EAN consensus review on prevention, diagnosis and management of tick-borne encephalitis

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Background and purpose: Tick-borne encephalitis (TBE) is an infection of the central nervous system (CNS) caused by tick-borne encephalitis virus (TBEV) and transmitted by ticks, with a variety of clinical manifestations. The incidence of TBE in Europe is increasing due to an extended season of the infection and the enlargement of endemic areas. Our objectives are to provide recommendations on the prevention, diagnosis and management of TBE, based on evidence or consensus decisions.

Methods: For systematic evaluation, the literature was searched from 1970 to 2015 (including early online publications of 2016), and recommendations were based on evidence or consensus decisions of the Task Force when evidence-based data were not available.

Recommendations: Vaccination against TBE is recommended for all age groups above 1 year in highly endemic areas ($\geq$5 cases/100 000/year), but also for individuals at risk in areas with a lower incidence. Travellers to endemic areas should be vaccinated if their visits will include extensive outdoor activities. Post-exposure prophylaxis after a tick bite is not recommended. A case of TBE is defined by the presence of clinical signs of meningitis, meningoencephalitis or meningoencephalomyelitis with cerebrospinal fluid (CSF) pleocytosis ($>5 \times 10^6$ cells/l) and the presence of specific TBEV serum immunoglobulin M (IgM) and IgG antibodies, CSF IgM antibodies or TBEV IgG seroconversion. TBEV-specific polymerase chain reaction in blood is diagnostic in the first viremic phase but it is not sensitive in the second phase of TBE with clinical manifestations of CNS inflammation. Lumbar puncture should be performed in all patients with suspected CNS infection unless there are contraindications. Imaging of the brain and spinal cord has a low sensitivity and a low specificity, but it is useful for differential diagnosis. No effective antiviral or immunomodulating therapy is available for TBE; therefore the treatment is symptomatic. Patients with a potentially life threatening meningoencephalitis or meningoencephalomyelitis should be admitted to an intensive care unit. In the case of brain oedema, analgosedation should be deepened; osmotherapy and corticosteroids are not routinely recommended. If intracranial pressure is increased, therapeutic hypothermia or decompressive craniectomy might be considered. Seizures should be treated as any other symptomatic epileptic seizures.

Conclusions: Tick-borne encephalitis is a viral CNS infection that may result in long-term neurological sequelae. Since its incidence in Europe is increasing due to broadening of endemic areas and prolongation of the tick activity season, the health burden of TBE is enlarging. There is no effective antiviral treatment for TBE, but the disease may be effectively prevented by vaccination.

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Introduction

Tick-borne encephalitis (TBE) is an infection of the central nervous system (CNS) caused by the tick-borne encephalitis virus (TBEV) that is transmitted by infected ticks or, rarely, by unpasteurized dairy products. A considerable increase in TBE morbidity has been observed in Europe over the decades, but different developments with fluctuations including periodical decreases of cases in some countries have been reported in recent years. However, a tendency for increase of areas and prolongation of the season has occurred across large endemic regions of Europe and Asia [1–3]. The risk of TBE is related to occupational exposure, outdoor leisure activities and travelling from non-endemic to endemic regions. The European Centre for Disease Prevention and Control (ECDC) included TBE in the list of notifiable diseases in the European Union (EU) in September 2012, as a disease with available preventive measures but causing significant morbidity [3–5].

Infection with TBEV is usually asymptomatic but can cause serious CNS inflammation. There is no effective antiviral treatment for TBE but patients need symptomatic treatment, including emergency management and intensive care interventions in severe cases. As immunization is an important measure to prevent TBE, morbidity of the disease could be reduced by improving awareness about TBEV infection, vaccination campaigns in endemic areas and recommendations for travellers [4–6].

The purpose of the Task Force on the Diagnosis and Management of TBE of the European Academy of Neurology (EAN) was to systematically review relevant publications on the diagnosis and management of TBE and to generate a consensus review to provide recommendations on the clinical management of TBE, based on evidence or consensus decisions. There are no previous guidelines on the management of TBE.

Methods and search strategy

The literature was searched from 1970 to 2015 using the MEDLINE, Embase and Cochrane Library databases that allowed a few early online articles dated for final publication in 2016 also to be included. A systematic search for original publications, review articles and meta-analyses, book chapters and guidelines was performed in English, German, Russian and Swedish languages by following keywords for 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, children, pediatric, outcome, prognosis. A total of 6749 references were retrieved, and of these 263 were selected for development of the recommendations.

The consensus review was developed according to Brainin *et al.* (2004), rating the evidence of studies as Class I–IV (with Class I the highest evidence) and the recommendations as Levels A–C (with Level A the highest rating) [7]. When evidence-based data were not available, consensus decisions based on good clinical practice and experience (Good Practice Points, GPP), were created by the Task Force, using the nominal group technique during the two Task Force meetings, followed by the modified Delphi process for further revising and finalizing the recommendations [8].

Epidemiology

The epidemiology of TBE comprises geographical distribution, age aspects, the influence of landscape, agricultural activities, leisure time activities, migration and travel of populations as well as political and climate changes occurring in the respective region [1,2,6]. The total number of annual cases is estimated to be up to 13 000 in the Eurasian northern hemisphere where this zoonotic flavivirus infection constitutes the most important tick-borne viral disease [6,9–11].

In nature, TBEV is propagated in a cycle involving permanently infected ticks and small mammals, e.g. rodents. The virus transmission occurs horizontally between ticks – as vectors – and vertebrate hosts [12]. Co-feeding of infected and non-infected ticks on the same host as well as transstadial and transovarial transmission of the virus play a major role in TBEV transmission [9,13]. Most TBEV infections of humans occur following a bite by an infected tick but a bite by an infected tick does not necessarily lead to an antibody response and only rarely results in clinical symptoms [14]. Alimentary routes of TBEV transmission by consuming raw milk or milk products, mainly from goats, are also possible [15–19]. The principal vector of the European TBEV subtype is *Ixodes ricinus* and for the other two (Siberian/Far Eastern) subtypes *Ixodes persulcatus* [2,9,11]. The epidemiology of TBE is influenced by the biology of ixodid ticks and their ecology, weather and climate, leisure time activities, land cover, land use, land tenure, travel and migration [4,9,20–23]. TBE is distributed in an endemic pattern, usually not occurring as epidemics; the natural foci cover a wide geographical area ranging from northern and eastern Asia, Russia, and northern and central Europe to more southern parts in the Balkans, Turkey, Greece and Italy [1,9]. Whereas the TBEV subtypes are closely related to the presence of the respective tick vectors, co-circulation of two or all three subtypes has been demonstrated in Finland and the Baltic states [24–26].

The incidence of TBE in European countries including Russia is shown in Fig. 1 [1,6,12,27–44]. Austria is a country with decreasing annual incidence to 1/100 000 due to vaccination; however, the occurrence of TBE is higher in unvaccinated tourists and Austrians [3,9,37]. Also in Sweden, a high risk for TBE in the unvaccinated population has been demonstrated [40].

