MANAGEMENT AND PROGNOSIS OF SEVERE TRAUMATIC BRAIN INJURY

Part I: **Guidelines for the Management of Severe Traumatic Brain Injury**

Part II: **Early Indicators of Prognosis in Severe Traumatic Brain Injury**

A joint project of the

Brain Trauma Foundation

**American Association of Neurological Surgeons,
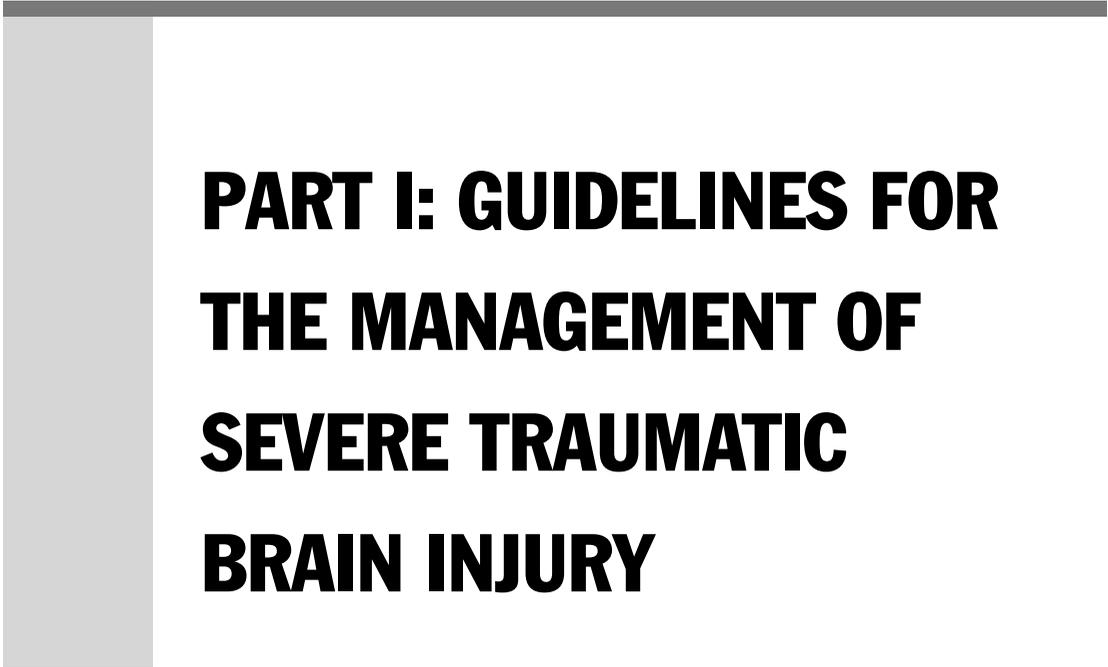Joint Section on Neurotrauma and Critical Care**

MANAGEMENT AND PROGNOSIS OF SEVERE TRAUMATIC BRAIN INJURY

DISCLAIMER OF LIABILITY

The information contained in the *Management and Prognosis of Severe Traumatic Brain Injury (Part I and II)* reflects the current state of knowledge at the time of publication, February 2000. The information is designed to provide accurate and authoritative information in regard to the subject matter covered. In view of the fact that there will be future developments in scientific information and technology, it is anticipated that there will be periodic review and updating of these guidelines. These guidelines are distributed with the understanding that the Brain Trauma Foundation, the American Association of Neurological Surgeons, and the other organizations that have collaborated in the development of these g uidelines are not engaged in rendering professional medical services. If medical advice or assistance is required, the services of a competent physician should be sought. The recommendations contained in these guidelines may not be appropriate for use in all circumstances. The decision to adopt any particular recommendation contained in the *Management and Prognosis of Severe Traumatic Brain Injury (Part I and II)* must be made by a treating physician in the light of all the facts and circumstances surrounding each particular case and on the basis of the available resources.

PART I: GUIDELINES FOR THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY

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GUIDELINES FOR THE MANAGEMENT OF SEVERE TRUAMATIC BRAIN INJURY

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INTRODUCTION

Traumatic Brain Injury (TBI), a clinical problem treated frequently by neurosurgeons, is a major cause of disability, death, and economic cost to our society. In the past two decades, we have increased remarkably our understanding of the pathophysiology of TBI. One of the central concepts that emerged from clinical and laboratory research is that all neurological damage does not occur at the moment of impact, but evolves over the ensuing hours and days. Furthermore, we now recognize the deleterious effects of these various delayed insults to the injured brain at the clinical and biochemical levels. This has led to an interest in developing better monitoring and treatment methods as well as the development of new pharmaceuticals, all of which show great promise in improving the outcome for patients who have suffered a brain injury.

Past efforts to develop guidelines for the management of patients with severe TBI relied on authors' expert opinion and practice experience and, therefore, had an element of subjectivity. Recently, with the advent of a methodology to develop guideline documents based on scientific method, there has been a dramatic increase in clinical practice guidelines with subsequent reports showing improvement in patient care and a reduction in medical time and cost.[1] The interest in developing guidelines for TBI intensified after a national study documented considerable variability in the management of patients with severe TBI.[2]

The task force authors developing the *Guidelines for the Management of Severe Traumatic Brain Injury* used a meticulous process relying on scientific evidence rather than expert opinion. In addition, the task force authors actively involved representatives of national and international medical societies and individuals with demonstrated expertise and interest in the care of patients with severe TBI.

These guidelines address key issues relating to the management of severe TBI in adult patients with a Glasgow Coma Scale score of 3-8. They are by no means an exhaustive treatise on severe TBI. Because of the enormous effort required to develop evidence-based guidelines, the task force authors selected topics that were deemed to have an impact on outcomes in patients with severe TBI. Other important aspects of patient management that were not covered in the present effort will be considered for study in subsequent editions of this document. Examples of such topics include indications for neurosurgical intervention, special consideration in pediatric head injury, the management of penetrating head injury, sedation and paralysis in the TBI patient, and the economics of TBI. We intend that these guidelines will be continually improved in response to new scientific evidence.

Our intent is that the *Guidelines for the Management of Severe Traumatic Brain Injury* will clearly state the current scientific basis for our clinical practice. For most clinical practice parameters,

scientific evidence is insufficient for standards of care, as is generally the case in most of current medical practice. Upgrading clinical practice parameters from option to guideline to standard will require focused, well-designed, and carefully implemented clinical research trials.

Process Used in Development of These Guidelines

These guidelines are comprised of fourteen topics ranging from trauma systems and prehospital resuscitation to monitoring and treatment of intracranial hypertension and intensive care. In 1993, a head injury guidelines task force was formed and supported by the Brain Trauma Foundation (BTF). Members of the task force were selected based on their academic expertise in head injury. BTF is a nonprofit organization dedicated to improving the outcome of brain trauma patients through education and clinical research. BTF financially supports and maintains these guidelines in a cooperative agreement with the American Association of Neurological Surgeons (AANS).

Initially, each author on the task force was assigned a topic and conducted a MEDLINE search, reviewed and graded clinical articles pertinent to the topic, then wrote a report. These reports were reviewed, critiqued, and revised by the entire task force and by representatives of various medical societies, individuals with expertise in head injury care, and members of the AANS Guidelines and Outcomes Committee. The document was critiqued in detail by a group of European neurosurgeons with expertise in neurotrauma (see European Advisory Committee listing).

In April 1995, the document was reviewed and approved by the AANS Guidelines and Outcomes Committee and the AANS Board of Directors. The guidelines were also reviewed by the American Academy of Neurology, the American College of Surgeons, the American College of Emergency Physicians, the American Society of Neuroradiology, the Society for Critical Care Medicine, the American Association of Neuroscience Nurses, and the American Academy of Physical Medicine and Rehabilitation. In 1998 the task force authors met to review the 1995 version of the guidelines and to update the scientific evidence and make other necessary changes. The term Head Injury as used in the original guidelines title was removed in favor of Traumatic Brain Injury, which reflected a more prevalent usage in the literature reviews.

Degrees of Certainty

In assessing the degree of certainty associated with a particular recommendation, the following terminology is the most widely accepted and is used in this document:

Standards: represent accepted principles of patient management that reflect a *high degree of clinical certainty.*

Guidelines: represent a particular strategy or range of management strategies that reflect a *moderate degree of clinical certainty.*

Options: are the remaining strategies for patient management for which there is *unclear clinical certainty.*

Note that the term "guideline" is used both in a global sense, i.e., clinical practice guidelines, as well as in a more specific sense, as noted above.

Classification of Evidence

When assessing the value of therapies or interventions, the available data is classified into one of three categories according to the following criteria[*]:

Class I evidence: Prospective, randomized, controlled trials (PRCT)—the gold standard of clinical trials. However, some may be poorly designed, lack sufficient patient numbers, or suffer from other methodological inadequacies.

Class II evidence: Clinical studies in which the data was collected prospectively, and retrospective analyses that were based on clearly reliable data. Types of studies so classified include: observational studies, cohort studies, prevalence studies, and case control studies.

Class III evidence: Most studies based on retrospectively collected data. Evidence used in this class indicates clinical series, databases or registries, case reviews, case reports, and expert opinion with some support from animal studies.

Technology Assessment: The assessment of technology, such as intracranial pressure monitoring devices, does not lend itself to classification in the above-mentioned format. Thus, for technology assessment the devices were evaluated in terms of their accuracy, reliability, therapeutic potential, and cost effectiveness.

Correlation Between Evidence and Recommendations

Standards are generally based on Class I evidence. However, strong Class II evidence may form the basis for a standard, especially if the issue does not lend itself to testing in a randomized format. Conversely, weak or contradictory Class I evidence may not be able to support a standard.

Guidelines are usually based on Class II evidence or a preponderance of Class III evidence.

Options are usually based on Class III evidence and are clearly much less useful except for educational purposes and in guiding future studies.

Attributes of Clinical Practice Guidelines

To ensure the development of scientifically sound, clinically relevant guidelines that are applicable to the day-to-day practice of medicine, the American Medical Association (AMA) developed a list of attributes that are listed here in an abbreviated form.[3]

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*A single study may be of a different class depending on the parameter in each topic.

Attribute I	Practice guidelines should be developed by or in conjunction with physician organizations and should be characterized by
	• scientific and clinical expertise in the content areas of the parameters.
	• broad-base representation of physicians likely to be affected by the parameters.

Attribute II	Relevant scientific literature and expert clinical opinion should be reviewed as evidenced by
	• a description of the process of the review.
	• a description of the evidence reviewed.
	• the specialty affiliations and other credentials of the physician organizations, groups, and individuals conducting the review.
	• a description of the methods used to evaluate the scientific literature and other appropriate research findings.
	• the rationale for including or excluding studies is noted.
	• the process for selection of clinical experts/reviewers is noted or available on request.
	• at least two-thirds of clinical experts/reviewers were actively involved in clinical practice in relevant clinical areas.
	• the clinical experts/reviewers thoroughly reviewed and assessed the scientific literature.

Attribute III	Practice parameters should be as comprehensive and specific as possible.

Attribute IV	Practice parameters should be based on current information. There should be provisions for periodic reviews and revisions, when appropriate.

Attribute V	The guidelines should be widely disseminated.

Every effort has been made in the formulation of the *Guidelines for the Management of Severe Traumatic Brain Injury* to achieve these ideals.

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TRAUMA SYSTEMS

I. Recommendations

A. Standards

There are insufficient data to support a treatment standard for this topic.

B. Guidelines

All regions should have an organized trauma care system.

C. Options

As delineated in the American College of Surgeons Committee on Trauma *Resources for Optimal Care of the Injured Patient: 1999,*[1] neurosurgeons should have an organized and responsive system of care for patients with neurotrauma. They should initiate neurotrauma care planning including prehospital management and triage, direct trauma center transport, maintain appropriate call schedules, review trauma care records for quality improvement, and participate in trauma education programs.

Trauma facilities treating patients with severe or moderate head injury must have a neurosurgery service, an in-house trauma surgeon, a neurosurgeon promptly available, and a continuously staffed and available operating room, intensive care unit, and laboratory with proper equipment for treating neurotrauma patients. A CT scanner must be immediately available at all times.

In rural or occasionally weather-bound communities without a neurosurgeon, a surgeon should be trained to perform accurate neurological assessment and to initiate immediate neurotrauma care. Such a surgeon also should be trained to perform life-saving surgical treatment of an extracerebral hematoma in a deteriorating patient.

II. Overview

Trauma causes about 150,000 deaths in the United States each year, about one-third are due to fatal head injuries.[23] One million American traumatic brain injury (TBI) victims are treated and released from hospital emergency departments annually[3] and 230,000 of these survivors require inpatient care.[4] Every year another 10,000 persons sustain spinal cord injuries; some 200,000 people in the United States live with the disabilities caused by these injuries. While there is no way to adequately characterize the human costs, the total (direct and indirect) costs of TBI is

estimated at $37.8 billion in 1985 dollars.[8] Thus, trauma, including neurotrauma, is a serious public health problem requiring continuing improvement in the care of injured patients. Trauma system development and organization and better injury prevention appear to be lowering death and disability from intentional and unintentional injury, and should be available to all people in the United States and other countries.

III. Process

A MEDLINE search from 1966 to 1998 identified articles with the key words "trauma systems" and "outcome." Twenty-three relevant manuscripts were used as a basis to assess the value of trauma systems. The guideline and options listed are derived from studies in trauma and neurotrauma care from a variety of peer-reviewed and other articles. *Resources for Optimal Care of the Injured Patient: 1999,*[1] published by the American College of Surgeons Committee on Trauma, provides the basis for most recommendations regarding trauma hospital organization. This document, originally published in 1976, is written, reviewed, and revised regularly by highly recognized North American trauma surgeons. Revision of the next document begins as soon as the latest version is completed; the 1999 version was employed here.

IV. Scientific Foundation

Since the late 1970s, various investigators have tried to demonstrate the efficacy of trauma systems. Early studies generally attempted to show that excessive, "preventable" trauma deaths occurred in regions without organized trauma care[2,7,21] but this methodology was criticized as being too subjective.[22] Additional studies relied on series of patients treated at one or more trauma centers and compared them with those treated within a region[18] or across the United States[8] using prospectively collected, standardized data for severity and outcome. In all comparisons between organized and non-organized trauma systems, patient outcome was worse without organization. Implementing a trauma system in Quebec reduced mortality by 50%[16], and reduced mortality of TBI patients in Oregon by 20%.[10] In the rural setting, ACS Level II trauma center guideline implementation more than doubled survival in head-injured patients.[11] A number of studies and their methodologies have been summarized.[9,14] There are no published data suggesting that unorganized trauma care is superior to organized systems. Published reports indicate that centers treating larger volumes of trauma have better patient outcomes than centers with fewer injured patient encounters.[19] However, morbidity, mortality, and length of stay does not seem to vary significantly with individual trauma surgeon case volume.[13] One report states that organized Level II trauma centers with attending trauma surgeons who are available but not "in-house" have outcomes as good as those with surgeons present in the hospital at all times.[20] However, in-house attending surgeons at another center achieved better than expected survival in patients who had blunt or penetrating trauma treated within 20 minutes of hospital arrival[15] (both of these studies examined data prospectively collected at their center against data collected prospectively at many trauma centers across the United States). Treatment of severely injured patients at a local hospital with subsequent transfer to a trauma center nearly doubles mortality in both the adult,[18] and pediatric populations.[19]

Organization of Neurotrauma Care

Several kinds of arrangements can provide optimal management of trauma, including neurotrauma, and depend on the presence and interest of the local neurosurgeon, trauma surgeon, emergency physician, and critical care specialist. The injured patient, particularly the patient with injury to several body regions, must have a surgeon available for overall management. A trauma surgeon or an appropriately qualified neurosurgeon may fill this role in collaboration with the Trauma Service. He or she most often assumes overall responsibility in patients with isolated head or spinal cord injuries, and in multitrauma patients after their other injuries have stabilized and when management of neurotrauma is the most pressing problem. When multiple organ injuries require active treatment, appropriate consultants may be called on to deliver care for respiratory, nutritional, infectious, and hematological needs.[1,12]

The surgeon qualified for the care of trauma patients is defined as a board certified, Advanced Trauma Life Support (ATLS) certified surgeon with active trauma clinical involvement, continuing medical education, and participation in national or regional trauma organizations.[1] The *Resources for Optimal Care* document further directs the surgeon's practice in the following areas: emergency intervention, critical care, acute care, and discharge planning.[1]

That same document[1] also directs neurosurgical involvement in the care of the injured patient. Neurosurgeons should participate in defining prehospital care in their region including on-site resuscitation and trauma center referral criteria, and in training emergency medical providers in the early management of neurotrauma. It is imperative that neurosurgeons define and maintain on-call schedules and formulate trauma center bypass procedures when a neurosurgeon is unavailable to treat injured patients, and be available when called to provide trauma care. They must ensure that the trauma facility has adequate computed tomography scanning capabilities, and operating room and intensive care resources for patients to be treated optimally. Neurosurgeons also should participate in the trauma system's review, quality improvement, and teaching efforts within their hospital and trauma system.

Prehospital care and emergency department treatment of patients with neurotrauma may have profound importance in their ultimate morbidity and mortality. Many key individuals provide critically important patient care in the early minutes and hours after trauma, including appropriately credentialed emergency physicians, anesthesiologists, emergency medical technicians and paramedics, and emergency department and operating room nurses, among others, whose skills and training are essential in the management of these critically injured patients. Because treatment of nervous system injury must be done correctly, involvement by neurosurgeons in the planning and implementation of treatment protocols is extremely important, along with input from other trauma specialists. Reviews of specific treatments are given in the following sections in these neurotrauma guidelines.

V. Summary

Published case series and cohort comparison studies of patients treated in regions where planned trauma systems are in place compared to regions without trauma systems, or before and after instituting a trauma system, conclude that mortality is reduced after major trauma in patients treated in a trauma system. For optimal care of neurotrauma, neurosurgeons should be involved in the planning and implementation of trauma systems and in support of a system once it is in place.

VI. Key Issues for Future Investigation

In order to establish trauma system development as a standard for treatment, a prospective study would have to compare the outcome of treatment of patients randomly taken to hospitals within and without a planned trauma system. This would be required both for trauma patients in general, and for neurotrauma patients in particular. Given the preponderance of data supporting trauma systems, such studies are unlikely to be undertaken.

VII. Evidentiary Table

ACS-COT,[1] 1999

Description of Study: Guidelines for organization of trauma centers and trauma personnel. Defined by expert opinion and supported by published data where possible.

Classification: Class III Study

Conclusions: Trauma is a surgical disease, and neurotrauma care should be planned and managed by neurosurgeons in concert with other trauma surgeons. Trauma systems and hospitals should be defined and maintained according to these guidelines.

Campbell,[2] 1989

Description of Study: Retrospective case series in an undesignated trauma system showing 23% "preventable" deaths other than head injury judged by group review. (n = 452)

Classification: Class III Study

Conclusions: Study demonstrates that a self-designation system without regulatory control results in a high percentage of preventable trauma deaths.

Hoyt,[5] 1989

Description of Study: Retrospective analysis of indications for operating room (OR) resuscitation of trauma patients with cardiac arrest, persistent hypotension despite resuscitation, or uncontrolled external hemorrhage. (n = 323)

Classification: Class III Study

Conclusions: No patients survived after blunt trauma and cardiopulmonary arrest. Patients with blunt trauma who have persistent hypotension rarely have surgery started within 20 minutes of injury. They can be resuscitated in the emergency department. Only patients with penetrating chest and abdominal injuries who have persistent hypotension after resuscitation may benefit from OR resuscitation.

VII. Evidentiary Table (continued)

Johnson,[6] 1995

Description of Study: This study compared the mortality of 98 children who sustained severe head injury and were transported directly to a pediatric trauma center, with those who were first taken to the closest hospital and later transferred.

Classification: Class III Study

Conclusions: Mortality for children taken directly to the pediatric trauma center was 27%; for those taken to the closest hospital first it was 50%.

Kreis,[7] 1986

Description of Study: Retrospective case series in an undesignated trauma system showing 21% "preventable" non-CNS deaths judged by group review. A Level I trauma center had a 12% preventable mortality rate compared with 21% in planned Level II centers and 30% at 16 other hospitals. (n = 1,201)

Classification: Class III Study

Conclusions: The authors concluded that severely injured patients should be triaged and taken to trauma centers and that there is a need for an organized trauma system.

Mendelhoff,[9] 1991

Description of Study: Review of trauma system studies and implications for public policy.

Classification: Review

Conclusions: Evidence suggests that the introduction of trauma systems in urban areas can prevent deaths at a relatively low cost. The federal government should require states or regional organizations to designate appropriate hospitals as trauma centers and to mandate the development of transfer agreements among hospitals.

Mullins,[10] 1996

Description of Study: Evaluated the influence of implementing the Oregon state-wide trauma system on admission distribution and risk of death using a before and after comparison.

Classification: Class III Study

Conclusions: The Oregon trauma system resulted in reduction in risk of trauma-related death.

Norwood,[11] 1995

Description of Study: This study compared outcome of trauma patients before and after a rural hospital implemented Level II trauma center guidelines using as a study group of patients with a calculated survival of 25%.

Classification: Class III Study

Conclusions: Survival of patients before meeting trauma center criteria was 13% and after the survival increased to 30%.

Pitts,[12] 1987

Description of Study: Editorial comment on the need for neurosurgeon involvement in neurotrauma care and planning.

Classification: Class III Study

Conclusions: It is essential for neurosurgeons to take an active role in defining triage schemes for neurotrauma, in helping establish the needed hospital organization for neurotrauma care, in maintaining appropriate call schedules, and in helping in trauma education and quality assurance.

Roy,[14] 1987

Description of Study: Review of published literature on the value of local and regional trauma care systems, emphasizing study methodology. Evidence in the reports includes case series reports, before and after studies, and intersystem comparisons.

Classification: Review

Conclusions: The literature overwhelmingly suggests that the main determinants of survival are the adequacy of resuscitation and the early recognition of serious injuries.

Sampalis,[16] 1995

Description of Study: The study evaluated the impact of trauma center development and designation on mortality in Quebec, Canada, comparing mortality before and after the trauma system was implemented.

Classification: Class III Study

Conclusions: There was a significant reduction in trauma-related mortality after implementing a trauma system.

VII. Evidentiary Table (continued)

Sampalis,[15] 1997

Description of Study: The outcome of severely injured patients (including head trauma) who were transported directly to trauma centers was compared to patients of similar injury severity who were transferred to a trauma center after first being transported to a less specialized, local institution (n = 1,608)

Classification: Class III Study

Conclusions: This study showed that severely head-injured patients transported directly from the scene to Level 1 trauma centers is associated with a significant reduction in mortality.

Shackford,[17] 1987

Description of Study: Analysis of patients admitted after traumatic injury, of whom 283 were severely injured (trauma score < 8). Of those who had sufficient data (n=189) to compare with a national cohort study that provided a model for predicting survival in patients, actual survival was 29% whereas predicted survival (Ps) was 18%. In patients with penetrating injury, Ps was 8% and actual survival was 20%. (n = 3393)

Classification: Class II Study

Conclusions: The improved survival was attributed to the integration of prehospital and hospital care and expeditious surgery.

Smith J,[18] 1990

Description of Study: Analysis of data abstracted from computerized discharge information about patients with femoral shaft fractures requiring operation over a one-year period in two states. (n=1,332)

Classification: Class II Study

Conclusions: Patients treated in trauma care centers had significantly fewer deaths and complications than in non-trauma centers.

Smith R,[19] 1990

Description of Study: A cohort analysis was performed on data from severely injured patients using three statistical methods to determine the relationship between trauma center volume and mortality. (n = 1,643)

Classification: Class II Study

Conclusions: Low-volume trauma centers (fewer than 140 patients annually) had significantly higher mortality when adjusted for head injury than did high-volume trauma centers (more than 200 patients annually) (p < .04).

Thompson,[20] 1992

Description of Study: Cohort analysis of trauma admissions at a Level II trauma center showed no difference between survival in that center and survival among patients in the Major Trauma Outcome Study (n > 15,000). Whether the trauma surgeon was on call out of the hospital did not adversely affect survival in patients with severe thoracoabdominal injury, compared with the trauma surgeon available in-house. (n = 3,689)

Classification: Class II Study

Conclusions: Level II trauma centers can achieve mortality rates equal to those shown in a large multicenter trauma study, and trauma surgeons promptly available from outside a hospital can produce mortality rates equal to in-house trauma surgeons.

West,[21] 1979

Description of Study: Retrospective case series of motor-vehicle trauma victims in two California counties, one with a trauma system (n = 92) and another without (n = 90). About two-thirds of the non-CNS deaths and one-third of the CNS deaths in the county with no trauma system were judged by the authors to be potentially preventable. Only one death in the county with a trauma system was judged to be potentially preventable.

Classification: Class III Study

Conclusions: The authors suggested that survival rates for major trauma can be improved by an organized system of trauma care.

Wilson,[22] 1992

Description of Study: Compared three methods by which a panel identified preventable trauma deaths other than from head injury, showing different rates of preventable deaths among the three methods.

Classification: Class II Study

Conclusions: Precise determination of preventable deaths is difficult and should not be used to measure institutional quality of care. The authors recommended that assessment of performance should be based on the study of patient population outcomes, rather than on subjective methods in which individual cases are reviewed.

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INITIAL MANAGEMENT

I.   Recommendations

A.   Standards

There are insufficient data to support a treatment standard for this topic.

B.   Guidelines

There are insufficient data to support a treatment guideline for this topic.

C.   Options

The first priority for the head-injured patient is complete and rapid physiologic resuscitation. No specific treatment should be directed at intracranial hypertension in the absence of signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial explanations. When either signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial explanations are present, however, the physician should assume that intracranial hypertension is present and treat it aggressively. Hyperventilation should be rapidly established. The administration of mannitol is desirable but only under conditions of adequate volume resuscitation.

Sedation and neuromuscular blockade can be useful in optimizing transport of the head injury patient. However, both treatments interfere with the neurological examination. In the absence of outcome-based studies, the choice of sedative is left to the physician. Neuromuscular blockade should be employed when sedation alone proves inadequate and short-acting agents should be used when possible.

II.   Overview

Although there is no present technology for its quantification, intracranial hypertension has the potential to exert a detrimental influence on outcome during the period between injury and insertion of an intracranial pressure (ICP) monitoring device. Unfortunately, not only do all treatment modalities for intracranial hypertension have serious potential complications, but many of them can directly interfere with resuscitation procedures (e.g., use of diuretics). The efficacy of cardiopulmonary resuscitation in improving survival from trauma in general is well accepted. In addition, the acknowledged negative influence of secondary insults such as hypotension and hypoxia on outcome from severe head injury establishes systemic

resuscitation as the critical foundation upon which treatment of intracranial hypertension must be based. Therefore, in the absence of obvious evidence of elevated ICP, any presumptive or prophylactic treatment must be consistent with optimal systemic resuscitation.

Alternatively, signs of transtentorial herniation are strong evidence of intracranial hypertension and should initiate rapid treatment to lower ICP. Under such circumstances, it is necessary to reassess the balance of cerebral and systemic priorities for the individual situation.

III. Process

The process leading to this section differs from that of the other chapters in this document in that many of the conclusions have been derived from analyses outlined in those other sections. In particular, material from the sections on hyperventilation, mannitol, and management of blood pressure and oxygenation were incorporated. The summary sections from these chapters are reproduced here and the relevant articles included in the evidentiary table.

For the subject of sedation, a MEDLINE search from 1966 to 1998 was undertaken using the following key words: "head injury," "sedation," and "human subjects." This produced 45 references that were reviewed for clinical relevance and outcome orientation. No articles met these criteria.

For the subject of neuromuscular blockade, a MEDLINE search from 1966 to 1998 was undertaken using the following key words: "head injury" (and "neuromuscular blockade" or "pharmacologic paralysis" or "relaxation") and "human subjects." This produced 15 references that were reviewed for clinical relevance and outcome orientation. One article met these criteria.

IV. Scientific Foundation

There is a dearth of data focused on the efficacy of head-injury specific resuscitation therapy with respect to either the subsequent in-hospital neurologic course or outcome. Therefore, all therapeutic conclusions regarding protocols must remain at the level of treatment options.

Sedation

Approaches to sedation and neuromuscular blockade in the severely head-injured patient vary widely and there is evidence that both sedation and pharmacologic relaxation influence the initial evaluation and treatment of the neurotrauma patient.[10] Unfortunately, there have been no studies on the influence of sedation on outcome from severe head injury.[5] Therefore, decisions about the use of sedation and the choice of agents are left to the practitioner to make based on individual circumstances.

Neuromuscular Blockade

There has been only one study (Class II) of the influence of neuromuscular blockade on outcome from severe head injury. Hsiang, et al., studied the effect on outcome in 514 severe head injuries entered into the Traumatic Coma Data Bank of prophylactic neuromuscular blockade (i.e., pharmacologic paralysis beginning early in the patient's course and lasting at least 12 hours not administered for control of intracranial hypertension).[9] They reported that such use of neuromuscular blockade was associated with a longer intensive care unit course, a higher incidence of pneumonia, and a trend toward more frequent sepsis without providing an improvement in outcome. They suggested that neuromuscular blockade should be reserved for

specific indications (e.g. intracranial hypertension, transport, etc.) rather than be routinely administered to severe head injury patients.

Blood Pressure and Oxygenation

Early, post-injury episodes of hypotension or hypoxia greatly increase the morbidity and mortality from severe head injury. The literature contains no adequate definition of their actual physiologic values. However, there is abundant Class II evidence suggesting that early hypotension, defined as a single observation of a systolic blood pressure of less than 90 mm Hg, or hypoxia, defined as apnea or cyanosis in the field, or a PaO_2 less than 60 mm Hg by arterial blood gas analysis, are associated with increased mortality and morbidity.[4, 6, 14] With respect to the efficacy of early treatment, there is now evidence from post-hoc (Class II) analysis of data from a prospective, randomized, controlled trial that enhanced blood pressure resuscitation improves outcome from severe head injury.[19]

A recent single-center, prospective, randomized, controlled trial suggested that delayed resuscitation was more beneficial than immediate resuscitation in improving outcome from penetrating torso injuries.[1] Notably, head injury patients were specifically excluded from this trial. Therefore, the concept of delayed resuscitation cannot be considered applicable in head injury.

Mannitol

There are two Class I studies[16, 18] and one Class II study[7] that can be used to support mannitol in ICP control (see mannitol chapter).

Hyperventilation

Hyperventilation provides a reduction in ICP by causing cerebral vasoconstriction and a subsequent reduction in cerebral blood flow (CBF). Research conducted over the past 20 years clearly demonstrates that CBF during the first day after injury is less than half that of normal individuals[2, 3, 11] and that there is a risk of causing cerebral ischemia when aggressive hyperventilation is employed.[13] These findings are corroborated by arteriovenous oxygen content difference and jugular venous saturation measurements.[15, 17] Aggressive hyperventilation (arterial $PaCO_2$ < 30 mm Hg) will reduce CBF values even further but will not consistently cause a reduction of ICP and may cause loss of autoregulation.[13] While the CBF level at which irreversible ischemia occurs has not been clearly established, ischemic cell changes are seen in 90% of those who die following severe head injury.[8] A recent, prospective, randomized study found improved outcome at 3 and 6 months when prophylactic hyperventilation was not used as compared to when it was.[12] Thus, limiting the use of hyperventilation following severe head injury may help improve neurologic recovery following injury or, at least, avoid iatrogenic cerebral ischemia.

Committee Consensus

Consistent with the analyses outlined above and discussed elsewhere in this document, the recommended management approach (Class III—treatment option) is that the management of the severe head injury patient prior to ICP monitoring be predicated on clinical evidence of intracranial hypertension as manifest by signs of herniation. These signs include unilateral or bilateral pupillary dilatation, asymmetric pupillary reactivity, motor posturing, or other

evidence of deterioration of the neurologic examination. The most convincing evidence of the development of intracranial hypertension is the witnessed evolution of one or more of these signs.

Successful systemic resuscitation is fundamental to maintaining the possibility of satisfactory neurologic recovery. Therefore, the Advanced Trauma Life Support (ATLS) evaluation remains the first priority. The considerations contained in this chapter are to be applied within the framework of the ATLS approach. An algorithm describing an approach to the resuscitation of the severe head injury patient is presented in Figure 1 (page 26).

Management in the Absence of Clinical Signs of Herniation

In the absence of clinical evidence of transtentorial herniation, sedation and pharmacologic relaxation should be used when indicated for safe and efficient patient transport. The confusion and agitation frequently attendant to head injury often makes sedation desirable. Pharmacologic relaxation, however, has the undesirable effect of limiting the neurologic exam to the pupils and, on arrival at the hospital, the CT scan. Therefore, its use in the absence of evidence of herniation should be limited to situations where sedation alone is not sufficient to optimize safe and efficient patient transport and resuscitation. When used, short-acting agents are strongly preferred.

This protocol opinion does not support the "prophylactic" administration of mannitol due to its volume-depleting diuretic effect. In addition, although it might be desirable to approximate the lower end of the normal range of $PaCO_2$ during transport of a suspected brain injury, the risk of exacerbating early ischemia (see hyperventilation chapter) outweighs the questionable benefit in the patient without evidence of herniation. Therefore, the protocol option derived here recommends ventilatory parameters consistent with optimal oxygenation and "normal" ventilation.

Management in the Presence of Clinical Signs of Herniation

When there is evidence of transtentorial herniation (or progressive neurologic deterioration not attributable to extracranial explanations), aggressive treatment of suspected intracranial hypertension is indicated. Hyperventilation is easily accomplished by increasing the ventilatory rate and does not depend on or interfere with successful volume resuscitation. Because hypotension can produce both neurologic deterioration and intracranial hypertension, the use of mannitol is less desirable unless adequate volume resuscitation has been accomplished (see mannitol chapter). If complete volume resuscitation has been attained, however, mannitol should be administered by bolus infusion. Under these circumstances, it is critical that the patient be transported to the hospital with utmost haste.

V. Summary

The fundamental goals of resuscitation of the head-injured patient are the restoration of circulating volume, blood pressure, oxygenation, and ventilation. The physician should initiate maneuvers that serve to lower ICP and do not interfere with these aims as early as possible during resuscitation of any patient with a head injury. Treatment modalities such as hyperventilation and mannitol administration that have the potential of exacerbating intracranial ischemia or interfering with resuscitation should be reserved for patients who show signs of intracranial hypertension such as evidence of herniation or neurologic deterioration.

VI. Key Issues for Future Investigation

The key issues discussed in all the chapters relevant to this section are germane to this discussion. Specific to this section is the question of combining these modalities into a protocol and testing the efficacy of that protocol in optimizing resuscitation and improving outcome from severe head injury. The "prophylactic" treatment of intracranial hypertension in patients suspected of severe head injury is of particular interest and would lend itself to a prospective, randomized trial.

INITIAL MANAGEMENT

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        ┌─────────────────────────┐
        │   SEVERE HEAD INJURY    │
        │      GCS 8 or Less      │
        └─────────────────────────┘
                     │
                     ▼
┌──────────────────┐   ┌─────────────────┐
│    Emergency     │   │   ATLS Trauma   │
│   Diagnostic     │◄─►│   Evaluation    │
│  or Therapeutic  │   └─────────────────┘
│    Procedures    │            │
│   as Indicated   │            ▼
└──────────────────┘
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Endotracheal Intubation
Fluid Resuscitation
Ventilation
  (PaCO$_2$ 35 mm Hg)
Oxygenation
Sedation
± Pharmacologic Paralysis
  (short acting)

Herniation?*
Deterioration?*   YES → ± Hyperventilation*
   ± Mannitiol (1 g/kg)*

CT Scan   YES → Resolution?

