Neurologic Emergencies in the ICU

Thomas P. Bleck MD MCCM FNCS

Professor of Neurology, Northwestern University Feinberg School of Medicine; and
Professor Emeritus of Neurological Sciences, Neurosurgery, Medicine, and Anesthesiology, Rush Medical College

NORTHWESTERN UNIVERSITY
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SCHOOL OF MEDICINE

Disclosures

- Research support from NIAID, NINDS, AHA
- Consultant for USAMRICD (nerve agent protection)
- DSMB chair for a phase 3 study of allopregnanolone for status epilepticus
- DSMB chair for a phase 3 study of brexanolone in postpartum depression

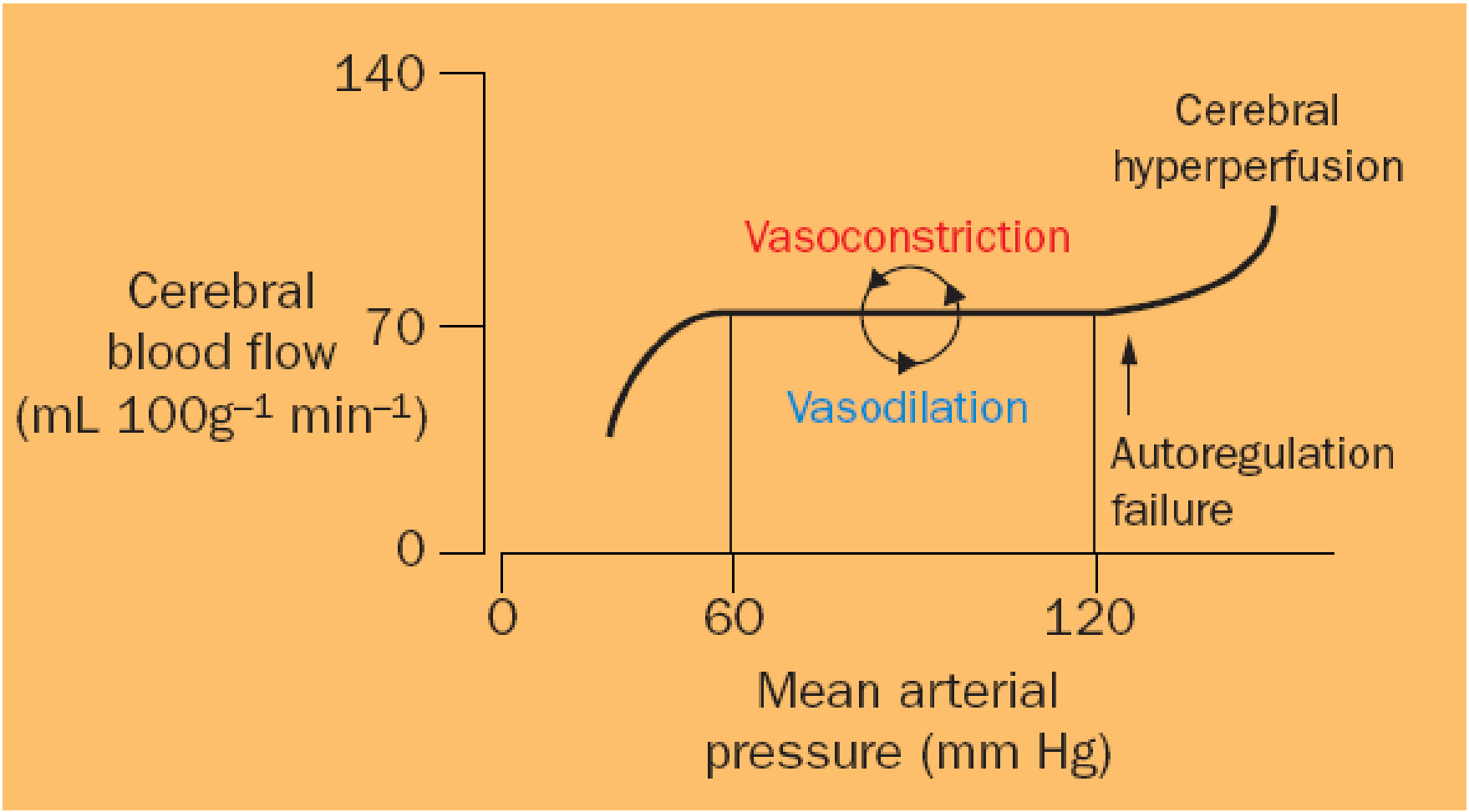
- Associate editor, **Critical Care Medicine**

- Many of the treatments discussed are not approved by the FDA for SE.

Cerebral blood flow and ICP

- The major determinant of cerebral blood flow is the extracellular potassium concentration, which determines the caliber of arterioles
  - We can affect this primarily by changing pH
  - The $PaCO_2$ effect on CBF is almost completely due to the change in pH rather than a direct effect of CO_2
- Other important factors include mean arterial pressure, the PaO_2, and intracranial pressure

Rosner view of cerebral blood flow



Cerebral vasomotor reactivity testing in head injury: the link between pressure and flow

E W Lang, J Lagopoulos, J Griffith, K Yip, A Yam, Y Mudaliar, H M Mehdorn, N W C Dorsch

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See end of article for authors' affiliations

Correspondence to: Dr Erhard W Lang, Department of Neurosurgery, Weimarer Strasse 8, D-24106 Kiel, Germany

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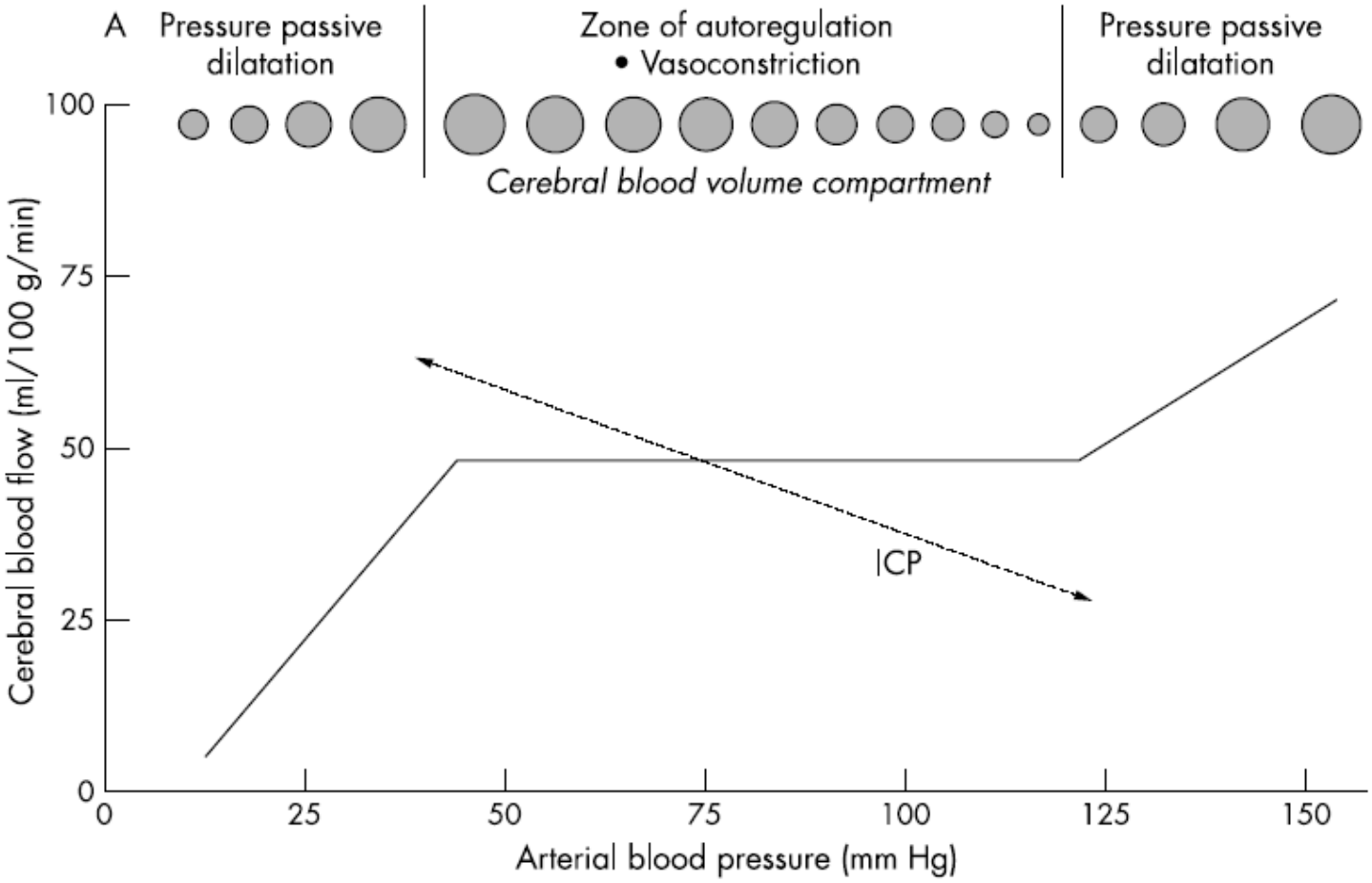
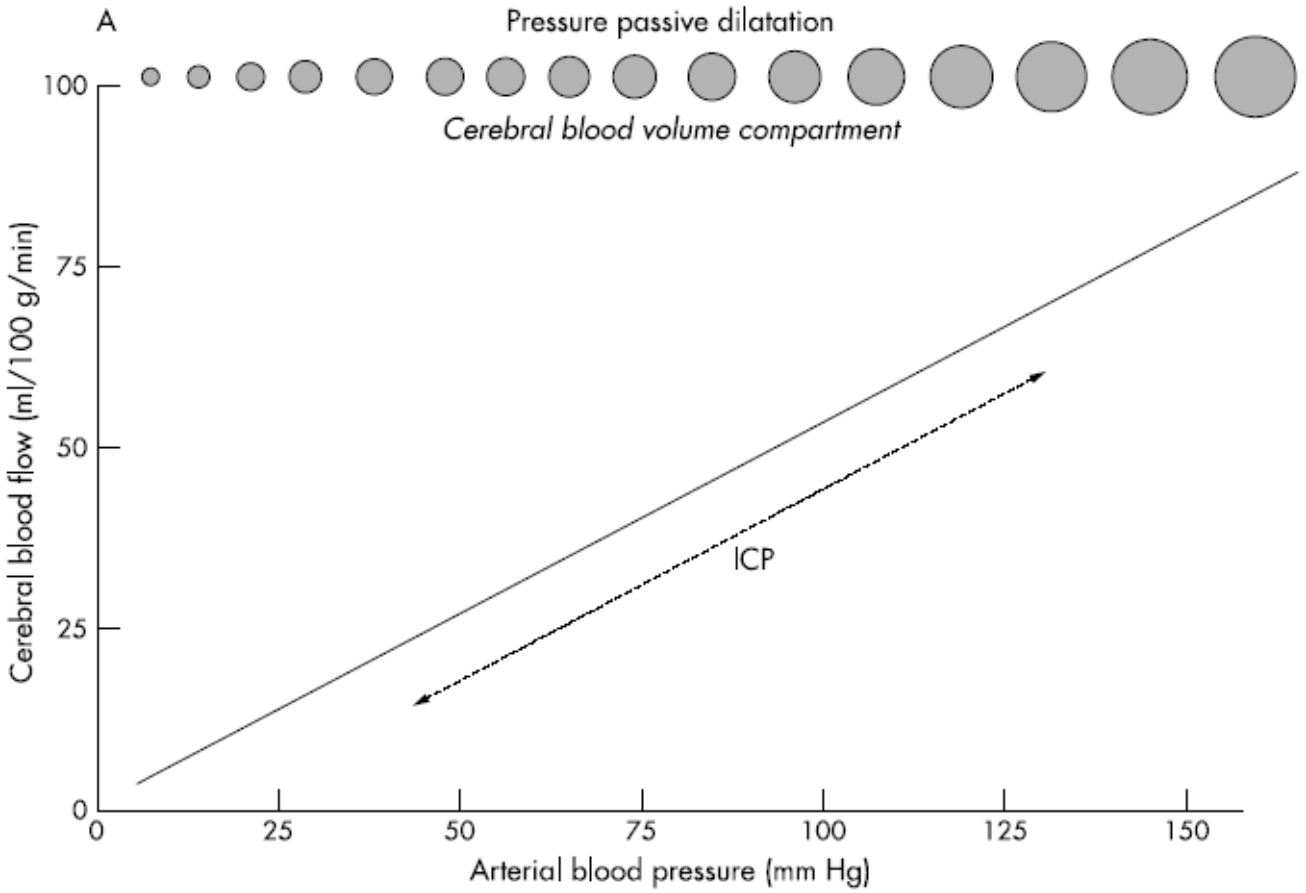
Background: It has been suggested that a moving correlation index between mean arterial blood pressure and intracranial pressure, called PRx, can be used to monitor and quantify cerebral vasomotor reactivity in patients with head injury.
Objectives: To validate this index and study its relation with cerebral blood flow velocity and cerebral autoregulation; and to identify variables associated with impairment or preservation of cerebral vasomotor reactivity.
Methods: The PRx was validated in a prospective study of 40 head injured patients. A PRx value of less than 0.3 indicates intact cerebral vasomotor reactivity, and a value of more than 0.3, impaired reactivity. Arterial blood pressure, intracranial pressure, mean cerebral perfusion pressure, and cerebral blood flow velocity, measured bilaterally with transcranial Doppler ultrasound, were recorded. Dynamic cerebrovascular autoregulation was measured using a moving correlation coefficient between arterial blood pressure and cerebral blood flow velocity, the Mx, for each cerebral hemisphere. All variables were compared in patients with intact and impaired cerebral vasomotor reactivity.
Results: No correlation between arterial blood pressure or cerebral perfusion pressure and cerebral blood flow velocity was seen in 19 patients with intact cerebral vasomotor reactivity. In contrast, the correlation between these variables was significant in 21 patients with impaired cerebral vasomotor reactivity, whose cerebral autoregulation was reduced. There was no correlation with intracranial pressure, arterial blood pressure, cerebral perfusion pressure, or interhemispheric cerebral autoregulation differences, but the values for these indices were largely within normal limits.
Conclusions: The PRx is valid for monitoring and quantifying cerebral vasomotor reactivity in patients with head injury. This intracranial pressure based index reflects changes in cerebral blood flow and cerebral autoregulatory capacity, suggesting a close link between blood flow and intracranial pressure in head injured patients. This explains why increases in arterial blood pressure and cerebral perfusion pressure may be useful for reducing intracranial pressure in selected head injured patients (those with intact cerebral vasomotor reactivity).

Intact autoregulation



Defective autoregulation



J Neurosurg 97:1045–1053, 2002

Efficacy of hyperventilation, blood pressure elevation, and metabolic suppression therapy in controlling intracranial pressure after head injury

Matthias Oertel, M.D., Daniel F. Kelly, M.D., Jae Hong Lee, M.D., M.P.H., David L. McArthur, Ph.D., M.P.H., Thomas C. Glenn, Ph.D., Paul Vespa, M.D., W. John Boscardin, Ph.D., David A. Hovda, Ph.D., and Neil A. Martin, M.D.

TABLE 1

Results of global vasoreactivity tests

Subject of Test	No. of Studies	Parameter	Mean ± SD*	Abnormal (%)†
baseline CBF	55	global CBF (ml/100 g/min)	39 ± 13‡	
hyperventilation	57	CO_2 reactivity (mm Hg)	3.2 ± 1.5	12.5
induced hypertension	55	pressure autoregulation (%)	64 ± 70	55.4
metabolic suppression	43	metabolic reactivity (%)	16 ± 11	88.4

* SD = standard deviation.

† Percent of studies with abnormal vasoreactivity. Normal CO_2 reactivity is defined as 3.7 ± 0.5%/mm Hg $PaCO_2$; normal pressure autoregulation is defined as a PAI greater than 70%; and normal metabolic suppression is defined as a decrease in CO_2-corrected V_{MCA} of 30% or more after the patient has undergone administration of high-dose propofol, according to Lee, et al.

‡ Of the baseline ^{133}Xe CBF studies, data from one study (1.8%) demonstrated global ischemia, which was defined as global CBF lower than 20 ml/100 g/min, and data from 10 studies (18%) showed absolute hyperemia, which was defined as global CBF higher than 55 ml/100 g/min, according to Kelly, et al., 1996, and Obrist, et al.

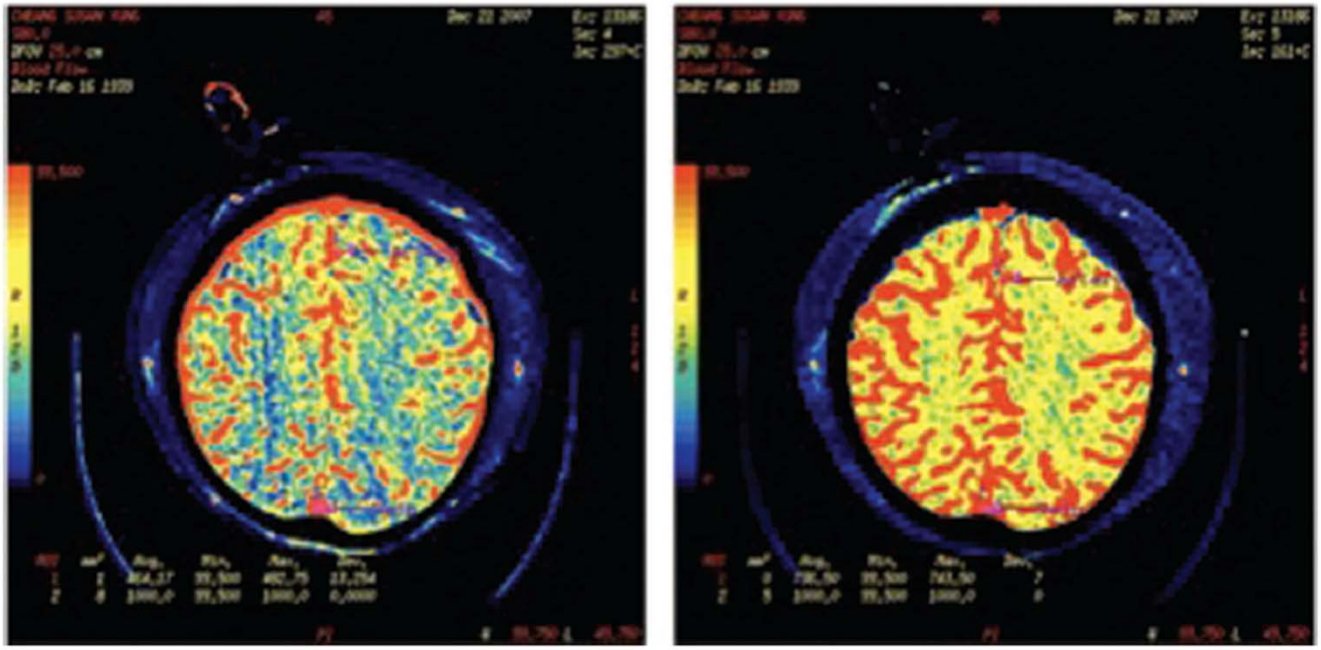


Figure 2. Left, CTP at baseline CPP of 59. Right, CTP at CPP of 76. Note diffuse increase in CBF at elevated CPP, consistent with disrupted autoregulation.

