Thieme

Tick-borne Encephalitis (TBE)*

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ABSTRACT

Tick-borne encephalitis (TBE) is an acute inflammation of the nervous system caused by a virus of the same name. Reservoirs for the TBE viruses are small rodents of the forest and meadows and rarely also goats, which explains the spatial limitation to endemic areas ("natural foci"). TBE virus is transmitted mainly by ticks, but occasionally also by products from non-pasteurized goat's milk. Infections can occur throughout the year, but most of the diseases present during the high summer months. More than 90 % of infections occur during leisure time. However, it is a typical occupational disease for farmers and foresters. In approximately 70 % of the patients, TBE manifests itself with a two-phase fever course.

After an incubation period of 5–28 days, the patients first develop a general feeling of illness, headaches and fever (prodromal phase). After a temporary improvement, a new episode of fever marks the beginning of the second phase of the disease a few days later. This is manifested in about 50 % of the cases as isolated meningitis, in 40 % as meningoencephalitis and in 10 % as meningoencephalomyelitis. Frequently, there are quantitative and qualitative disturbances of consciousness and ataxia. The early onset of swallowing and speech disturbances, paralysis of the facial and throat muscles as well as the need for assisted ventilation indicates an unfavorable prognosis. In children and adolescents, TBE is often unspecific with the symptoms of a flu infection and thus more benign than in adults. With age, not only the course is more serious, but also the number of residual deficits increases.

The diagnosis is based on history with stays in a risk area, the neurological symptoms with marked impairment of the general condition, the demonstration of TBE-specific IgM and IgG antibodies in the blood and a pleocytosis in the CSF. No specific treatment for TBE is known so far, but TBE can be successfully prevented by active immunization. Vaccination is recommended for all persons who stay repeatedly in a risk area.

Clinical Treatment Pathway

Diagnosis

- Stay in a TBE risk area
- Significantly reduced general condition with high fever and headaches
- Neurological deficits such as disturbances of consciousness and balance, paralysis of cranial nerves or extremities
- Evidence of TBE-specific IgM and IgG antibodies in blood
- Pleocytosis in CSF (normal cell count in extremely rare cases)
- Elevated TBE-specific antibody index at the latest 4 weeks after start of symptoms (in the event of doubt)

Therapeutic procedure

- In the first 72 h, review of neurological findings and vital capacity every 6 h (due to possibility of rapid development of brain stem encephalitis and/or myelitis requiring assisted ventilation)
- There is no specific antiviral treatment available. Nothing is known about the possible efficacy of immunomodulators.
- Fever reduction only if > 39 °C
- Analgesia and seizure treatment as required
- Rehabilitation as required

What's New?

Forgotten booster shots are no reason to repeat primary immunization. Every vaccination counts. Therefore the number of previous vaccinations determines the number of additional vaccinations needed to attain immunity from TBE [1].

* The text of the guidelines and the conflict of interest declaration are located at www.dgn.org/leitlinien and www.awmf.de

Most Important Recommendation at a Glance

Because the course of TBE is often serious and more than one-third of those infected suffer permanent neurological damage, active vaccination for TBE is recommended for all persons over the age of 3 who repeatedly stay in risk areas.

Introduction: Scope and Purpose of the Guidelines

Why guidelines are necessary

TBE is a disease with an elevated risk of subsequent damage, disability and death. It can be prevented by immunization, which is recommended only for at-risk persons. These guidelines are designed to support argumentation for an individual indication for vaccination.

Objectives of the guidelines

These guidelines are intended to provide information on the risk of TBE infection, disease course, diagnosis, prognosis, and the possibility to prevent the disease through vaccination.

Patient target group

All persons who plan on spending time in a TBE risk area.

Care area

Outpatient care for prevention and diagnosis; inpatient care for diagnosis, treatment, follow-up care, rehabilitation and assessment.

Target audience

Practicing general practitioners, internists, neurologists, pediatricians. Neurologists in acute-care clinics and rehabilitation facilities, consultants, and those interested in vaccines.

Key words

TBE, tick-borne encephalitis, meningitis, encephalitis, myelitis. ICD 10: A84.1.

