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Guidelines for Quality Management of Apallic Syndrome / Vegetative State

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Abstract

Introduction: Epidemiology in Europe shows constantly increasing figures for the apallic syndrome (AS)/vegetative state (VS) as a consequence of advanced rescue, emergency services, intensive care treatment after acute brain damage and high-standard activating home nursing for completely dependent end-stage cases secondary to progressive neurological disease. Management of patients in irreversible permanent AS/VS has been the subject of sustained scientific and moral-legal debate over the past decade.

Methods: A task force on guidelines for quality management of AS/VS was set up under the auspices of the Scientific Panel Neurotraumatology of the European Federation of Neurological Societies to address key issues relating to AS/VS prevalence and quality management. Collection and analysis of scientific data on class II (III) evidence from the literature and recommendations based on the best practice as resulting from the task force members' expertise are in accordance with EFNS Guidance regulations.

Findings: The overall incidence of new AS/VS full stage cases all etiology is 0.5–2/100.000 population per year. About one third are traumatic and two thirds non traumatic cases. Increasing figures for hypoxic brain damage and progressive neurological disease have been noticed. The main conceptual criticism is based on the assessment and diagnosis of all different AS/VS stages based solely on behavioural findings without knowing the exact or uniform pathogenesis or neuropathological findings and the uncertainty of clinical assessment due to varying inclusion criteria. No special diagnostics, no specific medical management can be recommended for class II or III AS treatment and rehabilitation. This is why sine qua non diagnostics of the clinical features and appropriate treatment of AS/VS patients of "AS full, remission, defect and end stages" require further professional training and expertise for doctors and rehabilitation personnel.

Interpretation: Management of AS aims at the social reintegration of patients or has to guarantee humanistic active nursing if treatment fails. Outcome depends on the cause and duration of AS/VS as well as patient's age. There is no single AS/VS specific laboratory investigation, no specific regimen or stimulating intervention to be recommended for improving higher cerebral functioning. Quality management requires at least 3

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years of advanced training and permanent education to gain approval of qualification for AS/VS treatment and expertise. Sine qua non areas covering AS/VS institutions for early and long-term rehabilitation are required on a population base (prevalence of 2/100.000/year) to quicken functional restoration and to prevent or treat complications. Caring homes are needed for respectful humane nursing including basal sensor-motor stimulating techniques. Passive euthanasia is considered an act of mercy by physicians in terms of withholding treatment; however, ethical and legal issues with regard to withdrawal of nutrition and hydration and end of life discussions raise deep concerns. The aim of the guideline is to provide management guidance (on the best medical evidence class II and III or task force expertise) for neurologists, neurosurgeons, other physicians working with AS/VS patients, neurorehabilitation personnel, patients, next-of-kin, and health authorities.

Key Words
Apallic syndrome · Vegetative state · Neurorehabilitation · Functional assessment · Outcome following severe brain damage · Management guideline · Multidisciplinary neurotraumatology · Withdrawal of nutrition and hydration · Evidence-based medicine

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Objectives

Task force consensus opinion in Central and East Europe on the term apallic syndrome (AS), as coined by Kretschmer [1], i.e. to describe patients who are awake but unresponsive secondary to traumatic and nontraumatic causes of brain damage, is well established, understood, and still used in neuroscience and clinical practice [2–16]. In contrast, the term vegetative state (VS), first introduced as *persistent vegetative state* after brain damage by Jennett and Plum [17], has currently found widespread use in the English and American literature, despite major concerns and ongoing controversy over the meaning of VS nomenclature [17–51]. This has critically been reviewed by Shewmon [52]. Jennett [37] himself recommended to definitively drop the attribute *P (persistent)* following his prior (1996) concerns, also for *permanent* [26, 30]. As a result of modern emergency and intensive care medical treatment and diagnostic neuroimaging, many patients who would have died in the past increasingly survive acute traumatic and nontraumatic brain damage and chronic progressive neurological diseases, however, at the expense of full AS, remission defect or end stage, respectively. For Europe prevalence of AS in hospital cases is reported to be 0.5–2/100.000 population/year, about one quarter to one-third secondary to acute traumatic and roughly 70% following acute nontraumatic brain damage and chronic neurological diseases [2, 5, 18, 26, 28, 29, 37, 54, 59, 60]. Over the past two decades, especially designed institutions for early neurological–neurosurgical rehabilitation (ENNR) of apallic patients after severe brain damage and nursing homes for permanent attention stimulating care of completely disabled patients have been established in Europe, thanks to national medical-social health authorities, public and private care providers, and care givers on a legal provision insurance basis [2, 14, 15, 27, 28, 60–65]. Rehabilitation aims to confirm the diagnosis, enable improvement, manage disabling complications and support the patients' families and social reintegration [2, 26, 37, 66]. Functional outcome has been shown to depend on the cause, duration of AS/VS, and patient's age [2, 26, 37, 47, 53]. There is no single specific laboratory investigation, no specific medical treatment, no specific rehabilitative regimen or stimulating intervention that can be recommended on evidence class II (or III) level to improve higher cerebral mental cognitive functioning and independent social outcome [2, 15, 23, 28, 30, 49, 51, 65, 66]. The purpose of this contribution is to recommend quality management for patients suffering from full stage and emerging from AS of different functional stages as a consequence of posttraumatic and non-traumatic brain damage, needing an even better early assessment and ongoing monitoring of impaired functioning [2, 6, 22, 26, 27, 34, 37, 54, 60, 67–72]. Neurorehabilitation aimes at social reintegration or adequate humane nursing care [6, 14]. Peer-reviewed statements of minimum and desirable standards for guidance in the practice of AS management are considered in this paper, based on best available evidence without having the intention of legally binding implications in individual cases.

Search Strategy and Scientific Basis

We have restricted ourselves to review medical evidence of AS quality management in consulting the Cochrane Library and bibliographic databases (e.g., MEDLINE), textbooks, and journals for an analysis of previous guideline documents and recommendations. Using the key words we searched for collection of new data from original scientific papers (referee-based and

non-refereed journals) and books including the older literature (different languages), especially German which is usually not reflected in English reviews. Scientific contributions of class II or III evidence (AANS Guidelines 1995) were found not to be specifically focused on the treatment of AS but are recommended in general for assessment, medical treatment, and neurorehabilitation after severe brain damage [73]. At present there is no class I evidence management available for AS or VS. From MEDLINE research over the last decade only a few references could be found on AS but some 640 for VS/PVS.

Doctors' inexperience and disagreement with regard to the diagnosis of AS is reflected in the literature [26, 36, 37, 106, 121–129]. Therefore, we collected reports on best practice and extensively used the task force members' expertise of AS management as each of them has been in charge of and responsible for AS management in all kinds of specialized rehabilitation institutions for at least 10 years. Furthermore, use has been made of the expertise of KvW, E.OS, A.R., and PWSch who were members of the *German Task force on Neuro-logical–Neurosurgical Rehabilitation* and the Coma Remission Scale (Table 3) in 1993 and 2000 [6, 14, 63]. G.Z. has coordinated and participated in the Aspen Conference for PVS management (Seville 1996) together with J.LC, F.G., KvW, and K.A. [49]. In view of our major concerns on ethical and legal issues in Europe, including some international variations and controversies as compared to the US and non-European countries, we confined ourselves to address these issues in the light of the latest review of Jennett [37] and the statements of Andrews, Ashwal, Giacino, Gigli et al., Shewmon, Schönle, and Zasler [33].

Background

Full stage AS has clinically been defined in three do mains: (a) anatomy, (b) behavior, and (c) self-awareness (consciousness) [2–5, 9, 11, 13, 17, 21–26, 28, 30, 32, 37, 38, 40, 41, 43, 49, 50, 51, 152, 157, 158]. *Apallic* syndrome is the clinical manifestation of a functional multimodular disconnection syndrome with signs and symptoms of a *pathological neurobehavioral syndrome* that cannot be explained by or taken for *a conditio sine qua non* of an anatomically completed and permanent disconnection of neocortical structures and of higher cerebral functioning. *Apallic* was coined from the Latin *pallium* which in English means overcoat (pallium) [1, 9], as it had become evident during recovery from full stage AS at times of different early remission stages by demonstrating some primitive awareness of self and environment and the capacity to experience pain. "Since this state has first been described (*by Kretschmer in 1940*), it has provoked intense debate among health professionals, clinical scientists, moral philosophers and lawyers." quote Jennett [37], who in 1972 coined the term *persistent vegetative state (PVS)* (100 together with Plum) [17]. Since PVS has become part of the Glasgow Outcome Scale (GOS) for functional assessment after traumatic brain injury (TBI) [74], this term is now in widespread use for the assessment or description of outcome after traumatic and nontraumatic brain damage. Conceptual criticism of VS terminology used has been reviewed by Jennett [37] and Shewmon [52]. "Consensus opinion seems to be in the English literature that the term VS is meanwhile so well entrenched in neuroscience that it would be difficult, if not impossible, to alter the term to a more appropriate one which has a more meaningful and humanized outcome for all patients involved", quote Zasler [33]. European neurologists, neurosurgeons, neurorehabilitation physicians and physiatrists might keep on using the term *apallic syndrome for AS full stage*, that can also be an *end stage*, and for all *AS remission stages* of partially recovered functioning as well as for the final *AS (defect stage)*. For publications in the English language, the term AS should be connected with VS according to bibliographic databases [22–38] as for example research in MEDLINE revealed some 640 VS but only few AS references listed for the last decade.