TABLE 1. Table Summarizing Results

CPA	Age (yr)*	GCS	ISS	ICP	ICP Change*	CPP
Intact	29	5.5	38	22	1.5	63
Disrupted	52	5.5	36	21	3.8	58.4

beat-to-beat (transient) variations in CPP. This is a significantly different challenge to the autoregulatory mechanism than a sustained infusion of neosynephrine. We hypothesize that dCPA and sCPA techniques may actually measure different aspects of global CPA and that the difference in the

Therapeutic approaches to intracranial hypertension

- 1918: tentorial incision (Cushing)
- 1923: osmotic diuretics (Fay)
- 1955: hypothermia (Sedzimir)
- 1957: hyperventilation (Furness)
- 1960: ventricular drainage (Lundberg)
- 1961: steroids (Gailich and French)
- 1971: decompressive craniectomy (Ransohoff *et al*; Kjellberg *et al*)
- 1973: barbiturates (Shapiro *et al*)

Management (I)

- resuscitation and airway management
  - avoid hypoxia and hypotension
  - concomitant cervical spine lesions
  - methods of intubation
    - orotracheal with inline traction
      - no nasal tubes (tracheal or gastric)
    - fiberoptic
    - videolaryngoscopic
  - posture and head position
    - effects on ICP and CPP
  - premedication
    - intravenous lidocaine, propofol, or etomidate to blunt ICP increase with intubation
      - topical anesthesia is **not** effective

Management (II)

- mannitol
  - potential mechanisms of action
  - dose: start at 0.25 gm/kg q4h
- hypertonic saline
  - may be more effective than mannitol, and effect lasts longer
  - may be used in dialysis patients
- ***maintain even fluid balance***
- sedation
- analgesia

Management (III)

- ventilatory management
  - aim for modest hypocapnea
  - reserve hyperventilation for emergencies
- NMJ blockade
  - use nondepolarizing agent (e.g., cisatracurium)
  - mechanism unknown, but may be related to abdominal compartment syndrome
- CSF drainage
- high-dose barbiturates (e.g., pentobarbital)
  - 5 mg/kg load, then 1 - 10 mg/kg/hr titrated to ICP

Management (IV)

- resection of mass lesions
- craniectomy
  - early craniectomy
    - sparing pial blood supply from compression
  - late craniectomy for salvage
    - prevention of herniation
- hypothermia
  - lowers ICP reliably but no effect on outcome
  - avoiding hyperthermia

Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial

*Jeannette Hofmeijer, L Jaap Kappelle, Ale Algra, G Johan Amelink, Jan van Gijn, H Bart van der Worp, for the HAMLET investigators**

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See Reflection and Reaction
page 303

*HAMLET investigators listed at end of report

Department of Neurology, Rijnstate Hospital, Arnhem, Netherlands (J Hofmeijer MD); **Department of Neurology** (L J Kappelle MD, A Algra MD, J van Gijn FRCP, H B van der Worp MD, J Hofmeijer), **Julius Centre for Health Sciences and Primary Care** (A Algra), **and Department of Neurosurgery** (G J Amelink MD), **Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, Netherlands**

Correspondence to:
J Hofmeijer, Rijnstate Hospital, Neurology, Wagnerlaan 55, Arnhem, Netherlands
jhofmeijer@alysis.nl

Summary

Background Patients with space-occupying hemispheric infarctions have a poor prognosis, with case fatality rates of up to 80%. In a pooled analysis of randomised trials, surgical decompression within 48 h of stroke onset reduced case fatality and improved functional outcome; however, the effect of surgery after longer intervals is unknown. The aim of HAMLET was to assess the effect of decompressive surgery within 4 days of the onset of symptoms in patients with space-occupying hemispheric infarction.

Methods Patients with space-occupying hemispheric infarction were randomly assigned within 4 days of stroke onset to surgical decompression or best medical treatment. The primary outcome measure was the modified Rankin scale (mRS) score at 1 year, which was dichotomised between good (0–3) and poor (4–6) outcome. Other outcome measures were the dichotomy of mRS score between 4 and 5, case fatality, quality of life, and symptoms of depression. Analysis was by intention to treat. This trial is registered, ISRCTN94237756.

Findings Between November, 2002, and October, 2007, 64 patients were included; 32 were randomly assigned to surgical decompression and 32 to best medical treatment. Surgical decompression had no effect on the primary outcome measure (absolute risk reduction [ARR] 0%, 95% CI –21 to 21) but did reduce case fatality (ARR 38%, 15 to 60). In a meta-analysis of patients in DECIMAL (DEcompressive Craniectomy In MALignant middle cerebral artery infarction), DESTINY (DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY), and HAMLET who were randomised within 48 h of stroke onset, surgical decompression reduced poor outcome (ARR 16%, –0·1 to 33) and case fatality (ARR 50%, 34 to 66).

Interpretation Surgical decompression reduces case fatality and poor outcome in patients with space-occupying infarctions who are treated within 48 h of stroke onset. There is no evidence that this operation improves functional outcome when it is delayed for up to 96 h after stroke onset. The decision to perform the operation should depend on the emphasis patients and relatives attribute to survival and dependency.

ORIGINAL ARTICLE

Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension

P.J. Hutchinson, A.G. Kolias, I.S. Timofeev, E.A. Corteen, M. Czosnyka, J. Timothy, I. Anderson, D.O. Bulters, A. Belli, C.A. Eynon, J. Wadley, A.D. Mendelow, P.M. Mitchell, M.H. Wilson, G. Critchley, J. Sahuquillo, A. Unterberg, F. Servadei, G.M. Teasdale, J.D. Pickard, D.K. Menon, G.D. Murray, and P.J. Kirkpatrick, for the RESCUEicp Trial Collaborators*

ABSTRACT

BACKGROUND

The effect of decompressive craniectomy on clinical outcomes in patients with refractory traumatic intracranial hypertension remains unclear.

METHODS

From 2004 through 2014, we randomly assigned 408 patients, 10 to 65 years of age, with traumatic brain injury and refractory elevated intracranial pressure (>25 mm Hg) to undergo decompressive craniectomy or receive ongoing medical care. The primary outcome was the rating on the Extended Glasgow Outcome Scale (GOS-E) (an 8-point scale, ranging from death to "upper good recovery" [no injury-related problems]) at 6 months. The primary-outcome measure was analyzed with an ordinal method based on the proportional-odds model. If the model was rejected, that would indicate a significant difference in the GOS-E distribution, and results would be reported descriptively.

RESULTS

The GOS-E distribution differed between the two groups (P<0.001). The proportional-odds assumption was rejected, and therefore results are reported descriptively. At 6 months, the GOS-E distributions were as follows: death, 26.9% among 201 patients in the surgical group versus 48.9% among 188 patients in the medical group; vegetative state, 8.5% versus 2.1%; lower severe disability (dependent on others for care), 21.9% versus 14.4%; upper severe disability (independent at home), 15.4% versus 8.0%; moderate disability, 23.4% versus 19.7%; and good recovery, 4.0% versus 6.9%. At 12 months, the GOS-E distributions were as follows: death, 30.4% among 194 surgical patients versus 52.0% among 179 medical patients; vegetative state, 6.2% versus 1.7%; lower severe disability, 18.0% versus 14.0%; upper severe disability, 13.4% versus 3.9%; moderate disability, 22.2% versus 20.1%; and good recovery, 9.8% versus 8.4%. Surgical patients had fewer hours than medical patients with intracranial pressure above 25 mm Hg after randomization (median, 5.0 vs. 17.0 hours; P<0.001) but had a higher rate of adverse events (16.3% vs. 9.2%, P=0.03).

CONCLUSIONS

At 6 months, decompressive craniectomy in patients with traumatic brain injury and refractory intracranial hypertension resulted in lower mortality and higher rates of vegetative state, lower severe disability, and upper severe disability than medical care. The rates of moderate disability and good recovery were similar in the two groups. (Funded by the Medical Research Council and others; RESCUEicp Current Controlled Trials number, ISRCTN66202560.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hutchinson at the Division of Neurosurgery, Box 167, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, United Kingdom, or at pjah2@cam.ac.uk.

*A complete list of investigators in the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial is provided in the Supplementary Appendix, available at NEJM.org.

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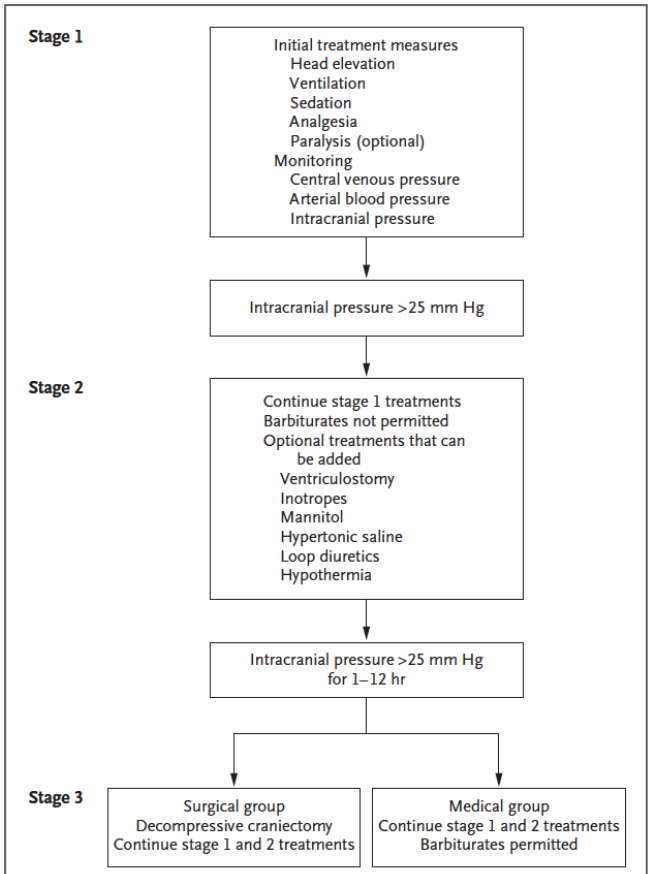
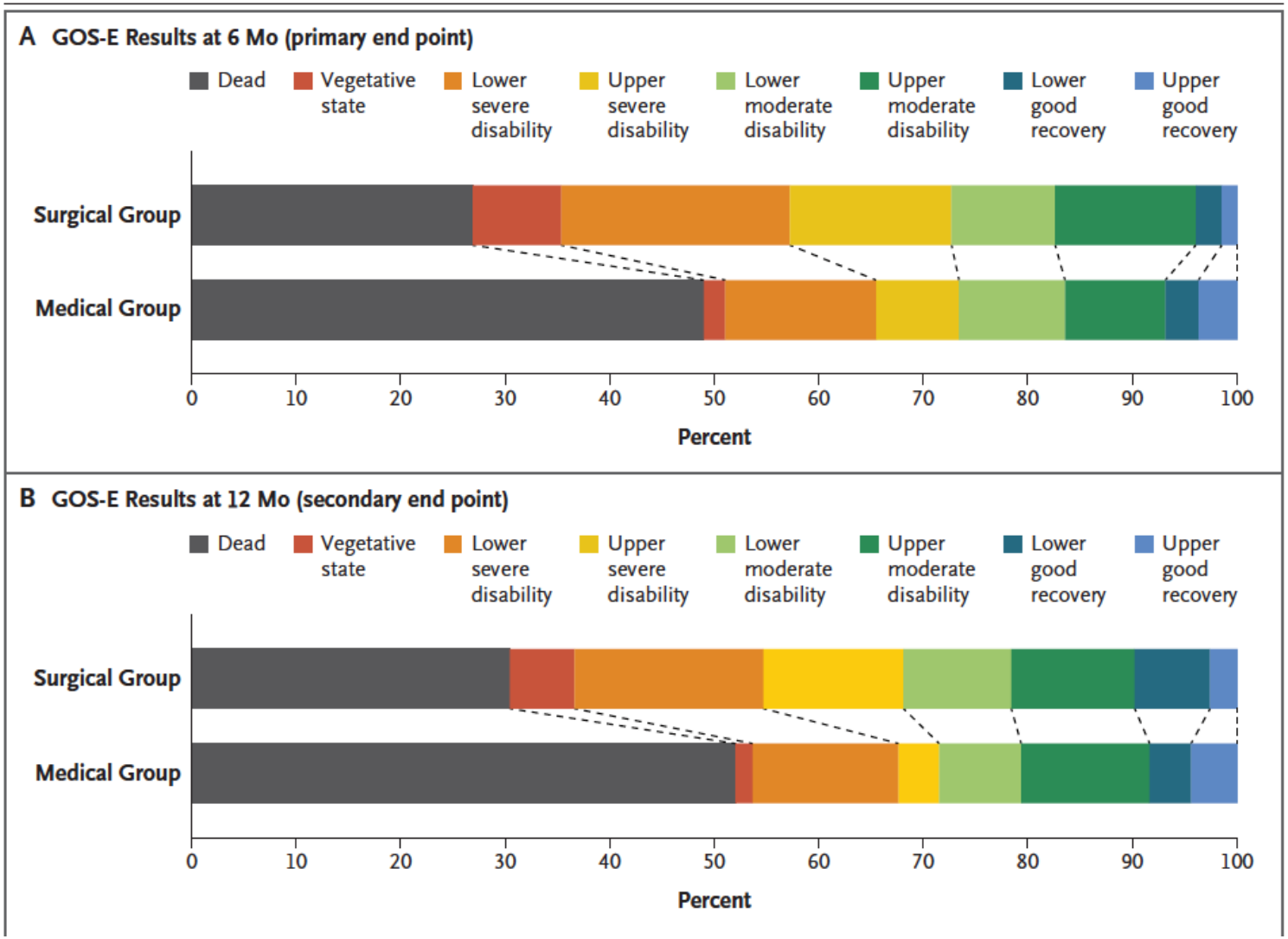


Figure 1. Stages of Therapeutic Management.

Agreement for participation was obtained from the nearest relative or a person who had been designated to give consent preemptively on admission of the patient in order to avoid delays in treatment. Randomization was performed after stage 2 if the intracranial pressure was more than 25 mm Hg for 1 to 12 hours. The protocol stages 1 and 2 reflected the therapeutic protocols that were followed in the participating units.


A GOS-E Results at 6 Mo (primary end point)
Dead
Vegetative state
Lower severe disability
Upper severe disability
Lower moderate disability
Upper moderate disability
Lower good recovery
Upper good recovery
Surgical Group
Medical Group
0
10
20
30
40
50
60
70
80
90
100
Percent
B GOS-E Results at 12 Mo (secondary end point)
Dead
Vegetative state
Lower severe disability
Upper severe disability
Lower moderate disability
Upper moderate disability
Lower good recovery
Upper good recovery
Surgical Group
Medical Group
0
10
20
30
40
50
60
70
80
90
100
Percent

Management (V)

- brain oxygen measurement and optimization
  - increase FiO_2, decrease minute ventilation slightly, transfuse PRBCs, lower core temperature
- antiseizure drugs
  - phenytoin 20 mg/kg for one week for trauma
    - most have moved to levetiracetam, without real data
  - other conditions uncertain
- nutrition and GI bleeding prophylaxis
- thromboembolism prophylaxis

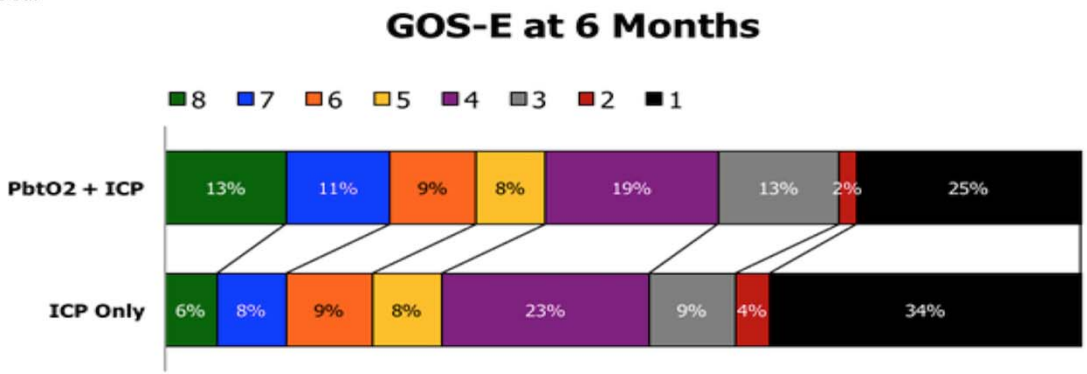
Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial*

David O. Okonkwo, MD, PhD[1]; Lori A. Shutter, MD[2]; Carol Moore, MA[3]; Nancy R. Temkin, PhD[3]; Ava M. Puccio, RN, PhD[1]; Christopher J. Madden, MD[4]; Norberto Andaluz, MD[5]; Randall M. Chesnut, MD[6]; M. Ross Bullock, MD, PhD[7]; Gerald A. Grant, MD, FACS[8]; John McGregor, MD[9]; Michael Weaver, PhD[9]; Jack Jallo, MD, PhD[10]; Peter D. LeRoux, MD, FACS[11]; Dick Moberg, MSE[12]; Jason Barber, MS[13]; Christos Lazaridis, MD[14]; Ramon R. Diaz-Arrastia, MD, PhD[14]

Measurements and Main Results: A management protocol based on brain tissue oxygenation and intracranial pressure monitoring reduced the proportion of time with brain tissue hypoxia after severe traumatic brain injury (0.45 in intracranial pressure–only group and 0.16 in intracranial pressure plus brain tissue oxygenation group; $p < 0.0001$). Intracranial pressure control was similar in both groups. Safety and feasibility of the tiered treatment protocol were confirmed. There were no procedure-related complications. Treatment of secondary injury after severe traumatic brain injury based on brain tissue oxygenation and intracranial pressure values was consistent with reduced mortality and increased proportions of patients with good recovery compared with intracranial pressure–only management; however, the study was not powered for clinical efficacy.