Surgical Lesion?   YES

Resolution?   NO → Operating Theater

Surgical Lesion?   NO → Intensive Care Unit

Monitor ICP

Treat Intracranial Hypertension

* Only in the presence of signs of herniation or progressive neurologic deterioration not attributable to extracranial factors.

FIG 1. Initial resuscitation of the severe head injury patient (treatment option).

VII. Evidentiary Table: The Integration of Brain-Specific Treatments Into the Initial Resuscitation of the Severe Head Injury Patient

Bickell,[1] 1994

Description of Study: Single-center, prospective, randomized, controlled trial to determine the effects of delaying fluid resuscitation until the time of operative intervention in 598 adult hypotensive patients with penetrating injuries to the torso. This study excluded patients with head injuries. Survival to discharge was improved in the delayed resuscitation group.

Classification: Class I Study

Conclusions: Delaying resuscitation in patients with penetrating torso wounds but without severe head injuries may improve outcome.

Bouma,[2] 1991

Description of Study: Cohort studies of 186 patients with severe TBI designed to measure early CBF after injury and correlate it with outcome.

Classification: Class II Study

Conclusions: The mean CBF during the first 6 hours after injury was 22.5 ± 5.2 ml/100 g/min and CBF was highest at 36-42 hours after injury.

Bouma,[3] 1992

Description of Study: Cohort studies of very early cerebral blood flow (CBF) in 35 patients with severe traumatic brain injury (TBI) studied a mean of 3.1 ± 2.1 hours after injury.

Classification: Class II Study

Conclusions: Global or regional CBF less than 18 ml/100 g/min, defined as ischemic threshold, was found in 31.4% of the patients.

Chesnut,[4] 1993

Description of Study: A prospective study of 717 severe head injury patients admitted consecutively to four centers investigated the effect on outcome of hypotension (systolic blood pressure [SBP] < 90 mm Hg) occurring from injury through resuscitation. Hypotension was a statistically independent predictor of outcome. A single episode of hypotension during this period increased mortality 150% and also increased morbidity. Patients whose hypotension was not corrected in the field had a worse outcome than those who were corrected by time of arrival.

Classification: Class II Study

Conclusions: Early hypotension (SBP < 90 mm Hg) significantly increases mortality in a statistically independent manner.

Fearnside,[6] 1993

Description of Study: A prospective study of 315 severe head injury patients admitted consecutively to a single center with respect to prehospital and in-hospital predictors of outcome. Hypotension (SBP < 90 mm Hg) was an independent predictor of increased mortality and morbidity.

Classification: Class II Study

Conclusions: Hypotension (SBP < 90 mm Hg) occurring at any time during a patient's course independently predicts worse outcome.

Gaab,[7] 1990

Title of Study: A Comparative Analysis of THAM (Tris-buffer) in Traumatic Brain Edema. (n = 21 patients, not randomized.)

Classification: Class II Study

Conclusions: Mannitol boluses produced a 32% reduction in ICP and the effect was seen for 60 minutes. THAM was "at least as effective as mannitol."

Graham,[8] 1988

Description of Study: Histologic study of 71 victims of fatal severe TBI who had no premortem evidence (clinical, radiologic, or pathologic) of elevated ICP.

Classification: Class II Study

Conclusions: Ischemic cell changes were found in 70% of the brains.

Hsiang,[9] 1994

Description of Study: A prospective study of 514 severe head injury patients admitted consecutively to four centers investigated the effect on outcome of prophylactic neuromuscular blockade (i.e., pharmacologic paralysis beginning early in the patient's course and lasting at least 12 hours not administered for control of intracranial hypertension). Such use of neuromuscular blockade was associated with a longer intensive care unit course, a higher incidence of pneumonia, and a trend toward more frequent sepsis without providing an improvement in outcome.

Classification: Class I Study

Conclusions: Neuromuscular blockade should be reserved for specific indications (e.g., intracranial hypertension, transport, etc.) rather than be routinely administered to severe head injury patients.

Marion,[11] 1991

Description of Study: Cohort study of 32 patients with severe TBI aimed at defining temporal changes in CBF that occur during the first 5 days after injury.

Classification: Class II Study

Conclusions: Mean CBF in the first 1-4 hours after injury was 27 ml/100 g/min, and CBF was always lowest during the first 12-24 hours after injury. Regional CBF was substantially heterogeneous.

Muizelaar,[12] 1991

Description of Study: Prospective, randomized clinical trial of 77 patients with severe TBI comparing clinical outcome for a group hyperventilated to a $PaCO_2$ of 25 ± 2 mm Hg for 5 days after injury and a group with a $PaCO_2$ kept at 35 ± 2 mm Hg during that period.

Classification: Class I Study

Conclusions: At 3 and 6 months after injury, the patient with an initial Glasgow Coma Scale (GCS) motor score of 4-5 had a significantly better outcome if they were not hyperventilated.

Obrist,[13] 1984

Description of Study: Cohort study of 31 patients with severe TBI in whom the effect of aggressive hyperventilation on ICP, CBF, and arteriovenous difference in oxygen content $(AVdO_2)$ was examined.

Classification: Class II Study

Conclusions: Hyperventilation had a much more direct effect on CBF reduction (29 of 31 patients) than it did on ICP reduction (15 of 31 patients). Aggressive hyperventilation in 10 patients ($PaCO_2$ of 23.2 ± 2.8 mm Hg) led to $AVdO_2$ values of 10.5 ± 0.7 vol% and CBF values of 18.6 ± 4.4 ml/100 g/min.

Pigula,[14] 1993

Description of Study: Fifty-eight children (< 17 years) with severe head injuries were prospectively studied for the effect of hypotension (SBP < 90 mm Hg) on outcome. An episode of hypotension decreased survival fourfold. This finding was confirmed in a concomitant analysis of the effect of hypotension on outcome in 509 patients in the National Pediatric Trauma Registry. Hypotension appeared to eliminate any neuroprotective mechanisms normally afforded by age.

Classification: Class II Study

Conclusions: The detrimental effects of hypotension (SBP < 90 mm Hg) on outcome appear to extend to children.

Robertson,[15] 1992

Description of Study: Cohort study of 102 patients with severe head injury examining the time course and relationship of $AVdO_2$, CBF, and ICP.

Classification: Class II Study

Conclusions: $AVdO_2$ values were always widest during the first 24 hours after injury.

Schwartz,[16] 1984

Title of Study: The University of Toronto Head Injury Treatment Study: A Prospective, Randomized Comparison on Pentobarbital and Mannitol.

Classification: Class I Study

Conclusions: Prospective, randomized comparison of mannitol vs barbiturates for ICP control. Crossover permitted. Sequential analysis (n=59). Pentobarbital was not significantly better than mannitol. Mannitol group had better outcome mortality, 41% vs 77%. Cerebral perfusion pressure (CPP) was much better with mannitol than barbiturates (75 mm Hg vs 45 mm Hg).

Sheinberg,[17] 1992

Description of Study: Cohort study of jugular venous Oxygen (O_2) saturation in 45 patients with severe head injury monitored for 1-8 days.

Classification: Class II Study

Conclusions: Hyperventilation was the second most common identifiable cause of jugular venous desaturations (O_2 saturation < 50%), and was the cause for desaturation in 10 of 33 cases.

Smith,[18] 1986

Title of Study: Comparison of Two Mannitol Regimens in Patients with Severe Head Injury, Undergoing Intracranial Pressure Monitoring: Effect of Bolus Mannitol Given Only When ICP > 25 mm Hg, versus "Empirical Mannitol" (every 2 hours until serum osmolarity (OSM) 310, or neurodeterioration).

Classification: Class I Study

Conclusions: No difference between ICP-directed and empiric mannitol use. ICP smoother and lower in empiric group. (Power too low to detect an effect (n = 8), randomized.)

VII.   Evidentiary Table (continued)

Vassar,[19] 1993

Description of Study: Prospective, randomized, controlled, multicenter trial comparing the efficacy of administering 250 ml of hypertonic saline vs normal saline as the initial resuscitation fluid in facilitating the resuscitation and improving the outcome of hypotensive trauma patients. In this trial, the hypertonic saline group had significantly improved blood pressure responses and decreased overall fluid requirements. Although there was an associated improvement in survival for the overall group, it did not reach statistical significance. Post-hoc analysis of the severe head injury group (Class II analysis), however, revealed that the hypertonic saline group had a statistically significant improvement in survival-to-discharge.

Classification: Class II Study

Conclusions: Raising the blood pressure in hypotensive, severe head injury patients improves outcome in proportion to the efficacy of the resuscitation.

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RESUSCITATION OF BLOOD PRESSURE AND OXYGENATION

I. Recommendations

A. Standards

There are insufficient data to support a treatment standard for this topic.

B. Guidelines

Hypotension (systolic blood pressure [SBP] < 90 mm Hg) or hypoxia (apnea, cyanosis, or an Oxygen (O_2) saturation < 90% in the field or a PaO_2 < 60 mm Hg) must be monitored and scrupulously avoided, if possible, or corrected immediately in severe traumatic brain injury (TBI) patients.

C. Options

The mean arterial blood pressure should be maintained above 90 mm Hg through the infusion of fluids throughout the patient's course to attempt to maintain cerebral perfusion pressure (CPP) greater than 70 mm Hg. Patients with a Glasgow Coma Scale (GCS) score less than 9, who are unable to maintain their airway or who remain hypoxemic despite supplemental O_2, require that their airway be secured, preferably by endotracheal intubation.

II. Overview

For ethical reasons, a prospective, controlled study concerning the effects of hypotension or hypoxia on outcome from severe head injury has never been done. Nevertheless, there is a growing body of evidence that secondary insults occur frequently and exert a profound, adverse influence on outcome from severe head injury. This effect appears to be more profound than results when hypoxic or hypotensive episodes of similar magnitude occur in trauma patients without neurologic involvement. Therefore, we need to determine if there is any strong evidence that suggests threshold values for oxygenation and blood pressure support.

III. Process

A MEDLINE search from 1966 to 1998 was undertaken using the following key words: "head injury" (and "hypoxia" or "hypotension") and "human subject"; and "head injury" (and "field" or "pre-hospital" or "prehospital") and ("treatment" or "management" or "resuscitation"). The resultant references found to be directly relevant regarding outcome analysis and clinical orientation were individually reviewed for design, content, and relevance. The results of this review were then incorporated into the analysis presented here.

IV. Scientific Foundation

Hypoxemia

In head-injured patients, significant secondary brain injury results from systemic hypotension and hypoxemia.[25] An English study revealed that 44% of TBI victims were hypoxemic in the field or ambulance, with documented O_2 saturations between 75%-90% in 28% of the patients and O_2 saturations less than 75% in 16% of the patients.[24] A study in Ireland documented hypoxemia in 27% of TBI patients on arrival to the closest emergency department.[4] These adult population findings are similar to those in a retrospective, pediatric, severe TBI study, where 13% of the patients were hypoxemic and 6% were hypercarbic.[12] These hypoxemic episodes have also been associated with statistically significant worse outcomes in the patients. In Italy, 55% of helicopter transported TBI patients were hypoxemic prior to intubation.[25] Of the hypoxemic patients, 46% did not have concomitant hypotension. In non-hypoxemic patients, mortality was 14.3% with a 4.8% rate of severe disability. However, in patients with documented O_2 saturations less than 60%, the mortality rate was 50% and all of the survivors were severely disabled.

Hypotension

The deleterious influence of hypoxemia and hypotension on the outcome of severe head injury was also demonstrated by the analysis of a large (717 patients), prospectively collected data set from the Traumatic Coma Data Bank (TCDB; Class II studies).[3,13] Hypoxemia and hypotension each occurred in over one-third of severe head injury patients. The TCDB study demonstrated that prehospital hypotension (a single observation of a SBP < 90 mm Hg) or hypoxia (apnea/cyanosis in the field or a PaO_2 < 60 mm Hg by arterial blood gas analysis) were among the five most powerful predictors of outcome. These predictors were statistically independent of the other major predictors such as age, admission Glasgow Coma Scale (GCS) score, admission GCS motor score, intracranial diagnosis, and pupillary status. A single episode of hypotension was associated with increased morbidity and a doubling of mortality as compared with a matched group of patients without hypotension.[3] N.B.

A Class II study from Australia supports the above findings, particularly regarding the effects of hypotension on outcome.[5] A retrospective review of prospectively collected data in children less than 17 years of age also corroborated these results.[19] Here, hypotension markedly increased morbidity and mortality independently of other predictors of outcome, eliminating the improvement in survival generally afforded by youth. These data validate similar retrospectively analyzed Class II and III reports published previously.[6,8,10,11,15-18,20,23]

N.B. The question of the influence of hypoxia and hypotension on outcome is not subjectable to manipulative investigation. In addition, no prospective studies with concomitant cohort controls have been performed or are likely to be undertaken due to ethical considerations. Therefore, the large, prospectively collected, observational data set from the TCDB is the best information on the subject that can be expected to be available. Given the size and nature of this study and the unequivocal nature of the results, the avoidance of hypotension (SBP ≤ 90 mm Hg) and hypoxia (PaO_2 ≤ 60 mm Hg) during the early post-injury period can be supported at the level of a guideline, if not a treatment standard.

Airway Management

The role of active airway management including endotracheal intubation (ETI) for TBI patients has not been well studied. A prehospital study[9] to investigate the relationship between GCS score and the need for intubation within 30 minutes of Emergency Department (ED) arrival determined that 100% of TBI patients with a GCS score of 3-5 required ETI (27% in the field, 72% in the ED). Additionally, 72% of TBI patients with a GCS score of 6-7 required ETI (27% in the field, 36% in the ED), and 61% of TBI patients with a GCS score of 8-9 required ETI (8% in the field, 53% in the ED). Prehospital intubation is associated with significantly enhanced survival in TBI patients. A retrospective, case control study with severe trauma victims (including head injury), compared patients who underwent prehospital intubation with those who did not.[31] Mortality was significantly reduced in intubated patients, particularly in the lowest GCS score and isolated head injury subsets.[26-30]

Resuscitation Fluids

A Class I study has never directly addressed the efficacy of preventing or correcting early hypotension to improve outcome. The American College of Surgeons advocates the rapid infusion of two liters of Ringer's lactate or normal saline as an initial resuscitative crystalloid bolus.[1] However, resuscitation prior to definitive surgical hemostasis may cause displacement of hemostatic clots, hemodilution, and worsen secondary blood loss and mortality in penetrating torso trauma.[2] The Advanced Trauma Life Support course and most textbooks advise the judicious use of fluid in treating TBI patients from concerns that fluid may augment cerebral edema and intracranial pressure (ICP). However, in multitrauma patients with head injury, Scalea demonstrated a lack of relationship between amount of fluid or blood infused and ICP.[22] Hypertonic saline and mannitol have been advocated as resuscitation fluids in addition to the reduction of intracranial hypertension.

Clinically, mannitol is routinely used to reduce ICP in TBI patients with intracranial hypertension. However, mannitol's osmotic diuresis may cause volume deficits, hypotension, and subsequent secondary brain injury. The prehospital administration of mannitol versus placebo in TBI patients showed no difference in mortality; however, in the treatment group SBP fell significantly two hours after hospital arrival, but comparing all time periods there was no substantial difference.[21]

Hypertonic saline has been demonstrated to reduce ICP in patients with TBI and intracranial hypertension.[7] Subgroup, post-hoc analysis of severe TBI patients in a prospective, randomized, placebo-controlled, multicenter trial demonstrated both a higher SBP and enhanced survival in trauma patients resuscitated with hypertonic saline instead of crystalloid.[14] This data strongly suggests that elevating the blood pressure in hypotensive, severe head injury patients improves outcome. Meta-analysis of TBI patients who received hypertonic saline/dextran are about twice as likely to survive as those who receive standard therapy.[30] Other studies show either no difference or improved survival utilizing hypertonic saline with or without dextran over isotonic saline for fluid resuscitation, with most benefit in the subgroup of patients with an initial GCS score less than 9.[27-29]

Resuscitation End-Points

The value of 90 mm Hg as a systolic pressure threshold for hypotension has arisen in a rather arbitrary fashion and is more of a statistical than a physiologic parameter. Given the evidence on the influence of cerebral perfusion pressure (CPP) on outcome, it is possible that systolic pressures significantly higher than 90 mm Hg would be desirable during the prehospital and resuscitation phase, but no studies have been performed thus far to corroborate this. The importance of mean arterial pressure, as opposed to systolic pressure, should also be stressed, not only because of its role in calculating CPP, but because the lack of a consistent relationship between systolic and mean pressures makes calculations based on systolic values unreliable. It may be valuable to maintain mean arterial pressures considerably above those represented by systolic pressures of 90 mm Hg throughout the patient's course. However, once ICP monitoring has been established, manipulation of blood pressure should be guided by CPP management.

V.   Summary

Early post-injury episodes of hypotension or hypoxia greatly increase morbidity and mortality from severe head injury. At present, the defining level of hypotension and hypoxia is unclear in these patients. However, ample Class II evidence exists regarding hypotension, defined as a single observation of an SBP of less than 90 mm Hg, or hypoxia, defined as apnea/cyanosis in the field or a PaO_2 less than 60 mm Hg by arterial blood gas analysis, to warrant the formation of guidelines stating that these values must be avoided, if possible, or rapidly corrected in severe head injury patients.[1,5,19] A significant proportion of adult and pediatric TBI patients are discovered to be hypoxemic or hypotensive in the prehospital setting. Patients with severe head injury that are intubated in the prehospital setting appear to have better outcomes. Strong Class II evidence suggests that raising the blood pressure in hypotensive, severe head injury patients improves outcome in proportion to the efficacy of the resuscitation.[17,26]

VI. Key Issues for Future Investigation

The major questions for resuscitating the severe head injury patient are the critical values for duration and magnitude of hypotensive episodes and the optimal resuscitation protocol (hypertonic or isotonic solutions, colloids, route of administration, etc.) affecting neurological outcome. The former question is not a subject for a controlled trial for ethical reasons and, therefore, would be best addressed using a prospective data collection study with high resolution collection of prehospital blood pressure data, correlating this with outcome. The latter question can be studied in prospective, randomized investigations, several of which are presently underway. Finally, because the actual parameter of interest is CPP, a simple, non-invasive method of determining ICP in the field warrants development.

VII. Evidentiary Table: Resuscitation of Blood Pressure and Oxygenation

Chesnut,[3] 1993

Description of Study: A prospective study of 717 consecutive severe head injury patients admitted to four centers investigated the effect on outcome of hypotension (SBP < 90 mm Hg) occurring from injury through resuscitation. Hypotension was a statistically independent predictor of outcome. A single episode of hypotension during this period doubled mortality and also increased morbidity. Patients whose hypotension was not corrected in the field had a worse outcome than those who were corrected by time of arrival.

Classification: Class II Study

Conclusions: Hypotension was a statistically independent predictor of outcome. A single episode of hypotension during this period doubled mortality and also increased morbidity. Patients whose hypotension was not corrected in the field had a worse outcome than those whose hypotension was corrected by time of ED arrival.

Cooke,[4] 1995

Description of Study: A prospective audit of 131 patients with severe head injury evaluating the early management of these patients in Northern Ireland.

Classification: Class III Study

Conclusions: 27% of patients were hypoxemic on arrival to the ED.

Fearnside,[5] 1993

Description of Study: A prospective study of prehospital and in-hospital predictors of outcome in 315 consecutive severe head injury patients admitted to a single trauma center. Hypotension (SBP < 90 mm Hg) was an independent predictor of increased morbidity and mortality.

Classification: Class II Study

Conclusions: Hypotension (SBP < 90 mm Hg) occurring at any time during a patient's course, independently predicts worse outcome.

Gentleman,[6] 1992

Description of Study: A retrospective study of 600 severe head injury patients in three cohorts evaluated regarding the influence of hypotension on outcome and the effect of improved prehospital care in decreasing its incidence and negative impact.

Classification: Class III Study

Conclusions: Improving prehospital management decreased the incidence of hypotension but its impact on outcome in patients suffering hypotensive insults maintained as a statistically significant, independent predictor of poor outcome. Management strategies that prevent or minimize hypotension in the prehospital phase improves outcome from severe head injury.

VII. Evidentiary Table (continued)

Hill,[8] 1993

Description of Study: A retrospective study of prehospital and ED resuscitative management of 40 consecutive, multitrauma patients. Hypotension (SBP ≤ 80 mm Hg) correlated strongly with fatal outcomes. Hemorrhagic hypovolemia was the major etiology of hypotension.

Classification: Class III Study

Conclusions: Improving the management of hypovolemic hypotension is a major potential mechanism for improving the outcome from severe head injury.

Hsiao,[9] 1993

Description of Study: A retrospective trauma registry–based study of 120 patients with a GCS less than 14 that evaluated the need for emergency intubation in the field or ED and evaluated CT scan findings.

Classification: Class III Study

Conclusions: Patients with a GCS score of 3-5 were all intubated and 73% had abnormal CT scans; 73% of patients with a GCS score of 6-7 were intubated and 36% had CT scan abnormalities; 62% of patients with a GCS score of 8-9 were intubated and 62% had CT scan abnormalities; 20% of patients with a GCS score of 10-13 required intubation and 23% had abnormal CT scans.

Jeffreys,[10] 1981

Description of Study: A retrospective review of hospital records in 190 head injury patients who died after admission. Hypotension was one of the four most common avoidable factors correlated with death.

Classification: Class III Study

Conclusions: Early hypotension appears to be a common and avoidable cause of death in severe head injury patients.

Kohi,[11] 1984

Description of Study: A retrospective evaluation of 67 severe head injury patients seen over a six-month period were correlated with 6-month outcome. For a given GCS score, the presence of hypotension resulted in a worse outcome than would have been predicted.

Classification: Class III Study

Conclusions: Early hypotension increases the mortality and worsens the prognosis of survivors in severe head injury.

VII. Evidentiary Table (continued)

Kokoska,[12] 1998

Description of Study: A retrospective chart review of 72 pediatric patients admitted to a single center with a GCS score of 6-8; primarily evaluated morbidity from hypotension with a brief mention of hypoxemia.

Classification: Class III Study

Conclusions: Thirteen percent of patients had a documented hypoxic episode, and 6% had hypercarbia. The exact location (prehospital, ED, OR, PICU) of these episodes was not given. Hypoxemia and hypercarbia could not be related to outcome.

Marmarou,[13] 1991

Description of Study: From a prospectively collected database of 1,030 severe head injury patients; all 428 patients who met ICU monitoring criteria were analyzed for monitoring parameters that determined outcome and their threshold values. The two most critical values were the proportion of hourly ICP readings greater than 20 mm Hg and the proportion of hourly SBP readings less than 80 mm Hg.

Classification: Class II Study

Conclusions: The incidence of morbidity and mortality resulting from severe head injury is strongly related to ICP and hypotension measured during the course of ICP management.

Miller,[15] 1982

Description of Study: A prospective study of 225 severely head-injured patients regarding the influence of secondary insults on outcome. Hypotension (SBP < 95 mm Hg) was significantly associated with increased morbidity and mortality. The predictive independence of hypotension in comparison to other associated factors, however, was not investigated.

Classification: Class II Study

Conclusions: A strong statistical relationship exists between early hypotension and increased morbidity and mortality in patients with severe head injury.

Miller,[16] 1978

Description of Study: One hundred consecutive severe head injury patients were prospectively studied regarding the influence of secondary insults on outcome (report of first 100 patients in subsequent report of 225 patients [vide supra]). Hypotension (SBP < 95 mm Hg) associated with a trend (not statistically significant) toward worse outcome in entire cohort. This trend met statistical significance for patients without mass lesions. Seminal report relating early hypotension to increased morbidity and mortality. Influence of hypotension on outcome not analyzed independently from other associated factors.

Classification: Class II Study

Conclusions: This is the first prospective report implicating early hypotension as a major predictor of increased morbidity and mortality from severe head injury.

VII. Evidentiary Table (continued)

Narayan,[17] 1982

Description of Study: Retrospective analysis of 207 consecutively admitted severe head injury patients. Management included aggressive attempts to control ICP using a threshold of 20 mm Hg. Outcome was significantly correlated with the ability to control ICP.

Classification: Class III Study

Conclusions: ICP control using a threshold of 20 mm Hg as a part of an overall aggressive treatment approach to severe head injury may be associated with improved outcome.

Pietropaoli,[18] 1992

Description of Study: A retrospective review of the impact of hypotension (SBP < 90 mm Hg) on 53 otherwise normotensive severe head injury patients who required early surgery (within 72 hours of injury). The mortality rate was 82% in the group with hypotension and 25% in the normotensive group (p < 0.001). The duration of intraoperative hypotension was inversely correlated with Glasgow Outcome Scale score using linear regression (R = -0.30, p = 0.02).

Classification: Class III Study

Conclusions: Early surgery with intraoperative hypotension is significantly correlated with increased mortality from severe head injury in a duration-dependent fashion.

Pigula,[19] 1993

Description of Study: Fifty-eight children (< 17 years old) with severe head injuries were prospectively studied for the effect of hypotension (SBP < 90 mm Hg) on outcome. An episode of hypotension decreased survival fourfold. This finding was confirmed in a concomitant analysis of the effect of hypotension on outcome in 509 patients in the National Pediatric Trauma Registry. Hypotension appeared to eliminate any neuroprotective mechanisms normally afforded by age.

Classification: Class II Study

Conclusions: The detrimental effects of hypotension (SBP < 90 mm Hg) on outcome appear to extend to children.

Rose,[20] 1977

Description of Study: A retrospective review of hospital and necropsy records of 116 head injury patients who were known to have talked before dying. Hypotension was a major avoidable factor related to the increased mortality in this group.

Classification: Class III Study

Conclusions: Hypotension is a major avoidable cause of increased mortality in patients with moderate head injury.

VII. Evidentiary Table (continued)

Sayre,[21] 1996

Description of Study: A prospective, randomized, double-blind, placebo-controlled clinical trial of 41 patients over a one-year period at a university-based Level I trauma center. All patients were endotracheally-intubated head trauma victims with a GCS score less than 12 evaluated within 6 hours of injury.

Classification: Class II Study

Conclusions: Out-of-hospital administration of mannitol did not significantly change systolic blood pressure in this group of head-injured, multiple trauma patients. There is an insufficient number of patients in this pilot study to assess whether out-of-hospital administration of mannitol to head-injured patients is beneficial overall.

Seelig,[23] 1986

Description of Study: A study of all patients (n = 160) with an ICP of 30 mm Hg during the first 72 hours after injury from a prospectively collected database of severe head injury patients (n = 348). The incidence and severity of intracranial hypertension and increased overall mortality were significantly correlated with systemic hypotension. The statistical independence of hypotension as a predictor was not evaluated.

Classification: Class II Study

Conclusions: Early hypotension is significantly correlated with increased incidence and severity of intracranial hypertension and increased mortality.

Silverston,[24] 1989

Description of Study: A study of 25 consecutive trauma patients, including head injury, which evaluated the use of non-invasive pulse oximetry in the field and in a moving ambulance.

Classification: Class III Study

Conclusions: 16% of patients had an SaO_2 less than 75%, and an additional 28% were between 75% and 90%. There were no demonstrated difficulties in using the pulse oximeter in the field or ambulance.

Stocchetti,[25] 1996

Description of Study: A cohort study of 50 trauma patients transported from the scene by helicopter, which evaluated the incidence and effect of hypoxemia and hypotension on outcome.

Classification: Class III Study

Conclusions: Fifty-five percent of patients were hypoxic ($SaO_2 < 90\%$) and 24% were hypotensive. Both hypoxemia and hypotension negatively affected outcome, however, the degree to which each independently affected the outcome was not studied.

VII. Evidentiary Table (continued)

Vassar,[26] 1990

Description of Study: A prospective, randomized, double-blind, clinical trial of 106 patients over an 8-month period. Intracranial hemorrhage was present in 28 (26%) patients.

Classification: Class II Study

Conclusions: No adverse effects of rapid infusion of 7.5% NaCl or 7.5% NaCl/6% dextran 70 were noted. Nor were any beneficial effects noted. There was no evidence of potentiating intracranial bleeding. There were no cases of central pontine myelinolysis; however, patients with severe pre-existing disease were excluded from the study.

Vassar,[27] 1991

Description of Study: A prospective, randomized, double-blind, multicenter clinical trial of 166 hypotensive patients over a 44-month period. Fifty-three of these patients (32%) had a severe head injury (defined as an AIS score for the head of 4, 5, or 6).

Classification: Class II Study

Conclusions: Survival was not significantly different in the total patient group. The survival rate of severely head-injured patients to hospital discharge was significantly higher for those who received hypertonic saline/dextran (HSD) (32% of patients with HSD vs 16% in patients with LR) when using logistic regression analysis.

Vassar,[28] 1993

Description of Study: A prospective, randomized, double-blind, multicenter trial comparing the efficacy of administering 250 ml of hypertonic saline vs normal saline as the initial resuscitation fluid in 194 hypotensive trauma patients over a 15-month period. 144 of these patients (74%) had a severe brain injury (defined as an abbreviated injury score [AIS] for the head of 4, 5, or 6). Here, hypertonic saline significantly increased blood pressure and decreased overall fluid requirements. Post-hoc analysis of the severe head injury group (Class II analysis) revealed that the hypertonic saline group had a statistically significant improvement in survival-to-discharge. However, the improvement in overall survival was not statistically significant.

Classification: Class II Study

Conclusions: Raising the blood pressure in the hypotensive, severe head injury patient improves outcome in proportion to the efficacy of the resuscitation. Prehospital administration of 7.5% sodium chloride to hypotensive trauma patients was associated with a significant increase in blood pressure compared with infusion of Lactated Ringer's (LR) solution. The survivors in the LR and hypertonic saline (HS) groups had significantly higher blood pressures than the non-survivors. There was no significant increase in the overall survival of patients with severe brain injuries, however, the survival rate in the HS group was higher than that in the LR group for the cohort with a baseline GCS score of 8 or less.

Vassar,[29] 1993

Description of Study: Prospective, randomized, double-blind, controlled clinical trial of 258 hypotensive patients over 31 months at a university-based trauma center. Twenty-seven of these patients (10%) had a severe head injury (defined as an AIS score for the head of 4, 5, or 6 only for anatomic lesions).

Classification: Class I Study

Conclusions: The administration of 7.5% NaCl (HS) and 7.5% NaCl/6% dextran 70 (HSD) caused no neurologic abnormalities. On the contrary, their use was associated with improvement in survival (as compared with predicted survival) in the patients with low initial GCS score (< 8) and in patients with anatomic confirmation of severe cerebral damage. It appeared that the dextran added little to improvement in survival when compared with HS alone. HS solutions did increase the blood pressure response in all patients.

Wade,[30] 1997

Description of Study: Cohort analysis of individual patient data from a previously published prospective, randomized, double-blind trial of HSD in patients with TBI and hypotension. TBI was defined as an AIS score for the head of 4 or greater. Hypotension was defined as an SBP of 90 mm Hg or less. 1,395 data records were analyzed from six separate studies; 233 patients were then included in this review. Eighty patients were treated in the ED and 143 were treated in the prehospital phase.

Classification: Class II Study

Conclusions: There was no statistically significant difference in overall survival when HS was retrospectively compared with normal saline. Logistic regression analysis was performed on patients with TBI showing an odds ratio of 1:92 for 24-hour survival, and 2:12 for survival until discharge. Thus, patients with TBI in the presence of hypotension who received HSD were approximately twice as likely to survive as those who received saline. This was statistically significant ($p = 0.048$).

Winchell,[31] 1997

Description of Study: A retrospective, case control study of patients with severe head injury and a field GCS score less than 9 and head or neck AIS score greater than 4. This study compared patients who underwent prehospital endotracheal intubation with those who did not.

Classification: Class III Study

Conclusions: Prehospital endotracheal intubation was associated with a statistically significant improved survival.

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INDICATIONS FOR INTRACRANIAL PRESSURE MONITORING

I. Recommendations

A. Standards

There are insufficient data to support a treatment standard for this topic.

B. Guidelines

Intracranial pressure (ICP) monitoring is appropriate in patients with severe head injury with an abnormal admission CT scan. Severe head injury is defined as a Glasgow Coma Scale (GCS) score of 3-8 after cardiopulmonary resuscitation. An abnormal CT scan of the head is one that reveals hematomas, contusions, edema, or compressed basal cisterns.

ICP monitoring is appropriate in patients with severe head injury with a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, systolic blood pressure (SBP) < 90 mm Hg.

ICP monitoring is not routinely indicated in patients with mild or moderate head injury. However, a physician may choose to monitor ICP in certain conscious patients with traumatic mass lesions.

II. Overview

It is now clear that only part of the damage to the brain during head trauma occurs at the moment of impact. Numerous secondary insults compound the initial damage in the ensuing hours and days. A large body of published data since the late 1970s reports that significant reductions in mortality and morbidity can be achieved in patients with severe head injury by using intensive management protocols.[2,32,38] These protocols emphasize early intubation, rapid transportation to an appropriate trauma care facility, prompt resuscitation, early CT scanning, and immediate evacuation of intracranial mass lesions, followed by meticulous management in an Intensive Care Unit (ICU) setting. Compared to earlier studies that had reported a mortality rate of approximately 50%,[21] these efforts resulted in a 36% mortality rate from severe head injury in the Traumatic Coma Data Bank (TCDB).[30]

Normal ICP is between 0-10 mm Hg (0-136 mm water). Different authors have used 15, 20, or 25 mm Hg as the arbitrary upper limit, beyond which treatment is initiated. Most centers use

20 mm Hg as the upper limit. However, an adequate cerebral perfusion pressure (CPP) is probably more important than the ICP per se. (CPP = mean arterial blood pressure – ICP.)

The main objective of intensive monitoring is to help the physician maintain adequate cerebral perfusion and oxygenation and avoid medical and surgical complications while the brain recovers.[1] Strong evidence links systemic hypotension with poorer outcomes in head-injured patients.[8] The basis of this association appears to be adequate cerebral perfusion.[6,33,46] While earlier severe head injury studies concentrated on the importance of ICP elevations per se,[37,42] current evidence emphasizes the importance of the CPP.[46] Thus, in a hypotensive patient, even a marginally elevated ICP could be harmful. Conversely, a somewhat elevated blood presure (BP) could protect against brain ischemia in a patient with high ICP.

The only way to reliably determine the CPP is to continuously monitor ICP and BP. While BP monitoring is standard practice in the ICU setting, ICP monitoring is not yet universally used. The technique has some associated risks and requires a certain commitment of time, personnel, training, and expense. However, virtually all major head injury centers use ICP monitoring in guiding management, and it is an integral part of intensive care in these centers. It has therefore become difficult, if not impossible, in most centers, to perform a study that would single out ICP monitoring as the sole intervention to be tested. This chapter seeks to define the body of evidence available on this subject and to arrive at conclusions based on this evidence.

This section addresses three key questions related to ICP monitoring of patients with head injury:
1. Which patients are at high risk for ICP elevation?
2. How does ICP data help in patient management?
3. Does ICP monitoring improve outcome?

III. Process

We conducted a MEDLINE search from 1966 to 1998 using the following key terms: "head injury," "intracranial pressure," "intracranial hypertension," and "intracranial pressure monitoring."

Only English language literature was reviewed. A search of "head injury and intracranial pressure" resulted in 753 articles that were cited on MEDLINE. "Head injury and intracranial hypertension" resulted in 146 articles cited. We narrowed the list down to papers that dealt specifically with clinical ICP monitoring, using the following terms: "head injury" and "intracranial pressure monitoring" (41 articles); "intracranial pressure" and "monitoring" and "indications" (27 articles). We reviewed these articles and included the relevant ones in this analysis, along with certain other articles identified from other sources. We chose papers that reported outcome and excluded those in which ICP was only incidentally relevant. No articles were excluded because of their conclusion alone.