In total, TBE is a growing concern in Europe as in some risk areas an increase of TBE has been observed.
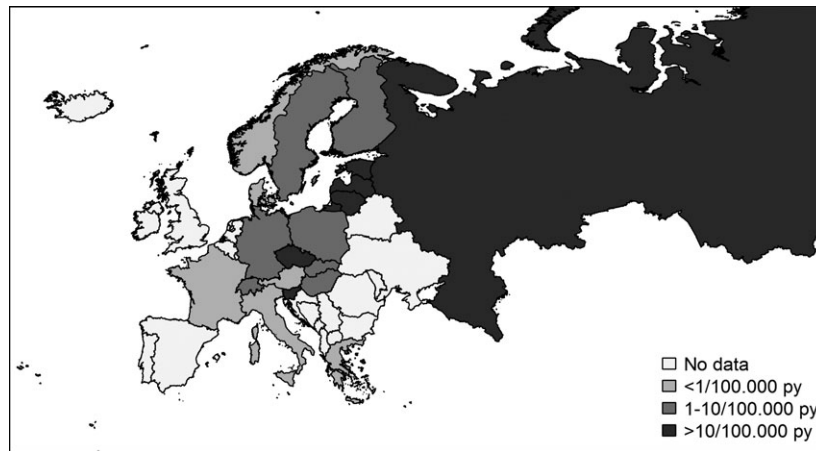
Figure 1 Annual incidence rates of tick-borne encephalitis per 100 000 inhabitants in the European countries.

Surveillance and notification schemes are not uniform and not mandatory in all European countries, diagnostic procedures vary, and the European case definition has only recently been proposed by the ECDC [41–43]. Therefore, the European network for the diagnostics of imported viral diseases contacted 31 European countries, 28 of which participated in a survey [2]. In 16 of these, TBE cases are mandatorily notifiable: Austria, Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Latvia, Lithuania, Norway, Poland, Russia, Slovakia, Slovenia, Sweden, Switzerland. In the other 10 countries TBE is not notifiable (Belgium, Bulgaria, Denmark, France, Italy, Malta, Portugal, Spain, The Netherlands, UK) [2,10,44]. Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Italy, Latvia, Lithuania, Russia, Slovenia, Sweden, Switzerland and France have reported an expanding distribution of TBE [1,24,25,28–30,32,37–39,45–47]. The countries with the highest reported annual incidence rates were the Czech Republic (incidence rate 10/100 000), Estonia (13.3/100 000), Latvia (14.6/100 000), Lithuania (18.5/100 000) and Slovenia (18.6/100 000) [2,29,30].

Besides the spread of TBEV and the prevalence of *Ixodes ricinus* in north and west directions, new endemic foci have been documented in parts of Siberia, Mongolia, northern China, the Korean peninsula, Kyrgyzstan, Armenia, Azerbaijan, Uzbekistan and Kazakhstan, also at altitudes of up to 2000 m. Thus, a horizontal and vertical expansion of prevalence at the margins of the known endemic areas can be seen [1,2,42]. The risk of contracting TBE is assessed to be 1:10 000 person-months for non-vaccinated tourists who spend 4 weeks in endemic areas of Austria [9,37]. TBE has become an important issue in travel medicine due to the risk for travellers to rural endemic areas, and implementation of risk strategies have been suggested by the World Health Organization (WHO) [4,48].

As a result of climatic changes, TBEV infected ticks might become more abundant [31,49–51]. Cold harsh winters may cause an abrupt decline in deer numbers, forcing host-seeking ticks to feed on other animals, thus enhancing the number of ticks feeding on reservoir competent rodents. Warm humid weather in spring and summertime, causing prolonged vegetation periods, permits nymphs and adult ticks to seek for hosts during an extended period. Also warm weather conditions stimulating people to spend time outdoors and increased occupational and recreational exposure are risk factors for TBE [23,27,31,51,52].

Virology

The TBEV is a flavivirus that belongs to a group of viruses transmitted via hard (ixodid) or soft (argasid) ticks. The vectors are able to support viral multiplication and to deliver it to the recipient vertebrate host. The tick vector also plays the role of a long-term reservoir of the virus [1,53]. The viral genome RNA by itself is infectious and produces virus progeny if introduced into susceptible cells [54]. Heparan sulfate is the major host cell receptor [55].

Most members of this *Flavivirus* genus are arthropod-borne. There are three recognized TBEV subtypes: European or Western, Siberian and Far Eastern. The European subtype of TBEV predominates in Europe; however, all three subtypes are present in the Eastern part of the continent. In addition, TBEV is very closely related with only up to 5%–6% genetic and antigenic variation to louping-ill virus which is regarded as the fourth subtype of TBEV [56]. Immunization with a vaccine based on the European subtype showed cross-protection against the Siberian and Far Eastern subtypes [57,58].

Vertebrate hosts of TBEV are small forest mammals, especially rodents but also goats, sheep and cattle [59]. TBEV causes a fatal disease mainly with diffuse meningoencephalitis in certain suckling and adult laboratory animals such as mice and rats [60]. The virus can persist in milk and survives an acid gastric environment but is inactivated by pasteurization [16,18].

Table 1 Vaccines against tick-borne encephalitis (TBE)

Vaccine	Encepur® Encepur® Children	FSME-IMMUN®/TicoVac® FSME-IMMUN® Junior/ TicoVac® Children	TBE-Moscow	EnceVir
TBEV strain	European: K23	European: Neudörfl	Far Eastern: Sofjin	Far Eastern: 205
Antigen content	1.5 μg (adults) 0.75 μg (children)	2.4 μg (adults) 1.2 μg (children)	0.5–0.75 μg	2.0–2.5 μg
Stabilizer	Sucrose	Human albumin	Human albumin	Human albumin
Ingredients	Traces of formaldehyde, gentamicin, neomycin		Traces of formaldehyde, protamine sulfate	
Immunization schedule after the initial dose of vaccine				
Second dose	1–3 months	1–3 months	1–7 months	5–7 months
Third dose	9–12 months	5–12 months	12 months	12 months
First booster	3 years	3 years	3 years	3 years
Next boosters	5 years (3)[a]	5 years (3)[b]	3 years	3 years

TBEV, tick-borne encephalitis virus. [a]3 years for patients older than 50 years; [b]3 years for patients older than 60 years.

The virus initially multiplies at the site of inoculation, mainly in the dendritic skin cells, which transmit the virus to local lymph nodes where lymphocytes get infected and eventually spread the infection systemically. Following replication in lymphatic organs, the TBEV reaches the brain via the circulation and crossing the blood−brain barrier. Once endothelial cells in the brain are infected, the TBEV enters the parenchyma. Meninges show diffuse infiltration by lymphocytes and neutrophils, more pronounced around the cerebellum. Infection is observed all over the CNS but involves particularly the brainstem, cerebellum, basal ganglia, thalamus and spinal cord [55,60]. Immunological response may contribute to brain tissue damage, and the inflammatory reaction mediated by CD8^{+} T cells induces neuronal damage and could lead to a fatal outcome [61]. Increased levels of cytokines, chemokines, growth factors, interferons and interleukins in serum or cerebrospinal fluid (CSF) confirm activation of inflammatory mediators in TBE [62–64]. Following TBE, immunoglobulin G (IgG) antibodies persist for a lifetime and provide immunity [65].

Vaccination

Prevention of TBE

Immunization remains the best prevention of TBE as there is no specific therapy. TBE vaccines are based on formalin inactivated strains of TBEV, produced in cell cultures. Four widely used vaccines are available. Two of them are based on the European subtype TBEV strains. FSME-IMMUN®/TicoVac® has been produced by Baxter (Vienna, Austria) but Pfizer is a marketing authorization holder at present. Encepur®, which has been produced by Novartis (Marburg, Germany), is marketed by GlaxoSmithKline. The European vaccines are produced according to the WHO Good Manufacturing Practice Guidelines and registered by the European Medicines Agency (EMA) [66]. Two other vaccines based on the Far Eastern subtype, TBE-Moscow (Chumakov Institute, Moscow) and EnceVir (Microgen, Tomsk) are manufactured in Russia and are not authorized by the EMA (Table 1) [67–71]. Additionally, a TBE vaccine based on the Far Eastern subtype is produced and marketed in China by the Changchun Institute of Biological Products [71]. Specific Ig for post-exposure prophylaxis is no longer available in Europe, and not recommended as it may cause a more severe course of TBE [69,72–76]. Non-specific prevention strategies include removal of ticks, use of repellents and adequate clothing when there is a risk for contact with ticks, and pasteurization of milk [71].

