Recommendations for a Patient with Confirmed Acute Necrotizing Encephalopathy (ANE)

ANE International — International ANE Clinical and Research Contributors

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Disclaimer: *These preliminary recommendations are intended to support clinical decision-making and do not replace individual clinical judgement. This document is under review for formal peer-reviewed publication. Please refer to the published version once available.*

Acute Necrotizing Encephalopathy (ANE) is a rare and often rapidly progressive neurologic condition, typically triggered by viral infections (especially influenza). Irreversible brain injury or death may occur if not promptly identified and managed. ANE may occur sporadically or in patients with pathogenic mutations in the RANBP2 gene. Recurrences may occur, particularly in patients with mutations of the RANBP2 gene. Emergency management focuses on rapid stabilization and preventing the risk for neurological injury. Preventative measures are also discussed below.

As ANE is a very rare disorder, patients and parents might face physicians who are not familiar with the condition. Quick, adequate analysis and treatment lead to a better outcome. Therefore, these recommendations are made to help parents and patients get optimal care in emergent situations. Parents and patients are owners of the document and hand it over to their treating physician.

This document contains recommendations for 3 situations:

I. Treatment guidance for the care of children with known ANE when families face an emergent situation
II. Information on the aftercare and rehabilitation.
III. General recommendations for children in between episodes

Background Information

Acute necrotizing encephalopathy (ANE) is a neurological syndrome in which bilateral intracranial lesions develop within a few days after the onset of an illness episode, typically in the thalami, brainstem, and/or cerebellum. ANE is always preceded by a febrile illness, usually caused by a viral pathogen. It is a life-threatening condition, with one-third of patients dying in the acute phase. This condition is typically due to a mutation in the RANBP2 gene and is inherited in an autosomal dominant manner with penetrance of around 40%. Gene carriers can also remain asymptomatic.

The first episode usually occurs in childhood but can also appear in (young) adulthood. About half of the patients will experience a recurrence, and a small subset may have multiple recurrences. Early recognition and treatment with corticosteroids in such cases can likely favorably influence the course of the disease.

Triggering Pathogens

- Many viral infections have been associated with ANE, including influenza A, influenza B, parainfluenza, human herpesvirus 6, coxsackievirus, SARS-CoV-2, and enteroviruses.
- The only bacterial pathogen associated with ANE is Mycoplasma pneumoniae.

Presentation of ANE

Acute encephalopathy/ANE induced by infection should be considered if:

- There are signs of a viral infection in the preceding days, such as fever, coughing/sneezing, vomiting, diarrhea, and malaise.
- Neurological symptoms occur within hours to several days after the first signs of a viral infection. The most common symptoms are lethargy progressing to coma and/or seizures (50%). Other symptoms may include hallucinations, ataxia, hypotonia, hypertonia, and decerebrate/decorticate posturing.

