European Guidelines on Management of Tick Borne Encephalitis: a Focus on Intensive Care

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Why tick borne encephalitis (TBE) guidelines?

- A growing public health concern
- A notifiable disease in the EU (2012)
- Causes significant morbidity, long term sequelae
- Available preventive measures
- Increasing endemic areas in Europe and Asia
- Prolongation of season
- Important issue of travel medicine
- Underestimated risk
Background

• No previous guidelines
• No standards and no etiologic treatment
• Management recommendations published mostly for prevention but not for treatment
  – WHO position paper on vaccines against TBE (by GRADE system)
  – International Scientific Working Group on TBE (ISW-TBE)
• Regulations in the EU
  – European Centre of Disease Prevention (ECDC): epidemiology; diagnostic criteria
  – EC Decision on case definitions of communicable diseases
  – European Surveillance reports
• Interdisciplinary: neurology, infectious diseases, intensive care

Sections of TBE guidelines

1. Epidemiology
2. Virology
3. Vaccination
4. Clinical characteristics and diagnosis
5. Therapy
6. Outcome and prognosis
7. TBE in children
Literature search

- 1970-2013
- No language restriction
- Databases
  - MEDLINE
  - EMBASE
  - Cochrane Library
- Full articles
  - Original articles
  - Reviews and meta-analyses
  - Regulations: WHO, EU, ECDC
- 6408 references retrieved
- 229 references used

Keywords: TBE +
- epidemiology, etiology, virology
- prevention, vaccine, vaccination, antibodies
- clinical picture, manifestations, diagnosis, differential diagnosis
- laboratory testing, cerebrospinal fluid/CSF, serology, serological tests, polymerase chain reaction/PCR
- imaging
- treatment, therapy, emergency, intensive care
- brain oedema, temperature, seizure
- rehabilitation
- outcome, prognosis
- children, paediatric

GRADE: the Grading of Recommendation Assessment, Development and Evaluation

- Assessment of quality of evidence for every outcome
  - downgrading and
  - upgrading factors
- Assessment of balance between advantages and disadvantages
- Judgement about the direction and strength of recommendation

Quality of evidence:
- High
- Moderate
- Low
- Very low

Direction:
- For
- Against

Strength:
- Strong
- Weak

Recommendations: (1) (2) (3) (4)
Vaccination

• Epidemiology is a basis for vaccination
• Highest risk: Russia, Baltic states, Slovenia, Czech
• TBE virus – in the family Flaviviridae
  – Subtypes: (1) European (Western); (2) Siberian; (3) Far Eastern
• 4 vaccines
  – Based on European subtype: FSME-Immun and Encepur
  – Based on Far Eastern subtype: TBE-Moscow and EnceVir
• Specific immune globulin for post-exposure prophylaxis

Vaccination

+ 
• WHO position paper based on GRADE system
• European vaccines approved by the European Medicines Agency – data
• Many studies available
• Experience of Austria

−
• No data on Russian vaccines – not appropriate for recommendations
• No data on breakthrough case rates in vaccinated population

Questions
  Efficacy and safety?
  Who to vaccinate?
  Schedule - booster interval?
  Cross-protection?
  Post-exposure prophylaxis?
Recommendation on vaccination with European vaccines

- For all age groups above 1 year in the highly endemic areas (≥5 cases/100000/year)
- For individuals at risk in areas with a lower incidence
- Travellers to endemic areas (if outdoor activities)
- The first booster immunization dose is recommended 3 years after the third primary vaccination dose, and later boosters every 5 years for people younger than 60 years and every 3 years for people older than 60 years
- Adults may be effectively and safely boosted with a different vaccine (FSME-Immun or Encepur).

GRADE: high quality of evidence; (1) strong recommendation for using vaccination against TBE.

Recommendation on post-exposure prophylaxis

- It is not recommended to use post-exposure prophylaxis after a tick bite.

GRADE: low quality of evidence; (3) weak recommendation against using post-exposure prophylaxis.

Clinical characteristics and diagnosis

- Biphasic course
- Various syndromes: (1) meningitic; (2) encephalitis; (3) myelitis
- Differential diagnosis from meningitis and encephalitis caused by other viruses, and other tick borne diseases

Questions:
- Method of choice for laboratory diagnosis of TBE?
- When to perform lumbar puncture?
- Case definition: clinical and laboratory criteria?
- Is imaging recommended for diagnosis?
**Recommendation on antibody detection**

- Detection of TBEV IgM and IgG antibodies in a serum by ELISA is the method of choice for diagnosis of TBE.
- In areas with possible exposure to other pathogenic flaviviruses (yellow fever, Dengue, West Nile virus), the virus neutralisation test should be used to assess the specific immunity against TBEV.
- **GRADE: high quality of evidence; (1) strong recommendation for using specific antibody detection for diagnosis of TBE**

**Recommendation on PCR diagnostics**

- TBEV specific PCR is diagnostic in the first viremic phase. It is not sensitive in the second phase of TBE.
- **moderate quality of evidence; (2) weak recommendation for using PCR.**

