Endemic Neuroinfectious Diseases in Arizona: West Nile Virus and Coccidiomycosis

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West Nile Virus
1. Review the epidemiology of systemic and neuroinvasive west nile virus (WNV) and coccidioidomycosis infections
2. Review the components of the neuroaxis. Discuss which locations may be affected by neuroinvasive WNV and coccidioidomycosis and the common presentations of each syndrome.
3. Learn how to evaluate for and ultimately diagnose neuroinvasive WNV and coccidioidomycosis.
4. Review patient cases, each with a different clinical syndrome.
5. Discuss the management of neuroinvasive WNV and coccidioidomycosis and the most common complications.
West Nile Virus (WNV)- Systemic

• Mosquito born illness
• June to October
• 2–14-day incubation period

• ~ 20% of cases are symptomatic
• Symptoms:
  • Flu-like illness
  • Fever
  • Nausea, vomiting
  • Diarrhea
  • Myalgias
  • HA
  • LAD
  • +/- Rash (trunk, limbs)
West Nile Virus Activity by State – United States, 2021
(as of January 11, 2022)
West Nile Virus (WNV)- Neuroinvasive

- Most common cause of endemic viral encephalitis in the US
- 1/150 patients known to be infected with WNV will have neurologic involvement
- Most at risk:
  - Advanced age, >60
  - Immunosuppressed state: organ transplantation
  - Chronic illness: HTN, DM
- Symptoms depend on which part of the nervous system is affected.
  - Headache, AMS/coma, weakness, bulbar symptoms, tremor, parkinsonism
What is the NeuroAxis?

- Cerebrum
- Basal Ganglia
- Cerebellum
- Brainstem
- Spinal Cord
- Motor Neuron
- Neuromuscular Junction
- Peripheral Nerve
- Muscle
- Autonomic
• Meningitis (meninges)
  • Headache, photo/phonophobia, meningismus

• Encephalitis (brain)
  • AMS, coma
  • Basal ganglia
    • Movement disorders: Parkinsonism, tremors, myoclonus
  • Rhombencephalitis- Brainstem and cerebellum
    • Bulbar dysfunction
    • CN palsies: 7th is most common
    • Incoordination, ataxia
    • Gait dysfunction

• Cortex
  • Seizures, less common
Clinical Syndromes

- **Myelitis (spinal cord)**
  - Anterior horn cell (motor neuron)
    - Weakness:
      - typically asymmetric
      - quadra/para paresis/plegia
      - Respiratory muscle weakness
  
- **Radiculitis (nerve root)**
  - Weakness: flaccid paralysis, asymmetric, one limb

- **Combination**

- +/- **Autonomic dysfunction**
  - Parainfectious
  - Orthostatic hypotension
West Nile Virus Neuroinvasive Disease Incidence by State – United States, 2021
(as of January 11, 2022)
West Nile Virus (WNV)- Diagnosis

- Serum Testing
  - WBC, inflammatory markers
  - Antibodies +/- PCR
- Cerebral Spinal Fluid (CSF) Testing
  - Pleocytosis = elevated WBC
    - Average 226
    - Lymphocytic predominant
    - Can be neutrophilic (PMN) predominant initially, can last 48 hrs to 1 wk
  - Protein: mildly elevated
  - Glucose: normal
  - Antibodies
    - IgM by ELISA
      - Best for diagnosis of acute infection
      - May not be positive for up to 7 days after sx onset
        - Consider repeat CSF testing
      - May remain positive for months to >1 year
  - RT-PCR
    - Highly specific but less sensitivity than ab testing
    - Less useful the longer the sample is taken from time of symptom onset
- Other diagnostics: MR (brain, spinal cord), EMG, EEG
West Nile Virus (WNV)- Management

• No approved vaccines or treatments

• Supportive care:
  • IV fluids
  • Fever management, acetaminophen
  • Headache and nausea/vomiting management
  • Monitoring for elevated ICP, seizures, bulbar/respiratory dysfunction, and autonomic symptoms
  • Therapy evaluations, rehab

• Unclear evidence:
  • IVIG, Interferon-alpha, ribavirin, acyclovir, steroids
"There is no specific treatment for West Nile virus (WNV) disease; clinical management is supportive. Patients with severe meningeal symptoms often require pain control for headaches and antiemetic therapy and rehydration for associated nausea and vomiting. Patients with encephalitis require close monitoring for the development of elevated intracranial pressure and seizures. Patients with encephalitis or poliomyelitis should be monitored for inability to protect their airway. Acute neuromuscular respiratory failure may develop rapidly, and prolonged ventilatory support may be required."