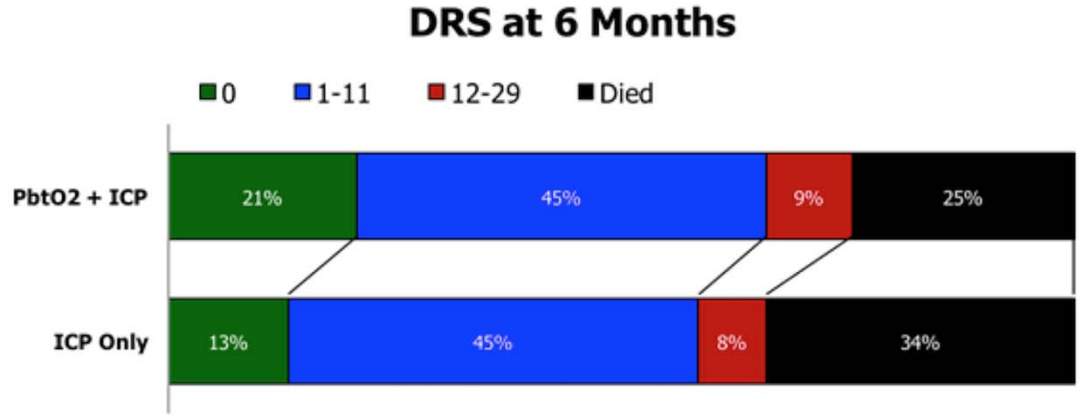
Crit Care Med 2017;45:1907–1914

Figure 3a.



8 = Upper Good Recovery; 7 = Lower Good Recovery; 6 = Upper Moderate Disability; 5 = Lower Moderate Disability; 4 = Upper Severity Disability; 3 = Lower Severe Disability; 2 = Vegetative State; 1 = Dead

Figure 3b.



0 = no disability; 1-11 = Mild to Moderate Disability; 12-29 = Severe Disability to Vegetative State

Study Protocol

Brain Oxygen Optimization in Severe Traumatic Brain Injury—Phase 3 (BOOST-3)

Study Chair:
Ramon Diaz-Arrastia, MD, PhD

Supported by:
The National Institute of Neurological Disorders and Stroke (NINDS)
U01 NS099046

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair;
Teri Ackerson, BSN, RN; Opeolu M. Adeoye, MD, MS, FAHA;
Nicholas C. Bambakidis, MD, FAHA; Kyra Becker, MD, FAHA; José Biller, MD, FAHA;
Michael Brown, MD, MSc; Bart M. Demaerschalk, MD, MSc, FAHA;
Brian Hoh, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Chelsea S. Kidwell, MD, FAHA;
Thabele M. Leslie-Mazwi, MD; Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA;
Phillip A. Scott, MD, MBA, FAHA; Kevin N. Sheth, MD, FAHA;
Andrew M. Southerland, MD, MSc, FAHA; Deborah V. Summers, MSN, RN, FAHA;
David L. Tirschwell, MD, MSc, FAHA; on behalf of the American Heart Association Stroke Council

2.2.2. IV Alteplase Eligibility (Continued)	COR	LOE	New, Revised, or Unchanged
2. In patients eligible for IV alteplase, because benefit of therapy is time dependent, treatment should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging.	I	B-NR	New recommendation.
NCCT was the only neuroimaging modality used in the NINDS rt-PA trial and in ECASS III and is therefore sufficient neuroimaging for decisions about IV alteplase in most patients.[48,49] Multimodal CT and MRI, including diffusion and perfusion imaging, are not necessary when the diagnosis of ischemic stroke is very likely, and their performance may delay time-sensitive administration of IV alteplase. In some cases, particularly when there is substantial diagnostic uncertainty, advanced imaging may be beneficial.			See Table XX in online Data Supplement 1.
3. In patients with AIS who awake with stroke symptoms or have unclear time of onset > 4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition.	IIa	B-R	New recommendation.
The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) randomized 503 patients with AIS who awoke with stroke or had unclear time of onset >4.5 hours from last known well and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the middle cerebral artery (MCA), NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. The trial was terminated early for lack of funding before the designated 800 patients were randomized. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well was slightly over 10 hours. At baseline, one-third of the patients had vessel occlusion on time-of-flight MRA, and three-quarters of the FLAIR lesions were <9 mL. The end point of an mRS score of 0 to 1 at 90 days was achieved in 53.3% of the IV alteplase group and in 41.8% of the placebo group (P=0.02).[88]			See Table XIX in online Data Supplement 1

2.2.3. Mechanical Thrombectomy Eligibility–Vessel Imaging	COR	LOE	New, Revised, or Unchanged
1. For patients who otherwise meet criteria for mechanical thrombectomy, noninvasive vessel imaging of the intracranial arteries is recommended during the initial imaging evaluation.	I	A	Recommendation reworded for clarity from 2015 Endovascular. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording.
2. For patients with suspected LVO who have not had noninvasive vessel imaging as part of their initial imaging assessment for stroke, noninvasive vessel imaging should then be obtained as quickly as possible (eg, during alteplase infusion if feasible).	I	A	Recommendation revised from 2015 Endovascular. COR and LOE unchanged.
A recent systematic review evaluated the accuracy of prediction instruments for diagnosing LVO.[4] In the setting where confirmed ischemic stroke patients would be assessed by a neurologist or emergency physician in the ED, the authors suggested that the NIHSS score is the best of the LVO prediction instruments. According to their meta-analysis, a threshold of ≥10 would provide the optimal balance between sensitivity (73%) and specificity (74%). To maximize sensitivity (at the cost of lower specificity), a threshold of ≥6 would have 87% sensitivity and 52% specificity. However, even this low threshold misses some cases with LVO, whereas the low specificity indicates that false-positives will be common. The sensitivity of CTA and MRA compared with the gold standard of catheter angiography ranges from 87% to 100%, with CTA having greater accuracy than MRA.[95,96] Pivotal trials of mechanical thrombectomy all required noninvasive CTA or MRA diagnosis of LVO as an inclusion criterion.			See Tables XVII and XXII in online Data Supplement 1.
3. In patients with suspected intracranial LVO and no history of renal impairment, who otherwise meet criteria for mechanical thrombectomy, it is reasonable to proceed with CTA if indicated before obtaining a serum creatinine concentration.	IIa	B-NR	New recommendation.
Analyses from a number of observational studies suggest that the risk of contrast-induced nephropathy secondary to CTA imaging is relatively low, particularly in patients without a history of renal impairment. Moreover, waiting for these laboratory results may lead to delays in mechanical thrombectomy.[97–102]			See Table XXIII in online Data Supplement 1.
4. In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, may be reasonable to provide useful information on patient eligibility and endovascular procedural planning.	IIb	C-EO	New recommendation.
Knowledge of vessel anatomy and presence of extracranial vessel dissections, stenoses, and occlusions may assist in planning endovascular procedures or identifying patients ineligible for treatment because of vessel tortuosity or inability to access the intracranial vasculature.			

2.2.4. Mechanical Thrombectomy Eligibility–Multimodal Imaging	COR	LOE	New, Revised, or Unchanged
1. When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window.	I	A	New recommendation.
The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical-core mismatch (a combination of age-adjusted NIHSS score and age-adjusted core infarct size on CTP or DW-MRI) as an eligibility criterion to select patients with large anterior circulation vessel occlusion for mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in functional outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33% [95% CI, 21–44]; posterior probability of superiority >0.999).[51] The DEFUSE 3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67 [95% CI, 1.60–4.48]; *P*<0.0001).[52] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice.[51,52]			See Table XVII in online Data Supplement 1.
2. When evaluating patients with AIS within 6 hours of last known normal with LVO and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≥6, selection for mechanical thrombectomy based on CT and CTA or MRI and MRA is recommended in preference to performance of additional imaging such as perfusion studies.	I	B-NR	New recommendation.
Of the 6 RCTs that independently demonstrated clinical benefit of mechanical thrombectomy with stent retrievers when performed <6 hours from stroke onset, 4 trials (REVASCAT [Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset], SWIFT PRIME [Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment], EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial], and ESCAPE)[105–108] used some form of advanced imaging to determine eligibility, whereas 2 (THRACE [Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke] and MR CLEAN)[109,110] required only NCCT and demonstration of LVO. Because the last 2 studies independently demonstrated benefit in the treated group, the role of additional imaging-based eligibility criteria is not well established and could lead to the exclusion of patients who would benefit from treatment and are therefore not indicated at this time. Further RCTs may be helpful to determine whether advanced imaging paradigms using CTP, CTA, and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, are beneficial for selecting patients for reperfusion therapy who are within 6 hours of symptom onset and have an ASPECTS <6.			See Table XVII in online Data Supplement 1.

Table 5. Options to Treat Arterial Hypertension in Patients With AIS Who Are Candidates for Emergency Reperfusion Therapy*

COR IIb	LOE C-EO
Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg:	
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or	
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
Other agents (eg, hydralazine, enalaprilat) may also be considered	
If BP is not maintained ≤185/110 mm Hg, do not administer alteplase	
Management of BP during and after alteplase or other emergency reperfusion therapy to maintain BP ≤180/105 mm Hg:	
Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6 h, and then every hour for 16 h	
If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:	
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or	
Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside	

3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR.	**IIa**	**B-R**	New recommendation.
The WAKE-UP RCT randomized 503 patients with AIS who awoke with stroke or had unclear time of onset and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the MCA, NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well to symptom recognition was ≈7 hours and to alteplase administration slightly over 10 hours. The primary end point of an mRS score 0 to 1 at 90 days was achieved in 53.3% of the alteplase group and in 41.8% of the placebo group (P=0.02). Only 20% had LVO of the intracranial internal carotid or proximal middle cerebral arteries.[88]			See Table XIX in online Data Supplement 1.

3.5.3. Mild Stroke	COR	LOE	New, Revised, or Unchanged
1. For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	I	B-R	Recommendation revised from 2015 IV Alteplase. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
2. For otherwise eligible patients with mild disabling stroke symptoms, IV alteplase may be reasonable for patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	IIb	B-NR	New recommendation.
3. For otherwise eligible patients with mild nondisabling stroke symptoms (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	III: No Benefit	B-R	New recommendation.
4. For otherwise eligible patients with mild non-disabling stroke symptoms (NIHSS 0–5), IV alteplase is not recommended for patients who could be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.	III: No Benefit	C-LD	New recommendation.

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	**IIb**	**B-R**	New recommendation.
IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).[178] This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (P=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; P=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (P=0.23) or 0 to 2 (P=0.06). sICH rates were 1% in both groups.			See Table XLIII in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	**IIb**	**B-R**	New recommendation.
IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[179–182] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[182] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XLIII in online Data Supplement 1.

3.9. Antiplatelet Treatment (Continued)	COR	LOE	New, Revised, or Unchanged
2. In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.	I	A	New recommendation.
3. In patients with BP ≥220/120 mm Hg who did not receive IV alteplase or mechanical thrombectomy and have no comorbid conditions requiring urgent antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.	IIb	C-EO	New recommendation.

Table 6. Management of Symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase for Treatment of AIS

COR IIb	LOE C-EO
Stop alteplase infusion	
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match	
Emergent nonenhanced head CT	
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

Table 7. Management of Orolingual Angioedema Associated With IV Alteplase Administration for AIS

COR IIb	LOE C-EO
Maintain airway	
Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.	
Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation.	
Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.	
Discontinue IV alteplase infusion and hold ACE inhibitors	
Administer IV methylprednisolone 125 mg	
Administer IV diphenhydramine 50 mg	
Administer ranitidine 50 mg IV or famotidine 20 mg IV	
If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL	
Icatibant, a selective bradykinin B_2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed a total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACE inhibitor-related angioedema	
Supportive care	

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Diederik W J Dippel, Peter J Mitchell, Andrew M Demchuk, Antoni Dávalos, Charles B L M Majoie, Aad van der Lugt, Maria A de Miquel, Geoffrey A Donnan, Yvo B W E M Roos, Alain Bonafe, Reza Jahan, Hans-Christoph Diener, Lucie A van den Berg, Elad I Levy, Olvert A Berkhemer, Vitor M Pereira, Jeremy Rempel, Mònica Millán, Stephen M Davis, Daniel Roy, John Thornton, Luis San Román, Marc Ribó, Debbie Beumer, Bruce Stouch, Scott Brown, Bruce C V Campbell, Robert J van Oostenbrugge, Jeffrey L Saver, Michael D Hill, Tudor G Jovin, for the HERMES collaborators

Summary

Background In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included.

Methods We formed the HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December, 2010, and December, 2014. In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days. By direct access to the study databases, we extracted individual patient data that we used to assess the primary outcome of reduced disability on mRS at 90 days in the pooled population and examine heterogeneity of this treatment effect across prespecified subgroups. To account for between-trial variance we used mixed-effects modelling with random effects for parameters of interest. We then used mixed-effects ordinal logistic regression models to calculate common odds ratios (cOR) for the primary outcome in the whole population (shift analysis) and in subgroups after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale score), site of occlusion (internal carotid artery *vs* M1 segment of middle cerebral artery *vs* M2 segment of middle cerebral artery), intravenous alteplase (yes *vs* no), baseline Alberta Stroke Program Early CT score, and time from stroke onset to randomisation.

Findings We analysed individual data for 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to control). Endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted cOR 2·49, 95% CI 1·76–3·53; p<0·0001). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2·6. Subgroup analysis of the primary endpoint showed no heterogeneity of treatment effect across prespecified subgroups for reduced disability ($p_{interaction}$=0·43). Effect sizes favouring endovascular thrombectomy over control were present in several strata of special interest, including in patients aged 80 years or older (cOR 3·68, 95% CI 1·95–6·92), those randomised more than 300 min after symptom onset (1·76, 1·05–2·97), and those not eligible for intravenous alteplase (2·43, 1·30–4·55). Mortality at 90 days and risk of parenchymal haematoma and symptomatic intracranial haemorrhage did not differ between populations.

Interpretation Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. These findings will have global implications on structuring systems of care to provide timely treatment to patients with acute ischaemic stroke due to large vessel occlusion.

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See **Comment** page 1695

Departments of Clinical Neuroscience and Radiology, Hotchkiss Brain Institute, Cummings School of Medicine, University of Calgary, Calgary, AB, Canada (Prof M Goyal MD, B K Menon MD, Prof A M Demchuk MD, Prof M D Hill MD); **Maastricht University Medical Center, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, Netherlands** (W H van Zwam MD, D Beumer MD, Prof R J van Oostenbrugge MD); **Erasmus MC University Medical Center, Rotterdam, Netherlands** (Prof D W J Dippel MD, Prof A van der Lugt MD); **Department of Radiology (Prof P J Mitchell MBBS) and Department of Medicine and Neurology, Melbourne Brain Centre** (Prof S M Davis MD, B C V Campbell MD), **Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia; Hospital Germans Trias y Pujol, Barcelona, Spain** (Prof A Dávalos MD); **Academic Medical Center, Amsterdam, Netherlands** (Prof C B L M Majoie MD, Prof Y B W E M Roos MD, O A Berkhemer MD, L A van den Berg MD); **Hospital**

Modified Rankin scale

0 No symptoms at all

1 No significant disability despite symptoms; able to carry out all usual duties and activities

2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 Moderate disability; requiring some help, but able to walk without assistance

4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 Dead

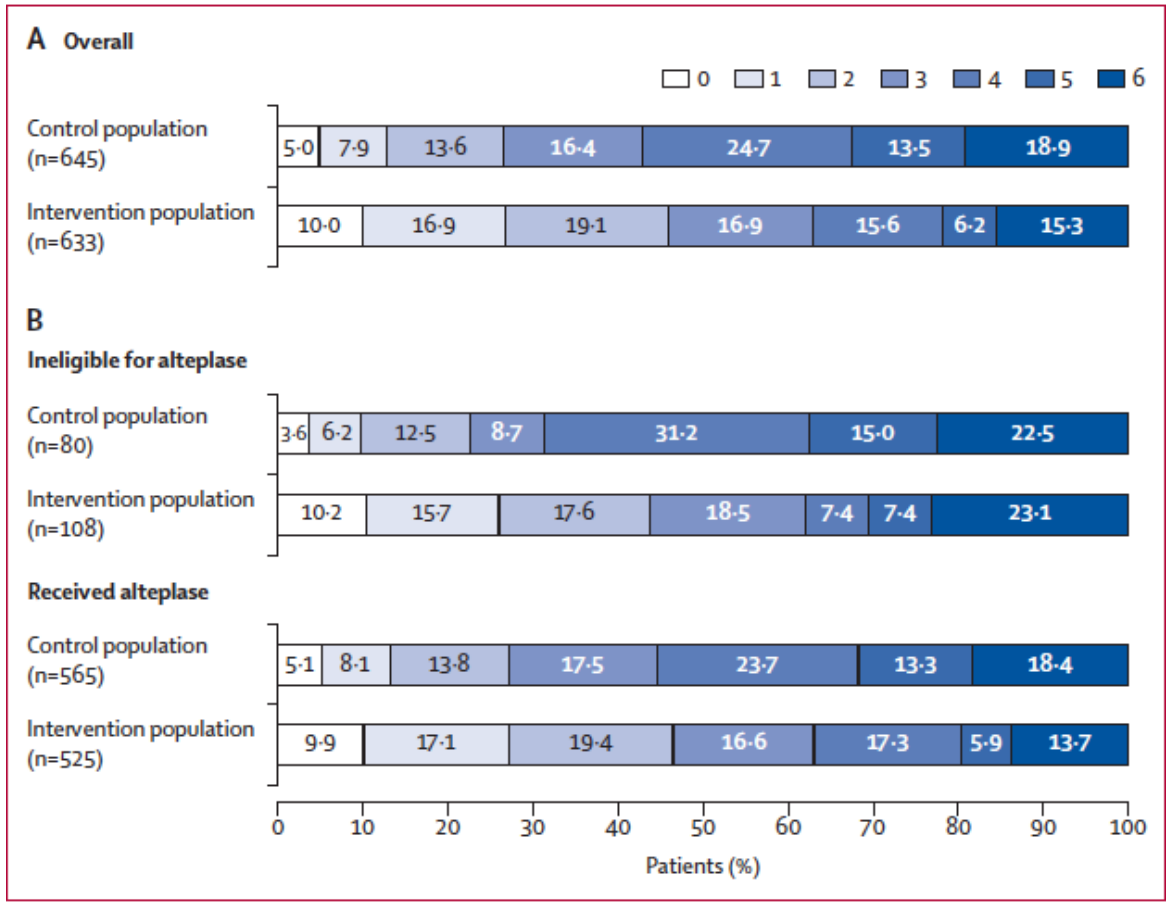

Figure 1: **Scores on the modified Rankin Scale at 90 days**
Distribution of scores at 90 days in the intervention and control groups in the overall trial population (A) and for patients treated with, or ineligible for, intravenous alteplase (B). Distributions for other subgroups shown in appendix pp 5–11.