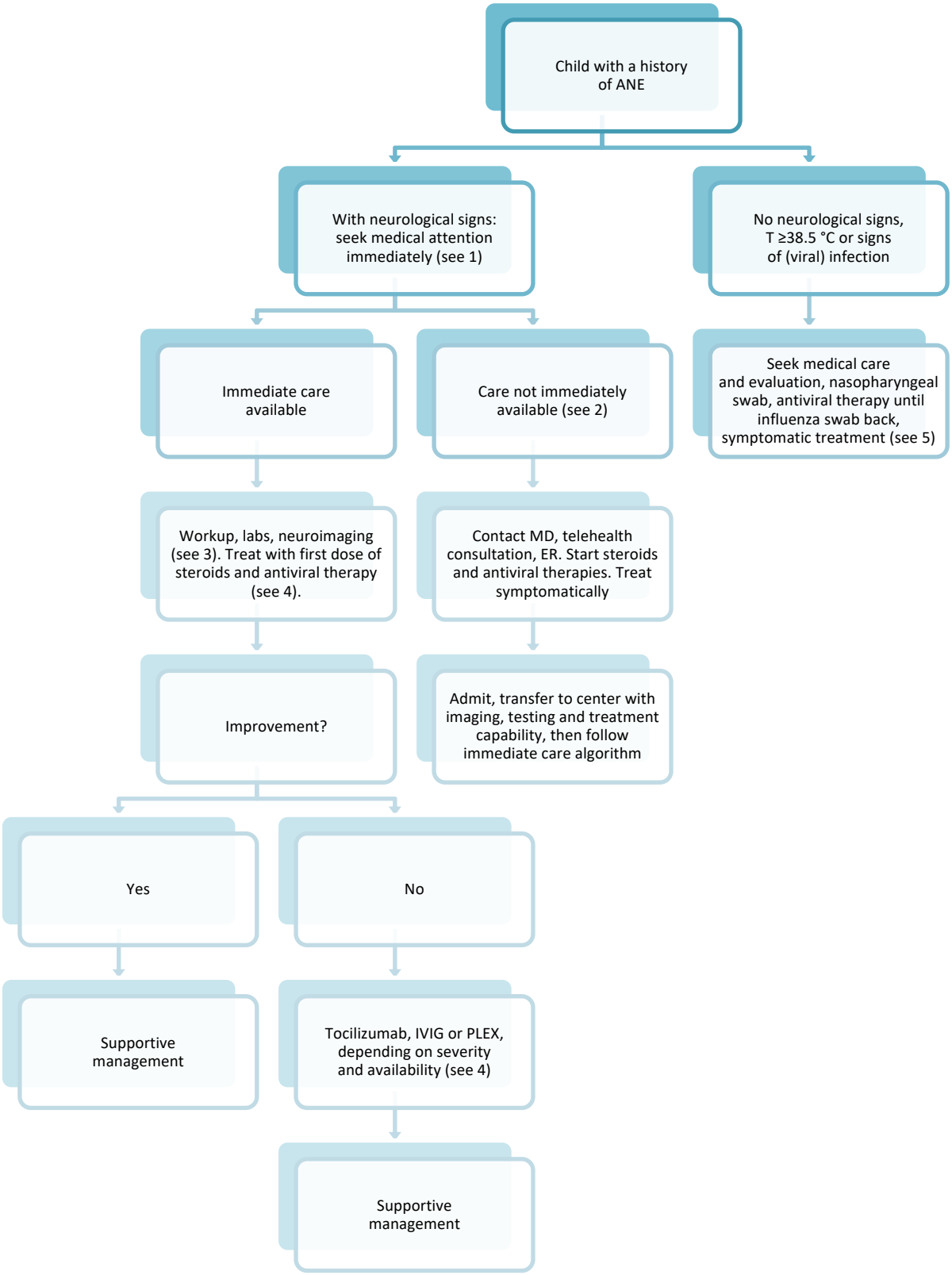

Figure 1. Emergency care algorithm for a child with a known history of ANE.
Bracketed numbers (see 1–5) refer to the correspondingly numbered sections in Part I.

Part I. Emergency clinical protocol for a patient with confirmed ANE in case *of a new* neurological deficit

The reference numbers in the flowchart correspond to the numbers below.

1. Patient with confirmed ANE in case *of a new* neurological symptom

In case of neurological symptoms, the patient contacts the emergency department.

- The parents inform the pediatrician about the emergency protocol and make clear the presence of neurological symptoms, for instance altered consciousness, seizures, ataxia and/or muscle weakness.
- Mild neurological symptoms can occur in neurologically compromised children in case of a viral illness. If there is uncertainty about recurrence of ANE, treat the patient as having a recurrence and admit for observation.

2. If care is not immediately available

If rapid access to medical care is not possible, parents start at home, preferably after (video) consultation with the pediatrician, methylprednisolone 1.5 mg/kg with a maximum of 50 mg per day or prednisolone 2 mg/kg with a maximum of 60 mg per day.

3. Diagnostic workup

Diagnostics

- **Laboratory Tests:**
  - CBC and WBC-differential, renal function, electrolytes, glucose, CRP, ESR
  - Liver function tests (elevated AST/ALT is common in ANE)
  - Test for influenza on pharyngeal swab, preferably multiplex PCR. If negative: consider broader viral diagnostics.
  - Serum storage (for additional testing)

- **Neuroimaging:**
  - **Urgent Brain MRI** preferred
  - CT scan if MRI is not immediately available. Note that CT scans can initially be with no abnormalities.

