



Complete Summary

GUIDELINE TITLE

Viral encephalitis: a review of diagnostic methods and guidelines for management.

BIBLIOGRAPHIC SOURCE(S)

Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, Kennedy PG. Viral encephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol 2005 May;12(5):331-43. [76 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Viral encephalitis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Infectious Diseases
Internal Medicine
Neurology

INTENDED USERS

Emergency Medical Technicians/Paramedics
Physicians

GUIDELINE OBJECTIVE(S)

To address the optimal clinical approach to central nervous system infections caused by viruses

TARGET POPULATION

Patients presenting with or suspected of having viral encephalitis

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Medical history
2. Physical examination (general and neurological)
3. Diagnostic investigations:
 - General work-up (peripheral blood count and cellular morphology, erythrocyte sedimentation rate, blood cultures, chest x-ray)
 - Electroencephalography (EEG)
 - Analysis of cerebrospinal fluid (CSF) for protein, glucose, and cellular analysis
 - Serology
 - Polymerase chain reaction (PCR) amplification
 - Neuroimaging (preferably by magnetic resonance imaging [MRI])
 - Viral culture
 - Brain biopsy for difficult cases

Management/Treatment/Prevention

1. Hospitalization with an access to intensive care units and supportive therapy
2. Acyclovir (vidarabine if acyclovir is not tolerated)
3. Ganciclovir
4. Foscarnet
5. Pleconaril
6. Corticosteroids as an adjunct treatment
7. Surgical decompression
8. Preventive measures including immunization

MAJOR OUTCOMES CONSIDERED

- Usefulness, sensitivity, and specificity of diagnostic tests
- Effectiveness of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (National Library of Medicine) was searched for relevant literature from 1966 to May 2004. The search included reports of research in human beings only and in English. The search terms selected were: "viral encephalitis," "encephalitis," "meningoencephalitis," and "encephalopathy." Then the search was limited using the terms "diagnosis," "MR," "positron emission tomography" (PET), "single photon emission tomography" (SPECT), "electroencephalography" (EEG), "cerebrospinal fluid," "pathology," "treatment/" and "antiviral therapy." Review articles and book chapters were also included if they were considered to provide comprehensive reviews of the topic. The final choice of literature and the references included was based on the judgment of their relevance to the subject.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- a. Randomization concealment
- b. Primary outcome(s) is/are clearly defined
- c. Exclusion/inclusion criteria are clearly defined
- d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations were reached by consensus of all Task Force participants appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS) and were also based on their awareness and clinical experience. Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good practice points (GPP).

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points (GPPs) Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good practice points

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (Hughes RAC, Barnes MP, Baron J, Brainin M [2001]. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces. *Eur J Neurol* 8:549-550).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Recommendations for Diagnostic Tests

Viral encephalitis is still an evolving discipline in medicine. The emergence of new, and re-emergence of old, pathogens and the constant search for specific therapeutic measures, unavailable in most viral encephalitis cases, suggests that the following years will bring new developments in diagnosis and therapy. At present, adherence to a strict protocol of diagnostic investigations is recommended and includes:

Study	Finding	Level of Recommendation	Class of Evidence
LP	Cells: 5 to 500 white blood cells, mainly lymphocytes; May be xanthochromic with red blood cells. Glucose: normal (rarely reduced). Protein: >50 mg/dL	A	II
Serology	CSF and serum	B	II
PCR	Major aid in diagnosis (CSF) May be false negative in the first 2 days of disease	A	I
EEG	Early and sensitive. Non-specific. May identify focal abnormalities	C	III
Imaging	MRI is usually more sensitive than CT, demonstrating high signal intensity lesion on T2-weighted and FLAIR images.	B	II
Viral culture	Only rarely useful		
Brain biopsy	Highly sensitive Not used routinely	C	III and GPP

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; FLAIR, fluid-attenuation inversion recovery; LP, lumbar puncture; MRI, magnetic resonance imaging; PCR, polymerase chain reaction

Recommendations for Therapeutic Interventions

The following are the specific and symptomatic therapeutic measures available for viral encephalitis:

Interventions	Class of Evidence	Level of Recommendation
Acyclovir for HSE	II	A
Acyclovir for suspected viral encephalitis	IV	(--)
Acyclovir for VZV encephalitis	IV	(--)

Interventions	Class of Evidence	Level of Recommendation
Ganciclovir and/foscarnet for CMV encephalitis	IV	(--)
Acyclovir or ganciclovir for B virus encephalitis	IV	(--)
Pleconaril for enterovirus encephalitis	Not available	(--)
Corticosteroids for viral encephalitis	IV	
Surgical decompression	IV	

Abbreviations: CMV, cytomegalovirus; HSE, herpes simplex encephalitis; VZV, varicella-zoster virus

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

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Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- a. Randomization concealment
- b. Primary outcome(s) is/are clearly defined
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- d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points (GPPs) Where there was lack of evidence but consensus was clear the Task Force members have stated their opinion as good practice points

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of viral encephalitis

POTENTIAL HARMS

Diagnostic Tests

Polymerase chain reaction (PCR) may render false-negative results in the first 2 days of disease

Adverse Effects of Medication

- As more than 80% of acyclovir in circulation is excreted unchanged in urine, renal impairment can rapidly precipitate acyclovir toxicity and therapeutic doses should be adjusted according to the renal clearance.
- Adverse effects of corticosteroids include gastrointestinal haemorrhage, secondary fever, and infections.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

IMPLEMENTATION TOOLS

Staff Training/Competency Material

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 May

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: I. Steiner, Laboratory of Neurovirology, Department of Neurology, Hadassah University Hospital, Jerusalem, Israel; H. Budka, Institute of Neurology, Medical University of Vienna, Vienna, Austria; A. Chaudhuri, Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK; M. Koskiniemi, Department of Virology, Haartman Institute; K. Sainio, Department of Clinical Neurophysiology; O. Salonen, Helsinki Medical Imaging Center, University of Helsinki, Helsinki, Finland; P. G. E.

Kennedy, Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the [European Federation of Neurological Societies Web site](#).

Print copies: Available from Dr I. Steiner, Department of Neurology, Hadassah University Hospital, PO Box 12 000, Jerusalem, 91 120, Israel; Phone: 972 2 6776952; Fax: 972 2 6437782; E-mail: isteiner@md2.huji.ac.il

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol*. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the [European Federation of Neurological Societies Web site](#).
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the [European Federation of Neurological Societies Web site](#).
- Continuing Medical Education questions available from the [European Journal of Neurology Web site](#).

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on December 4, 2006. The information was verified by the guideline developer on January 15, 2007.

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