- Patients older than 80 years had at least as great a benefit as younger patients (OR 3.68).
- Patients treated more than 300 minutes from stroke onset still benefitted (OR 2.43); most stopped enrolling at six hours.
- Patients not eligible for intravenous rt-PA still benefitted (OR 2.43).
- Intracranial bleeding was not significantly different between the treated patients and the controls.
- Mortality was slightly better, but not significantly so, in the thrombectomy group (15.3% vs 18.9%).

Other AHA/ASA recommendations

- No acute therapeutic anticoagulation
  - Prophylaxis for DVT OK
    - (when to start anticoagulation in AF for secondary prevention uncertain)
- ASA within 48 hours
    - (we give in ambulance or on ED arrival; crush or give rectally unless swallowing has been cleared)
- Uncertainty about blood pressure augmentation or volume expansion

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REVIEW

Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference

Michael N. Diringer · Thomas P. Bleck · J. Claude Hemphill III · David Menon · Lori Shutter · Paul Vespa · Nicolas Bruder · E. Sander Connolly Jr. · Giuseppe Citerio · Daryl Gress · Daniel Hänggi · Brian L. Hoh · Giuseppe Lanzino · Peter Le Roux · Alejandro Rabinstein · Erich Schmutzhard · Nino Stocchetti · Jose I. Suarez · Miriam Treggiari · Ming-Yuan Tseng · Mervyn D. I. Vergouwen · Stefan Wolf · Gregory Zipfel

Critical care issues: rebleeding

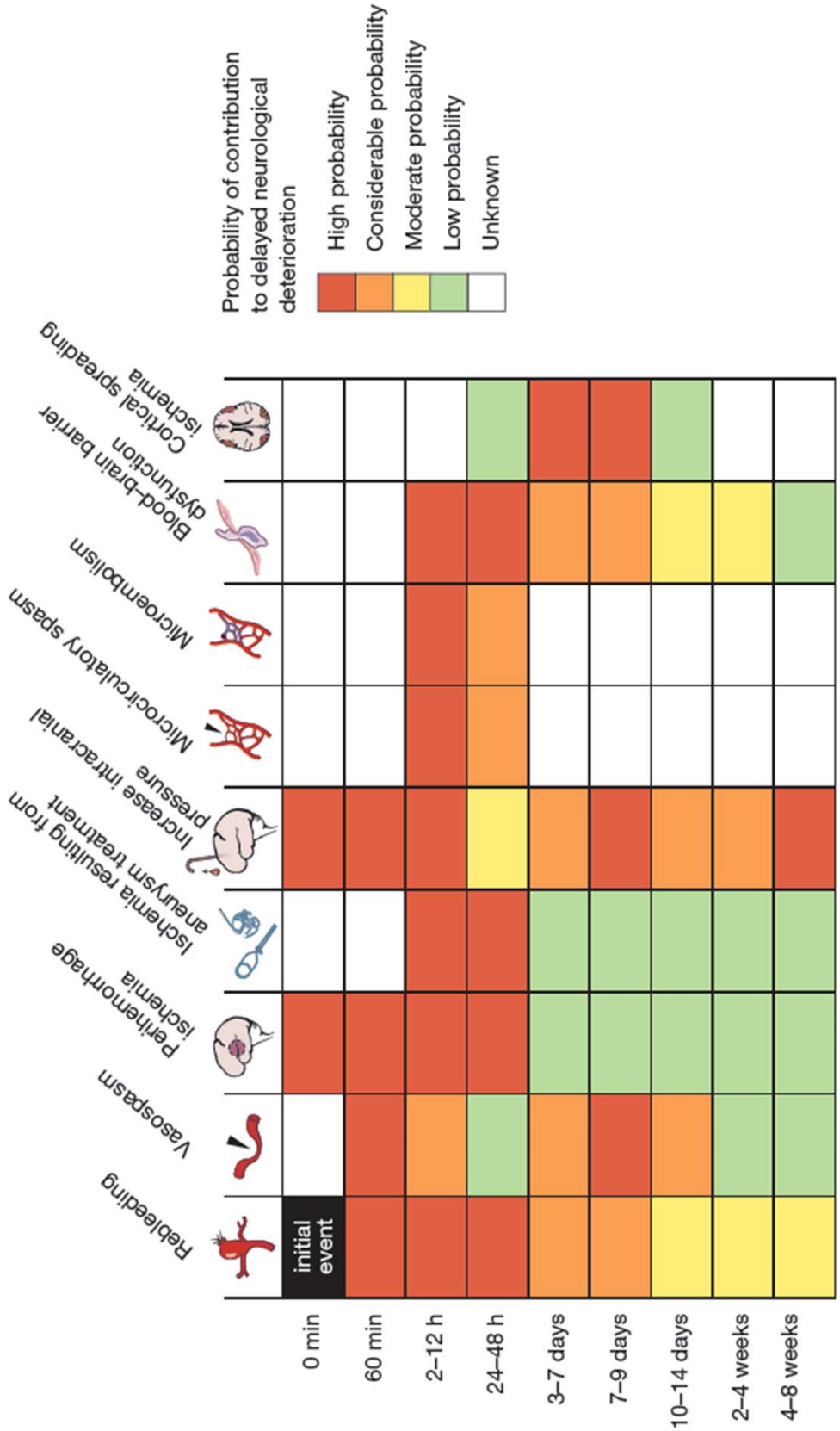
- Unsecured aneurysms:
  - 9% – 17% rebleed on day 0, then
  - 1.5%/day for next 13 days [∴ up to 36% for 2 weeks]
- Antifibrinolytic therapy (e.g., aminocaproic acid)
  - may be useful between presentation and early surgery
- Blood pressure management
  - labetalol, hydralazine, nicardipine
- Analgesia
- Minimal or no sedation to allow examination

Critical care issues: neurogenic pulmonary edema

- Symptomatic pulmonary edema occurs in about 20% of SAH patients
  - detectable oxygenation abnormalities occur in 80%
- Potential mechanisms:
  - hypersympathetic state
  - cardiogenic pulmonary edema
  - neurogenic pulmonary edema
- Management

Cerebral vasospasm after subarachnoid hemorrhage: the emerging revolution

R Loch Macdonald*, Ryszard M Pluta and John H Zhang

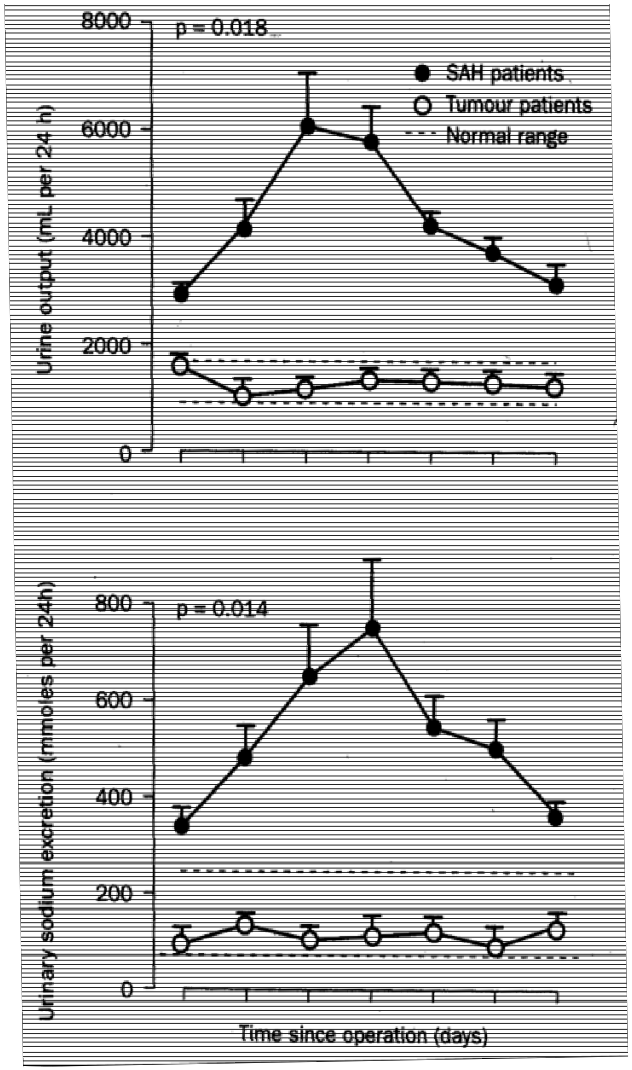


Critical care issues: vasospasm and delayed ischemic damage

- Prophylaxis
  - clot removal
  - volume expansion
  - nimodipine
  - free radical scavengers
- Management
  - volume expansion
  - induced hypertension
  - angioplasty
  - intra-arterial verapamil or nicardipine

Critical care issues: cerebral salt wasting

- Pathophysiology
  - natriuretic peptides
- Diagnosis
  - physical signs of volume depletion unreliable in SAH
  - hypo-osmolar serum with concentrated urine (not SIADH)
  - normal or elevated serum uric acid
- Management
  - volume repletion
  - hypertonic sodium chloride



Berendes *et al* **Lancet** 1997;349:245-9

mini review http://www.kidney-international.org

Is it cerebral or renal salt wasting?

John K. Maesaka[1,2], Louis J. Imbriano[1,2], Nicole M. Ali[1,2] and Ekambaram Ilamathi[1,2]

[1]Division of Nephrology and Hypertension, Department of Medicine, Winthrop-University Hospital, Mineola, New York, USA and [2]SUNY Medical School at Stony Brook, Stony Brook, New York, USA

Euvolemia in SIADH and ECV depletion in RSW are the only variables that differentiate SIADH from RSW on first encounter, but clinical assessment of ECV is inaccurate.[6] Treatment for RSW, however, can be initiated if FEphosphate is >20% on first encounter.[2] Moreover, exceptions and misconceptions have fueled this controversy, although it can be concluded that RSW is a clinical entity that is more common than is perceived and must now be considered in those without cerebral disease.[1,2]

Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial

Sanne M Dorhout Mees, Ale Algra, W Peter Vandertop, Fop van Kooten, Hans A J M Kuijsten, Jelis Boiten, Robert J van Oostenbrugge, Rustam Al-Shahi Salman, Pablo M Lavados, Gabriel J E Rinkel, Walter M van den Bergh

Summary

Background Magnesium sulphate is a neuroprotective agent that might improve outcome after aneurysmal subarachnoid haemorrhage by reducing the occurrence or improving the outcome of delayed cerebral ischaemia. We did a trial to test whether magnesium therapy improves outcome after aneurysmal subarachnoid haemorrhage.

Methods We did this phase 3 randomised, placebo-controlled trial in eight centres in Europe and South America. We randomly assigned (with computer-generated random numbers, with permuted blocks of four, stratified by centre) patients aged 18 years or older with an aneurysmal pattern of subarachnoid haemorrhage on brain imaging who were admitted to hospital within 4 days of haemorrhage, to receive intravenous magnesium sulphate, 64 mmol/day, or placebo. We excluded patients with renal failure or bodyweight lower than 50 kg. Patients, treating physicians, and investigators assessing outcomes and analysing data were masked to the allocation. The primary outcome was poor outcome—defined as a score of 4–5 on the modified Rankin Scale—3 months after subarachnoid haemorrhage, or death. We analysed results by intention to treat. We also updated a previous meta-analysis of trials of magnesium treatment for aneurysmal subarachnoid haemorrhage. This study is registered with controlled-trials.com (ISRCTN 68742385) and the EU Clinical Trials Register (EudraCT 2006-003523-36).

Findings 1204 patients were enrolled, one of whom had his treatment allocation lost. 606 patients were assigned to the magnesium group (two lost to follow-up), 597 to the placebo (one lost to follow-up). 158 patients (26·2%) had poor outcome in the magnesium group compared with 151 (25·3%) in the placebo group (risk ratio [RR] 1·03, 95% CI 0·85–1·25). Our updated meta-analysis of seven randomised trials involving 2047 patients shows that magnesium is not superior to placebo for reduction of poor outcome after aneurysmal subarachnoid haemorrhage (RR 0·96, 95% CI 0·86–1·08).

Interpretation Intravenous magnesium sulphate does not improve clinical outcome after aneurysmal subarachnoid haemorrhage, therefore routine administration of magnesium cannot be recommended.

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Utrecht Stroke Center, Department of Neurology and Neurosurgery, Rudolf Magnus Institute of Neurosciences (S M Dorhout Mees MD, Prof A Algra MD, Prof G J E Rinkel MD), **Julius Center for Health Sciences and Primary Care** (Prof A Algra), **Department of Intensive Care Medicine** (W M van den Bergh MD), **University Medical Center Utrecht, Utrecht, The Netherlands; Neurosurgical Center Amsterdam, Academic Medical Center Amsterdam and VU University Medical Center, Amsterdam, The Netherlands** (Prof W P Vandertop MD); **Department of Neurology, Erasmus Medical Center Rotterdam, Rotterdam,**

SAH prognosis

- Sudden death prior to medical attention in about 20%
- Of the remainder, with early aneurysm obliteration,
  - 58% regained premorbid level of function
    - as high as 67% in some centers
  - 9% moderately disabled
  - 2% vegetative
  - 26% dead

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society

J. Claude Hemphill III, MD, MAS, FAHA, Chair; Steven M. Greenberg, MD, PhD, Vice-Chair; Craig S. Anderson, MD, PhD; Kyra Becker, MD, FAHA; Bernard R. Bendok, MD, MS, FAHA; Mary Cushman, MD, MSc, FAHA; Gordon L. Fung, MD, MPH, PhD, FAHA; Joshua N. Goldstein, MD, PhD, FAHA; R. Loch Macdonald, MD, PhD, FRCS; Pamela H. Mitchell, RN, PhD, FAHA; Phillip A. Scott, MD, FAHA; Magdy H. Selim, MD, PhD; Daniel Woo, MD, MS; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology

Purpose—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of spontaneous intracerebral hemorrhage.

Methods—A formal literature search of PubMed was performed through the end of August 2013. The writing committee met by teleconference to discuss narrative text and recommendations. Recommendations follow the American Heart Association/American Stroke Association methods of classifying the level of certainty of the treatment effect and the class of evidence. Prerelease review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Oversight Committee and Stroke Council Leadership Committee.

Results—Evidence-based guidelines are presented for the care of patients with acute intracerebral hemorrhage. Topics focused on diagnosis, management of coagulopathy and blood pressure, prevention and control of secondary brain injury and intracranial pressure, the role of surgery, outcome prediction, rehabilitation, secondary prevention, and future considerations. Results of new phase 3 trials were incorporated.

Conclusions—Intracerebral hemorrhage remains a serious condition for which early aggressive care is warranted. These guidelines provide a framework for goal-directed treatment of the patient with intracerebral hemorrhage.
(*Stroke*. 2015;46:000-000. DOI: 10.1161/STR.0000000000000069.)

Intracerebral hemorrhage

- Phase III trial of rFVIIa did **not** show benefit at three months
  - No further trials planned at present
  - Perhaps a role in anticoagulant overdose-related hemorrhage but no good data
    - Need > 120 mg/dL fibrinogen for rFVIIa to work
- Current suggestion of prothrombin complex concentrate for warfarin overdose
- No established treatment for dabigatran or Xa antagonist-related hemorrhages
- Catheter-based clot lysis trials show promise
  - MISTIE: parenchymal clot
  - CLEAR: intraventricular clot

Intracerebral hemorrhage

- Lower blood pressure ‘as tolerated’
  - Labetalol, nicardipine to lower MAP ~15%
  - ATACH-2, INTERACT did not find better outcome with ‘intensive’ BP lowering
- No good data on pulmonary embolism prophylaxis
  - We start unfractionated heparin SQ within 24 hours

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DOI 10.1007/s12028-015-0222-x

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REVIEW ARTICLE

Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine

Jennifer A. Frontera[1] · John J. Lewin III[2] · Alejandro A. Rabinstein[3] · Imo P. Aisiku[4] · Anne W. Alexandrov[5,6] · Aaron M. Cook[7] · Gregory J. del Zoppo[8] · Monisha A. Kumar[9] · Ellinor I. B. Peerschke[10] · Michael F. Stiefel[11] · Jeanne S Teitelbaum[12] · Katja E. Wartenberg[13] · Cindy L. Zerfoss[14]

Table 3 Composition of common prothrombin complex concentrates (IU per 100 IU of Factor IX)

Trade name	Factor II	Factor VII	Factor IX	Factor X	Protein C	Protein S	Protein Z	Antithrombin III	Heparin
3-factor products									
Bebulin[a]	100	<5	100	100	–	–	–	–	<0.15[b]
Preconativ	83.3	–	100	83.3	–	–	–	–	–
Proplex-T	50	400	100	50	–	–	–	–	<1.5
Prothrombinex-HT	100	Low	100	100	–	–	–	5	40
Profilnine SD[a]	150	35	100	100	–	–	–	–	–
4-factor products									
Beriplex (Kcentra[a])	106.9	55.1	100	141.4	120.7	86.2	124.1	2.1	1.7
Cofact	56–140	28–80	100	56–140	–	–	–	<0.6	–
Kaskadil	148	40	100	160	–	–	–	–	20
Octaplex	50–129	50–129	100	50–129	50–129	50–129	–	–	20–48

[a] Indicates FDA approval in US

[b] indicates IU per 1 unit factor IX

Activated Prothrombin Complex Concentrate Versus 4-Factor Prothrombin Complex Concentrate for Vitamin K-Antagonist Reversal*

A. Shaun Rowe, PharmD, FNCS[1]; Scott K. Dietrich, PharmD[2]; John W. Phillips, PharmD[3]; Kaci E. Foster, PharmD[1]; Joshua R. Canter, BS[1]

Objectives: To compare the international normalized ratio normalization efficacy of activated prothrombin complex concentrates and 4-factor prothrombin complex concentrates and to evaluate the thrombotic complications in patients treated with these products for warfarin-associated hemorrhage.

Design: Retrospective, Multicenter Cohort.

Setting: Large, Community, Teaching Hospital.

Patients: Patients greater than 18 years old and received either activated prothrombin complex concentrate or 4-factor prothrombin complex concentrate for the treatment of warfarin-associated hemorrhage. We excluded those patients who received either agent for an indication other than warfarin-associated hemorrhage, pregnant, had a baseline international normalized ratio of less than 2, received a massive transfusion as defined by hospital protocol, received plasma for treatment of warfarin-associated hemorrhage, or were treated for an acute warfarin ingestion.

Interventions: Patients in the activated prothrombin complex concentrate group (enrolled from one hospital) with an international normalized ratio of less than 5 received 500 IU and those with an international normalized ratio greater than 5 received 1,000 IU. Patients in the 4-factor prothrombin complex concentrate (enrolled from a separate hospital) group received the Food and Drug Administration approved dosing algorithm.