Definitions and Basic Information

Synonyms

Tick encephalitis, Central European encephalitis (CEE), tick-born encephalitis (TBE), Kumlinge disease, Siberian tick-borne encephalitis

Pathogens

Tick-borne encephalitis (TBE) is an acute inflammation of the brain, spinal cord and meninges caused by a virus of the same name. The TBE virus contains a plus-strand RNA which codes for three structural proteins and seven additional proteins. The RNA is encapsulated in a capsid protein and an additional lipid shell containing the membrane protein (M) and the envelope protein (E). In infection or immunization, the virus-neutralizing immune response targets this E glycoprotein. In a comparison of the three subtypes of TBE (European, Siberian, Far Eastern), there was a 97 % match of glycoprotein E, meaning that vaccination against the European subtype is effective against the other two [2, 3].

Transmission

The main reservoirs for TBE viruses are small forest and field rodents and, in rare cases, goats. TBE viruses are transmitted primarily by ticks (Ixodes ricinus in Western Europe, Ixodes persulcatus in Eastern Europe, Russia, and Asia); only about 70 % of those infected can recall being bitten [4]. Depending on the region, 0.1–5 % of ticks are infected with the virus, although higher prevalence rates were found in individual regions of southeastern Germany [5]. Mature ticks are usually found in vegetation 30–60 cm from the ground, less frequently as high as 1.5 m; they do not fall from trees. They can occur in mountain regions up to a geographic height of approx. 1 500 m above sea level. They become active at approx. 6–8 °C, and a local humidity of > 80 % is also important. The TBE viruses are transmitted within the first few hours after the tick bite. In rare cases the virus can come from infected goat's milk (cheese from unpasteurized milk) [6–8].

Most infections occur between March and November, peaking during the summer months. However, infections can occur throughout the entire year depending on weather conditions.

Epidemiology

Epidemiological studies show that > 90 % of infections are acquired during leisure time [4]. The clinical manifestation rate of the TBE virus infection is approx. 33 %. The varying courses of the disease can be explained by differences in individual resistance levels and the virulence and number of transmitted viruses [9, 10].

In Germany, a TBE risk area is defined as a district or region in which the number of transmitted TBE diseases is significantly higher than the expected incidence of 1 in 100 000 inhabitants. Neither Austria, Switzerland nor other European countries have corresponding definitions for risk areas, where they are generally called distribution areas.

TBE risk areas in Germany

https://www.rki.de/DE/Content/InfAZ/F/FSME/Karte_FSME.pdf?__blob=publicationFile

TBE distribution areas in Austria

http://www.zecken.de/de/fsme/fsme-europa

TBE distribution areas (natural foci, endemic areas) in Switzerland

https://map.geo.admin.ch/?layers=ch.bag.zecken-fsme-impfung&topic=ech&lang=de&bgLayer=ch.swisstopo.pixelkarte-farbe&layers_opacity=0.75
Tick-borne encephalitis, distribution of endemic areas. Date: 2015 (PDF)

Principal symptoms

In approx. 70 % of patients, TBE has a biphasic course of fever. An average 10-day incubation period (5–28 days) is initially followed by a prodromal phase of approx. 1 week of general malaise, headaches,

fever and occasionally abdominal pain. Serology and CSF can still be unremarkable at this point in time. After a temporary improvement, a new episode of fever marks the beginning of the second phase of the disease a few days later. This second phase manifests in approx. 50 % of cases as meningitis, in approx. 40 % as meningoencephalitis, and in approx. 10 % as meningoencephalomyelitis [4]. In rare cases, fever is the sole clinical feature of TBE [11].

The clinical symptoms of the purely meningeal form of TBE are not substantially different from other forms of viral meningitis; however general health is frequently more severely affected, headaches are more intense, and the fever is often very pronounced. Ataxia, impaired consciousness, and paralysis of the extremities and cranial nerves are primarily signs of meningoencephalitis. Meningoencephalomyelitis manifests primarily in the area of the anterior horns and is therefore associated with flaccid paralysis of the musculature of the extremities. Because it frequently occurs in association with brain stem encephalitis, there are often swallowing and speech disturbances, paralysis of the facial and throat muscles, and respiratory paralysis. An isolated myelitis [12–15] or radiculitis [16] and disease progression without an initial fever or pleocytosis [17, 18] occur as infrequently as autonomic regulation disturbances [19]. As age increases, the overall course of TBE is more serious and it more frequently leaves behind persistent deficits [4].

In children and adolescents, TBE is often nonspecific with symptoms of a flu infection and is thus more benign than in adults [20, 21]. In recent years, however, there have been reports of children with protracted neurological dysfunction [11, 22–34]. The youngest child with a TBE virus infection was 17 days old [25]. The primary clinical presentation was a focal seizure with subsequent hemiparesis that did not diminish after 2 months. Brain MRI initially showed brain edema of the entire left hemisphere with atrophy in this area two months later.The further disease course is unknown.

