Bispebjerg Hospital

FACULTY OF HEALTH SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

ICH Guideline fra European Stroke Organisation

- Hanne Christensen, professor, overlæge, dr.med., FESO

Tilknytning (seneste 2 år)

- Medlem af ESO's guideline udvalg, medforfatter på flere guidelines
- Formand for ESO's counsil of fellows
- Medforfatter INCH-studiet
- Advisory Boards
  - International Advisory Board Amgen
  - Global Advisory Board Astra Zeneca
- Honorar for foredrag/undervisning
  - Bayer, BMS, Boehringer-Ingelheim, Covidien, Institut for Rationel Farmakoterapi, KAP-H (Kvalitet i almen praksis, RegionH
- Kongresrejser
  - Boehringer-Ingelheim

Baggrund for ESO guidelines

- Ønsket om at udvikle Europæiske guidelines på et højt fagligt niveau
- Ønsket om at anvende GRADE-principperne – en systematisk tilgang – 'gennemsigtigt og fornuftigt'
- Dedikation til 'evidence based medicine – in contrast to eminence based medicine'
- Guidelines kan oversættes til andre sprog – DSFA har påtaget sig denne opgave

Organisation og fremgangsmåde

- Guideline-gruppen – som refererer til bestyrelse og forretningsudvalg i ESO – leder arbejdet; formand Prof Thorsten Steiner
- Der afholdes kurser i GRADE halvårligt (Cochrane-gruppen fra Freiburg samt medlemmer af guideline-gruppen underviser)
- Potentielle deltagere i arbejdet samt allerede udpegede deltager
- Guidelines skal følge SOP – se senere..
- Guidelines sendes i review i guideline-gruppe og publiceres efter peer review proces hidtil i IJS, fremtidigt i EJS

SOP'en

Guidelines

The European Stroke Organisation Guidelines: a standard operating procedure

George Ntaios[1]*, Natan M. Bornstein[2], Valeria Caso[3], Hanne Christensen[4], Jacques De Keyser[5,6], Hans-Christoph Diener[7], Exuperio Diez-Tejedor[8], Jose M. Ferro[9], Gary A. Ford[10], Armin Grau[11], Emanuella Keller[12], Didier Leys[13], David Russell[14], Danilo Toni[15], Guillaume Turc[16], Bart Van der Worp[17], Nils Wahlgren[18], and Thorsten Steiner[19,20] for the European Stroke Organisation

IJS 2015

- Øger gennemsigtighed og sikrer kvalitet gennem fast procedure

Udvikling af guideline, jfr. SOP

Table 6 Summary of actions toward a Guideline Document

Responsible	Steps for the working group	GRADE steps according to Schünemann *et al.* (23)	Actions	Time schedule (weeks)
Module leader	1		Assemble the working group	4
MWG	2	1	Ask a specific management question to be answered by a recommendation.	4
MWG		2	Identify all important outcomes for every health care question.	
MWG		3	Judge the relative importance of outcomes	
GC; external reviewers			Comment on and approve PICO questions	
MWG; Cochrane Stroke Registry Group	3	4	Perform literature search; identify and summarize all relevant evidence in evidence profiles.	4
PICO group	4	5	Grade the quality of evidence for each outcome.	4
PICO group		6	Decide on the overall quality of evidence across outcomes.	
PICO group		7	Include judgments about the underlying values and preferences related to the management options and outcomes.	
PICO group		8	Decide on the balance of desirable and undesirable effects	
PICO group		9	Decide on the balance of net benefits and cost.	
MWG		10	Grade the strength of recommendation.	
MWG		11	Formulate a recommendation	
MWG	5		Preparation of the Guideline Document	6
GC, external reviewers and ESO fellows	6		Review	12
MWG			Integration of changes	
GC			Review/approval	
EC			Review	
MWG			Integration of changes	
EC			Review/approval	
Module leader			Submission	
Total				34

GRADE- principper, resume

- Styrken af evidens: hvor sikre er vi på om dette er rigtigt?
- Styrken af anbefalingen: hvor vigtigt synes vi dette er?
- Forhold kan op og ned-graderes
- PICO-spørgsmål (**p**opulation **i**ntervention **c**onparator **o**utcome)
- systematisk søgning
- meta-analyse
- Grading: grundlag for op- eller nedgradering
- Diskussion, konsensus, eventuelt ved Delphi

PICO-spørgsmål

- Population – hvilken patient-population handler dette om?
- Intervention – hvilken intervention?
- Comparator- i sammenligning med hvad?
- Outcome – hvilket endepunkt? –endepunkter i GRADE skal som udgangspunkt være patient-relevante, dvs fx funktion eller mortalitet, ikke en diameter på en skanning eller lign
- Hos patienter med sICH i pladehæmmerbehandling, nedsætter infusion af trombocytter i sammenligning med placebo, mortalitet indenfor 3 måneder?