Measurements and Main Results: A total of 158 patients were included in the final analysis (activated prothrombin complex concentrate = 118; 4-factor prothrombin complex concentrate = 40). Those in the 4-factor prothrombin complex concentrate group had a higher pretreatment international normalized ratio (2.7±1.8 vs 3.5±2.9; $p = 0.0164$). However, the posttreatment international normalized ratio was similar between the groups. In addition, even when controlling for differences in the pretreatment international normalized ratio, there was no difference in the ability to achieve a posttreatment international normalized ratio of less than 1.4 (odds ratio, 0.753 [95% CI, 0.637–0.890]; $p = 0.0009$). Those in the activated prothrombin complex concentrate group did have higher odds of achieving a posttreatment international normalized ratio of less than 1.2 (odds ratio, 3.23 [95% CI, 1.34–7.81]; $p = 0.0088$). There was only one posttreatment thrombotic complication reported.

Conclusions: A low, fixed dose of activated prothrombin complex concentrate was as effective as standard dose 4-factor prothrombin complex concentrate for normalization of international normalized ratio. In addition, we did not see an increase in thrombotic events. (*Crit Care Med* 2018; 46:943–948)

DNR in ICH = self-fulfilling prophecy

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Do-not-resuscitate orders and predictive models after intracerebral hemorrhage

D.B. Zahuranec, MD, MS
L.B. Morgenstern, MD
B.N. Sánchez, PhD
K. Resnicow, PhD
D.B. White, MD, MAS
J.C. Hemphill III, MD, MAS

Address correspondence and reprint requests to Dr. Darin B. Zahuranec, University of Michigan Cardiovascular Center, 1500 East Medical Center Drive, SPC#5855, Ann Arbor, MI 48109-5855
zdarin@umich.edu

ABSTRACT

Objective: To quantify the accuracy of commonly used intracerebral hemorrhage (ICH) predictive models in ICH patients with and without early do-not-resuscitate orders (DNR).

Methods: Spontaneous ICH cases (n = 487) from the Brain Attack Surveillance in Corpus Christi study (2000–2003) and the University of California, San Francisco (June 2001–May 2004) were included. Three models (the ICH Score, the Cincinnati model, and the ICH grading scale [ICH-GS]) were compared to observed 30-day mortality with a χ^2 goodness-of-fit test first overall and then stratified by early DNR orders.

Results: Median age was 71 years, 49% were female, median Glasgow Coma Scale score was 12, median ICH volume was 13 cm^3, and 35% had early DNR orders. Overall observed 30-day mortality was 42.7% (95% confidence interval [CI] 38.3–47.1), with the average model-predicted 30-day mortality for the ICH Score, Cincinnati model, and ICH-GS at 39.9% ($p = 0.005$), 40.4% ($p = 0.007$), and 53.9% ($p < 0.001$). However, for patients with early DNR orders, the observed 30-day mortality was 83.5% (95% CI 78.0–89.1), with the models predicting mortality of 64.8% ($p < 0.001$), 57.2% ($p < 0.001$), and 77.8% ($p = 0.02$). For patients without early DNR orders, the observed 30-day mortality was 20.8% (95% CI 16.5–25.7), with the models predicting mortality of 26.6% ($p = 0.05$), 31.4% ($p < 0.001$), and 41.1% ($p < 0.001$).

Conclusions: ICH prognostic model performance is substantially impacted when stratifying by early DNR status, possibly giving a false sense of model accuracy when DNR status is not considered. Clinicians should be cautious when applying these predictive models to individual patients.

Neurology® 2010;75:1–1

Component	Criteria	Points
GCS	3-4	2
	5-12	1
	13-15	0
ICH Volume (cc)	>= 30 cc	1
	< 30 cc	0
Intraventricular Hemorrhage	Yes	1
	No	0
Infratentorial Origin	Yes	1
	No	0
Age	>= 80 y	1
	< 80 y	0
Total		0-6

ICH score and 30 day mortality

	original	Morgenstern 2014
1	17	10
2	30	18
3	75	22
4+	95	50

neurocritical care society Neurocrit Care (2016) 24:47–60
DOI 10.1007/s12028-015-0221-y

CrossMark

REVIEW ARTICLE

Prophylaxis of Venous Thrombosis in Neurocritical Care Patients: An Evidence-Based Guideline: A Statement for Healthcare Professionals from the Neurocritical Care Society

Paul Nyquist[1] · Cynthia Bautista[2] · Draga Jichici[3] · Joseph Burns[4] · Sanjeev Chhangani[5] · Michele DeFilippis[6] · Fernando D. Goldenberg[7] · Keri Kim[8] · Xi Liu-DeRyke[9] · William Mack[10] · Kim Meyer[11]

Neurogenic respiratory failure

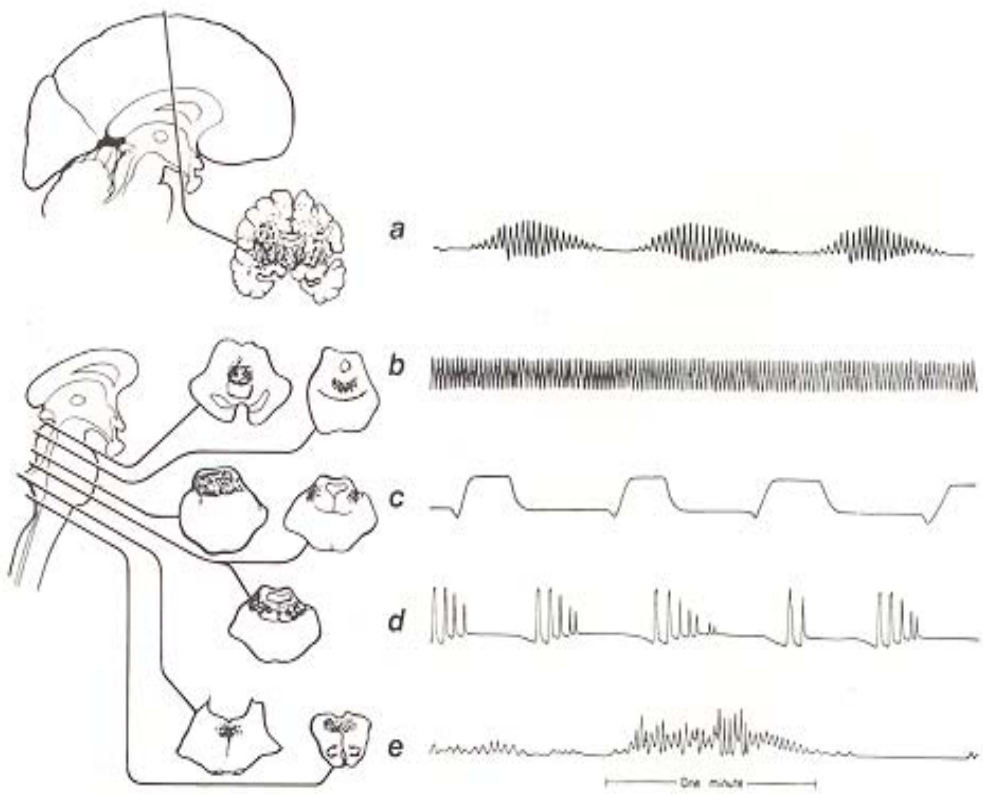
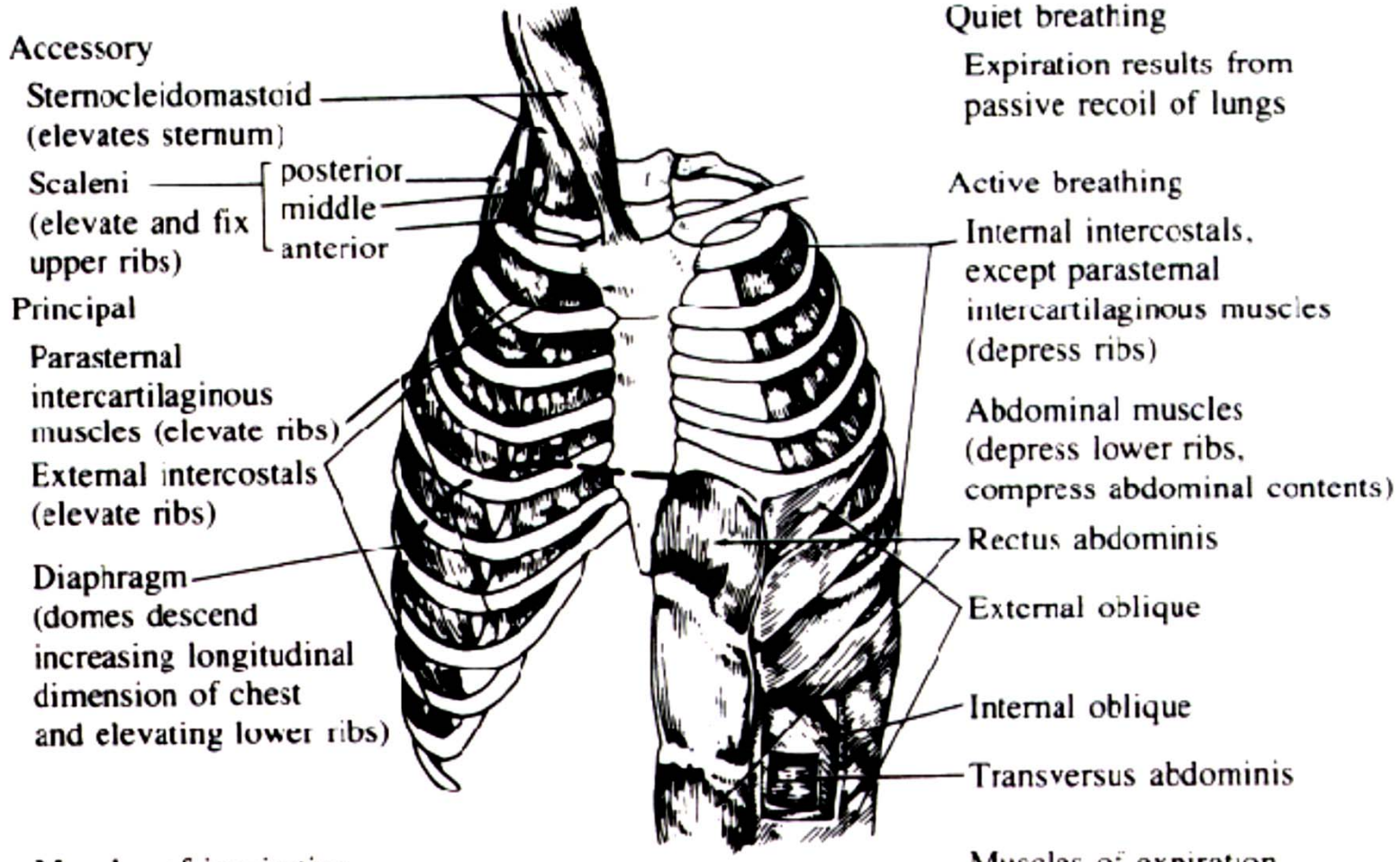


Figure 6. Abnormal respiratory patterns associated with pathologic lesions (shaded areas) at various levels of the brain. Tracings by chest-abdomen pneumograph, inspiration reads up. **a,** Cheyne-Strokes respiration. **b,** Central neurogenic hyperventilation. **c,** Apneusis. **d,** Cluster breathing. **e,** Ataxic breathing.

Neurogenic ventilatory disturbance syndromes: spinal cord disorders

- lesions above or at C4
- lesions between C4 – T8
- diffuse disorders
  - e.g., tetanus
- anterior horn cell disorders
  - e.g., ALS, West Nile myelitis


Accessory
Sternocleidomastoid (elevates sternum)
Scaleni (elevate and fix upper ribs)
posterior
middle
anterior
Principal
Parasternal intercartilaginous muscles (elevate ribs)
External intercostals (elevate ribs)
Diaphragm (domes descend increasing longitudinal dimension of chest and elevating lower ribs)
Muscles of inspiration
Quiet breathing
Expiration results from passive recoil of lungs
Active breathing
Internal intercostals, except parasternal intercartilaginous muscles (depress ribs)
Abdominal muscles (depress lower ribs, compress abdominal contents)
Rectus abdominis
External oblique
Internal oblique
Transversus abdominis
Muscles of expiration

Neurogenic ventilatory disturbance syndromes: peripheral nerve disorders

- Guillain-Barré syndrome
  - Newly recognized cause: SARS-Cov-2
- chronic inflammatory polyneuropathy
- diphtheritic neuropathy
- porphyric neuropathy
- tick paralysis
  - *Dermacentor* ticks
- ciguatera
- saxitoxin (and other nerve toxins)
- thallium intoxication
- acute hyperkalemic paralysis
- heavy metals
  - e.g., arsenic

General management of GBS

- Good ICU care is the most important part of management
  - Prevention of VAC and VTE
  - Nutrition
- Autonomic dysfunction is now the major cause of death
  - Sinus tachycardia is the most common manifestation
    - A few develop bradycardia requiring pacing
  - Alteration in blood pressure control is the most dangerous

Immunologic management of Guillain – Barré Syndrome

- Many, if not most, cases of GBS result from cross-reacting antibodies aimed at an infecting organism
- Effective immune therapies are aimed at decreasing anti-myelin or anti-axonal antibodies
- Steroids and other more global immune suppressants are not useful
  - Except that steroids may help with neuritic pain

Immunologic management of Guillain – Barré Syndrome

- Plasma exchange decreases the time on mechanical ventilation and the time to independently ambulation by 50%
- Must be started within 14 days of onset to be effective
  - The earlier, the better
  - Five exchanges totaling 200 – 250 mL/kg over about 10 days

Immunologic management of Guillain – Barré Syndrome

- Some will give a second course of PE if the first is ineffective

"A second marriage is the triumph of hope over experience."

-- **Samuel Johnson**

- French cooperative trial:
  - Treatment decreases likelihood of progression when started while patients still ambulatory
  - Four treatments better than two for bedbound patients
  - Six no better than four for ventilated patients

Ann Neurol 1997;41:298-306

Immunologic management of Guillain – Barré Syndrome

- Intravenous immunoglobulin
  - 2 gms/kg over 2 – 5 days
- Randomized trial (383 patients) of PE vs. IVIg: no difference in outcome (Lancet 1997;349: 225-230)
  - PE followed by IVIg showed a slight, insignificant advantage over either individually

Critical illness polyneuropathy

- Incidence: common in septic patients
- Clinical features: flaccid limbs and respiratory weakness
- Electrophysiology: axonal degeneration of motor and sensory fibers
- Creatine kinase: near normal
- Muscle biopsy: denervation atrophy, mild necrosis

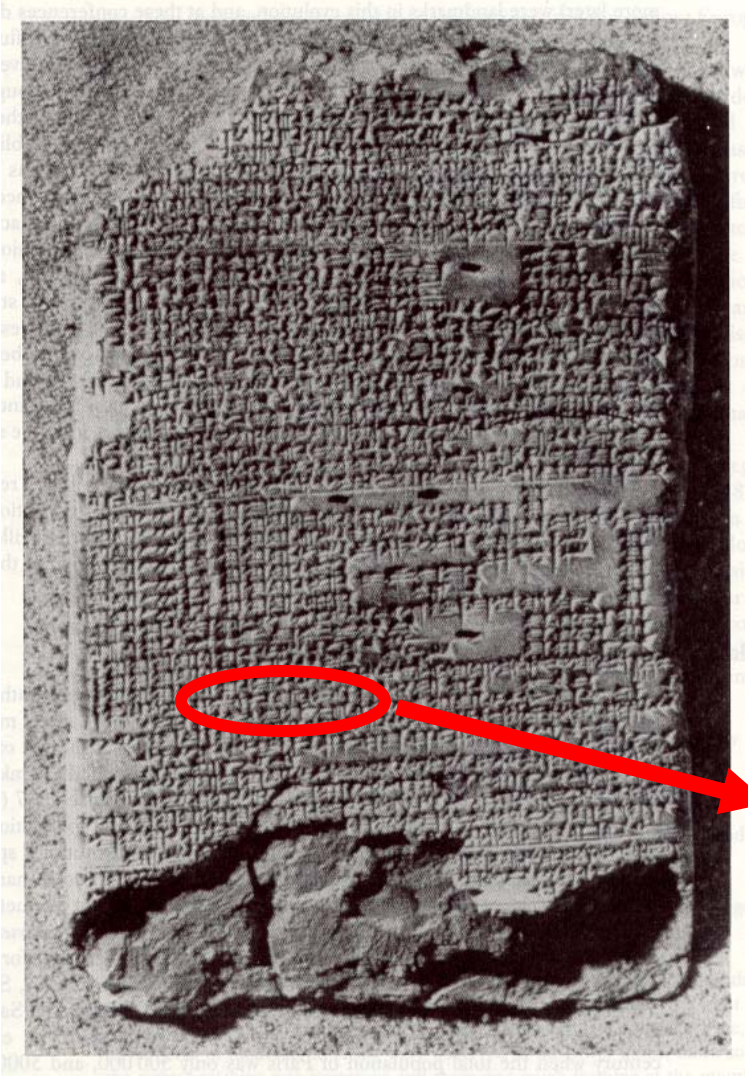
Neurogenic ventilatory disturbance syndromes: neuromuscular junction disorders

- prolonged effect of NMJ blockade
- myasthenia gravis
- botulism
- organophosphate intoxication
- hypermagnesemia
- tick paralysis
  - *Ixodes* ticks
- snake bites

Neurogenic ventilatory disturbance syndromes: muscle disorders

- rhabdomyolysis
- polymyositis/demato-myositis
- acid maltase deficiency
- carnitine palmityl-transferase deficiency
- nemaline rod myopathy
- acute hypokalemic paralysis
- acute hypophosphatemic paralysis
- stonefish myotoxin poisoning
- barium poisoning
- trichinosis

Status epilepticus

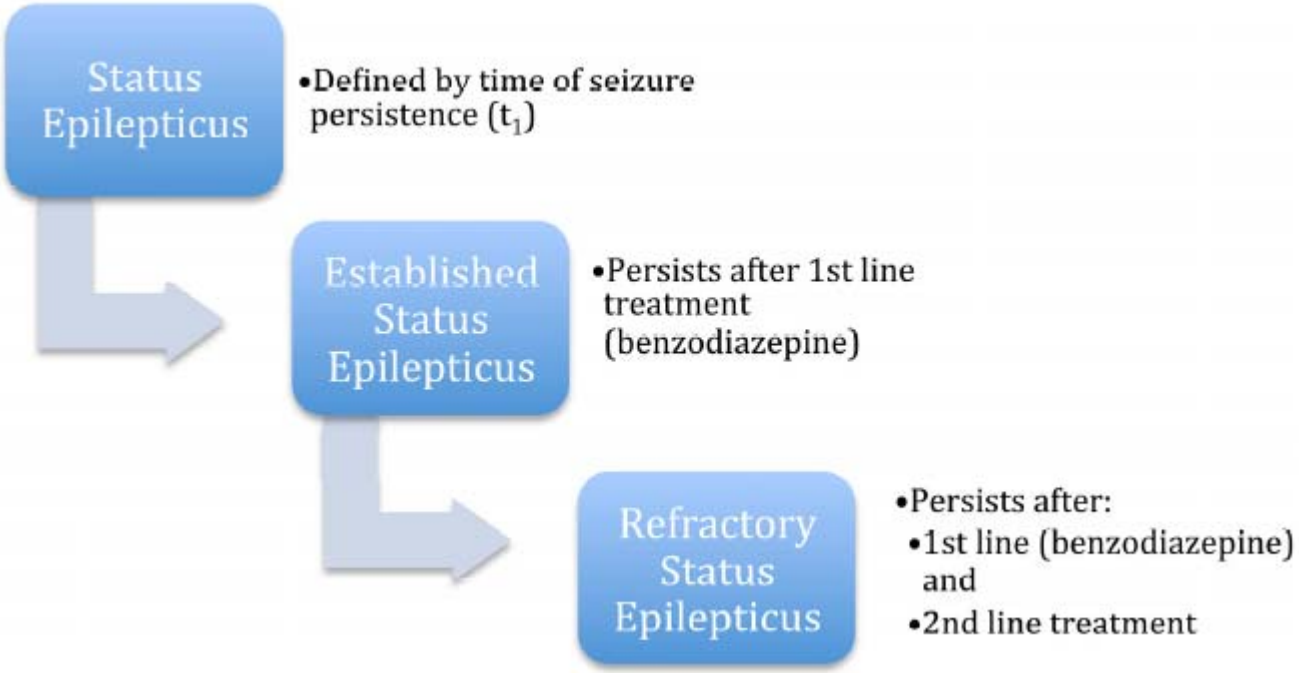


First known description of status epilepticus (Sakikku cuneiform, ca. 700 B.C)

give a benzo !