Immunization strategies and schedules

Public immunization strategies against TBE are considered according to the local endemic situation, based on risk assessment on regional and country levels [9,77,78]. In areas where the disease is highly endemic (≥5 cases/100 000/year), WHO recommends that vaccination should be offered to all age groups above 1 year of age. In regions with a moderate or low TBE incidence (<5 cases/100 000/year), immunization should target individuals at risk, i.e. those working under high risk conditions or having outdoor activities. Travellers from non-endemic to endemic areas should be vaccinated if extensive outdoor activities are expected [4,45,69,79,80]. Immunization offers the most effective protection against TBE as demonstrated in practice by the Austrian vaccination programme [71,81,82]. Cost-effectiveness studies on TBE vaccines have been performed in Slovenia, Sweden, Finland and Estonia, demonstrating economic saving related to decreased incidence, especially of severe cases, but not for all ages [83]. A survey in Sweden showed the importance of subsidy to increase the vaccination rate in risk areas [84].

The European vaccines are licensed for use in adults and children older than 1 year. Primary immunization consists of three doses, followed by booster doses (Table 1) [69,71,85]. The interval after the initial dose may be reduced to 1–2 weeks for rapid protection. Investigations comparing rapid immunization (vaccination on days 0, 7 and 21) versus conventional schedules of Encepur® revealed a similar protection efficacy [86,87]. The Russian vaccines are licensed for adults and children older than 3 years (Table 1) but are not authorized by the EMA for use in the EU [69,88].

Studies on currently available TBE vaccines have demonstrated long-lasting immune responses with persistence of neutralizing antibodies over 5 years, supporting extension of the interval between booster doses [69,89–91]. Interrupted schedules should be resumed without repeating previous doses but continued by the regular schedule, determined by the number of previously completed vaccination doses. Studies to assess the effectiveness of delayed booster vaccination doses of both Encepur® and FSME-IMMUN® demonstrated a typical booster antibody response, and irregular vaccination schedules showed re-established adequate protection in 93%–99% of subjects [81,92–95].

Efficacy and safety of immunization

Vaccination is highly effective and TBE incidence has decreased substantially in TBEV endemic regions with successful vaccination programmes [53,87]. Randomized controlled trials in large populations have shown a high immunogenicity with a strong antibody induction and a low rate of adverse events following TBE vaccination [69,78,89,96,97]. A Cochrane review summarized 11 vaccine trials, amongst them four randomized studies on licensed European vaccines (Encepur® and FSME-IMMUN®) with a total of 5063 participants: the vaccinees reached seroconversion rates of 92%–100% [85]. In Austria, during 2000–2011, the overall field effectiveness of European vaccines was 96%–99% for regularly vaccinated persons and 91%–92% in irregular schedule [77]. Studies on persistence of immunity show a long-term seroprotection that may last up to 10 years, but there is an age-related decline in immunocompetence since the seroprotection rates in people over 50–60 years were significantly lower than in younger individuals [69,98–100]. In a Swedish study in older individuals, age and the number of vaccine doses were shown as the most important factors determining the immunological response [101]. However, despite decreasing levels, healthy elderly people are able to produce antibodies in response to vaccination with similar avidity and functional activity as young individuals [102]. Caution is needed in vaccination of patients with autoimmune diseases or immunocompromised condition. A decreased immunological response compared to healthy controls was shown in thymectomized children and in HIV-positive patients with lower CD4 counts, although they achieved protective antibody titres after the full course of vaccination [71,103,104].

For vaccination by the conventional schedule, adults may be effectively and safely boosted with different European vaccines as strains used in FSME-IMMUN®/TicoVac® and Encepur® are antigenetically closely related [89,105]. *In vivo* and *in vitro* studies have shown that the European vaccines protect against all TBEV subtypes circulating in endemic areas of Europe and Asia, indicating equally potent cross-protection [57,58,78,106]. An animal study in Far Eastern Russia detecting the antibodies to the Far Eastern subtype of TBE after vaccination with two European and two Russian vaccines demonstrated a high seroconversion rate and high and stable antibody levels [107]. A meta-analysis of 14 studies demonstrated high seroconversion rates against Far Eastern and Siberian subtypes of TBE after immunization with both European vaccines [108].

Breakthrough TBE after vaccination is rare. Altogether 25 cases were reported in Austria during 2002–2008 and 27 cases in Sweden throughout 2000–2008, with the majority (70%) of patients over 50 years old, but also a paediatric case has been described [109–112]. In Slovenia, seven (0.7%) out of 1036 patients with TBE during 2000–2006 had received at least two doses of vaccine, and three of these (all were females over 50 years) had completed the primary vaccination [113]. In a Swiss epidemiological study in 2005–2011, 33 TBE patients (3.1%), with a median age of 53 years, had received a complete vaccination series that can be referred to as a failure of vaccination [47]. The Austrian experience with almost 7 million vaccinated persons confirms that breakthrough TBE is rare and tends to occur in older age: increase of the vaccination coverage in Austria was not accompanied by an increase in the absolute annual numbers of breakthrough disease [82].

All current vaccines have been consistently described as moderately reactogenic but without being causally associated with severe adverse reactions. A Cochrane review summarizing 11 vaccine trials showed that adverse events were frequently reported (mild local reactions such as transient redness and pain at the site of injection in up to 45% of the cases; fever in 0.6%–9%; and headache, muscle and joint pain, or fatigue with a minor frequency), but none of the adverse events was considered serious [78,85,96]. However, occurrence of high fever and allergic reactions has been reported due to EnceVir (one of the two Russian vaccines) that is currently not recommended by Russian authorities for use in children up to 17 years [69].

Recommendations

1 Vaccination against TBE with the European vaccines is recommended for all age groups above 1 year in the highly endemic areas (≥5 cases/100 000/year) and for individuals at risk in areas with a lower incidence. Travellers to endemic areas should be vaccinated if their visits will include extensive outdoor activities. (Level A)

2 Recommended intervals are 1–3 months between doses 1 and 2, and 5–12 months (FSME-IMMUN®/TicoVac®) or 9–12 months (Encepur®) between doses 2 and 3. The first booster dose is recommended 3 years after the third primary vaccination dose, and further boosters every 5 years, whilst in persons aged above 60 years (for FSME IMMUN®/TicoVac®) or above 50 years (for Encepur®) boosters are recommended at 3 year intervals. Interrupted schedules should be continued without repeating previous doses. Adults may be effectively and safely boosted with a different vaccine (FSME-IMMUN®/TicoVac® or Encepur®). (Level A)

3 There is a strong evidence that both European vaccines induce a high level of seropositivity against all TBE subtypes. (Level A)

4 Post-exposure prophylaxis after a tick bite is not recommended. (GPP)

Clinical characteristics and diagnosis

Clinical characteristics

About two-thirds of TBEV infections are asymptomatic [13,114,115]. The incubation period of TBE is on average 7–14 days after a tick bite (range 2–28 days), being shorter after milk-borne transmission. One-third of patients do not report or recall a tick bite. For the disease caused by the European subtype of TBEV, a biphasic course is characteristic: the initial viremic phase presenting with fever, headache, muscle pain and fatigue, lasting 2–7 days, is followed by an afebrile period of 2–10 days. In the second phase, fever reappears and is accompanied by signs and symptoms of CNS inflammation [13,114–117].