There have been rare reports of double infections with the TBE virus and Borrelia burgdoferi s.l.; such cases usually had very severe clinical features [35, 36].

Typical symptoms of TBE

- Significantly impaired general health
- High fever
- Headaches
- Balance problems
- Qualitative and quantitative disturbances in consciousness (incl. severe sleepiness, disorientation)
- Cranial nerve paralysis (facial paralysis, difficulty hearing, swallowing and speaking)
- Paralysis of the arms and legs
- Twitching of the facial muscles (myoclonus) and the extremities

Diagnosis

Preamble

The diagnosis of TBE is based on an history with a stay in a risk area, possible recall of tick bite, a prodromal phase with flu-like symptoms, typical neurological symptomatology of headaches and fever, evidence of inflammatory changes in the blood and CSF, and presence of TBE-specific IgM and IgG antibodies in the blood [37].

Flow chart

Tentative clinical diagnosis → serology → CSF analysis

Diagnosis

Blood analysis usually indicates leukocytosis in excess of 10 000 (3 000–40 000) cells/µl, accelerated blood sedimentation rate (5–120 in the first hour) and/or an increase in C-reactive protein (1–60 mg/dl) [4].

Approx. 2–4 weeks after the tick bite, serological tests first show TBE-specific IgM antibodies; 1–2 weeks thereafter specific IgG antibodies are also present. Along with the corresponding clinical symptoms and lack of TBE vaccination, only the simultaneous detection of IgM and IgG antibodies for the TBE virus in the blood substantiates acute infection. Isolated or only slightly elevated IgM antibodies (without IgG) are also found as a cross-reaction against other flaviviruses or other types of immune stimulation and therefore do not confirm the diagnosis [38]. However if the concentrations of TBE-specific IgM antibodies are significantly elevated at the time of acute illness, they can serve as a valuable diagnostic indicator (but not proof) of the corresponding infection [39]. In these cases, testing for IgG antibodies should be repeated approx. 1–4 weeks later to confirm the diagnosis.

In rare cases (e. g., immunodeficiencies,-suppression, vaccination failure), no IgM antibodies are detected. In such cases, the significant increase in IgG antibodies after > 2 weeks, the determination of intrathecal synthesis of TBE-specific IgG antibodies in the CSF (antibody index), detection of TBE RNA in the CSF via PCR, or the avidity determination of IgG antibodies [40] can be used to confirm diagnosis (in order of practicability) [41].

Lactate in CSF is usually normal or slightly elevated (< 3.5 mmol/l) [42].

Further diagnostics

Among the imaging technologies, magnetic resonance imaging is most useful for the often initially necessary differential diagnosis from herpes simplex encephalitis. Unlike the latter, in nearly 20 % of patients TBE shows signal changes primarily in the thalamus and corpus callosum [4, 43, 44]. Occasionally, especially with immune deficiencies/suppression/modulation, areas of inflammation can be seen in other areas of the brain and spinal cord [45–49]. Because there is no verifiable correlation between these signal anomalies and the severity or prognosis of the disease, there is no compelling indication to perform an MRI [4].

Differential diagnosis

Neuroborreliosis is seldom associated with high fever and severe impact on general health as usually observed in TBE. Headaches tend to be uncommon in adults with neuroborreliosis (although they are frequent in children), whereas Bannwarth syndrome is especially marked by pain in the extremities and occasionally the torso. Sensory disturbances occur very rarely in TBE, whereas they are frequent in neuroborreliosis [50].

Differential diagnosis for herpes encephalitis (HSE) requires an MRI of the brain that shows the typical changes in the temporal re-

gion associated with HSE and a positive PCR for HSV in the cerebral spinal fluid. An antiviral treatment for HSE should be administered as a precaution until a definitive diagnosis is made.

Treatment

General recommendations for treatment

There is no specific treatment for TBE. Due to the risk of worsening immune defenses, immune-modulating drugs such as glucocorticoids should be avoided in particular. Fevers, headaches and seizures are treated symptomatically. A general reduction in fever is not recommended due to immune issues, although fever usually drops with acetaminophen or metamizole treatment for headaches. Fore severe headaches NSAID's such as diclofenac or ibuprofen can be used, if not adequately effective, opioids. Approximately 5 % of patients require treatment in intensive care due to respiratory paralysis or seriously impaired consciousness. Certain neurological functional problems require physical, occupational and speech therapy.

Prognosis

Approximately 40 % of TBE patients require long-term rehabilitation (phase B –D) [51].

