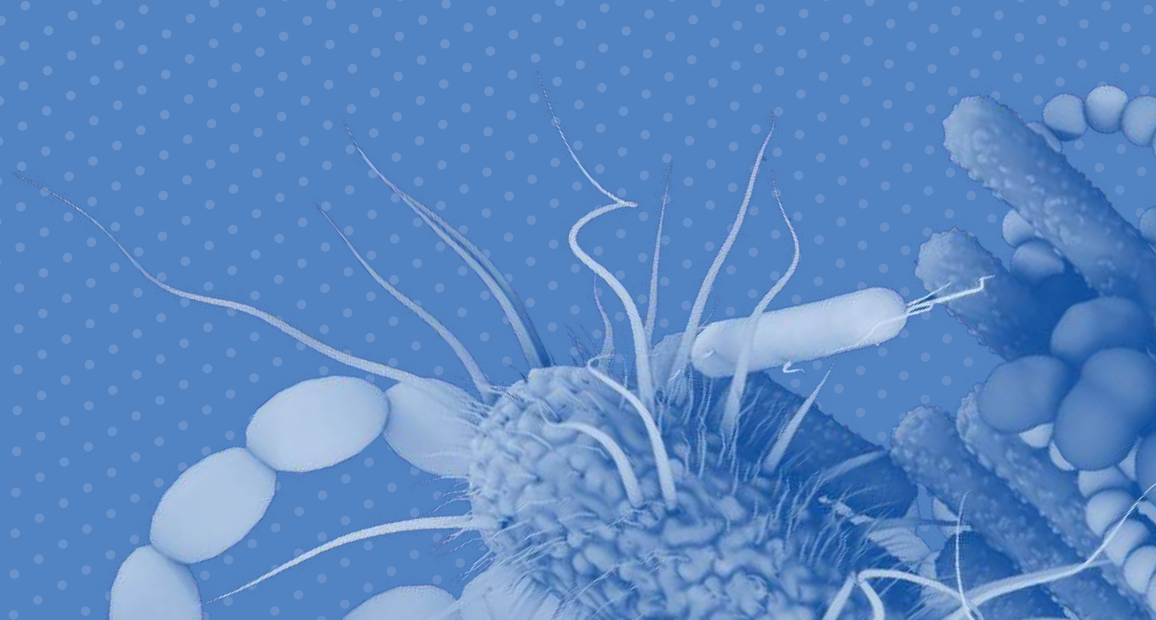
delvedetect
CEREBROSPINAL FLUID

▸ ME in Immunocompromised Patients

Metagenomic Next-Generation Sequencing for Meningitis and Encephalitis Diagnosis in Immunocompromised Patients



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Contents

Meningitis and encephalitis in immunocompromised patients: unknown etiology, atypical pathogens, diminished immune response

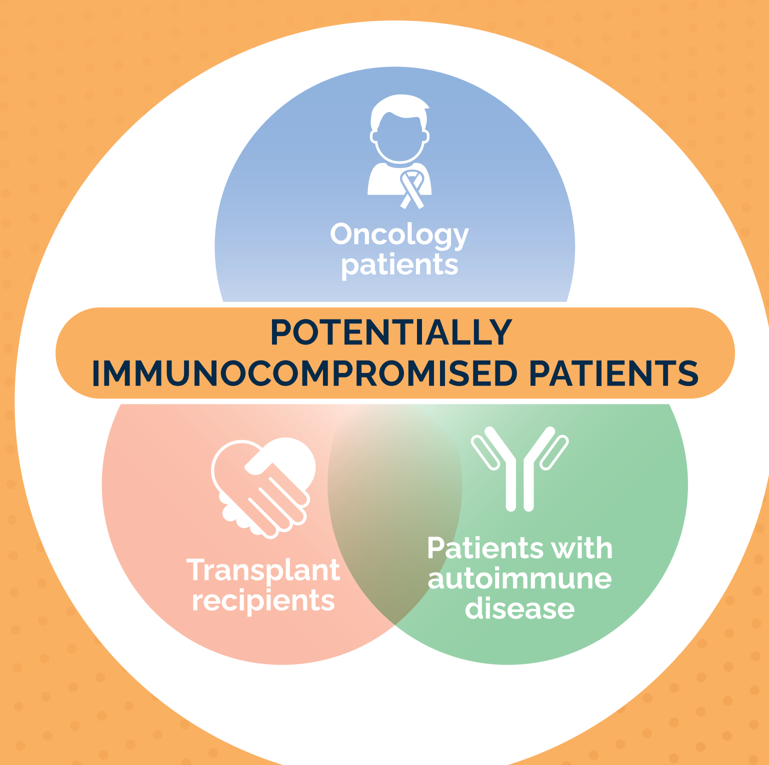
Meningitis and encephalitis (ME) remain undiagnosed in up to 50% of cases due to the limited scope, sensitivity, and speed of diagnostics currently used as standard of care[1,2]. A leading cause of ME is central nervous system (CNS) infections. However, in immunocompromised (IC) patients, the absence of a normal inflammatory response, including diminished or absent leukocytosis, can obscure typical signs of infection. Thus, the expected markers for infection can be masked and diagnosis and appropriate management may be delayed.[11,12,13]