Gerstenbrand [3–5, 9, 106] has described manifold causes and typical clinical pictures of all AS states based on anatomical brain pathology and clinical pathophysiology [8, 10, 13, 21, 74–76, 79–87, 91–96, 117, 123]. Clinical assessment and correct diagnosis of AS presupposes additional, qualified education and some years of personal expertise in AS management in order to prevent misdiagnoses and maltreatment [4, 9, 23, 26, 27, 50, 51, 60, 67–69, 109, 116, 118, 120–129, 158]. Coma is defined as the pathological status of a patient who cannot be aroused to a wakeful state and whose eyes are continuously closed and do not open on command or on receipt of nociceptive stimuli [119]. Unfortunately, misleading either the phenotype (for example, posttraumatic catatonia, coma prolongé, and prolonged coma) or a single sign and symptom describing historical terminology (for example, hypersomnie, akinetischer Mutismus, Wachkoma, Coma vigile, postcomatose unawareness, Decerebrations syndrome), is still in use confusing the correct diagnosis and management of AS patients [2, 17, 30, 32–34, 36,

43, 52, 53, 55, 100, 102–104, 106–107, 109, 120]. We recommend not to use misleading terms any more that should definitively be abandoned in neuroscience and by doctor's for use in the lay press. The term *Minimally Conscious State (MCS)*, however, introduced by Giacino et al. [121] that may be a final stage or a transition state from VS to recovery might be a helpful adjunct for patients emerging from AS to describe evidence of limited but clearly discernible selfor environmental awareness on a reproducible or sustained basis by one or more neurobehavioral criteria as they can be observed in patients emerging from AS full to early remission stage [2, 31, 32, 37, 44]. However, the different neurobehavioral stages of the Symptomatic transitory psychotic AS have to be assessed and described more precisely. From the extensive literature of the past few years, we restricted ourselves to refer to only some meaningful contributions that attempted to clarify the clinical neurobehavioral criteria for the assessment and management of AS [22–31, 37, 48–55, 67–74, 100, 118–122, 134]. A nomenclature to be used uniformly for patients with severe alterations of consciousness was formulated by the American Congress of Rehabilitation Medicine [23] and reviewed by Andrews [26]. For a number of AS patients it has been demonstrated that recovery of impaired higher cerebral functioning of the sensory motor system, awareness and cognition is possible but requires careful clinical assessment and individualized rehabilitative interventions that, however, still rely on empirical approaches [2, 33, 37, 50, 51, 57, 91–94, 130, 151, 156]. Promising new developments using functional MRI and acoustic evoked potentials are going to change the historical diagnose of AS/VS [143, 144] as they show appropriate neural response to the meaning of spoken instructions through functional brain activity in vegetative stage [83, 84, 87, 143, 144, 149]. Gerhard [8] was able to demonstrate primary upper (bulbar) brain stem lesions in patients after TBI who had survived in full stage AS for several months. Primary damage within the midbrain structures, basal ganglia up to the neocortical regions were previously described in AS and reviewed by Kinney et al. [80, 81], see also [37]. Concerning pathological brain lesions as demonstrated by neuroimaging for AS, Firsching and co workers performed a prospective MRI study on acute severe TBI and have shown that AS was never observed in the absence of bilateral mesencephalic damage, and bilateral lesions of the pons and of the lower medulla oblongata were predictors of fatal outcome in children and adults [75, 95, 124–126].

Results

Etiology

The main causes for AS full, remission, defect, and end states can be summarized as the following [2, 5, 9, 18, 21, 22, 26, 28, 29, 36, 53, 59, 77, 78, 80, 91, 106, 120, 164, 180, 181]:

(1) Acute brain damage
(1.1) Acute traumatic brain damage (direct impact): acute traumatic brain injury (TBI)
(1.2) Acute nontraumatic brain damage
(1.2.1) Hypoxic–anoxic, hypoxemic, ischemic (secondary to cardiac arrest, strangulation, CO, perinatal asphyxia)
(1.2.2) Metabolic (for example, hepatic, renal, diabetic, drug-, mercury-, snake venom(viper), plant-, animal poisoning, etc.)
(1.2.3) Postencephalitic
(2) Chronic degenerative brain damage
(2.1) Alzheimer's disease, Pick's disease, Huntington's disease
(2.2) Inflammatory (for example, Creutzfeldt–Jacob disease, Multiple Sclerosis, etc.)
(2.3) Vascular circular disturbances, progressive course
(2.4) Metabolic (for example, chronic hepatic failure, Marchiafava–Bignami disease, etc.) end stage, no remission possible
(3) Chronic progressive brain disease
(3.1) Chronic progressive intoxication (for example, Minamata-F.G. Mangan intoxication, etc.)
(3.2) Chronic endogen intoxication (for example, chronic hepatic failure, thyreotoxic) partial remission possible
(4) Congenital (*Developmental malformations*): severe microencephaly, hydranencephaly, Liss-Encephaly, (decorticate) hydrocephalus, anencephaly, and others.

Prevalence

The prevalence of AS in European countries with regard to its etiology and regional distribution, patient's age and sex, concomitant organ failures, and risk factors is not exactly known because of (a) regionally dependent differences in the incidence of traumatic and nontraumatic causes, (b) question of mistaken diagnosis, (c) confusion over correct naming and etiology [2, 15, 37, 59, 60, 127–129, 134–136] by using national codes and the international classification of diseases like ICD 9 when only recently ICD 10 was introduced into clinical practice. Key to ICD-9 diagnosis used: 348.9 AS; 800.7: open/closed skull fracture with AS; 801.7:Skull fracture with AS; 803.7

other fractures with AS; 804.7 multiple fractures with involvement of the skull or of the face with other bones with AS; 851.5: cerebral contusion with AS; 852.5: subarachnoid hemorrhage (SAH) with AS; 854.5: intracranial injury with AS. There were 31 adults and one child. Causes of in-hospital patients were two posttraumatic and 11 nontraumatic brain damage (= 3 cardiac arrests, 2 myocardial infarctions, 2 strokes, 1 hypovolemic shock, 1 status asthmaticus, 2 cerebral hemorrhages) while in nursing homes the findings were comparable, i.e. 26% posttraumatic and 14 (74%) nontraumatic cases (4 myocardial infarctions, 3 cardiac arrests, 3 intoxications, 2 drownings, 2 intracerebral hemorrhages). The ICD code is G 93.80 for AS treatment which does not reflect the severity of brain damage and etiology. The cause of AS is coded by G 93.1 for hypoxic brain lesion, S 06.20 for diffuse brain damage, I 61.6 intracerebral mass hemorrhage, G 30.9 Mb Alzheimer. In case AS G 93.80 is in combination with code of procedures 8–552 for early neurorehabilitation, this AS patient will be assessed as B 43Z and no costs will be refunded for the first 2 weeks of clinical treatment; thereafter, from days 14–28, a flat rate will be paid including all treatment costs. However, in the case the AS patient stays longer than 28 days in the early rehabilitation unit, the individually assessed local daily recompensation will be paid for the patient covering all expenses of in-hospital treatment from the first day. Using data collected from care givers or insurance companies might be risky and lead to false statistics of AS when diagnosis of the most expensive brain damage is mentioned for medical care money considerations in the managed care system of our days [14, 15, 59–61, 127]. One has to be aware that patients suspected to be AS patients are often wrongly diagnosed by general practitioners and specialists, as it was the case in 43% of patients checked by Andrews et al. [60, 67, 94, 128, 134–136]. Prevalence of posttraumatic AS, as derived from the literature, is reported to be 0.5–2/100.000 population per year [2, 37]. Prevalence of posttraumatic AS is reported to be approximately one-third of all causes with a clear tendency toward increasing figures for nontraumatic hypoxemic cases [105]. Research data from France, Italy, and Belgium show a national annual incidence of 0.9–2/100.000 population [29, 53, 55, 100–102] while for Israel (retrospective analysis) the incidence of posttraumatic AS at 1 month was 0.4–0.5/100.000 population per year [2]. In Austria [89, 105] the prevalence of AS (traumatic and nontraumatic causes) on an in-patient population basis for Vienna was found to be 1.9/100.000 in the year 2001 and 1.7/100.000 in 2003 (by ICD 9 and new ICD 10 code 780.03) when 9% out of 78 patients had mistaken diagnosis [59, 60]. In *Germany* (Hannover and Münster areas), a prospective-controlled multicenter study showed al posttraumatic incidence of 0.13/ 100.000 in-patients/year out of 6.782 acute TBI in adults while it was zero for children within the first year in 2000/2001 [15].

