Patients that have undergone cardiopulmonary resuscitation have a poor prognosis. Fewer than 5% survive resuscitation on average in rural areas (1), while in cities up to a third survive (2). About 80% of surviving patients remain comatose for some time after resuscitation, and most of them have a decidedly poor outcome. They either die soon afterward or else survive with severe, irreversible brain damage causing permanent unconsciousness, a persistent vegetative state, or a lasting, severe neurological deficit with permanent dependence on nursing care (3, 4).

More and more people are now writing “living wills” stating that, in case of irreversible unconsciousness or very severe, permanent brain damage, no therapeutic measures should be undertaken except for appropriate palliative treatment. If a patient who has written such a document were to survive cardiopulmonary resuscitation with a definitively poor prognosis, then treating this patient with all of the available measures of intensive-care medicine would be against the patient’s expressed wishes and, therefore, impermissible. Even if the patient has not written a living will, the nature and extent of intensive-care measures should be reassessed over the course of the patient’s illness on the basis of the individual findings, and then modified accordingly, because, as soon as the prognosis becomes definitively unfavorable, many treatments that are medically feasible are no longer either reasonable or desirable.

A definitively poor prognosis should be discussed with the patient’s family as soon as it is determined. No unrealistic hopes should be nurtured, because, if the patient survives the acute phase, the family will be faced with many problems of a scope that they usually, and understandably, have no clear conception of in advance. In this paper, the authors present the definitive indicators of a poor prognosis that were consistently found in multiple studies involving large groups of patients. We will refer to three meta-analyses (5–7) and to the original articles underlying these studies; the literature that we discuss was found by a Medline search on the term “cardiopulmonary resuscitation,” in connection with the terms “anoxic encephalopathy,” “hypoxic encephalopathy,” “prognosis,” “coma,” “electro-

SUMMARY
Introduction: Most comatose survivors of cardiopulmonary resuscitation (CPR) have a poor prognosis. Reliable predictors of a poor outcome are described derived from large groups of patients not treated with therapeutic hypothermia after resuscitation. Methods: Selective literature review, focused on 3 meta-analyses and on articles found by a Medline search. Results: Within 3 days post-CPR, the following signs reliably predict a poor outcome: bilaterally absent pupillary light response, bilaterally absent corneal reflexes, absent motor responses to pain, burst suppression-EEG, isoelectric EEG, bilaterally absent cortical responses following median nerve stimulation, and an elevation of neuron-specific enolase. Generalized myoclonus within 24 h after CPR is also a reliable predictor of poor outcome. Discussion: The expectation of a poor outcome should be communicated to the relatives and the appropriate level of care discussed. Where the combination of clinical, electrophysiological, and biochemical findings indicate a poor prognosis, treatment restrictions should be discussed.

Key words: resuscitation, hypoxia, prognosis, myoclonus, EEG
physiological studies,” “EEG,” “SSEP,” “biochemical markers,” and “NSE.” Death, permanent unconsciousness, and a persistent vegetative state were considered by all authors to be unfavorable outcomes. The authors of the present paper also consider a severe neurological deficit with permanent dependence on nursing care to be an unfavorable outcome, as do the authors of a number of studies in the literature. Based on the data that we evaluated, we present an algorithm that has emerged from many years’ experience in the interdisciplinary treatment of these patients.

**Parameters for the prognostic assessment of resuscitated patients**

**Demographic and preclinical data**
- Age
- Underlying illnesses, comorbidities
- Etiology of cardiac arrest
- Type of cardiac arrhythmia
- Observed or non-observed cardiac arrest
- Immediate life-saving measures (chest compression and mouth-to-mouth ventilation)
- (Estimated) interval from collapse to arrival of the emergency medical team
- Spontaneous respiration on arrival of the emergency medical team
- (Estimated) interval from collapse to return of spontaneous circulation
- Total adrenalin dose during resuscitation
- Pupillary light responses after return of spontaneous circulation
- Cough/gag reflex after return of spontaneous circulation
- Glasgow Coma Score after return of spontaneous circulation
- Spontaneous respiration after return of spontaneous circulation

**Clinical findings**
- Generalized myoclonus
- Pupillary light responses on hospital admission and 1 and 3 days thereafter
- Corneal reflexes on hospital admission and 1 and 3 days thereafter
- Response to painful stimuli on the third day
- Glasgow Coma Score on admission
- APACHE-II score in the first 24 hours
- Vestibulo-ocular reflex on day 3
- Cough/gag reflex on day 3
- Duration of unconsciousness

**Laboratory studies**
- Neuron-specific enolase in the serum in the first 72 hours after resuscitation
- S-100 protein in the serum 24 hours after resuscitation
- Serum glucose on hospital admission and 12 and 24 hours thereafter