GRADE: definition af kvalitet af evidens

Table 3 Definitions, implications, and symbols of grades of quality of evidence

Grade	Definition	Implication	Symbol
High	We are very confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕
Low	We have limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the true effect.	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.	Any estimate of effect is very uncertain.	⊕

Table 4 Criteria for assigning grade of evidence

Type of evidence
- Randomized trial: high
- Observational study: low
- Any other evidence: very low

Decrease grade if:
- Limitation in study design or execution (risk of bias) (↓1 or ↓2 levels)
- Inconsistency of results (↓1 or ↓2 levels)
- Indirectness of evidence (↓1 or ↓2 levels)
- Imprecise or sparse data ((↓1 or ↓2 levels)
- Publication bias (↓1 or ↓2 levels)

Increase grade if:
- Strong evidence of association: significant relative risk of >2 (<0·5) based on consistent evidence from two or more observational studies, with no plausible confounders (↑1 level)
- Very strong evidence of association: significant relative risk of >5 (<0·2) based on direct evidence with no major threats to validity (↑2 levels)
- Dose response gradient (↑1 level)
- All plausible confounders would have reduced the demonstrated effect or increase the effect if no effect was observed (↑1 level)

Styrken af anbefalingen

Table 5 Definitions and symbols of categories of strength of recommendation

Category	Definition	Symbol
Strong for an intervention	The desirable effects of an intervention outweigh its undesirable effects.	↑↑
Weak for an intervention	The desirable effects probably outweigh the undesirable effects but appreciable uncertainty exists.	↑?
Weak against an intervention	The undesirable effects probably outweigh the desirable effects but appreciable uncertainty exists.	↓?
Strong against an intervention	The undesirable effects of an intervention outweigh its desirable effects	↓↓

Delphi metoden

- Ved uenighed
- Arbejdsgruppens formænd agerer mediatorer; udsender det/de kritiske spørgsmål til gruppens medlemmer
- Medlemmerne svarer individuelt og kun til mediatorerne, som kategoriserer svar anonymt
- Dette fremlægges i gruppen mhp konsensus
- Fordele er inddragelse og demokratisering; herunder at give lige meget taletid til alle medlemmer og fjerne diskussionen fra det interpersonelle plan

European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage

Thorsten Steiner[1,2], Rustam Al-Shahi Salman[3], Ronnie Beer[4], Hanne Christensen[5], Charlotte Cordonnier[6], Laszlo Csiba[7], Michael Forsting[8], Sagi Harnof[9], Catharina J. M. Klijn[10], Derk Krieger[5], A. David Mendelow[11], Carlos Molina[12], Joan Montaner[12], Karsten Overgaard[5], Jesper Petersson[13], Risto O. Roine[14], Erich Schmutzhard[4], Karsten Schwerdtfeger[15], Christian Stapf[16], Turgut Tatlisumak[17], Brenda M. Thomas[18], Danilo Toni[19], Andreas Unterberg[20], and Markus Wagner[21]*

IJS 2014

De fleste PICO spørgsmål gennemgås –
der henvises til publikationen for fuldstændighed, referencer etc.

Indlæggelse på akut apopleksiafsnit

(1) For adults with ICH, does management on an acute stroke unit (ASU) in comparison with care on a general ward improve outcome?

Recommendation
Acute stroke unit care reduces both death and dependency for patients with ICH in comparison with care on a general ward.
Quality of evidence: High
Strength of recommendation: Strong

Der foreligger ikke RTC ang indlæggelse på ICU, neurokirurgisk afdeling eller lignende, kun vedrørende akut apopleksiafsnit, hvor der findes en ca. 20% reduktion i risiko for død og afhængighed.
Observationelle studier sparsomme og af ikke optimal kvalitet.
Der kan derfor ikke laves anbefalinger angående andre organisations-former, studier ønskes

Blodtryksreduktion

(2) For adults with acute ICH, does altering blood pressure to a particular target or with a specific agent compared with an alternative target or agent improve outcome?

