Prognosis of Coma after therapeutic hypothermia:

Critical Care Journal Club
Dean Bell
Heather Smith
When cardiac arrest occurs, either as standstill or as ventricular fibrillation, the circulation must be restored promptly; otherwise anoxia will result in irreversible damage. There are two techniques that may be used to meet the emergency: one is to open the chest and massage the heart directly and the other is to accomplish the same end by a new method of closed-chest cardiac massage. The latter method is described in this communication. The closed-chest alternating current defibrillator that was developed in our laboratories has proved to be an effective and reliable means of arresting ventricular fibrillation. Its counter-shock must be sent through the chest promptly, or else cardiac anoxia will have developed to such a degree that the heart will no longer be able to resume forceable contractions without assistance. Our experience has indicated that external defibrillation is not likely to be followed by the return of spontaneous heart action, unless the counter-shock is applied within less than 10 seconds.

Cardiac resuscitation after cardiac arrest or ventricular fibrillation has been limited by the need for open thoracotomy and direct cardiac massage. As a result of exhaustive animal experimentation a method of external transthoracic cardiac massage has been developed. Immediate resuscitative measures can now be initiated to give not only mouth-to-nose artificial respiration but also adequate cardiac massage without thoracotomy. The use of this technique on 20 patients has given an over-all permanent survival rate of 70%. Anyone, anywhere, can now initiate cardiac resuscitative procedures. All that is needed are two hands.
**Background—Post Arrest Prognosis**

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Prognostic importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965</td>
<td>Hockaday et al.</td>
<td>Suppressed to flattened EEG</td>
</tr>
<tr>
<td>1974</td>
<td>Willoughby and Leach</td>
<td>Absent motor response</td>
</tr>
<tr>
<td>1974</td>
<td>Bell and Hodgson</td>
<td>Duration of coma</td>
</tr>
<tr>
<td>1977</td>
<td>Snyder et al.</td>
<td>Abnormal brainstem reflexes</td>
</tr>
<tr>
<td>1978</td>
<td>Caronna and Finkelstein</td>
<td>Duration of coma and abnormal flexor or extensor responses</td>
</tr>
<tr>
<td>1978</td>
<td>Jørgensen and Malchow-Møller</td>
<td>Pattern of improvement</td>
</tr>
<tr>
<td>1985</td>
<td>Levy et al.</td>
<td>Combination of 3 waiting days, abnormal motor responses or abnormal brainstem reflexes</td>
</tr>
<tr>
<td>1988</td>
<td>Krumholz et al.</td>
<td>Status epilepticus and myoclonus status</td>
</tr>
<tr>
<td>1997</td>
<td>Fogel et al.</td>
<td>Increased serum neuron specific enolase</td>
</tr>
<tr>
<td>2000</td>
<td>Madl et al.</td>
<td>Absent cortical SSEP</td>
</tr>
<tr>
<td>2004</td>
<td>Johkura et al.</td>
<td>Forced vertical gaze</td>
</tr>
</tbody>
</table>

EEG = electroencephalogram; SSEP = somatosensory evoked potentials.

* Observations by neurologists.

Predicting Outcome From Hypoxic-Ischemic Coma

David E. Levy, MD; John J. Caronna, MD; Burton H. Singer, PhD; Robert H. Lapinski, PhD; Halina Frydman, PhD; Fred Plum, MD

- Outcome from coma caused by cerebral hypoxia-ischemia (eg, cardiac arrest) was compared with serial neurological findings in 210 patients. Thirteen percent of patients regained independent function at some point during the first postarrest year. Computer application of new multivariate techniques to the prospectively observed findings generated easily utilized rules that classified patients by likely outcome. At the time of initial examination, 52 patients (one fourth of the total population) had absent pupillary light reflexes, and none of these patients ever regained independent daily function. By contrast, the initial presence of pupillary light reflexes, the development of spontaneous eye movements that were roving conjugate or better, and the findings of extensor, flexor, or withdrawal responses to pain identified a smaller group of 27 patients, 11 (41%) of whom regained independence in their daily lives. By 24 hours after onset, 93 poor-outcome patients were identified by motor responses that were absent, extensor, or flexor and by spontaneous eye movements that were neither orienting nor roving conjugate; only one regained independent function. This contrasts with recovery in 19 (63%) of 30 patients who at that time showed improvement in their eye-opening responses and obeyed commands or had motor responses that were withdrawal or localizing. Similarly simple rules distinguished between good- and poor-prognosis patients on postarrest days 3, 7, and 14.