IV. Scientific Foundation

Which Patients Are at High Risk for ICP Elevation? (Table 1)

Mild and Moderate Head Injury

It is generally believed that head injury patients who are following commands (GCS 9-15) are at relatively low risk for intracranial hypertension (ICH) and may be followed with sequential neurological examinations. Less than 3% of patients with mild head injury (GCS 14 and 15) and about 10%-20% of those with moderate head injury (GCS 9-13) will deteriorate into coma and be classified with severe head injury. Thus, routine ICP monitoring is not indicated in patients with mild or moderate head injury. However, the treating physician may elect to monitor ICP in certain conscious patients with traumatic mass lesions.

Severe Head Injury

The correlation between high ICP and a poorer outcome in patients with severe head injury has been amply demonstrated by several groups.[2,22,27,29,30,38,41,51] An extensive body of clinical experience now indicates that lowering elevated ICP reduces the risk of herniation and ensures adequate cerebral perfusion, thus maximizing the likelihood of recovery.[11,38,42]

Given that placement of an ICP monitor is associated with a small risk of complications (see ICP monitoring technology chapter),[36,42] it is reasonable to try to limit its use to patients who are most at risk of ICH.

Patients with a GCS score of 8 or less (comatose patients) are the high-risk group.[29,42] However, even within this group, some patients are more likely to suffer ICH than others. In 1982, Narayan, et al., reported a prospective studied series of patients with severe closed head injury and found that in comatose head injury patients with an abnormal CT scan, the incidence of ICH was between 53%-63%.[42] In contrast, patients with a normal CT scan at admission had a relatively low incidence of ICP elevation (13%). However, within the normal CT group, if patients demonstrated at least two of three adverse features (age over 40 years, unilateral or bilateral motor posturing, or SBP < 90 mm Hg), their risk of ICH was similar to that of patients with abnormal CT scans.

In 1994, O'Sullivan, et al., reported on 8 patients with severe head injury whose admission CT scan did not show a mass lesion, midline shift, or effaced basal cisterns, and yet elevated ICP (> 20 mm Hg for 5 minutes or more) was recorded in 7 of the 8 patients.[44] It seems reasonable to conclude that the more carefully one looks for episodes of ICH, the more likely one is to find them. However, the majority of the patients at increased risk may be identifiable by the previously listed features.[13,40]

In 1979, Marshall, et al., reported the results of standardized aggressive treatment of 100 consecutive patients with severe head injury.[32] ICH (ICP > 15 mm Hg) was present in 55% of the patients. Based on this high incidence of ICH, these authors recommended continuous monitoring of ICP in patients with severe head injury.

In 1986, Lobato, et al., reported on 46 severe head injury patients who had completely normal CT scans during days 1 to 7 after head trauma.[25] These patients represented approximately 10% of a series of 448 cases. These authors reported that "sustained elevation of the ICP was not seen in these patients, indicating that ICP monitoring may be omitted in cases with a normal scan." However, because one-third of the patients with a normal admission scan

developed new pathology within the first few days of injury, the authors recommended a strategy for follow-up scanning.

In 1990, Eisenberg, et al., reporting on the TCDB study, also concluded that "severely head-injured patients whose initial CT scan does not show a mass lesion, midline shift, or abnormal cisterns, have a 10%-15% chance of developing elevated pressure."[11] This study analyzed the CT scans of 753 prospectively studied patients treated in a uniform fashion at four major head injury research centers in the United States between 1984 and 1987.

In 1991, Marmarou, et al., reported on the relationship between ICP and blood pressure in determining outcome following severe head injury.[29] In the TCDB database of 1,030 patients, 428 patients who underwent ICP monitoring from within 18 hours post-injury to at least 60 hours post-injury were analyzed. In addition to the factors of age, admission motor score, and admission pupillary response, the factor most predictive of outcome was the proportion of ICP measurements greater than 20 mm Hg. The next most significant factor was the proportion of mean blood pressure (BP) measurements less than 80 mm Hg.

In 1993, Gopinath, et al., studied the relationship between physiological thresholds and outcome.[17] In a large cohort of uniformly managed patients on whom data was prospectively collected, separate analyses revealed that outcome was adversely affected when ICP was over 25 mm Hg, mean arterial blood pressure under 80 mm Hg, and CPP under 60 mm Hg.

Thus, ICP monitoring is justified in all comatose head injury patients. However, patients with normal CT scans are at lower risk for ICH if they have only one or none of the factors cited above.

How Does ICP Data Influence Patient Management? (Table 2)

Although ventriculostomies can serve as a therapeutic tool for raised ICP by allowing CSF drainage, ICP monitoring is primarily a means for guiding therapy.[12,26] Just as it is impossible to achieve optimal control of blood pressure or blood sugar without appropriate monitoring, it is not possible to treat ICP accurately without knowing what it is. It has been known for several decades that one cannot ascertain ICP simply by observing clinical signs such as pupillary size and reactivity or motor response until the patient has herniated.[4,26]

ICP data allow a clinician to manage the head-injured patient based on objective data. There is good evidence that virtually all therapies used to control ICP are double-edged swords. Severe prolonged hyperventilation has been conclusively shown in a prospective randomized study to worsen outcome in severe head-injured patients.[39] Recent evidence based on jugular venous oxygen saturation monitoring ($SjvO_2$) indicates that severe hyperventilation ($PaCO_2 < 25$) causes ischemic episodes probably by constricting the cerebral vasculature.[18,45,50] Yet hyperventilation is still widely used in head injury patients to reduce ICP without monitoring ICP.[15]

The response of ICP to mannitol is unpredictable in a given patient—both in extent and duration.[31,34] Furthermore, there is evidence that cumulative doses of mannitol can exacerbate brain edema by leaking into the interstitium.[23] However, mannitol is empirically used in head-injured patients with periodic serum osmolality measurements often used as the sole limiting criterion.

Sedation, analgesia, and chemical paralysis are now used routinely in the acute management of severe head injury. These interventions prevent a patient from hurting him/herself externally, and even more importantly, prevent blood pressure elevations and associated

ICP surges. However, these agents make it difficult, if not impossible, to interpret the clinical exam. ICP data are valuable in this setting for the early detection of developing brain swelling or mass lesions. However, paralysis should not be used if sedation and analgesia are adequate.[7]

An extreme example of sedation/paralysis is the use of barbiturate coma for ICP control. ICP monitoring is critical in this instance, both to decide when this risky therapy needs to be initiated and when it can be tapered off. There is Class I evidence showing that barbiturates are effective in reducing ICH when all other measures have failed. Furthermore, patients in whom the ICP could be thus controlled had a significantly better outcome than those in whom it could not.[10]

ICP monitoring has achieved widespread use in nontraumatic neurological disorders such as subarachnoid hemorrhage and hydrocephalus, and to a lesser extent in brain tumors, infarctions, intracerebral hemorrhages, and infections (encephalitis, meningitis, cysticercosis). In Reye's syndrome, which is characterized by brain swelling, there is Class II evidence that ICP monitoring and a management protocol similar to that used for severe head injury can reduce mortality and morbidity.[20]

Finally, the value of ICP data is not confined to guiding therapy. ICP data are strong predictors of outcome.[32,38,41] Patients with normal ICP have the best prognosis, whereas those with controllable ICH do less well and those with uncontrollable pressures do the worst.[41] Strong evidence indicates that ICP data can increase the confidence of outcome predictions that are based on the clinical examination alone.[29,41] Thus, ICP data can help the clinician to predict outcome with greater certainty and thus counsel the patients' families more accurately. ICP data may also allow more appropriate allocation of resources.

Does ICP Monitoring Improve Outcome? (Table 3)

Proving the Effectiveness of an Intervention
To prove that any therapy or intervention (such as ICP monitoring) improves mortality from head injury from 35% to 25% with an alpha of 5% ($p < 0.05$) and a beta of 20% (power 80%) requires a sample size of 349 in each treatment arm.[5] In other words, to prove that ICP monitoring per se improves mortality would require a prospective, randomized study with [698 + 10%] = 768 patients. Because most busy trauma centers can enter only about 50 severe head injury patients annually into such studies, this would require a multicenter design and take 4-5 years to complete. The cost of such an undertaking would be over $5 million, based on past experience.

A study of this nature has not been performed for the following reasons: 1) ICP monitoring has become an integral part of the management of severe head injury in virtually all head injury research centers. Hence, it would be difficult to design a study in which a group of patients would not be monitored, or would be treated according to an empiric protocol independent of the ICP; 2) the ethical basis for such a study may be questionable; 3) with several promising drugs becoming available for clinical trials, enthusiasm is limited for embarking on a study of a technique that is considered to be indispensable by most experts in the field; 4) such a study was proposed by the centers that comprised the TCDB but was not funded by the National Institutes of Health (NIH).

Evidence in Support of ICP Monitoring

In 1977, Jennett, et al., reported on the outcome from severe head injury in three countries.[21] The mortality figures in comatose patients (GCS < 8 for at least 6 hours) from all centers was close to 50%. Soon thereafter, Becker, et al., from Richmond reported a significantly reduced mortality (30%) by use of an intensive management protocol that included ICP monitoring.[2,38]

Around the same time, similar improvements in outcome with similar intensive protocols were being reported by other centers.[32,47] In 1982, Saul and Ducker reported a prospective trial in which 127 patients with a GCS score of 7 or less were treated with mannitol and cerebrospinal fluid (CSF) drainage for an ICP of over 20-25 mm Hg. The next 106 severely head-injured patients were similarly treated but at a lower ICP level (15 mm Hg). They found that the mortality was 46% in the former group and 28% in the latter group (p < 0.0005). The treatment at a lower ICP level reduced the incidence of an ICP greater than 25 mm Hg from 34% to 25% (p < 0.05).[47] The fact that the two groups were treated during two different time periods is an uncontrollable variable.

In 1988, Eisenberg, et al., reported a multicenter study of the use of pentobarbital to treat patients with ICP elevations refractory to simpler measures.[10] In this study, patients whose ICP could be controlled had a much better outcome than those in whom it could not be controlled. Because all decisions relative to therapy were based on ICP data, monitoring of this physiological parameter was central to therapy.

In 1989, Colohan, et al., reported a comparative study of the outcome from head injury in Charlottesville, Virginia, and New Delhi, India.[9] All head injury patients admitted to a university hospital in these two cities for more than 4 hours were included in the study (Charlottesville, 822 patients; New Delhi, 551 patients). In both centers, the flaccid patients (GCS motor score of 1) did uniformly poorly and those patients who were following commands (GCS motor score of 6) did uniformly well. The patients that demonstrated extension, abnormal flexion, or flexion withdrawal (GCSm = 2, 3, 4) had a lower mortality rate in Charlottesville (40.9%) than in New Delhi (56.2%), but the number of patients was not sufficient to reach statistical significance. One striking difference in mortality did exist, and this was in the patients who localized to painful stimuli (GCSm = 5). In this group, the mortality was 2.5 times greater in New Delhi (12.5%) than in Charlottesville (4.8%) (p < 0.01). The use of ICP monitoring and better critical care in Charlottesville was presumably responsible for this difference. However, several other factors may be responsible.

In 1991, the TCDB, consisting of four head injury research centers in the United States, reported a mortality rate of 36% in patients with a GCS score of 8 or less.[29] ICP monitoring was central to the management of patients in all four centers.

Recently, Ghajar, et al., reported a non-randomized study in which a comparison was made between 34 patients who were treated with ICP monitoring and ventricular drainage for ICP greater than 15 mm Hg and 15 patients who did not receive ICP monitors and were not treated for ICH.[16] Patients with a GCS score of 7 or below for 24 hours or more were included in the study. Patients were assigned to one group according to which attending neurosurgeon was on call on the day of admission. Mortality in the monitored group was 12% and in the non-monitored group 53%. An analysis of 14 series of head injury patients in the United States suggested that the use of ventricular drainage shows lower mortality in series that use CSF drainage routinely (21%) as compared to sometimes (35%) or never (43%) (see Tables 4 and 5).[14] The non-randomized nature of these analyses should be kept in mind.

Evidence Against the Value of ICP Monitoring

In 1983, Stuart, et al., reported a prospective series of 100 consecutive patients with severe head injury treated in Queensland, Australia, between 1979 and 1981.[49] These patients were comatose for at least 6 hours post-injury. ICP monitoring was not carried out in this series and assisted ventilation was used in 43 patients. The incidence of surgical hematomas was 52%. The mortality rate in this series was 34%, with 49% of patients achieving a good or moderately disabled outcome. While this report seems to throw into question the value of intensive therapies if comparable results can be achieved without them, it should be noted that this study highlights the difficulties inherent in comparing disparate patient groups. Fifty-five percent of the patients in this series were transferred from facilities a great distance away from the neurosurgical center (11 km to over 300 km). The authors of this study note that "mortality rates decreased with increasing distance of transfer, and this probably represents both natural and medical selection. Many of the most severely injured do not survive long enough to reach a major center, and medical officers are reluctant to send a patient a long distance if the prognosis is "hopeless." The selection bias of this local circumstance undermines the comparability of this study to the predominantly urban series that are in the literature.

In 1986, Smith, et al., reported a prospective, randomized study of 80 patients with severe head injury (GCS ≤ 8).[48] All patients were intubated and moderately hyperventilated, ICP was monitored with bolts, and CT of the head was obtained every 2 to 3 days. Group I received mannitol for ICP greater than 25 mm Hg and pentobarbital for ICP greater than 35 mm Hg. Group II empirically received 0.25 gm/kg/2 hr. The mortality in the specifically treated group was 35%, while in the empirically treated group it was 42%. Although suggesting a better outcome in Group I, the difference was not statistically significant. This study was limited by its sample size. As noted earlier, it would have taken 349 patients in each group (rather than about 40) to demonstrate a 10% improvement in mortality.

V.   Summary

ICP monitoring per se has never been subjected to a prospective, randomized clinical trial (PRCT) to establish its efficacy (or lack thereof) in improving outcome from severe head injury. Hence, there are insufficient data to support its use as a standard. However, there is a large body of published clinical experience that indicates that ICP monitoring: 1) helps in the earlier detection of intracranial mass lesions, 2) can limit the indiscriminate use of therapies to control ICP, which themselves can be potentially harmful, 3) can reduce ICP by CSF drainage and thus improve cerebral perfusion, 4) helps in determining prognosis, and 5) may improve outcome. ICP monitoring is therefore used by most head injury experts in the United States and is accepted as a relatively low-risk, high-yield, modest-cost intervention. Comatose head injury patients (GCS 3-8) with abnormal CT scans should undergo ICP monitoring. Comatose patients with normal CT scans have a much lower incidence of ICH unless they have two or more of the following features at admission: age over 40, unilateral or bilateral motor posturing, or a systolic blood pressure (SBP) of less than 90 mm Hg. ICP monitoring in patients with a normal CT scan with two or more of these risk factors is suggested as a guideline. Routine ICP monitoring is not indicated in patients with mild or moderate head injury. However, it may be undertaken in certain conscious patients with traumatic mass lesions at the discretion of the treating physician.

VI. Key Issues for Future Investigation

A prospective, randomized, clinical trial of ICP monitoring would be extremely useful in establishing the value of this technique. However, it is not clear that such a trial will ever be performed. Most head injury experts consider ICP or CPP to be the primary basis for ICU management decisions in the care of the severe head-injured patient. However, some neurosurgeons do not routinely monitor ICP in severe head injury patients, demand proof that it makes a difference, and believe that the risks do not justify the benefits. A PRCT would require approximately 700 patients with severe head injury to demonstrate a 10% difference in mortality. One would need a multicentered trial at a cost of at least $5 million. The management of the non-monitored group would remain problematic. Such a trial was proposed to the NIH a few years ago but was not funded. There is a NIH-funded trial currently underway comparing traditional ICP management to management aimed at maintaining a certain CPP in severe head injury patients. This study may provide the type of Class I data that is required without randomizing one group of patients to a non-monitored arm.

VII. Evidentiary Tables
Table 1: Which Patients Are at High Risk for ICP Elevation?

Eisenberg,[10] 1988

Description of Study: In a multicenter study, 73 patients with severe head injury and elevated ICP refractory to all standard measures were prospectively randomized to receive either a regimen that included high-dose pentobarbital or one that was similar but did not include pentobarbital.

Classification: Class I Study

Conclusions: Patients whose ICP could be controlled with pentobarbital had a much better outcome than those in whom it could not be controlled. At 1 month, 92% of the patients who responded to treatment survived and 83% who did not respond had died.

Eisenberg,[11] 1990

Description of Study: Prospective multicenter study (TCDB) in which the authors examined the CT scans of 753 patients with severe head injury who were treated in a consistent fashion.

Classification: Class II Study

Conclusions: Severely head-injured patients whose initial CT scan does not show a mass lesion, midline shift, or abnormal cisterns have a 10-15% chance of developing elevated pressure.

Feldman,[13] 1994

Description of Study: Letter to the editor.

Classification: Class III Study

Conclusions: Response to O'Sullivan paper.

Abbreviations: GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state; D, dead

VII. Evidentiary Table 1 (continued)

Gopinath,[17] 1993

Description of Study: ICP, MABP, CPP, $ETCO_2$, $SjvO_2$, and SaO_2 were continuously monitored in 163 severely head-injured patients to determine the critical values for these parameters and to relate them to outcome.

Classification: Class II Study

Conclusions: It was determined in separate analyses that outcome was adversely affected when ICP was greater than 25 mm Hg, MABP less than 80 mm Hg, and CPP less than 60 mm Hg.

Johnston,[22] 1970

Description of Study: Observational study of 32 patients with severe head injury. All patients had continuous ICP monitoring to observe the effects of elevated ICP vs normal ICP.

Classification: Class II Study

Conclusions: In Group I (ICP < 20 mm Hg) 5 of 9 patients died; in Group II (ICP = 20-40 mm Hg) 6 of 11 patients died; in Group III (ICP > 40 mm Hg) 8 of 12 patients died and 3 remained in coma.

Lobato,[25] 1986

Description of Study: Study of 46 severe head injury patients who had normal CT scans days 1 through 7 post-injury.

Classification: Class II Study

Conclusions: "A sustained elevation of ICP was not seen in these patients, indicating that ICP monitoring may be omitted in cases with a normal scan." However, a strategy for controlled scanning was recommended because 1 of 3 patients with a normal admission scan developed new pathology within the first few days of injury.

Lundberg,[27] 1965

Description of Study: Thirty patients underwent ICP monitoring to examine the variations of ICP during the acute post-injury stage.

Classification: Class II Study

Conclusions: Uncontrollable ICP greater than 40 mm Hg usually led to a poor outcome.

Marmarou,[29] 1991

Description of Study: A study of 428 severely head-injured patients from the TCDB. Described the relationship between raised ICP (> 20 mm Hg), hypotension, and outcome.

Classification: Class II Study

Conclusions: The proportion of ICP measurements greater than 20 mm Hg was highly significant in explaining outcome (p < 0.0001). As ICP > 20 increased, more favorable outcomes (G/MD) became less likely while worse outcomes (V/D) became more likely. The next most significant factor in predicting outcome was the proportion of mean blood pressure (BP) measurements less than 80 mm Hg. Patients with a GCS less than 8 are at high risk of developing ICH.

Marshall,[30] 1991

Description of Study: The outcome of severe head injury was prospectively studied in 746 patients enrolled in the TCDB. All patients were managed by a relatively "homogeneous" protocol that included ICP monitoring.

Classification: Class II Study

Conclusions: Among the patients with nonsurgical lesions, the mortality rate was higher in those having an increased likelihood of elevated ICP greater than 25 mm Hg (diffuse injury III and IV).

Marshall,[32] 1979

Description of Study: Results of a study in which 100 consecutive patients with severe head injury were managed using a standardized intensive protocol that included ICP monitoring.

Classification: Class II Study

Conclusions: ICH (ICP > 15 mm Hg) was present in 55% of the patients. ICP monitoring to control ICH was recommended in patients with severe head injury.

Miller,[36] 1987

Description of Study: Review of ICP monitoring.

Classification: Class III Study

Conclusions: ICP monitoring is associated with an infection rate of about 6% and a major hemorrhage rate of 1-2%.

Abbreviations: GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state; D, dead

VII. Evidentiary Table 1 (continued)

Miller,[37] 1977

Description of Study: Series of 160 consecutive patients with severe head injury whose ICP was continuously monitored to determine the frequency, extent, and significance of ICH.

Classification: Class II Study

Conclusions: 82% of patients had elevated ICP on admission, (i.e., ICP > 20 mm Hg in 44% and > 40 mm Hg in 10%). Patients with an ICP greater than 40 mm Hg and those with diffuse brain injury and an ICP greater than 10 mm Hg on admission had a poor outcome. It was recommended that ICP monitoring be included in the management of severely head-injured patients.

Miller,[38] 1981

Description of Study: Series of 225 prospective, consecutive patients with severe head injury managed by a uniform and intensive protocol in an effort to relate outcome to several clinical variables.

Classification: Class II Study

Conclusions: Factors important in predicting a poor outcome included: presence of intracranial hematoma; increasing age; abnormal motor responses; impaired or absent eye movements or pupil light reflexes; early hypotension, hypoxemia, or hypercarbia; and elevation of ICP greater than 20 mm Hg despite artificial ventilation.

Narayan,[40] 1994

Description of Study: Letter to the editor.

Classification: Class III Study

Conclusions: Response to O'Sullivan paper.

Narayan,[41] 1981

Description of Study: Clinical signs, multimodality evoked potentials, CT scan, and ICP data were prospectively recorded and analyzed in 133 severely head-injured patients to ascertain their accuracy and relative value in predicting one of two categories of outcome.

Classification: Class II Study

Conclusions: An ICP greater than 20 mm Hg that required treatment was associated with a significantly poorer prognosis (36% G/MD) than if the ICP was less than 20 mm Hg (80% G/MD).

Abbreviations: GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state; D, dead

Narayan,[42] 1982

Description of Study: 207 consecutive patients with severe head injury who underwent ICP monitoring were analyzed to determine the efficacy and need of ICP monitoring.

Classification: Class II Study

Conclusions: Elevation of ICP at any stage was associated with a significantly poorer outcome (27% G, 16% MD) as compared to patients with normal ICP courses (59% G, 18% MD) (p < 0.0001). Patients with persistently elevated ICPs refractory to therapy almost always died. A 6.3% infection rate and a 1.4% hemorrhage rate was encountered. Comatose patients with an abnormal CT scan had a 53%-63% incidence of ICH, while patients with a normal CT scan at admission had a 13% incidence of ICP elevation; however, in patients with normal CT scans with 2 of the 3 adverse features (age greater than 40 years, uni- or bilateral posturing, or SBP < 90 mm Hg), the incidence of ICH was 60%. Patients with a GCS score 8 or less are at high risk for of developing ICH, especially if their CT scan is abnormal.

O'Sullivan,[44] 1994

Description of Study: Eight patients with severe head injury whose admission CT scan did not show a mass lesion, midline shift, or effaced basal cisterns had continuous ICP, BP, and CPP monitoring to determine what percentage would develop ICH under intensive monitoring and data acquisition.

Classification: Class II Study

Conclusions: Seven of the 8 patients developed ICH (ICP ≥ 20 mm Hg for more than 5 minutes). Reduced CPP of 60 mm Hg or less for more than 5 minutes was recorded in 5 of the 8 patients. The authors concluded that in patients with severe head injury, episodes of ICH occur even in normal CT scans.

Troupp,[51] 1965

Description of Study: Series of 9 patients with severe head injury in whom the ICP was continuously recorded for 3-14 days after injury.

Classification: Class III Study

Conclusions: An ICP less than 30 mm Hg indicated a good prognosis (4 of the 5 patients recovered favorably, 1 patient died due to an unrelated complication); in the absence of a removable hematoma, sustained ICP greater than 30 mm Hg indicated a poor prognosis (3 of the 4 patients died).

Abbreviations: GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state; D, dead

Table 2: How Does ICP Data Influence Patient Management?

Browder,[4] 1936

Description of Study: Case review study of 23 cases of head injury to ascertain the relationship of BP, pulse rate, and CSF pressure for diagnosis, prognosis, and treatment in severe head injury.

Classification: Class III Study

Conclusions: The "classical pattern of signs," consisting of steady rise above normal levels of blood pressure, steady fall in pulse rate, decrease in respiratory rate, stupor, coma, vomiting, etc., which had been held to indicate that ICP was increasing, was not seen in this series.

Chesnut,[7] 1994

Description of Study: Retrospective review of data from 514 TCDB patients to investigate the efficacy of early, routine use of neuromuscular blocking agents for ICP management: Group 1 (n = 239) patients were pharmacologically paralyzed; Group 2 (n=275) patients were not pharmacologically paralyzed.

Classification: Class II Study

Conclusions: The final GCS scores for the two groups were not significantly different in those G/MD survivors. Group 2 had a higher mortality rate (39%) than Group 1 (24%), however, there were more SD/V survivors in Group 1 (21% vs 13% and 8% vs 4%, respectively). The authors recommended that routine early management of head-injured patients in the ICU should be accomplished using sedation alone, and neuromuscular blockade should be generally reserved for patients with ICH who require escalation of treatment intensity.

Eisenberg,[10] 1988

Description of Study: In a multicenter study, 73 patients with severe head injury and refractory elevation of ICP were prospectively randomized to receive either a regimen that included high-dose pentobarbital or one that was similar but did not include pentobarbital.

Classification: Class I Study

Conclusions: Patients whose ICP could be controlled with pentobarbital had a much better outcome than those in whom it could not be controlled; at 1 month, 92% of the patients who responded to treatment survived and 83% who did not respond had died.

Feldman,[12] 1993

Description of Study: Review of ICP monitoring.

Classification: Class III Study

Conclusions: Although ventriculostomies can serve as a therapeutic tool for raised ICP by allowing cerebrospinal fluid drainage, ICP monitoring is primarily a means for guiding therapy.

Abbreviations: GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state; D, dead

VII. Evidentiary Table 2 (continued)

Ghajar,[15] 1995

Description of Study: Telephone survey of hospitals that care for head injury patients to determine standard practices.

Classification: Class III Study

Conclusions: A large number of hospitals were using measures to reduce ICP, such as hyperventilation and mannitol, without monitoring the ICP.

Gopinath,[18] 1994

Description of Study: 116 severely head-injured patients had continuous $SjvO_2$ monitoring during days 1-5 after injury to examine the relationship between episodes of jugular venous desaturation ($SjvO_2 < 50\%$ for more than 10 minutes) and neurological outcome.

Classification: Class II Study

Conclusions: 90% of patients with multiple desaturations and 74% of patients with one desaturation had a poor neurological outcome as compared with 55% of patients with no episodes of desaturation. The incidence of desaturation was significantly associated with a poor outcome ($p = 0.03$).

Jenkins,[20] 1987

Description of Study: Direct measurements of arterial blood pressure and ICP were recorded in 39 patients with Reye's Syndrome (stage 2 and beyond) ranging in age from 3-6 months to 5 years 11 months.

Classification: Class II Study

Conclusions: Thirty-three of the 39 patients survived, and 27 made a full recovery. Measurement of CPP proved to be a better guide to prognosis and management than ICP alone. ICP monitoring was considered mandatory in all but the mildest cases of Reye's syndrome.

Lundberg,[26] 1960

Description of Study: Early experience with ICP monitoring in patients.

Classification: Class II Study

Conclusions: ICP monitoring can be undertaken safely.

Marshall,[31] 1978

Description of Study: Eight patients with severe head injury and who received ICP monitoring were studied to determine the dose-response relationship, the osmotic gradient required, and the time course of ICP reduction produced by mannitol.

Classification: Class II Study

Conclusions: It was seen that smaller and more frequent doses of mannitol are as effective in reducing ICP as larger doses.

VII. Evidentiary Table 2 (continued)

Marshall,[32] 1979

Description of Study: Results of a study in which 100 consecutive patients with severe head injury were managed using a standardized intensive protocol that included ICP monitoring.

Classification: Class II Study

Conclusions: ICH (ICP > 15 mm Hg) was present in 55% of the patients. ICP monitoring to control ICH was recommended in patients with severe head injury.

Mendelow,[34] 1985

Description of Study: The effect of mannitol on CPP, ICP, and CBF was studied in 55 patients with severe head injury.

Classification: Class II Study

Conclusions: Mannitol consistently reduced ICP and increased CPP and CBF 10-20 minutes after infusion.

Miller,[38] 1981

Description of Study: Clinical series of 225 prospective, consecutive patients with severe head injury managed with a uniform and intensive protocol in order to detect a link between outcome and several clinical variables.

Classification: Class II Study

Conclusions: Factors important in predicting a poor outcome included: presence of intracranial hematoma; increasing age; abnormal motor responses; impaired or absent eye movements or pupil light reflexes; early hypotension, hypoxemia, or hypercarbia; elevation of ICP (> 20 mm Hg) despite artificial ventilation.

Muizelaar,[39] 1991

Description of Study: A prospective, randomized trial on 113 severely head-injured patients, using three groups: control, hyperventilated, and hyperventilated and THAM.

Classification: Class I Study

Conclusions: Prophylactic hyperventilation proved harmful in head-injured patients with motor scores of 4-5; when sustained hyperventilation was necessary for ICP control, its harmful effects might have been partially overcome by THAM.

Narayan,[41] 1981

Description of Study: Clinical signs, MEPs, CT scans, and ICP data were prospectively recorded and analyzed in 133 severely head-injured patients to ascertain their accuracy and relative value, either individually or in various combinations, in predicting one of two categories of outcome.

Classification: Class II Study

Conclusions: An ICP greater than 20 mm Hg that required treatment was associated with a significantly poorer prognosis (36% G/MD) than if the ICP was less than 20 mm Hg (80% G/MD).

Robertson,[45] 1992

Description of Study: CBF and other physiological variables were measured repeatedly for up to 10 days after severe head injury in 102 patients, and CBF levels were related to outcome.

Classification: Class II Study

Conclusions: A reduced CBF was significantly associated with an unfavorable outcome.

Sheinberg,[50] 1992

Description of Study: Continuous measurement of $SjvO_2$ with a fiberoptic catheter was performed on 45 patients with severe head injury as a method of detecting cerebral ischemia.

Classification: Class II Study

Conclusions: Hypocarbia ($PaCO_2 < 28$ mm Hg) was one cause of 10 jugular venous oxygen desaturation episodes ($SjvO_2 < 50\%$ for more than 15 minutes).

Table 3: Does ICP Monitoring Improve Outcome?

Becker,[2] 1977

Description of Study: 160 patients with severe head injury were managed with a standardized protocol that emphasized early diagnosis and evacuation of mass lesions, artificial ventilation, control of ICH by monitoring ICP, and aggressive medical therapy.

Classification: Class II Study

Conclusions: A 30% mortality rate was reported by this study as compared to the 50% mortality rate reported from the three centers in Jennett, et al., 1977.

Colohan,[9] 1989

Description of Study: A comparative prospective study of 551 patients with head injury in New Delhi, India, and 822 patients in Charlottesville, Virginia.

Classification: Class II Study

Conclusions: In patients who localized to painful stimuli (GCS motor=5), the mortality was 2.5 times greater in New Delhi (12.5%) than in Charlottesville (4.8%) (p < 0.01). The use of ICP monitoring and better critical care were among the factors believed to be responsible for this difference.

Eisenberg,[10] 1988

Description of Study: In a multicenter study, 73 patients with severe head injury and elevated ICP were prospectively randomized to receive either a regimen that included high-dose pentobarbital or one that was similar but did not include pentobarbital.

Classification: Class I Study

Conclusions: Because all decisions relative to therapy were based on ICP data, ICP monitoring was pertinent to therapy. Patients whose ICP could be controlled with pentobarbital had a much better outcome than those in whom it could not be controlled; at 1 month 92% of the patients who responded to treatment survived and 83% who did not respond had died.

Ghajar,[14] 1995

Description of Study: A meta analysis of 14 U.S. series of head injury that report the use of ventricular drainage for therapeutic measures.

Classification: Class III Study

Conclusions: A 28% mortality was found in series that use CSF drainage routinely as compared to 34% mortality that use it sometimes and 44% that never use CSF drainage.

Ghajar,[16] 1993

Description of Study: Prospective, non-randomized cohort study of 49 consecutive severely head-injured patients: Group 1 (34 patients) received ICP monitoring and CSF drainage when ICP was greater than 15 mm Hg; Group 2 (15 patients) received no ICP monitoring and were not treated for ICH.

Classification: Class II Study

Conclusions: Mortality in Group 1 was 12% and in Group 2 was 53%.

VII. Evidentiary Table 3 (continued)

Jennett,[21] 1977

Description of Study: Early characteristics and late outcome after severe head injury were reported in 700 cases in three countries (Scotland, The Netherlands, and United States). ICP monitoring was not routinely used.

Classification: Class II Study

Conclusions: Mortality figures in comatose patients (GCS ≤ 8 or less for at least 6 hours) from all centers was close to 50%.

Marmarou,[29] 1991

Description of Study: A study of 428 severely head-injured patients form the TCDB describing the relationship between raised ICP (> 20 mm Hg), hypotension, and outcome.

Classification: Class II Study

Conclusions: A mortality rate of 36% was reported. ICP management was central to this study.

Marshall,[30] 1991

Description of Study: The outcome of severe head injury was prospectively studied in 746 patients enrolled in the TCDB. All patients were managed by a relatively "homogeneous" protocol that included ICP monitoring.

Classification: Class II Study

Conclusions: A mortality rate of 36% was reported as compared to the 50% mortality rate reported in Jennett, et al., 1977.

Marshall,[32] 1979

Description of Study: Results of a study in which 100 consecutive patients with severe head injury were managed using a standardized intensive protocol that included ICP monitoring.

Classification: Class II Study

Conclusions: A mortality rate of 28% was reported as compared to the 50% mortality rate reported in Jennett, et al., 1977.

Miller,[38] 1981

Description of Study: Clinical series of 225 prospective, consecutive patients with severe head injury managed with a uniform and intensive protocol in order to relate outcome to several clinical variables.

Classification: Class II Study

Conclusions: This study reported a 34% mortality rate, an improvement compared to the 1977 Jennett, et al., report of a 50% mortality from three centers. This series met the 6 -hour requirement used in the Jennett report.

VII.   Evidentiary Table 3 (continued)

Saul,[47] 1982

Description of Study: Prospective study of 127 severely head-injured patients who were treated with mannitol and CSF drainage for an ICP at 20 to 25 mm Hg, and 106 patients who were treated similarly except at a lower ICP (>15 mm Hg) level.

Classification: Class II Study

Conclusions: Mortality was 46% in the 127 patients treated for an ICP at 20-25 mm Hg and only 28% in the 106 patients treated at an ICP threshold of 15 mm Hg.

Smith,[48] 1986

Description of Study: A prospective, randomized study of 80 patients with severe head injury to assess the benefit of ICP monitoring with two regimens of mannitol administration: Group I received mannitol for an ICP greater than 25 mm Hg and Group II received empirical mannitol therapy irrespective of ICP.

Classification: Class II Study

Conclusions: No statistically significant differences in mortality rate or neurological outcome were demonstrated between the two groups. This study was limited by its sample size, an n = 349. Patients in each group would have been necessary to demonstrate a 10% improvement in mortality.

Stuart,[49] 1983

Description of Study: A retrospective analysis of 100 cases of severe head injury in Queensland, Australia, where ICP was not monitored. Patients who did not survive transportation to the tertiary neurosurgical center (often several hundred miles away) were not included in the analysis.