The frequency of neurological signs has been variable in epidemiological studies and case series (Table 2). Meningitis occurring in about half of the adult patients is characterized by fever, headache, nausea, vomiting and nuchal rigidity. Meningoencephalitis seen in about 40% of adult patients may be manifested by a range of neurological symptoms and signs: seizures, pareses, ataxia, movement disorders, speech disorder, sensory impairment, and rarely brainstem symptoms with cranial nerve abnormalities. Mental disorders including impaired consciousness, amnesia, cognitive impairment, behavioural changes, psychosis, delirium and insomnia may occur. The myelitic form is rare (4%–15%), usually being associated with meningoencephalitis, and manifests with flaccid paralysis when motoneurons, radices or peripheral nerves are involved (poliomyelitic or polyradiculoneuritic forms, commonly seen in upper limbs and neck), or rarely with spastic pareses [5,30,118–123]. Occasionally, autonomic disorders have been described in patients with TBE [124,125]. In endemic areas, concomitant TBE and Lyme neuroborreliosis may occur with more severe clinical course [126–128]. The severity of the illness increases with age [13,116,129].

A chronic form of TBE associated with the Siberian subtype of TBEV that may manifest with epilepsia partialis continua has been described in Siberia and the Far East [130–133]. A progressive form is unusual in Europe but two cases have been described in Lithuania [116]. After an acute TBE caused by the European subtype of TBEV, a post-encephalitic syndrome has been reported in 35%–58% of patients, with neuropsychiatric disorders including cognitive deficits and depression, headache, hearing and vision disturbances, and imbalance as the most frequent symptoms, [114,116–118,123,134].

Tick-borne encephalitis should be differentiated primarily from an aseptic meningitis or encephalitis caused by other viruses including West Nile virus, Japanese encephalitis virus, herpes simplex virus, other herpes viruses and enteroviruses, and other diseases transmitted by ticks such as Lyme neuroborreliosis, human granulocytic anaplasmosis, babesiosis, tularemia and tick-transmitted rickettsioses [65,114,135].

Laboratory testing

Blood
In the initial phase of TBE, leukopenia and/or thrombocytopenia are often present. In the encephalitic (second) phase, platelet counts are in the normal range whilst leukocyte count is normal or mildly elevated [13,114].

Serological testing
A confirmed diagnosis of TBE is established by the detection of specific IgM and IgG serum antibodies, usually by highly sensitive and specific enzyme-linked immunosorbent assay (ELISA) [65,114,136]. Generally, comparison of commercial serological diagnostic methods has shown good sensitivity and good agreement between different methods but lack of specificity demonstrating a limitation of cross-reactivity amongst flaviviruses [137,138]. Earlier studies on quality control assessment for serological diagnosis of TBE in different laboratories revealed correct results for at least 90% of samples by 33 of 40 laboratories for IgM, and in 16 of 42 laboratories for IgG, demonstrating the need for standardized quality measures [139,140]. A recently developed multiplex ELISA array might offer additional advantages for simultaneous identification of different Flaviviridae infections [141]. Serological distinction of TBEV subtypes has not been available but a novel μ-capture enzyme immunoassay using the antigens of Siberian and European strains could be a valuable diagnostic instrument to distinguish these two subtypes [142].

Immunoglobulin M antibodies may be detectable for several months after the infection, whereas IgG antibodies persist over a lifetime and prevent TBE [5,65,114]; however, individual variations of antibody populations have been shown [143]. Compared to vaccinees, neutralizing antibody titres are higher and do not show an age-dependent decrease in individuals with past TBE [144].

To avoid a false positive diagnosis, in potential cases for cross-reactivity with other flaviviruses, a confirmatory neutralization assay (the most specific test available) is recommended [13,137,138]. Rarely IgM antibody quantification may be needed, to avoid interference factors in the serodiagnosis of TBE [102].

In patients who have been vaccinated but develop TBE, immunological response is characterized by delayed development of the specific IgM response, together with a rapid increase of IgG antibodies in the serum. For confirmation of TBE diagnosis in these cases, demonstration of intrathecal synthesis of TBEV antibodies is needed [65,113,114].

Recommendation. Detection of TBEV IgM and IgG antibodies in serum by ELISA is the method of choice for diagnosis of TBE. In areas with possible exposure to

Table 2 Clinical manifestations in the acute stage of tick-borne encephalitis

Country, years	Sweden, 1991–1993	Latvia, 1973–2009	Lithuania, 1998–1999	Poland, 1993–2008	Slovenia, 2000–2004
Author, year [reference]	Günther et al., 1997 [118]	Karelis et al., 2012 [30]	Mickiene et al., 2002 [116]	Czupryna et al., 2011 [119]	Logar et al., 2006 [129]
Study design	Prospective	Retrospective	Prospective follow-up	Retrospective	Retrospective
Number of patients	85	228	133	687	448
Men/women ratio (%)	54/46		55/45	63/37	61/39
Age	15–78 years	22–82 years	≥16 years	15–82 years	15–89 years
Notice of tick bite (%)	77		68	44	72
Biphasic course	87		72		56
Clinical form (%)	Meningitis 55.3	Meningitis 77.5[a]	Meningitis 43.6	Meningitis 41	Meningitis 36.4
	Meningoencephalitis, encephalitis or myelitis 44.7	Meningoencephalitis 13.2	Meningoencephalitis, encephalitis or myelitis 56.4	Meningoencephalitis 51.3	Meningoencephalitis 60
		Meningoencephalomyelitis 9.3		Meningoencephalomyelitis 7.6	Meningoencephalomyelitis 3.6
Clinical symptoms (%)	Emotional instability 28.2	Meningeal signs 90.4	Headache 95.5	Headache 93.4	Headache 96
	Ataxia 25.9	Headache 84	Ataxia 26.3	Meningeal signs 92.4	Fever 92.4
	Impaired consciousness 20	Ataxia 34.1	Tremor 21.8	Nausea 55.4	Meningeal signs 70.3
	Sensory impairment 12.9	Impaired consciousness 19.3	Impaired consciousness 18.8	Dizziness 46.7	Tremor 40.2
	Spinal nerve paralysis 10.6	Spinal nerve paralysis 14.9	Emotional instability 15	Vomiting 35.4	Nausea 38.8
	Dysphasia 9.4	Cranial nerve palsy 11	Concentration decrease 11.3	Cognitive disorder 31.9	Vomiting 38.2
	Tremor 9.4	Seizures 9.1	Cognitive disorder 9.8	Impaired consciousness 26.2	Dizziness 16.5
	Concentration decrease 5.9	Sensory impairment 7.9	Cranial nerve palsy 5.3	Emotional instability 16.3	Impaired consciousness 10
	Cognitive disorder 3.5	Dysphasia 1.8	Spinal nerve paralysis 3.8	Ataxia 14.1	Pareses 3.8
	Cranial nerve palsy 2.4		Dysphasia 3.8	Pareses 8.5	Spinal nerve paralysis 3.6
	Respiratory insufficiency 1.2			Spinal nerve paralysis 6.4	Respiratory insufficiency 1.6
				Cranial nerve palsy 3	Cranial nerve palsy 1.1
				Sensory impairment 2.1	
Risk factors for a severe illness	Increasing age, male gender		Increasing age, monophasic disease	Increasing age	Increasing age, pareses, oedema cerebri, urine retention

[a]Hospital data 1994–2006.