The meningeal form has the best prognosis and is usually without sequelae. Patients with meningoencephalitis frequently suffer from neurasthenic symptoms (headaches, increased tiredness, decreased resilience, emotional instability) that persist over several weeks. Some patients experience temporary and even permanent difficulties with concentration and memory, coordination, speech, hearing as well as paralysis. Only partial recovery is expected in approximately 20 % of patients with meningoencephalitis [4, 51–59].

Encephalomyelitis has the poorest prognosis. Of 57 patients followed over 10 years, only 20 % recovered completely; 50 % had permanent deficits and 30 % died from the sequelae of the disease [60].

Usually there is no significant improvement of symptoms persisting three years after the acute illness phase in patients with encephalitic or myelitic form of TBE [52, 54, 60].

The prognosis of TBE is, however, often better in children than adults, although follow-up neuropsychological testing revealed deficits not cited in previous surveys in up to one third of the children and adolescents tested [11, 22–34].

Description of risk

In risk areas, the average incidence of ticks with the TBE virus is approx. 1:50 and the clinical manifestation rate approx. 1:3. Therefore the risk of contracting TBE from a tick bite is approx. 1:150, and 1:500 for developing severe sequelae.

Prophylaxis

Recommended vaccinations

All clinical experience (there are no related prospective studies) indicates that going through TBE (verified by significantly elevated IgG antibodies in the blood) gives one life-long immunity that does not require booster shots.

According to the Standing Committee on Vaccination (STIKO), the recommendations for TBE vaccination in Germany are as follows:

- **Travel vaccinations** for stays in TBE risk areas outside of Germany,
- **Indicated vaccinations** for persons in Germany who stay in TBE risk areas and for persons who are occupationally at risk.

In Austria, TBE vaccinations are recommended for all persons over the age of 1 who live in or travel to an endemic area. Infants over the age of six months can be vaccinated after careful risk/benefit analysis. The booster intervals are the same as those recommended in Germany. For the valid vaccination schedule for Austria, see http://www.bmg.gv.at.

In Switzerland, the Swiss Federal Office of Public Health (FOPH) recommends vaccinating all adults and children (generally over the age of 6) who live in or occasionally travel to an endemic area (http://www.bag.admin.ch/themen/medizin/00682/00684/01069/index.html?lang=de).

After a primary immunization of 3 doses, a booster vaccination is recommended only every 10 years (Bull BAG 2006; No. 13: 225-31.24.3.2006; and Bull BAG 2013; No. 18: 305-307. 30.04.2013).

Active vaccination

Active immunization against TBE protects against infection from all three subtypes [61, 62]. The complete primary immunization provides initial protection for a minimum of three years. Primary immunization consists of three injections, the second given 1–3 months after the first and the third 9–12 months after the second. The first booster should be given 3 years thereafter; those under 50 (60 in Austria) require a booster no later than 5 years thereafter, and those over the age of 50 (60 in Austria) require a booster after 3 years. A recently published study on children and adolescents up to the age of 15 years indicated that the interval for the initial booster for Encepur Children, but not for FSME Immun-Junior, could be extended from 3 to 5 years [63].

In Switzerland, booster vaccinations are recommended only every 10 years. The corresponding vaccines can be used interchangeably (exception: fast immunization) [64–66].

Forgotten booster shots are no reason to repeat primary immunization as long as the latter was performed lege artis. Based on the number of prior vaccinations, the following procedure is recommended [1]:

- One previous vaccination: Administer one TBE vaccination and another 5–12 months later to complete primary vaccination. Administer first booster three years later and additional boosters after 3–5 years, depending on age
- Two previous vaccinations: Administer one TBE vaccination to complete primary vaccination. Administer first booster three years later and additional boosters after 3–5 years, depending on age
- Three previous vaccinations: Administer one booster and additional boosters after 3–5 years, depending on age
- Four or more previous vaccinations: Administer the next TBE vaccination and additional boosters depending on age 3–5 years after the last TBE vaccination

Contraindications for vaccination include acute illness, an anaphylactic reaction to an earlier vaccination or a component of the

▶ **Table 1** Vaccines in German speaking countries: Dose in relation to age.

Germany	Austria	Switzerland	Age group
Encepur Children®	Encepur 0.25 Children®	Encepur Children®	Ages 1–11
Encepur Adults®	Encepur 0.5 Adults®	Encepur N®	Over 12 years of age
FSME-Immun® Junior	FSME-Immun® 0.25 Junior	FSME-Immun® 0.25 Junior	Ages 1–15
FSME-Immun®	FSME-Immun 0.5®	FSME-Immun® CC	Over 16 years of age

vaccine. Vaccination during pregnancy requires careful risk assessment. There is no experience with vaccinating pregnant women.