Classification: Class II Study

Conclusions: The mortality rate was 34%, and 49% of patients achieved a good or moderately disabled outcome. It is suggested that the outcome compares favorably with series in which ICP was monitored. However, the selection bias of this study undermines its comparability to the predominantly urban series that are in the literature.

Table 4: Comparison of Outcome: Fourteen U.S. Studies

First Author	number of patients	GCS	ICP Monitor*	CSF Drain	Rx at ICP (mm Hg)	OUTCOME G/MD (%)	Dead (%)
Jaggi[19]	64	≤ 9	bolt	0	> 20	47%	53%
Colohan[9]	122	≤ 8	bolt	0	> 20	—	41
Smith[48]	37	≤ 8	bolt	0	> 25	54	35
Wald[52]	170	≤ 8	epidural	0	> 20	48	41
Saul I[47]	127	≤ 7	ventric, bolt	+/0	> 25	—	46
Saul II[47]	106	≤ 7	ventric, bolt	+/0	> 15	54	28
Bowers[3]	200	≤ 7	ventric, bolt†	+/0	> 20/25	52	36
Becker[2]	160	≤ 9	ventric, bolt	+/0	> 25/40	60	30
Miller[37]	225	≤ 9	ventric, bolt	+/0	> 25	56	34
Muizelaar[39]	113	≤ 8	ventric, bolt	+/0	> 25	39	34
Marion[28]	68	≤ 8	ventric	+	‡	51	18
Narayan[42]	207	≤ 9	ventric	+	> 25	57	34
Rosner[46]	34	≤ 7	ventric	+	‡	68	21
Ghajar[16]	34	≤ 7	ventric	+	15	59	12

GCS = Glasgow Coma Score; ICP = intracranial pressure; CSF = cerebrospinal fluid;
GOS = Glasgow Outcome Scale; G = good recovery; MD = moderate disability
*ICP monitor deemed ventric if ventriculostomy was used in more than 90% of patients
† only 41% of patients were monitored
‡ cerebral perfusion pressure maintained at 70-80 mm Hg
0 = not used; + = used
— = data unavailable

Table 5: Average Outcomes from Studies Based on CSF Drainage Category

CSF Drainage Category	Independent (%)	Dead (%)
Never (0)	49.7%	43.0%
Sometimes (+/0)	52.2	34.7
Routinely (+)	58.8	21.3

Adapted from Ghajar[14], 1996.

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INTRACRANIAL PRESSURE TREATMENT THRESHOLD

I.   Recommendations
   A. Standards
       There are insufficient data to support a treatment standard for this topic.
   B. Guidelines
       Intracranial pressure (ICP) treatment should be initiated at an upper threshold of
       20-25 mm Hg.
   C. Options
       Interpretation and treatment of ICP based on any threshold should be corroborated
       by frequent clinical examination and cerebral perfusion pressure (CPP) data.

II.   Overview
Quantitative guidelines are needed for ICP management. The impact of ICP on outcome from severe head injury appears to lie in its role 1) in determining CPP, and 2) as an indicator of mass effect. Because CPP can be managed by manipulation of arterial pressure to a great extent, the issue of herniation is more determinant of the ICP threshold. The goal is to balance the risks of herniation against the iatrogenic risks of overtreatment.

III. Process
A MEDLINE search back to 1966 was undertaken using the following query: "intracranial hypertension" or "ICP" or "intracranial pressure" and "head injury" and "treatment" or "management" or "resuscitation" and "threshold" or "level" and "human subject". This produced 146 references. Of these, 46 were found to be directly relevant to clinical orientation and the issue of relating ICP treatment threshold to outcome. These references were individually reviewed for design, content, and relevance. The results of this review were then incorporated into the analysis presented here.

IV. Scientific Foundation
No prospective, randomized trials compare ICP treatment thresholds. The largest study using prospectively collected, observational data, controlling for a large number of confounding prognostic variables, analyzed the mean ICP in 5 mm Hg steps against outcome in a logistic regression model and found 20 mm Hg to be the optimal predictive value. [3]

These values are in keeping with small, non-controlled reports suggesting a range of 15-25 mm Hg.[4,6,7] The report by Saul and Ducker changed the ICP threshold from 25 mm Hg to 15 mm Hg in two sequentially treated groups of patients and found an associated decrease in mortality from 46% to 28%.[7] However, differences in protocols between the first and second treatment periods confound the determination of the independent influence of lowering the ICP treatment threshold on outcome.

The study by Eisenberg, et al., is the only prospective, double-blind, placebo-controlled study demonstrating improved outcome attributable to lowering ICP.[2] Their lowest ICP thresholds were 25 mm Hg in patients without craniectomy and 15 mm Hg in patients following craniectomy. However, they defined additional ICP thresholds at higher pressures and shorter durations (see barbiturates chapter for details) and they did not stratify outcome by threshold.

Patients can herniate at ICPs less than 20-25 mm Hg. The likelihood of herniation depends on the location of an intracranial mass lesion.[1,5] In the report by Marshall, et al., pupillary abnormalities occurred with ICP values as low as 18 mm Hg. Therefore, at all points, any chosen threshold must be closely and repeatedly corroborated with the clinical exam and CT imaging in an individual patient.

Adequate CPP values can generally be maintained with ICPs of greater than 20-25 mm Hg. In addition, the ICPs at which patients begin to show signs of herniation can also occasionally be greater than 20-25 mm Hg. Therefore, in select cases, a higher limit of acceptable ICPs may be chosen as long as an adequate CPP can be maintained.

V.   Summary

An absolute ICP threshold that is uniformly applicable is unlikely to exist. Current data, however, support 20-25 mm Hg as an upper threshold above which treatment to lower ICP should generally be initiated.[2,3,7]

VI. Key Issues for Future Investigation

The critical value of ICP and its interaction with CPP is the major unanswered question. As we recognize the importance of CPP and improve our ability to safely maintain an adequate CPP somewhat independently of ICP, the issue of an absolute value for ICP appears to be most closely related to the risk of herniation that seems to vary between patients and within patients over the course of their therapy. If a method to estimate this "herniation pressure" can be developed and the range of values wherein CPP is independent of mean arterial and intracranial pressures can be determined, more concrete treatment thresholds for ICP and CPP will be forthcoming.

VII. Evidentiary Table

Andrews,[1] 1988

Description of Study: Retrospective review of the clinical course and CT scans of 45 patients with supratentorial intracerebral hematomas to determine the effect of hematoma location on clinical course and outcome. Signs of herniation were significantly more common with temporal or temporoparietal lesions. Clot size of 30 cc was the threshold value for increased incidence of herniation.

Classification: Class III Study

Conclusions: Factors other than ICP (such as location of mass lesion) must be considered in guiding treatment.

VII. Evidentiary Table (continued)

Eisenberg,[2] 1998

Description of Study: Prospective, multicenter study wherein 73 severe head injury patients, whose ICP was not controllable using "conventional therapy," were randomly assigned to a high-dose pentobarbital vs placebo-control regimen. Dependent variable was ability to control ICP below 20 mm Hg. The outcome for study patients whose ICP could be kept below 20 mm Hg using either regimen was significantly better than those whose ICP could not be controlled.

Classification: Class II Study (with respect to ICP threshold)

Conclusions: Improved outcome when ICP could be controlled using a threshold of 20 mm Hg.

Marmarou,[3] 1991

Description of Study: From a prospectively collected database of 1,030 severe head injury patients, all 428 patients who met ICU monitoring criteria were analyzed for monitoring parameters that determined outcome and their threshold values. The ICP threshold most predictive of 6-month outcome was determined using logistic regression, evaluating values from 0-80 mm Hg in increments of 5 mm Hg. The threshold value of 20 mm Hg was found to best correlate with outcome. The proportion of hourly ICP reading greater then 20 mm Hg was a significant and powerful independent determinant of outcome. Notably, the four centers used ICP treatment thresholds of 20-25 mm Hg. The degree by which this confounds the regression statistics is unclear.

Classification: Class II Study

Conclusions: The incidence of morbiditly and mortality resulting from severe head injury is strongly related to ICP control wherein 20 mm Hg is the most predictive threshold.

Marshall,[4] 1979

Description of Study: Retrospective review of 100 consecutively admitted severe head injury patients. Patients managed employing a regimen including ICP monitoring using a threshold of 15 mm Hg as a part of an aggressive approach to treatment had improved outcome compared to published reports using less ICP-intensive therapy.

Data Class: Class III Study

Conclusions: ICP control using a threshold of 15 mm Hg as a part of an overall aggressive treatment approach to severe had injury may be associated with improved outcome.

Marshall,[5] 1983

Description of Study: Reported 14 patients with oval pupils felt to be due to elevated ICP. Associated ICP values ranged from 18-38 mm Hg. The pupil normalized in 9 of these patients when the ICP was reduced.

Classification: Class III Study

Conclusions: Signs of herniation due to intracranial hypertension can occur associated with a wide range of ICP values. ICP treatment thresholds should be tempered using other clinical values in individual patients.

Narayan,[6] 1982

Description of Study: Retrospective analysis of the courses of 207 consecutively admitted severe head injury patients. Management included aggressive attempts to control ICP using a threshold of 20 mm Hg. Outcome was significantly correlated with the ability to control ICP.

Classification: Class III Study

Conclusions: ICP control using a threshold of 20 mm Hg as a part of an overall aggressive treatment approach to severe head injury may be associated with improved outcome.

Saul,[7] 1982

Description of Study: A series of 127 severe head injury patients whose ICP treatment was initiated at 20-25 mm Hg, not using a strict treatment protocol, was compared with a subsequent group of 106 patients with similar injury characteristics who received treatment under a strict protocol at an ICP threshold of 15 mm Hg. Other treatment aspects had not been changed. The 46% mortality in the first group was significantly greater then the 28% mortality in the second group.

Classification: Class III Study

Conclusions: Suggests an increase in mortality if ICP maintains above a threshold between 15 and 25 mm Hg.

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RECOMMENDATIONS FOR INTRACRANIAL PRESSURE MONITORING TECHNOLOGY

I.   Recommendations*

In the current state of technology the ventricular catheter connected to an external strain gauge is the most accurate, low-cost, and reliable method of monitoring intracranial pressure (ICP). It also allows therapeutic cerebrospinal fluid drainage. ICP transduction via fiberoptic or strain gauge devices placed in ventricular catheters provide similar benefits, but at a higher cost.

Parenchymal ICP monitoring with fiberoptic or strain gauge catheter tip transduction is similar to ventricular ICP monitoring but has the potential for measurement drift.

Subarachnoid, subdural, and epidural monitors (fluid coupled or pneumatic) are currently less accurate.

II. Overview

In patients for whom ICP monitoring is indicated, a decision as to what type of monitoring device to use must be made. The optimal ICP monitoring device is one that is accurate, reliable, cost effective, and causes minimal patient morbidity. We reviewed the scientific literature on ICP monitoring and propose a ranking based on the currently available technology.

III. Process

A computerized literature search of MEDLINE from 1975 to January 1998 using the search words "monitor" and "intracranial pressure" found 4,290 articles, of which 1,000 articles were found to be pertinent to data in humans. Scientific publications on ICP monitoring devices used clinically and reporting accuracy or complications were reviewed in depth. Case reports were excluded.

*The assessment of ICP monitoring technology does not lend itself to classification of evidence as in other guideline sections. Thus, the ICP devices were evaluated in terms of their accuracy, reliability, therapeutic potential, and cost effectiveness.

IV. Scientific Foundation

The scientific discussion of ICP monitoring technology is divided into the following sections:

    A. ICP monitoring device accuracy and stability
    B. Optimal intracranial location of monitor
    C. Complications
    D. Cost

A. ICP monitoring device accuracy and stability (Table 1)

The Association for the Advancement of Medical Instrumentation (AAMI) has developed the American National Standard for Intracranial Pressure Monitoring Devices in association with a Neurosurgery committee.[4]

The purpose of this standard is to provide labeling, safety, and performance requirements, and to test methods that will help enssure a reasonable level of safety and effectiveness of devices intended for use in the measurement of ICP.

According to AAMI's standard, an ICP device should have the following specifications:

- Pressure range 0-100 mm Hg
- Accuracy ± 2 mm Hg in range of 0-20 mm Hg
- Maximum error 10% in range of 20-100 mm Hg

Current ICP monitors allow pressure transduction by external strain gauge, catheter tip strain gauge, or catheter tip fiberoptic technology. External strain gauge transducers are coupled to the patient's intracranial space via fluid filled lines, whereas catheter tip transducer technologies are placed intracranially. External strain gauge transducers are accurate[17] and can be recalibrated, but obstruction of the fluid couple can cause inaccuracy. In addition, the external transducer must be consistently maintained at a fixed reference point relative to the patient's head to avoid measurement error.

Catheter tip strain gauge or fiberoptic devices are calibrated prior to intracranial insertion and cannot be recalibrated once inserted (without an associated ventricular catheter). Consequently, if the device measurement drifts and is not recalibrated, there is potential for an inaccurate measurement, especially if the ICP monitor is used for several days.

There is potential for significant ICP measurement drift with fiberoptic pressure transduction[1,6,31,41] and strain gauge pressure transduction[34,36] in the parenchymal space. However, other studies of catheter tip strain gauge ICP devices have demonstrated low or negligible drift over 5 days.[6,18] The accuracy of a pressure transduction device can be assessed by placing the device within the lumen of a ventricular catheter and comparing the fluid coupled ventricular pressure reading to

the device being tested. Catheter tip fiberoptic and strain gauge devices tested in this manner show differences (greater than ± 2mm Hg) compared to ventricular ICP readings.[9,10,15,16,18] This method of pressure transduction comparison may be erroneous when the ventricular catheter is misplaced or occluded.[38]

B. Optimal intracranial location of monitor

A pressure transduction device for ICP monitoring can be placed in the epidural, subdural, subarachnoid, parenchymal, or ventricular location.

Historically, ventricular ICP is used as the reference standard in comparing the accuracy of ICP monitors in other intracranial compartments. It also has the therapeutic benefit of draining cerebrospinal fluid (CSF) in the event of intracranial hypertension. The potential risks of catheter misplacement, infection, hemorrhage, and obstruction have lead to alternative intracranial sites for ICP monitoring.

The ensuing statements can be generated from reviewing the pertinent literature:

- Ventricular pressure measurement is the reference standard for ICP monitoring. [4,9,10,12, 15, 16, 18, 25, 27, 28, 34, 36, 37, 39, 40, 45, 48]

- ICP measurement by parenchymal catheter tip strain gauge pressure transduction[34, 36, 41] or subdural catheter fluid coupled device is similar to ventricular ICP. However, some investigators have found that subdural and parenchymal fiberoptic catheter tip pressure monitoring does not always correlate well with ventricular ICP.[9, 15, 16, 39]

- Fluid coupled epidural devices or subarachnoid bolts[4, 8, 13, 25, 27, 28, 45] and pneumatic epidural devices[1,2, 37,40] are less accurate than ventricular ICP monitors. Significant differences in readings have been demonstrated between catheter tip strain gauge ICP devices that are placed in the parenchyma versus in the subdural space.[19]

C. Complications

ICP monitoring complications include infection, hemorrhage, malfunction, obstruction, or malposition. While these complications rarely produce long-term morbidity in patients, they can increase costs by requiring replacement of the monitor, and they can give inaccurate ICP readings.

Most studies define infection as a positive CSF culture in ventricular and subarachnoid bolt monitors, or a positive culture of the intracranial device. A better definition would be bacterial colonization of the device rather than infection, because there have been no reports in large prospective studies of clinically significant intracranial infections associated with ICP monitoring devices.[26, 29] Colonization of the ICP devices increases significantly after five days of implantation[26, 33] and, when detected, is treated by removal of the device. Irrigation of fluid coupled ICP devices significantly increases bacterial colonization leading, in one study,[2] to an increase from 6% to 19% (the higher rate was excluded in the subsequent analysis of ICP device complications). ICP catheter infection reductions have been reported with

changes in insertion techniques, antibiotic prophylaxis, maintainence, and CSF sampling methods.[3, 23, 35] However these observational studies are limited by insufficient or unreported numbers of trauma patients.

In reviewing the literature on ICP device colonization, there were 13 articles pertinent to ventriculostomy,[11, 14, 18, 20, 22, 26, 29, 30, 33, 43, 44, 46, 48] three for subarachnoid bolt,[9, 29, 30] 6 for subdural catheters,[11, 19, 22, 28, 30, 47] and 3 for parenchymal strain gauge and fiberoptic catheter tip devices.[1, 6, 34] The average rate of bacterial colonization was 5% for ventricular (range: 0-9.5%), 5% for subarachnoid (range: 0-10%), 5% for subdural (range:1-13%), and 14% in parenchymally placed catheter tip strain gauge or fiberoptic devices. Even though these studies document increasing bacterial colonization of all ICP devices over time, clinically significant intracranial infections are uncommon.

Hemorrhage associated with an ICP device is not defined in the majority of reports reviewed in terms of volume of hematoma on head CT or morbidity. In order to assess the incidence of hematomas, case report articles were excluded. There were five articles on ventriculostomy associated hematomas[14,29, 30, 33, 41] reporting an average incidence of 1.1% versus one article each on subarachnoid bolts (no hematomas),[30] subdural catheters (no hematomas),[30] catheter tip strain gauge devices (no hematomas),[34] and three in parenchymal fiberoptic catheter tip devices[31, 48] that were associated with an average of 2.8% hematomas. Overall, the incidence of hematomas with all ICP devices is 1.4%. Significant hematomas requiring surgical evacuation occurred in 0.5% of patients in published reports with more than 200 patients requiring ICP monitoring.[29, 33, 41]

Malfunction or obstruction in fluid coupled ventricular catheters, subarachnoid bolts, or subdural catheters has been reported as 6.3%, 16%, and 10.5%, respectively.[4, 5, 30] With ICP measurements greater than 50 mm Hg, higher rates of obstruction and loss of signal are noted.[24] In reports of ventricular catheter malposition, 3% of patients needed operative revision.[32, 33, 42] Malfunction has been reported in parenchymal and ventricular pressure fiberoptic catheter tip transducer devices from 9% to 40%,[6, 9, 10, 21, 41, 48] requiring reinsertion of a new fiberoptic device.

As delineated above, each type of pressure transduction system and intracranial location of the monitor has a profile of potential complications. Calibration, monitoring for infection, and checking fluid coupled devices for obstruction are necessary tasks in maintaining an optimal ICP monitoring system. Table 2 summarizes each type of ICP monitor by the parameters discussed above.

D. **Cost**

A cost analysis of the various ICP devices was done using currently available prices (Tables 3 and 4). The average cost of the intracranial, extracranial, and pressure transducer disposable components for ICP monitors is shown in Table 2. The nondisposable hardware costs that need to be purchased with fiberoptic and strain

gauge catheter tip ICP devices range from $820 to $6,235 per bed (Table 3). Generally, fluid coupled ICP systems were less than half the cost of other systems.

V.   Ranking of ICP Monitoring Technology

ICP monitoring devices have been ranked based on their accuracy, stability, and ability to drain CSF.

1.   Intraventricular devices—fluid coupled catheter with an external strain gauge or catheter tip pressure transducer
2.   Parenchymal catheter tip pressure transducer devices
3.   Subdural devices—catheter tip pressure transducer or fluid coupled catheter with an external strain gauge
4.   Subarachnoid fluid coupled device with an external strain gauge
5.   Epidural devices

VI. Summary

In patients who require ICP monitoring, a ventricular catheter connected to an external strain gauge transducer or catheter tip pressure transducer device is the most accurate and reliable method of monitoring ICP and enables therapeutic CSF drainage. Clinically significant infections or hemorrhage associated with ICP devices causing patient morbidity are rare and should not deter the decision to monitor ICP.

Parenchymal catheter tip pressure transducer devices measure ICP similar to ventricular ICP pressure but have the potential for significant measurement differences and drift due to the inability to recalibrate. These devices are advantageous when ventricular ICP is not obtained or if there is obstruction in the fluid couple. Subarachnoid or subdural fluid coupled devices and epidural ICP devices are currently less accurate.

VII. Key Issues for Further Investigation

■   The specifications standard for ICP monitoring should include *in vivo* clinical ICP drift measurement. *In vitro* testing of devices does not necessarily reflect clinical performance. Specifications for ICP devices should be reviewed in the context of what data is useful in the management of patients that require ICP monitoring.

■   Is there normally a difference in pressure between ventricular and parenchymal ICP? Studies measuring both simultaneously report both positive and negative differences. These studies may be difficult to interpret if the ICP device is inaccurate. A study of parenchymal and ventricular ICP measurements using an accurate catheter tip transducer device would be useful.

■   Does parenchymal monitoring in or near a contusion site provide ICP data that improves ICP management and outcome compared to other sites of ICP monitoring?

■   Recommendations for the use of prophylactic antibiotics, surgical technique, ICP data collection, monitoring for complications, and timing for removal of ICP monitoring devices need to be developed.

- Further improvement in ICP monitoring technology should focus on developing an ICP device that can provide ventricular CSF drainage and parenchymal ICP measurement simultaneously. This would allow *in situ* recalibration and give accurate ICP measurements in case of fluid obstruction or when CSF is actively drained.

VIII. Evidentiary Tables:
Table 1: ICP Monitoring Device Accuracy and Stability

Artru,[1] 1992

Description of Study: A prospective study of parenchymal fiberoptic catheter tip ICP monitors in 100 patients.

Conclusions: Daily baseline drift of 0.3 mm Hg.

Barlow,[4] 1985

Description of Study: Simultaneous recording of ventricular fluid coupled ICP compared to a subdural fluid coupled catheter in 10 patients and a subdural catheter tip pressure transducer device in another 10 patients.

Conclusions: Compared to ventricular ICP, 44% of the subdural fluid coupled device measurements and 72% of the subdural catheter tip pressure transducer devices were within a 10 mm Hg range.

Bavetta,[6] 1997

Description of Study: A prospective study of 101 fiberoptic pressure transducers (52 subdural and 42 ventricular) in 86 patients.

Conclusion: An average of -3.3 mm Hg zero drift was noted each day up to 5 days after insertion. 10% of devices had functional failure.

Bruder,[8] 1995

Description of Study: Comparison of an epidural ICP monitor and a parenchymal fiberoptic catheter tip ICP monitor in 10 severe head injury patients.

Conclusions: There was a lack of measurement agreement with the epidural ICP on average 9 mm Hg higher (range: 10-28 mm Hg) than parenchymal ICP.

Chambers,[10] 1993

Description of Study: Simultaneous recording of ventricular fluid coupled ICP compared to a fiberoptic catheter tip pressure transducer device at the tip of the ventricular catheter in 10 patients.

Conclusions: 60% of the ICP readings with the fiberoptic device were within 2 mm Hg of the ventricular fluid coupled ICP readings.

VIII. Evidentiary Table (continued)

Chambers,[9] 1990

Description of Study: ICP recordings between a ventricular fluid coupled system in 10 patients compared to a subdural fiberoptic catheter tip pressure transducer and the same device situated in the ventricular catheter in another 10 patients.

Conclusions: 54% and 74% of the fiberoptic subdural and fiberoptic ventricular ICP readings, respectively, were within 5 mm Hg of the ventricular fluid coupled ICP measurements.

Czech,[12] 1993

Description of Study: Comparison of simultaneous ICP recordings in 15 patients using a ventricular fluid coupled ICP monitoring system and an epidural pneumatic ICP monitoring device.

Conclusions: In the majority of comparisons the epidural device ICP measurements were different from ventricular ICP recordings with deviations between -20 and +12 mm Hg.

Dearden,[13] 1984

Description of Study: Assessment of ICP measurement accuracy in a subarachnoid/subdural fluid coupled bolt device using an infusion test in 18 patients.

Conclusions: Device read ICP accurately according to infusion test 48% of the time.

Gambardella,[15] 1992

Description of Study: Comparison of a parenchymal fiberoptic catheter tip pressure transduction device to ventricular fluid coupled ICP readings in 18 adults patients.

Conclusions: 55% of parenchymal fiberoptic ICP readings were 5 mm Hg higher or lower than ventricular ICP measurements.

Gambardella,[16] 1993

Description of Study: Comparison of parenchymal fiberoptic catheter tip pressure transduction device to ventricular fluid coupled ICP readings in 12 pediatric patients.

Conclusions: ICP values obtained by the parenchymal fiberoptic device were 3 ± 2 mm Hg lower than ventricular ICP readings.

Gopinath,[18] 1995

Description of Study: Evaluation of the measurement accuracy and drift of a new catheter tip strain gauge ICP device. The device was placed in the lumen of a ventricular catheter in 25 patients.

Conclusions: No significant measurement drift was noted over an average of four days. The device was 63% accurate (within 2 mm Hg) compared to ventricular ICP recordings.

VIII. Evidentiary Table (continued)

Gray,[19] 1996

Description of Study: Comparison of ICP readings in 15 patients using catheter tip strain gauge devices simultaneously in parenchymal and subdural locations.

Conclusions: ICP measurement differences of greater than 4 mm Hg were noted in 30% of the readings. Daily baseline drift of 0.3 mm Hg in parenchymal location.

Holloway,[20] 1996

Description of Study: A retrospective analysis of 584 patients in head injury databanks with regard to ventriculostomy infection rates and duration of monitoring.

Conclusions: Infection rate peaks within 10 days for an overall rate of 10.4% with a significant association with septicemia, pneumonia, craniotomy, IVH, and operated depressed skull fractures. The average duration of ICP monitoring was 6.7 days and the average time to onset of infection was 6.8 days.

Jensen,[21] 1997

Description of Study: Parenchymal fiberoptic catheter tip pressure studied in 98 children (average age of 9 years old).

Conclusions: 13% functional device failure rate and 7% catheter tip cultures positive. No positive cultures in devices placed in the operating room.

Mendelow,[27] 1983

Description of Study: Simultaneous recordings of ICP using two types of subdural fluid coupled bolt devices and a ventricular catheter fluid coupled system in 31 patients.

Conclusions: ICP recordings were within 10 mm Hg of ventricular ICP in 41% of the recordings using one type of bolt and 58% using the other kind.

Mollman,[28] 1988

Description of Study: Simultaneous recordings of ICP using a subdural/subarachnoid fluid coupled catheter and a ventricular fluid coupled catheter in 31 patients.

Conclusions: The difference between the ICP readings was -0.12 mm Hg with a standard deviation of 5.29 mm Hg.

Ostrup,[31] 1987

Description of Study: Comparison of ICP readings between a parenchymal fiberoptic catheter tip pressure transducer device and ventricular fluid coupled catheter or subarachnoid bolt in 15 adults and 5 children.

Conclusions: Measurement drift up to 1 mm Hg per day. Parenchymal ICP readings were generally within 2-5 mm Hg of ventricular or subarachnoid ICP measurements.

VIII. Evidentiary Table (continued)

Piek and Bock,[34] 1990

Description of Study: In a series of 100 patients, 13 had simultaneous ICP recordings from a parenchymal strain gauge catheter tip pressure transducer device and a ventricular fluid coupled catheter.

Conclusions: An initial drift up to 4 mm Hg in the first day. Parenchymal ICP measurements were generally 4-8 mm Hg below ventricular ICP.

Piek,[36] 1987

Description of Study: Simultaneous recording of ICP using a parenchymal strain gauge catheter tip pressure transducer device and a ventricular fluid coupled catheter in 7 patients.

Conclusions: Parenchymal ICP was 4-12 mm Hg lower than ventricular ICP but parallel changes in pressure were noted.

Piek and Raes,[35] 1996

Description of Study: Clinical experience with a new combined ventricular catheter and built-in strain gauge sensor at tip in 13 patients (3 head injury).

Conclusions: Initial drift less than 4 mm Hg over 4 days and pressure difference less than 5 mm Hg.

Powell and Crockard,[37] 1985

Description of Study: Simultaneous recording of ICP using an epidural pneumatic pressure transducer and a ventricular fluid coupled catheter in 17 patients.

Conclusions: Marked differences in pressure up to 30 mm Hg were recorded.

Schickner and Young,[39] 1992

Description of Study: Comparison of ICP readings between a parenchymal fiberoptic catheter tip pressure transducer device and ventricular fluid coupled catheter in 10 patients.

Conclusions: 66% of the parenchymal fiberoptic measurements exceeded ventricular ICP and 21% were lower. Absolute pressure differences of up to 40 mm Hg were recorded.

Schwarz,[40] 1992

Description of Study: Comparison of ICP readings between an epidural pneumatic pressure transducer device and a subdural strain gauge, subdural fiberoptic, or ventricular fluid coupled catheter in 6 patients.

Conclusions: ICP readings from the epidural device correlated with the other device readings in only one case.

VIII. Evidentiary Table (continued)

Shapiro,[41] 1996

Description of Study: Review of clinical performance of parenchymal fiberoptic catheter tip ICP monitors in 244 patients (180 head injury) of which 51 also had ventricular catheter placement.

Conclusions: A strong correlation was found between initial parenchymal and ventricular measurements. Fiberoptic breakage and malfunction was seen in 17% and 14% of patients, respectively. The mean length of monitoring was 7 days.

Weaver,[45] 1982

Description of Study: Comparison of ICP measurements between two subarachnoid fluid coupled pressure transducers in the same patient. Twenty patients were studied, 4 of them had unilateral mass lesions.

Conclusions: More than 50% of patients demonstrated significant differences in ICP. Patients harboring intracranial mass lesions showing clear differences.

Table 2: Ranking and Evidenciary Table for ICP Monitoring Technologies

Device Location		Method of Pressure Transduction	CSF Drainage	Accuracy	Recalibration	(1998) Cost (in dollars)	Complications (mean %) Infection, Hemorrhage, Malfunction
Ventricular	1	FC external strain gauge	+	+	+	$212	5.4[11, 14, 18, 20, 22, 26, 29, 30, 33, 43, 44, 46, 48], 1.1[14, 29, 30, 33, 44], 5[4, 30, 32, 33, 42]
	2	FC strain gauge catheter tip	+	+	+	420	3[18], 0[18], 0[18]
	3	FC fiberoptic catheter tip	+	+	+	375	n/a[23], n/a, 24.5[9,10]
Parenchymal	4	Strain gauge catheter tip	–	–	–	305	15[19], 0[34], n/a
	5	Fiberoptic catheter tip	–	–	–	345	9.4[21], 2.8[1,31,48], 15.6[6, 10, 21, 41,48]
Subarachnoid	6	FC external strain gauge	–	–	+	91	5[11,29,30], 0[30], 16[30]
Subdural	7	Strain gauge catheter tip	–	–	–	305	13[19], n/a, 30[4]
	8	Fiberoptic catheter tip	–	–	–	355	n/a, n/a, 16[5]
	9	FC external strain gauge	–	–	+	101	3.8[11,22,28,30,47], 0[30], 10.5[4,30]
Epidural	10	FC external strain gauge	–	–	+	n/a	n/a, n/a, 33[25]
	11	Pneumatic	–	–	+	n/a	n/a, n/a, 7.1[12]

*See Table 3 for device manufacturers

n/a Data not available

FC = Fluid Coupled

Table 3: Cost (1998) of ICP Monitoring Devices

Device Location		Method of Pressure Transduction	Product Description & Catalog Number	Disposable Pressure Transducer Cost (in dollars)	Reusable Display Monitor and/or Calibration Device (in dollars)
Ventricular	1	FC external strain gauge	Ventricular Catheter[a] External CSF Drainage Bag[a] Sorenson Transpac IV (Abbott #42584-05)	$212	–
	2	FC strain gauge catheter tip	External CSF Drainage Bag MicroSensor Ventricular Kit (Codman #82-6633)	420	$ 820
	3	FC strain gauge catheter tip	Ventcontrol MTC, Draeger Medical Germany (HD480122042)	375	820
	4	FC fiberoptic catheter tip	External CSF Drainage Bag[a] Micro Ventricular Bolt Pressure Monitoring Kit (Camino #110-4HM))	433	6,250
Parenchymal	5	Strain gauge catheter tip	MicroSensor Skull Bolt Kit (Codman #82-6632) Sensodyn (B. Braun AG) Germany	305[d] n/a	820 n/a
	6	Fiberoptic catheter tip	OLM Intracranial Pressure Monitoring System (Camino #110-4B)	345	6,250
Subarachnoid	7	FC external strain gauge	Disposable Bolt System (Codman #80-1198) Sorenson Transpac IV (Abbott #42584-05)	91[d]	–
Subdural	8	Strain gauge catheter tip	MicroSensor Basic Kit (Codman #82-6631)	305	820
			MMI·Gaeltec Model ICT/b Intracranial Catheter Tip Pressure Transducer (Gaeltec #ICT/b)	355	1,705
	9	Fiberoptic catheter tip	Post Craniotomy Subdural Pressure Monitoring Kit (Camino #110-4G)		6,250
	10	FC external strain gauge	Ventricular Catheter and Sorenson Transpac IV (Abbott #42584-05)	–	101
Epidural	11	FC external strain gauge	Plastimed Transducer, France	n/a	n/a
	12	Pneumatic	Speigelberg Transducer, Germany	n/a	n/a
			Ladd/Steritek ICP Monitoring System (Ladd # P1500)	n/a	n/a

[a]Generic

[b]Average Price (see Table 2)

[c]n/a, Data not available

[d]Estimate

[e]For 61/10 uses

Manufacture names may have changed due to business changes.

Table 4: Average Cost (1998) of Ventricular Catheters and CSF Drainage Systems

Product	Manufacturer	Product Description & Catalog Number	Unit Price	Average Price
Ventricular Catheter	Cordis (Electa)	Intraventricular Monitoring Catheter (#910-130A)	$ 73	
	P.S. Medical (Medtronics)	EDM Ventricular Catheter (#46118)	75	
	Clinical Neuro Systems	Ventricular Catheter (#10-400)	37	
	Camino Heyer-Schulte NeuroCare L.P.	Ventricular Catheter (#060)	55	
				$60
External CSF Drainage System	Cordis (Electa)	External Drainage Set (#910-112A)	130	
	P.S. Medical (Medtronics)	EDMS-II External Drain without Catheter (#46128)	175	
	Codman Johnson & Johnson Professional, Inc.	External Drainage II (#82-1721)	99	
	Camino Heyer-Schulte NeuroCare L.P.	Ventricular Drainage System (NL850-8300N)	110	
	Clinical Neuro Systems	MoniTorr ICP External Drainage Bag System (#10-150)	40	
	Phoenix Medical	Ventricular Drainage System PFV-1	110	
				111

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GUIDELINES FOR CEREBRAL PERFUSION PRESSURE

I.   Recommendations

1. Standards
    There are insufficient data to support treatment standards for this topic.
2. Guidelines
    There are insufficient data to support treatment guidelines for this topic.
3. Options
    Cerebral perfusion pressure (CPP) should be maintained at a minimum of 70 mm Hg.

II. Overview

Cerebral ischemia may be the single most important secondary event affecting outcome following severe traumatic brain injury (TBI).[29] The CPP, defined as the mean arterial blood pressure (MABP) minus intracranial pressure (ICP), is the physiologic variable that defines the pressure gradient driving cerebral blood flow (CBF) and metabolic delivery and is, therefore, closely related to ischemia. Based on previous studies that document a significant incidence of post-traumatic vasospasm, as well as changes in pressure and metabolic autoregulation, it is clear that cerebral vascular resistance is altered (often increased) by trauma. A low CPP may jeopardize regions of the brain with pre-existing ischemia, and enhancing intravascular hydrostatic pressure by increasing CPP can help to improve cerebral perfusion. In most cases, CPP is amendable to clinical manipulation, and enhancement of CPP may help to avoid both global and regional ischemia.