Assessment

[2, 4, 18, 22–26, 30, 32, 37, 41, 43, 48, 50, 51, 53, 60, 60, 67, 69, 71, 85, 116, 127, 130]

Neurobehavioral Assessment (Task Force Consensus on Best Practice)

Full Stage AS (Table 1, [3, 4])

This is a separate entity, characterized by the classical symptoms and signs of *wakefulness without awareness of self and environment* and related to signs and symptoms of functional disinhibition of the upper brainstem. Regarding the reported high level of AS/VS misdiagnosis [127–129] we would like to suggest a practical education in AS management for at least three years like in other sub-specialities. This should qualify the doctor too to furnish the expert opinion concerning the right diagnose of a (permanent) AS full stage and early remission stages [6, 14, 54, 67, 69, 72, 132–135]. Detailed assessment is important if the reported high level of misdiagnosis is to be avoided [127, 67–69]. Evaluation needs a considerable amount of time, measured in weeks rather than hours, and during different day times, if varying levels of function are to be identified and correctly classified on a special questionnaire. The ability to generate a behavioural response fluctuates from day to day, hour to hour, and even from minute to minute. Sampling of spontaneous behavior, structured intervals with the aid of care staff and/or relatives is important. Continuous documentation of patient's functioning on special charts, of all interventions, laboratory tests, medication, and secondary complications is essential. For physical and mental-cognitive neurobehavioral assessment we recommend best performance as assessed by all team members of the German coma remission scale (CRS) that was the one best able to detect subtle changes and fluctuations in neurobehavior and which is used by all task force members (Table 3). For later recovery states, the early Barthel index and the FIM have shown complementary results (see also [121, 131, 132a]). *The SMART* (Sensory Modality Assessment and Rehabilitation Technique) is widely used in the UK and many

parts of Europe and has been the method used to detect that as many as 43% of patients thought to be in the VS were actually aware [67–69, 133–137]. There is a lot of merit too in the Royal College of physicians concept of what is required and what is compatible with the VS diagnosis [37].

AS Remission Stage (Table 2 [3, 4])

Recovery from AS is defined as the ability to establish visual and or oral contact with the outer world (surrounding environment) and to reproducibly obey meaningful commands.

First signs and symptoms of AS remission stage (= 80% of full stage AS) that is known as awakening without awareness are *spontaneous eye movements and focusing, eye tracking* (with or without turn of the head in the direction of sudden noise or movements). Thereafter, the patient becomes regularly able to follow reproducible simple commands in a predictable manner while recovering consciousness.

Laboratory Investigations

Up to now there is no single AS specific laboratory parameter available that can be recommended for diagnosis and/or prognosis [2, 14, 26, 30, 31, 36, 37, 50, 53, 100, 138, 157].

Electrophysiology

SSEPs, event-related potentials, and conventional cortical electroencephalogram (EEG) recordings are recommended as routine laboratory investigations for early assessment and monitoring of recovery while pharmaco-EEG studies are still experimental. EEG was found to be not specifically helpful in assessing AS stages and prognosis because of the wide range of abnormalities during full stage AS and remission stages [13]. EEG shows the typical sleep–wake cycles. Computerized EEG analysis and pharmaco-EEG were demonstrated to provide some prognostic information when the arousal effect obeyed as desynchronization with shifting of the power spectra to faster frequency bands *may proceed clinical restoration* of consciousness for weeks and even months (on class II evidence A [2, 16, 131, 138, 147]). Somatosensory evoked potentials have been proposed as acceptable predictor of output in the early phase of coma and AS with a higher predictive value above 90% compared to EEG reactivity in two thirds comparable to GCS (class 2 evidence) [17]. Differently from post-anoxic, in post-traumatic coma the presence of normal SSEPs, has a favourable predictive value both for awakening and disability [82]. Median nerve SSEPs correlate with outcome in hypoxic AS cases (Binder H and Saltuari L, unpublished data). Laureys et al. in a PET study on patients in full stage AS, recorded a cascade of functional disconnection of auditory evoked potentials along the auditory cortical pathway, from the primary auditory area to parietal associative and limbic areas, when the primary auditory cortex was activated by appropriate stimulation and a brain stem response was recorded [83, 140–142, 169].

Kotchoubey et al. [139] observed P 300 responses in 14 AS patients and 19 cases of minimal responsiveness. Recently in a large non-selected sample of VS patients he demonstrated habituation of the N1 in a group of VS patients indicating for the first time ever elementary learning process in VS [140]. He too showed evidence of cortical learning by analyzing the N1 amplitude decrement in a large non-selected sample of VS [143]. Schoenle et al. [87] tested the existence of cognitive capabilities in AS by using the N-400 ERPs paradigm and reported significantly more intact semantic capabilities (= 76.7%) for brain injured "near AS" than AS patients (12%).

Neuroimaging

No current diagnostic methods for functional assessment permit long-term prognosis being made on a single finding during AS full and remission stages. Cranial computerized tomography (CCT) and functional magnetic resonance imaging (MRI) have become the gold standard, when available. We recommend central activating drug PET and/or SPECT studies for selected cases [144, 146, 147].

CCT and MRI have proved to be of high diagnostic sensitivity but without any AS specificity for demonstrating brain pathologies, e.g., brain atrophy and diffuse axonal injury (DAI) secondary to shearing injuries. Primarily bilateral brain lesions within the upper brainstem, pons, and mesencephalon in early MRI imaging have shown to be of significant prognostic value. Promising new developments of functional MRI studies demonstrate a residual functional capacity in VS and minimally conscious patients (MCP) to activate large integrative networks. Data from Laureys laboratory [83, 84] did not allow differentiating AS from MCP by overall decreased cerebral metabolism, but fMRI studies with the aid of a simple auditory activation paradigm made this possible when each and every of five MSP demonstrated a more widespread activation than did any of the 15 AS patients.

PET and SPECT cerebral blood flow (CBF) studies on cerebral metabolism in AS have revealed a 40– 50% reduction of normal values [84]. Pathophysiology showed that coma could be assumed at a persistent flow rate below 20 ml/100 g per minute that provokes definitive cortical cell loss and atrophy. Reduced CBF in AS patients, mainly in the basal ganglia and mesencephalon, was demonstrated [32]. Fluor-Glucose–PET studies before and after pharmacological stimulation can demonstrate the extent of functional metabolic brain damage and CFB in AS full and remission stages. Recent PET studies have indicated that some AS patients are unconscious not just because of a global loss of neuronal function, but due to an altered activity in a critical fronto-parietal cortical network and the abolished functional connections within this network and with nonspecific thalamic nuclei. Recovery of consciousness is dependent on restoration of this cortico–thalamo–cortical interaction (Literature see Laureys). Kanno et al. [146] used CBF and PET studies for intravenous drug stimulation tests to activate brain metabolism of comatose and VS patients secondary to hypoxic brain damage. FES spinal cord stimulation is only indicated that in the case CBF is > 20 ml/100 g per minute and PET or SPECT show an increase of brain metabolism after stimulation [88–90, 96, 97, 146, 147].

Neurorehabilitation

The spectrum of neurorehabilitation comprises the ongoing chain of interventions by an interdisciplinary team that should start immediately after the acute impact on the brain and is aimed at patients' reintegration [2, 6, 14, 31, 39, 42, 44, 45, 61, 63, 64, 66, 98–100, 134, 135, 137, 149, 156].

Medical Treatment

In neuropsychiatry, there is no specific drug therapy pharmacologically to be recommended for attention and arousal of patients in AS full and remission stage. Medical treatment has to be prophylactic and symptomatic according to the individual situation. Pharmacological interactions of drugs, side effects on brain metabolism, and recovery of functioning as well as complications should be known and avoided (neuroplasticity and body functions). In general, arousal is generated by the reticular activating system (RAS) which provides a background excitatory tone for the CNS. While sedatives depress stimulants increase the activity of the RAS. Acetylcholine (ACh) norepineh-

Table 1. Apallic syndrome full stage (modified from Gerstenbrand [3] and the Royal College of Physician Working Group 1996).

1. *Four clinical criteria all to be fulfilled* (characterized by signs and symptoms of disinhibition of the brainstem, comparable with the neurophysiological status of a newborn): No evidence of awareness of self or environment. No volitional response to visual, auditory, tactile, or noxious stimuli. No evidence of language comprehension or expression. Cycles of eye closure and opening simulating sleep and waking (sleep–waking condition such as in the new-born)
2. Sufficiently preserved hypothalamic and brain stem function to maintain respiration and circulation
3. The eyes are in divergent position can neither focus objects nor follow them; blinking reflex positive; diameter of pupils changing (enlarged–diminished); retained pupillary response to light; oculo-cephalic reflex – doll-head phenomenon – partly positive
4. No nystagmus but conjugate or disconjugate tonic response to caloric testing. No visual fixation, tracking of moving objects with eyes or response to menace
5. Decerebrate positioning (brain damage of internal capsule affecting the corticospinal tracts) with adducted upper limbs and flexed position of arms, palms, and fingers, and flexed – extended position of both legs, with plantar flexion of the feet and stretched position of the trunk, spastic increased muscle tonus (rigido-spasticity). Stereotype movements with lack of spontaneous and meaningful finalizing movements of face, limbs, and trunk. Maybe occasional movements of head and eyes toward sound movement, and trunk and limbs in purposeless way. Decerebrate body position (midbrain syndrome) spasticity with upper limbs extended in adduction and hyperpronation and the lower limbs extended with plantar flexion of the feet
6. Demonstrate primitive motor patterns such as chewing–suckling automatism (spontaneous and elicitable by stimuli), and may have oral and rasping reflexes, musculus mentalis reflexes, startle myoclonus, tonus regulating reflexes (symmetric, asymmetric neck reflex)
7. Disinhibiting of the autonomic regulating system that may provoke primitive emotional reactions and mass movements of trunk and limbs which are accompanied by vegetative reactions
8. Swallowing reflex may be preserved in most patients
9. Grimace to pain. May have roving eye movements
10. Incontinence of bladder and bowel. Spontaneous blinking and usually retained papillary and corneal responses to ice-water caloric testing; cilio-spinal reflex positive

Table 2. Innsbruck AS remission scale (eight phases when emerging from full stage [3]).