CNS infections in immunocompromised patients

Patients with compromised immune systems face predisposing risk factors for infection due to either treatment-related effects or underlying immune impairment. Disruption of the blood brain barrier may occur for multiple reasons including:

- A result of the installation of support or monitoring procedures like shunts, ventricular reservoirs, through cranial surgery
- Chemotherapy and/or radiation associated loss in mucosal integrity
- Immune deficits which can increase the risk of CNS infections, but not necessarily impact the blood-brain barrier[2]

Populations at risk include patients with cancer, hematopoietic and solid organ transplant recipients, and individuals with autoimmune or inflammatory conditions receiving immunomodulatory or immunosuppressive therapies.



Potentially Immunocompromised Populations at Risk for CNS Infection

Oncology Patients

Individuals undergoing chemotherapy for hematologic malignancies (such as leukemia and lymphoma) or solid tumors frequently have neutropenia, mucosal barrier injury, and impaired cellular and humoral immunity. This increases susceptibility to both common and opportunistic CNS pathogens, including bacteria (e.g., *Listeria*, *Nocardia*), viruses (e.g., HSV, VZV, JC virus), and fungi (e.g., *Cryptococcus*, *Aspergillus*).

A multicenter study noted that patients undergoing cancer chemotherapy, particularly those receiving checkpoint inhibitors like Atezolizumab, can develop drug-related encephalitis or aseptic meningitis, with over 80% of cases occurring within two weeks of starting therapy. Immune checkpoint inhibitor-related encephalitis is characterized by lymphocytic pleocytosis and elevated cerebrospinal fluid (CSF) protein and typically responds to corticosteroids or other immunosuppressive therapy, though some cases require further treatments like IVIG or rituximab. Autoimmune encephalitis is also increasingly seen in this population, sometimes with atypical or attenuated presentations such as fewer seizures or movement disorders, compared to in immunocompetent patients. This continues to highlight challenges in diagnosing autoimmune encephalitis in the setting of immunocompromised state many of these patients are in.[3,4,5]

Transplant Recipients

Both hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients require prolonged immunosuppressive therapy to prevent graft rejection or graft-versus-host disease. These patients are vulnerable to a broad spectrum of CNS infections, often with unusual or rare pathogens, with the risk and spectrum of infections influenced by timing post-transplant, type of organ transplanted, and immunosuppressive regimen. Common etiologies include viral (CMV, HHV-6, EBV, JC virus), fungal (*Aspergillus*, *Mucorales*), and bacterial infections (*Nocardia*, *Mycobacteria*).

A large French cohort of kidney transplant patients reported a distinct spectrum of CNS pathogens, with common causes including *Cryptococcus neoformans* (20%), varicella-zoster virus (13.5%), *Mycobacterium tuberculosis* (5.5%), and *Enterobacteriaceae* (4.5%). Typical pathogens of the general population (such as *Streptococcus pneumoniae* and *Neisseria meningitidis*) were rare or absent. Studies of solid organ transplant recipients have identified fatal cases of meningoencephalitis due to lymphocytic choriomeningitis virus (LCMV), with diagnosis often achieved through advanced molecular techniques like metagenomic next-generation sequencing (mNGS). In pediatric transplant recipients, HHV-6 meningoencephalitis can require prolonged antiviral therapy and vigilant monitoring for antiviral resistance.[6,7,8]

Patients with Autoimmune Disease

Those receiving chronic corticosteroids, biologic agents (e.g., TNF-alpha inhibitors, rituximab), or other immunomodulators for conditions such as rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel disease, are also at heightened risk for CNS infections. These therapies can cause profound lymphocyte or neutrophil dysfunction, leading to both typical and opportunistic CNS infections, including viral (HSV, VZV), bacterial (including *Listeria* and *Mycobacteria*), and fungal (e.g., *Coccidioides*, *Histoplasma*) causes.