Recommendation
In acute ICH within 6 h of onset, intensive blood pressure reduction (systolic target <140 mmHg in <1 h) is safe and may be superior to a systolic target <180 mmHg. No specific agent can be recommended.
Quality of evidence: Moderate
Strength of recommendation: Weak

Baseret på INTERACT-&2
ENOS senere vist sig neurtralt
ATACH-2 ?????

Hæmostase-fremmende medicinsk behandling uden tidligere antitrombotika

(3) For adults with acute ICH not associated with antithrombotic drug use, do hemostatic drugs compared with standard care improve outcome at six-months?

Recommendation
We do not recommend the use of rFVIIa for adults with acute spontaneous ICH not associated with antithrombotic drug use outside ongoing trials.
Quality of evidence: High
Strength of recommendation: Strong

Baseret på FAST/NovoSeven

THE LANCET Neurology

Medscape Medical News > Conference News

Platelet Transfusion Harmful in ICH Patients on Antiplatelets

Sue Hughes

May 12, 2016

The primary outcome was shift toward death or dependence, rated on the modified Rankin Scale (mRS) at 3 months, analyzed by ordinal logistic regression, and adjusted for stratification variables and the Intracerebral Hemorrhage Score.

Results showed that the odds of death or dependence at 3 months were higher in the platelet transfusion group than in the standard care group (adjusted common odds ratio [OR], 2.05; 95% confidence interval [CI], 1.18 - 3.56; *P* = .0114).

Prof Michael Hennerici, MD, Jennifer Kollmer, MD, Henning Stetefeld, MD, Katja E Wartenberg, MD, Prof Christian Weimar, MD, Prof Werner Hacke, MD, Prof Roland Veltkamp, MD

Operation & dræn (supratentoriel ICH)

(6) For adults with suprater
toma evacuation compared

8 out of 14 RCTs published
that surgery seemed effective
ness level [especially Glasgow
in patients who were randomi
ICH symptom onset (49).

Quality of evidence: Very low
Strength of recommendation

Additional information: The Minimally Invasive Surgery plus Recombinant Tissue Plasminogen Activator (MISTIE) II RCT compared minimally invasive surgery plus recombinant tissue plasminogen activator with medical treatment in 118 patients with acute supratentorial ICH and found reductions in hematoma and edema volume from intervention, but no overall difference in clinical outcomes (50). MISTIE III is ongoing to investigate clinical outcome (modified Rankin Scale at three-months) and safety (mortality, rebleeding, and infection at one-month) (NCT01827046).

(8) For adults with supratentorial ICH, does EVD with intraventricular thrombolysis compared with EVD with placebo improve outcome?

Recommendation
In the absence of RCTs, we cannot r
dations about how, when, and for w
bined with intrathecal thrombolysis
Quality of evidence: Very low
Stength of recommendation: None

Additional information: It seems reasonable to apply an EVD in case of clinical or neuroradiological signs of hydrocephalus, which is supported indirectly by small non-randomized studies of intraventricular fibrinolysis for IVH compared with no treatment (5,51–55). Endoscopy compared with EVD for thalamic ICH with ventricular extension reduced length of stay and the need for shunting, but there was no difference in clinical outcome (51).

Infratentoriel ICH

Additional information: Small, retrospective, observational studies suggest that initial neurological condition, level of consciousness, evidence of brain stem compression, and a tight posterior fossa on imaging are associated with outcome and might influence the decision to evacuate infratentorial ICH (58). The following indications for surgery have been proposed: obliteration of the fourth ventricle regardless of clinical symptoms or ICH size (59), GCS score <14 (60,61), hematoma diameter >30–40 mm (60,61), and hematoma volume not less than 7 cm^3 (62). Observational studies of the effect of surgery on cerebellar ICH have been inconsistent (61,63–66). An EVD usually is inserted in cases of infratentorial ICH with associated hydrocephalus (59). In a retrospective study on 39 cases of ICH within posterior fossa, CSF-drainage alone frequently required a second operation for hematoma evacuation (66).

ICP-monitorering

(10) For adults with ICH, does intracranial pressure (ICP) monitoring improve outcome in comparison to no ICP monitoring?

We could not identify any completed RCTs of ICP monitoring for acute spontaneous ICH.

Recommendation

In the absence of RCTs we cannot not make strong recommendations about how, when, and for whom invasive monitoring of intracranial pressure should be performed for patients with acute ICH.