1. Optical fixation, primitive emotional reactions minimal differentiated, motor primitive patterns diminished
2. Optical tracking: differentiation of emotional reactions, aim directed on motor primitive patterns, mass movements partly directed, diminishing of the flexed stretch position, spastic and Parkinson's symptoms observed
3. Obeying simple commands; emotional reactions responding to the situation (positive and negative), organized primitive motor patterns; grasping reflex and oral reflexes (initial Klüver Bucy symptoms); patient accepts oral feeding; beginning of finalized movements,
4. Klüver Bucy full syndrome: grasping, bringing the object to the mouth without recognizing the object, interest in the genital region, react to simple orders, primitive sounds
5. Post-Klüver Bucy phase: residual arm flexion and lower limb flexion-extension movements of head, trunk and extremities become more finalized, simple words are produced
6. Korsakow syndrome, somnolence, residual spasticity and extrapyramidal symptoms and primitive motor patterns present, first going practised
7. Amnestic psychosyndrome, residual motor disturbances, residual primitive motor patterns
8. Organic psychosyndrome with local and diffuse neurological deficits

The defect (end-)stage is characterized by more or less local, regional and diffuse deficits of higher cerebral functioning

rine (NE), dopamine (DA), and serotonin (5-HT) are all involved in this system as major neurotransmitters (limbic system = emotion and RAS = arousal contribute jointly to overall arousal levels and attention). In the treatment of neuro-psychiatric, -psychological deficit syndromes, in addition to unspecific catecholaminergic psychostimulating agents, in particular dopamine agonists, are successfully applied. While there is little evidence that any medication can help the person to emerge from the AS full state condition clinical experience suggests that there may be some response from neurostimulants, doperminergic, or antidepressant medications for those in the minimally consciousness state [148, 149]. Administered in sufficiently high doses, bromocriptine, and pergolide have been shown to have a particularly favorable effect in patients with deficits of a pronounced psychomotor character, meaning, that these appear to be particularly indicated in connection with a lack of drive and apathy. Sympathicomimetic drugs such as amphetamine would have the same effects as a cholinergic blocking agent in disinhibiting or releasing the inhibited behavior. In several studies, reversal of permanent-appearing behavioral loss had been provoked by amphetamine injection. Amphetamine, as a typical psychopharmalogical stimulant compound, releases the monamines noradrenaline, dopamine, and serotonin from presynaptic terminals and inhibits their reuptake from synaptic cleft with secondary alleviation of injury-induced functional depression of structures remote from the injury site (diaschisis) [16, 98, 149, 151, 151]. The senior author has used successfully amphetamine for arousal of comatose and AS individuals between 1965 and 1990 when it was no longer licensed in Germany so that is was replaced by weaker amphetamine drugs [166]. The effect of pyritinol is attributable to a pyritinol-induced release of acetylcholine at the synapses within the mesencephalic structures and to an increased cortical postsynaptic reaction of the cholinergic system [131, 147]. In [63], von Wild reported for the first time on the unexpected neurobehavioral arousal effect Botulinum toxin A application for the treatment of central neurogenic spasticity in 5 out of 12 subjects who were in full state AS for several weeks and months secondary to severe TBI or stroke, despite intensive early neurorehabilitation interventions. Ten days after the first (single) local intramuscularly application of 200 MU Btx (upper and lower limbs) 5 out of 12 subjects regained awareness and later on consciousness that was measured with aid of the coma-remission scale (CRS) when the score improved (permanently) from 9 to more than 18 points [151]. This pharmacological effect may be explained either by blocking and release of peripheral pain in the treated limb or by direct central effect to the RAS system due to an influence to the cholinergic system with an increase of local cerebral blood perfusion, as it was demonstrated to happen during Kanno's direct spinal cord stimulation. For more details, we refer to pharmacological textbooks.

Early Neurological–Neurosurgical Rehabilitation

Following the German task force Guidelines for ENNR [14, 61, 99, 108, 115, 141, 151], we recommend the establishment of special units for AS early rehabilitation (15–20 beds each) on a population based incidence of 2/100.000 to support (spontaneous) recovery and to quicken restitution of impaired higher cortical functioning, preserving and supporting brain plasticity and – at the same time – to prevent secondary and tertiary complications. Staff, equipment, and room requirements and therapeutic interventions needing a multi

disciplinary team approach are described elsewhere in detail [6, 61–64]. For AS patients who do not recover from AS full stage or early remission stages despite all rehabilitative efforts over 3–6 months, activating nursing care is indicated depending on the consultation of the treatment team and the relatives after careful information and explaining the given situation. Nursing at home and during home care has to provide ongoing physical and mental-cognitive therapies for activation of partly or completely dependent, disabled subjects of AS full or early remission end stage to maintain patient's personal dignity and hygiene [24–29, 53–57]. These patients, provided they do not suffer from progressive neurological brain damage AS, should have the legal right to be reassessed for functional recovery on an ENNR basis. The follow-up should be every 6 months after patient's discharge for about 3 weeks each until 3 years from the event. It was demonstrated that AS patients after acute brain damage may need 3 to 6 and up to 12 months of ENNR treatment. Secondary, tertiary, and quarterly complications are frequent in AS after brain damage and hinder clinical remission by functional restoration. Biochemical emergency laboratory, one mobile X-ray machine, CCT should readily be available within 15 min transport. Therefore, we recommend to establish the ENNR unit either as part of a neurological or neurosurgical department or at a rehabilitation hospital that provides direct access and transfer of the patient to the X-ray, neurosurgical and general surgical and internal medicine departments, or guarantees on-call consultation service of all doctors that might be needed at all times [63, 108]. A therapy room for medical interventions is needed for example for local Botox R application, phenol injections and casting [14, 61, 110, 151].

It must be stressed that up to now there is no class II or III evidence proving the effectiveness and efficiency of one single specific neurorehabilitative intervention to quicken and arouse awareness, consciousness, and higher brain mental-cognitive functioning in AS patients [42–46, 98, 100, 120–122]. ENNR cut-off point [61, 87] depends on the assessment of patient's best functional recovery as accepted for Germany. For ENNR of AS patients, we recommend a CRS (Table 3) sum score of 24 points (maximal score) together with an early rehabilitation Barthel index of + 40 points. Patients with CRS sum score of 10 points over 6 weeks were demonstrated not to recover from functional impairment in the long run [15, 115]. Younger AS patients after brain trauma have been shown to have a better outcome than older and non traumatic cases [2, 4, 15, 18, 19, 26, 37, 111, 153, 154]. ERBI was first described by Schönle [156]).

The Impact of the Cause on the Outcome

In the current literature, a ratio of one-third posttraumatic to two third nontraumatic AS cases (with > 70% cerbrovascular and one-fifth anoxia/hypoglycemia cases is reported [2, 37]. New figures that were carefully reassessed by AS expert H.B. and his co-workers [15, 59, 60, 155] showed an in-patient prevalence (intensive care or ENNR, hospital, and nursing homes) of roughly 25% posttraumatic cases, 50% nontraumatic, and about 25% AS suffering from progressive brain damage [91]. These data are in line with the figures recently reviewed and reported by Jennett [37] and Dolce et al. [2] in 2002.

Diagnosis and Assessment

Brain Pathology

We would like to refer to publications of Adams et al. [21, 75, 76], and Ule et al., p. 104, Jellinger, p. 88, Grcefic, p. 109, Peters and Rothemund, p. 78, Gerstenbrand, p. 82, in Dalle Ore [106], Jennett et al. [11, 37] and also to references [8, 10, 105, 116, 117, 123, 158, 164, 176].

The comparison by Adams et al. of 35 posttraumatic with 14 nontraumatic AS patients who had survived for at least 1 month after the impact on 80% showed abnormalities in the thalamus after TBI. Of those who survived some 3 months after TBI, 96% had thalamic damage and only 14% had brain stem damage [91]. In ischemic-hypoxic cases analyzed by Adams, extensive necrosis was present in the cerebral neocortex almost always in conjunction with thalamic damage because of the selective vulnerability of the gray matter in the cerebral hemispheres. But in some cases relative sparing of the cortex was found with the main damage in the thalamus and corpus callosum. In traumatic cases the dominant lesion is diffuse damage to the subcortical white matter (diffuse axonal injury, DAI). DAI was first described by Strich in 1956 as the result of shearing forces. This was subsequently confirmed by Adams et al. in experimental studies in nonhuman primate as a primary lesion by nonimpact angular acceleration of the head without secondary hypoxia or ischemia having occurred. Adams et al. [75] coined the term DAI and defined three grades of severity of the lesions in humans (1989). Jellinger and others claimed that this type of brain damage in AS patients is secondary to hypoxia and ischemia because of high intracranial pressure.

Table 3. Coma remission scale (CRS) (German Task Force of Neurological–Neurosurgical Early Rehabilitation 1993/2000; von Wild 2000) [6].