**Electrophysiological studies**
- Electroencephalography (EEG): burst-suppression EEG, isoelectric EEG
- Somatosensory evoked potentials (SEP): bilateral loss of N20 on median nerve stimulation

**Radiological and nuclear medical studies**
- Computerized tomography
- Magnetic resonance tomography
- Hexamethylpropyleneamine oxime single-photon emission computerized tomography (HMPAO-SPECT)
- Positron emission tomography (PET)

*Indicator of a poor prognosis*
Prognostic possibilities

More than 100 individual parameters have been studied to date with respect to their prognostic significance for patients who have undergone cardiopulmonary resuscitation (CPR). Only a small number of clinical, electrophysiological, and biochemical findings have been consistently found to be independent, definitive indicators of a poor prognosis in multiple studies involving large numbers of patients (11). The prognostic definitiveness of these parameters, however, applies only to patients who were not treated with hypothermia after resuscitation. A recent multicenter study has shown that mortality can be significantly reduced in a certain, well-defined group of resuscitated patients by treatment with mild hypothermia (ca. 33°C) for 24 hours. 56 of 137 patients treated with hypothermia died (41%), as compared to 76 of 138 normothermic patients in the control group (55%; \( p = 0.02 \)) (12). The percentage of patients with a good outcome was also significantly higher: 75 of 136 hypothermic patients (55%), versus 54 of 137 normothermic patients (39%; \( p = 0.009 \)) (12). These findings led to a recommendation that successful cardiopulmonary resuscitation should be followed by 24 hours of hypothermia, but this mode of treatment has not yet been put to widespread use (13). Much effort will be needed before the recommended guidelines can become standard treatment in practice and thereby improve outcomes in this group of patients. Until this happens, the prognostic parameters to be discussed individually below will still be of great use.

Prerequisites for prognostic assessment

Proper clinical and electrophysiological examinations can only be performed if no sedating medications affect the results. It makes sense, therefore, to refrain from treating patients with any sedatives that have a long half-life (such as barbiturates) in the first three days after cardiopulmonary resuscitation. If substances with a short half-life (such as propofol) are used instead, they can be discontinued shortly before the examination so as not to affect the results.

Maximum diagnostic certainty is obviously desirable when the prognosis of resuscitated patients is to be assessed. A poor prognosis should not be determined on the basis of a single finding, but rather on the basis of a consistent constellation of prognostically unfavorable findings. In practice, this means that a poor prognosis can be assumed with a sufficient degree of certainty when the clinical, electrophysiological, and biochemical findings are all unfavorable. When this principle is adhered to, the prognosis can be definitively assessed within 3 days after cardiopulmonary resuscitation (5–11).

It should be borne in mind that, while certain clinical, electrophysiological, and biochemical findings indeed definitively indicate a poor prognosis, their absence does not imply that the prognosis is good. Thus, for example, bilateral loss of cortical somatosensory evoked potentials in response to median nerve stimulation is a definitive sign of a poor prognosis, but the presence of these potentials is not a definitive sign of a good prognosis. Similarly, a significant decrease in the amplitude of the electroencephalographic response to auditory stimuli is a definitive sign of a poor prognosis, but an increase in this response is not a definitive sign of a good prognosis.

### Table 1

The prognosis of patients in coma with generalized myoclonus within 24 hours of cardiopulmonary resuscitation

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Died</th>
<th>Vegetative state</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butenuth &amp; Kubicki 1971 (e1)</td>
<td>12</td>
<td>12</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Celesia et al. 1988 (e2)</td>
<td>13</td>
<td>8</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Krumholz et al. 1988 (e3)</td>
<td>19</td>
<td>19</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Jumao-as &amp; Brenner 1990 (e4)</td>
<td>11</td>
<td>11</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Young et al. 1990 (13)</td>
<td>15</td>
<td>15</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Wijdicks et al. 1994 (e5)</td>
<td>40</td>
<td>40</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Reeves et al. 1997 (e6)</td>
<td>9</td>
<td>9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Authors’ experience</td>
<td>83</td>
<td>77</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>Overall</td>
<td>202</td>
<td>191</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>
elevation of the serum concentration of neuron-specific enolase definitively portends a bad outcome, but a normal or only mildly elevated concentration of this substance does not necessarily imply that the outcome will be good.

**Clinical predictors of a poor outcome**

Three large meta-analyses (5–7) of studies performed on this topic came to the unanimous conclusion that the following findings indicate a poor prognosis:

- loss of the pupillary light responses,
- loss of the corneal reflexes,
- lack of motor response to noxious stimulation.

Booth et al. (5) state that loss of the pupillary light responses and loss of the corneal reflexes are already definitively unfavorable prognostic signs 24 hours after resuscitation, while Zandbergen et al. (6) consider these signs to be definitive only three days after resuscitation. On the other hand, Wijdicks et al. (7) consider the loss of these reflexes at any time in the first three days to be prognostically unfavorable. The lack of a motor response to noxious stimulation of the face and limbs is considered by all three groups to indicate a poor prognosis if the finding is made three days after resuscitation (5–7).