Quality of evidence: Very low

Strength of recommendation: None

Ikke kirurgiske interventioner til nedsættelse af ICP (mannitol, glycerol, hyperton Nacl, barbiturater etc)

Additional information: Hypertonic saline (3%) was tested in one nonrandomized feasibility study in patients with supratentorial ICH, leading to less perihematomal edema and a trend in mortality figures in favor of treatment when compared with 64 historical controls (75). Invasive mild hypothermia (35°C) started within 12 h of symptom onset for 10 days in 10 patients with ICH resulted in reduced peri-hematomal edema volumes and increased the chance of survival when compared with 25 patients who were not treated (76). Several nonrandomized studies compared decompressive craniectomy plus hematoma evacuation with hematoma evacuation alone with conflicting results (77–79).

Feber

(12) For adults with ICH, does prevention and early treatment of fever (by pharmacological or physical means) compared with conventional fever management improve outcome?

Recommendation
There is insufficient evidence from RCTs to make strong recommendations on whether, when, and for whom preventive or early fever treatment should be given after acute ICH.
Quality of evidence: Low
Strength of recommendation: Weak

PAIS, observationelle studier

Forebyggelse af VTE

(13a) For adults with ICH, do physical or pharmacological interventions to prevent deep vein thrombosis/pulmonary

evidence of an effect on clinical outcomes (100). In the CLOTS-3 RCT comparing IPC versus no IPC for immobile patients with stroke, IPC was superior for the prevention of the primary outcome of proximal DVT within 30 days (8·5% vs. 12·1%; OR 0·65, 95% CI 0·51–0·84; $P = 0·001$), patients with ICH seemed to benefit at least as much as patients with ischemic stroke (OR 0·36, 95% CI 0·17–0·75 vs. OR 0·72, 95% CI 0·55–0·93; $P = 0·057$), and IPC may be superior for the prevention of death within six-months (adjusted HR 0·86, 95% CI 0·74–0·99; $P = 0·042$) (101).

t or long graduated compression of DVT. We recommend inter- ssion to improve outcome and

Additional information: Subcutaneous low-dose, unfractionated heparin after acute ICH DVT prophylaxis did not show harm, but was not superior to elastic stockings, in a nonrandomized comparison (200 with heparin plus elastic stockings vs. 258 with elastic stockings only) (104). A retrospective study included

Quality of evidence: Low

Strength of recommendation: Weak

Epilepsi

(14a) For adults with ICH, do prophylactic antiepileptic drugs (AEDs) compared with no AEDs reduce the occurrence of seizures/epilepsy or improve outcome?

Recommendation:
There is insufficient evidence from RCTs to make strong recommendations on whether preventive antiepileptic treatment should be used after ICH for the prevention of seizures or improvement of outcome in the long term.
Quality of evidence: Low
Strength of recommendation: Weak

Mangler generelt evidens, også ang. iskæmisk apopleksi

(14b) For patients with ICH suffering from an early seizure, do long-term AEDs compared with no AEDs reduce the risk of epilepsy?

Recommendation:
There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom AEDs should be given to reduce the risk of epilepsy after ICH.
Quality of evidence: Low
Strength of recommendation: Weak

Antihypertensiva efter ICH som sekundær profylakse

(17) For adults who had suffered an ICH, does subsequent

Additional information: There is no evidence on a specific blood pressure target or choice of antihypertensive drug, as this varies between RCTs (132,134–136). Adherence to antihypertensive treatment after stroke relates to support from carers (137) and health professionals as well as a realistic perception of risk and benefits of the treatment; however, nonadherence is frequently reported (138).

Strength of recommendation: Strong

Ret begrænset data fra mest fra PROGRESS, men er up-graded da det Vurderes usandsynligt at flere/større studier vil ændre anbefalingen

Genoptagelse af antitrombotika?

(18). For adults with ICH who had been on antithrombotic d ti o

The proportion of patients with ICH who had been taking antithrombotic drugs for thrombotic diseases before the time of their ICH increased over time in one community-based study (139). Short-term outcome appears worse for patients who have been taking antiplatelet drugs (140) or anticoagulant drugs pre-ICH. However, the dilemma for the patients who survive is whether to resume their antithrombotic drugs for secondary prevention against thrombotic diseases or to discontinue their antiplatelet drugs lest they should raise the risk of recurrent ICH and/or worsen the outcome of any recurrence. RCTs have not been performed to address this treatment dilemma.