"Various drugs have been evaluated or empirically used for WNV disease, However, none have shown specific benefit to date."

Prevention: “No WNV vaccines are licensed for use in humans.” “Community-level mosquito control programs.” “Personal protective measures: mosquito repellents, wearing long-sleeved shirts and long pants, and limiting outdoor exposure from dusk to dawn. Using air conditioning, installing window and door screens, and reducing mosquito breeding sites around the home”
“No specific therapy of proven benefit for West Nile virus infection exists. Isolated case reports and small series describe both benefit and lack of effect from treatment with IVIg containing high-titer anti-West Nile virus antibodies and with interferon alfa. A multicenter randomized controlled trial of a high-titer anti–West Nile virus IVIg preparation was conducted by the Collaborative Antiviral Study Group (CASG) and did not show evidence of a therapeutic benefit. A phase 2/3 trial to evaluate the safety and efficacy of a humanized monoclonal antibody directed against an epitope on the West Nile virus envelope glycoprotein was closed because of low enrollment (NCT00515385). Isolated reports of use of corticosteroids in patients with West Nile virus acute flaccid paralysis and brainstem disease do not permit any conclusions about efficacy.”
Outcomes

Systemic:
• Most people with systemic WNV limited to a febrile illness will completely recover
  • Fatigue and weakness can last for weeks or months

Neuroinvasive:
• Morbidity
  • Movement disorders
    • 6 months: 40%
    • 18 months: 20%
  • Encephalitis
    • 3 months: 50% ongoing cognitive issues, decreased motor speed
• Mortality
  • Severe encephalitis or severe acute flaccid paralysis
  • ~5-12% of people with neuroinvasive WNV will die
• Greater M/M in immunocompromised individuals
Coccidiomycosis
Coccidioidomycosis - Systemic

- Fungal infection
- Soil and dust in endemic areas
- 60% infected humans – asymptomatic or mild respiratory symptoms
- 40% infected humans – symptomatic disease 1-4 weeks after exposure
  - 5-10% will have serious and/or long term pulmonary issues
- Most frequently seen as a community acquired pneumonia, under-recognized
- Symptoms:
  - Fever
  - Cough
  - Dyspnea
  - Headache (21%)
  - Fatigue, malaise
  - Myalgias, arthralgias, rash
Coccidioidomycosis: average incidence of reported infections per 100,000 people, by county 2011–2017

https://www.cdc.gov/fungal/diseases/coccidioidomycosis/maps.html
Estimated Areas with Coccidioidomycosis: Worldwide

https://www.cdc.gov/fungal/diseases/coccidioidomycosis/maps.html
Coccidioidomycosis - Neuroinvasive

- **Chronic** infection
- 1-8% of new cocci infections are disseminated
  - CNS 17%
  - Others: skin, bones (vertebral), joints

- Most at risk:
  - Pregnancy
  - Advanced age
  - Immunosuppressed state: HIV/AIDS
  - Chronic illness: Diabetes
  - Race/ethnicities: Black and Filipino

- Signs and symptoms depend on which part of the nervous system is affected
  - Headache, AMS/coma, cognitive complaints, cranial nerve palsies, gait dysfunction, weakness
Headache: Systemic Infection or Meningitis?

• Headache
  • Predominant symptom, persistent (> 1 week), worsening
  • High pressure components: worse with valsalva, bending over, laying down

• Nausea, vomiting

• Neuro Symptoms
  • AMS, confusion
  • Gait difficulties
  • Other focal neurologic signs/symptoms

• When in doubt, perform LP and analyze CSF
  • CSF will remain abnl for weeks-months and beyond, even after antifungal therapy has been initiated

• Perform neuroimaging prior to LP
  • Especially if concern for CNS abscess and/or patient is immunocompromised

• Absence of HA, neuro signs/symptoms- high negative predictive value
  • If not present, CSF analysis is not helpful
XIII. In Patients With Newly Diagnosed Coccidioidal Infection, Should a Lumbar Puncture Be Performed?