Myoclonus appearing in a comatose patient in the first 24 hours after cardiopulmonary resuscitation (early post-anoxic myoclonus) is a further prognostically unfavorable clinical sign. This type of myoclonus consists of rapid, "lightning-like" twitching of individual muscles or muscle groups that occurs spontaneously and typically increases markedly after an external stimulus, e.g., touching the patient, endotracheal suction, or an auditory stimulus.
It is mainly seen in the face, the muscles of the shoulder and upper arm, and the diaphragm. Myoclonus of this type is sometimes very mild, e.g., restricted to the face, but at other times so massive that it causes the bed to shake. More than 90% of these patients die, most of them in the first 7 days, while the few who survive remain in a persistent vegetative state (table 1) (7, 11, 14, 15, e1–e6). Although there have been rare reports of a more favorable course, these should be viewed critically, as the clinical descriptions of some of these patients give rise to doubt as to whether they truly had early post-anoxic myoclonus. In other patients, multifocal action myoclonus after recovery of consciousness was misinterpreted as early post-anoxic myoclonus (15). The authors do not know of any patient who had generalized early post-anoxic myoclonus combined with an EEG finding of burst-suppression, an isoelectric tracing (at 20 µV/cm), or continuous, generalized epileptiform discharges who then went on to have a favorable course.

Electrophysiological predictors of a poor outcome

The largest amount of experience in the prognostic assessment of resuscitated patients has been obtained with electroencephalography (EEG) and somatosensory evoked potentials (SEP). It should be noted, however, that EEG cannot provide any prognostically useful information in the first 6 to 8 hours after resuscitation, because certain findings that unequivocally portend a poor prognosis if present at later times do not preclude a good outcome if they are seen this early. Beyond the 6-to-8-hour interval, certain EEG findings do allow definitive prognostication, as shown by many studies that have been performed since the 1970’s. Specifically, a burst-suppression EEG pattern (diagram 1) or the absence of cerebral electrical activity in the first 2 (to 3) days after resuscitation are definitive signs of impending death or a persistent vegetative state (6, 7, 9–11, 14, 15, e1–e6, e8–e13).

The loss of cortical somatosensory evoked potentials in response to median nerve stimulation at any time in the first week after resuscitation is likewise a definitive sign of a poor prognosis (6, 7, 9–11, e10, e14–18). This finding is only valid if the potentials over the brachial plexus and/or the spinal cord are still present. An initial report suggests that the unfavorable prognostic significance of this finding applies to patients who have been treated with 24 hours of hypothermia as well as to those who have not (18). Although the SEP is less likely to be influenced by sedating drugs than the EEG, it should nonetheless be recorded in the absence of such drugs to maximize diagnostic certainty. The patient should not be under the influence of sedatives anyway, as these would interfere with the clinical examination.

Biochemical predictors of a poor outcome

Loss of cells in the cerebral cortex is accompanied by the release of certain metabolic enzymes that are detectable in the serum. In particular, measurement of the serum concentration of neuron-specific enolase (NSE) can be performed routinely and cheaply in any large laboratory and has been found to be very useful. A significantly elevated serum NSE level in the first few days after resuscitation indicates a poor prognosis (table 2) (6, 7, 9–11, e19–e27). The recently published large-scale prospective study by Zandbergen et al. (10), involving 407 patients, is particularly instructive: all patients whose serum NSE levels exceeded 33 µg/l in the first 72 hours after resuscitation had a poor outcome, i.e., they died or were still comatose one month later. Thus, experience suggests that this finding is incompatible with a later regaining of consciousness (19). The brain damage is so severe that nothing better than a permanent vegetative state or a so-called minimally responsive syndrome can be expected.

It cannot yet be determined whether, and to what extent, this borderline value is still valid for patients that have been treated with hypothermia for 24 hours after resuscitation. According to an initial report, NSE levels in the first 48 hours after resuscitation are lower in such patients than in normothermic patients. The NSE level falls between 24 and 48
hours after resuscitation significantly more often in patients treated with hyperthermia than in normothermic patients; this drop was also associated with a better outcome (20).

S-100 protein also appears to permit the reliable prediction of a poor outcome 24 hours after resuscitation (e22, e24–28), but there has been less experience to date with this parameter than with NSE. In the authors' view, only a significantly elevated serum NSE level should currently be considered a definitive biochemical indicator of a poor prognosis.