Checkpoint inhibitor–associated autoimmune encephalitis has emerged as an important cause, accounting for more than 10% of encephalitis cases in immunocompromised cohorts. Immune-related encephalitis often requires corticosteroids or other immunosuppression for management, and discontinuation of the inciting immunotherapy is standard practice, though relapse is rare. Diagnostic sensitivity for CNS autoimmunity can be limited, especially in those receiving biologic agents, emphasizing the need for high clinical suspicion and multimodal diagnostic testing.[9,10]

Delve Detect: comprehensive, agnostic, hypothesis-free detection of pathogens

Delve Detect is a metagenomic next-generation sequencing (mNGS) test that enables comprehensive, hypothesis-free identification of viruses (RNA and DNA), bacteria, fungi and parasites in a single sample. Delve Detect CSF's mNGS platform uses an unbiased approach to sequencing: sequencing DNA and RNA, including both cellular and cell-free nucleic acid in a single, 1 mL sample of cerebrospinal fluid (CSF). The process includes nucleic acid extraction, library preparation, sequencing, and bioinformatic analysis to identify the microorganisms present by mapping the detected sequences to an extensive microbial database of over 68,000 pathogens.

delvedetect

Delve Detect's results are rapid, crucial information that can quickly guide clinicians toward a definitive infectious diagnosis or help pivot the investigation toward a non-infectious etiology.

Detectable Microorganisms by Delve Detect

>68,000

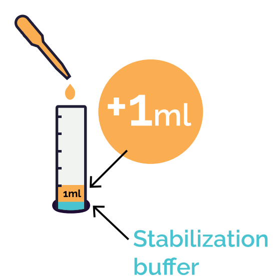
Bacteria

Viruses (RNA and DNA)

Fungi

Parasites

Results available the next day after sample received



1 mL of CSF sent in Delve Detect kit, **shipped at room temperature**

Includes **expert medical consultation** via Clinical Microbial Sequencing Boards

UCSF

Delve Bio is the home of UCSF's CSF mNGS testing and exclusive licensee of UCSF's mNGS platform

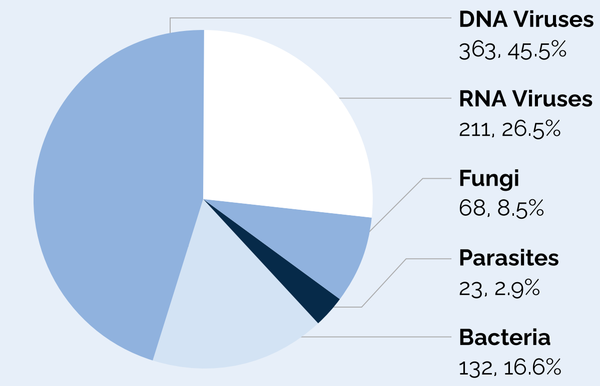
Delve Detect CSF for the diagnosis of suspected infectious meningitis and encephalitis

Delve Detect's results are rapid, crucial information that can quickly guide clinicians toward a definitive infectious diagnosis or help pivot the investigation toward a non-infectious etiology. Large scale analysis of nearly 5000 CSF samples over 7 years of testing at UCSF was published in Nature Medicine and demonstrated:

437 Unique Pathogens Detected

Broad Pathogen Detection

The pathogen diversity in CSF far exceeds the number of pathogens detected by conventional microbiological testing. In a 7 year analysis of the clinical use of CSF mNGS, over 400 unique pathogens were uncovered.[1]



22% Additional Diagnostic Yield

mNGS has been shown to improve diagnostic yield in suspected central nervous system (CNS) infections, especially in cases where routine microbiological testing (such as culture and targeted PCR) fails to identify a pathogen.[1]

97% Positive Predictive Value

CSF mNGS exhibited positive predictive (PPV) and negative predictive (NPV) values of 97% and 92%, compared to the clinically adjudicated final diagnosis, along with a specificity of 99.6% and accuracy of 93% for the diagnosis of CNS infections.[1]

86% Sensitivity

The sensitivity of mNGS testing increased to 86% when comparing to diagnoses made by CSF direct detection assays (direct testing of the CSF to identify pathogens via methods like culture, antigen testing, and nucleic acid amplification testing [NAAT]) which justifies the use of diagnostic mNGS testing for hospitalized patients with suspected CNS infection.[1]