Table 3 Definition of a case: criteria for the diagnosis of tick-borne encephalitis (TBE) [41,42,114][a]

	Confirmed TBE	Probable TBE	
Clinical criteria	Symptoms of CNS inflammation: meningitis, meningoencephalitis or encephalomyelitis	Symptoms of CNS inflammation: meningitis, meningoencephalitis or encephalomyelitis	Symptoms of CNS inflammation: meningitis, meningoencephalitis or encephalomyelitis
	+	+	+
Epidemiological link	Yes	Yes	No
	+	+	+
CSF findings	Pleocytosis >5 × 10^6 cells/l	Pleocytosis >5 × 10^6 cells/l	Pleocytosis >5 × 10^6 cells/l
	+	+	+
Microbiological/ serological criteria	• TBE-specific IgM *and* IgG antibodies[b] in serum; or • TBE-specific IgM antibodies in CSF; or • seroconversion or four-fold increase of TBE-specific IgG antibodies in paired serum samples; or • detection of TBE viral nucleic acid in a clinical specimen	No	TBE-specific IgM antibodies in a single serum sample

CNS, central nervous system; CSF, cerebrospinal fluid; Ig, immunoglobulin. [a]ECDC/EU definitions were designed for reporting; [b]the antibodies used in the ELISA methods are cross-reactive with other flaviviruses. In patients immunized against TBE, an intrathecal synthesis of TBEV-specific antibodies in the CSF should be shown.

other pathogenic flaviviruses (yellow fever, Dengue, West Nile virus), the virus neutralization test should be used to assess the specific immunity against TBEV. (Level A)

Polymerase chain reaction (PCR)
Polymerase chain reaction is a method often used for the diagnosis of various viral CNS infections. New TBEV-specific tests have allowed rapid detection of viral RNA in the blood, but only in the first (viremic) period before the seroconversion and manifestations of CNS inflammation. Therefore PCR in blood is a relevant method for detection of TBEV in the initial phase of TBE, but has no diagnostic value in the second phase of TBE and is not a suitable method for detection of TBEV in CSF. In fatal encephalitic cases, TBEV can be detected in the brain tissue by PCR [65,114,145–148]. In a few cases, TBEV RNA was detected in urine by PCR in the encephalitic phase of TBE [149]. However, the value of this diagnostic approach needs further evaluation.

Recommendation. Tick-borne encephalitis virus specific PCR in blood is diagnostic only in the first, viremic phase. It is not sensitive and cannot be used in the second phase with clinical manifestations of TBE. (Level B)

Cerebrospinal fluid (CSF)
Patients with suspected TBE need a diagnostic lumbar puncture [150–152]. In the case of possible brain oedema, i.e. impaired consciousness, focal neurological signs, bradycardia, seizures or papilloedema, brain imaging is mandatory prior to lumbar puncture to exclude conditions that may increase intracranial pressure (ICP). Other contraindications include local infections at the puncture site, congenital abnormalities and coagulopathies [115,150,152,153].

For TBE, moderately raised CSF protein and mononuclear pleocytosis ranging from 6 × 10^6 to 1200 × 10^6 cells/l but normal glucose and lactate levels are characteristic [5,115,136]. Exceptionally, TBE has been demonstrated without CSF pleocytosis [154]. Early

after the disease onset, TBEV-specific antibodies can be found in the CSF in half the patients, but they are detectable in almost all patients within 10 days [65].
Recommendation. Lumbar puncture should be performed in all patients with suspected CNS infection unless there are clinical contraindications: signs of increased ICP including focal signs and seizures, coagulopathy or local skin infection. CSF pleocytosis >5 × 10^6 cells/l is a diagnostic marker for TBE in the presence of specific IgM and IgG serum antibodies and the corresponding clinical picture. (Level A)

Case definition

The case definition and criteria for the diagnosis of TBE have been established by the ECDC for reporting communicable diseases to the Community network and approved in the Commission Implementing Decision of the European Parliament and of the Council in 2012 [41–43]. A case of TBE is defined by the following diagnostic criteria: the presence of clinical signs of meningitis, meningoencephalitis or meningoencephalomyelitis, an epidemiological link, CSF pleocytosis (>5 × 10^6 cells/l), and demonstration of recent TBEV infection by the presence of specific serum IgM and IgG antibodies (Table 3). In clinical practice, also for probable cases, full available management should be applied. For the reliable diagnosis of TBE in persons vaccinated against TBE previously, demonstration of intrathecal synthesis of TBEV antibodies is needed [65,114].

• Clinical criteria: any person with symptoms/signs of inflammation of the CNS (e.g. meningitis, meningoencephalitis, encephalomyelitis).
• Laboratory criteria for a confirmed case: at least one of the following five:
  1 TBE-specific IgM *and* IgG antibodies in serum;
  2 TBE-specific IgM antibodies in CSF;
  3 seroconversion or four-fold increase of TBE-specific IgG antibodies in paired serum samples;
  4 detection of TBE viral nucleic acid in blood by PCR;

5 isolation of TBE virus from a clinical specimen.
- Laboratory criteria for a probable case: detection of TBE-specific IgM antibodies in a single serum sample.
- Epidemiological criteria: exposure to ticks in a TBE endemic area, or a common source (unpasteurized dairy products).
- Case classification
  1 Confirmed case: any person meeting the clinical and laboratory criteria for a confirmed case.
  2 Probable case: any person meeting the clinical criteria and CSF findings, with TBE-specific IgM antibodies in a single serum sample, *or* any person meeting the clinical criteria and CSF findings, with an epidemiological link.

Recommendation
The EAN Task Force on TBE suggests using combined diagnostic criteria based on the EU decision on case definition and clinical presentations (Table 3). (Level B)

Imaging

Magnetic resonance imaging (MRI) abnormalities
Magnetic resonance imaging findings in the brain include increased signal intensity on T2-weighted and fluid attenuated inversion recovery images in the thalamus, basal ganglia, internal capsule, splenium, cerebellum, peduncles and brainstem [73,74,117,155–165]. Most common are thalamic lesions that can be unilateral or bilateral, multifocal or more diffuse in character [162]. In patients with myelitis and radiculitis spinal MRI has shown increased signal intensity on T2-weighted images in the spinal cord with a predilection to the anterior horns [157,158,162,166–170].

Sensitivity and specificity of MRI findings
Magnetic resonance imaging of the brain was performed in 102 of 656 TBE patients described in a German prospective study during 1994–1998 [117]. Abnormalities were found in 18 of 102 patients (18%), in 11 of 64 (17%) with meningoencephalitis, in seven of 25 (29%) with meningoencephalomyelitis, and in none of 13 (0%) patients with meningitis. Single case reports and small case series have reported brain MRI abnormalities in 26 of 40 (65%) examined patients [73,155–163,166–172]. Spinal MRI abnormalities have been reported in single case reports and small case series in 11 of 16 (69%) examined patients (eight with encephalomyeloradiculitis, three with encephalomyelitis, two with isolated radiculitis and one with myeloradiculitis [157,158,162,166–171].

Studies of specificity are lacking. It is considered to be low since similar MRI findings are reported in several other conditions: demyelinating, ischaemic, autoimmune, other infectious and toxic disorders of the brain, and vascular disorders of the cord and nerve roots [162].