III. Process

A MEDLINE search for the headings of "cerebral perfusion pressure" and "brain injury" was performed for the period of 1970-1998; 266 references were generated and 44 dealt with clinical brain injury—17 of these studies provided outcome data. One of the clinical studies prospectively randomized patients into groups treated at different CPP levels. Several of the studies were randomized, prospective trials of other therapies in conjunction with CPP management and involved sequential and prospective accumulation of physiologic data.

IV. Scientific Foundation

The rationale for attempting to optimize CPP arises from the increasing evidence that CBF is typically very low following TBI and, in many cases, may be near the ischemic threshold.[4,5,17,21,33] CBF in the vicinity of post-traumatic contusions and subdural hematomas is reduced even further than global CBF.[28,39] Low CBF values may be caused by compression of cerebral vessels from mass lesions but also may be related to reduced cerebral metabolism in comatose patients[31] or to post-traumatic vasospasm, as has been documented in as many as 40% of these patients.[40] Although there is debate about the absolute CBF value below which irreversible ischemia will occur, it is apparent from histologic analysis of the brains of those who die following TBI that ischemia is very common.[11,16,38]

The adverse consequences of failure to maintain an adequate CPP following severe TBI are well described. In a prospective study of 21 patients with severe TBI in whom brain tissue pO_2 ($tipO_2$) was monitored, ischemic episodes defined as a $tipO_2$ less than 10 mm Hg for greater than 15 minutes during the first week after injury were associated with unfavorable neurologic outcomes.[19] Elevation of the CPP from 32 ± 2 to 67 ± 4 mm Hg improved $tipO_2$ by 62%. Raising CPP above 68 did not cause a further increase in $tipO_2$, however. In their analysis of multiple physiologic variables monitored for these patients, a CPP greater than 60 mm Hg emerged as the most important factor determining a sufficient brain tissue pO_2. Several studies document worsened clinical outcomes in TBI patients who have had hypotensive episodes (systolic blood pressure [SBP] <90 mm Hg) during the first several hours or days after their injury.[8,18,32] A significant inverse relationship between outcome and elevated ICP has been reported[1,25] and hypotension has been shown to cause an increase in ICP in those with intact cerebral vascular autoregulation.[2,3] There is experimental evidence that a decline in blood pressure is responsible for a sudden increase in ICP (plateau waves) and that such waves can be aborted by increasing the blood pressure.[35] There also is evidence that autoregulatory vasodilation in response to hypotension may be as high as 65% above baseline vessel diameters.[20]

In a prospective study of 11 patients with severe TBI, changes in CPP resulting from spontaneous fluctuations in MABP and ICP induced highly significant alterations in SjO_2 in all patients and at all periods after trauma.[30] Such changes in the SjO_2 were thought to be caused by changes in CBF induced by alterations in CPP. However, in a separate prospective study of 66 patients with severe TBI, a multivariate statistical analysis of these and other physiologic variables found no correlation between CPP and CBF, CPP and $AVdO_2$, or CPP and $CMRO_2$, for CPPs ranging from 60-130 mm Hg.[13]

It has been argued that the hypertensive therapy needed in some head-injured patients to maintain an adequate CPP can cause an increase in ICP and poor outcome.[26,27] The effect of artifical blood pressure elevation on ICP and CBF has been systematically studied in patients with severe TBI. Bauma and Muizelaar studied 35 patients and found that elevation of the MABP from 92 ± 10 mm Hg to 123 ± 8 mm Hg led to only a slight (insignificant) increase in ICP in those patients with intact autoregulation (less than 1% change in CBF).[2] In the group with defective autoregulation, as defined by a $53\% \pm 20\%$ increase in CBF, there was actually a significant decrease in the mean ICP. In 14 patients with severe TBI, Bruce, et al., found that artificially increasing the SBP by 30 mm Hg caused an average increase in ICP of only 4 mm Hg, and in 3 cases the ICP actually decreased.[6] In a subgroup of these patients with defective autoregulation, as defined by an increase of CBF of 7 ml/100 g/min or more with the increased blood pressure, ICP

increased by only 3 mm Hg or less in 4 patients, although it increased by 13 and 27 mm Hg in the other 2 patients.

These studies clearly demonstrate that ICP usually changes very little when blood pressure is increased by as much as 30 mm Hg in head-injured patients, and this is true regardless of the status of autoregulation. Because loss of autoregulation is defined as an increase in CBF when the blood pressure is increased, there is no direct relationship between CBF and ICP. Thus, a moderate increase in blood pressure, as might be induced to maintain an adequate CPP, should not be expected to cause an increase in ICP in most TBI patients.

When there is loss of autoregulation, the reason for a minimal increase, or even decrease, in ICP despite a substantial increase in CBF is not intuitively obvious. In some cases, crystalloid is used to enhance intravascular volume and increase the blood pressure, and it is possible that the subsequent hemodilution and decreased blood viscosity lead to a decreased transit time of blood through the brain. Under these circumstances, cerebral blood volume could decrease out of proportion to an increase in CBF.[2] In the studies cited, however, blood pressure was increased with the use of vasopressor agents, not volume. An alternative explanation is that the physiologic characteristics of autoregulation are altered by severe brain injury, but autoregulation usually is not lost.[36] Those patients thought to have lost autoregulation based on the criterion of Bauma and Muizelaar[2] or Bruce, et al.,[6] may in fact have had a trauma-induced increase in blood pressure at which autoregulation vasoconstriction begins (a shift of the autoregulatory curve to the right).[14,15]

The level at which CPP is best maintained is not entirely clear, but several clinical studies suggest that 70-80 mm Hg may be the critical threshold. Perhaps the largest prospective cohort series of patients managed with the intention of keeping the CPP above 70 mm Hg is that of Rosner.[37] He described the outcomes for 158 patients in whom the CPP was kept at least 70 mm Hg at all times. The mean CPP in the group was in fact 83 ± 14 mm Hg. The ICP averaged 27 ± 12 mm Hg in these patients. Outcomes at 10.5 months after injury were mortality of 29%, moderate disability of 20%, and good recovery of 39%. Rosner found an 80% favorable recovery rate for the 71% of his patients who survived and suggested that these results compared quite favorably with those of the Traumatic Coma Data Bank (TCDB).

McGraw developed a model relating outcome to CPP.[27] When CPP was greater than 80 mm Hg, mortality was 35%-40%. When CPP was decreased below this level, mortality progressively increased by 20% for each 10 mm Hg epoch, such that when CPP was less than 60 mm Hg, mortality was about 95%. Morbidity and neurologic deterioration were reliably ($p < 0.02$) associated with decrementing CPP. In a subsequent retrospective analysis of 136 patients with severe TBI, this group reported that all patients whose average CPP fell below 60 mm Hg for more than 33% of the hourly measurements obtained on the second day following injury died.[7] However, these reports were retrospective observations in which there had been no effort to manage patients according to CPP. The primary management goal was to maintain ICP less than 22 mm Hg, patients were treated with dehydration and aggressive hyperventilation, and overall mortality was 54%.

Outcomes have been reported for prospective TBI studies in which CPP was actively maintained at about 70 mm Hg.[10,15,22,36,41] The mortality documented in these studies ranged from 5%-35%, with a mean of 21% for the patients with a Glasgow Coma Scale (GCS) score of 3-7. This was a substantial reduction from the 40% mortality rate reported for the TCDB patients within the same GCS score range.[24] When morbidity was considered, the percent of good recoveries and moderate disabilities was 54%, as opposed to 37% in the TCDB database.

Thus, there did not appear to be adverse clinical outcomes when CPP was actively maintained. However, it could not be concluded that the improved outcomes in these studies were a result of CPP management because none were randomized, prospective trials of this treatment. In some of the reports, another treatment was actually the focus of the study, and maintenance of CPP above 70 mm Hg was only a part of routine management.[10,22]

Several studies suggest that monitoring and management of CPP alone may not be enough to improve outcomes. In a prospective, interventional study of 353 patients with severe TBI, Cruz found that outcome at 6 months after injury was significantly better in the 178 patients who had monitoring and management of cerebral extraction of oxygen along with CPP as compared with 175 patients undergoing monitoring and management of CPP alone.[12] Robertson, et al., completed a prospective, controlled, randomized trial of 189 adult patients with a GCS score ± 5 within 12 hours of head injury (closed and gun shot wound [GSW]).[34] Patients were randomized to an "ICP-targeted protocol" where CPP was kept above 50 mm Hg, or to a "CBF-targeted protocol" where CPP was kept above 70 mm Hg. They found no significant difference in 3/6 month Glasgow Outcome Scale (GOS) or Disability Rating Scale (DRS) scores, or in ICP. There was a significant increase in the incidence of adult respiratory distress syndrome (ARDS) in the "CBF-targeted" group.

Most studies have shown a strong inverse relationship between outcome and ICP, independent of other clinical variables.[1,9,23,25] It could be argued that the poor outcomes observed in the McGraw study[27] were in fact due to high ICP, as ICP varied to a much greater extent than the MABP. To establish the significance of CPP management, a prospective clinical trial will be needed to demonstrate that outcomes are improved when CPP is kept above 70-80 mm Hg even when ICP increases to levels well above the previously reported critical thresholds of 20-25 mm Hg.

V.   Summary

Maintenance of a CPP greater than 70 mm Hg is a therapeutic option that may be associated with a substantial reduction in mortality and improvement in quality of survival, and is likely to enhance perfusion to ischemic regions of the brain following severe TBI. No study has demonstrated that the incidence of intracranial hypertension, morbidity, or mortality is increased by the active maintenance of CPP above 70 mm Hg, even if this means normalizing the intravascular volume or inducing systemic hypertension.

VI. Key Issues for Future Investigation

Controlled, prospective, randomized studies comparing CPP-based management vs ICP-based management of head-injured patients will be needed to determine if the former will lead to improved outcomes. Such studies should attempt to determine at which level CPP should be optimally maintained, and for which types of brain injury. A recent prospective study of CBF-based management has contributed to but not directly addressed this question because $PaCO_2$ also was an independent variable in that study design.

VII. Evidentiary Table

Changaris,[7] 1987

Description of Study: Retrospective analysis of the relationship between 1-year outcomes and initial CPP in 136 patients with severe TBI.

Classification: Class III Study

Conclusions: All patients with CPP less than 60 mm Hg on the second post-injury day died; more patients had a good outcome than died when CPP was greater than 80 mm Hg.

Clifton,[10] 1993

Description of Study: Prospective clinical trial of therapeutic hypothermia in which a CPP greater than 70 mm Hg was actively maintained in all 46 patients.

Classification: Class II Study

Conclusions: Overall mortality rate was 35%, and good recovery rate was 45%.

Fortune,[15] 1994

Description of Study: Prospective study of the relationship of jugular venous oxygen saturation to outcome in 14 TBI patients who also had their CPP actively maintained above 70 mm Hg.

Classification: Class II Study

Conclusions: Mortality rate was 14%.

Marion,[21] 1993

Description of Study: Prospective clinical trial of therapeutic hypothermia in which CPP greater than 70 mm Hg was actively maintained in all 40 patients.

Classification: Class II Study

Conclusions: Overall mortality rate was 5%, and good recovery rate 50%.

McGraw,[27] 1989

Description of Study: Retrospective analysis of the relationship between 1-year outcomes and initial CPP in 221 patients with severe TBI.

Classification: Class III Study

Conclusions: The likelihood of good outcomes was significantly higher and of death significantly lower ($p < 0.001$) if CPP was greater than 80 mm Hg.

Rosner and Daughton,[36] 1990

Description of Study: Prospective study of outcomes in 34 TBI patients who were managed by actively keeping CPP above 70 mm Hg.

Classification: Class II Study

Conclusions: The mortality rate was 21%, and good recovery rate was 68%.

Yoshida,[41] 1993

Description of Study: Prospective study of the effect of barbiturate therapy on the CPP threshold for good outcome in 32 patients with severe TBI.

Classification: Class II Study

Conclusions: Barbiturates lowered the threshold of CPP at which good recovery was likely; without barbiturates a CPP above 70 mm Hg was necessary for good outcomes.

Bouma and Muizelaar,[2] 1990

Description of Study: Prospective study of the effect of artificial blood pressure elevation on the ICP and CBF in 35 patients with severe TBI.

Classification: Class II Study

Conclusions: When MABP was increased by 30 mm Hg, an insignificant increase in ICP occurred in patients with intact autoregulation, and there was a significant decrease in ICP (despite a 53% increase in CBF) in patients with defective autoregulation.

Bruce,[6] 1973

Description of Study: Prospective study of the effect of artifical blood pressure elevation on the ICP and CBF in 14 patients with severe TBI.

Classification: Class II Study

Conclusions: When SBP was artificially increased by 30 mm Hg, the average ICP increase was 4 mm Hg; ICP actually decreased in 3 cases; in the subgroup with defective autoregulation, ICP increased no more than 3 mm Hg in 4 of 7 patients.

VII. Evidentiary Table (continued)

Robertson,[34] 1998

Description of Study: Prospective, randomized clinical trial of 189 patients with severe TBI (15% with GSW) comparing ICP-targeted therapy with CBF-targeted therapy. CPP was maintained above 50 mm Hg in the former group, and above 70 mm Hg in the latter group.

Classification: Class I Study

Conclusions: No significant difference in 3/6 month GOS or DRS between the two groups. The incidence of ARDS was significantly higher in CBF-targeted groups.

Kiening,[19] 1997

Description of Study: Prospective cohort study of 21 patients with severe TBI in which the effect of CPP on brain tissue pO_2 was determined.

Classification: Class II Study

Conclusions: Elevation of CPP from 32-67 mm Hg significantly improved brain tissue pO_2. Further increases in the CPP did not alter brain tissue pO_2.

Cruz,[12] 1998

Description of Study: Prospective cohort study of 353 patients with severe TBI in which 178 underwent continuous monitoring and management of cerebral O_2 extraction and CPP, and 175 patients had only monitoring and management of CPP.

Classification: Class II Study

Conclusions: Outcome at 6 months after injury was significantly better in those who had monitoring and management of cerebral extraction of O_2 as well as CPP.

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HYPERVENTILATION

I. Recommendations

A. Standards

   In the absence of increased intracranial pressure (ICP), chronic prolonged hyperventilation therapy ($PaCO_2 \le 25$ mm Hg) should be avoided after severe traumatic brain injury (TBI).

B. Guidelines

   The use of prophylactic hyperventilation ($PaCO_2 \le 35$ mm Hg) therapy during the first 24 hours after severe TBI should be avoided because it can compromise cerebral perfusion during a time when cerebral blood flow (CBF) is reduced.

C. Options

   Hyperventilation therapy may be necessary for brief periods when there is acute neurologic deterioration, or for longer periods if there is intracranial hypertension refractory to sedation, paralysis, cerebrospinal fluid (CSF) drainage, and osmotic diuretics.

   Jugular venous oxygen saturation (SjO_2), arterial jugular venous oxygen ($AVdO_2$) content differences, brain tissue oxygen monitoring, and CBF monitoring may help to identify cerebral ischemia if hyperventilation, resulting in $PaCO_2$ values less than 30 mm Hg, is necessary.

II. Overview

Aggressive hyperventilation (arterial $PaCO_2 \le 25$ mm Hg) has been a cornerstone in the management of severe TBI for more than 20 years because it can cause a rapid reduction of ICP. Brain swelling and elevated ICP develop in 40% of patients with severe TBI,[32] and high or uncontrolled ICP is one of the most common causes of death and neurologic disability after TBI.[1,30,36] Therefore, most clinicians have assumed that hyperventilation benefits all patients with severe TBI.

   However, hyperventilation reduces ICP by causing cerebral vasoconstriction and a subsequent reduction in CBF.[40] Research conducted over the past 20 years clearly demonstrates that CBF during the first day after injury is less than half that of normal individuals,[4, 5, 11, 17, 25, 29, 33, 42, 45, 47] and that there is a risk of causing cerebral ischemia with aggressive hyperventilation. Histologic evidence of cerebral ischemia has been found in most victims of severe TBI who

die.[21, 22, 44] A prospective, randomized study found improved outcome at 3 and 6 months when prophylactic hyperventilation was not used as compared to when it was.[34]

Thus, limiting the use of hyperventilation following severe TBI may help improve neurologic recovery following injury, or at least avoid iatrogenic cerebral ischemia.

III. Process

The development of these guidelines began with an extensive review of all of the pertinent literature published during the past 25 years. Approximately 600 citations were acquired by computerized search of the National Library of Medicine using the following MeSH headings in combination with "head injuries": "ischemia," "jugular vein," "regional blood flow," "perfusion," and "hyperventilation." Abstracts from the publications were reviewed and relevant articles selected to develop the guidelines. We focused on four specific areas: cerebral blood flow (30 articles reviewed); arterial jugular venous oxygen content differences ($AVdO_2$*)(7 articles reviewed); jugular venous oxygen saturation analysis (SjO_2*)(6 articles reviewed); and hyperventilation (16 articles reviewed). All of these articles were cohort studies of more than 8 patients (Class II) and were published in peer reviewed journals except for 5:—1 was a controlled, randomized prospective clinical trial[34] (Class I) and 4 were case reports or reviews[11, 40, 41, 47] (Class III).

IV. Scientific Foundation

Post-traumatic Cerebral Physiology

CBF is lowest during the first 24 hours after injury, and increases for at least three days thereafter except in patients who have uncontrollable ICP and die.[4, 11, 25, 29, 33, 42, 45] CBF is typically less than 30 cc/100 g/min during the first 8 hours after injury, and may be less than 20 cc/100 g/min during the first four hours after injury in patients with the worst injuries.[4, 5, 11, 17, 45, 47]

The CBF threshold for irreversible ischemia or infarction in TBI is not clearly established. Obrist has suggested that TBI causes a depression of cerebral metabolism, and that the reduced CBF that occurs following TBI may in many cases be appropriate for the metabolic needs of the brain.[26] However, in a positron emission tomography (PET) study of 16 patients with clinical and CT evidence of hemispheric stroke, studied at a mean of 23 hours after the onset of symptoms, Heiss found that the mean CBF was 16.7 ± 7.95 cc/100 g/min at the center of the infarct and 31.0 ± 10.65 cc/100 g/min in the zone immediately adjacent to the infarct.[24]

In severe TBI, CBF is lowest in patients with subdural hematomas, diffuse injuries, and hypotension, and highest in those with epidural hematomas or normal CT scans.[5, 29, 38, 45, 47] There is a direct correlation between CBF and Glasgow Coma Scale (GCS) score or outcome, but only during the first 24 hours after injury.[4, 29] A change in CBF does not necessarily correlate with a change in ICP; in some cases, an increase in CBF actually causes a decrease in ICP.[3, 39]

There is an inverse relationship between $AVdO_2$ values and CBF values during the first 24 hours after injury, except in patients with subdural hematomas.[4, 6, 33, 39, 43] $AVdO_2$ values exceeding 9 vol% probably indicate cerebral ischemia.[20, 39]

Jugular venous oxygen saturation is normally greater than 50%, and values less than 50% are considered desaturations. Profound or prolonged episodes of desaturation are associated with a poor outcome.[10, 48] Desaturations are most common with low CBF.[48] Hypocapnia is

* See Glossary on page 114.

associated with desaturations: in 6 patients Cruz found that the mean SjO_2 was $45 \pm 8\%$ when the arterial $PaCO_2$ was less than 22 mm Hg; and when the pCO_2 was increased by 10 mm Hg in these patients, the SjO_2 was $59 \pm 3.2\%$.[13] Sheinberg and colleagues identified an arterial $PaCO_2$ less than 28 mm Hg as the cause for desaturation in 10 of 33 patients.[48]

Recent studies continue to demonstrate decreased CBF and widened $AVdO_2$ after severe TBI, as well as a low $CMRO_2$ and abnormal CO_2 vasoresponsivity.[15,31,37] Several studies conclude that there is narrowed microcirculation and persistent vasoconstriction and that post-traumatic vasospasm may occur in as many as 43% of patients who suffer a severe TBI.[23,27,35,54] Wide variability of CO_2 vasoresponsivity surrounding contusions has been documented.[31] PET studies have shown an increase in the cerebral metabolic rate for glucose surrounding contusions or underlying subdural hematomas in some patients.[36,53]

Hyperventilation

The normal response to hyperventilation was studied by Raichle in a group of healthy volunteers: 40% decrease in CBF 30 minutes after decreasing the $PaCO_2$ by 15-20 mm Hg; 4 hours later there was an increase in CBF to 90% of baseline; when the original $PaCO_2$ was restored there was an overshoot in CBF of 31%.[41]

A study of cerebral blood volume, measured with the 99M-tc-labeled red blood cells (RBC), and simultaneous CBF measurements using carotid duplex scanning found that a reduction of the $PaCO_2$ to 26 mm Hg led to a 7.2% decrease in cerebral blood volume, but a 30.7% decrease in CBF.[18] Thus, the change in CBF was far greater than the change in cerebral blood volume caused by hyperventilation. This study is particularly important because of the established interrelationships between ICP, CBF, and cerebral blood volume, and hyperventilation. As a static measurement, cerebral blood volume is directly related to ICP. The dynamic parameter of CBF is not directly related to ICP and yet it is the physiologic parameter directly affected by hyperventilation. In global terms, at least, hyperventilation will usually cause a reduction in CBF, thereby potentially limiting flow of blood to ischemic areas of the brain. However, CBF changes are not necessarily related to changes in cerebral blood volume.

The relative CO_2 vasoresponsivity in severe TBI is a 3% change in CBF per torr change in $PaCO_2$, but is lower with a lower CBF.[6,7,39] A low CO_2 vasoresponsivity is associated with a poor outcome.[28,39,51] Local CO_2 vasoresponsivity differs from global values by more than 50% in a substantial number of patients.[28] In some patients, cerebral autoregulation is preserved with normocapnia, and lost with hypocapnia.[8] In some cases, hyperventilation can actually cause an increase in ICP: Crockard found an increase in ICP in 4 of 14 patients associated with a decrease in $PaCO_2$ to 25-30 mm Hg,[9] and Obrist found a decrease in ICP with hyperventilation in only 15 of 31 patients, but there was a decrease in CBF in 29 of them.[39] Aggressive hyperventilation can cause $AVdO_2$ and CBF values that most consider at or near the ischemic thresholds: in 10 patients with a $PaCO_2$ of 23.2 ± 2.8, Obrist found that the $AVdO_2$ was 10.5 ± 0.7 and CBF was 18.6 ± 4.4.[39]

During the past four years (1994 to 1998) blood flow studies using both the xenon techniques as well as the local thermodiffusion technique have continued to demonstrate a significant decrease in CBF associated with hyperventilation.[14,19,49,50] In a recent xenon CT CBF study, the incidence of 2 centimeter in diameter regions of CBF with blood flows less than 18 ml/100 g/min increased from 28.9% to 73.1% when the $PaCO_2$ was decreased from 35 mm Hg to 25 mm Hg.[50] Several studies also document an increased incidence of jugular venous

desaturations ($SjO_2 < 50\%$) associated with the use of hyperventilation.[46] Recent studies of the use of brain tissue oxygen levels have shown that hyperventilation is frequently associated with a significant decrease in brain tissue oxygen.[16, 26, 52]

One study has suggested that hyperventilation can "improve cerebral glucose utilization following trauma." In that study, jugular bulb monitoring was used to demonstrate an increase in cerebral glucose extraction when the $PaCO_2$ was lowered to below 25 mm Hg in some patients.[12] However, there is no evidence that this is desirable and certainly no evidence that the change in glucose extraction is associated with an improved outcome following severe TBI. Because of substantial variability in the metabolic values measured between the right and left jugular venous samples, and because jugular venous samples measure global cerebral metabolism in the face of significant regional metabolic heterogeneity, this observation is not thought to provide a rationale for changing the recommendations regarding the use of hyperventilation following severe TBI.

In 1991, Muizelaar, et al.,[34] published the results of a prospective, randomized clinical study in which 77 patients with severe TBI were randomized to a group treated with chronic prophylactic hyperventilation for 5 days after injury ($PaCO_2$ of 25 ± 2 mm Hg), or to a group kept relatively normocapneic during that time ($PaCO_2$ of 35 ± 2 mm Hg). At 3 and 6 months after injury, patients with an initial GCS motor score of 4-5 who were in the hyperventilation group had a significantly worse outcome than did those in the normocapneic group. Statistically significant differences between the two groups were not found at one year after injury. However, this lack of significance can be attributed to a type II statistical error because there were substantially fewer patients available for follow-up one year after injury.

V. Summary

Chronic prophylactic hyperventilation therapy should be avoided during the first 5 days after severe TBI, and particularly during the first 24 hours. CBF measurements in patients with severe TBI demonstrate that blood flow early after injury is low, and strongly suggest that in the first few hours after injury the absolute values approach those consistent with ischemia. These findings are corroborated by $AVdO_2$ and SjO_2 and brain tissue O_2 measurements. Hyperventilation will reduce CBF values even further, but will not consistently cause a reduction of ICP and may cause loss of autoregulation. The cerebral vascular response to hypocapnia is reduced in those with the most severe injuries (subdural hematomas and diffuse contusions), and there is substantial local variability in perfusion. While the CBF level at which irreversible ischemia occurs has not been clearly established, ischemic cell change has been demonstrated in 90% of those who die following TBI, and there is PET evidence that such damage is likely to occur when CBF drops below 15-20 cc/100 g/min. A prospective, randomized clinical trial has determined that outcomes are worse when TBI patients are treated with chronic prophylactic hyperventilation therapy.

Within the standard, guideline, and options, specific $PaCO_2$ thresholds have been described that are different for each of the three parameters. These individual thresholds were selected based on the preponderance of literature supporting those thresholds in the contexts of the statements that included them. With the exception of the threshold included for the standard in this guideline, it is emphasized that the $PaCO_2$ threshold is not as important as the general concept of hyperventilation. The preponderance of the physiologic literature concludes that

hyperventilation during the first few days following severe TBI, whatever the threshold, is potentially deleterious in that it can promote cerebral ischemia.

VI. Key Issues for Future Investigation

Prospective, randomized, clinical trials are needed to establish if short-term hyperventilation during the first 24 hours after injury is deleterious. In addition, such trials should determine if systemic neuromuscular paralysis and controlled mechanical ventilation is beneficial for those who spontaneously hyperventilate following severe TBI.

VII. Evidentiary Tables

Table 1: Clinical CBF, Metabolic, and Physiologic Measurements following Severe TBI

Fieschi,[17] 1974

Description of Study: Cohort study of CBF in 12 patients with severe TBI designed to describe the temporal changes in CBF during the first few days after injury.

Classification: Class II Study

Conclusions: CBF was always lowest during first 12 hours after injury, with mean values of 17 and 28 ml/100 g/min, respectively, for those who died and who survived.

Bouma,[5] 1992

Description of Study: Cohort study of very early CBF in 35 patients with severe TBI studied a mean of 3.1 ± 2.1 hours after injury.

Classification: Class II Study

Conclusions: Global or regional, CBF of less than 18 ml/100 g/min, defined as ischemic threshold, was found in 31.4% of the patients.

Muizelaar,[33] 1989

Description of Study: Cohort of 32 children with severe TBI in which CBF was determined over time during first several days after injury.

Classification: Class II Study

Conclusions: CBF was lowest during the first 24 hours after injury.

Marion,[29] 1991

Description of Study: Cohort study of 32 patients with severe TBI aimed at defining temporal changes in CBF that occur during the first 5 days after injury.

Classification: Class II Study

Conclusions: Mean CBF in the first 1-4 hours after injury was 27 ml/100 g/min, and CBF was always lowest during the first 12-24 hours after injury. Regional CBF was substantially heterogeneous.

Bouma,[4] 1991

Description of Study: Cohort study of 186 patients with severe TBI designed to measure early CBF after injury and correlate it with outcome.

Classification: Class II Study

Conclusions: The mean CBF during the first 6 hours after injury was 22.5 ± 5.2 ml/100 g/min, and CBF was highest at 36-42 hours after injury.

Salvant and Muizelaar,[45] 1993

Description of Study: Cohort study of 54 patients with severe TBI and subdural hematoma, designed to define temporal changes in CBF and the effect of the hematoma on regional CBF.

Classification: Class II Study

Conclusions: The lowest CBF was always seen during the first 24 hours after injury. In the hemisphere with the subdural hematoma, 9% of patients had a CBF less than 18 ml/100 g/min.

Newell,[37] 1997

Description of Study: Cohort study of 22 patients designed to measure CO_2 vasoresponsivity using transcranial Doppler within 48 hours of the injury.

Classification: Class II Study

Conclusions: There was diminished CO_2 reactivity in most patients within 48 hours after injury.

Hadani,[23] 1997

Description of Study: Cohort study of 32 patients studied with TCD to determine the incidence of vasospasm.

Classification: Class II Study

Conclusions: Blood flow velocities compatible with vasospasm were found in 43% of the patients in either the basilar artery, the middle cerebral artery, or both. The peak of vasospasm was at 4 to 5 days after injury.

Muizelaar,[35] 1997

Description of Study: Cohort study of 71 patients with severe TBI. Mean transit time was studied using rapid sequence CT scanning after a bolus infusion of intravenous contrast solution.

Classification: Class II Study

Conclusions: The mean transit time was significantly prolonged after TBI and suggested an increase in cerebrovascular resistance due to narrowing of the microvasculature, consistent with early cerebral ischemia

Yoshihara,[54] 1995

Description of Study: Cohort study of 49 patients with severe TBI in whom the pressure volume index and ICP were studied to determine the resistance of cerebrovasculature.

Classification: Class II Study

Conclusions: Resistance vessels in the brain are in a state of persistent vasoconstriction following TBI.

Bergsneider,[2] 1997

Description of Study: Cohort study of 28 patients with severe TBI using PET scanning to determine regional cerebral glucose metabolism.

Classification: Class II Study

Conclusions: Increased glucose metabolism was documented surrounding cerebral contusions and underlying subdural hematomas in several patients with severe TBI.

Table 2: Histologic Evidence for Ischemia Following TBI and Evidence of Widened Arterial Jugular Venous Oxygen Content Differences (AVdO$_2$) Early After Injury

Graham,[22] 1988

Description of Study: Histologic study of 71 victims of fatal severe TBI who had no pre-mortem evidence (clinical, radiologic, or pathologic) of elevated ICP.

Classification: Class II Study

Conclusions: Ischemic cell changes were found in 70% of the brains.

Ross,[44] 1993

Description of Study: Histologic study of 37 victims of fatal severe TBI to determine the incidence of ischemic cell change in the basal ganglia.

Classification: Class II Study

Conclusions: Loss of thalamic reticular neurons was found in 89% of cases.

Bouma,[4] 1991

Description of Study: Cohort study of 186 patients with severe TBI to determine the time course of CBF and AVdO$_2$ changes early after injury.

Classification: Class II Study

Conclusions: AVdO$_2$ values were widest (7.1 $\pm$ 1.5 vol%) during the first 4-6 hours after injury and decreased to 4.2 $\pm$ 1.7 vol% at 36-42 hours

Robertson,[43] 1992

Description of Study: Cohort study of 102 patients with severe TBI examining the time course and relationship of $AVdO_2$, CBF, and ICP.

Classification: Class II Study

Conclusions: $AVdO_2$ values were always widest during the first 24 hours after injury.

Table 3: Effects of Hyperventilation on CBF, AVdO$_2$, SjO$_2$, Brain Tissue pO$_2$, and Clinical Outcome

Obrist,[39] 1984

Description of Study: Cohort study of 31 patients with severe TBI in whom the effect of aggressive hyperventilation on ICP, CBF, and $AVdO_2$ was examined.

Classification: Class II Study

Conclusions: Hyperventilation had a much more direct effect on CBF reduction (29 of 31 patients) than it did on ICP reduction (15 of 31 patients). Aggressive hyperventilation in 10 patients ($PaCO_2$ -23.2 $\pm$ 2.8 mm Hg) led to $AVdO_2$ values of 10.5 $\pm$ 0.7 vol% and CBF values of 18.6 $\pm$ 4.4 ml/100 g/min.

Sheinberg,[48] 1992

Description of Study: Cohort study of SjO_2 in 45 patients with severe TBI monitored for 1 to 8 days.

Classification: Class II Study

Conclusions: Hyperventilation was the second most common identifiable cause for jugular venous desaturations (O_2 sat. < 50%), and was the cause for desaturations in 10 of 33 cases.

Cruz,[13] 1991

Description of Study: Cohort study of 6 patients with severe TBI undergoing continuous SjO_2 monitoring for 48 hours after injury.

Classification: Class II Study

Conclusions: Jugular venous O_2 desaturations (45.5 $\pm$ 8%) were observed in all 6 patients during aggressive hyperventilation, and the O_2 saturation improved to greater than 50% in all cases with withdrawal of hyperventilation.

VII. Evidentiary Table 3 (continued)

Muizelaar,[34] 1991

Description of Study: Prospective, randomized, clinical trial of 77 patients with severe TBI comparing clinical outcome for a group hyperventilated to a $PaCO_2$ of 25 $\pm$ 2 mm Hg for 5 days after injury, and a group with $PaCO_2$ kept at 35 $\pm$ 2 mm Hg during that time.

Classification: Class II Study

Conclusions: At 3 and 6 months after injury, the patients with an initial GCS motor score of 4 to 5 had a significantly better outcome if they were not hyperventilated.

Fortune,[18] 1995

Description of Study: Cohort study of 8 normal individuals. Cerebral blood volume was measured with 99M-tc-labeled RBC and CBF was measured with carotid duplex scanning.

Classification: Class II Study

Conclusions: Decreasing the $PaCO_2$ to 26 mm Hg caused a 7.2% decrease in cerebral blood volume, but a 30.7% decrease in cerebral blood flow. Thus, changes in cerebral blood flow were much greater than changes in cerebral blood volume.

Skippen,[50] 1997

Description of Study: Cohort study of 23 children with severe TBI studied using xenon CT CBF techniques and SjO_2 to correlate cerebral oxygen consumption with changes in CBF.

Classification: Class II Study

Conclusions: Cerebral oxygen consumption decreased out of proportion to CBF following TBI. Frequency of one or more 2 cm regions of low CBF (CBF < 18 ml/100 g/min) when the pCO_2 was greater than 35 mm Hg was 28.9%. If the $PaCO_2$ was lowered to 25 mm Hg, the frequency was 73.1%.

Dings,[16] 1996

Description of Study: Cohort study of 22 patients with severe TBI studied using a brain tissue oxygen sensor to determine the effect of hyperventilation on brain tissue pO_2.

Classification: Class II Study

Conclusions: Six of 22 patients had a reduction of brain tissue oxygen into ischemic ranges following hyperventilation.

Dahl,[14] 1996

Description of Study: Cohort study of 14 patients with severe TBI studied with xenon[133] CBF techniques to evaluate the effect of hyperventilation.

Classification: Class II Study

Conclusions: Reduction of $PaCO_2$ to less than 28 mm Hg caused a decrease in the CBF of 12% and an increase in the $AVdO_2$ of 34%.

van Santbrink,[52] 1996

Description of Study: Cohort study of 22 patients with severe TBI in whom the brain tissue oxygen was monitored and the effects of hyperventilation studied.

Classification: Class II Study

Conclusions: Hyperventilation decreased brain tissue oxygen in most of the patients studied.

Cruz,[12] 1995

Description of Study: Cohort study of 33 patients with severe TBI in whom jugular venous glucose extraction was measured.

Classification: Class II Study

Conclusions: A reduction of the $PaCO_2$ to less than 25 mm Hg increased glucose extraction into "normal" ranges in some patients.

Kiening,[26] 1997

Description of Study: Cohort study of 13 patients with severe TBI studied using brain tissue oxygen monitoring.

Classification: Class II Study

Conclusions: A reduction of the $PaCO_2$ from 29 mm Hg to 21 mm Hg lead to a significant reduction of the brain tissue pO_2 from 31 mm Hg to 14 mm Hg.