Key Advantages of Delve Detect CSF for Immunocompromised Patients

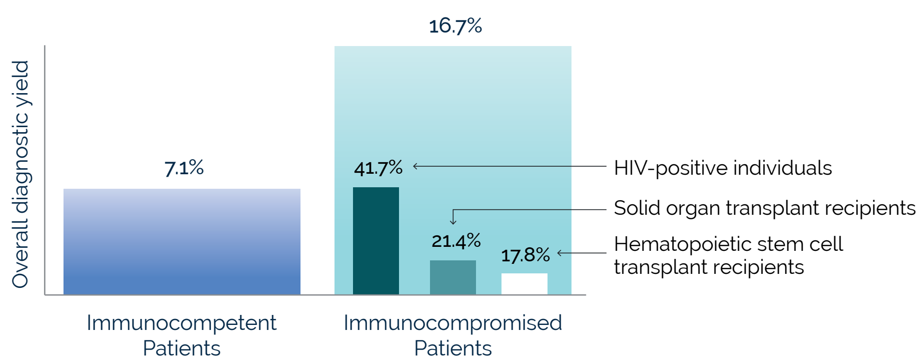
The key advantages of using Delve Detect mNGS for immunocompromised patients suspected of having central nervous system (CNS) infections include enhanced diagnostic yield, unbiased and broad pathogen detection (especially crucial for opportunistic infections), and the ability to guide early, targeted clinical intervention.

1. Greater Diagnostic Yield and Sensitivity for Complex Cases

mNGS of CSF demonstrates a higher rate of successful pathogen identification in this population compared to immunocompetent patients and conventional methods:

Higher Diagnostic Yield: In the Nature study across over 1000 patients for which clinical and laboratory characteristics were analyzed over 7 years of testing, the overall diagnostic yield of mNGS was significantly higher in immunocompromised patients (16.7%) compared to immunocompetent patients (7.1%).[1] The yield was particularly high in specific high-risk groups, such as HIV-positive individuals (41.7%), solid organ transplant recipients (21.4%), and hematopoietic stem cell transplant recipients (17.8%).[1]

Overall diagnostic yield of CSF mNGS across 7 years

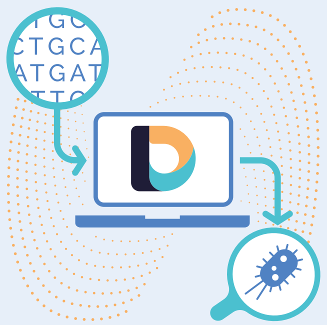


This enhanced sensitivity highlights mNGS's critical role in identifying infections in populations susceptible to opportunistic pathogens, such as *Cryptococcus neoformans*, *Toxoplasma gondii*, and *Coccidioides* species, which are often identified late or excluded from conventional diagnostic workup. The test also identified invasive mold infections like *Aspergillus* and *Fusarium* species as well as viral infections like JC virus, which have high morbidity and mortality particularly when diagnosis is delayed. These findings highlight mNGS as a crucial tool that can enable early, targeted intervention in this diagnostically challenging and highly vulnerable group.[1]

In the 2019 Precision Diagnosis of Acute Infectious Diseases (PDAID) study of 204 hospitalized patients, 83 patients (40.7%) of whom were immunocompromised, mNGS alone identified 13 (22%) of 58 total infections that were missed by conventional testing. Infections diagnosed solely by mNGS included St. Louis encephalitis virus, hepatitis E virus, and *Streptococcus agalactiae*. mNGS also identified orthogonally confirmed detections, including MW polyomavirus in an immunocompromised child with meningoencephalitis (of unclear clinical significance), and Epstein-Barr virus (EBV) in a patient with EBV-positive primary hepatic lymphoma and associated encephalitis.[19]

Detection Despite Atypical Presentation: Immunocompromised patients often lack typical signs of infection, such as fever or cerebrospinal fluid (CSF) pleocytosis (elevated white blood cell count). The ability of mNGS to detect pathogens even when CSF inflammation is minimal is critical, as the absence of CSF inflammation is observed in more than half of confirmed CNS infections in immunocompromised patients.[14]

2. Comprehensive and Unbiased Pathogen Detection for Opportunistic, Atypical, Fastidious, and Unexpected Pathogens



Delve's curated database of **>68,000 organisms**

Immunocompromised patients are susceptible to a vast and often unexpected array of opportunistic, fastidious, and emerging pathogens that targeted tests frequently miss due to difficulty to culture or lack of test coverage. Delve Detect's unbiased approach addresses this diagnostic gap via:

Identification of Opportunistic Pathogens: Delve Detect's detection of DNA and RNA virus, bacteria, fungi, and parasites enables it to identify organisms prone to late diagnosis in immunosuppressed hosts, including fungi such as *Cryptococcus neoformans*, Toxoplasma *gondii*, and *Coccidioides* species. It also identifies invasive mold infections like *Aspergillus* and *Fusarium* species, and viral infections such as JC virus (the agent of Progressive Multifocal Leukoencephalopathy or PML), all of which carry high morbidity when diagnosis is delayed.