(JAMA 1985;253:1420-1426)
Predicting the Outcome From Hypoxic-Ischemic Coma: Medical and Ethical Implications

In a recent issue of The Journal, Levy et al. have presented a summary of their work on the outcome of coma in 210 patients with brain hypoxia or ischemia. This work is an extension of previous publications. The statistics are somber: 57% of patients died without opening their eyes, 20% attained only the vegetative state, and only 13% recovered independent function. The authors believe that simple clinical data could have predicted the outcome in many of the 87% of patients who did not achieve independent function, data such as fixed pupils on the first day or absent or posturing motor responses after three days. The authors draw several conclusions about the care of comatose patients from these data.

See also p 1171.

Two features of this article are of particular interest: the general applicability of its prognostic factors for predicting outcome from ischemic/hypoxic coma and the ethical implications of such predictions for decision making in comatose states.
“The major reservations in applying the data of Levy et al result from the methodology, however. Even within this retrospective study, the predictive power of any single item is limited. Pupillary dilation on the initial examination is considered a poor prognostic feature, for example; with it there is 95% confidence that the percentage of patients who will recover independent function is somewhere between 0% and 7%. There is therefore a one-in-20 chance that 7% of patients with this finding might achieve independent function, despite its use as a sign of poor outcome. Neither this finding nor any other is a certain predictor of prolonged coma. Most important, the data are retrospective. As the authors correctly point out, no definite statements can be made without prospective testing. Although this does not diminish the importance of this report as a preliminary study, it makes any firm prognostic conclusions difficult to support.”

Early Prognosis in Anoxic Coma: An Analysis of the Major Clinical Criteria

Christopher M. DeGiorgio, M.D.,* and D. Alan Shewmon, M.D.**

The Clarence Herbert case¹ has had substantial impact on the care of comatose patients in the state of California and in the nation as a whole, yet the medical details demonstrate the dangers implicit in early coma prognosis. In this article, the major coma prognosis criteria are applied to this and to another illustrative case involving an early prognosis of “hopelessness,” but with a very different outcome. The criteria are also analyzed from medical and statistical perspectives and recommendations regarding their use in treatment decisions are made.

“1. Withdrawal of hydration, nutrition, and life support based on current prognostic criteria is not justified, as it will lead to appropriate deaths of comatose patients who would otherwise have recovered with good outcome/moderate disability.

2. Coma prognosis based on neurologic signs and electrophysiologic tests should serve only as a general estimate of eventual outcome. Assessments of "hopelessness" or "irreversibility" based on clinical signs are unjustified early in coma and should not be communicated, unqualified, to patients' families.

3. Life support should not be discontinued during the first and probably second month into coma solely on the basis of poor prognosis.

4. Much more data need to be gathered before prognostic criteria can be developed that are reliable enough for application to individual patients.”

Is This Patient Dead, Vegetative, or Severely Neurologically Impaired? Assessing Outcome for Comatose Survivors of Cardiac Arrest

Christopher M. Booth, MD
Robert H. Boone, MD, MSc
George Tomlinson, PhD
Allan S. Detsky, MD, PhD, FRCPC

CLINICAL SCENARIO
Case 1
A 65-year-old man experienced a witnessed ventricular fibrillation cardiac arrest at home 24 hours ago. A neighbor had performed cardiopulmonary resuscitation for 5 minutes until the paramedics arrived and performed successful defibrillation. His electrocardiogram revealed a large anterior myocardial infarction for which he underwent urgent coronary angioplasty. Although still unresponsive, he withdraws from a painful stimulus and his pupillary and corneal reflexes are present. The family asks you about his chance of meaningful recovery.