Sensitivity of computed tomography (CT) findings
Computed tomography of the brain is considered to be less sensitive than MRI in the diagnosis of encephalitis but is recommended in the emergency setting before lumbar puncture when brain oedema is suspected, or for differential diagnostic purposes if MRI is not available [150,152].
Recommendation. Brain and spinal MRI may show diverse pathology in about 20% of TBE patients. Imaging of the brain and spinal cord has low sensitivity and low specificity in the diagnosis of TBE, but it is suggested that it is used for differential diagnosis and exclusion of brain oedema. (Level C)

Therapy

Tick-borne encephalitis should be considered in every patient with meningitis, encephalitis or myelitis in a TBEV endemic area; the diagnosis is most likely when a tick bite has occurred within the incubation period for TBE [114,115,158,173–175]. Patients with severe encephalitis should be empirically treated with intravenous acyclovir (10 mg/kg three times daily) until herpes simplex virus encephalitis is ruled out [135,136,150,176]. There is no specific treatment for TBE but symptomatic treatment should be introduced when indicated: antipyretics and analgesics, antiemetics, therapies for epileptic seizures and cerebral oedema, respiratory and circulatory support, control of electrolyte and fluid balance, and treating neurological and systemic complications, to avoid secondary neuronal damage [114,152,153,174].

Emergency management

Figure 2 delineates the algorithm of diagnostic and therapeutic interventions in a patient with acute meningitis or meningoencephalitis, suggestive for TBE in the emergency setting. If neurological and/or systemic signs and symptoms indicate a potentially life threatening course of the disease, immediate admission to and management in a (neuro)intensive care unit (ICU) is mandatory [153,175]. Delayed ICU admission of patients with severe acute encephalitis is associated with a worse prognosis [177]. Up to 12% of hospitalized TBE patients are treated in an ICU, and artificial ventilation is needed in up to 7% of TBE patients [114,117,129].

A recent meta-analysis on ICP and cerebral perfusion pressure (CPP) monitoring in non-traumatic brain injury patients concluded that continuous ICP/CPP monitoring with an invasive device should be considered in all conditions including meningitis and encephalitis that may lead to severe brain oedema and elevated ICP, although there are limited data and low evidence [178]. If ICP is elevated (20–25 mmHg) or CPP is dangerously low (50–60 mmHg), immediate follow-up neuroimaging is mandatory [153,175]. In the case of severe brain oedema invasive multimodal neuromonitoring might allow the metabolic distress of brain tissue to be detected at the earliest possible point in time [179].

As epileptic seizures are a frequent complication of CNS infections, critical care monitoring should include electroencephalography (EEG) for diagnostic and
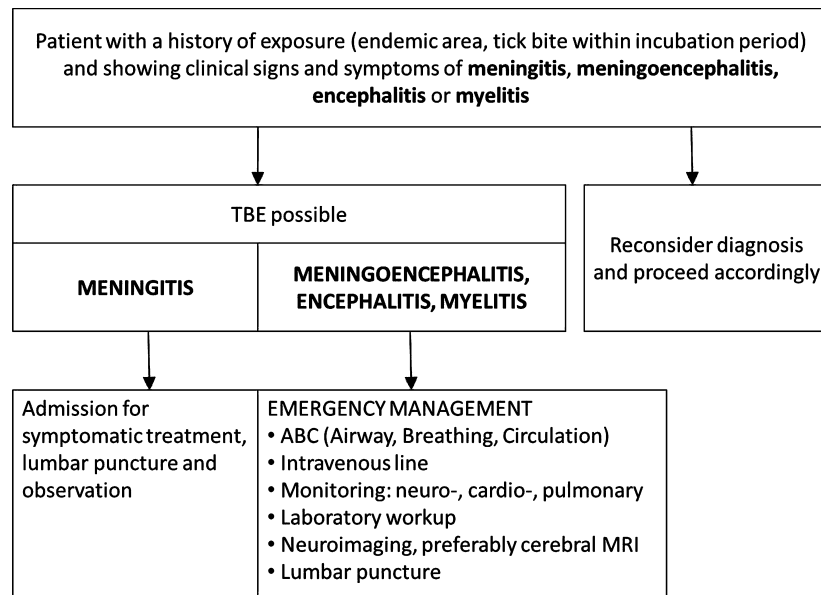
Figure 2 Management algorithm for a patient with suspected tick-borne encephalitis virus meningitis, encephalitis or myelitis in emergency settings.

prognostic information [180], and continuous EEG monitoring for at least 48 h is recommended in patients with persistent unconsciousness, to evaluate intermittent non-convulsive seizures or even persistent non-convulsive status epilepticus [150,153,181,182].

Recommendation
Every patient with a potentially life threatening course of meningoencephalitis, encephalitis or myelitis should be admitted to and managed in a (neuro) ICU (Fig. 2). If clinical signs and symptoms, electrophysiology and/or neuroimaging indicate increased ICP or status epilepticus, ICP/CPP monitoring, temperature management and, if available, continuous EEG monitoring are indispensable. (Level C)

Symptomatic treatment

Brain oedema
Encephalitic brain oedema may be diffuse or focal involving brainstem, basal ganglia or thalami. It is still a matter of discussion whether encephalitic brain oedema responds to 'conventional' anti-oedematous therapy with corticosteroids, osmotherapy (mannitol, hypertonic saline), analgosedation, cautious hyperventilation, hypothermia or neurosurgical intervention (decompressive hemicraniectomy) [11,183–185].

In high quality prospective randomized trials of non-viral infectious/inflammatory brain oedema (e.g. bacterial meningitis or cerebral malaria), dexamethasone has been shown to be of limited efficacy [186–188]. There are no specific randomized trials with dexamethasone in TBE but observational population studies have shown prolonged hospitalization to be associated with

administration of dexamethasone compared to patients receiving only symptomatic treatment [114,116,119]. Continuous osmotherapy has clearly yielded a negative result with increased morbidity and mortality, but osmotherapy as boluses restricted to a period of maximally 1–2 days may be considered by general suggestions for management of encephalitis, as there are no specific studies on osmotherapy for TBE [183,184,189–192].

A few patients with severe viral encephalitis, the majority of them with TBE, have been successfully subjected to therapeutic hypothermia. It has influenced positively the progressive development of increased ICP and, likewise, the progressive deterioration of CPP [181,182,192–196]. Decompressive craniectomy for encephalitis patients with malignant brain oedema and brainstem compression is a potentially lifesaving neurosurgical intervention; although there are no randomized trials, case series show a good recovery [193–199]. A favourable long-term outcome after surgical intervention has been demonstrated in observational studies, with a better prognosis in viral encephalitis than in bacterial encephalitis [200,201]. Therefore, therapeutic hypothermia and in selected cases decompressive craniectomy might be considered as a second line treatment of increased ICP in TBE in otherwise refractory cases; the first line is deepening of analgosedation [183–185].

Epileptic seizures
Viral encephalitis may manifest with early seizures or even status epilepticus (convulsive or non-convulsive) in the early phase; early seizures increase a risk for late post-encephalitic epilepsy [130,202,203]. Isolated seizures need to be treated as any other symptomatic epileptic seizure. Further, the therapy of rarely occurring symptomatic status

epilepticus in TBE does not differ from the management of status epilepticus due to other causes, escalating the therapy from intravenous benzodiazepines (such as lorazepam or diazepam), fosphenytoin, valproic acid, levetiracetam, and eventually to anaesthesia with ketamine, propofol, midazolam or barbiturates; antiepileptic drugs are given concomitantly with anaesthetics. Barbiturates may only be given if an ICP monitoring probe is in place and the patient is on continuous EEG monitoring [182,203]. In refractory status epilepticus, the aim must be to achieve a burst suppression pattern on EEG. However, in most cases the outcome is generally poor [204,205]. In super-refractory status epilepticus, when general anaesthetics have failed to control seizures, hypothermia, electrical brain stimulation and immunosuppressive therapies have been described as possible therapeutic options but none of these invasive treatment recommendations is based upon randomized trials [182,206–208]. There is insufficient evidence for the use of antiepileptic drugs to prevent seizures in viral encephalitis [209].