Recommendation

21. In patients with recently diagnosed coccidioidal infection, we recommend lumbar puncture with CSF analysis only in patients with unusual, worsening, or persistent headache with altered mental status, unexplained nausea or vomiting, or new focal neurologic deficits (strong, moderate).
Clinical Syndromes

Meningitis (meninges), basilar
- Most common neurologic manifestation*
- Chronic, indolent time course
- High pressure headache: worse when supine and pending over, wakes from sleep, worse w/ Valsalva
- Meningismus
- Papilledema
- Elevated OP can be present with meningitis without hydrocephalous

Encephalitis (brain)
- Basilar/posterior fossa
  - Multiple cranial neuropathies
    - Diplopia
  - Cognitive changes, lethargy, coma
  - Emotional lability
  - Gait instability

Meningo/Encephalitis
Clinical Syndromes

Hydrocephalous
• Communicating > obstructive
• High pressure headache
• Papilledema
• Confusion, AMS, stupor
• Diplopia
• Gait disturbance
• Urinary incontinence

Coccidioidomas- abscesses
• Multiple locations:
  • Brain (basilar/posterior fossa)
  • Spinal cord (intramedullary),
  • Boney spine (intradural, paravertebral)
• Cerebral edema
Clinical Syndromes

Vasculitis
- Small vessel, basilar
- Ischemic strokes
  - Basal ganglia, thalamus, and white matter
- Arterial aneurysms
  - Subarachnoid hemorrhage

Myelitis (spinal cord)
- Weakness/sensory disturbance: symmetric, para/quadra paresis/plegia
- Bowel/bladder dysfunction
- Associated edema

Radiculitis (nerve root)

Arachnoiditis
- Nerve root clumping
- Most common in lumbar spine
- Lumbar pain, neurogenic bladder, lower extremity weakness

Syrinx
- Fluid-filled cavity
- Spinal cord (cervical and thoracic) or brain stem

Combination
Coccidioidomycosis - Diagnosis

Cerebral Spinal Fluid (CSF)

- Pleocytosis = elevated WBC
  - 20-2000
  - Lymphocytic predominant. Eosinophilic predominant is classic but not typically seen. Neutrophilic predominant can be seen as well.

- Elevated protein
  - Very high? Think about hydrocephalus

- Hypoglycorrhachia = low glucose
  - <40

- Elevated opening pressure
  - Can be seen with meningitis and hydrocephalus
Coccidioidomycosis- Diagnosis

Cerebral Spinal Fluid (CSF) continued

• Antibody testing
  • CF > EIA
• Antigen testing
• PCR lacks sensitivity
• Fungal culture (<10-30%) and direct microscopy are not sensitive but are diagnostic if positive
Coccidioidomycosis- Diagnosis

• Serum Testing
  • Antibody testing
    • EIA and ID with complement fixation
    • ~70% sensitive
  • Antigen testing

• MR imaging
  • Brain
    • Hydrocephalous, basilar inflammation, CVA, coccidiodoma
  • Spinal cord
  • Spine- juxtadural infection

• Urine antigen testing

• Bronchoalveolar lavage (BAL)
  • PCR testing
Coccidioidomycosis- Management

• LIFELONG AZOLE THERAPY
  • Fluconazole: 400–800*mg PO daily
• 80% chance of relapse if discontinued
• If stable and/or improving, no need for repeat CSF or neuroimaging
• Follow serum serologies, titers
Coccidioidomycosis- Management

• Fluconazole failure?
  • ~20% of patients with neuroinvasive disease
  • Increase fluconazole to 1200mg daily
  • Other azole options
    • Itraconazole 200mg PO BID–TID
    • Voriconazole 200–400mg PO BID
    • Posaconazole DR 300mg PO daily
    • Isavuconazole
  • Intrathecal Amphotericin B deoxycholate
Coccidioidomycosis - Management

- Daily LPs → VP Shunt
  - Hydrocephalous
- Steroids
  - Vasculitis: decreases risk of recurrent stroke
  - Cerebral edema associated with abscesses
  - Short course with rapid titration if used
- Surgery
  - Abscess drainage should be considered, especially if large
Outcomes

• Untreated cocci meningitis is nearly always fatal - early detection and initiation of treatment is critical.

• Continue lifelong anti-fungal medications
  • If taken off, 80% chance patient will have relapse of disease

• Development of hydrocephalus portents a worse outcome
  • Mortality approaches 10% even with shunting
  • 12.5 fold increase in mortality compared to those who do not develop hydrocephalous