Vaccines

In 2015, the vaccines Encepur Children and Encepur Adults were sold by Novartis to Glaxo Smith Kline; FSME-Immun Junior and FSME-Immun were sold by Baxter to Pfizer. The names of the medications were retained. (▶ **Table 1**)

Vaccination failure and reactions/complications

The risk of vaccination failure after a complete primary vaccination is estimated at approx. 1/800 000 per year. In most cases, the affected individuals were >50 years of age, explainable to some degree due to age-related weakness of the immune system [67]. In individual cases, however, no plausible explanation could be found [68]. Furthermore, current studies found indications of insufficient immunization in some individuals over the age of 50 when antibodies were measured as surrogate markers of success. Because persons in this age group are increasingly interested in TBE vaccination, testing of a modified vaccination schedule appears warranted [69, 70]. Because vaccine protection can ultimately be determined only by measuring the neutralizing antibodies, which is possible only in scientific studies, only regular boosters can be recommended at the present time.

Vaccination is generally well tolerated. As with all vaccines injected intramuscularly, local reactions can develop at the injection site with temporary pain, redness, and swelling (up to 10 %). Systemic reactions observed include general malaise, flu-like symptoms and fever, especially after the first vaccination (up to 10 %).

According to calculations based on the number of vaccine doses sold between 2002 and 2009 (data from Baxter and Novartis) and the number of suspected cases in the same time period assessed by the Paul Ehrlich Institute (one confirmed and 66 probable cases, personal report from Dr. Keller-Stanislawski), the risk of neurological complications is 1.5 per million vaccinations, far below that of the tetanus vaccination (10 per 1 million vaccinations).

What to do after a tick bite in a TBE risk area

Passive vaccination, i. e., post-exposure administration of a specific hyperimmunoglobulin, is no longer offered by manufacturers and is therefore not possible.

Due to a lack of clinical, epidemiological and experimental data, active immunization immediately after a tick bite in a risk area is generally not recommended.

For related recommendations in Austria, see the current vaccination schedule at: http://bmg.gv.at.

General protective measures

Measures to prevent tick-borne infections include wearing clothing that provides snug, gap-free coverage; avoiding brush; using repellents; and checking the body for ticks and removing them as quickly as possible. Repellents, however, provide only partial coverage and only for a few hours; the measures described do not guarantee protection from infection.

Mandatory reporting

In Germany, TBE is an occupational illness No. 3102 and must be reported to the relevant health authorities. Furthermore, diagnosing laboratories must report the disease to the responsible health authorities.

Coordination of Care

Prevention: outpatient

Diagnosis and treatment: Due to the risk of rapid and dramatic deterioration (respiratory insufficiency), patients with suspected TBE should always be hospitalized.

Editorial Committee

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Declaration of Interests

The declarations of interests of all members of the guidelines group were reviewed by an independent conflict of interest officer of the German Neurological Society (DGN) for related conflicts of interest. In his opinion, there are no conflicts of interest that would limit the objectivity of the contributions.

"Wolfgang Jilg and especially Sebastian Rauer have multiple connections with industry as paid consultants and experts, receiving in some cases not insignificant honoraria. These connections, however, do not represent any thematically relevant conflict of interest in the preparation of the guidelines, because none of the pharmaceutical companies indicated manufactures TBE vaccines. The remaining authors have no connections to industry. Therefore more than 50 % of the editorial committee have no conflicts of interest. The proven technical competency of the authors and the composition of the editorial committee guarantee the objectivity of the guidelines."

The detailed declarations of interest of all participants in accordance with the Association of the Scientific Medical Societies in Germany (AWMF) are retained by the coordinator and can be requested by legitimate parties.

Guideline Development Methodology

Members of the guideline group

The Guideline Committee of the DGN selected the lead author and other members of the guideline group.

Research and selection of scientific evidence

The literature was selected through PubMed using the following search terms: Tick-borne encephalitis, TBE, diagnostic procedure, treatment, prevention, symptoms, follow-up, sequelae, vaccination. The corresponding publications were considered with respect to their relevance for practicing physicians, clinicians, and those interested in vaccines.

Consensus-building procedure

These guidelines were prepared using a modified Delphi method and corrected by the Guideline Committee of the DGN.

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Conflict of interest

See conflict of interest declaration at www.dgn.org/leitlinien.

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