Detection of Atypical and Fastidious Pathogens: mNGS successfully detects species that are difficult or impossible to culture, such as *Mycobacterium tuberculosis* (a common concern in immunocompromised patients) and *Tropheryma whipplei*.[11] It also identified *Nocardia farcinica* in a patient treated empirically with antibiotics.[19]

Diagnosis of Unexpected Agents: The test's broad detection capabilities identified rare or emerging infections in immunocompromised patients who were severely ill and had broad or ambiguous clinical presentations. Examples include:

- Potosi virus (POTV) and Lone Star virus (LSV), two bunyaviruses detected in immunocompromised patients with fatal meningoencephalitis. In these arbovirus cases, serologic testing was problematic due to the patients' severe immunosuppression (e.g., B-cell depletion from rituximab or hypogammaglobulinemia).[14]
- St. Louis Encephalitis Virus (SLEV) in an elderly immunocompromised patient (mantle cell lymphoma and chemotherapy), a pathogen that was not initially considered in the differential and for which serologic testing proved negative.[15]

3. Facilitating Time-Sensitive, Targeted Clinical Management

With most results available the next day, after sample receipt, Delve Detect's rapid and definitive results enable clinicians to move quickly from broad empirical therapy to targeted intervention. This is essential in critically-ill immunocompromised patients where timely pathogen identification is urgent.

Next Day

Results available the next day after sample received

Guiding Targeted Treatment of Unexpected Pathogens: Positive mNGS results can help guide the initiation of appropriate, targeted treatment, especially in cases where an unexpected or atypical pathogen may be the cause of infection.

- For example, CSF mNGS identified Hepatitis E Virus (HEV) in a transplant recipient with meningoencephalitis, allowing for successful treatment with ribavirin.[21]
- In another case, mNGS provided an actionable diagnosis of neuroleptospirosis (*Leptospira santarosai*) in an immunocompromised child when conventional tests were negative, leading to immediate targeted treatment with penicillin G.[20]

De-escalating Antimicrobials: When mNGS provides a definitive diagnosis or helps rule out infection, it can support the clinical decision to discontinue unnecessary broad-spectrum empirical antimicrobial therapy (e.g., stopping vancomycin, meropenem, or acyclovir), especially critical for immunocompromised patients with complex workups.

Expediting Non-Infectious Diagnoses: A negative mNGS result can increase confidence that an active infection is unlikely, which is crucial for distinguishing between infectious and non-infectious causes of neuroinflammation, such as autoimmune encephalitis. This confidence can allow clinicians to more quickly consider initiating alternative treatments such as corticosteroids or biologics. For instance, one case involved CNS lymphoma and encephalitis where mNGS identified only Epstein-Barr virus (EBV)[19], supporting the decision to discontinue empiric antimicrobials and initiate chemotherapy and immunosuppressive agents. With a reported negative predictive value of 92.3% in CNS infections[1], mNGS can help clinicians determine when to safely de-escalate antimicrobial use and shift diagnostic focus when an infectious cause is considered less likely, ultimately reducing patient risk and resource use as well as expediting appropriate care.

92% NPV in CNS infections

Identifying Nosocomial and Community Causes for Meningitis: Delve Detect can identify a large spectrum of microbial organisms, including those that cause typical community-acquired meningitis and nosocomial meningitis, which can be associated with CNS shunts or hardware. CSF collected by all methods is acceptable for testing, including lumbar puncture, shunt fluid, and surgical collection.

Case 1: Diagnosis of St Louis encephalitis Diagnosis of St. Louis Encephalitis Virus (SLEV) via Unbiased mNGS of CSF[14]

DAY 0

Acute illness and inconclusive testing

A 68-year-old man with a history of coronary artery disease, hypertension, and on chemotherapy. mantle cell lymphoma.

Admitted to the hospital after experiencing 2 days of fever, chills, lethargy, confusion, and new-onset urinary incontinence.

DAYS 1-2

Unrevealing imaging and empiric therapy

The patient's initial workup in the hospital included MRI of the brain (unrevealing) and lung imaging. Imaging of the lungs revealed inflammatory pneumonitis, after which the patient was started on empirical therapy (vancomycin, meropenem, and levofloxacin).

DAYS 3-9

Expanded therapy and continued negative results

On day 3 in the hospital, the patient became acutely hypoxic with worsening altered mental status (AMS). The patient was intubated and transferred to the ICU. Lumbar puncture (LP) revealed CSF pleocytosis, and empiric therapy was continued with acyclovir and antifungal therapy added to his regimen.