**Consequences of a foreseeably poor outcome**

If the clinical, electrophysiological, and biochemical findings unanimously point to a poor prognosis, one can no longer assume that the patient will regain his or her premorbid functional level or survive with only mild neurological impairment. Irreversible brain damage has occurred of such severity that nothing better than a permanent vegetative state or a persistent, severe neurologic deficit with permanent dependence on nursing care can be expected. This fact must be discussed with the patient's family, who naturally are filled with the hope that, having been successfully resuscitated, the patient will soon wake up. They then observe, to their distress, that the patient remains unconscious. The poor prognosis often comes as a surprise to them, and multiple discussions are often needed so that they will not just understand the situation, but also be able to come to terms with all of its consequences. These discussions should be carried out in a quiet and relaxed setting, yet with the full clarity that they require. It should be made clear that severe brain damage has occurred leading to an irretrievable loss of all of the higher functions of the brain. Conscious perception of the environment is no longer possible, and any reaction to external stimulation will be absent or, at best, fragmentary.

The authors do not know of the existence of any specific guidelines for patients with a poor prognosis after cardiopulmonary resuscitation. The general recommendations for the treatment of severely ill patients in intensive care whose prognosis is poor are, of course,
also applicable to patients with very severe hypoxic brain damage (7, 21, 22, 23). If the patient's poor prognosis has been established beyond any reasonable doubt, then the goals of therapy should be reassessed and the nature and extent of any further intensive treatment measures should be discussed, both within the medical team and with the patient's family (7, 21, 22, 23). If the patient has issued a living will stating that, in case of irreversible unconsciousness or severe, permanent brain damage, no treatment should be given aside from the appropriate palliative measures, then this should obviously be respected and the treatment should be correspondingly limited (diagram 2). The same also holds if it has become clear, through discussion with the patient's family, that he or she would have regarded a syndrome of severe neurological impairment as an intolerable condition to be in (diagram 2).

If the patient's wishes, or presumed wishes, cannot be determined, then the authors think it is appropriate to consider a limitation of treatment as long as no member of the treating team has any reasonable doubt about the poor prognosis. A permanent vegetative state or very severe neurological deficit with permanent dependence on nursing care, which is the best outcome that can be expected in such cases, is, in our opinion, not a goal that should be pursued with the entire armamentarium of intensive care medicine. There is no hurry to cut back on treatment, however, and we do not suggest that all medications should be discontinued as rapidly as possible. Instead, the medications that are used to support cardiovascular function can be incrementally reduced, and extubation should be a goal once the patient starts to breathe spontaneously again, which often happens within one week. We think it is appropriate to give morphine; in our experience, patients' families often desire this in order to ensure that the patient does not suffer, even if conscious perception of pain seems unlikely in view of the massive brain damage that has been sustained.

**Conclusions**

The overriding principle of intensive care medicine is that each individual patient should receive the best possible treatment, yet not everything that can be done is appropriate or desirable for every patient. For comatose survivors of cardiopulmonary resuscitation whose
prognosis is poor, i.e., for patients who can be expected either to die or to emerge from intensive care with a persistent vegetative state or, at best, a severe neurological deficit with permanent dependence on nursing care, the possible withdrawal of intensive medical treatment should be evaluated and discussed. Obviously, maximal diagnostic certainty is required in such cases, i.e., a poor outcome can only be predicted in a patient that has not been treated with hypothermia and only if the clinical examination, the EEG or SEP, and the serum NSE level all indicate a poor prognosis.

It is not currently known with certainty whether these parameters are also applicable to patients who have been treated with hypothermia for 24 hours after resuscitation. The prognostic significance of bilateral loss of the cortical component of the median nerve SEP seems to apply to hypothermic patients as well, according to an initial report (19). Myoclonus or tonic-clonic seizures are often not recognizable during therapeutic hypothermia, because patients are generally given muscle relaxants to prevent shivering (24). These clinical findings can only be looked for and assessed once the patient’s temperature has returned to normal. An initial report on the course of the serum NSE level in patients treated with hypothermia has shown that their values are lower than those of normothermic patients and also decline more often after the first day (19). Thus, more studies are necessary to provide a definite answer to the question whether the known indicators of a poor prognosis after cardiopulmonary resuscitation are also applicable after 24 hours of hypothermia. Now that the care of patients after cardiopulmonary resuscitation is increasingly oriented to published guidelines, it should be easier to perform this type of research. Studies such as the prospective trial on acute anoxic brain injury (PROGANOX) that has been initiated by the Interdisciplinary Task Force on Coma of the German Interdisciplinary Association for Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin, DIVI) are very important, because the basic problem of prognosis and its implications for the continuation or limitation of intensive treatment is particularly relevant to this group of patients.

Conflict of Interest Statement
The authors declare that no conflict of interest exists as defined by the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 29 November 2006; final version accepted on 21 June 2007.

Translated from the original German by Ethan Taub, M.D.

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For e-references please refer to the additional references listed below.

Dtsch Arztebl 2007; 104(42): A 2879–85 | www.aerzteblatt.de

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