Case 2
A 26-year-old woman presented to the emergency department with severe pleuritic chest pain and dyspnea. While waiting for a computed tomographic scan in the radiology department, she had an asystolic cardiac arrest. The resuscitation lasted 20 minutes, after which she was found to have reactive pupils. Three days later the family is considering withdrawing care because she is still comatose. On exami

Context Most survivors of cardiac arrest are comatose after resuscitation, and meaningful neurological recovery occurs in a small proportion of cases. Treatment can be lengthy, expensive, and often difficult for families and caregivers. Physical examination is potentially useful in this clinical scenario, and the information obtained may help physicians and families make accurate decisions about treatment and/or withdrawal of care.

Objective To determine the precision and accuracy of the clinical examination in predicting poor outcome in post-cardiac arrest coma.

Data Sources and Study Selection We searched MEDLINE for English-language articles (1966-2003) using the terms coma, cardiac arrest, prognosis, physical examination, sensitivity and specificity, and observer variation. Other sources came from bibliographies of retrieved articles and physical examination textbooks. Studies were included if they assessed the precision and accuracy of the clinical examination in prognosis of post–cardiac arrest coma in adults. Eleven studies, involving 1914 patients, met our inclusion criteria.

Data Extraction Two authors independently reviewed each study to determine eligibility, abstract data, and classify methodological quality using predetermined criteria. Disagreement was resolved by consensus.

Data Synthesis Summary likelihood ratios (LRs) were calculated from random effects models. Five clinical signs were found to strongly predict death or poor neurological outcome: absent corneal reflexes at 24 hours (LR, 12.9; 95% confidence interval [CI], 2.0-68.7), absent pupillary response at 24 hours (LR, 10.2; 95% CI, 1.8-48.6), absent withdrawal response to pain at 24 hours (LR, 4.2; 95% CI, 2.2-9.8), no motor response at 24 hours (LR, 4.9; 95% CI, 1.6-13.0), and no motor response at 72 hours (LR, 9.2; 95% CI, 2.1-49.4). The proportion of individuals’ dying or having a poor neurological outcome was calculated by pooling the outcome data from the 11 studies (n=1914) and used as an estimate of the pretest probability of poor outcome. The random effects estimate of poor outcome was 77% (95% CI, 72%-80%). The highest LR increases the pretest probability by 77% to a posttest probability of 97% (95% CI, 87%-100%). No clinical findings were found to have LRs that strongly predicted good neurological outcome.

Conclusions Simple physical examination maneuvers strongly predict death or poor outcome in comatose survivors of cardiac arrest. The most useful signs occur at 24 hours after cardiac arrest, and earlier prognosis should not be made by clinical examination alone. These data provide prognostic information, rather than treatment recommendations, which must be made on an individual basis incorporating many other variables.

CME available online at www.jama.com

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The Rational Clinical Examination Section Editors: David L. Sine, MD, MHS, Durham Veterans Affairs Medical Center and Duke University Medical Center, Durham, NC; Drummond Rennie, MD, Deputy Editor, JAMA.
Pretest Probability (pre hypothermia)

- Outcome data from 11 studies in 14 publications pooled.
- Sample size of 1914 comatose survivors of cardiac arrest.
- Pretest probability represents best estimate of death or poor neurologic outcome following cardiac arrest.

Booth et al. JAMA 2004; 291:870-879
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77% (95% CI, 72%-80%)

Booth et al. JAMA 2004; 291:870-879
## 24 Hour Predictors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Likelihood ratio</th>
<th>95% CI for LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent Corneal</td>
<td>12.9</td>
<td>2.0-68.7</td>
</tr>
<tr>
<td>Absent pupillary light reflexes</td>
<td>10.2</td>
<td>1.8-48.6</td>
</tr>
<tr>
<td>Absent motor</td>
<td>4.9</td>
<td>1.6-13.0</td>
</tr>
<tr>
<td>Absent withdrawal</td>
<td>4.7</td>
<td>2.2-9.8</td>
</tr>
</tbody>
</table>

Booth et al JAMA 2004; 291:870-879
# 72 Hour Predictors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Likelihood ratio</th>
<th>95% CI for LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent Pupil response</td>
<td>3.4</td>
<td>0.5-23.6</td>
</tr>
<tr>
<td>Absent Motor response</td>
<td>9.2</td>
<td>2.1-49.4</td>
</tr>
</tbody>
</table>