Repeat LPs on day 9 showed consistent pleocytosis while all microbiological tests for CSF, blood, and bronchoalveolar lavage were negative, along with a workup for non-infectious causes.

SLEV DIAGNOSED (DAYS 9+)

mNGS identifies SLEV in CSF sample

From the CSF collected on day 9, mNGS identified SLEV with >99% of the genome sequence identical to SLEV isolates from mosquitos in southwestern USA. This case demonstrated that SLEV can be acquired in the U.S. after re-introduction of the virus in the local mosquito population.

Further mNGS testing of CSF collected from day 3 of hospitalization substantiated the finding and was also positive for SLEV. The diagnosis was later confirmed by PCR and viral culture.

CASE OUTCOME

CDC confirmatory testing

Although mNGS was able to positively identify SLEV as the pathogen, the information came later in the course of treatment, with the patient already in critical condition. Following discussion about the SLEV diagnosis and prognosis, on day 23 in the hospital, the patient was transitioned to comfort care and died on day 24. The mNGS diagnosis of SLEV provided provided reassurance and closure to the family. SLEV was later confirmed postmortem by the CDC via PCR and culture testing.

While this patient ultimately died from his infection, the case highlights the potential value of an unbiased approach to infectious disease diagnosis:

1. Ability to diagnose unexpected severe infection
2. Enables detection of rare pathogen with limited testing options
3. Supports public health infectious agent detection and epidemiology

Case studies

All testing done for SLEV case prior to mNGS

All Microbiology Testing Negative

Blood Studies
Bacterial cultures
Fungal cultures
Mycobacterial culture
Aspergillus antigen EIA
Adenovirus PCR
CMV DNA quantitative PCR
EBV DNA quantitative PCR
Enterovirus RNA
HSV-1 and HSV-2 PCR
HHV-6 PCR
HIV RNA quantitative PCR
HBV DNA quantitative PCR
Leptospira DNA
Parvovirus B19 DNA
VZV DNA, qualitative PCR
Cryptococcal antigen

CSF Studies
HSV 1&2 PCR
Fungal culture
Bacterial culture
Coccidioides Ab CF, ID
CMV PCR
EBV PCR
HHV-6 PCR
JC polyomavirus DNA, PCR
Mycobacterial culture
MTb DNA
Meningoencephalitis antibody
VDRL
VZV Ab lgG
West Nile virus RNA

Respiratory Secretion Testing
Bacterial culture
Fungal culture
Respiratory virus panel
Mycoplasma pneumoniae PCR
HSV-1 and HSV-2 PCR
CMV PCR
Pneumocystis DFA
Mycobacterial culture
Legionella culture and urinary Ag

Serological Testing
Coccidiodes lgG/lgM
Coccidioides complement fixation
HCV Ab
HBV (core Ab and hepatitis B e Ab)
Mycobacterium tuberculosis-quantiferon gold
Q fever antibody
RPR

Case 2: Diagnosis of Hepatitis E Virus (HEV) meningoencephalitis (ME) in a lung transplant recipient via metagenomic sequencing[21]

DAY 0

Hospital admission and unclear symptoms

A 58-year old woman with a history of idiopathic pulmonary fibrosis status post bilateral lung transplant in 2011, presented with migraines, hypercoagulability, and multiple sclerosis (MS) on chronic immunosuppression was admitted to the hospital with terrible headaches following and 5 years of word-finding difficulty and speech slurring, 1 year of recurrent dizziness, and 1 month of lower extremity weakness.

DAYS 1-3

Complex patient history and empiric antimicrobials

Upon admission the patient was in moderate distress and sleepy, with a fever of 38.3˚C. MRI revealed baseline periventricular, subcortical, and juxtacortical T2/FLAIR white matter intensities associated with her MS but no acute changes. Evaluation of recent patient history and medications revealed no obvious infection drivers. The patient also had outpatient usage of various immunosuppressive medications for her lung transplant and MS, antimicrobial prophylaxis anticoagulation, and pain medications, including an intrathecal morphine pump. She was started on empiric antimicrobials.

DAYS 3-6

Inconclusive microbiological studies and patient discharge

With the patient's ongoing symptoms, a lumbar puncture (LP) was performed on day 3. The LP revealed a lymphocytic pleocytosis. All microbiological tests run on the blood, CSF, from a nasopharyngeal swab, from peritoneal fluid, were negative.