Bleck classification of status epilepticus

1. Status epilepticus
2. Not status epilepticus
3. Not sure
4. Post-anoxic myoclonus is not a form of status epilepticus



Journal of *Clinical Medicine*

MDPI

Review

Treatment of Established Status Epilepticus

Jessica J. Falco-Walter * and Thomas Bleck

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

ABSTRACT

BACKGROUND

Early termination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes. For faster and more reliable administration, paramedics increasingly use an intramuscular route.

METHODS

This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus treated by paramedics. Subjects whose convulsions had persisted for more than 5 minutes and who were still convulsing after paramedics arrived were given the study medication by either intramuscular autoinjector or intravenous infusion. The primary outcome was absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, recurrent seizures, and timing of treatment relative to the cessation of convulsive seizures. This trial tested the hypothesis that intramuscular midazolam was noninferior to intravenous lorazepam by a margin of 10 percentage points.

RESULTS

At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the intramuscular-midazolam group and in 282 of 445 (63.4%) in the intravenous-lorazepam group (absolute difference, 10 percentage points; 95% confidence interval, 4.0 to 16.1; P<0.001 for both noninferiority and superiority). The two treatment groups were similar with respect to need for endotracheal intubation (14.1% of subjects with intramuscular midazolam and 14.4% with intravenous lorazepam) and recurrence of seizures (11.4% and 10.6%, respectively). Among subjects whose seizures ceased before arrival in the emergency department, the median times to active treatment were 1.2 minutes in the intramuscular-midazolam group and 4.8 minutes in the intravenous-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 minutes and 1.6 minutes. Adverse-event rates were similar in the two groups.

CONCLUSIONS

For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation. (Funded by the National Institute of Neurological Disorders and Stroke and others; ClinicalTrials.gov number, NCT00809146.)

From the Department of Emergency Medicine, University of Michigan, Ann Arbor (R.S., W.B.); the Department of Medicine, Division of Biostatistics and Epidemiology, Medical University of South Carolina, Charleston (V.D., Y.P.); the Department of Neurology, University of California, San Francisco, San Francisco (D.L.); the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (R.C.); and the Department of Emergency Medicine, University of Cincinnati, Cincinnati (A.P.). Address reprint requests to Dr. Silbergleit at the Department of Emergency Medicine, Suite 3100, 24 Frank Lloyd Wright Dr., Ann Arbor, MI 48105, or at robert.silbergleit@umich.edu.

*The Neurological Emergencies Treatment Trials (NETT) investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1107494) was updated on February 16, 2012.

N Engl J Med 2012;366:591-600.

- 40 kg: MDZ 10 mg, LRZ 4 mg)
- 13-40 kg *apply the neurosurgical dose rule*

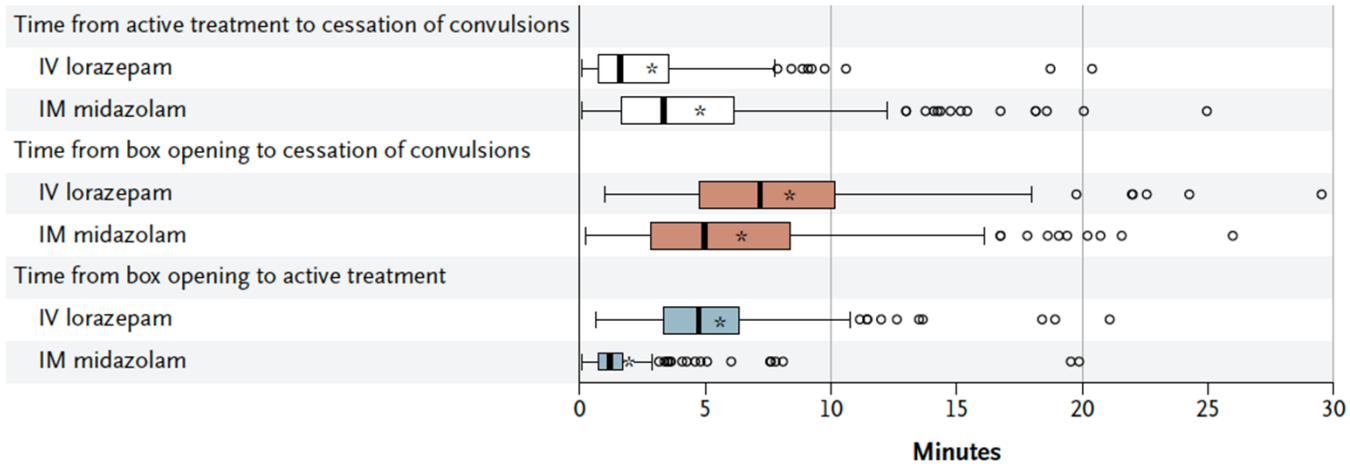
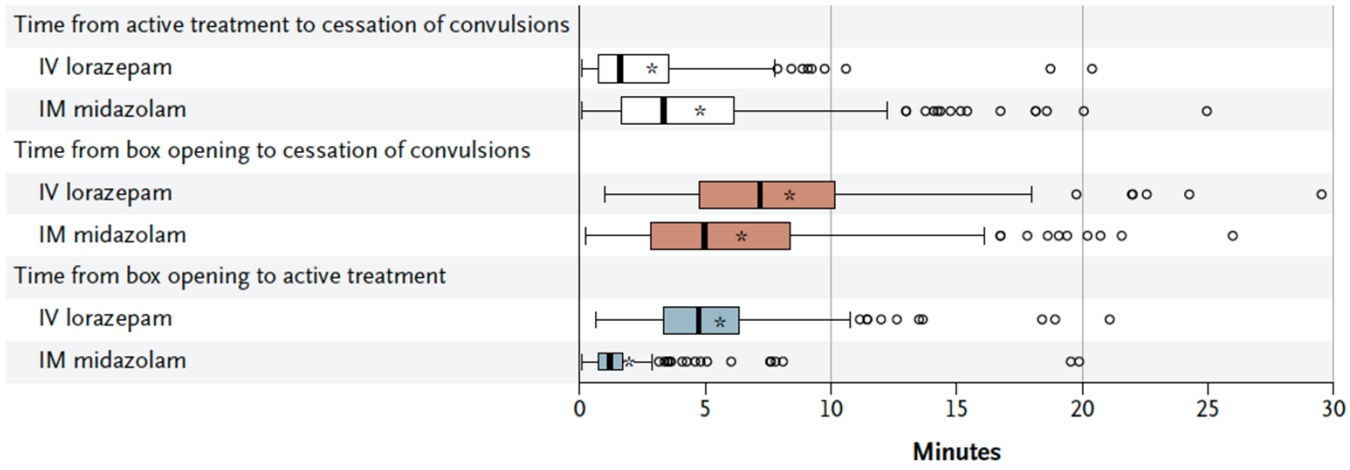


Figure 3. Intervals between Active Treatment and Cessation of Convulsions, Box Opening and Cessation of Convulsions, and Box Opening and Active Treatment.

The shorter time to IM drug administration was offset by the faster onset of action after IV drug administration, resulting in similar latency periods until convulsions were terminated. Time to IV administration includes the nominal time (about 20 seconds) needed to administer the drug by means of IM autoinjector. Asterisks indicate means, boxes interquartile ranges, bold vertical lines within boxes medians, I bars 1.5 times the interquartile range, and circles outliers.

- 40 kg: MDZ 10 mg, LRZ 4 mg)
- 13-40 kg: *just cut the dose in half*



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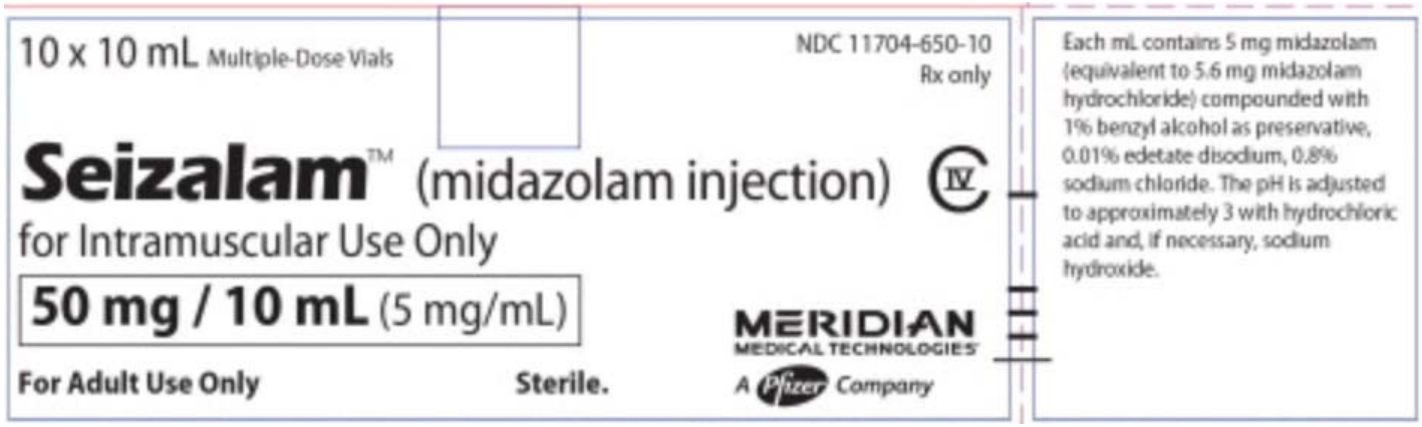

1 INDICATIONS AND USAGE

Seizalam is indicated for the treatment of status epilepticus in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of Seizalam is 10 mg, administered by intramuscular injection.

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Three Anticonvulsant Medications for Status Epilepticus

MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

No significant difference in rates of seizure cessation or in safety

J. Kapur et al. 10.1056/NEJMoa1905795

Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial

James M Chamberlain, Jaideep Kapur, Shlomo Shinnar, Jordan Elm, Maija Holsti, Lynn Babcock, Alex Rogers, William Barsan, James Cloyd, Daniel Lowenstein, Thomas P Bleck, Robin Conwit, Caitlyn Meinzer, Hannah Cock, Nathan B Fountain, Ellen Underwood, Jason T Connor, Robert Silbergleit, for the Neurological Emergencies Treatment Trials and the Pediatric Emergency Care Applied Research Network investigators†*

Summary

Background Benzodiazepine-refractory, or established, status epilepticus is thought to be of similar pathophysiology in children and adults, but differences in underlying aetiology and pharmacodynamics might differentially affect response to therapy. In the Established Status Epilepticus Treatment Trial (ESETT) we compared the efficacy and safety of levetiracetam, fosphenytoin, and valproate in established status epilepticus, and here we describe our results after extending enrolment in children to compare outcomes in three age groups.

Methods In this multicentre, double-blind, response-adaptive, randomised controlled trial, we recruited patients from 58 hospital emergency departments across the USA. Patients were eligible for inclusion if they were aged 2 years or older, had been treated for a generalised convulsive seizure of longer than 5 min duration with adequate doses of benzodiazepines, and continued to have persistent or recurrent convulsions in the emergency department for at least 5 min and no more than 30 min after the last dose of benzodiazepine. Patients were randomly assigned in a response-adaptive manner, using Bayesian methods and stratified by age group (<18 years, 18–65 years, and >65 years), to levetiracetam, fosphenytoin, or valproate. All patients, investigators, study staff, and pharmacists were masked to treatment allocation. The primary outcome was absence of clinically apparent seizures with improved consciousness and without additional antiseizure medication at 1 h from start of drug infusion. The primary safety outcome was life-threatening hypotension or cardiac arrhythmia. The efficacy and safety outcomes were analysed by intention to treat. This study is registered in ClinicalTrials.gov, NCT01960075.

Findings Between Nov 3, 2015, and Dec 29, 2018, we enrolled 478 patients and 462 unique patients were included: 225 children (aged <18 years), 186 adults (18–65 years), and 51 older adults (>65 years). 175 (38%) patients were randomly assigned to levetiracetam, 142 (31%) to fosphenyltoin, and 145 (31%) were to valproate. Baseline characteristics were balanced across treatments within age groups. The primary efficacy outcome was met in those treated with levetiracetam for 52% (95% credible interval 41–62) of children, 44% (33–55) of adults, and 37% (19–59) of older adults; with fosphenytoin in 49% (38–61) of children, 46% (34–59) of adults, and 35% (17–59) of older adults; and with valproate in 52% (41–63) of children, 46% (34–58) of adults, and 47% (25–70) of older adults. No differences were detected in efficacy or primary safety outcome by drug within each age group. With the exception of endotracheal intubation in children, secondary safety outcomes did not significantly differ by drug within each age group.

Interpretation Children, adults, and older adults with established status epilepticus respond similarly to levetiracetam, fosphenytoin, and valproate, with treatment success in approximately half of patients. Any of the three drugs can be considered as a potential first-choice, second-line drug for benzodiazepine-refractory status epilepticus.

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See Online/Comment
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*Listed in the appendix (pp 2–8)

†Listed in the appendix (pp 2–8)

Division of Emergency Medicine Children's National Hospital, Washington, DC, USA (Prof J M Chamberlain MD); **Department of Neurology, University of Virginia Health Sciences Center, Charlottesville, VA, USA** (Prof J Kapur MBBS, Prof N B Fountain MD); **Neurology, Pediatrics and Epidemiology and Population Health Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA** (Prof S Shinnar MD); **Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA** (J Elm PhD, C Meinzer PhD, E Underwood MS); **Division of Pediatric Emergency Medicine, University of Utah, Salt Lake City, UT, USA** (M Holsti MD); **Division of Pediatric Emergency Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, USA** (Prof L Babcock MD);

	Children (aged <18 years; n=225)	Adults (aged 18–65 years; n=186)	Older adults (aged >65 years; n=51)
Levetiracetam	85	71	19
Primary outcome	44 (52%; 41–62)	31 (44%; 33–55)	7 (37%; 19–59)
Probability treatment is the most effective	0·37	0·22	0·22
Probability treatment is the least effective	0·27	0·44	0·40
Fosphenytoin	71	54	17
Primary outcome	35 (49%; 38–61)	25 (46%; 34–59)	6 (35%; 17–59)
Probability treatment is the most effective	0·22	0·41	0·19
Probability treatment is the least effective	0·47	0·27	0·46
Valproate	69	61	15
Primary outcome	36 (52%; 41–63)	28 (46%; 34–58)	7 (47%; 25–70)
Probability treatment is the most effective	0·41	0·37	0·59
Probability treatment is the least effective	0·26	0·29	0·14

Data are n, n (%; 95% credible interval), or probability.

***Table 2*: Efficacy analysis by age group**

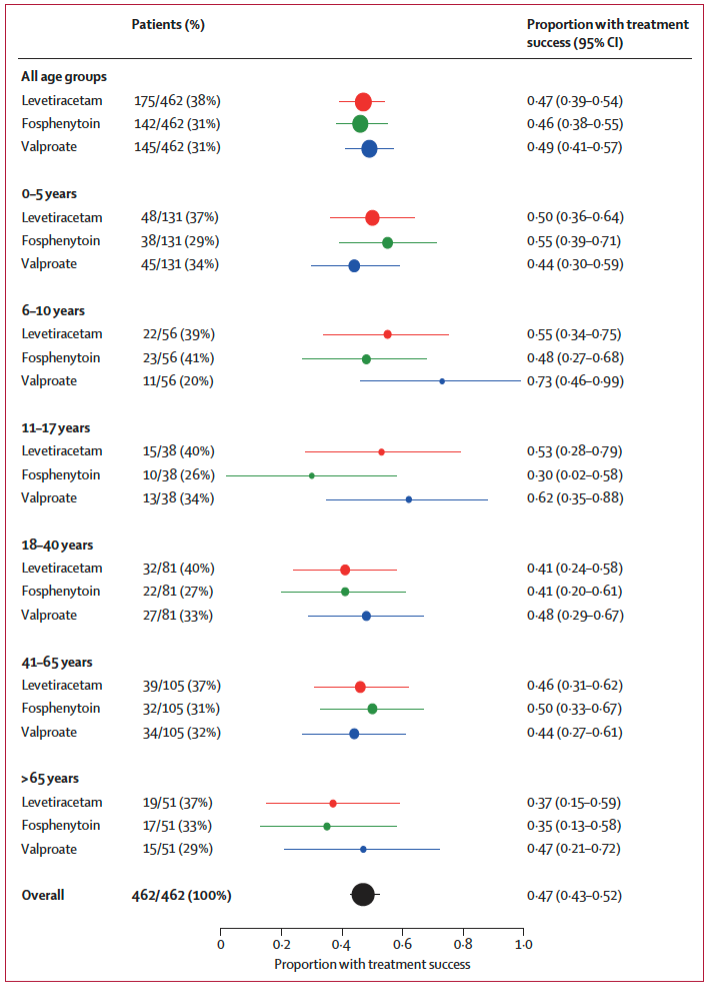


***Figure 3*: Forest plot of proportion of treatment success for the primary outcome by age ranges, post hoc**
The size of the circle in each row is representative of the number of patients in that group and the error bars show 95% CIs. These narrower age groupings were determined post hoc.