Booth et al JAMA 2004; 291:870-879
Prediction of poor outcome within the first 3 days of postanoxic coma

E.G.J. Zandbergen, MD; A. Hijdra, PhD; J.H.T.M. Koelman, PhD; A.A.M. Hart, PhD; P.E. Vos, PhD; M.M. Verbeek, PhD; and R.J. de Haan, PhD, for the PROPAC Study Group*

Abstract—Objective: To determine the optimal timing of somatosensory evoked potential (SSEP) recordings and the additional value of clinical and biochemical variables for the prediction of poor outcome in patients who remain comatose after cardiopulmonary resuscitation (CPR). Methods: A prospective cohort study was conducted in 32 intensive care units including adult patients still unconscious 24 hours after CPR. Clinical, neurophysiologic, and biochemical variables were recorded 24, 48, and 72 hours after CPR and related to death or persisting unconsciousness after 1 month. Results: Of 407 included patients, 356 (87%) had a poor outcome. In 301 of 305 patients unconscious at 72 hours, at least one SSEP was recorded, and in 136 (45%), at least one recording showed bilateral absence of N20. All these patients had a poor outcome (95% CI of false positive rate 0 to 3%), irrespective of the timing of SSEP. In the same 305 patients, neuron-specific enolase (NSE) was determined at least once in 231, and all 138 (60%) with a value >33 μg/L at any time had a poor outcome (95% CI of false positive rate 0 to 3%). The test results of SSEP and NSE overlapped only partially. The performance of all clinical tests was inferior to SSEP and NSE testing, with lower prevalences of abnormal test results and wider 95% CI of false positive rates. Conclusion: Poor outcome in postanoxic coma can be reliably predicted with somatosensory evoked potentials and neuron-specific enolase as early as 24 hours after cardiopulmonary resuscitation in a substantial number of patients.

NEUROLOGY 2006;66:62–68
<table>
<thead>
<tr>
<th>Variable/time after CPR, h</th>
<th>Patients tested, n (patients without treatment restrictions)</th>
<th>Abnormal test result, % (95% CI)</th>
<th>False positive rate,* % (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No SSEP (N20) bilaterally</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>24</td>
<td>254 (193)</td>
<td>38 (32–44)</td>
<td>0 (0–4)</td>
<td>29 (2–454)</td>
</tr>
<tr>
<td>48</td>
<td>246 (164)</td>
<td>36 (30–42)</td>
<td>0 (0–4)</td>
<td>27 (2–427)</td>
</tr>
<tr>
<td>72</td>
<td>281 (170)</td>
<td>41 (35–46)</td>
<td>0 (0–3)</td>
<td>25 (2–394)</td>
</tr>
<tr>
<td>24–72†</td>
<td>301 (175)</td>
<td>45‡ (40–51)</td>
<td>0 (0–3)</td>
<td>25 (2–383)</td>
</tr>
<tr>
<td>EEG no activity ≥20 µV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>282 (165)</td>
<td>28 (23–33)</td>
<td>0 (0–5)</td>
<td>17 (1–272)</td>
</tr>
<tr>
<td>EEG burst-suppression pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>276 (163)</td>
<td>8 (5–12)</td>
<td>0 (0–15)</td>
<td>5 (0–81)</td>
</tr>
<tr>
<td>EEG status epilepticus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>282 (166)</td>
<td>9 (6–13)</td>
<td>7 (1–24)</td>
<td>1 (0–5)</td>
</tr>
</tbody>
</table>

* Patients with abnormal test result and favorable outcome/all patients with abnormal test result (1 − positive predictive value).
† Refers to 305 patients who were still comatose after 72 h and in whom SSEP testing had been performed at least once.
‡ At least one abnormal test result.