However, on day 6 the patient's condition improved except for a mild persistent headache, and the differential diagnosis included viral meningoencephalitis or tacrolimus toxicity. The patient was discharged on day 6.

POST-PATIENT DISCHARGE

mNGS leads to diagnosis of HEV-associated ME

Due to the unknown etiology of the patient's meningoencephalitis, the patient's CSF from day 3 of her hospitalization was analyzed by mNGS.

The mNGS result revealed HEV, related to viral strains from Japan and Southeast Asia. The diagnosis was communicated to the patient and review of the patient's health records indicated potential signs of infection post-lung transplant. The case was reported to the United Network for Organ Sharing donor safety net. Testing of stored donor serum was positive for HEV IgG and IgM antibody but negative for HEV RNA.

CASE OUTCOME

Patient recovery and confirmation of HEV infection from transplant donor

The patient was readmitted two-weeks after discharge with new, worsening symptoms: decompensated liver disease, encephalopathy, asterixis, ascites, and cirrhosis by abdominal ultrasound and liver elastography. Following the HEV mNGS results, HEV infection was confirmed by serum and plasma testing. The patient was then treated with ribavirin and low-dose diuretics. This led to decline in HEV RNA, normalization of transaminases, and improvement in ascites, edema, and mentation.

mNGS testing of the CSF was able to:

1. **Identify HEV as the cause of the patient's meningoencephalitis** in a challenging case
2. **Inform targeted treatment leading to eventual patient recovery.**
3. **Identify of the first case of presumptive HEV transmission via lung transplantation.**

Case studies

All testing done for HEV ME case prior to mNGS

All Microbiology Testing Negative

FIRST HOSPITAL ADMISSION

Blood

CMV DNA quantitative PCR negative
Cryptococcal Ag negative
EBV PCR detected <10
HSV-1/2 PCR negative
Fungal culture negative
Bacterial culture negative
Toxoplasma gondii DNA PCR negative
MTB Quantiferon-Gold assay negative
Adenovirus DNA PCR negative
Parvovirus B19 DNA PCR negative
West Nile IgG / IgM negative
Rickettsia RMSF and typhus IgG / IgM negative
Varicella zoster DNA PCR negative
Coccidioides IgG and IgM EIA negative
Hepatitis A Ab total negative
Hepatitis A Ab IgM negative

CSF

Cryptococcal Ag negative
Enterovirus PCR negative
Fungal culture negative
Bacterial Gram stain and culture negative
VZV PCR negative
HSV-1/2 PCR negative
CMV DNA quantitative PCR negative

Nasopharyngeal swab

Respiratory Virus Panel (RVP) PCR negative

MRI brain: Stable periventricular and subcortical and juxtacortical
T2/FLAIR white matter intensities w/T1 hypointensity

Abdominal ultrasound:
Normal liver size, homogeneous in echogenicity. Normal spleen size. No ascites. Normally distended gallbladder containing sludge, without stones.

SECOND HOSPITAL ADMISSION

Blood

Hepatitis A IgM negative
Hepatitis B core IgM negative
Hepatitis B surface antigen negative
Hepatitis C Antibody negative
HBV DNA PCR negative
Cryptococcal antigen negative
HIV 4th generation Ag/Ab negative
JCV Ab 2.31 [>0.40 positive]
RPR negative
Aspergillus antigen EIA negative
Coccidioides IgG/IgM EIA negative
Toxoplasma gondii DNA PCR negative

Peritoneal fluid

Bacterial gram stain and culture negative

MRI brain: Unchanged

Abdominal ultrasound: Cirrhotic appearing liver without focal lesion, patent hepatic vessels. Small volume ascites. Spleen upper normal in size.

Liver ultrasound elastography: shear wave liver stiffness 2.1 m/sec consistent with METAVIR score of F3-F4