McLaughlin and Marion,[31] 1996

Description of Study: Cohort study of 7 patients with severe TBI studied with stable xenon CT CBF to determine the range of CO_2 vasoresponsivity surrounding cerebral contusions.

Classification: Class II Study

Conclusions: CO_2 vasoresponsivity in tissue surrounding post-traumatic cerebral contusions ranged from 0.4% to 9.1%, and within the contusion it ranged from 0 to 7.6%.

Schneider,[46] 1995

Description of Study: Cohort study of 54 patients with severe TBI; SjO_2 was measured to determine the incidence and causes of jugular venous oxygen desaturations.

Classification: Class II Study

Conclusions: Hyperventilation was the second most common identifiable cause for jugular venous oxygen desaturations.

Sioutos,[49] 1995

Description of Study: Thirty-seven patients with severe TBI studied with thermodiffusion CBF monitoring to determine the effects of hyperventilation on local CBF.

Classification: Class II Study

Conclusions: One-third of the patients had a CBF of less than 18 ml/100 g/min following TBI and hyperventilation decreased CBF even further in those patients.

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Glossary

AVdO$_2$: This abbreviation refers to the oxygen content difference between jugular venous blood and arterial blood. A catheter is placed into the jugular bulb, and simultaneous blood samples are withdrawn from this catheter and from the arterial circulation for determination of their O_2 content.

SjO$_2$: The level of oxygen saturation in jugular venous blood. An O_2 saturation monitoring probe is placed percutaneously into the internal jugular vein and threaded into the jugular bulb. When connected to a monitor specially designed for this device, one can obtain continuous O_2 saturation readings. Jugular venous saturations of greater than 50% are considered optimal.

THE USE OF MANNITOL

I. Recommendations

A. Standards

There are insufficient data to support a treatment standard for this topic.

B. Guidelines

Mannitol is effective for control of raised intracranial pressure (ICP) after severe head injury. Effective doses range from 0.25 g/kg body weight to 1 gm/kg body weight.

C. Options

1. The indications for the use of mannitol prior to ICP monitoring are signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial explanations. However, hypovolemia should be avoided by fluid replacement.

2. Serum osmolarity should be kept below 320 mOsm because of concern for renal failure.

3. Euvolemia should be maintained by adequate fluid replacement. A Foley catheter is essential in these patients.

4. Intermittent boluses may be more effective than continuous infusion.

II. Overview

The administration of mannitol has become a cornerstone of management of head-injured patients, particularly in the acute phase when suspected or actual raised ICP may be present. However, it has never been subjected to a controlled clinical trial against placebo. Although there is much data regarding its mechanism of action, there are few studies that validate different regimens of mannitol usage. Recently, mannitol has been advocated as a "small volume resuscitation fluid" for the acute phase resuscitation of patients with hypotension and concomitant brain injury.

III. Process

"Mannitol" was listed 147 times associated with "brain trauma" in MEDLINE in a search of the past 25 years' literature, to January 1998. The majority of these citations were descriptive, discussing the use of mannitol, among other modalities, in head injury management or

emergency trauma care. Only 4 of these citations were comparative studies or claimed an effect for mannitol alone on outcome. Forty-one citations were selected for review because they focused on the mechanism of action of mannitol or its effect on outcome or critically reviewed its role in head trauma management. The most important of these are summarized in the evidentiary table.

IV. Scientific Foundation

Over the past 20 years, mannitol has replaced other osmotic diuretics.[1,2,5,7,8,16,17,22,24] Its beneficial effects on ICP, cerebral perfusion pressure (CPP), cerebral blood flow (CBF), brain metabolism, and its short-term beneficial effect on neurological outcome, are widely accepted as a result of many mechanistic studies performed in humans and animal models.[5,25,30,31,33] There is still controversy regarding the exact mechanism or mechanisms by which it exerts its beneficial effect, and it is probable that it has two distinct effects in the brain that include:[13,29]

1) an immediate plasma expanding effect that reduces the hematocrit, reduces blood viscosity, increases cerebral blood flow, and increases cerebral oxygen delivery.[1,4,14,18,25,29,30,31,35] These rheological effects probably explain why mannitol reduces ICP within a few minutes of its administration, and why its effect on ICP is most marked in patients with low CPP (< 70).[24,29,30,35] This plasma expanding effect is best accomplished with bolus administration.

2) the osmotic effect of mannitol is delayed for 15-30 minutes while gradients are established between plasma and cells.[1] Its effects persist for a variable period—90 minutes to 6 or more hours, depending on the clinical conditions.[2,4,7,13,23,24,40] Mannitol is excreted entirely in the urine, and a significant risk of acute renal failure (acute tubular necrosis) exists if mannitol is administered in large doses, particularly if serum osmolarity exceeds 320 mOsm.[2,9] Patients may be more prone to renal failure if other potentially nephrotoxic drugs are being administered, or in the presence of sepsis, or pre-existing renal disease.[2,9,22,25] Mannitol markedly raises the urinary osmolarity and specific gravity so that these cannot be used to diagnose diabetes insipidus in patients on large doses of mannitol. Mannitol, in common with other osmotics, is known to cause "opening" of the blood-brain barrier, meaning that both mannitol and other small molecules concurrently in the circulation may pass into brain.[3,13,15,19] This effect becomes harmful after many doses have been given, because mannitol may accumulate in the brain causing a reverse osmotic shift and raising brain osmolarity, thus theoretically exacerbating ICP by increasing brain cellular swelling.[2,3,6,19,38] The accumulation of mannitol in the brain is most marked when mannitol is in the circulation for long periods, as occurs with continuous infusion administration.[1,2,38,39]

Thus, it is recommended that mannitol should be administered as repeated boluses, rather than continuous infusion.[6,16,17,25,26,27]

Recently, mannitol has become popular as "a small volume resuscitation fluid," and has often been compared with hypertonic saline (7.5%). Mannitol has particularly been advocated in this role for patients with coexistent shock due to systemic injuries and head injury.[14,18,38,40,43] The theoretical concern that mannitol might jeopardize myocardial function and reduce cardiac output during shock has not been seen in studies in animal models, and it has been recommended by some as a first stage resuscitation fluid, along with colloids, in patients with head injury[10,11,20,38,42,43] and coexistent hypovolemia.

The use of concomitant diuretics such as furosemide, along with mannitol boluses, has been advocated, but few data exist to support this.[36, 41]

On theoretical grounds mannitol may be "neuroprotective" in circumstances of borderline ischemia, because it increases CBF and CPP. However, in animal studies, no consistent effect has been found in reducing lesion size, in infarct, or in trauma models.[21,44]

The administration of mannitol has become common practice in the management of head injured patients with suspected or actual raised ICP, but it has never been subjected to a controlled clinical trial against placebo. A single, well-conducted randomized trial has been performed in Canada to compare mannitol against barbiturates for control of high ICP after head injury.[37] Mannitol was superior to barbiturates, improving CPP, ICP, and outcome. Only 59 eligible patients were studied, precluding a statistically significant effect on outcome. Smith, et al., also compared bolus mannitol therapy given whenever ICP exceeded 25 mm Hg, versus empirical small bolus administration every 2 hours.[39] This was, in fact, a trial of ICP-directed therapy versus non–ICP driven management. Unfortunately, no conclusions can be drawn regarding the effectiveness of mannitol, because it was given to both groups. Fortune, et al., recently studied 22 patients who received ventriculostomy drainage, mannitol, or hyperventilation, to control raised ICP. The effect on ICP, CPP, and jugular vein oxygen saturation was measured 20 minutes after each therapy. Mannitol was the most effective in lowering ICP and improving jugular oxygen saturation (SjO_2). ICP fell by 7.4 ± 0.7 mm Hg, in 90% of observations.[12] Mannitol volume, administered per day, is an important component of the "therapy intensity level," or "TIL", and is thus an indicator of the usefulness of other therapies in control of ICP.[8, 32]

V.   Summary

There are two Class I studies (Schwartz et al.[37,] and Smith et al.[39]) and one Class II study (Gaab, et al.[13]), and a large body of "Class III" data (see table) that can be used to support mannitol. The evidence supporting use of mannitol for ICP control is sufficiently strong to warrant guideline status.

Mannitol is effective in reducing ICP and its use is recommended as a guideline in the management of traumatic intracranial hypertension. Serum osmolalities greater than 320 mOsm and hypovolemia should be avoided. There is some data to suggest that bolus administration is preferable to continuous infusion.

VI. Evidentiary Table

Becker and Vries,[2] 1972

Description of Study: The alleviation of increased ICP by chronic administration of osmotic agents. Retrospective analysis over an epoch of ICU care.

Data Class: Class III Study

Conclusions: Continuous infusion of mannitol offers no advantage over bolus use. Mannitol often causes renal failure when continued if serum osmolarity exceeds 320 mOSm.

Cold,[6] 1990

Description of Study: Cerebral blood flow in acute head injury. Review of mechanistic animal studies and $CBF/CMRO_2$/autoregulatory effects in human head injury.

Data Class: N/A REVIEW

Conclusions: Mannitol increases blood flow, CVP, cardiac output, and $CMRO_2$; it decreases hematocrit, blood viscosity, CBF, and ICP, especially when ICP is high. Reverse osmotic effects suggest single bolus use is best.

Cruz,[7] 1990

Description of Study: Continuous monitoring of cerebral oxygenation in acute brain injury: injection of mannitol during hyperventilation. (n=10 adults)

Data Class: Class III Study

Conclusions: Mannitol restores jugular vein O_2 saturation to normal levels when profound hyperventilation makes the brain ischemic.

Eisenberg,[8] 1988

Description of Study: High-dose barbiturate control of elevated ICP in patients with severe head injury. A trial of barbiturates in patients who fail ICP control with conventional measures (n=925).

Data Class: Class II Study

Conclusions: By inference, mannitol, hyperventilation, and CSF drainage are effective for ICP control in 78% of severe head injury patients.

Feldman and Fish[10], 1991

Description of Study: Resuscitation fluids for a patient with head injury and hypovolemic shock. Review of animal and human data.

Data Class: N/A REVIEW

Conclusions: Mannitol plus blood/colloid is effective for resuscitation of shocked head injury patients.

VI.   Evidentiary Table (continued)

Freshman,[11] 1993

Description of Study: Hypertonic saline (7.5%) versus mannitol: a comparison for treatment of acute head injuries. Balloon model of high ICP using sheep.

Data Class: Class III Study

Conclusions: ICP reduction and brain water content was the same with mannitol (20%) and hypertonic saline.

Fortune,[11] 1995

Description of Study: Comparison between ventricular drain, mannitol, and hyperventilation in 22 severe TBI patients: effect on ICP, SjO_2, AVO_2.

Data Class: Class II Study

Conclusions: Mannitol "increased the $CBF/CMRO_2$ ratio 5 times more than ventricular drainage," and lowered ICP 7.4 ± 0.7 mm Hg.

Gaab,[13] 1990

Description of Study: A comparative analysis of tromethamine (THAM) in traumatic brain edema. (n=21 patients, not randomized).

Data Class: Class II Study

Conclusions: Mannitol boluses produced a 32% reduction in ICP, and the effect was seen for 69 minutes. THAM was "at least as effective as Mannitol."

Israel,[14] 1988

Description of Study: Hemodynamic effect of mannitol in a canine model of concomitant increased ICP and shock. Hemorrhagic hypertension model in dogs.

Data Class: Class III Study

Conclusions: Mannitol had no harmful effects on CPP, mean arterial blood pressure, or cardiac output when given in shocked dogs with high ICP; its beneficial effect on ICP was marked.

James,[16] 1980

Description of Study: Methodology for the control of ICP with hypertonic mannitol. Retrospective study based on ICU usage patterns.

Data Class: Class III Study

Conclusions: Effect becomes less after multiple doses—especially greater than 3-4 doses/24 hours. Hyperventilation initially avoids any risk of ICP "spike" in first minutes.

VI. Evidentiary Table (continued)

Kuroda,[21] 1994

Description of Study: Effect of NMDA antagonists upon raised ICP: Studies in the rat acute subdural hematoma model. Rat neuroprotection study.

Data Class: Class III Study

Conclusions: Mannitol had no effect on ischemic brain damage after subdural hematoma.

Marshall,[23] 1978

Description of Study: Mannitol dose requirements in brain-injured patients. Uncontrolled, mechanistic study.

Data Class: Class III Study

Conclusions: An osmotic gradient of 10 mOSm or more is effective in lowering ICP. Fast i.v. infusion of 0.5-1 gm/kg is best; effect begins at 2 minutes, lasts 6-8 hours, or more.

Mendelow,[25] 1985

Description of Study: Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. Retrospective, mechanistic, multi-endpoint study.

Data Class: Class III Study

Conclusions: Mannitol consistently improved mean arterial blood pressure, CPP, and CBF, and lowered ICP by 10-20 minutes after infusion; the effect was greater with diffuse injury and in normal hemisphere. CBF increase was greatest when CPP was less than 50 mm Hg. (Rheologic effect is important.)

Miller,[27] 1975

Description of Study: Effect of mannitol and steroid therapy on intracranial volume-pressure relationships in patients. Observations in an ICU head injury population, using pressure/volume index, etc., as endpoint.

Data Class: Class III Study

Conclusions: Brain compliance and V/P response improves rapidly after mannitol infusion; probably a rheological effect.

VI. Evidentiary Table (continued)

Miller,[28] 1993

Description of Study: Management of intracranial hypertension in head injury: Matching treatment with cause. Uncontrolled, unmatched cohorts, crossover allowed.

Data Class: Class II Study

Conclusions: Mannitol is the "single agent of choice" for ICP control after severe head injury. It was effective alone in 25% of cases with high ICP (in a series of 208 patients). Hypnotic drugs may work better for a small subgroup; ± 5% with "milder injury" plus vascular engorgement.

Muizelaar,[31] 1984

Description of Study: Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. Uncontrolled, mechanistic study.

Data Class: Class III Study

Conclusions: Mannitol works best on ICP when autoregulation is intact; suggests rheologic effect is more important than osmotic effect.

Nath and Galbraith,[33] 1986

Description of Study: The effect of mannitol on cerebral white matter water content. (n=8 patients) Mechanistic study.

Data Class: Class III Study

Conclusions: Brain water in damaged white matter fell by 6% over 15 minutes after low-dose mannitol (0.28 gm/Kg).

Rosner,[35] 1987

Description of Study: Cerebral perfusion pressure: A hemodynamic mechanism of mannitol and post-mannitol hemograms. Prospective, mechanistic study.

Data Class: Class II Study

Conclusions: Mannitol works best when CPP is less than 70 mm Hg, suggesting its rheological effect is more important and more active when cerebral microvessels are dilated maximally.

Schwatz,[37] 1984

Description of Study: Prospective, randomized comparison of mannitol vs. barbiturates for ICP control. Crossover permitted. Sequential analysis n=59.

Data Class: Class I Study

Conclusions: "Pentobarbital was not significantly better than mannitol." Mannitol group had better outcome mortality-41% vs. 77%. CPP was better maintained with mannitol than barbiturates (75 mm Hg vs. 45 mm Hg).

VI. Evidentiary Table (continued)

Smith,[39] 1984

Description of Study: Comparison of two mannitol regimens in patients with severe head injury, undergoing intracranial pressure monitoring: effect of bolus mannitol given only when ICP > 25 mm Hg, versus "empirical mannitol" (every 2 hours until serum osmolarity >310 mOSm/liter or neurodeterioration).

Data Class: Class I Study

Conclusions: No difference between ICP-directed and empiric mannitol use. ICP was smoother and lower in empiric group. (Power too low to detect an effect, n=80, randomized.)

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THE USE OF BARBITURATES IN THE CONTROL OF INTRACRANIAL HYPERTENSION

I.   Recommendations

A. Standard

There are insufficient data to support a treatment standard for this topic.

B. Guideline

High-dose barbiturate therapy may be considered in hemodynamically stable salvageable severe head injury patients with intracranial hypertension refractory to maximal medical and surgical intracranial pressure (ICP) lowering therapy.

II. Overview

Currently, it is estimated that 10%-15% of patients admitted with severe head injury will ultimately manifest medically and surgically intractable elevated ICP with an associated mortality of 84%-100%.[7,11,12]

High-dose barbiturates have been known since the 1930s to have ICP lowering effects.[5] However, their well-known risks and complications have limited their applications to the most extreme of clinical situations.

Recently Goodman, et al., have used microdialysis to study the neurochemical alterations in patients under barbiturate coma.[4] These authors found that indication of thiopental coma to manage ICPs above 40 mm Hg in patients was associated with a 37% reduction in lactate, a 59% reduction in glutamate, and a 66% reduction in aspartate in the brain's extracellular space.

Barbiturates appear to exert their cerebral protective and ICP lowering effects through several distinct mechanisms: alterations in vascular tone, suppression of metabolism, and inhibition of free radical mediated lipid peroxidation.[2,6] The most important effect may relate to coupling of cerebral blood flow to regional metabolic demands such that the lower the metabolic requirements, the less the cerebral blood flow and related cerebral blood volume with subsequent beneficial effects on ICP and global cerebral perfusion.

Cruz recently reported a potential adverse effect of pentobarbital coma on global cerebrovenous oxygenation in outcome in a group of 151 patients prospectively studied utilizing jugular bulb oxyhemoglobin saturations (SjO_2).[1] All patients were placed on pentobarbital for ICPs greater than 40 mm Hg. Outcomes were significantly worse (p < 0.0001) in patients who developed decreases in SjO_2 to levels below 45% than in those whose SjO_2 remained at or above 45%:31% vs 70% good recovery/moderate disability; 40% vs 16.5% severe disability; 29% vs 13.5% vegetative/dead. These findings would suggest that in certain patients

pentobarbital may induce oligemic hypoxia and that simultaneous monitoring of arteriovenous saturation may be considered when this therapeutic modality is utilized.

A number of barbiturates have been studied with the most information available on pentobarbital. All will suppress metabolism. However, little is known about comparative efficacy to recommend one agent over another except in relationship to their particular pharmacologic properties. Considerably more, however, is known about the potential complications of the use of a therapy that is essentially the institution of a general anesthetic in a non–operating room environment.

The use of barbiturates is based on two postulates: 1) that barbiturates can effect long-term ICP control when other treatments have failed, and 2) that absolute ICP control improves ultimate outcome.

III. Process

A second MEDLINE search from 1994 to January 1998 was undertaken using the following key terms: "barbiturates," "etomidate," "head injury," "ICP treatment," "pentobarbital," an "thiopental." This resulted in 406 citations. The abstracts of all citations were reviewed yielding four clinically pertinent articles. One was a Class I study, with the remaining three Class II.

IV. Scientific Foundation

A number of case series and case reports document the ability of barbiturates to lower ICP when other treatments have failed. The first such report was by Shapiro, et al., in 1979.[17] In 1979, Marshall, et al., were the first to report not only ICP control but also improved outcome with the use of barbiturates. In this case series, 25 patients with an ICP greater than 40 mm Hg were treated. Of the 19 patients in whom ICP control was effected, 50% had a good recovery, while 83% of those in whom barbiturates failed to control ICP died.[10] In a subsequent report of 15 additional patients, identical results were obtained.[15] Similarly, Rea's case series of 27 patients demonstrated that, when ICP can be controlled by barbiturates, the mortality rate was only 33% compared to 75% when control could not be accomplished.[14]

Prophylactic Use of Barbiturates

Of the three barbiturate randomized controlled trials (RCTs), two examined early prophylactic administration and neither demonstrated significant clinical benefits. In 1984, Schwartz, et al., compared barbiturates to mannitol as the initial therapy for ICP elevations and found no improvement in outcome, noting that when diffuse injury was present, barbiturate-treated patients faired much worse.[16] Patients with ICPs greater than 25 mm Hg for more than 15 minutes were randomly assigned to a pentobarbital or mannitol treatment group. In patients who underwent evacuation of hematomas, mortalities were 40% and 43%, respectively, for the pentobarbital and mannitol treatment groups. However, in patients with diffuse injury, there was a 77% mortality in those receiving pentobarbital compared to 41% with mannitol. Additionally, these authors noted a significant decrement in cerebral perfusion pressure (CPP) in the pentobarbital-treated group.

In 1985, Ward, et al., reported on a RCT of pentobarbital in 53 consecutive head-injured patients who had an acute intradural hematoma or whose best motor response was abnormal flexion or extension. There was no significant difference in one-year Glasgow Outcome Scale

(GOS) scores between treated and untreated patients, while 6 in each group died from uncontrollable ICP. The highly undesirable side effect of hypotension (systolic blood pressure [SBP] < 80 mm Hg) occurred in 54% of the barbiturate-treated patients compared to 7% of the controls.[18]

Refractory Intracranial Hypertension

In 1988, Eisenberg, et al. reported the results of a five-center, RCT of high-dose barbiturate therapy for intractable ICP elevation in patients with Glasgow Coma Scale (GCS) scores 4 to 8[3]. The control of ICP was the primary outcome measure, although mortality was also assessed. The patients were randomly allocated to barbiturate treatment when standard conventional therapy failed.

Patients in the control group were electively "crossed over" to barbiturate treatment at specific "ICP treatment failure" levels. There were 36 controls and 37 treated patients; however, 32 of the controls ultimately "crossed over" to barbiturate treatment. The odds of ICP control were two times greater with barbiturate treatment and four times greater when adjusted for cardiovascular "complications." The likelihood of survival for barbiturate responders was 92% at one month compared to 17% for non-responders. Of all deaths, 80% were due to uncontrollable ICP. At six months, 36% of responders and 90% of non-responders were vegetative or had died. Due to the study design, the effects of barbiturate treatment on outcome other than mortality cannot be conclusively determined.

Pre-randomization cardiac "complications" were carefully evaluated and appeared to show a possible important interaction with barbiturate therapy. The primary cardiovascular complication reported was hypotension. In those patients with pre-randomization hypotension, control of ICP with either barbiturate treatment or conventional treatment had a similar chance of success (24% vs 29%).[3] A summary figure of efficacy of barbiturates and ICP control and outcome is presented in Table 1.

Therapeutic Regimens

While a number of agents have proven efficacious in lowering ICP, pentobarbital has been most often used clinically. A study by Levy, et al., (1995) randomized 7 patients to treatment with either pentobarbital or etomidate when the ICP was greater than 20 mm Hg for more than 20 minutes despite maximal medical treatment.[8] There was no significant difference in ICP lowering effect between the two drugs. With etomidate the SBP did drop to a mean of 103.9 compared to 92.9 mm Hg with pentobarbital. Likewise, cardiac output dropped to 4.5 liters per minute with etomidate as compared to 4.0 liters per minute with pentobarbital. Neither of these cardiovascular changes were statistically significant. Additionally, all three of the patients who received etomidate developed significant renal compromise. This was felt to be due to a toxic accumulation of the carrier agent propylene glycol. A number of therapeutic regimens using pentobarbital have been applied, all requiring a loading dose followed by a maintenance infusion. The Eisenberg RCT used the following protocol[3]:

Loading dose: 10 mgm/kg over 30 minutes
                5 mgm/kg every hour x 3 doses

Maintenance: 1 mgm/kg/hr

Even though a goal of therapy is to establish serum pentobarbital levels in the range of 3-4 mgm%, available literature suggests a poor correlation among serum level, therapeutic benefit, and systemic complications. A more reliable form of monitoring is the electroencephalographic pattern of burst suppression. Near maximal reductions in cerebral metabolism and cerebral blood flow (CBF) occur when burst suppression is induced.

Table 1: Barbiturate - ICP Control versus Outcome

Series	Number of Patients	Mortality Rate Responders	Mortality Rate Non-Responders	Class
Marshall (1979)	25	21%	82%	III
Eisenberg (1988)	37	8	83	I
Lobato (1988)	47	69	100	III
Nordstrom (1988)	19	25	63	III

V.   Summary

High-dose barbiturate therapy is efficacious in lowering ICP and decreasing mortality in the setting of uncontrollable ICP refractory to all other conventional medical and surgical ICP-lowering treatments. Utilization of barbiturates for the prophylactic treatment of ICP is not indicated. The potential complications attendant on this form of therapy mandate that its use be limited to critical care providers and that appropriate systemic monitoring be undertaken to avoid or treat any hemodynamic instability.

When barbiturate coma is utilized, consideration should also be given to monitoring arteriovenous oxygen saturation as some patients treated in this fashion may develop oligemic cerebral hypoxia.

VI. Key Issues for Future Investigation

Subsequent studies have attempted to identify certain subsets of head-injured patients who might respond favorably to barbiturate treatment. Lobato, et al., based on his experience with 55 patients, and suggested that barbiturates increase the chance for survival in the setting of post-traumatic unilateral hemispheric swelling. Survival was seen only in those patients whose ICP responded to barbiturates.[9] Nordstrom, et al., demonstrated a correlation in 19 patients between cerebral vasoreactivity, the beneficial effects of barbiturate therapy, and clinical outcome in 19 patients. The only patients to respond favorably to barbiturate ICP control (50% good recovery, 25% mortality) were those who exhibited a retained cerebrovascular autoregulatory response. Of those with an impaired response, ICP was not controlled with barbiturates with a resultant 64% mortality.[13]

It thus remains to be determined if various subsets of head-injured patients might benefit from the early administration of barbiturates.

The effects of barbiturate-medicated ICP control on quality of survival after severe head injury remain, for the most part, unknown. Further studies will be required to adequately address outcomes utilizing the Glasgow Outcome Scale (GOS) score, Disability Rating Scale, Functional Independence Measures, and Neuropsychological Testing.

Additional studies might also be considered that examine the comparative clinical efficacy of different barbiturates such as etomidate, pentobarbital, and thiopental.

VII. Evidentiary Table

Schwartz,[16] 1984

Description of Study: Randomized trial of pentobarbital vs mannitol as primary therapy for ICP elevations above 25 mm Hg.

Classification: Class I Study

Conclusions: Pentobarbital, when used as prophylactic treatment for ICP, provided no benefits in patients with intracranial mass lesions (mortality was 40% in pentobarbital group vs 43% in mannitol). In patients with diffuse injury, pentobarbital treatment was detrimental (mortality was 77% vs 41% in mannitol group).

Ward,[18] 1985

Description of Study: Randomized trial of pentobarbital vs standard treatment in 53 patients with risk factors for potential ICP elevations.

Classification: Class I Study

Conclusions: No significant difference in either mortality or one-year GOS score was found between treatment groups. However, hypotension (SBP < 80 mm Hg) occurred in 54% of the pentobarbital-treated patients compared to 7% in the other group.

Eisenberg,[3] 1988

Description of Study: Randomized trial of pentobarbital for medically refractory ICP elevations in 36 controls and 37 treated patients. Crossover design allowed 32 of the 36 controls to receive pentobarbital.

Classification: Class I Study

Conclusions: The likelihood of survival for those patients whose ICP responded to barbiturate therapy was 92% compared to 17% when control was not effected. In those patients with pre-randomization hypotension, barbiturates produced no benefits.

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THE ROLE OF STEROIDS

I.   Recommendations

A. Standards

The use of steroids is not recommended for improving outcome or reducing intracranial pressure (ICP) in patients with severe head injury.

B. Guidelines

None

C. Options

None

II.   Overview

Steroids were introduced in the early 1960s as a treatment for brain edema. Experimental evidence accumulated that steroids were useful in the restoration of altered vascular permeability in experimental brain edema,[20] reduction of cerebrospinal fluid production,[24] attenuation of free radical production, and other beneficial effects in experimental models.[3,4,15,17,20,21] The administration of glucocorticoids to patients with brain tumors often resulted in marked clinical improvement, and glucocorticoids were found to be beneficial when administered in the perioperative period to patients undergoing brain tumor surgery. French and Galicich reported a strong clinical benefit of glucocorticoids in cases of brain edema and found glucocorticoids especially beneficial in patients with brain tumors.[9] Renaudin, et al., in 1973 reported a beneficial effect of high-dose glucocorticoids in patients with brain tumor who were refractory to conventional doses.[22]

Glucocorticoids became commonly administered to patients undergoing a variety of neurosurgical procedures and became commonplace in the treatment of severe head injury. Gobiet, et al., in 1976 compared low-dose and high-dose Decadron to a previous control group of severely head-injured patients and reported it to be of benefit in the high-dose group.[12] Faupel, et al., in 1976 performed a double-blind trial and reported a favorable dose-related effect on mortality in head-injured patients using glucocorticoid treatment.[8] Subsequently, six major studies of glucocorticoid in severe head injury were conducted that evaluated clinical outcome ICP or both. None of these studies showed a substantial benefit of glucocorticoid therapy in these patients.[2,5,6,11,14,23] More recently, trials in head-injured patients have been completed using the synthetic glucocorticoid, triamcinolone,[13] the 21-aminosteroid tirilazad,[7,19] and also a trial using ultra-high-dose dexamethasone.[10] None of these trials have indicated an

overall beneficial effect of steroids on outcome. Moreover a recent meta-analysis of trials of steroids in head injury has revealed no overall beneficial effect of steroids on outcome.[1]

III. Process

A computer search was performed using MEDLINE for the period from 1966 to 1998 by using the key terms "head injury" and "steroids." A total of 60 documents were found. In addition, reference lists from the major clinical trials of steroid treatment in head injury and a recent meta-analysis of trials of steroids in head injury were examined. All clinical studies of steroids and head injury in humans were examined and reviewed in detail.

IV. Scientific Foundation

Gudeman, et al., reported the effects of high-dose methylprednisolone on ICP and volume-pressure response in 20 patients with severe head injury.[14] Patients were given 40 mg of methylprednisolone every 6 hours for the first 24 hours and the dose was increased to 2 g loading dose and 500 mg methylprednisolone every 6 hours for the following 24 hours. There was no significant change in the ICP or volume-pressure response between the two intervals. There was a 50% incidence of gastrointestinal bleeding and an 85% incidence of hyperglycemia in the treated group.

Cooper, et al., in 1979 reported a prospective, double-blind study of dexamethasone in patients with severe head injury.[5] Ninety-seven patients were stratified for severity and treated with placebo, low-dose dexamethasone 60 mg/day, or high-dose dexamethasone 96 mg/day. Seventy-six patients were available for clinical follow-up and ICP was measured in 51 patients. The results showed no difference in outcome, ICP, or serial neurologic examinations among the groups.

Saul, et al., in 1981 reported a prospective, randomized clinical trial in 100 patients. One group received methylprednisolone 5 mg/kg/day versus a control group that received no drug.[23] There was no statistically significant difference in outcome between the treated and non-treated groups at 6 months. This study reports a benefit of steroids in a small group of patients based on a subgroup analysis. This analysis indicated that in the subgroup of patients who improved during the first 3 days after head injury, the steroid-treated group fared better when compared with the placebo group.

Braakman, et al., reported the results of a large prospective, double-blind trial on the effect of dexamethasone on severely head-injured patients in 1983.[2] A total of 161 patients were randomized to placebo or high-dose dexamethasone (100 mg/day) followed by a tapering dose. There was no difference in 1 month survival or 6-month outcome between the two groups.

Giannotta, et al., in 1984 reported a prospective, double-blind clinical trial of 88 patients comparing placebo, low-dose methylprednisolone 1.5 mg/kg loading, followed by a tapering dose, with high-dose methylprednisolone 30 mg/kg loading, followed by a tapering dose.[14] The data did not show a beneficial effect of either low-dose or high-dose methylprednisolone compared with placebo. Subgroup analysis revealed an increased survival and improved speech function in patients under age 40 when the high dose was compared against the low dose and placebo groups combined.

Dearden, et al., in 1986, reported the results of a prospective, double-blind study on the effect of high-dose dexamethasone on outcome and ICP in 130 severely head-injured patients.[6] Patients were randomized to receive drug or placebo. No differences in ICP trends or 6-month outcome were seen.

Gaab, et al., in 1994, reported the results of a prospective, randomized, double-blind multicenter trial on the efficacy and safety of ultra-high-dose dexamethasone on outcome in patients with moderate and severe head injury.[10] The trial enrolled 300 patients, randomized to placebo or dexamethasone: 500 mg within 3 hours of injury, followed by 200 mg after 3 hours, then 200 mg every 6 hours for 8 doses for a total dexamethasone dose of 2.3 g, given within 51 hours. Glasgow Outcome Scale (GOS) score at 10-14 months following injury, and also time from injury until Glasgow Coma Scale (GCS) score reached 8 or greater, were used as primary endpoints. The results of the trial revealed no differences between placebo and drug-treated patients in either primary endpoints. This trial has the advantages of having a large number of patients who were treated early following injury, and with very high doses of medication.

Grumme, et al., in 1995, reported the results of a prospective, controlled, multicenter trial of the synthetic corticosteroid, triamcinolone on outcome in severely head-injured patients.[13] This trial randomized 396 patients to either placebo or steroids using triamcinolone 200 mg within 4 hours of injury followed by 40 mg every 8 hours for 4 days, followed by 20 mg every 8 hours for 4 days. The primary outcome measures were GOS at the time of discharge and at 12 months following injury. There was a trend toward better outcome in the steroid treated group, which was not statistically significant. Subgroup analysis revealed a better outcome in patients with focal lesions who had GCS scores of less than 8. The improvement in outcome in this subgroup was reported as significant. Multiple subgroups were analyzed, however, and if the results are corrected for multiple comparisons, then the difference in outcome in this subgroup is not statistically significant.

Marshall, et al., in 1998,[19] and Kassell, et al., in 1996[18], reported the results of two large prospective, randomized, controlled trials of the synthetic 21-amino steroid, tirilazad mesylate, on outcome in severely head-injured patients, one in North America and the other in Europe and Australia.[7] There is experimental evidence that this compound may be more effective than glucocorticoids against specific mechanisms that occur in brain injury, and higher doses can be used without glucocorticoid side effects.[15,16] The North American trial enrolled 1,170 patients and the European trial enrolled 1,128 patients. No overall benefit on outcome in head-injured patients was detected in either trial. Subgroup analysis in the European trial indicated that male patients with subarachnoid hemorrhage on their initial CT scan, who were on active drug, had a better outcome.

Alderson, et al., in 1997, reported the results of a systematic review of randomized controlled trials of corticosteroids in acute traumatic brain injury (TBI).[1] Many of the trials mentioned above, as well as additional unpublished data, were included in this analysis. The data presented indicate that there was no evidence for a beneficial effect of steroids to improve outcome in head-injured patients. Analysis of the trials with the best blinding of groups revealed the summary odds ratio for death was 1.04 (0.83 to 1.30), and for death and disability was 0.97 (0.77 to 1.23). The authors stated that a lack of benefit from steroids remained uncertain, and recommended that a larger trial of greater than 20,000 patients to detect a possible beneficial effect of steroids be conducted.

V.   Summary

The majority of available evidence indicates that steroids do not improve outcome or lower ICP in severely head-injured patients. The routine use of steroids is not recommended for these purposes.

VI. Key Issues for Future Investigation

Data analysis from the trials of the 21-aminosteroid tirilizad is ongoing. It is possible that based on the results of subgroup analysis from these trials further studies, such as in patients with traumatic subarachnoid hemorrhage, may be proposed. A future trial in patients with more severe head injuries with focal lesions may determine if this subgroup of patients may benefit from triamcinolone.

VII. Evidentiary Table

Braakman,[2] 1983

Description of Study: Prospective, double-blind study, randomized 161 patients with severe head injury to placebo or high-dose dexamethasone (100 mg day followed by tapering dose).

Classification: Class I Study

Conclusions: No significant difference in 1-month survival of 6-month outcome.

	Active Treatment	Placebo
Dead	54 %	58%
Good recovery	17.3	15

Cooper,[5] 1979

Description of Study: Prospective, double-blind study of 97 patients with severe head injury, stratified for severity, and treated with placebo 60 mg/day or 96 mg/day of dexamethasone; 76 patients available for follow-up at 6 months.