CPR = cardiopulmonary resuscitation; SSEP = somatosensory evoked potential.
### Table 3 Prediction of poor outcome with biochemical variables

<table>
<thead>
<tr>
<th>Variable/time after CPR, h</th>
<th>Patients tested, n (patients without treatment restrictions)</th>
<th>Abnormal test result, % (95% CI)</th>
<th>False positive rate,* % (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE &gt; 33 µg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>272 (206)</td>
<td>42 (36–48)</td>
<td>0 (0–3)</td>
<td>36 (2–563)</td>
</tr>
<tr>
<td>48</td>
<td>241 (157)</td>
<td>52 (46–59)</td>
<td>0 (0–3)</td>
<td>45 (3–715)</td>
</tr>
<tr>
<td>72</td>
<td>209 (108)</td>
<td>46 (40–53)</td>
<td>0 (0–4)</td>
<td>39 (3–610)</td>
</tr>
<tr>
<td>24–72†</td>
<td>231 (110)</td>
<td>60‡ (53–66)</td>
<td>0 (0–3)</td>
<td>23 (2–357)</td>
</tr>
<tr>
<td>S100b &gt; 0.7 µg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>273 (207)</td>
<td>45 (40–51)</td>
<td>3 (1–8)</td>
<td>5 (2–12)</td>
</tr>
<tr>
<td>48</td>
<td>238 (155)</td>
<td>44 (38–50)</td>
<td>2 (0–7)</td>
<td>9 (2–36)</td>
</tr>
<tr>
<td>72</td>
<td>207 (108)</td>
<td>35 (29–42)</td>
<td>0 (0–5)</td>
<td>30 (2–466)</td>
</tr>
<tr>
<td>24–72†</td>
<td>230 (110)</td>
<td>53‡ (46–59)</td>
<td>2 (1–7)</td>
<td>3 (1–9)</td>
</tr>
</tbody>
</table>

* Patients with abnormal test result and favorable outcome/all patients with abnormal test result (1 – positive predictive value).
† Refers to 305 patients who were still comatose after 72 h and in whom NSE or S100b testing had been performed at least once.
‡ At least one abnormal test result.

CPR = cardiopulmonary resuscitation; NSE = neuron-specific enolase.
### Table 4 Prediction of poor outcome with clinical variables

<table>
<thead>
<tr>
<th>Variable/time after CPR, h</th>
<th>Patients tested, n (patients without treatment restrictions)</th>
<th>Abnormal test result, % (95% CI)</th>
<th>False positive rate,* % (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APACHE-II score &gt;25</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 24</td>
<td>366 (274)</td>
<td>51 (46–56)</td>
<td>8 (4–12)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td><strong>Circulation unstable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>394 (299)</td>
<td>57 (52–62)</td>
<td>14 (10–19)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td>48</td>
<td>353 (238)</td>
<td>47 (41–52)</td>
<td>10 (6–15)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>72</td>
<td>298 (175)</td>
<td>39 (34–45)</td>
<td>8 (4–14)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td><strong>Epilepsy or myoclonus (no status)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>374 (301)</td>
<td>33 (29–38)</td>
<td>6 (3–12)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>48</td>
<td>341 (237)</td>
<td>19 (14–23)</td>
<td>6 (2–16)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>72</td>
<td>292 (177)</td>
<td>14 (10–18)</td>
<td>2 (0–13)</td>
<td>4 (1–29)</td>
</tr>
<tr>
<td><strong>Myoclonus status</strong></td>
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<td></td>
</tr>
<tr>
<td>24</td>
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<td>4 (2–6)</td>
<td>0 (0–21)</td>
<td>5 (0–81)</td>
</tr>
<tr>
<td>48</td>
<td>350 (237)</td>
<td>1 (0–3)</td>
<td>0 (0–52)</td>
<td>1 (0–25)</td>
</tr>
<tr>
<td>72</td>
<td>300 (177)</td>
<td>2 (1–4)</td>
<td>0 (0–52)</td>
<td>1 (0–20)</td>
</tr>
<tr>
<td><strong>Status epilepticus</strong></td>
<td></td>
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<tr>
<td>24</td>
<td>395 (301)</td>
<td>2 (1–4)</td>
<td>0 (0–41)</td>
<td>2 (0–39)</td>
</tr>
<tr>
<td>48</td>
<td>351 (237)</td>
<td>1 (0–3)</td>
<td>0 (0–60)</td>
<td>1 (0–21)</td>
</tr>
<tr>
<td>72</td>
<td>300 (177)</td>
<td>1 (0–3)</td>
<td>0 (0–71)</td>
<td>1 (0–14)</td>
</tr>
<tr>
<td><strong>No pupillary or corneal reflexes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>386 (301)</td>
<td>12 (9–16)</td>
<td>4 (0–14)</td>
<td>4 (1–15)</td>
</tr>
<tr>
<td>48</td>
<td>338 (236)</td>
<td>12 (8–15)</td>
<td>2 (0–13)</td>
<td>5 (1–36)</td>
</tr>
<tr>
<td>72</td>
<td>289 (177)</td>
<td>13 (9–17)</td>
<td>0 (0–9)</td>
<td>8 (1–121)</td>
</tr>
<tr>
<td><strong>No motor response</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>395 (300)</td>
<td>59 (54–64)</td>
<td>9 (6–14)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>48</td>
<td>351 (236)</td>
<td>44 (38–50)</td>
<td>6 (3–10)</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>72</td>
<td>300 (177)</td>
<td>35 (29–42)</td>
<td>5 (2–9)</td>
<td>2 (1–4)</td>
</tr>
</tbody>
</table>