References

1. Pruitt AA. Central Nervous System Infections in Immunocompromised Patients. *Curr Neurol Neurosci Rep*. 2021;21(7):37. Published 2021 May 26. doi:10.1007/s11910-021-01119-w
2. Kolchinski A, Li M, Habis R, et al. Encephalitis in Immunocompromised vs Immunocompetent Patients: A Comparative Study. *Open Forum Infect Dis*. 2025;12(7):ofaf332. Published 2025 Jun 11. doi:10.1093/ofid/ofaf332
3. Yan Q, Hu Y, Liu X, Xia H. Clinical characteristics, diagnosis, treatment, and prognosis of Atezolizumab-induced encephalitis, aseptic meningitis or meningoencephalitis. *Frontiers in Human Neuroscience*. 2025;19. doi:https://doi.org/10.3389/fnhum.2025.1443463
4. Buckley MW, Balaji Warner A, Brahmer J, et al. Immune-related encephalitis after immune checkpoint inhibitor therapy. *The Oncologist*. Published online July 26, 2024. doi:https://doi.org/10.1093/oncolo/oyae186
5. Sayyad LE, Smith KL, Sadigh KS, et al. Severe Non-Donor-Derived Lymphocytic Choriomeningitis Virus Infection in Two Solid Organ Transplant Recipients. *Open Forum Infectious Diseases*. 2025;12(2). doi:https://doi.org/10.1093/ofid/ofaf002
6. Thomas SJ, Ouellette CP. Viral meningoencephalitis in pediatric solid organ or hematopoietic cell transplant recipients: a diagnostic and therapeutic approach. *Frontiers in Pediatrics*. 2024;12. doi:https://doi.org/10.3389/fped.2024.1259088
7. Tamzali Y, Scemla A, Bonduelle T, et al. Specificities of Meningitis and Meningo-Encephalitis After Kidney Transplantation: A French Retrospective Cohort Study. *Transpl Int*. 2023;36:10765. Published 2023 Jan 18. doi:10.3389/ti.2023.10765
8. Buckley MW, Balaji Warner A, Brahmer J, et al. Immune-related encephalitis after immune checkpoint inhibitor therapy. *The Oncologist*. Published online July 26, 2024. doi:https://doi.org/10.1093/oncolo/oyae186
9. Kolchinski A, Li M, Habis R, et al. Encephalitis in Immunocompromised vs Immunocompetent Patients: A Comparative Study. *Open Forum Infect Dis*. 2025;12(7):ofaf332. Published 2025 Jun 11. doi:10.1093/ofid/ofaf332
10. Zimmer AJ, Burke VE, Bloch KC. Central Nervous System Infections. *Microbiol Spectr*. 2016;4(3):10.1128/microbiolspec.DMIH2-0012-2015. doi:10.1128/microbiolspec.DMIH2-0012-2015
11. Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. *Clin Infect Dis*. 2003;36(6):731-742.
12. Granerod J, Tam CC, Crowcroft NS, Davies NWS, Borchert M, Thomas SL. Challenge of the unknown. A systematic review of acute encephalitis in non-outbreak situations. *Neurology*. 2010;75(10):924-932.
13. Chiu CY, Godasi RR, Hughes HR, et al. Two human cases of fatal meningoencephalitis associated with Potosi and Lone Star virus infections, United States, 2020-2023. Emerg *Infect Dis*. 2025;31(2):215-221.
14. Chiu CY, Coffey LL, Murkey J, et al. Diagnosis of fatal human case of st. Louis encephalitis virus infection by metagenomic sequencing, California, 2016. *Emerg Infect Dis*. 2017;23(10):1964-1968.
15. Gould CV, Free RJ, Bhatnagar J, et al. Transmission of yellow fever vaccine virus through blood transfusion and organ transplantation in the USA in 2021: report of an investigation. *Lancet Microbe*. 2023;4(9):e711-e721.
16. Fridey JL, Stramer SL, Nambiar A, et al. Sepsis from an apheresis platelet contaminated with Acinetobacter calcoaceticus/baumannii complex bacteria and Staphylococcus saprophyticus after pathogen reduction. *Transfusion*. 2020;60(9):1960-1969.
17. Crawford E, Kamm J, Miller S, et al. Investigating transfusion-related sepsis using culture-independent metagenomic sequencing. *Clin Infect Dis*. 2020;71(5):1179-1185.
18. Wilson MR, Sample HA, Zorn KC, et al. Clinical Metagenomic Sequencing for Diagnosis of Meningitis and Encephalitis. *New England Journal of Medicine*. 2019;380(24):2327-2340. doi:https://doi.org/10.1056/nejmoa1803396
19. Wilson MR, Tyler KL. The Current Status of Next-Generation Sequencing for Diagnosis of Central Nervous System Infections. *JAMA Neurol*. 2022;79(11):1095-1096. doi:10.1001/jamaneurol.2022.2287
20. Wilson MR, Naccache SN, Samayoa E, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing. *N Engl J Med*. 2014;370(25):2408-2417. doi:10.1056/NEJMoa1401268
21. Murkey JA, Chew KW, Carlson M, et al. Hepatitis E Virus-Associated Meningoencephalitis in a Lung Transplant Recipient Diagnosed by Clinical Metagenomic Sequencing. *Open Forum Infect Dis*. 2017;4(3):ofx121. Published 2017 Jun 13. doi:10.1093/ofid/ofx121

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