Recommendations.

1 Corticosteroids should not be used routinely. (Level C)
2 Continuous osmotherapy has a negative result but osmotherapy as boluses could be considered only for maximally 1–2 days. (GPP)
3 If ICP continues to be elevated and CPP is dangerously decreased, therapeutic hypothermia might be effective. (GPP)
4 In single cases, decompressive craniectomy might be considered. (GPP)
5 Epileptic seizures or status should be treated with intravenous benzodiazepines, fosphenytoin, valproic acid, levetiracetam or anaesthetics as any other symptomatic epileptic seizures. (Level C)

Antiviral treatment and immunomodulation

There are no convincing prospective randomized trials with antivirals, although possible antiviral properties of a variety of drugs have been indicated [173,174,210–218]. Some drugs have been shown to exert an antiviral effect in murine TBE models [219–222]. Antiviral activity of several compounds against TBE in experiments in cell cultures and *in vitro* experiments to inhibit replication of TBEV by RNA interference may lead to prospects for further trials [223–230].

There are no reports on plasma exchange therapy for TBE, but there are a few case reports on intravenous Ig for treatment of viral encephalitis, including a case of TBE with improvement of dysautonomic symptoms, that do not prove evidence for indication of its use [112,231]. Currently, there is no evidence-based antiviral medication approved for TBE, but several compounds have a potential to be investigated in clinical trials [174].

Recommendation

There is no evidence on effective antiviral or immunomodulating therapies for treatment of TBE. (GPP)

Outcome and prognosis

Case fatality rate

The reported case fatality rate in TBE caused by the European TBEV is around 1% [30,116–118,134,232,234] (Table 4). Case fatality rates for disease caused by the two other TBEV subtypes are generally higher, but the data are very limited. In the Primorsky territory in Russia, where the Far Eastern subtype of TBEV predominates, the reported mean case fatality rate was 33% for the 'focal form' and 6.4% for the 'meningeal form' during a period of 25 years [234]. In western Siberia, where the Siberian TBEV subtype predominates, the reported annual case fatality rate varied between 1.8% and 3% over a period of 20 years [131].

Long-term outcome

Case series with a follow-up time of 6 months or more show that 26%–46% of patients with TBE caused by the European TBEV subtype report incomplete recovery (Table 4). Neuropsychological sequelae such as impaired memory and concentration and reduced stress tolerance are commonly reported. The most frequent types of neurological sequelae are shoulder amyotrophy, cranial nerve paresis, hemiparesis or paraparesis, and impaired balance and coordination [116,232]. A follow-up MRI study of patients with severe TBE demonstrated that cortico-subcortical atrophy with enlarged ventricles was more marked on follow-up examination compared to the initial imaging [164].

The frequency of sequelae after TBE caused by the Far Eastern or Siberian subtypes is unknown. In the retrospective case series from Latvia (Table 4), where all three subtypes of TBEV occur, sequelae were reported in 63% of patients, including a high rate of permanent pareses [30]. However, these results may be biased by a high proportion of non-responders.

Some publications report a progressive form of TBE [131,235–237]. This condition is poorly defined, and it is not clear whether the progressive symptoms are due to ongoing infection or other mechanisms or are causally related to TBE infection. One of the two patients classified as having a progressive form of the disease from Lithuania, reported in Table 4, developed internuclear ophthalmoplegia and hemiplegia accompanied by MRI lesions 1 year after the onset of TBE and responded well to high dose methylprednisolone and plasma exchange, indicating immune-mediated mechanisms [116].

Risk factors for incomplete recovery and death

As expected, a severe course of TBE in the acute phase is associated with a non-favourable outcome [30,47,116–118,121,157,238,239]. A study of patients with a myelitic course of TBE showed that 51% of the patients suffered from persistent pareses or other impairments during 1–10 years after the acute disease [240]. However, also in

Table 4 Long-term outcome after tick-borne encephalitis (TBE)

Country	Sweden		Latvia	Lithuania	Slovenia
Virus subtype	European		European/Siberian/Far Eastern	European	European
Author, year [reference]	Haglund et al., 1996 [232]	Günther et al., 1997 [118]	Karelis et al., 2012 [30]	Mickiene et al., 2002 [116]	Tomazic et al., 1996 [233]
Study design	Retrospective	Prospective	Retrospective	Prospective	Prospective
	Interview	Physical examination	Questionnaire	Physical examination	Questionnaire
	Physical examination of patients reporting sequelae			Neuropsychiatric questionnaire	
Number of patients	143	85	482 contacted	133	492
Lost at follow-up	35	2	382 non-responders	15	6
Men/women	61/43 (54%/46%)	46/39 (54%/46%)	43/57 (43%/57%)		332/160 (67%/33%)
Age	11–74 years	15–78 years	22–82 years	≥16 years	All ages
Inclusion period	1978–1987	1991–1993	1994–2005	1998–1999	1994
Follow-up time	Median 47 months (20–133)	Median 12 months	Mean 6.5 years (1–13)	Median 16 months (10–23)	6 months
Case fatality rate[a]	1.4%	0	0%–1.3%	0.7%	0.2%
Sequelae	36% (40/114)	40% (33/83)	63% (63/100)	46% (54/117)	26%
	• mild 8%		• mild 20%	• mild 15%	
	• moderate 15%		• moderate 27%	• moderate 22%	
	• severe 13%		• severe 16%	• severe 9%	
Distribution of sequelae	Mental 29	Headache 9	Fatigue 61	Headache 24	Headache 110
	Balance/tremor 15	Memory 9	Headache 58	Memory 23	Fatigue 105
	Headache 11	Concentration 7	Dizziness 40	Emotional instability 22	Concentration 74
	Hearing 8	Ataxia 6	Coordination 39	Concentration 18	Pain 54
	Pain 4	Spinal nerve paralysis 5	Muscle wasting 20	Tremor 10	Tremor 50
	Vision 4	Dysphasia 5	Shoulder paresis 14	Ataxia 7	Sweating 27
	Paralysis 3	Dysaesthesia 2	Hemiparesis 13	Hemiparesis 4	Pareses 11
	Photophobia 3	Hearing 2	Cranial nerve paresis 2	Spinal nerve paralysis 3	Mental 7
	Weakness 3	Phono/photophobia 1		Progressive form 2	Consciousness 1
	Parkinsonism 1	Tremor 2			
	Smell 1				
Risk factors for sequelae	Increasing age	None identified	Focal forms of acute TBE	Encephalitic form of acute TBE (OR 4.066, P < 0.001)	Double infection (TBE and Lyme neuroborreliosis)

Case series reviewing more than 50 mainly adult patients comprising all kinds of acute TBE manifestations with at least 6 months follow-up time; available detailed method descriptions are included. OR, odds ratio. [a]Only deaths due to TBE.

patients with a serious acute illness, a favourable outcome is possible [168,241–243].

Higher age is associated with a non-favourable outcome [157,243,244]. A case series with 114 patients revealed that individuals with sequelae after TBE had higher age compared to those with complete recovery ($P = 0.006$) [232]. Another study, comparing the course of TBE in adults ($n = 318$) and seniors above 60 years ($n = 130$), found a higher case fatality rate ($P = 0.024$) and a more serious disease course amongst seniors [129]. Other identified risk factors are abnormal findings on MRI, CSF cell count $>300 \times 10^6$ cells/l and impaired blood−brain barrier (total protein >600 mg/l) [117].