* Patients with abnormal test result and favorable outcome/all patients with abnormal test result (1 = positive predictive value).

CPR = cardiopulmonary resuscitation; APACHE-II = Acute Physiology and Chronic Health Evaluation.
Practice Parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

E.F.M. Wijdicks, MD; A. Hjdra, MD; G.B. Young, MD; C.L. Bassetti, MD; and S. Wiebe, MD

Neurology 2006; 67: 203-210
2006 American Academy Neurology Algorithm

FPR=false positive rate

Neurology 2006; 67: 203-210
“When data could be abstracted from the articles, we calculated sensitivity, false-positive rate (FPR) \((1 - \text{specificity})\), and corresponding 95% CI.”

“We chose to report our calculation of the FPR because clinicians need to be informed about the ability of the clinical examination and laboratory tests to predict poor outcome with a high level of certainty (low FPR).”

“We calculated 95% CIs for sensitivity and FPR using Wilson’s method, as recommended by Altman et al.”

Normal Approximation Method of the Binomial Confidence Interval

The equation for the Normal Approximation for the Binomial CI is shown below.

\[ p \pm z_{1-\alpha/2} \sqrt{\frac{p(1-p)}{n}} \]

where \( p \) = proportion of interest  
\( n \) = sample size  
\( \alpha \) = desired confidence  
\( z_{1-\alpha/2} \) = “z value” for desired level of confidence  
\( z_{1-\alpha/2} = 1.96 \) for 95% confidence  
\( z_{1-\alpha/2} = 2.57 \) for 99% confidence  
\( z_{1-\alpha/2} = 3 \) for 99.73% confidence

Using our previous example, if a poll of 50 likely voters resulted in 29 expressing their desire to vote for Mr. Gubinator, the resulting 95% CI would be calculated as follows.

\[ p = \frac{29}{50} = .58 \]

\[ CI = p \pm z_{1-\alpha/2} \sqrt{\frac{p(1-p)}{n}} \]

\[ CI = .58 \pm 1.96 \sqrt{\frac{.58(1-.58)}{50}} \]

\[ CI = .58 \pm .14 \]

Thus, we would be 95% confident that the proportion of the target population (all voters in Calisota) who intend to vote for Mr. Gubernator falls between 44% and 72%.
Exact Confidence Interval

The deficiencies in the Normal Approximation were addressed by Clopper and Pearson when they developed the Clopper-Pearson method which is commonly referred to as the “Exact Confidence Interval” [3]. Instead of using a Normal Approximation, the Exact CI inverts two single-tailed Binomial test at the desired alpha. Specifically, the Exact CI is range from $p_{lb}$ to $p_{ub}$ that satisfies the following conditions [2].

$$\sum_{k=0}^{k} \binom{n}{k} p_{UB}^k (1 - p_{UB})^{n-k} = \frac{\alpha}{2}$$

$$\sum_{k=x}^{n} \binom{n}{k} p_{LB}^k (1 - p_{LB})^{n-k} = \frac{\alpha}{2}$$

The population proportion falls in the range $p_{lb}$ to $p_{ub}$ where:

- $p_{lb}$ is the confidence interval lower bound
- $p_{ub}$ is the confidence interval upper bound
- $n$ is the number of trials
- $k$ is the number of successes in $n$ trials
- $\alpha$ is the desired confidence interval
Given an observation $p$, there are, potentially, two values of $P$ which would place $p$ at the outermost limits of a confidence interval about $P$. See Figure 4. What we can do, therefore, is search for values of $P$ which satisfy the formula used to characterise the Normal approximation to the Binomial about $P$. Now we have the following definitions:

\begin{align}
\text{population mean } \mu &= P, \\
\text{population standard deviation } \sigma &= \sqrt{P(1-P)/n}, \\
\text{population confidence interval } (E^-, E^+) &= (P - z\sigma, P + z\sigma).
\end{align}

Wallis S. Binomial confidence intervals and contingency tests: mathematical fundamentals and the evaluation of alternative methods
However the following **interval equality principle** must hold, where $e^-$ and $e^+$ are the lower and upper bounds of a sample interval for any error level $\alpha$:

$$e^- = P_1 \iff E_1^+ = p \text{ where } P_1 < p, \text{ and}$$

$$e^+ = P_2 \iff E_2^- = p \text{ where } P_2 > p.$$  \hspace{1cm} (3)

If the lower bound for $p$ (labelled $e^-$) is a possible population mean $P_1$, then the upper bound of $P_1$ would be $p$, and vice-versa. Since we have formulae for the upper and lower intervals of a population confidence interval, we can attempt to find values for $P_1$ and $P_2$ which satisfy $p = E_1^+ = P_1 + z.\sigma_1$ and $p = E_2^- = P_2 - z.\sigma_2$. With a computer we can perform a search process to converge on the correct values.
The score interval can be broken down into two parts on either side of the plus/minus (‘±’) sign:

1) a relocated centre estimate \( p' = \left( p + \frac{z^2}{2n} \right) \left/ \left( 1 + \frac{z^2}{n} \right) \right. \) and

2) a corrected standard deviation \( s' = \sqrt{\frac{p(1-p)}{n} + \frac{z^2}{4n^2}} \left/ \left( 1 + \frac{z^2}{n} \right) \right. \),

such that \( w^- = p' - z.s' \) and \( w^+ = p' + z.s' \). \(^3\) We will use lower case \( w \) to refer to the Wilson interval.
If Nothing Goes Wrong, Is Everything All Right?
Interpreting Zero Numerators
James A. Hanley, PhD, Abby Lippman-Hand, PhD

If Nothing Goes Wrong, Is Everything All Right?
Interpreting Zero Numerators

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To be 95% confident that our interval estimate of the long-run risk is correct, a simple rule (of unknown origin) can be applied. This “rule of three” states that if none of \( n \) patients shows the event about which we are concerned, we can be 95% confident that the chance of this event is at most three in \( n \) (ie, \( 3/n \)). In other words, the upper 95% confidence limit of a 0/\( n \) rate is approximately \( 3/n \). (This approximation is remarkably good: when \( n \) is larger than 30, the rule of three agrees with the exact calculation to the nearest percentage point; below 30, it slightly overestimates the risk, but then the
MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOThERMIA AFTER CARDIAC ARREST STUDY GROUP*

AUSTRALIAN STUDY N ENGL J MED 2002; 346:557-63

INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

Hypothermia after cardiac arrest: Results

<table>
<thead>
<tr>
<th>Must Cool</th>
<th>Could Cool</th>
<th>Do Not Cool</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Witnessed Vfib or V tach</td>
<td>• Unwitnessed arrest that fits other criteria</td>
<td>• Time to ACLS over 30 minutes</td>
</tr>
<tr>
<td>• Time to ACLS ≤ 15 min</td>
<td>• Asystole or PEA if other criteria met</td>
<td>• ACLS time over 60 minutes</td>
</tr>
<tr>
<td>• Total ACLS time ≤ 60 min</td>
<td>• ≥ 8 hours since ROSC</td>
<td>• Over 24 hours since ROSC</td>
</tr>
<tr>
<td>• GCS ≤ 9</td>
<td>• systolic BP ≥ 90 mm Hg (pressors OK)</td>
<td>• GCS ≥ 10 or improving rapidly</td>
</tr>
<tr>
<td>• ≤ 8 hours since ROSC</td>
<td>• ≤ 8 hours since ROSC</td>
<td>• Comatose state prior to cardiac arrest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Terminal illness preceding arrest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oxygen saturation under 85% for more than 15 minutes after ROSC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Known preexisting pathological coagulopathy that cannot be reversed</td>
</tr>
</tbody>
</table>
Prognostication after Cardiac Arrest and Hypothermia: A Prospective Study