Front page **Patient name:**

Date:	
Investigator (initials):	

1. Arousability/attention (to any stimulus)

Attention span for 1 minute or longer	5	
Attention remains on stimulus (longer than 5 sec)	4	
Turning towards a stimulus	3	
Spontaneous eye opening	2	
Eye opening in response to pain	1	
None	0	

2. Motoric response (minus 6 points from max. attainable sum if tetraplegic)

Spontaneous grasping (also from prone position)	6	
Localized movement in response to pain	5	
Body posture recognizable	4	
Unspecific movement in response to pain (vegetative or spastic pattern)	3	
Flexion in response to pain	2	
Extension in response to pain	1	
None	0	

3. Response to acoustic stimuli (e.g. clicker) (minus 3 points from max. attainable sum if deaf)

Recognizes a well-acquainted voice, music, etc.	3	
Eye opening, turning of head, perhaps smiling	2	
Vegetative reaction (startle)	1	
None	0	

4. Response to visual stimuli (minus 4 points from max. attainable sum if blind)

Recognizes pictures, persons, objects	4	
Follows pictures, persons, objects	3	
Fixates on pictures, persons, objects	2	
Occasional, random eye movements	1	
None	0	

5. Response to tactile stimuli

Recognizes by touching/feeling	3	
Spontaneous, targeted grasping (if blind), albeit without comprehension of sense	2	
Only vegetative response to passive touching	1	
None	0	

6. Speech motor (logomotor) response (tracheotomy = 3 if lips can be heard to utter guttural sounds/seen to mime "letters")

At least one understandably articulated word	3	
Unintelligible (unarticulated) sounds	2	
Groaning, screaming, coughing (emotional, vegetative tinged)	1	
No phonetics/articulation audible/recognizable	0	

Sum score:		
Max. Attainable score (of 24) for this patient		

Table 3 guidance (back)

1. Arousability/attention

5 pts: Patient can direct his/her attention towards an interesting stimulus for at least 1 minute (perceivable by vision, hearing, or touching; stimulus: persons, objects, noises, music, voices, etc.) without being diverted by secondary stimuli.

4 pts: Attention fixed to a stimulus for a discernible moment (fixation with the eyes, grasping, and feeling or "pricking up of ears"); patient is, however, easily diverted or "switches off".

3 pts: Patient turns to source of stimulus by moving eyes, head, or body; patient follows moving objects. Vegetative reactions should also be observed (patient capable only of vegetative reaction).

2 pts: Spontaneous opening of eyes without any external stimulus, e.g. in connection with a sleep-waking-state rhythm.

2. Motoric response

6 pts: Patient spontaneously grasps hold of held-out everyday objects (only if patient's vision function is intact, otherwise lay object on back of patient's hand). OR patient able to respond to such gestures with an invitational character only with a delay or inconsistently, yet adequately, due to paralysis or contraction.

Note regarding the following items (use of pain stimuli):

The pain stimuli must be applied to the various limbs and to the body trunk, since there may be regional stimulus-perception impairments; pain stimuli can take the form e.g. of a gentle twisting pinch of a fold of skin, pressure applied to a fingernail fold, tickling of the nose.

5 pts: Patient responds to pain stimuli defensively after localization, by a targeted and adequate measure, e.g. pushing away, sweeping motions of the hand, etc.

4 pts: The patient should be seated upright: tests for the sense of balance and/or posture by slight pushes applied to the body (corrective movements of trunk or extremities).

3 pts: Untargeted withdrawal from pain stimulus or merely vegetative reactions (tachycardia, tachypnea, agitation) or increase of spastic pattern.

2 pts: Strong, hardly resolvable flexion, especially in the arms/elbows. Legs may stretch out.

1 pt: Typical "decerebrate rigidity" with spastic extension of all extremities, in many cases opisthotonus (dorsal overextension/hyperlordosis).

3. Response to acoustic stimuli (tests as a rule to be carried out beyond patient's field of vision !)

3 pts: Patient can recognize voices or music, i.e. he/she is able either to name the stimulus or to react in a differentiated manner (e.g. to certain pieces of music or persons with pleasure or defensively).

2 pts: Patient only opens eyes, fixates or turns to source of stimulus with his/her head, in some cases accompanied by emotional expressions such as smiling, crying, ...

1 pt: Rise in pulse and/or blood pressure, perspiration or agitation, excessive twitching of the body

1 pt: Rise in pulse and/or blood pressure, perspiration or agitation, excessive twitching of the body, slight triggering of eye blinking.

Note: Similar to the procedures applied when testing the motor responsiveness by the application of pain stimuli, the use of a clicker held directly next to each of the patient's ears (bilateral testing) suggests itself as the relatively strongest non-pain-involving stimulus for items 1 and 2; if the response is positive, the patient can be assumed to still be in possession of his/her hearing and the stimuli can be made more manifold.

4. Response to visual stimuli (must be presented without speaking or any other form of comment)

4 pts: Patient recognizes pictures, objects, portraits of familiar persons.

3 pts: Follows pictures etc. with the eyes without any sign of recognition or questioning, inconsistent recognition.

2 pts: Fixates moving pictures or objects without being able to follow them properly, or when picture/object moves outside patient's field of vision patient makes no attempt to keep track.

5. Response to tactile stimuli

3 pts: Patient capable of feeling and recognizing objects, hands of other persons, etc. even if his/her sense of vision is absent and the objects must be placed on the skin/in the hands; adequate response to stimuli in the area of the mouth/face (edible/inedible, e.g. response to a kiss).

2 pts: Touches, feels, and grasps targetedly, but without an adequate reaction.

1 pt: Unspecific response to stroking and touch (vegetative signs such as agitation, raised pulse).

6. Speech motor (logomotor) response

3 pts: Patient is capable of expressing an intelligible word, even if this is not related to the context or situation. Names also count as words here.

2 pts: Patient utters unintelligible sounds, e.g. slurred, also repetition of syllables or similar ("ma-ma", "au", ...).

Total score: In the event that certain channels of sense or motor systems are completely absent ("blind", "deaf", "plegic"), the point scores of the respective category must be subtracted from the maximum attainable score, e.g. 12/21 points instead of 12/24 points.

Neuroimaging (= living brain pathology) demonstrated new important findings as reported by the group of Firsching [124–126]. The authors observed from early traumatic brain lesions as demonstrated by early MRI after acute TBI in 175 children and adults (prospective study) that 98% of patients within bilateral pons lesions died and no single victim regained consciousness. One half of patients with bilateral mesencephalic lesions became apallic but without bilateral mesencephalic lesions no single TBI became apallic if recovery was otherwise possible. So it can be concluded that bilateral mesencephalic lesions are typical brain lesions in AS pathology.

Early Functional Assessment

The model of attention functions, as described by Mateer et al. [187, 188] became widely accepted. They divided attention into the following five categories. (a) Focused: the abilty to respond directly to specific stimuli; (b) sustained: the ability to maintain a consistent behavioral response during continuous and repetitive activity; (c) selective: the skill to maintain a behavioral or cognitive set in the face of competing stimuli; (d) alternating: the ability to shift focus of attention and move between tasks; (e) divided: the ability to respond simultaneously to multiple tasks. Having this in mind the careful assessment of functioning on a regularly basis (in the beginning 10 to 14 days, later on every 3–4 weeks) and documentation on special charts is a precondition for quality management of AS full and remission stage patients. The conscious interaction between the patient and the observer that is required in conventional neurological neurobehavioral examination is lacking in early AS stages. For functional examination the patient should be supine and undressed. The alignment of the body and head and the positioning of the limbs are observed. Hyperextension to opistotonus of the head and trunk are rare, whereas flexion of the head and upper body or lateral deviation of the head is more frequent. Each limb or pair of limbs can assume its own posture when the upper limbs are mostly flexed (decorticated posture) or seldom hyperextended. Lower limbs are mostly hyperextensive, but flexion is not exceptional. None of these postural positions have particular prognostic value and can revert completely within 4 months of AS. In contrast, tonic and postural disturbances may become permanent after this period. It is necessary to observe and to describe all spontaneous and evoked segmental movements. Observation of passive mobilization of limb segments and joints allows evaluation of the muscular tone, increasing spasticity, and the identification of complications, for example, shortening of tendons, blocked joints, and pathological ossification and bed sores. Behavioral examination of the AS patient requires attention, dedication, and experience in the observation and interpretation of every sign potentially conveying relevant information (see also [2–4, 28, 30, 37, 94, 104]). We recommend CRS (Table 3) as an assessment tool of choice during early functional recovery, for example, in combination with the EFBI, disability rating scale (DRS), functional independence measure (FIM), and Loewenstein communication scale (LCS) [2, 15, 19, 24, 26–30, 32, 35, 37, 43, 53, 67, 67–71, 94, 110, 112, 113, 119, 120, 130, 151, 157–159].

Restoration of Impaired Functioning

Gerstenbrand described a continuum model through a series of levels or phases that can clinically be defined [3, 4, 9]. In addition a number of discrete syndromes with specific patterns of recovery are known. Three neurological signs and symptoms have been identified by Quintieri et al. (2001) to be significant for a remarkable prognostic value predicting a favorable outcome from AS: the temporal development of spontaneous movements, disappearance of oral automatism, and eye tracking [2]. Analysis of prospectively collected data of monitored incidence and relevance of neurological signs in 70 patients every 14 days during the phase of remission from posttraumatic AS showed that if eye tracking and spontaneous mobility occurred, while oral automatism disappeared, in at least 75 days after TBI, this turned out to be a strong prognostic sign for a favorable outcome. About one-third of patients were discharged home being able to resume work or educational level. A moderate to severe degree of disability persisted in about 30% of AS in whom these signs had appeared late, e.g., more than 150 days after TBI. No recovery of consciousness occurred when no spontaneous mobility or eye tracking occurred and oral automatism was still present more than 200 days after trauma. A branching tree along with different sub-categories a patient may pass shows recovery in different domains [2, 3, 9, 18, 30, 32–34, 37, 41–51, 54–58, 67–72, 85–87, 92, 95, 96, 102–104, 107–112, 112, 112, 114, 118–122, 127–130, 137, 143–145, 148, 154–159, 166, 169].