- **Other**
  - EEG if epilepsy is suspected.
  - Consider alternative diagnoses (like bacterial or viral meningitis) and act in accordance with applicable guidelines.

4. Treatment of a new ANE episode

Medical Treatment

- **High-dose corticosteroids (As soon as possible):**
  - Methylprednisolone 30 mg/kg/day (max 1 g/day) IV for 3–5 days. In case of suspicion of a relapse of ANE start immediately.
- Consider combination treatment of steroids with tocilizumab or plasma-exchange (PLEX) (especially in severely affected children or children with ICU indication or brainstem-lesions). IVIG may be considered if no improvement with steroids.
- There is too little evidence to recommend targeted temperature management (core temperature reduction to 32-34 degrees Celsius).
- **Antiviral therapy:**
  - Oseltamivir if influenza suspected or confirmed (6 mg/kg per day orally in 2 doses) for at least 5 days.
  - Based on clinical judgment, empirical antimicrobial therapy should be started (until negativity of cultures is proven).
- **Symptomatic treatment:**
  - It might be beneficial to avoid fever > 37.5 degrees Celsius
  - There are no specific contraindications for the use of antipyretics in immune disorders: consider paracetamol and NSAIDs as symptomatic treatment to reduce fever and discomfort.

Supportive Care

- Seizure management: benzodiazepines (e.g., lorazepam or midazolam) followed by levetiracetam and other anti-seizure medication
- Intracranial pressure (ICP) monitoring and management if signs of raised ICP

5. Protocol for a patient with confirmed ANE in case of fever ***without*** neurological deficit

In case of a serious fever (≥38.5 degrees Celsius and looking sick) without neurological symptoms contact the emergency department.

- Inform your pediatrician about the protocol for fever and indicate the absence of neurological symptoms.

Diagnostics

- **Laboratory Tests:** Test for influenza on pharyngeal swab, preferably multiplex PCR. If negative: consider broader viral diagnostics.

Medical Treatment

- **Antiviral therapy:**
  - Prophylactic Oseltamivir if influenza suspected or confirmed (6 mg/kg/day orally in 2 doses).
- **Symptomatic treatment:**
  - There are no specific contraindications for use of antipyretics in auto-immune disorders: consider paracetamol and NSAIDs as symptomatic treatment.

Part II. General recommendations for (long-term) sequelae in children after an episode of ANE

Many families face sequelae of ANE in their child or family members and finding the right care for rehabilitation of neurological deficits or help in behavioral changes. Most patients qualify for intensive rehabilitation.

Long-term Planning

- Early initiation of rehabilitation (PT/OT/speech therapy)
- Follow-up with neurology for long-term sequelae
- Follow-up with (neuro)psychologist for psychological aspects of disease like fear and neuropsychological consequences.
- If neurological sequelae allow so: guided return to the education system/school is an important part of recovery.

A baseline MRI is recommended 6-12 months after an ANE episode.

Part III. General Recommendations and Preventive Measures for Children after an Episode of ANE in the Past

The main goal is prevention of recurrence in children with confirmed ANE in the past.

Recommendation for Vaccinations

- Yearly influenza and COVID-19 vaccinations for the patient and their family (injection)
- It is advised to follow national vaccination programs, also with live attenuated vaccines (only isolated reports of adverse effects)

Infection Prevention in Daily Life

- There is no need to avoid crowding like day care. Attending day care helps to build up the immune system and is important for psychosocial development.
- Avoid direct exposure to sick people. In case of seasonal frequent infections or influenza: wear a medical nose-mouth mask and hand disinfection.
- Basic hygiene: regular handwashing.

Other Preventive Strategies

- Any maintenance immunomodulation is not recommended, weighing risks and benefits. Possible treatments to reduce the threshold for relapses are the subject for future research.
- There is no place for regular maintenance treatment/immune modulation
- There are no specific contraindications for use of antipyretics in immune disorders: consider paracetamol and NSAIDs as symptomatic treatment.

Further information

- Information about the disease and a patient/parent support group:
  - https://aneinternational.org/
- Information about the ANE Clinical and Research Contributors:
  - https://aneinternational.org/ane-specialists-researchers-clinicians/