Continuous electroencephalography in the medical intensive care unit*

Mauro Oddo, MD; Emmanuel Carrera, MD; Jan Claassen, MD; Stephan A. Mayer, MD; Lawrence J. Hirsch, MD

Objectives: To examine predictors and the prognostic value of electrographic seizures (ESZs) and periodic epileptiform discharges (PEDs) in medical intensive care unit (MICU) patients without a primary acute neurologic condition.

Design: Retrospective study.

Setting: MICU in a university hospital.

Patients: A total of 201 consecutive patients admitted to the MICU between July 2004 and January 2007 without known acute neurologic injury and who underwent continuous electroencephalography monitoring (cEEG) for investigation of possible seizures or changes in mental status.

Intervention: None.

Measurements and Main Results: Median time from intensive care unit (ICU) admission to cEEG was 1 day (interquartile range 1–4). The majority of patients (60%) had sepsis as the primary admission diagnosis and 48% were comatose at the time of cEEG. Ten percent (n = 21) of patients had ESZs, 17% (n = 34) had PEDs, 5% (n = 10) had both, and 22% (n = 45) had either ESZs or PEDs. Seizures during cEEG were purely electrographic (no detectable clinical correlate) in the majority (67%) of patients. Patients with sepsis had a higher rate of ESZs or PEDs than those without sepsis (32% vs. 9%, $p < 0.001$). On multivariable analysis, sepsis at ICU admission was the only significant predictor of ESZs or PEDs (odds ratio 4.6, 95% confidence interval 1.9–12.7, $p = 0.002$). After controlling for age, coma, and organ dysfunction, the presence of ESZs or PEDs was associated with death or severe disability at hospital discharge (89% with ESZs or PEDs, vs. 39% if not; odds ratio 19.1, 95% confidence interval 6.3–74.6, $p < 0.001$).

Conclusion: In this retrospective study of MICU patients monitored with cEEG, ESZs and PEDs were frequent, predominantly in patients with sepsis. Seizures were mainly nonconvulsive. Both seizures and periodic discharges were associated with poor outcome. Prospective studies are warranted to determine more precisely the frequency and clinical impact of nonconvulsive seizures and periodic discharges, particularly in septic patients. (Crit Care Med 2009; 37:2051–2056)

KEY WORDS: acute brain dysfunction; ICU delirium; septic encephalopathy; sepsis-associated encephaloapathy; electrographic seizures; nonconvulsive seizures; medical ICU; outcome

Conclusion: In this retrospective study of MICU patients monitored with cEEG, ESZs and PEDs were frequent, predominantly in patients with sepsis. Seizures were mainly nonconvulsive. Both seizures and periodic discharges were associated with poor outcome. Prospective studies are warranted to determine more precisely the frequency and clinical impact of nonconvulsive seizures and periodic discharges, particularly in septic patients. (Crit Care Med 2009; 37:2051–2056)

New-onset refractory status epilepticus

Etiology, clinical features, and outcome

Nicolas Gaspard, MD, PhD
Brandon P. Foreman, MD
Vincent Alvarez, MD
Christian Cabrera Kang, MD
John C. Probasco, MD
Amy C. Jongeling
Emma Meyers, BSc
Alyssa Espinera, BSc
Kevin F. Haas, MD
Sarah E. Schmitt, MD
Elizabeth E. Gerard, MD
Teneille Gofton, MD
Peter W. Kaplan, MD
Jong W. Lee, MD
Benjamin Legros, MD
Jerzy P. Szaflarski, MD, PhD
Brandon M. Westover, MD, PhD

ABSTRACT

Objectives: The aims of this study were to determine the etiology, clinical features, and predictors of outcome of new-onset refractory status epilepticus.

Methods: Retrospective review of patients with refractory status epilepticus without etiology identified within 48 hours of admission between January 1, 2008, and December 31, 2013, in 13 academic medical centers. The primary outcome measure was poor functional outcome at discharge (defined as a score >3 on the modified Rankin Scale).

Results: Of 130 cases, 67 (52%) remained cryptogenic. The most common identified etiologies were autoimmune (19%) and paraneoplastic (18%) encephalitis. Full data were available in 125 cases (62 cryptogenic). Poor outcome occurred in 77 of 125 cases (62%), and 28 (22%) died. Predictors of poor outcome included duration of status epilepticus, use of anesthetics, and medical complications. Among the 63 patients with available follow-up data (median 9 months), functional status improved in 36 (57%); 79% had good or fair outcome at last follow-up, but epilepsy developed in 37% with most survivors (92%) remaining on antiseizure medications. Immune therapies were used less frequently in cryptogenic cases, despite a comparable prevalence of inflammatory CSF changes.

Conclusions: Autoimmune encephalitis is the most commonly identified cause of new-onset refractory status epilepticus, but half remain cryptogenic. Outcome at discharge is poor but improves during follow-up. Epilepsy develops in most cases. The role of anesthetics and immune therapies warrants further investigation. ***Neurology*® 2015;85:1604–1613**

High-dose benzodiazepines

- Midazolam
  - loading dose: 0.2 mg/kg
  - maintenance: 0.1-2.0 mg/kg/hr (2.0-40 μg/kg/min)
  - goal: seizure suppression
- Lorazepam
  - up to 9 mg/hr
  - goal: seizure suppression

Ketamine

- for refractory SE
  - dose uncertain
  - general (dissociative) anesthetic dose 1 **- 5** mg/kg, with infusion of 1 – 5 mg/kg/hr (20 **-** 80 µg/kg/min)
  - administer with a benzodiazepine in an attempt to decrease later psychiatric side effects

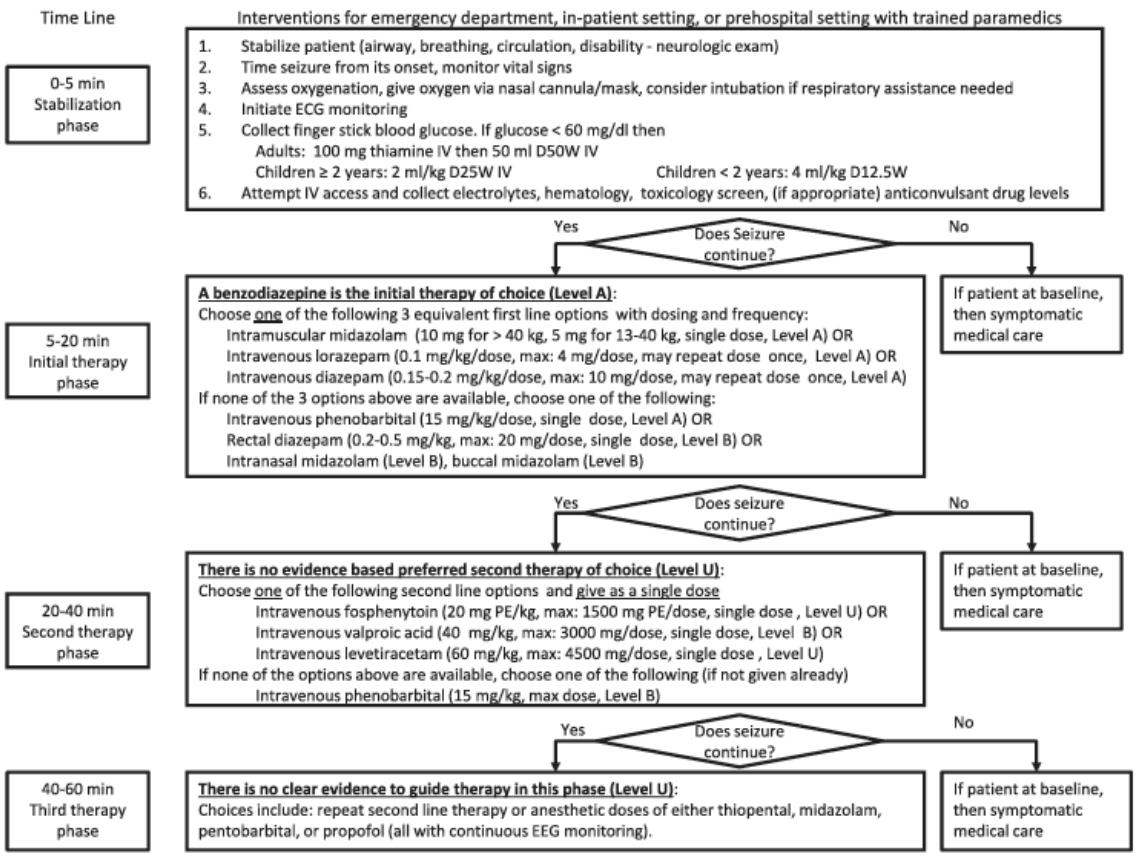


FIGURE 1. Proposed treatment algorithm for status epilepticus.

Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytical framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

Pathophysiology of head injury

- Primary injury
  - Result of immediate mechanical disruption of brain tissue
  - Can be prevented or reduced (e.g., air bags) but not ameliorated
- Secondary injury
  - Onset from minutes to months following injury
  - Most research focuses on the prevention or reduction of secondary injury

Secondary injury in head trauma

- hypoxia and hypotension are the two major causes of secondary CNS injury following head trauma
- even in the best intensive care units, these complications occur frequently
- preventing hypoxia and hypotension could have the greatest effect of any currently available treatment for head trauma
- herniation with tissue compression and vascular compromise
- avoid hyperthermia

Outcome after traumatic brain injury improved by an organized secondary insult program and standardized neurointensive care*

Kristin Elf, MD; Pelle Nilsson, MD, PhD; Per Enblad, MD, PhD

Objective: To evaluate today's refined neurosurgical intensive care of patients with traumatic brain injury after implementation of an organized secondary insult program focused on the importance of avoiding secondary brain damage together with a standardized treatment protocol system.

Design: Clinical observational patient study.

Patients: A total of 154 patients 16–79 yrs of age with acute head trauma and pathologic computed tomographic findings treated between 1996 and 1997.

Setting: Neurointensive care unit.

Interventions: None.

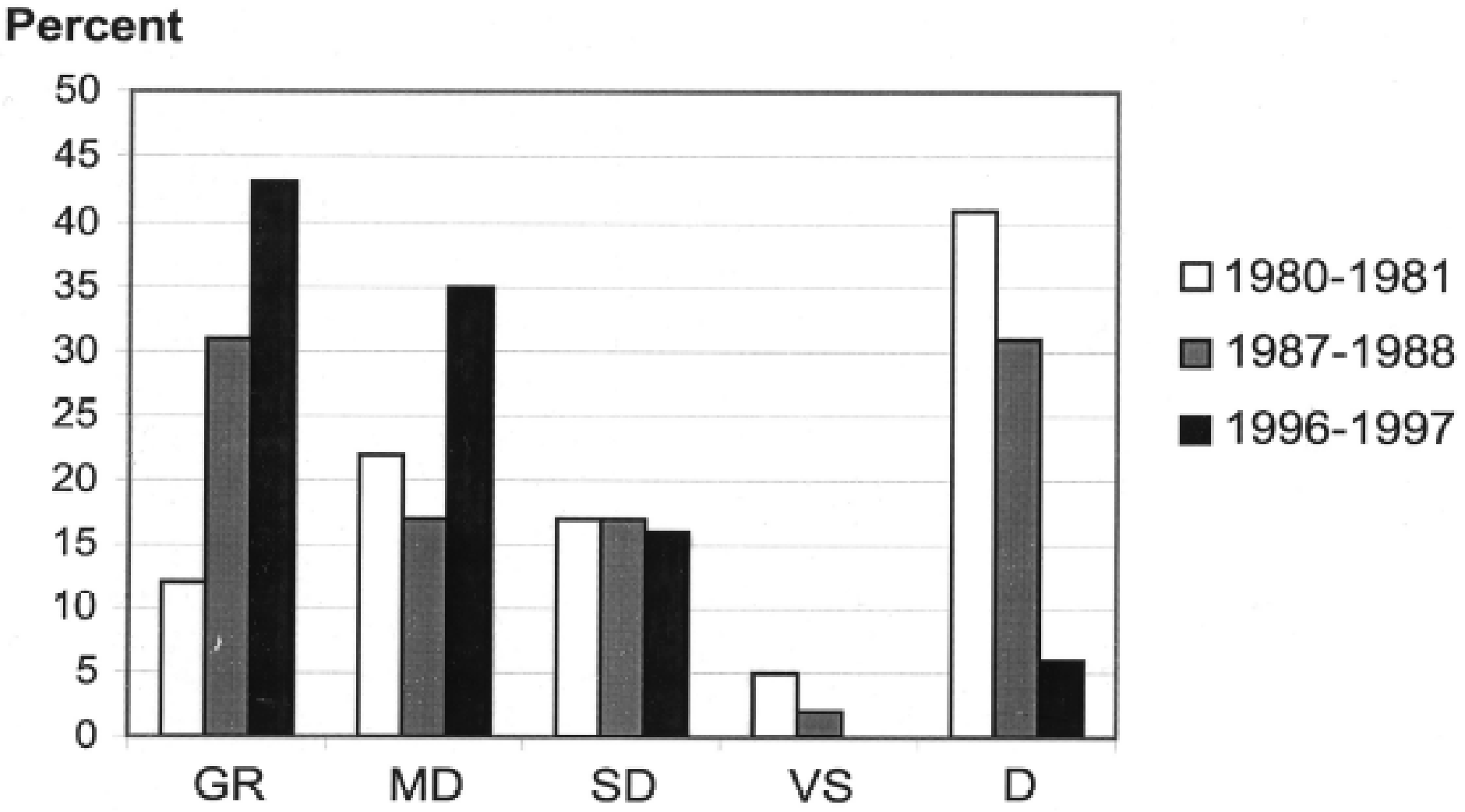
Measurements and Main Results: Good recovery was obtained in 44% of the patients, moderate disability in 35%, severe disability in 16%, and no patient remained in a vegetative state. Six percent of the patients died, but only two of these patients (1.3%) died as direct result of their head injury. When the results for patients with Glasgow Coma Scale motor scores of ≥4 were compared with the periods 1980–1981 (preneurosurgical intensive care) and 1987–1988 (basic neurosurgical intensive care), mortality had decreased from 40% in the first period to 27% in the second period and to 2.8% in the present series. Favorable outcome in the same group of patients had increased steadily from 40% in the first period, to 68% in the second period, and finally, to 84% in the present series.

Conclusions: The main observation in this hospital series of traumatic brain injury patients was a low rate of death directly caused by head injury and a high rate of favorable outcome. The comparison of patients with Glasgow Coma Scale motor scores of ≥4 with the previously reported results from the same unit indicate that substantial improvement in outcome has been achieved. (Crit Care Med 2002; 30:2129–2134)

KEY WORDS: traumatic brain injury; neurointensive care; secondary insults; standardized treatment protocol; outcome

Table 1. Neurosurgical intensive care treatment goals

Variable	Goal
ICP	≤20 mm Hg
CPP	60 mm Hg
Systolic blood pressure	≥100 mm Hg
CVP	0–5 mm Hg
Pco_2	4.0–4.5 kPa
Po_2	≥12 kPa
Sao_2	≥96%
B-glucose	5–10 mmol/L
Temperature	≤38°C


Percent
50
45
40
35
30
25
20
15
10
5
0
GR
MD
SD
VS
D
1980-1981
1987-1988
1996-1997

CRITICAL CARE MEDICINE

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Neurologic Critical Care

Neurologic complications of critical medical illnesses

THOMAS P. BLECK, MD, FCCM; MICHAEL C. SMITH, MD; SERGE J.-C. PIERRE-LOUIS, MD; JOSEPH J. JARES, MD; JOAN MURRAY, MD; CAROLYN A. HANSEN, MA, MSTAT

Objectives: **To identify the neurologic complications of critical medical illnesses, and to assess their effect on mortality rates and on medical ICU and hospital lengths of stay.**

Design: **Prospective clinical evaluation of all medical ICU admissions for 2 yrs.**

Setting: **A 14-bed, general medical intensive and coronary care unit in a large university hospital.**

Patients: **Patients (n = 1,850) admitted to the hospital, of whom 92 were admitted for primarily neurologic problems. Of the remaining 1,758 patients, 217 (12.3%) experienced a neurologic complication.**

Interventions: **None.**

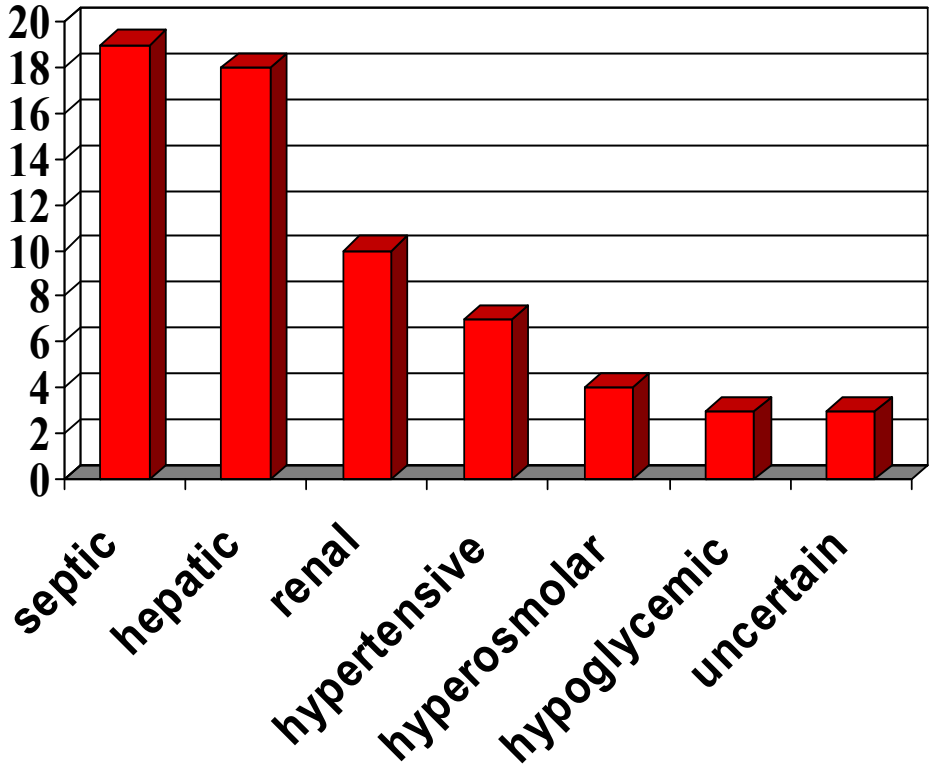
Measurements and Main Results: **Patients developing a neurologic complication while in the medical ICU demonstrated an increased risk of inhospital mortality when compared with patients who did not suffer such problems (45.7% vs. 26.6%; $p < .00001$). Patients with neurologic complications experienced 2.5-fold longer medical ICU stay times ($p < .001$) and almost two-fold longer hospital stay times ($p < .001$). Metabolic encephalopathy, seizures, hypoxic-ischemic encephalopathy, and stroke were the most common complications. Sepsis was the most frequent cause of encephalopathy, and cerebrovascular lesions were the most common cause of seizures. Formal neurologic consultations were requested in only 36% of these patients.**

Conclusions: **Neurologic complications are associated with increased mortality rates and longer medical ICU and hospital lengths of stay. These conditions are probably underrecognized at present. ICUs have the potential to serve as environments for neurologic teaching and research. (Crit Care Med 1993; 21:98–103)**

KEY WORDS: **critical care; intensive care; metabolic encephalopathy; neurologic complication; sepsis; seizure; stroke; neurology; brain injury; neuropathy; neurologic emergencies**

In the practice of critical care medicine, patients with secondary neurologic disorders constitute an underrecognized but highly important group. Because these complications occur in the course of critical illnesses and their therapies (such as neuromuscular junction blockade), which may mask common signs of neural dysfunction, recognition of these disorders is often delayed. Isensee and colleagues (1) evaluated 100 consecutive patients in a medical ICU within 72 hrs of their admission, to detect neurologic problems. Their study population included all medically ill patients in need of intensive care, exempting those patients with primarily cardiac problems. Eighteen of their patients were admitted primarily for acute neurologic disease,

Causes of encephalopathy in the MICU



Total patients = 1850

Bleck TP *et al* **Crit Care Med** 1993:21:98-103

The Neuropathology of Septic Shock

Tarek Sharshar[1,3]; Djillali Annane[1]; Geoffroy Lorin de la Grandmaison[2]; Jean Philippe Brouland[2]; Nicholas S Hopkinson[3]; Françoise Gray[2]

[1]Service de Réanimation Médicale, Hôpital Raymond Poincaré, Faculté de Médecine Paris-Ile de France Ouest, Garches, France.
[2]Service d'Anatomo-Pathologie et de Médecine Légale, Hôpital Raymond Poincaré, Faculté de Médecine Paris-Ile de France Ouest, Garches, France.
[3]National Heart and Lung Institute, Royal Brompton Hospital, United Kingdom.