Andrea O. Rossetti, MD,1 Mauro Oddo, MD,2 Giancarlo Logroscino, MD, PhD,3 and Peter W. Kaplan, MBBS, FRCP1,4

Objective: Current American Academy of Neurology (AAN) guidelines for outcome prediction in comatose survivors of cardiac arrest (CA) have been validated before the therapeutic hypothermia era (TH). We undertook this study to verify the prognostic value of clinical and electrophysiological variables in the TH setting.

Methods: A total of 111 consecutive comatose survivors of CA treated with TH were prospectively studied over a 3-year period. Neurological examination, electroencephalography (EEG), and somatosensory evoked potentials (SSEP) were performed immediately after TH, at normothermia and off sedation. Neurological recovery was assessed at 3 to 6 months, using Cerebral Performance Categories (CPC).

Results: Three clinical variables, assessed within 72 hours after CA, showed higher false-positive mortality predictions as compared with the AAN guidelines: incomplete brainstem reflexes recovery (4% vs 0%), myoclonus (7% vs 0%), and absent motor response to pain (24% vs 0%). Furthermore, unreactive EEG background was incompatible with good long-term neurological recovery (CPC 1–2) and strongly associated with in-hospital mortality (adjusted odds ratio for death, 15.4; 95% confidence interval, 3.3–71.9). The presence of at least 2 independent predictors out of 4 (incomplete brainstem reflexes, myoclonus, unreactive EEG, and absent cortical SSEP) accurately predicted poor long-term neurological recovery (positive predictive value = 1.00); EEG reactivity significantly improved the prognostication.

Interpretation: Our data show that TH may modify outcome prediction after CA, implying that some clinical features should be interpreted with more caution in this setting as compared with the AAN guidelines. EEG background reactivity is useful in determining the prognosis after CA treated with TH.

ANN NEUROL 2010;67:301–307
Prognosis in hypothermic era

No brain stem reflexes at any time (pupil, cornea, oculocephalic, cough)

Or

Day 1
Myoclonus Status Epilepticus

Or

Day 1-3
SSEP absent N20 responses*

Or

Day 1-3
Serum NSE >33 μg/L*

Or

Day 3
Absent pupil or corneal reflexes; extensor or absent motor response

Yes Brain Death testing

FPR 0% (0-8.8)

FPR 0.7% (0-3.7)

FPR 0% (0-3)

Neurology 2006; 67: 203-210
Prognosis in hypothermic era

Rossetti et al

FPR 3% (0-11%)

FPR 24% (13-40%)

(motor response)

Neurology 2006; 67: 203-210
Prognosis in hypothermic era

Prognosis in hypothermic era

No brain stem reflexes at any time (pupil, cornea, oculocephalic, cough)

Or

Day 1
Myoclonus Status Epilepticus

Or

Day 1-3
SSEP absent N20 responses*

Or

Day 1-3
Serum NSE >33 µg/L*

Or

Day 3
Absent pupil or corneal reflexes; extensor or absent motor response

Yes

Brain Death testing

Yes

Poor outcome

FPR 0% (0-8.8)

FPR 0.7% (0-3.7)

FPR 0% (0-3)

FPR 0% (0-3)

FPR 3% (0-11%)

FPR 24% (13-40%)

Neurology 2006; 67: 203-210

Rossetti et al

FPR 2%

Leithner 2010

FPR=2%

Fugate 2010

FPR=29%

FPR 29%

Neurology 2010; 67: 301-7

Ann Neurol 2010; 67: 301-7


The END

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