Secondary, Tertiary, and Quarterly Lesions (Complications)

Literature in general deals with main risk factors of patients suffering from severe brain damage during ICU treatment [2, 6, 15, 53, 59, 61, 108, 157, 177, 179,

186]. There is no specific management that can be recommended for AS patients at any stage regarding causes, treatment, and prevention of complications, mainly infections (respiratory tract and urinary tract infections, especially nosocomial infections). Prevalence of ICU acquired infections is listed elsewhere [53, 61, 177, 179]. Central venous and pulmonary artery catheter, urinary catheter, gastric stress ulceration prophylaxis, tracheotomy, increased length of stay (nosocomial infections increase length of stay), and negligence of hygienic standards among nursing staff are well-known risk factors to be prevented by special care. Management of spasticity follows the general rules of neurological diagnosis and treatment. Tertiary complications are known as tracheostoma, hydrocephalus, local changes of intracranial pressure and/or regional CBF (secondary to brain atrophy and large cranial skull bone defects), hypothalamo-pituitary hormonal insufficiency, and autonomic disorders (vegetative storm and dysautonomia). Periarticular ossifications (periarticular new bone formation P.N.B.F.) and pressure source, frequently observed in older times, are rare now, thanks to careful nursing and physiotherapy under chemistry lab controls [53, 56], while others like Sazbon state that the lab controls are not useful in this complication of AS. Sazbon et al. [103] published a natural history of P.N.B.F and stated that the appearance of this phenomenon is not so rare, appears in up to 70% of the patients. They concluded that it could be that the differences in the percentages from authors occurs due to different methods of research as most authors do a transversal cut of time, while they used periodical X-ray examination of all great 8 joints during 3 years [103].

Parkinsonian syndrome, as considered by Gerstenbrand [3, 10], is an obligatory phase during recovery from AS but in the Anglo-American literature is not generally recognized as posttraumatic extrapyramidal symptom. In Europe it refers to TBI survivors with DAI, a neuropathological pattern similar to that of vascular or encephalitic parkinsonism [116, 117], while in the Anglo-American literature reports are mainly on focal brain injury after TBI which only rarely cause a Parkinson-like syndrome [22–25, 37]. Swallowing disturbances are not specific but a major problem for all AS patients [53, 56]. Therefore, early percutaneous endoscopic gastrostomy (PEG) is recommended to guarantee appropriate hypercaloric nutrition (40–60 cal/kg/day and protein supplementation) and fluid balance. The interval between acute brain damage and recovery to first oral feeding was described to have some prognostic value [2, 7, 9, 31, 37, 53–56, 106–108, 114, 155, 157, 162, 163, 177, 179, 186].

Outcome

Probability of Outcome

Most AS patients regaining consciousness do so within the first 6 months [2, 37]. The American Multi-Society Task force has analyzed data of 754 cases who were *vegetative* at 1 month with 1 year follow-up from the English language literature, separately for traumatic and nontraumatc cases (class III evidence). Nontraumatic cases less often recovered, among these the hypoxic cases did worse than others. Children, especially after TBI, did somewhat better. Of the whole series 43% regained consciousness, ranging from 62% for TBI children to 13% nontraumatic children. The highest independence recovery rate was in children after TBI (27%) the lowest in nontraumatic adults (4%). Probability of various outcomes after 1 year was calculated for TBI cases as dead for 33% of adults and 9% of children who were apallic for 1 month while for nontraumatic cases figures were 53% and 22%, respectively. Thereafter, the rate of recovery decreases to 7–11% in adults and 17–22% in children [47, 111, 154]. Late recovery of a few AS/VS patients after 2 years and even later has been reported [24, 37, 50, 51]. Sazbon & Grosswasser did not find a significant statistical correlation between the initial Glasgow coma scale score and conscious recovery of vegetative patients when recovery of conscious was defined as the state where the patient maintains clinical relationship with the examiner either by visual, verbal, gestual, or motor contact. The influence of patient's age, cause, and duration of AS/VS on the recovery of consciousness and independence (GOS 4 and 5) or irreversible AS and death were clearly demonstrated by the American Multi-Society Task Force on PVS (1994). Concerns about the uncertainty of AS outcome is reflected in the European inquiry of over 2000 doctors in seven countries where 17% were very or quite confident of the ultimate outcome in less than 3 months, but 38% in 4– 6 months [35].

The reliability of CRS at day 40 of ENNR as a prognostic tool for the recovery of consciousness and independence over time was demonstrated by the senior author's group in a partly prospective analysis of GOS of 240 adults TBI between 6 months and 5 years after trauma (mean 26 months). Initial GCS was 8 or less in 66% of the cases, 15 (= 6%) were in AS stage at time of discharge. Only 1 out of 15 cases improved from GOS 2 to GOS 3, while 3 patients died and 11

remained in unchanged AS [108, 115]. All patients with fewer than 10 points CRS score on day 40 of ENNR reached GOS levels 1 and 2 only. No patient with a CRS sum score lower than 20 points on day 40 achieved GOS 4 or 5, while all patients with CRS (maximal) sum score of 24 points proceeded to a favorable independence of GOS 4 and 5. (1) Of the German prospective study of 6.783 acute TBI, only 258 patients (= 3.8%) received neurorehabilitation, 100 as ENNR (= 3.9%). Early GOS at the time of discharge was 1 = 4%; GOS 2 = 2.7%, GOS 3 = 37.3%, GOS 4 = 26.7%, GOS 5 = 29.3. The dynamic of functional restorations over time was demonstrated after 1 year when GOS 1 = 1.2%, GOS 2 = 1.7%, GOS 3 = 21.8%, GOS 4 = 36.2%, and GOS 5 = 39.1. (2) Stepan et al. [89, 105] reported an incidence of AS of all causes for Austria (Vienna region) of 1.9/100,000 AS, Thirteen patients (= 41%) were treated in acute care units (2 after TBI, 11 nontraumatic secondary to cardiac arrest (3), myocardial infarction (2), strokes (2), hypovolemic shock and status asthmaticus (2 each), and 2 cerebral hemorrhages) while 19 were in nursing homes (5 after TBI, 14 nontraumatic AS being myocardial infarctions, cardiac arrest, intoxications, drownings, and cerebral hemorrhages).

The shift in etiology from traumatic to nontraumatic AS causes of 1:4 to 1:5 in the series of Stepan et al. [56, 59, 60] is remarkable (class 2 evidence). Neurological signs that occur 6 months after the beginning of AS, for example, rabbit-snout, halfmoon pucker mouth, and Klippel signs never disappear and are a bad prognostic indication for the functional restoration of consciousness. This was recently confirmed when Dolce and Sazbon prospectively analyzed all neurological signs and symptoms with respect to 1 year outcome of 350 AS after TBI: up to 70% of patients regained a certain degree of consciousness and after 1 year one half of them finally reached GOS 4 and 5 while 20% were GOS 3, 10% = GOS 2 and 10% = GOS. But when compared to the nontraumatic AS group, 30–50% of apallic patients died (= GOS 1) and only 15% survived as GOS 2 while more than 30% reached GOS 3, and only 7% = GOS 4 or 5 (unpublished data).

Life Expectancy: Late Mortality

The survival of 10 and even more than 20 years is reported by the task force who calculated the probability of survival for more than 15 years as to be very low in patients vegetative at 1 month (less than 1 in 15,000–75,000) [37, 57, 58, 150].

One-third of the Multi-Society Task Force AS patients, apallic at 1 month after acute brain damage died within the first year. Mortality rate of AS cases 1 year after the impact has been found to increase by 8% for each extra year of survival between 1 and 10 years by reviewing 1000 AS cases [47]. Strauss et al. addressed the issue of different views with regard to mean life expectancy and median survival time (by which half of the patients will have died). For example, 15-year-old patients with AS for 1 year have a mean expectancy of 10.5 years but a median survival of only 5.2 years. However, if still vegetative after 4 years, these figures are 12.2 years and 7 years, respectively. Tube feeding increased the mortality of AS patients by 2.5 times. It is the latter that concerns lawyers in civil courts working to the "more probable than not" standard of proof, as Jennett [37] stressed. Outcome of disabled TBI patients between 5 and 21 years of age, 23% of whom had been followed over 5 years and more, was also analyzed by Strauss et al. in 1998, including the 21 AS cases that were found not to differ in life expectancy from the 109 others who were also immobile and tube fed at 6 months after TBI. For such male patients at age 15, remaining life expectancy was estimated to be 15 years as for a normal individual of 58 years. Comparing life expectancy with regard to physical mobility of AS children and those minimally conscious, Strauss et al. [111] observed for both groups – both were immobile – the same survival time for 8 years (65% and 63%) but it was significantly longer for minimally conscious children (81%) who were somewhat mobile.

We accept the statement of Jennett [37], who estimated that the probability of long survival should increase in those who survived the first year by four times in all cases and by five times in posttraumatic AS [150].