Corresponding author:
Françoise Gray, MD, PhD.
AP-HP Service d'Anatomo-Pathologie et de Médecine Légale Hôpital Raymond Poincaré, 104 boulevard Raymond Poincaré, F-92380 Garches, France.
(E-mail: francoise.gray@rpc.ap-hop-paris.fr)

The neuropathological correlates of encephalopathy and autonomic dysfunction in septic shock are unclear. We performed post mortem analysis of 5 brain areas susceptible to ischemia and 5 autonomic nuclei (AN) in 23 patients who had died in our intensive care unit (ICU) from septic shock and 8 dying from non-septic shock as well as 5 controls who had died suddenly from extracranial injury. Proinflammatory cytokine (IL1-β and TNF-α) and inducible nitric oxide synthase (iNOS) expression was assessed by immunocytochemistry. Abnormalities in septic shock were: hemorrhages (26%), hypercoagulability syndrome (9%), micro-abscesses (9%), multifocal necrotizing leukoencephalopathy (9%) and ischemia (100%). The incidence of cerebral hemorrhage or hypercoagulability syndrome was not related to clotting disturbances. The intensity of ischemia within susceptible areas was the same in both ICU groups, but more pronounced in the autonomic centers of septic patients (P<0.0001). Neuronal apoptosis assessed using anti-caspase 3 immunocytochemistry and in situ end labeling was more pronounced in the autonomic nuclei of septic patients. (P<0.0001). TNF-alpha expression did not differ between groups but vascular iNOS expression assessed by immunocytochemistry was higher in sepsis (P<0.0001) and correlated with autonomic center neuronal apoptosis (P<0.02). We conclude that septic shock is associated with diffuse cerebral damage and specific autonomic neuronal apoptosis which may be due to circulating factors particularly iNOS.

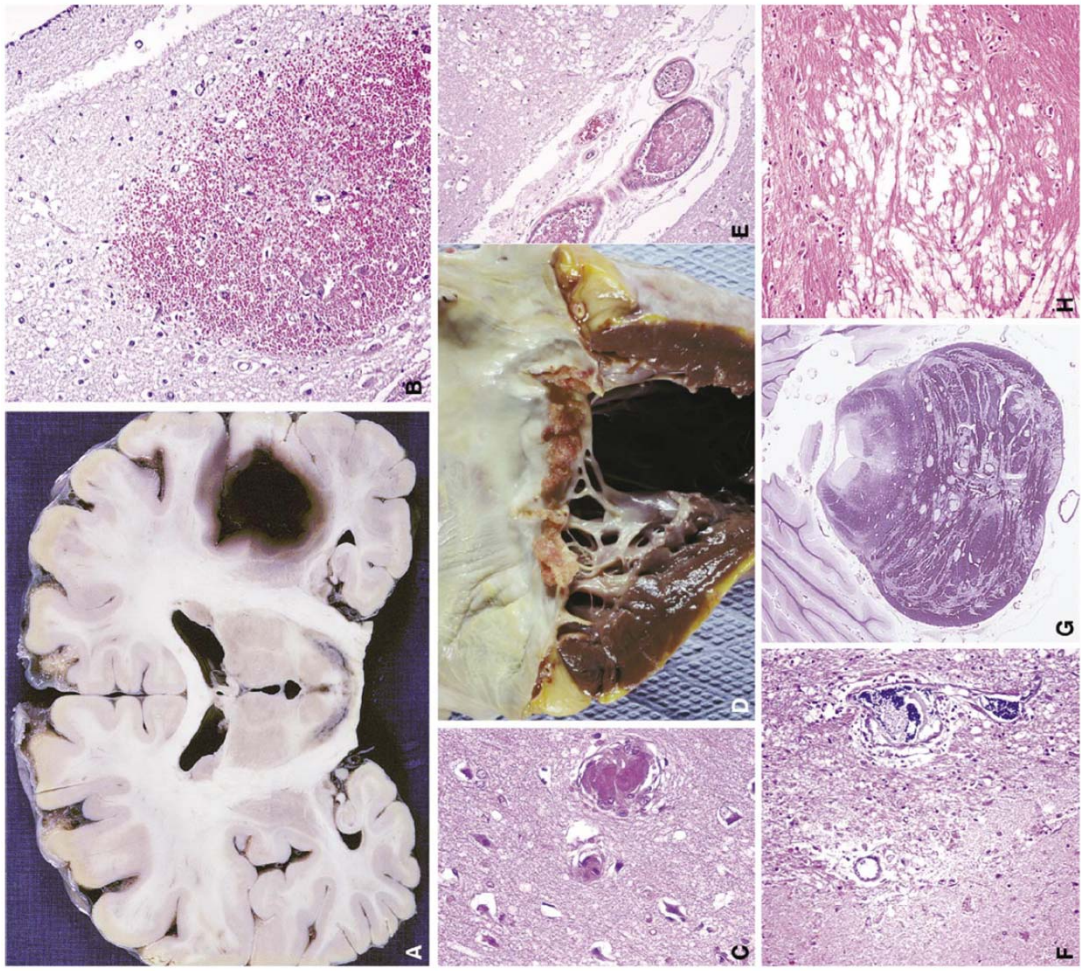
Brain Pathol 2004;14:21-33.

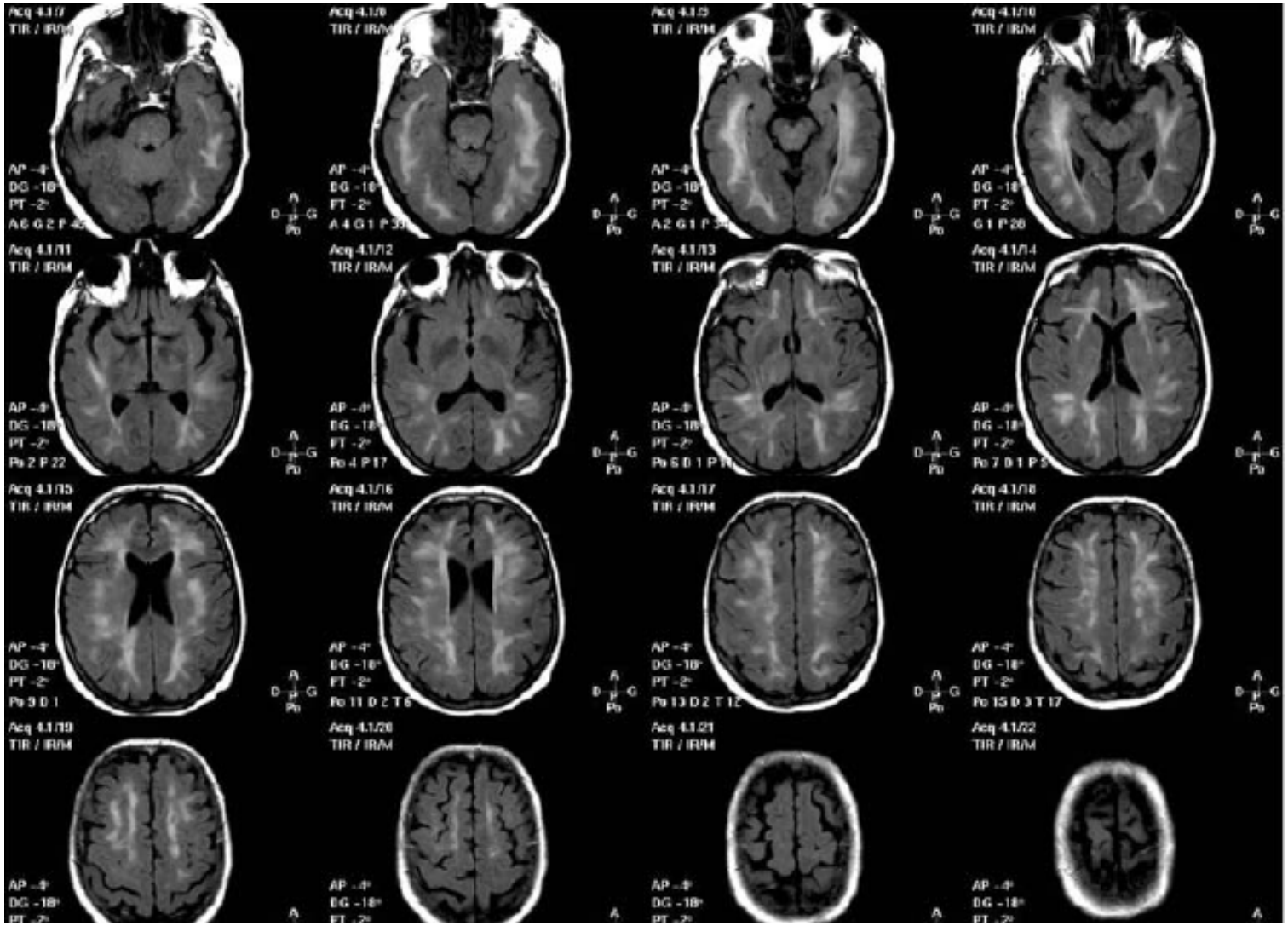
volved in the control of the cardiovascular system are damaged during septic shock.

PATIENTS AND METHODS

Study population. Patients. Twenty-three consecutive patients (group S) who died in the Intensive Care Unit (ICU) at University Hospital Raymond Poincaré (Garches, France), between January 1997 and December 1999, were enrolled when they met the following criteria for septic shock : *i)* systemic inflammatory response of less than 7 days duration, as defined by 2 or more of the following data: temperature above 38.3°C (>101.3°F) or below 35.6°C (<95°F), heart rate above 90 beats per minute, respiratory rate of more than 20 per minute or $PaCO_2$ of less than 32 mm

Figure 1. *Neuropathological changes in patients who died from septic shock.* **A.** Large leptomeningeal hemorrhage adjacent to the right scissure of Sylvius. **B.** Recent petechial hemorrhage in the right nucleus paraventricularis (H&E, ×100). **C.** Fibrinous microthrombi in a case with disseminted intravascular coagulation (H&E, ×200). **D.** Non bacterial thrombotic endocarditis, gross appearance of the heart. **E.** Same case as Figure 1D, distal fibrino-cruoric emboli in small leptomeningeal arteries; note recent ischemia in the underlying cortex (H&E, ×40). **F.** Septic emboli within a necrotic area (H&E, ×40). **G.** Multifocal necrotizing leukoencephalopathy; horizontal section of the upper pons (Luxol fast blue/cresyl violet). **H.** Multifocal necrotizing leukoencephalopathy, recent necrotic changes in the transverse pontine fibers (H&E, ×60).





ORIGINAL ARTICLE

Bacterial Dissemination to the Brain in Sepsis

Benjamin H. Singer[1,2], Robert P. Dickson[1,2], Scott J. Denstaedt[1], Michael W. Newstead[1], Kwi Kim[3], Nicole R. Falkowski[1], John R. Erb-Downward[1], Thomas M. Schmidt[3], Gary B. Huffnagle[1,3], and Theodore J. Standiford[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, and [3]Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, Michigan; and [2]Michigan Center for Integrative Research in Critical Care, Ann Arbor, Michigan

ORCID ID: 0000-0002-4721-6920 (B.H.S.).

Abstract

Rationale: Sepsis causes brain dysfunction and neuroinflammation. It is unknown whether neuroinflammation in sepsis is initiated by dissemination of bacteria to the brain and sustained by persistent infection, or whether neuroinflammation is a sterile process resulting solely from circulating inflammatory mediators.

Objectives: To determine if gut bacteria translocate to the brain during sepsis, and are associated with neuroinflammation.

Methods: Murine sepsis was induced using cecal ligation and puncture and sepsis survivor mice were compared with sham and unoperated control animals. Brain tissue of patients who died of sepsis was compared with patients who died of noninfectious causes. Bacterial taxa were characterized by 16S rRNA gene sequencing in both murine and human brain specimens; compared among sepsis and nonsepsis groups; and correlated with levels of S100A8, a marker of neuroinflammation using ~~PERMANOVA~~.

Measurements and Main Results: Viable gut-associated bacteria were enriched in the brains of mice 5 days after surviving abdominal sepsis ($P < 0.01$), and undetectable by 14 days. The community structure of brain-associated bacteria correlated with severity of neuroinflammation ($P < 0.001$). Furthermore, bacterial taxa detected in brains of humans who die of sepsis were distinct from those who died of noninfectious causes ($P < 0.001$), and correlated with S100A8/A9 expression ($P < 0.05$).

Conclusions: Although bacterial translocation is associated with acute neuroinflammation in murine sepsis, bacterial translocation did not result in chronic cerebral infection. Postmortem analysis of patients who die of sepsis suggests a role for bacteria in acute brain dysfunction in sepsis. Further work is needed to determine if modifying gut-associated bacterial communities modulates brain dysfunction after sepsis.

Keywords: inflammation; microbiome; S100A8; sepsis; cecal ligation and puncture

Sepsis-associated Encephalopathy Is Septic

… However, brain infection should be more systematically sought via brain imaging and cerebrospinal fluid analysis in the case of altered mental status in patients with sepsis.

In conclusion, the present study raises challenging issues about the mechanisms and consequences of bacterial dissemination into the brain during sepsis, emphasizes the necessity to rule out brain infection, and perhaps calls for reconsidering the duration of antibiotherapy in a patient with sepsis who is developing brain dysfunction. Finally, the article raises a semantic issue: should the term “sepsis-associated encephalopathy” be replaced by “sepsis-associated encephalitis”?

Mazaraud and Sharshar, AJRCCM 2018

What is limbic encephalitis?

- short-term memory disturbance
- confusion
- seizures
- personality changes
- hippocampal abnormalities on brain MRI
- ± hyponatremia

Table 1. Antibodies associated with encephalitides and seizures

Antibody	Syndrome	Clinical significance	Location of epitopes	Response to immunotherapy
Hu	Limbic, cortical encephalitis	High	Intracellular	Infrequent
CV2/CRMP5	Limbic encephalitis	High	Intracellular	Infrequent
Ma2	Limbic, diencephalon, upper brainstem encephalitis	High	Intracellular	Moderate
Amphiphysin	Limbic encephalitis, stiff-person syndrome	High	Intracellular	Poor
GAD	Limbic encephalitis, refractory epilepsy, stiff-person syndrome	Moderate	Intracellular	Moderate
VGKC (Kv1.1, Kv1.2)	Limbic encephalitis, Morvan's syndrome	High	Extracellular	Frequent
NMDAR (NR1)	Psychosis, dyskinesias, autonomic instability, hypoventilation	High	Extracellular	Frequent
NMDAR (NR2B or Gluϵ2)	Multiple types of encephalitides	Unclear[a]	Extra and intracellular	N/A
NMDAR (NR2A/2B)	Neuropsychiatric lupus	Low	Extracellular (DWEYS)[b]	N/A
AMPAR (GluR1/2)	Limbic encephalitis (frequent relapses)	N/A[c]	Extracellular	Frequent
AMPAR (GluR3)	Rasmussen's encephalitis	Low	Extracellular?	Infrequent/moderate
Thyroid peroxidase, thyroglobulin	Hashimoto's encephalitis	Low	Intracellular	Frequent

Italics indicate syndromes that are almost always paraneoplastic.

CRMP5, collapsin response mediator protein-5; GAD, glutamic acid decarboxylase; VGKC, voltage-gated potassium channels; NMDAR, *N*-methyl-D-aspartate receptor, AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

[a]Described in multiple unrelated disorders, including among others: limbic encephalitis, nonspecific encephalitis, viral encephalitis, and degenerative disorders.

[b]DWEYS pentapeptide consensus sequence present in NR2A and NR2B.

[c]N/A: not available, too early to assess significance.

Neuroprognostication postcardiac arrest: translating probabilities to individuals

Clifton W. Callaway

Purpose of review
Predicting neurological recovery in patients who are comatose after cardiac arrest is an important activity during postarrest care, and this prediction can affect survival. As no early test or clinical finding perfectly predicts potential for recovery, guidelines recommend using data from multiple examinations or tests to estimate patient prognosis.

Recent findings
Studies reported accuracy of initial clinical examination, progression of clinical examination, early (<24 h) brain imaging, electroencephalography (EEG), evoked potentials, later (>24 h) brain imaging, blood markers of brain injury, and cerebral oximetry for predicting good or poor outcome. In multiple cohorts, patients with status myoclonus with particular clinical or EEG features have potential for good outcome. When multiple tests were compared, each test provided independent information.

Summary
Absence of cortical functional recovery over time is detected using multiple testing modalities and remains strongly associated with poor outcome. Early recovery of cortical function increases the probability of good outcome. Concordant assessments from multiple tests increase confidence in prognostication.

- Talk on how critical illness affects the brain … and vice versa:

  https://www.youtube.com/watch?v=4DQ-loqaNLI