Few studies have followed patients beyond 12 months. One case series from Switzerland reported some remaining complaints in 32/56 (56%) after 1 year, 10/32 (31%) after 5 years and 4/6 (66%) after 10 years, but it is not specified whether any patients with sequelae after 1 year improved later [245]. A German study that followed patients with the encephalomyelitic form of TBE for 10 years found that the most important ameliorations occurred during the first year after the acute disease; thereafter improvements occurred, but fewer, lesser and more seldom [240].

Tick-borne encephalitis in children

In endemic areas, about 10% of encephalitis in childhood is caused by TBEV [243]. According to ECDC about 15% of all registered cases of TBE in Europe were subjects aged <19 years [42]. TBE is also the most common febrile illness after tick bites in endemic areas in Europe. On average 10%–20% of TBE cases occur in children less than 15 years. The annual incidence of TBE in children <15 years in endemic areas varies, ranging from 0.25 to 17.6 per 100 000 [246–248].

Tick-borne encephalitis mainly affects schoolchildren with a median age of 9 years, but cases in infants as young as 2 weeks old have been recorded [249]. In most studies, however, the youngest reported age has been 3 years. About a half to two-thirds of the children recall tick bites.

Clinical findings and diagnostics

Tick-borne encephalitis in children is a milder illness than in adults [250]. A recent retrospective study that included 38 TBE patients aged <16 years from Sweden demonstrated that less than 60% of children had a biphasic course similar to adults [251]. If a biphasic course is observed then similarly to adults the first phase appears in a median of 12 days after an incubation period as an acute non-specific febrile illness. The second phase starts 2–8 days after the end of the first one. In a review of 417 published cases, 70% of paediatric patients had meningitis, 29% meningoencephalitis and 1% meningoencephalomyelitis, whereas 85% of those with meningoencephalitis were older than 7 years [252]. Although about one-third of children admitted to hospital are severely ill, serious neurological symptoms such as ataxia, limb paresis, cranial nerve involvement, seizures or unconsciousness are significantly less frequent than in adults, and are seen in about 5% of patients [74,114,156]. Similarly to adults, MRI studies have demonstrated lesions in the brain white and grey matter including basal ganglia, but also cortically [153,165,253].

Laboratory findings and diagnostic criteria are in general similar to those seen in adults [247,248].

Outcome and follow-up

Serious consequences (e.g. lethal outcome or severe neurological disability) are rarely seen in paediatric TBE [254]. However, follow-up EEG showed slowing of the cortical activity in 11 out of 19 (58%) children with TBE in Germany [255]. Recent data from a study of eight children monitored for a year after TBE indicated that long-term morbidities (fatigue, headache and irritability) were common and were seen more frequently in TBE patients than in controls (patients treated for Lyme borreliosis). In addition, two patients had memory problems during the follow-up period [256]. In a recent study from Sweden in 55 children with TBE at a long-term follow-up, two-thirds of the children experienced residual problems with main complaints of cognitive disorder, headache, fatigue and irritability [246]. In children following TBE, a relationship of the working memory deficit with functional MRI findings was demonstrated [253]. These data suggest that long-term follow-up and larger studies using a control group are needed in paediatric patients with TBE.

Vaccination

Similarly to adults, immunization should be offered to all children living in or travelling to endemic areas [48,257]. This expert opinion is based on the observation of vaccine effectiveness in Austria, the Czech Republic and Slovenia that demonstrated a significant decline of TBE after the introduction of general immunization in Austria whereas no change or even an increase in the neighbouring countries was observed [69,78,89,258]. There is strong evidence that currently available vaccines protect children against TBE [69]. The general concepts of pre- and postexposure prophylaxis highlighted in the section above on vaccination also apply for the paediatric population.

For children aged 1–11 years both vaccines are available in paediatric formulations (FSME-IMMUN® Junior/TicoVac® Children and Encepur® Children). The paediatric versions of both vaccines are identical to the adult vaccine, the only difference being the dose, 0.25 ml and 0.5 ml, respectively. The conventional paediatric primary vaccination schedules for these vaccines consist of three doses administered at 0, 1–3 and 9–12 months for Encepur® Children, or at 0, 1–3 and 5–12 months for FSME-IMMUN® Junior/TicoVac® Children.

The 'head to head' comparison FSME-IMMUN® Junior/TicoVac® Children and Encepur® Children demonstrated high efficacy of both vaccines, long-term protection, and interchangeability of the vaccines within

Table 5 Summary of recommendations for management of tick-borne encephalitis (TBE)

	Interventions	Class of evidence[a]	Level of recommendation
Vaccination	Vaccination efficacy and safety	I	A
	Immunization schedules	I	A
	Cross-protection	I	A
	Post-exposure prophylaxis	III	GPP
	Vaccination in children	I	A
Diagnosis	Antibody detection	I	A
	PCR	II	B
	LP/CSF	I	A
	Case definition	II	B
	Imaging	II	C
Treatment	Emergency monitoring	III	C
	Corticosteroids (against their use)	III	C
	Osmotherapy	–	GPP
	Hypothermia	–	GPP
	Craniectomy	–	GPP
	Antiepileptic treatment	III	C
	Antivirals	IV	GPP

GPP, Good Practice Point; PCR, polymerase chain reaction; LP, lumbar puncture; CSF, cerebrospinal fluid. [a]Noted the highest evidence class rating for the studies used for the recommendation.

the primary immunization course; however, comparative immunogenicity evaluations of the two vaccines revealed somewhat controversial results that could be at least partly explained by employment of different methodologies in individual studies [259–262].

By comparing the rapid administration schedule (0, 7 and 21 days) to the conventional one (0, 28 and 300 days), it appeared that at day 300 99% vs. 90% of children, respectively, were seropositive according to neutralization test [86].

Recommendation
Vaccination is recommended for all age groups including children from the age of 1 year in highly endemic areas (≥5 cases/100 000/year) and for individuals at risk in areas with a lower incidence. Travellers to endemic areas should be vaccinated if their visits will include extensive outdoor activities. (Level A)

Treatment

There is no specific treatment for children with TBE but symptomatic treatment is available (see the 'Therapy' section). Corticosteroids in the treatment of childhood encephalitis have never been studied in controlled trials and are not recommended because of concerns that their immunosuppressive activity may increase viral replication and spread [263]. Antibiotics and acyclovir should be stopped immediately after the diagnosis of TBE is confirmed.

Conclusions

Tick-borne encephalitis is one of the most important human viral infections with an increasing health burden in Europe that might be attributed to occupational exposure, leisure time activities and climate changes affecting pathogen transmission. With increasing travel to endemic areas, TBE has become an international problem. The disease may result in long-term neurological sequelae including headache, fatigue and balance problems as the most frequent; incomplete recovery occurs in 26%–46% patients. No specific therapy is available but immunization remains the best prevention of TBE, and the example of Austria has shown that extended TBE vaccination is beneficial for both economic and healthcare prospects. A summary of recommendations for diagnosis and management of TBE is given in Table 5.

Disclosure of conflicts of interest

Pille Taba, Irja Lutsar, Unn Ljøstad, Ase Mygland, Iryna Levchenko, Franc Strle and Israel Steiner have no conflicts of interest to declare. Erich Schmutzhard has received speaker's honoraria from Baxter, Pia Forsberg is a member of the Baxter Advisory Board on Immunodeficiency Diseases (not related to TBE) and Unn Ljøstad has received speaker's honoraria from Novartis (not related to TBE).

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