Stimulation Techniques

Up to now there is no single specific drug or physical or technical stimulation technique to be recommended for the management of AS patients that guarantees recovery of consciousness, mental cognitive, and/or motor functioning [82, 148, 149, 169]. Sensory regulation, a more relevant concept than sensory stimulation, is applied as described in text books for neurological–neurosurgical ICU and ENNR treatment of patients after severe brain damage in form of (1) environmental stimulation and (2) structured stimulation [6, 15, 61, 68–72, 150, 161, 169, 170]. Activating nursing is the fundamental form of therapy in ENNR. With the help of basal stimulation by touching and posturing, the

patient's perception of his body and motions in connection with personal hygiene and when being dressed are enhanced in the sense of training active daily living (ADL). Bringing the patient in an upright and standing position (tilting bed/table) is a highly intensive central acting stimulus influencing arousal reactions. It has been demonstrated that in normal individuals, a neural system can be "dishabituated" by exposure to an alternative stimulus or a more intense stimulus, either in the same or in a different modality. He found significant changes after multimodal stimulation in some of his patients. The group of Dengler [167] showed that pathological cognitive processes after TBI (GCS > 3) can be improved by proprioceptive passive stimulation of the left forearm as demonstrated by shortening in the choice-reaction-time task latencies and amplitudes of the P 300 ERP component in patients with severe TBI when compared with healthy controls. Furthermore, foot sole stimulation that was first described and used in Russian space medicine can enhance awareness and cognition and may help to prevent bed rest inactivity atrophy of the muscular system of AS patients (F.G., personal communication).

Programs are directed at all five senses in a labor-intensive, systematic fashion [98]. The windows of potential responsiveness in AS are often short and can easily be missed. If any, a consistent program of specific stimulation should be used by all staff members and relatives to prevent over-stimulation. Reports of functional electrical stimulation (FES) to enhance awareness and consciousness are promising for some selected cases [39, 42, 44, 86, 88, 90, 93, 98, 100, 122, 143, 143, 145, 152, 160, 161, 168, 172].

Neurologic Music Therapy

Neurologic music therapy (NMT) is now recommended as regular rehabilitative intervention for patients in AS full and remission stage on a class 3 evidence [6, 61, 161, 170]. Thaut [160] suggests cognitive training through NMT by the application of his transformational design model (TDM) (for more details, see Thaut, pp. 192–3, Table 9.1) In general, music therapy is based on the belief that the self is more than a corporeal entity and that human beings are organized not mechanically but musically "in a harmonic complex of interacting rhythms and melodic contours", as Aldridge et al. [145] quoted. "Music therapy is the medium by which a coherent organization is regained, i.e. linking brain, body and mind". The music therapist aims at reaching the awareness of the patient that cannot be accessed through verbal communication. The music therapist improvises vocally to the breathing of the patient reflecting changes in intensity, tempo, and dynamics. This offers the patient a unique possibility to express his individual self. Music therapy on a two-patient basis and in small groups enhances personal and social integration following individuals' isolation and social withdrawal. Occupational Snoezel therapy aims at activation of sensual perception, practical experience of self-awareness and to induce relaxation and comfort (25–43 pp.) The senior author has shown on class IIA evidence (unpublished data) like others that during multisensorial stimulation the agitated patients can be calmed down and AS patients are aroused when they experience and enjoy the physical nearness and warmth of therapists.

Functional Electrical Stimulation (Class 2 and 3 evidence)

Hassler et al. have performed deep brain FES in AS full stage patients in 1969 [138]. Although a definitely effective modality of FES has not yet been established for treatment of AS full stage patients, deep brain stimulation (DBS), spinal dorsal column stimulation (SDCS), and median nerve stimulation have more and more often been performed over the last decade. Candidates have to be carefully selected. Laboratory electro-neurophysiological examination includes SSEP's and event-related potentials, trans-cranial magnetic stimulation (TCMS), and metabolic CBF studies [(CBF ‡ 30 ml/g/min), fSPECT scans (e.g., HMPAO Tc-99m single photon emission computed tomography) and 18 Fluor-Glucose–PETscan studies (positron emission tomography) of brain metabolism] [88–91, 146].

Deep Brain Stimulation

DBS might be indicated the patients with prolonged loss of consciousness extending over 3 months after acute brain damage. Yamamoto et al. [97] performed a prospective-controlled series of 26 cases (21 AS and 5 MCS) with DBS at 3 months after brain damage with a follow-up period of 10 years (class II evidence). In patients from 19 to 75 years (mean age 44 years), causes were nine cases each after TBI and after cerebrovascular insult and three secondary to anoxia. For chronic DBS by using chronically implanted flexible electrodes the selected target was the nucleus cuneiformis of the mesencephalic reticular formation that is located in the dorsal part of the nucleus ruber and ventral part of the deep layer of the superior colliculus in two cases of VS and the CM-pf complex by selection of the stimulating point in the nonspecific thalamic nucleus in another 19 VS individuals and 5 minimally

conscious state patients. Stimulation was given every 2–3 h for 30 min each during daytime. The frequency of stimulation was mostly fixed at 25 Hz, while the intensity was decided according to the response of each individual, being slightly higher than the threshold for inducing arousal response. Eight of 21 AS patients emerged from AS to obey verbal commands, but remained in a bedridden state except one. Four of the MCS patients recovered from the bedridden state and were able to enjoy life in their own home [171].

Dorsal Column Stimulation

Following Kanno's criteria [39, 88, 90, 146] that are based on class II and III evidence, dorsal column stimulation (DCS) might be an option for treatment especially for (1) relatively young patients (< 40 years), (2) patients with traumatic etiology, (3) patients without severe destruction of the thalamus and without marked cerebral atrophy on CT or MRI, (4) patients with CBF ‡ 20 ml/100 g per minute. Examination of regional blood flow (rCBF) during DCS with the aid of three-dimensional stereotactic region of interest template (3DSRT) was pre and postoperatively performed on 30 AS cases (8 after vascular, 13 TBI, 9 after anoxic brain damage). The CBF increase by 10% and more during DCS was observed in 25 of vascular, 38.5 of TBI, and 6% of anoxic group. SPECT, CT, EEG, and laboratory tests on catecholamine metabolism in CSF showed the effectiveness of therapy with a marked increase in J 3 CBF and CMRO2 during ongoing DCS and an increase in catecholamine metabolism and acethylcholine increase in CSF. Increased FDG metabolism and J 3 CBF increases were found with PET and SPECT in 42% but not in the remaining 58% of cases [171]. Kanno introduced dorsal column FES in 1985 for the arousal of AS patients. He and his coworkers up to now have treated 156 AS full stage patients at 6 months after acute brain damage (figures of 2005). The stimulation was inserted into the epidural space, midline reaching the stimulation to C2 level. The stimulation usually started at postoperative day 3 or 4. Stimulation was given for 10 h during daytime "until the time when the patient is recognized to be satisfactory improved" that is assessed having regained satisfactory awareness and meaningful repetitive reactions. Criteria for excellent response were showing meaningful response to verbal commands, speaking some meaningful words and oral eating by himself while the development of meaningful facial expression to painful stimuli, following finger movements of the examiner with his eyes and acoustic response to verbal commands with eye opening and closing was classified as a positive result. Stimulation was applied as following: amplitude 2.5–30 V, pulse width 120 ms, frequency 60 Hz, cycle on 15 min, cycle off 15 min RAMP 7 s [172]. Excellent responsiveness to DCS was observed in 43% of all cases. They were 62% TBI, no excellent but positive response in 32% after anoxic damage, 8% excellent, and 20% positive responses after cerebrovascular damage. Reports on the literature show 43–50% positive response using DCS [39, 88, 146].

Functional Electrical Right Median Nerve Stimulation (RMNS)

FES–RMNS was introduced by Cooper et al. [172, 173] in 1973 and is now recommended (class III A evidence) for arousal of comatose and apallic patients by increasing the brain blood flow and metabolism as it was shown by regional CBF studies and with the aid of biochemical analysis during stimulation therapy by means of increased central dopamine level and the regional concentration of Acetylcholine (Ach), a parasympathomimetical neurotransmitter substance in CSF and functional MRT within the area of the upper brain stem and basal ganglia [173]. In Cooper's prospective-controlled clinical study (class II evidence) on comatose TBI patients with the aid of battery powered, electrical neuromuscular stimulators trains of asymmetric biphasic pulses were supplied, delivered to the volar aspect of the right distal forearm over the median nerve surface rubber electrode measuring 2.5 cm^2 at an amplitude of 20 mA with a pulse width of 300 mys at 40 Hz for 20 s/min at each day for 2 weeks by either 12 or 8 h of stimulation. Patients were randomly assigned to a treated or control group where the sham stimulation was applied. GCS evaluators and families of the patients were blinded to the experimental assignment. All six patients with prolonged coma in the Liu series (2003) [174] underwent SPECT scans (HMPAO Tc 99m) for cerebral perfusion evaluation and neurotransmitter (Dopamine) quantification in CSF before right median nerve stimulation therapy of 8–10 h/day over 6 months. They were two TBI, one aneurysm, one hemorrhagic stroke and two hypoxic encephalopathy cases in chronic stage. Four patients gained consciousness between days 23 and 35 while the two hypoxic patients had no clinical improvement. Brain perfusion increased due to RMNS in all six cases and the elevation of neurotransmitters in CSF was found in five out of six patients. A number of well-documented prospective single case studies, mainly in Asia (Japan), have confirmed on class 3 evidence the previous clinical results [39, 90, 146, 172, 173].