**Recommendation on lumbar puncture to examine CSF**

- Lumbar puncture should be performed in all patients with suspected CNS infection unless there are clinical contraindications: presence of signs of intracranial pressure (ICP) including focal signs and symptoms, seizures, coagulopathy or local infection.
- An elevated CSF pleocytosis >5 cells/µl is a diagnostic marker for TBE in the presence of specific serum antibodies and corresponding clinical picture.
- **GRADE: moderate quality of evidence; (2) strong recommendation for using lumbar puncture and testing CSF**

**Recommendation on imaging**

- Imaging of the brain and spinal cord has low sensitivity and low specificity in the diagnosis of TBE, but it is useful for differential diagnosis.
- Brain and spinal MRI may show diverse pathology in about 20% of TBE patients.
- **GRADE: very low quality of evidence, based on good clinical practice and consensus; (2) weak recommendation for using imaging for diagnosis of TBE**
Definition of a case of TBE:
combined clinical criteria based on the EU decision
on case definition and clinical presentations

<table>
<thead>
<tr>
<th>Definition</th>
<th>Confirmed case</th>
<th>Probable case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and/or epidemiologic</td>
<td>Symptoms of CNS inflammation: meningitis, meningoencephalitis or encephalomyelitis, and an epidemiologic link</td>
<td>Symptoms of CNS inflammation: meningitis, meningoencephalitis or encephalomyelitis; or clinical criteria together with an epidemiologic link</td>
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<tr>
<td>criteria</td>
<td></td>
<td></td>
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<tr>
<td>CSF findings</td>
<td>Pleocytosis &gt;5 WBC/μl</td>
<td>Pleocytosis &gt;5 WBC/μl</td>
</tr>
<tr>
<td>Microbiological/serological criteria</td>
<td>- TBE specific IgM AND IgG antibodies** in blood; or - TBE specific IgM antibodies in CSF; or - Four-fold increase of TBE-specific antibodies in paired serum samples; or - Detection of TBE viral nucleic acid in a clinical specimen</td>
<td>TBE-specific IgM-antibodies in a single serum sample (if no epidemiologic link)</td>
</tr>
</tbody>
</table>

Treatment

- Problem: studies are available on neuroinfections but not specifically for TBE

- Questions:
  - What kind emergency interventions are recommended?
  - Which is an appropriate department to treat TBE?
  - What are recommended symptomatic treatment options?
  - Antiviral treatments and immunomodulation?
**Recommendation on emergency management**

- Every patient with a potentially life threatening course of meningoencephalitis, encephalitis and myelitis should be admitted to and managed in a (Neuro) ICU
- If clinical signs and symptoms, electrophysiology and/or neuroimaging indicate increased intracranial pressure or status epilepticus, intracranial pressure/ cerebral perfusion pressure (ICP/CPP) monitoring, temperature management and, if possible, continuous EEG monitoring are indispensable
- If ICP is elevated (20-25 mmHg) or CPP is dangerously low (50-60 mmHg), immediate follow-up neuroimaging is mandatory

**GRADE:** low quality of evidence, based on good clinical practice and consensus; (2) weak recommendation for emergency management
**Recommendation on symptomatic treatment**

- In case of brain edema, analgosedation should be deepened
- Osmotherapy could be considered exclusively as boluses and restricted to a period of maximally 1–2 days
- Corticosteroids should not be used routinely
- If ICP continues to be elevated and CPP is threateningly decreased, therapeutic hypothermia, and in single cases, decompressive craniectomy might be considered
- Epileptic seizures or status should be treated with intravenous benzodiazepines, phenytoin, valproic acid, levetiracetam, or anaesthesia as any other symptomatic epileptic seizures
- Low molecular weight heparins are suggested for prophylaxis of early deep vein thrombosis.

**GRADE:** generally, symptomatic treatment is of low quality of evidence, as it based on good clinical practice and consensus, and there are no specific studies in TBE; (2/3) weak recommendations for or against using symptomatic treatment.

**Grading by treatment options:**

- low quality of evidence, (3) weak recommendation against using corticosteroids – not suggested;
- moderate quality of evidence, (3) weak recommendation against using osmotherapy (including continuous infusion or prolonged osmotherapy) – not suggested;
- low quality of evidence, (2) weak recommendation for using hypothermia;
- very low quality of evidence, (2) weak recommendation for using decompressive craniectomy;
- low quality of evidence, (2) weak recommendation for using epilepsy treatment;
- low quality of evidence, (2) weak recommendation for using thrombosis prophylaxis.
**Recommendation on antiviral and immunomodulating treatment**

- No effective antiviral, immunomodulating or other adjunctive therapy, including neuroprotective therapy, is available for treatment of TBE

- **GRADE: very low quality of evidence; (3) weak recommendation against antiviral and immunomodulating treatment – not suggested.**

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**Conclusions**

- TBE is of increasing health burden in Europe
  - Occupational exposure, leisure time activities, climate changes
  - Travel to endemic areas – an international problem
- No previous guidelines on TBE
  - Lack of evidence on therapy specifically for TBE
  - Existing European surveillance and WHO position on vaccination

**New ENS/EFNS (EAN) guidelines on management of TBE:**
- Evidence based strong recommendations on vaccination
- High/moderate quality of evidence for diagnostic measures
- Consensus based recommendations on therapy
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