Classification: Class I Study

Conclusions: No significant difference was seen in 6-month outcome, serial neurological exams, or ICP.

	Low Dose	High Dose	Placebo
Bad outcome (SD, PVD, D)	56%	71%	63%
Good outcome (GR, MD)	44	29	37

Abbreviations: GR, good recovery; MD, moderate disability; SD, severe disability; PVS, persistent vegetative state; D, dead

Dearden,[6] 1986

Description of Study: Prospective, double-blind study of 130 patients with severe head injury, randomized to high-dose dexamethasone vs placebo. All patients were followed and outcome was analyzed. ICP trends in the two groups were also analyzed.

Classification: Class I Study

Conclusions: No significant difference in ICP trends or 6-month outcome between control and treated groups was found.

	Active Treatment	Placebo
Dead	49%	35.5%
Good Recovery	32	35.5

Faupel,[8] 1976

Description of Study: Prospective, double-blind trial of dexamethasone vs placebo in 95 patients with severe head injury.

Classification: Class I Study

Conclusions: Significant improvement in mortality in steroid-treated group; however, overall outcome was not improved. Of the active treatment groups, 25.4% were vegetative and 11.9% were severely disabled vs 3.6% and 7.1% in the control group.

	Active Treatment	Placebo
Good Outcome (GR, MD, SD)	39%	32%
Dead	24	57
Dead or Vegetative	49	61

Gaab,[10] 1994

Description of Study: Prospective, randomized, double-blind, multicenter trial of ultra-high-dose dexamethasone on outcome in 300 patients with moderate and severe head injury, randomized to placebo or dexamethasone: 500 mg within 3 hours of injury, followed by 200 mg after 3 hours, then 200 mg every 6 hours for 8 doses for a total dexamethasone dose of 2.3 g, given within 51 hours.

Classification: Class I Study

Conclusions: No significant difference in 12-month outcome or in time to improvement to GCS score greater than or equal to 8 in treatment group compared with placebo.

	Active Treatment	Placebo
Dead	14.3%	15.4%
Good Recovery	61.7	57.4

VII.   Evidentiary Table (continued)

Grumme,[13] 1995

Description of Study: Prospective, controlled, multicenter trial randomized 396 severely head-injured patients to either placebo or steroids using triamcinolone 200 mg within 4 hours of injury followed by 40 mg every 8 hours for 4 days, followed by 20 mg every 8 hours for 4 days.

Classification: Class I Study

Conclusions: A trend toward better outcome in treated group, but no significant difference in 12-month outcome or at the time of discharge from the hospital in treatment group compared with placebo.

At discharge	Active treatment	Placebo
Dead	16 %	21 %
Good recovery	49.2	40.7

Giannotta,[11] 1984

Description of Study: Prospective, double-blind study of 88 patients with severe head injury. Patients randomized to placebo, low-dose methylprednisolone (30 mg/kg/day) or high-dose methylprednisolone (100 mg/kg/day).

Classification: Class I Study

Conclusions: No significant difference in 6-month outcome in treatment groups compared with placebo. Subgroup analysis showed improved survival and speech function in patients under age 40 when high-dose group was compared to low-dose and placebo groups combined.

	Low Dose	High Dose	Placebo
Dead	55.8%	39.4%	43.7%
Good Recovery	14.7	18.4	25

Gobiet,[12] 1976

Description of Study: Cohort study of 93 head-injured patients. Compared low-dose and high-dose dexamethasone to cohort retrospectively.

Classification: Class II Study

Conclusions: Reported significant benefit in high-dose group on mortality.

	Low Dose	High Dose	Control
Dead	41.5%	23%	45.5%

Gudeman,[14] 1979

Description of Study: Examined the effect of two doses of methylprednisolone on ICP parameters only in 20 patients with severe head injury. Patients served as their own controls and two separate intervals were analyzed.

Classification: Class II Study

Conclusions: No significant difference in ICP or volume-pressure response was seen during an interval when the methylprednisolone dose was increased.

Marshall,[19] 1998 and Kassell,[18] 1996

Description of Study: Two large prospective, randomized, controlled trials of the synthetic 21-amino steroid, tirilizad mesylate, on outcome in severely head-injured patients, one in North America (1,120 patients) and the other in Europe and Australia (1,023 patients).

Classification: Class I Study

Conclusions: No overall benefit on outcome in head-injured patients was detected in either trial. Subgroup analysis in the European trial indicated that male patients with subarachnoid hemorrhage on their initial CT scan, who were on active drug, had a better outcome. Final data analysis is pending.

Saul,[23] 1981

Description of Study: Prospective, double-blind study of 100 patients with severe head injury, randomized to placebo or methylprednisolone 5 mg/kg/day.

Classification: Class I Study

Conclusions: No significant difference in outcome at 6 months. A subgroup of responders was identified who did better with active treatment; however, the trial was not designed to examine this group.

	Active Treatment	Placebo
Dead or Vegetative	38%	48%
Good Recovery or Disabled (GR, MD, SD)	62	52

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CRITICAL PATHWAY FOR THE TREATMENT OF ESTABLISHED INTRACRANIAL HYPERTENSION

I.   Introduction

A critical pathway, developed by consensus, is presented in Figure 1. We developed a treatment algorithm for established intracranial hypertension wherein the order of steps is determined by the risk/benefit ratio of individual treatment maneuvers. The considerations involved are outlined in the chapter specific to each step.

As discussed in the section on intracranial pressure (ICP) treatment threshold, the absolute value defining unacceptable intracranial hypertension is unclear. Although a general threshold of 20-25 mm Hg has been presented, there will be situations where such pressures are too high as well as instances where higher ICP values are acceptable. These considerations are relevant to the decision to pursue any step in the escalated treatment of ICP.

This critical pathway is a committee consensus and, therefore, must be viewed as Class III ("expert opinion") evidence. As such, it should be interpreted as a framework that may be useful in guiding an approach to treating intracranial hypertension. It can and should be modified in an individual case by any circumstances unique to the patient as well as by the response of the ICP to individual treatment steps.

II.   Critical Pathway

A number of general maneuvers may be applied together early during the treatment of intracranial hypertension. These include control of body temperature, seizure prophylaxis, elevation of the head of the bed, avoidance of jugular venous outflow obstruction, sedation ± pharmacologic paralysis, maintenance of adequate arterial oxygenation, and complete volume resuscitation to a cerebral perfusion pressure (CPP) of 70 mm Hg or more.

When a ventricular catheter is being used for ICP monitoring, cerebrospinal fluid (CSF) drainage should be used first for ICP elevations. Ventilation may be adjusted to establish a $PaCO_2$ at the low end of eucapnea (35 mm Hg).

When intracranial hypertension is maintained despite initiation of these general maneuvers, treatment modalities with a lower ratio of risk to benefit may be considered. If CSF drainage is ineffective in controlling ICP or is not available, the level of ventilation may be increased to obtain $PaCO_2$ levels of 30-35 mm Hg (0-5 mm Hg below the lower threshold of eucapnea). If available, measurement of cerebral blood flow or jugular venous saturation should be considered when hyperventilation is further increased. If mild hypocapnia is ineffective in controlling ICP, mannitol can be employed, limited by serum osmolarity levels of 320 mOsm/l.

The patient's volume status should be closely observed during mannitol administration and euvolemia to mild hypervolemia maintained by careful fluid replacement. At all times during the treatment of intracranial hypertension, the possibility of a surgical mass or an intracranial lesion should be considered. Therefore, under conditions of intractability or loss of ICP control or when second tier therapy is being contemplated, consideration should be given to repeating a CT scan.

For intracranial hypertension refractory to the above techniques, second tier therapies should be considered when it is the physician's opinion that the patient may benefit if ICP control can be accomplished. Second tier therapy includes both treatment modalities that have been proven effective in improving outcome, but have very significant complication rates (e.g., barbiturates). Additional second tier therapies are those that appear to effectively lower ICP, but remain unproven in their influence on outcome or the exact magnitude of their risk/benefit ratio. These latter modalities include hyperventilation to $PaCO_2$ less than 30 mm Hg, decompressive craniectomy, and hypertensive therapy. Barbiturates, the most thoroughly studied second tier approach, are covered here in a separate chapter. Ventilation to low $PaCO_2$ values is addressed in the hyperventilation section. The precise indications and implementation of second tier therapies in an individual patient are left to the discretion of the managing physician.

CRITICAL PATHWAY FOR TREATMENT OF INTRACRANIAL HYPERTENSION

FIG 1. Critical pathway for treatment of intracranial hypertension in the severe head injury patient (treatment option).
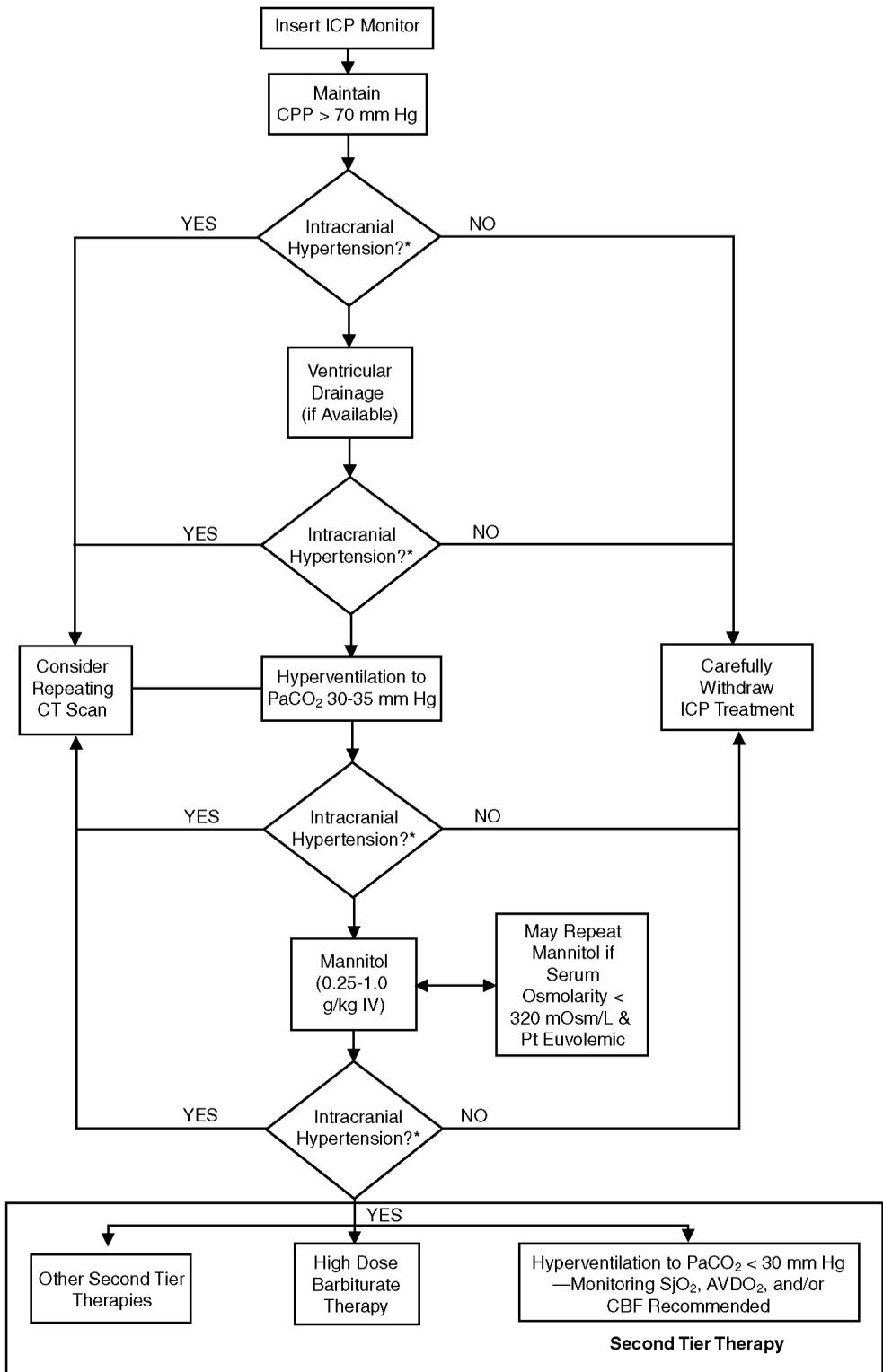
* Threshold of 20-25 mm Hg may be used. Other variable may be substituted in individual conditions.

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NUTRITION

I. Recommendations

    A. Standards

        There are insufficient data to support a treatment standard for this topic.

    B. Guidelines

        Replace 140% of resting metabolism expenditure in non-paralyzed patients and 100% of resting metabolism expenditure in paralyzed patients using enteral or parenteral formulas containing at least 15% of calories as protein by the seventh day after injury.

    C. Options

        The preferable option is use of jejunal feeding by gastrojejunostomy due to ease of use and avoidance of gastric intolerance.

II. Overview

The metabolic response to severe brain injury was systematically documented beginning in the early 1980s. There were occasional case reports of hypermetabolism in brain injury in prior years (Class III data). Up to this time a casual attitude toward nutritional replacement was usual in clinical practice. This was based on the assumption that, due to coma, metabolic requirements were reduced. Most of the research done beginning in 1980 consisted of measurements of metabolic expenditure, nitrogen loss, and cardiovascular parameters. These values were compared to well-established normative data and to the patterns documented in other injured patient groups (Class II data). Hypermetabolism and nitrogen wasting were well documented. At least 12 Class I studies have been completed. Nine Class I studies examined the effect of amount of feeding, type of feeding, route of feeding, and steroids on nitrogen balance and serum biochemistries. These studies made no statements regarding patient outcome (deleted phrase).

     One Class I study examined the effect of IGF-1 on the catabolic state and on outcome.[18] Two Class I studies examined the effect of the extent of nutritional replacement on patient outcome.[31,39] These showed that with nearly equivalent quantities of feeding, the mode of administration (parenteral or enteral) had no effect on neurologic outcome. Conflicting results were found with infection rate and nitrogen retention. One study reported that malnutrition increased mortality rate in head-injured patients. This study's methodology can be questioned due to an unexpectedly low mortality rate in the higher nutrition group and an unexpectedly

high mortality rate in the low nutrition group. It was judged that this study did not have the force to establish a standard.

III. Process

A MEDLINE search of the categories "brain injury" and "nutrition" was conducted for the years 1975 through 1997, and all publications published in English were reviewed. Only articles discussing nutritional data in patients with head injury were referenced in evidentiary tables and used as the primary source for conclusions. The methodology, results, and conclusions of each of these 29 references were studied.

IV. Scientific Foundation

1) The physician should aim for replacement of 140% of resting metabolism expenditure in non-paralyzed patients and 100% resting metabolism expenditure in paralyzed patients.

A number of publications have dealt with energy requirements after head injury.[2,4,6,8,9,10,13,14,17,25,27,33,34,35,38,41,43,47,49] The technique for measurement is indirect calorimetry, which measures the rate of oxygen utilization and gives energy expenditure by the known caloric yield of one liter of oxygen. Because caloric expenditure varies with age, sex, and body surface area, metabolic expenditure is expressed as a percent of normal at rest for a given patient. This value for each patient can be found in standard tables. Data from most investigators measuring metabolic expenditure in rested comatose patients with isolated head injury yielded a mean increase of approximately 140% of the expected metabolic expenditure with variations from 120%-250% of that expected. Of importance, only the data of Young, et al.,[47] and Deutschman, et al.,[9] are of nonsteroid-treated patients, and those agree with other calorimetric data in steroid-treated, head-injured patients.

Researchers found that, in head-injured patients, paralysis with pancuronium bromide or barbiturate coma decreased metabolic expenditure from a mean of 160% of that expected to 100%-120%. This finding suggests that a major part of the increased metabolic expenditure is related to muscle tone. Even with paralysis, energy expenditure remained elevated by 20%-30% in some patients.[4] In the first two weeks after injury, energy expenditure seems to rise regardless of neurological course. The duration of hypermetabolism beyond the first two weeks is not known.

At some point, the pathologically increased caloric requirements fueled by increased muscle tone and an altered hormonal milieu are replaced by the requirements that would normally accompany increased activity as the patient improves. Routine use of calorimetry has been recommended because of the high variability among patients and the relatively poor ability of predictive formulas to guide acute nutritional requirements.[43] The method is cumbersome and is rarely used in routine clinical practice. The resting metabolic expenditure for a 70 kg, 25-year-old male is 1,700 kcal/24 hr and for a 50 kg, 50-year-old female is 1,200 kcal/24 hr. Projected caloric needs would, therefore, be 2,400 kcal/24 hr for a 70 kg male.

Three randomized (Class I) studies have evaluated the relationship of level of caloric intake to patient outcomes.[16,36,48] Rapp showed that the consequence of severe undernutrition for a two-week period after injury was an increased mortality rate as compared to full replacement of measured calories by seven days.[36] In a subsequent study of brain injured patients, Young, et al., showed that with full replacement at three days after injury in the early

group (fed parenterally) as opposed to nine days after injury in the late feeding group (fed enterally), there were no changes in morbidity. [48] Patient outcome was better at three months but not at six months. Hadley randomized 45 patients with severe head injury to receive enteral or parenteral nutrition. While caloric intake between groups was not significantly different, the parenteral group had significantly better nitrogen intake. [16]

To achieve full caloric replacement by 7 days after injury, nutritional replacement is usually begun no later than 72 hours after injury. This is so because 2-3 days are required to gradually increase feedings to full replacement whether feeding is by jejunal or gastric route. [5,8,15,37,48] Intravenous hyperalimentation must also be started at levels below resting metabolism expenditure and advanced over 3 days. Whichever method is used in order to achieve full replacement, feedings are usually begun within 72 hours of injury.

2) Use an enteral or parenteral formula containing 15% of calories as protein. Nitrogen balance is defined as the difference between nitrogen intake and nitrogen excretion. For each gram of nitrogen measured in the urine (plus fecal loss), 6.25 g of protein have been catabolized. In normal and injured man, optimal protein utilization has been found to be heavily dependent upon the adequacy of caloric intake. Catabolism of protein, which yields only 4 kcal/g (as opposed to fat, which yields 8 kcal/g), makes up 10% or less of consumed calories in normal man. [12] After severe brain injury, not only do energy requirements rise greatly, but nitrogen excretion does also. The contribution of protein to consumed calories after head injury rises to levels as high as 30% (given 10 g/day nitrogen intake and full caloric replacement). [12] In a fasting normal human, nitrogen catabolism drops to levels as low as 3-5 gN/day. Fasting patients with severe brain injury continue to lose 14-25 gN/day, however. [14] The peak in nitrogen excretion appears to occur in the second week with improvement in nitrogen retention by the third week.

It is only after the third week that nitrogen balance can be achieved. Two publications address the question of steroid effect on nitrogen excretion and report that increased nitrogen excretion after brain injury is not the result of steroid administration. [37,47]

One can estimate the potential sequelae of these levels of nitrogen loss from the following facts. A 30% preoperative weight loss increased the morbidity and mortality of gastric surgery by tenfold. [41] It is, therefore, generally assumed that a 10%-15% weight loss in a bedfast patient is of little consequence, but that a 30% weight loss is potentially very deleterious. The average nitrogen loss of the fasting head-injured patient is 0.2 gN/kg/day (14 gN in 70 kg male), about double or triple the loss in the normal person, with values of fasting nitrogen loss of up to 25 gN/day frequently being seen. This level of nitrogen loss will produce a 10% decrease in lean mass in seven days; hence, underfeeding for a two-to-three week period could result in a 30% weight loss.

The desired level of reduction of nitrogen loss has not been quantified but is the subject of Class I studies. [5,11,15,19,22] These studies have not, however, examined patient outcome. The relative gains in nitrogen balance achieved with high protein feeding can be illustrated. Two matched groups of comatose head-injured patients were treated by caloric replacement with intakes of 17.6 ± 3.6 gN/day and 29.0 ± 5.3 gN/day, respectively, at 140% replacement of expended calories. [5] Data are from 7-day balance periods within the first two weeks after injury. A nitrogen balance of -9.2 ± 6.7 g/day was found in the lower protein group and a balance of -5.3 ± 5.0 g/day in the higher protein group. These data suggest that at a high

range of nitrogen intake (> 17 g/day), less than 50% of administered nitrogen is retained after head injury. Therefore, the level of nitrogen intake that generally results in less than 10 g nitrogen loss per day is 15-17 gN/day or 0.3-0.5 gN/kg/day. As it turns out, this value is about 20% of the caloric composition of a 50 kcal/kg/day feeding protocol. Twenty percent is the maximal protein content of most enteral feedings designed for the hypermetabolic patient. Twenty percent is the maximal amino acid content of most parenteral formulations for trauma patients, which generally contain more than 15% protein calories.

3) Jejunal feeding by gastrojejunostomy avoids gastric intolerance found in gastric feeding and the use of intravenous catheters required in total parenteral nutrition.

There are three options for the method of feeding. Some reports indicate that jejunal and parenteral replacement produce better nitrogen retention than gastric feeding. [15,16,19,48] Gastric alimentation has been used by some investigators.[5,37,48] Others have found altered gastric emptying or lower esophageal sphincter dysfunction to complicate gastric feeding.[27,28,29,40] There has been one Class I report and one Class II report indicating better tolerance of enteral feeding with jejunal rather than gastric administration.[5,22] In studies of both gastric and jejunal administration, it has been possible to achieve full caloric feeding in most patients by seven days after injury.[5,15,22,48]

Jejunal alimentation by endoscopic or fluroscopic, not blind, placement has practical advantages over gastric feeding. A higher percentage of patients tolerates jejunal rather than gastric feeding early after injury and less risk of aspiration is reported (presumably after extubation).[15,26,29,40] Increasingly parenteral nutrition is started early after injury until either gastric feedings are tolerated or a jejunal feeding tube can be placed or a procedure team is used to effect very early jejunal tube placement.[1,29]

Three potential advantages of enteral feeding are:
1. Less risk of hyperglycemia than with parenteral feeding
2. Lower theoretical risk of infection
3. Lower cost

Hyperglycemia has been shown to aggravate hypoxic ischemic brain injury in an extensive experimental literature. One study in experimental cortical contusion injury has shown that hyperglycemia exacerbates cortical contusion injury with superimposed ischemia.[3] In two Class II studies, hyperglycemia has been associated with worsened outcome. [24,46] Parenteral nutrition has not, however, been shown to aggravate hyperglycemia, though more insulin is required to maintain normoglycemia with parenteral nutrition than with enteral nutrition.[42]

The risk of infection has not been shown to be increased with parenteral nutrition as compared to enteral nutrition in brain injured patients.[1,46] Literature about patients with other kinds of trauma, however, suggests that use of enteral feedings reduces septic complications related to gut mucousal integrity and may decrease hypermetabolism. [20,21,23] Class I data in head injury patients indicates less insulin dependence and earlier improvement in visceral proteins with enteral nutrition than with parenteral nutrition.[42] Another Class I study, however, has shown no difference in recovery of visceral proteins. [1] The primary advantage of parenteral nutrition is that it is well tolerated. While in

laboratory animals parenteral nutrition may aggravate brain swelling, this has not been a clinical problem.[7,44,46] No clearly superior method of feeding has been demonstrated either in terms of nitrogen retention, complications, or outcome.

The daily cost of parenteral nutrition is higher than enteral nutrition.[1,29] The overall cost of care has not, however, been increased by use of parenteral nutrition.[1,29] This discrepancy could be related to increased costs associated with problems associated with placement or replacement of enteral feeding tubes.[29]

4) New data in a Class I study of 33 patients has shown achievement of positive nitrogen balance and some indication of improved outcome with administration of IGF-1. Further testing of neurotrophic factors in patients with brain injury will probably result from this study.

V.   Summary

Data show that starved head-injured patients lose sufficient nitrogen to reduce weight by 15% per week. Class II data show that 100%-140% replacement of resting metabolism expenditure with 15%-20% nitrogen calories reduces nitrogen loss. Data in non–head-injured patients show that a 30% weight loss increased mortality rate. Class I data suggests that non-feeding of head-injured patients by the first week increases mortality rate. The data strongly support feeding at least by the end of the first week. It has not been established that any method of feeding is better than another or that early feeding prior to seven days improves outcome. Based on the level of nitrogen wasting documented in head-injured patients and the nitrogen sparing effect of feeding, it is a guideline that full nutritional replacement be instituted by the seventh day.

VI.   Key Issues for Future Investigation

The effect found with IGF-1 in 33 patients could be definitively tested in a multicenter, prospective, randomized trial with a large sample size.

VII. Evidentiary Table

Borzotta,[1] 1994

Description of Study: Energy expenditure (MREE) and nitrogen excretion (UNN) measured in patients with severe head injury randomized to early parenteral (TPN, n=21) or jejunal (ENT, n=17) feeding with identical formulations. MREE rose to 2400 ± 531 kcal/day in both groups and remained at 135%-146% of predicted energy expenditure over 4 weeks. Nitrogen excretion peaked the second week at 33.4 (TPN) and 31.2 (ENT) gN/day. There was equal effectiveness in meeting nutritional goals, and infection rates and hospital costs were similar.

Classification: Class I Study

Conclusions: Authors concluded patients with head injuries are hypermetabolic for weeks, that only 27% are capable of spontaneously eating nutritional requirements by discharge, and either TPN or ENT support is equally effective when prescribed according to individual measurements of MREE and nitrogen excretion.

Bruder,[2] 1991

Description of Study: Nitrogen excretion and energy expenditure were measured simultaneously in 8 patients at 4 days and 18 days after injury. Patients were fed 13 ± 2g/day of Nitrogen. In sedated patients, RME was 104%-134% of expected and Nitrogen excretion was 17-23 g/day.

Classification: Class II Study

Conclusions: The authors recommended not feeding head-injured patients over 140% RME.

Clifton,[4] 1986

Description of Study: A nomogram is presented for estimation of RME at bedside of comatose, head-injured patients based on 312 days of measurement of energy expenditure in 57 patients. No predictors for nitrogen excretion were found.

Classification: Class II Study

Conclusions: The authors recommend use of a nomogram to estimate RME and measurement of nitrogen excretion to guide feeding.

Abbreviations: N = nitrogen; RME = resting metabolic expenditure; g = grams; TPN = total parenteral nutrition

VII.   Evidentiary Table (continued)

Clifton,[5] 1985

Description of Study: Twenty patients with severe brain injury were randomized to feeding with an enteral formula containing 14% protein calories or 22% protein calories. Patients were fed at 140% RME. Nitrogen balance was -9.2 ± 6.7 g/24 hr in the group fed 14%, and -5.3 ± 5.0 g/24 hr in the higher protein group. Patients were treated with steroids.

Classification: Class I Study

Conclusions: The authors conclude that high protein and caloric feedings can be delivered enterally. Increasing protein content may improve Nitrogen balance but not eliminate Nitrogen excretion.

Clifton,[6] 1984

Description of Study: Caloric expenditure and Nitrogen balance were measured in 14 steroid-treated, comatose, head-injured patients acutely and for 28 days after injury. Nitrogen intake was: 8.0 ± 6.1 g (days 1-3), 13.0 ± 7.3 g (days 4-6), and 11.2 ± 6.9 g (days 7-9). Nitrogen loss was 18.6 ± 6.4 g (days 1-3), 20.3 ± 6.5g (days 4-6), and 22.1 ± 6.0 g (days 7-9). Average RME was 138 and 37% of expected patients were steroid treated.

Classification: Class II Study

Conclusions: The authors recommended feeding 0.24 g/kg/day of Nitrogen.

Deutschman,[9] 1986

Description of Study: Ten patients with severe brain injury underwent measurements of oxygen consumption by arterial-venous oxygen measurement for the first 7 days after injury. Patients were not fed. Patients were found to be hypermetabolic initially but with resolution by 7 days. Nitrogen excretion was 12-14 g/day of Nitrogen. Steroids were administered.

Classification: Class II Study

Conclusions: The authors recommended 1.5-2.0 g protein/kg/24 hr tapered to 1.2-1.4 g protein/kg/24 hr by 7 days.

Dickerson,[10] 1990

Description of Study: In six patients with acute head injury, RME and Nitrogen excretion were measured acutely after injury. All patients received dexamethasone. Mean RME was 90 ± 31%. Urinary Nitrogen excretion was 16.5 ± 5.8 g/day.

Classification: Class II Study

Conclusions: Protein requirements are accentuated in excess of calorie needs in head-injured patients.

Fell,[13] 1984

Description of Study: Nitrogen excretion of 27 patients with acute neurosurgical injuries were compared with 23 patients with both neurosurgical and multisystem injuries. On days 1, 3, and 5, urinary Nitrogen excretion and serum electrolytes were measured. Patients were not fed.

Classification: Class II Study

Conclusions: Nitrogen excretion was -14.6 ± 3.2 g/day in patients with neurosurgical injuries and multisystem injuries, and -16.5 ± 3.1 g/day in patients with multisystem injuries.

Gadisseux,[14] 1984

Description of Study: Twenty-three comatose patients with severe brain injury had measurement of RME and Nitrogen excretion for 12 days following injury. Mean Nitrogen output was 199 ng/kg/day in fasted patients. Values of RME ranged from 43% to 234% Steroids were not used.

Classification: Class II Study

Conclusions: Nitrogen loss is similar to that of skeletal trauma. The peak increase in RME is 170%. Barbiturates and muscle relaxants diminish increased RME.

Grahm,[15] 1984

Description of Study: Thirty-two head-injured patients were randomized to nasojejunal or gastric feeding. Nitrogen balance in the nasojejunal group was -4.3 g/day vs -11.8 g/day in the gastric feeding group.

Classification: Class I Study

Conclusions: Nasojejunal feeding permitted increased caloric intake and improved Nitrogen balance.

Hadley,[16] 1986

Description of Study: Forty-five acute head trauma patients were randomized into two groups comparing the efficacy of TPN and enteral nutrition. TPN patients had significantly higher mean daily Nitrogen intakes ($p < 0.01$) and mean daily Nitrogen losses ($p < 0.001$) than nasogastrically fed patients; however, Nitrogen balance was not improved.

Classification: Class I Study

Conclusions: Patients with head injury who are fed larger Nitrogen loads have exaggerated Nitrogen losses.

VII. Evidentiary Table (continued)

Haider,[17] 1975

Description of Study: Twenty-seven patients with severe brain injury underwent measurement of RME and Nitrogen balance acutely after injury. Mean increase in RME is 170%. Metabolic rates decreased over time. Nitrogen loss was increased over normal.

Classification: Class II Study

Conclusions: Metabolic rate of brain-injured patients is increased.

Hatton, [18] 1997

Description of Study: Randomized study of 33 traumatic head-injured patients (18-59 years) to determine the effect of insulin-like growth factor-1 (IGF-1) on catabolic state and clinical outcome of head-injured patients.

Classification: Class I Study

Conclusions: Indications that pharmacological concentrations of IGF-1 may improve clinical outcome. There was substantial improvement in Nitrogen utilization in patients with moderate-to-severe head injury treated with IGF-1.

Hausmann,[19] 1985

Description of Study: Twenty patients with severe brain injury were randomized to feeding with combined enteral TPN and to TPN alone. No statistical differences could be observed in Nitrogen balance.

Classification: Class I Study

Conclusions: Addition of TPN to enteral nutrition did not produce metabolic differences.

Kirby,[22] 1991

Description of Study: Twenty-seven patients with severe brain injury underwent feeding with percutaneous endoscopic gastrojejunostomy. Average Nitrogen balance was -5.7 g/day.

Classification: Class II Study

Conclusions: The reduction in Nitrogen loss by this technique appeared equal or superior to gastric or TPN.

Lam,[24] 1991

Description of Study: The clinical course of 169 patients with moderate or severe brain injury was retrospectively reviewed and outcome correlated with serum glucose.

Classification: Class II Study

Conclusions: Among the more severely injured patients (GCS < 8), a serum glucose level greater than 200 mg/dl postoperatively was associated with a significantly worse outcome.

VII. Evidentiary Table (continued)

Long,[25] 1979

Description of Study: Metabolic expenditure and urinary Nitrogen loss was measured in patients after elective surgery, skeletal trauma, blunt trauma, head trauma with steroids, sepsis, burns, and normals.

Classification: Class II Study

Conclusions: Patients with head trauma and steroids had $0.34 \pm .1$ g/kg/day of nitrogen loss and 60.8 ± 6 % increase in RME.

Moore,[27] 1989

Description of Study: RME of 20 patients with severe brain injury was measured within 48 hours of admission.

Classification: Class II Study

Conclusions: RME was $160 \pm 37\%$ of expected.

Norton,[28] 1988

Description of Study: Twenty-three brain-injured patients were fed by gastric tube. The time from injury to initiation of full feeding was 11.5 days; 7 patients tolerated feeding within 7 days, 4 patients from days 7-10, and 12 patients after 10 days.

Classification: Class II Study

Conclusions: Tolerance of enteral feeding is inversely related to increased ICP and severity of brain injury.

Ott,[29] 1999

Description of Study: A retrospective analysis of early enteral feedings by endoscopic, blind, and percutaneous endoscopic gastrostomy jejunostomy (PEG/J) placement of small bowel feeding tubes in 57 patients.

Classification: Class II Study

Conclusions: Blind transpyloric feeding tube placement is rarely possible in head injury patients. Endoscopic access to small bowel permits tolerance of enteral feedings by most patients and is cheaper than parenteral nutrition.

VII. Evidentiary Table (continued)

Ott,[31] 1991

Description of Study: Liquid gastric emptying was measured during the first three weeks in 12 patients with severe head injury.

Classification: Class II Study

Conclusions: Delayed or abnormal gastric emptying was observed in most patients in the first two weeks after injury.

Ott,[32] 1988

Description of Study: Twenty severely brain-injured patients with GCS scores 4-9 were prospectively randomized to receive one of two standard amino acids formulas, starting with the first day of hospital admission up to day 14 post-injury. Nitrogen balance was -8 ± 2.1 g/day vs 1.8 ± 1.2 g/day.

Classification: Class I Study

Conclusions: The amino acid formula with increased leucine, isoleucine, valine tyrosine, and phenylalanine resulted in improved N balance.

Phillips,[33] 1987

Description of Study: Energy expenditures, Nitrogen excretion, and serum protein levels were studied from the time of hospital admission until two weeks after severe head injury in 8 adolescents and 4 children with GCS scores 3-8.

Classification: Class II Study

Conclusions: Head injury in the child and adolescent induced a metabolic response that includes increased energy expenditure and decreased serum albumin levels similar to those seen in adult head injuries.

Piek,[35] 1985

Description of Study: Fourteen patients suffering from severe head injury were followed for changes in amino acid and protein metabolism during the first 8 days after trauma. Patients were fed 15.7 g/day of Nitrogen and had an Nitrogen balance of -9.7 g/day on the eighth day.

Classification: Class II Study

Conclusions: Protein metabolism is increased after brain injury.

VII. Evidentiary Table (continued)

Rapp,[36] 1983

Description of Study: Thirty-eight head-injured patients were randomly assigned to receive TPN or enteral nutrition. There were no significant differences in severity of head injury by GCS score or other variables that influence outcome. Mean intake for the TPN group was 1,750 calories and 10.2 g/day of Nitrogen for the first 18 days. The TPN group got full nutritional replacement within 7 days of injury. The enteral group achieved 1,600 calories replacement by 14 days after injury. For the enteral nutrition group mean intake in the same period was 685 calories and 4.0 g/day of N. There were 8 deaths in the enteral nutrition group and none in the parenteral nutrition group in the first 18 days ($p < 0.001$).