Ethics

[7, 12, 22–30, 32–38, 40–51, 55–58, 68, 69, 72, 78, 91, 100–102, 104, 105, 118–122, 127, 128, 132, 137, 139, 143, 144, 150–157, 162, 163, 165, 166, 169, 175, 178, 182–186]

The main demand is to provide every AS patient, independent of his/her functional stage, with the medical treatment and rehabilitative measures needed over time (during early, postacute and long-term rehabilitation and activating nursing). It has become evident over the last decade that progress and intensity of rehabilitative interventions and medical caring insignificantly improved AS survival time. However, up to now one of the most difficult things to achieve is a controlled environment for apallic patients that can be created to meet the special needs of this group of individuals [2 pp. 13–17; 6, 53, 55pp. 4–7, 150]. In 2004, Oka et al. [150] reported on their analysis of life prognosis of AS patients that were treated with the aid of different medical care modalities. The first group was treated state of the art at their special 50 beds CRC department for vegetative patients after traffic accidents from 1985 until 2003 (49 patients/year = total of 931 patient–years and 144.404 days of medical treatment). The yearly mortality rate was only 1.2%. In contrary, for patients who have been discharged home to be cared in the community with financial support by the National Agency of Automotive Safety and Victims' Aid (NASVA) between 1980 and 2003, the averaged annual mortality rate was 15.2%. The authors concluded that good life prognosis can be expected from special units for AS medical care and humanistic nursing providing a clean environment, an adequate primary nursing system, and easy and quick access of medical care to prevent and treat secondary and tertiary complications [177, 179]. Nevertheless, the question of long-term survival is a matter of ongoing and controversial debate in the scientific literature and in the lay press. There are different opinions as to how long such patients could live and how long they do live in special rehabilitation centers, in nursing homes, or at their home with relatives. Jennett [37] pointed out that this may become more significant with the practice of limiting treatment once a vegetative state is declared (permanent is becoming more widely accepted), since long-term survivors are reported not to have benefited that impressively from modern methods of rehabilitative interventions and activating care, and some reports emphasized that care of a long survivor had been provided by an unsophisticated institution (Case III evidence).

The objective of the European survey, where doctors involved in the treatment of patients in "persistent vegetative state" were being interviewed, was to offer provisional orientation concerning the basic attitudes. When compared to other countries participating in the survey in Germany, the hypotheses were confirmed that doctors from different European countries – as far as the decision of withdrawing or withholding treatment is concerned – are guided by different basic attitudes. It has become apparent that due to important national differences it would not be advisable to recommend the European guidelines on the management of such patients for all countries but to respect and follow national legal decisions. Lanzerath et al. [40] concluded, and we follow their recommendations, that decisions taken will depend on the guiding ethical assumptions, and by doing so decisions can only be derived at considering each individual case (at Class II evidence).

According to the Helsinki Declaration of the World Health Organization [182], first published in 1964, and its numerous amendments, doctors today are obliged to use all available means to help their patient and to leave nothing untried.

If there is clinically no doubt as to the diagnosis of AS and when repeated assessments unequivocally demonstrate the irreversibility of full stage AS – notwithstanding best possible intensive-care therapy – and early rehabilitation measures over more than 6 months in the case of hypoxic AS and more than 12 months in the case of posttraumatic AS – then, in consideration of the specific facts of the individual case the question of further active therapy of the patient can be raised and also the issues of artificial nutrition and liquid intake via PEG probe. This decision must be made on the basis of concurrent diagnoses of two independent neurologists and/or neurosurgeons with proven expertise in the field of neurological intensive-care medicine and in the treatment of AS patients. Only on a such basis is it permissible to end all life-prolonging medical measures – or, more correctly, those that prolong the patient's suffering – and thus enable the AS patient to die in a way compatible with his rights as a human being. Providing and securing basic physical care, pain relief, maintenance of respiratory patency, and a sufficient supply of liquids and natural alimentation via the stomach are fundamental obligations demanded from the physician in terms of basic therapy.

The withdrawal of assisted nutrition and hydration is reported to be increasingly supported by some families, practicioners, scientific societies, and medical hospitals and nursing homes, once the condition of an apallic full stage or an early remission stage of minimally consciousness could be considered permanent

(for more details, concerning societal dimension and issues at stake for medical profession we refer on [178]). However, major ethical objections against the ending of artificial nutrition on medical advice and approval should be interpreted as arguments in favor of the value of human life, independent of the status of cerebral function, and that every such person without consciousness and/or with severest cognitive impairments has exactly the same dignity and right to live as a person who is healthy from the mental-cognitive viewpoint. Furthermore, there is the high moral value that must be attached to the love and engagement of the patient's relatives that develop during the time of the AS disorder for the irreversibly unconscious or severely impaired patient, especially when the patient is being cared for at his home by his next of kin. "Withdrawal of nutrition and hydration from apallic patients is a very difficult and sensitive issue for all people working with these patients and their relatives," K. Andrews quotes [27]. Andrews' expertise by carefully reading his publications illustrates the best state-of-the-art decision making as based on the scientific literature and intensive discussions by taking into account European legal aspects. There is nothing more to add but to claim for intensive experience and expertise in AS management before making any medical decision.

This devoted care is an expression of human solidarity, and the helpless AS patient is existentially reliant on the dedicated protection and the appropriate degree of care by society to a special degree. The Hippocratic Oath and our occidental culture place the physician under a special obligation to do his utmost to uphold the life of the patient and also to respect his death when time comes. The enlightened person of this day and age rightfully expects that the physician in charge of his treatment feels committed to both the indivisible value of life as such, but also to respecting the patient's will (witnessed and confirmed patient declaration). Enabling the patient to pass away by discontinuing artificial nutrition may not be misinterpreted as giving one person the permission to kill another as an active deed. The patient's right to self-determination is binding for all concerned and must be respected by the physician even in the cases when this will does not coincide with his (expert) medical opinion [12]. According to medical-legal interpretation, euthanasia is understood as the deliberate induction of the death of a person. Today, it is taken in the meaning of "mercy killing", an act taken to end a life that will shortly be over. In Austria and Germany and indeed in the majority of European and civilized countries, active euthanasia is subject to legal sanctions and is classed as a criminal act. Passive euthanasia, in contrast, is considered an act of mercy by the physician in the form of withholding treatment, i.e., he does not continue with his medical efforts to actively maintain the life of the dying or soon-to-die patient. This notwithstanding, the passive attitude does not relieve the physician and his assistants from their obligation to continue providing the patient with conscientious basic care and sufficient palliative and pain-relieving therapy on top of human attention [27, 33–35, 40, 127, 128, 178].

Commentary

For the management of AS patients, we accept a given prevalence of 1.5–2 AS per 100,000 population in Europe which health authorities and medical societies have to take into account when planning and running population based regional special ENNR centers. We recommend units of 15 to 20 AS patients according to the German Task Force Guidelines. Post-acute and long-term rehabilitation institutions and activating nursing homes must be provided on the same figures for prevalence, prognosis and life expectancy, respectively. Functional assessment of patients in AS full and remission stage is the indispensable basis for quality management in an adequate rehabilitation setting. During the first 3 years AS patients who have been diagnosed as nonrecovering consciousness and were discharged from specially designed environments for nursing or community-based home care should have the legal right to be routinely reassessed on an inpatient basis for every 6 months. CRS is recommended as a valid measuring tool for assessing early functional recovery for changes of neurobehavioral performance while SMART was demonstrated to be a reliable comprehensive and integrated assessment and treatment protocol for the AS and the minimally responsive patient. Patients' age, the cause of brain damage, and duration of AS after the acute brain damage are the most important prognostic factors. Only general but no specific laboratory examination findings can be recommended to corroborate the behavioral diagnosis of AS over time. PET, SPECT, and 3DSRT are helpful diagnostic adjuncts to examine regional CBF and brain metabolism before and after treatment. No specifically AS addressed treatment and especially tailored stimulation programs can be recommended. Best arousal and recovery of consciousness by invasive deep brain and dorsal spinal cord FES (DBS and DSCS) have been demonstrated in selective permanent AS full and early remission patients, especially in young patients

after trauma. Noninvasive right median nerve FES can be applied as an alternative. Quality management of apallic patients requires especially experienced physicians and therapists. (1) For expert opinion additional education in AS treatment including imaging techniques and electrophysiological diagnostics and social medicine of 3 years is recommended for neurologists, neurosurgeons, and physiatrists/rehabilitation-physicians. (2) Professional training has to take place partly in a scientifically approved special institution for ENNR (for example, by the World Federation of Neuro-rehabilitation – WFNR) and in an approved long-term rehabilitation institute, both providing 15 to 20 beds for the management of AS patients of all stages and a minimum of 30 cases/year. (3) The head of the special ENNR unit should have the professional experience of 5 years in functional rehabilitation of apallic patients. (4) He/she as an AS specialist will be qualified for legal expert opinion and for making the right medical decision when withdrawal of nutrition and hydration is questioned. (5) Advanced education and expertise in the treatment of AS patients is recommended and will improve quality management of AS and help respect apallic patients' human rights.

Major ethical objections against the ending of artificial nutrition and hydration on medical advice and approval should be interpreted as arguments in favor of the value of human life, independent of the status of brain functioning, and that every such person without consciousness and/or with severest cognitive impairments has exactly the same dignity and right to live as a person who is healthy from the mental-cognitive viewpoint. No consensus was reached among the authors with respect to this statement but the decision by consensus exists concerning the moralities of taking a medical decision only after careful and thoughtful evaluation of each individual patient's condition, his/her past medical history, future prospects and life expectancy to respect his/her confirmed last will to die humane. The decision to withdrawal nutrition and liquid is known to have a historical negative background in Europe. Renunciation of maximal therapy is in accordance with the Hippocratic ethics.

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