Classification: Class I Study

Conclusions: Early feeding reduces the mortality rate from head injury.

Robertson,[37] 1985

Description of Study: The effect of steroid administration on metabolic rate and Nitrogen excretion was examined in 20 head-injured patients alternately assigned to receive either methylprednisolone for 14 days or no steroid treatment. All patients had an increase in Nitrogen excretion through the second peak at day 11. The patients who received steroids had a 30% higher excretion of Nitrogen in the first 6 days, and had lower lymphocyte count and higher infection rates.

Classification: Class I Study

Conclusions: Exogenesis steroids increase Nitrogen excretion in head-injured patients.

Robertson,[38] 1984

Description of Study: Factors that influenced RME and the cardiovascular response associated with elevated RME were examined in 55 patients with penetrating and closed head injuries who were kept normovolemic and hyperalimented in the acute phase of injury.

Classification: Class II Study

Conclusions: Sedatives and muscle relaxants decreased RME. The lower the GCS score the higher the RME.

Robertson,[39] 1991

Description of Study: The role of intravenous infusion of glucose in limiting ketogenesis and the effect of glucose in cerebral metabolism were studied in 21 comatose patients.

Classification: Class II Study

Conclusions: Administration of glucose during the early recovery period of severe head injury is a major cause of ketogenesis and may increase production of lactic acid by the brain.

VII. Evidentiary Table (continued)

Saxe,[40] 1994

Description of Study: Study designed to identify role of lower esophageal sphincter (LES) function in gastric feeding complications of vomiting and aspiration pneumonitis in 16 head-injured patients (GCS < 12) within 72 hours of admission.

Classification: Class II Study

Conclusions: There is evidence that LES dysfunction accompanies acute head injury and contributes to aspiration pneumonitis after early gastric feeding. Authors recommend parenteral or jejunal feeding in patients with low GCS scores.

Suchner,[42] 1996

Description of Study: Thirty-four patients after emergency craniotomy were randomized to TPN versus enteral nutrition. The effects on nutritional status, gastrointestinal absorptive functional substrate tolerance was studied.

Classification: Class I Study

Conclusions: Enteral nutrition following neurosurgical procedures was associated with accelerated normalization of nutritional status and improved substrate tolerance. Enteral nutrition opposes early postoperative absorption disturbances of the small intestine.

Sunderland and Heilbrun,[43] 1992

Description of Study: 385 measurements were obtained in 102 patients with severe head injury and were compared with three predictive formulas. The best prediction when compared with measured RME was able to capture values of 25%-125% of predicted RME in only 56% of measurements.

Classification: Class II Study

Conclusions: The routine use of indirect calorimetry to guide caloric supplementation in patients with traumatic brain injury is warranted.

Young,[45] 1989

Description of Study: Serum glucose levels were followed in 59 consecutive brain-injured patients for up to 18 days after injury and correlated with outcome.

Classification: Class II Study

Conclusions: The patients with the highest peak admission 24-hour glucose levels had the worst 18-day neurologic outcome.

Young,[46] 1987

Description of Study: Fifty-one brain-injured patients with admission GCS scores 4-10 were randomized to receive TPN or enteral nutrition. The TPN group received higher cumulative intake of protein than the enteral nutrition group (8.75 vs 5.7 g/day of Nitrogen). Nitrogen balance was higher in the TPN group in the first week after injury. Caloric balance was higher in the TPN group (75% vs 59%). Infections, lymphocyte counts, and albumin levels were the same in both groups as was outcome. At 3 months the TPN group had a significantly more favorable outcome but at 6 months and 1 year the differences were not significant.

Classification: Class I Study

Conclusions: Neurological recovery from head injury occurs more rapidly in patients with better early nutritional support.

Young,[47] 1985

Description of Study: Energy production, substrate oxidation, serum protein levels, and weight change were studied in 16 non–steroid-treated patients with severe head injury. Mean energy expenditure was 140% of expected. Patients were given 1.5 g protein/day and in only 2 was there positive Nitrogen balance.

Classification: Class II Study

Conclusions: Head injury induces a profound traumatic response with increased energy expenditure, negative Nitrogen balance, weight loss, hypoalbuminemia, and altered substrate oxidation.

Young,[48] 1987

Description of Study: Ninety-six patients with severe brain injury were randomly assigned to TPN or enteral nutrition. The incidence of increased ICP was measured in both groups for a period of 18 days.

Classification: Class I Study

Conclusions: There was no difference in rate of increased ICP in the two groups.

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THE ROLE OF ANTISEIZURE PROPHYLAXIS FOLLOWING HEAD INJURY

I.   Recommendations

A. Standards

Prophylactic use of phenytoin, carbamazepine, phenobarbital or valproate is not recommended for preventing *late* post-traumatic seizures.

B. Guidelines

None

C. Options

It is recommended as a treatment option that anticonvulsants may be used to prevent *early* post-traumatic seizures in patients at high risk for seizures following head injury. Phenytoin and carbamazepine have been demonstrated to be effective in preventing early post-traumatic seizures. However, the available evidence does not indicate that prevention of early post-traumatic seizures improves outcome following head injury.

II.   Overview

Post-traumatic seizures are classified as *early*, occurring within 7 days of injury, or *late*, occurring after 7 days following injury.[11,13] It is desirable to prevent both *early and late* post-traumatic seizures. However, it is also desirable to avoid neurobehavioral and other side effects of medications that are ineffective in preventing seizures. Prophylaxis for PTS refers to the practice of administering anticonvulsants to patients following head injury to prevent the occurrence of seizures. The rationale for routine seizure prophyaxis is as follows. There is a relatively high incidence of post-traumatic seizures in head-injured patients, and there are potential benefits to preventing seizures following head injury.[11,13] The incidence of seizures following penetrating injuries is about 50% in patients followed for 15 years.[11] In civilian head injury studies that followed high-risk patients up to 36 months, the incidence of early post-traumatic seizures varied between 4% and 25%, and the incidence of late post-traumatic seizures varied between 9% and 42% in untreated patients.[2,6,11] In the acute period, seizures may precipitate adverse events in the injured brain because of elevations in intracranial pressure (ICP), blood pressure changes, changes in oxygen delivery, and also excess neurotransmitter release. The occurrence of seizures may also be associated with accidental injury, psychological effects, and loss of driving privileges. There has been a belief that prevention of early seizures may prevent the development of chronic epilepsy.[11,13] Experimental studies have supported the

idea that initial seizures may initiate kindling, which then may generate a permanent seizure focus. On the other hand, anticonvulsants have been associated with adverse side effects including rashes, Stevens-Johnson syndrome, hematologic abnormalities, ataxia, and neurobehavioral side effects.[2,11,13] It is therefore important to evaluate the efficacy and overall benefit of anticonvulsants used for the prevention of post-traumatic seizures. Certain risk factors have been identified that place head injured patients at increased risk for developing post-traumatic seizures.[10,13] These risk factors include:

- Glasgow Coma Scale (GCS) score less than 10
- Cortical contusion
- Depressed skull fracture
- Subdural hematoma
- Epidural hematoma
- Intracerebral hematoma
- Penetrating head wound
- Seizure within 24 hours of injury

Eight well-controlled studies of prophylaxis for PTS have been found. The scientific evidence supports the use of prophylactic anticonvulsants to prevent early PTS and does not support the use of those anticonvulsants studied thus far in preventing late PTS.

III. Process

A MEDLINE computer search using the key words "seizure" and "head injury" between 1966 and 1998, was performed. A total of 95 documents were found. In addition, the results of other National Institutes of Health–funded studies that have not been published and other clinical studies referred to in major review articles on post-traumatic seizures prophylaxis were reviewed. All clinical studies of seizure prophylaxis in head-injured patients were reviewed.

IV. Scientific Foundation

Early retrospective studies indicated that phenytoin was effective for the prevention of post-traumatic seizures.[12,14] A practice survey among U.S. neurosurgeons in late 1973 indicated that 60% used seizure prophylaxis for head-injured patients.[8] Subsequent prospective, double-blind trials, with one exception, failed to show a beneficial effect of phenytoin, or phenytoin combined with phenobarbital, in reducing the incidence of PTS.[11,13] Penry, et al., reported the results of a trial that enrolled 125 high-risk head injury patients randomized to placebo or a combination of phenytoin and phenobarbital.[7] Patients were treated for 18 months and then followed for an additional 18 months. The 36-month cumulative seizure rates were not significantly different (23% in the active group and 13% in the placebo group, p is not significant).

Young, et al., conducted a prospective, randomized, double-blind study of 244 head-injured patients and reported that phenytoin was not effective in preventing early or late post-traumatic seizures.[15,16] The incidence of early post-traumatic seizures was low in the placebo and treatment groups, however, which may have influenced the lack of protective effect of treatment on early post-traumatic seizures. No patient with a phenytoin plasma concentration of 12 ug/ml or higher had a seizure, however, and, therefore, the possibility remained that higher levels may have been more effective in preventing late post-traumatic seizures.

McQueen, et al., conducted a prospective, randomized, double-blind study of 164 patients receiving phenytoin or placebo for the prevention of late post-traumatic seizures.[5] No significant reduction in late post-traumatic seizures was found in the treatment group.

Glotzner, et al., evaluated the effect of carbamazepine in preventing early and late PTS in a prospective, randomized, double-blind study of 139 patients.[2] There was a significant reduction in the number of early post-traumatic seizures in the treated group, and no significant reduction in late post-traumatic seizures with treatment.

Pechadre, et al., conducted a prospective, randomized study of phenytoin in 86 patients for early and late post-traumatic seizures that was neither blinded nor placebo controlled.[6] There was a significant reduction in early post-traumatic seizures and also a significant reduction in late post-traumatic seizures in the acitve treatment groups. The incidence of late post-traumatic seizures was higher than in any of the similar trials, but the number of patients in the study was small.

Temkin, et al., reported the results of the largest prospective, randomized, double-blind, placebo-controlled trial to date, which randomized 404 patients to evaluate the effect of phenytoin on early and late post-traumatic seizures.[10] This trial was unique in that serum levels were independently monitored and dosages were adjusted so that therapeutic levels were maintained in at least 70% of the patients. Moreover, three-quarters of the patients who had levels monitored on the day of their first late seizure had therapeutic levels. There was a significant reduction in the incidence of early post-traumatic seizures in the treated group. There was no significant reduction in the incidence of late post-traumatic seizures in the treated group. The survival curves for the placebo and active treatment groups showed no significant difference. The neurobehavioral effect of phenytoin was also examined in this trial.

A secondary analysis has recently been performed on the data from the trial reported by Temkin, et al., to determine if treatment for early post-traumatic seizures was associated with significant drug-related adverse side effects. The occurrence of adverse drug effects during the first two weeks of treatment was low and not significantly different between the treated and placebo groups. Hypersensitivity reactions occurred in 0.6% of the phenytoin-treated group versus 0% in the placebo group (p = 1.0) during week 1, and 2.5% of phenytoin-treated patients versus 0% of placebo-treated patients (p = 0.12) for the first two weeks of treatment. Mortality was also similar in both groups. The results of the study indicate that the incidence of early PTS can be effectively reduced by prophylactic administration of phenytoin for one or two weeks without a significant increase in serious drug-related side effects.[3]

In another secondary analysis of the same trial, Dikmen, et al., found significantly impaired performance on neuropsychologic tests at one month after injury in severely head-injured patients maintained on phenytoin. However, the difference was not apparent at one year following injury.[1]

Manaka conducted a prospective, randomized, double-blind study of 126 patients receiving placebo or phenobarbital for the prevention of late post-traumatic seizures.[4] There was no significant reduction in late PTS in the active treatment group.

An additional prospective, randomized, double-blind study has been recently completed that evaluated the effect of valproate to reduce the incidence of early and late post-traumatic seizures.[9] The trial compared phenytoin to valproate for the prevention of early post-traumatic seizures, and valproate to placebo for the prevention of late post-traumatic seizures. The incidence of early post-traumatic seizures was similar in patients treated with either valproate or phenytoin. The incidence of late post-traumatic seizures was similar in patients treated with

phenytoin for one week and then placebo, or patients treated with valproate for either one month then placebo, or with valproate for six months. There was a trend toward a higher mortality in patients treated with valproate.

The majority of studies, therefore, indicate that anticonvulsants administered prophylactically reduce the incidence of early post-traumatic seizures but do not significantly reduce the incidence of late post-traumatic seizures.

V.   Summary

The majority of studies do not support the use of the prophylactic anticonvulsants studied thus far for the prevention of late post-traumatic seizures. Routine seizure prophylaxis later than one week following head injury is, therefore, not recommended. If late post-traumatic seizures occur, patients should be managed in accordance with standard approaches to patients with new onset seizures. Phenytoin and carbamazepine have been shown to reduce the incidence of early post-traumatic seizures. Valproate may also have a comparable effect to phenytoin on reducing early PTS but may also be associated with a higher mortality. It is, therefore, an option to use phenytoin or carbamazepine to prevent the occurrence of seizures in high-risk patients during the first week following head injury.

VI. Key Issues for Future Investigation

Additional studies may be needed to determine if reduction in early post traumatic seizures has an effect on outcome. Future trials of neuroprotectant agents that have antiepileptic activity, such as magnesium sulphate and other NMDA receptor antagonists, may futher reduce the incidence of post-traumatic seizures.

VII. Evidentiary Table

Glotzner,[2] 1983

Description of Study: Prospective, randomized, double-blind study of 139 patients treated with placebo or carbamazepine, and evaluated for early and late post-traumatic seizures. Theraputic levels were maintained in the majority of patients.

Classification: Class I Study

Conclusions: Showed significant reduction in early post-traumatic seizures and no significant effect on late post-traumatic seizures using therapeutic levels of carbamazepine

Seizure Rates

Early			Late		
% Active	% Placebo	p	% Active	% Placebo	p
10%	25%	0.016	27%	21%	ns

VII. Evidentiary Table (continued)

Manaka,[4] 1992

Description of Study: Prospective, randomized, double-blind study of 126 patients receiving placebo or phenobarbital for effect on late post-traumatic seizures. Treatment was started one month following head injury.

Classification: Class I Study

Conclusions: Showed no significant effect of phenobarbital on late post-traumatic seizures.

Seizure Rates

Early			Late		
% Active	% Placebo	p	% Active	% Placebo	p
(not studied)			16%	11%	ns

McQueen,[5] 1983

Description of Study: Prospective, randomized, double-blind study of 164 patients receiving phenytoin or placebo for late post-traumatic seizures.

Classification: Class I Study

Conclusions: Showed no significant effect of phenytoin on late post-traumatic seizures.

Seizure Rates

Early			Late		
% Active	% Placebo	p	% Active	% Placebo	p
(not studied)			10%	9%	ns

Pechadre,[6] 1991

Description of Study: Prospective, randomized study (not blinded or placebo controlled) of phenytoin or no drug in 86 patients for early and late post-traumatic seizures.

Classification: Class I Study

Conclusions: Showed significant reduction in early and late post-traumatic seizures by phenytoin.

Seizure Rates

Early			Late		
% Active	% No Drug	p	% Active	% No Drug	p
6%	24%	0.05	6%	42%	0.001

Penry,[7] 1979

Description of Study: Prospective, randomized, double-blind study of 125 patients receiving placebo or phenobarbital and phenytoin for late PTS. Low doses were used, and levels were not monitored.

Classification: Class I Study

Conclusions: Showed no significant effect of phenobarbital and phenytoin on late PTS. Results of study published as abstract.

Seizure Rates

Early			Late		
% Active	% Placebo	p	% Active	% Placebo	p
(not studied)			23%	13%	ns

Temkin,[10] 1990

Description of Study: Prospective, randomized, double-blind study of 404 patients receiving placebo vs phenytoin for the prevention of early and late post-traumatic seizures. Drug levels were monitored and were kept in the therapeutic range in the majority of patients. Patients were followed for 24 months.

Classification: Class I Study

Conclusions: Showed significant reduction in early PTS by phenytoin and no significant effect of phenytoin in preventing late PTS.

Seizure Rates

Early			Late		
% Active	% Placebo	p	% Active	% Placebo	p
4 %	14%	0.001	27%	21%	ns

Temkin,[9] 1997

Description of Study: Prospective, randomized, double-blind parallel group clinical trial of 380 patients at high risk for post-traumatic seizures assigned to either one week of phenytoin, one month of valproate, or six months of valproate.

Classification: Class I Study

Conclusions: Showed similar rates of early post-traumatic seizures in patients treated with either valproate or phenytoin. Showed no significant difference in late post-traumatic seizures in patients treated with either phenytoin for one week, or valproate for either one month or six months.

Seizure Rates

Early			Late			
% Phenytoin	% Valproate	p	% Placebo (phenytoin 1 wk)	% Valproate (1 mo)	(6 mos)	p
1.5%	4.5%	ns	14%	16%	23%	ns

Young,[15,16] 1983

Description of Study: Prospective, randomized, double-blind study of 244 patients receiving placebo vs phenytoin for the prevention of early and late PTS. Drug levels monitored.

Classification: Class I Study

Conclusions: Showed no significant effect of phenytoin on early or late PTS.

Seizure Rates

	Early			Late	
% Active	% Placebo	p	% Active	% Placebo	p
4 %	4%	ns	12%	11%	ns

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PART II: EARLY INDICATORS OF PROGNOSIS IN SEVERE TRAUMATIC BRAIN INJURY

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EARLY INDICATORS OF PROGNOSIS IN SEVERE TRAUMATIC BRAIN INJURY

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INTRODUCTION

The uncertainty that exists about the likely outcome after traumatic brain injury (TBI) is encapsulated in the Hippocratic aphorism: "No head injury is so serious that it should be despaired of nor so trivial that it can be ignored." Today, physicians' estimates of prognosis are still often unduly optimistic, unnecessarily pessimistic, or inappropriately ambiguous. [1,4,6,12] It still remains impossible to say with certainty what will be the future course of events in an individual patient, but intensive research in the last two decades has made it possible to be much more confident about what is likely to happen, and to consider prognosis in terms of probabilities rather than prophecies.

Prediction of outcome involves making probability statements that depend on a logical relationship between outcome and features encapsulated in antecedent, early data. The advances in prognosis reflect the establishment of methods for categorizing outcome[9] and early injury severity.[18] These became widely accepted[13] and led to multinational, multicenter studies[14] that identified the features about the patient, the injury, and the early clinical course with a distinctive, consistent relationship to outcome.[10,15] The subsequent chapters consider these various features, first with respect to the existence of a relationship to outcome, then the strength of the effect or interaction with outcome, and finally, the extent to which the effect is unique to the feature in question (almost never so) or how far there is interaction (interdependence) with other prognostic features.

Although clinicians usually attempt to take a wide range of factors into account when making clinical decisions and assessing prognosis, there is probably a redundancy in this effort to be complete. In practice, relatively few features have been found to contain most of the prognostic information,[3,10,17] These include the patient age, clinical indices indicating the severity of brain injury (e.g., the depth and duration of coma and other neurological abnormalities), and the results of investigation and imaging studies, particularly intracranial pressure (ICP) and computed tomography (CT) scanning, which disclose the nature of brain injury and its effects on intracranial dynamics. Even though there is little doubt regarding the importance of these features from clinical experience, there are still debates about the precise nature of their relationships and about exactly how the different features should be assessed, categorized, and—most importantly—utilized.

The identification of powerful, single prognostic factors is only one step toward a useful statement about prognosis. Unique relationships between the findings of a feature and outcome may apply only for the most extreme abnormalities found only in a tiny minority of patients. To be useful, prognostic statements need to be applicable across all severities of injury and capable

of being expressed in a way that indicates the likelihood of an individual patient achieving different outcomes at some future time. This depends on combining the information on the different individual prognostic features. Although a wide number of statistical approaches have been described, there is little difference in practice between the results that they produce. Also the details of calculation are much less important than the data that are employed.[17,19] Likewise, the results of prognostic calculations can be expressed in a number of ways that include mathematical probability,[8,10] graphical presentations,[2,5] and the methodology used in this document. The merits of different methods have not been established.

The utility of prognostic probabilities can be assessed by various criteria. One is "separation," in which a particular outcome is emphasized (e.g., by being assigned a very high probability). Separation has the benefit of conveying discrimination and a high degree of certainty; however, it runs the risk of being excessively confident and leading to extremes of prognosis—either falsely optimistic or falsely pessimistic. Perhaps a more desirable attribute is "faithfulness," that is, that the probabilites expressed relate reliably to what is likely to happen. Thus, the figure calculated should reflect the distribution of outcomes that occur in a series of patients allocated the respective probabilities of different outcomes. To do this effectively would require a large data set collected prospectively and with relevant patient follow-up.

Clearly, this type of approach cannot be used when reviewing published reports. The methodology described in the next section has been devised to fit the task of literature review while adhering to clinical epidemiological principles. Information about prognosis and predictive statements can be useful in a number of ways. From the start, concern about outcome is often foremost in the mind of the relative of severely brain-injured victims and realistic counseling is preferable to over pessimism—characterized as "hanging crepe"—or the raising of false hopes. An assessment of prognosis is crucial in research studies, both in determining the appropriate target population and in deciding if a given intervention has produced an outcome different from that which would have been expected. The place of prognosis in making decisions about the management of individual patients remains controversial. While many neurosurgeons acknowledge that it is an important factor in decision making,[2] others relegate prognosis to a minor or even nonexistent role, reflecting a range of attitudes arising from cultural and ethical differences as much as clinical convictions.

Although there are concerns that estimation of prognosis may be used to allocate (and in particular to withdraw) resources, and that this might worsen the outcome in some cases, this was not substantiated in a formal study.[16] In a large prospective trial, doctors, nurses, and other staff providing acute care for severe brain injuries were provided with predictions of the outcome in individual cases. Compared with control periods without predictions, there was no lessening of the use of intensive care resources nor an increase in the rate of decisions to limit treatment. Instead, there was a shift in the employment of aspects of intensive care from patients with a calculated high likelihood of poor outcome to those with a greater prospect of recovery, without an adverse affect to outcome in the former group.

The purpose of this exercise is to identify from the published medical literature those early clinical factors that may be prognostic for outcome. This will then suggest which early factors should be focused on in prospective database research in patients with TBI.

An estimate of a patient's prognosis should never be the only factor, and only rarely the main factor, in influencing clinical decisions. Instead, prognosis is simply one of the many factors that need to be considered in the clinical management of a severely brain-injured patient.

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Prognostic Parameters

for Traumatic Brain Injury Methodology

Introduction

With the publicity of *Guidelines for the Management of Severe Head Injury*, those interested in guideline development were exposed to evidence-based principles for determining therapeutic effectiveness. In this paradigm, study strength in terms of design is related directly to the strength of recommendations. Thus, Class I evidence (randomized controlled trials) gave rise to practice standards, Class II evidence (non-randomized cohort studies, case-control studies) supported weaker recommendations called guidelines, and all other evidence—including expert opinion—was given the designation of Class III and produced practice options. While this classification of evidence suits clinical studies related to therapy, it does not pertain to studies of prognosis, diagnostic tests, or clinical assessment. Therefore, the working group convened by the Brain Trauma Foundation, the American Association of Neurological Surgeons, the Neuro-trauma Committee of the World Health Organization, and the Brain Injury Association to evaluate the literature on prognostic indicators in head injury, had the task of developing a different model for making recommendations, while still adhering to the concepts of evidence-based practice.

Committed to continuing to utilize the principles of clinical epidemiology, the working group produced a model in which pertinent literature was qualitatively evaluated. In developing this model, it was recognized that the literature of interest would pertain to prognosis of treated brain-injured patients. It would, therefore, need to comply with standard measures of quality applicable to prognosis in order to minimize bias or systematic error as much as possible.

In addition, it was recognized that the clinical assessments of interest and their relationships to prognosis could be likened to diagnostic tests. In this scenario, the outcome of mortality or Glasgow Outcome Scale score is similar to the reference measure against which a diagnostic test is evaluated, whereas the prognostic indicator is like a diagnostic test. We might therefore, create a 2 x 2 table as follows:

	DEAD	ALIVE
PROGNOSTIC FACTOR PRESENT		
PROGNOSTIC FACTOR ABSENT		

With the data taken from appropriate articles, characteristics of sensitivity, predictive values, and, where applicable, likelihood ratios can be estimated. An additional aspect of this task that had to be acknowledged was that many of the prognostic indicators, as well as one of the outcome measures (Glasgow Outcome Scale), are clinical assessments, which need to be reliable and valid to be useful.

In summary, the criteria we elected to use for this task combined those for prognosis, diagnosis, and clinical assessment, as described below.

Methodology

The literature was searched, using the appropriate rubrics, via a computerized link to the National Library of Medicine in Washington, D.C., U.S.A. Additional references were found by examination of reference lists at the end of each journal article and through personal knowledge of the experts participating in the working group. Specific prognostic indicators were then examined separately, as shown in the sections that follow. Each paper was qualitatively evaluated according to criteria intended to establish study strength. These included:

1. Twenty-five or more patients in the series with complete follow-up.
2. Outcomes measured — Glasgow Outcome Scale or Mortality — at six months or more.
3. Data gathered prospectively, although retrospective examination from a database creating an ongoing cohort of patients could be used.
4. Glasgow Coma Scale score measured within 24 hours.
5. Appropriate statistics (e.g., multivariate analysis) used to include adjustment for prognostic variables.

It was then decided by the working group that papers thus evaluated could be classified in a similar fashion as those for therapeutic effectiveness, as indicated below:

CLASSIFICATION OF EVIDENCE ON PROGNOSIS	
CLASS I:	Those papers containing all of the above characteristics.
CLASS II:	Those papers containing four out of the five characteristics, including prospectively collected data.
CLASS III:	Those papers containing three or fewer of the above characteristics.

Further, in order to be able to calculate sensitivity, specificity, positive and negative predictive value, and, where applicable, likelihood ratios, the Bayesian table was constructed:

	DEAD	ALIVE
PROGNOSTIC FACTOR PRESENT	a	b
PROGNOSTIC FACTOR ABSENT	c	d

CLINICAL QUESTION	PROGNOSTIC ATTRIBUTE	CALCULATION
If a trauma patient reaches a certain outcome, how likely is she or he to have had a given prognostic indicator?	*Sensitivity*	$\dfrac{a}{a + c}$
If a trauma patient does not reach a certain outcome, how likely is she or he to have not had a given prognostic indicator?	*Specificity*	$\dfrac{d}{b + d}$
If a trauma patient has a given prognostic indicator, how likely is she or he to reach a certain outcome?	*Postive predictive value*	$\dfrac{a}{a + b}$
If a trauma patient does not have a given prognostic indicator, how likely is she or he to reach a certain outcome?	*Negative predictive value*	$\dfrac{d}{c + d}$

GLASGOW COMA SCALE SCORE

I. Conclusions

A. Which feature of the parameter is supported by Class I evidence and has at least a 70% positive predictive value? There is an increasing probability of poor outcome with a decreasing Glasgow Coma Scale (GCS) score in a continuous, stepwise manner.

B. Parameter measurements:
   1. How should it be measured?
      ■ It should be measured in a standardized way.
      ■ It must be obtained through interaction with the patient (e.g., application of a painful stimulus for patients unable to follow commands).
   2. When should it be measured for prognostic purposes?
      ■ Only after pulmonary and hemodynamic resuscitation.
      ■ After pharmacologic sedation or paralytic agents are metabolized.
   3. Who should measure it?
      ■ The GCS can be fairly reliably measured by trained medical personal.

II. Overview

The GCS was developed by Teasdale and Jennett in 1974 as an objective measure of the level of consciousness.[31] It has since become the most widely used clinical measure of the severity of injury in patients with severe traumatic brain injuries (TBIs). A number of studies have confirmed a fairly high degree of inter- and intra-rater reliability of the scale across observers with a wide variety of experience.[5,11,24,32]

III. Search Process

The titles and abstracts of approximately 500 journal articles were retrieved using a computerized search of the National Library of Medicine. The MESH heading "Glasgow Coma Scale" was used to search for articles published since the GCS was developed in 1974. The abstracts of all articles were reviewed and those articles that focused on the correlation between the acute GCS score (obtained within the first 24 hours) and outcome in patients with severe closed head injuries were selected for review of the entire article. This left 20 articles that dealt primarily with correlation of the GCS score and outcome, 8 articles that focused on the use of the initial GCS score to predict outcome, and 6 articles describing the reliability of the GCS score.

IV. Scientific Foundation

The modern, prehospital treatment of many TBI patients (sedation, pharmacologic paralysis, and/or intubation) complicates the early determination of valid GCS scores in nearly half of the patients admitted to trauma centers. A recent review of patients entered into various drug trials as part of the European Brain Injury Consortium revealed that the motor score was untestable in 28% of the patients at the time of admission to the neurosurgery service, and the full GCS score was untestable in 44% of the patients (Personal communication, A.I.R. Maas). In addition, a survey of major trauma centers in the United States found that there is substantial variability of practice regarding the assignment of the initial GCS score both within the hospital and among different hospitals when patients are admitted following such prehospital treatment.[22] In many cases, patients are assigned a GCS score even though they have received paralytic medication within minutes prior to the assessment. For those patients who were intubated prior to assessment of the initial GCS score, members of the Traumatic Coma Data Bank (TCDB) arbitrarily decide to assign a GCS verbal score of 1.1. This practice may significantly overestimate the severity of the injury, however. Gale, et al., found that the mortality rate for those with a true (testable) GCS score of 3-5 was 88%, while it was only 65% for those with the same GCS sum score when a verbal score of 1 was used because of endotracheal intubation.[12] Others also have found that prediction of outcome is less accurate if all three components of the GCS, and particularly eye opening, are not assessed.[4,18]

When assessing the motor sub-score, some controversy exists regarding the best location for applying a painful stimulus. Teasdale, et al., recommend stimulation of the nailbed initially, but recording the best response obtained from either arm to any stimulus.[32] In their study of observer variability, they found that, for inexperienced observers, interobserver variability was less when nailbed pressure was used. For those with more experience variability was less when supraorbital pressure was used.

Despite these concerns, the GCS score has been shown to have a significant correlation with outcome following severe TBI, both as the sum score,[7,8] or as just the motor component.[1,3,8,25] In a prospective study by Narayan a positive predictive value of 77% for a poor outcome (dead, vegetative, or severely disabled) was measured for patients with a GCS score of 3-5 and 26% poor predictive value for a GCS score 6-8 (see Evidentiary Table).[27] As is commonly done, this study grouped GCS measurements versus outcome. In a larger study each GCS level would have its own predictive value. For example, in a series of 315 TBI patients from Australia, a significant inverse correlation was demonstrated between the initial GCS score (obtained 6-48 hours after injury) and mortality.[10]

GCS score	Mortality
3	65%
4	45
5	35
6	24
7-13	10-15

In the United States, 746 patients with closed head injuries who were entered into the TCDB were reviewed to determine the relationship of the initial GCS score with outcome.[23] In this study, the interval from injury to outcome assessment was quite variable and ranged from 11 to

1199 days, with a median of 674 days. The morality rate for those with an initial post-traumatic GCS score of 3 was 78.4%; initial GCS score of 4, 55.9%; and initial GCS score of 5, 40.2%. Of note, however, is that 4.1%, 6.3%, and 12.2% of the three groups, respectively, had a good outcome.

In a large study of 46,977 head-injured patients the relationship between GCS scores 3-15 and mortality was investigated.[13] A sharp progressive increase in mortality was noted in patients who presented to the Emergency Room with a GCS score of 3-8.

In 109 adults with acute subdural hematomas, Phuenpathom also showed a significant inverse relationship with GCS score (best score within 24 hours) and mortality.[28]

GCS score	Mortality	Number of patients
3	100%	(37)
4	90	(9/10)
5	63	(5/8)
6	33	(2/6)
7	22	(2/9)
8-15	0	(39)

In a series of 115 patients with epidural hematomas, Kuday found that the initial GCS score was the single most important factor affecting outcome (p<0.00001).[21]

Because of the strong association with the initial GCS score and outcomes, a number of investigators have studied the predictive value of the initial GCS score using various logistic regression techniques.[2,16,20,30,33] Thatcher, et al., used multimodal statistical models to study the ability of the initial GCS score or the GCS score obtained at a mean of 7.5 days after the injury to predict outcome at one year after injury for 162 patients with TBI.[33] When based on the initial GCS score, only 68.6% of those predicted to have a good outcome and 76.5% of those predicted to have a poor outcome actually had such outcomes at one year. If the later GCS was used for predictions, there was a significant increase in the rate of correct predictions for a good outcome (80.6%), but the rate of correct predictions for a poor outcome remained essentially unchanged (78.6%).

Kaufman described the accuracy of outcome predictions of an experienced neurosurgeon for 100 patients with severe TBI.[20] Outcomes were categorized as dead/vegetative, severely disabled, or capable of independent survival, and were predicted based on the best GCS scores obtained within 24 hours after injury. Age, pupils, blood pressure, heart rate, laboratory values, and initial computed tomograpy (CT) scans were also considered. Correct prognosis was estimated in only 56% of the cases.

GOS	Predicted/Actual Outcomes
Dead/Vegetative	35/24
Severe Disability	23/11
Independent	42/65

The table reveals that predictions were best for very bad or very good outcomes. In addition, poor outcomes were overestimated by 32%-52%, while good outcomes were underestimated by 35%. In a study of 254 patients with severe TBI, Benzer used logistic regression methods to predict patient outcome based on the immediate post-traumatic GCS

score, and made correct predictions 82.68% of the time.[2]

It should be emphasized that most of these studies looked at the least discriminate scenario (e.g., reduction of potential outcomes to two or at most three groups). When attempts were made to predict more precisely into one of the five categories of the Glasgow Outcome Scale (GOS), the predictive accuracy of the initial GCS score was poor.[19]

V.   Summary

When considering the use of the initial GCS score for prognosis, the two most important problems are the reliability of the initial measurement, and its lack of precision for prediction of a good outcome if the initial GCS score is low. If the initial GCS score is reliably obtained and not tainted by prehospital medications or intubation, approximately 20% of the patients with the worst initial GCS score will survive and 8%-10% will have a functional survival (GOS 4-5).

VI. Key Issues for Further Investigation
  A.   The optimal time after injury for determining the initial GCS
  B.   When to assess the GCS score for those who have received paralytic or sedative medication
  C   Reliability of the prehospital GCS score

VII. Evidentiary Table

Fearnside,[10] 1998

Description of Study: Prospective study of 315 consecutive patients of all ages with severe TBI to identify factors responsible for morbidity and mortality.

Classification: Class II Study

Conclusions:

	GOS
GCS	**1**
3	65%
4	45
5	35
6	24
7-13	10-15

Marshall,[23] 1991

Description of Study: Prospective study of 746 consecutive patients with severe TBI to gather demographic and outcome data; adults.

Classification: Class II Study

Conclusions:

	GOS	
GCS	**1**	**4, 5**
3	78.4%	7.2%
4	55.9	14.4
5	40.2	29.3
6	21.2	50.5
7	17.6	68.9
8	11.3	77.4

VII. Evidentiary Table (continued)

Narayan,[27] 1989

Description of Study: Prospective study of 133 consecutive patients with severe TBI to identify factors responsible for morbidity and mortality; all ages.

Classification: Class I Study

Conclusions:

GCS	GOS 1	GOS 2, 3	GOS 4, 5	
3-5	62%	15%	23%	+PPV=77%
6-8	20	74		
9-11	18	76		

Beca,[1] 1995

Description of Study: Prospective study of 109 children with severe TBI to compare outcome prediction of somatosensory evoked potentials (SEPs) with GCS.

Classification: Class III Study

Conclusions:

GCS Motor	GOS 4, 5
1	0%
2-3	41-47
4-5	75-78

Braakman,[6] 1980

Description of Study: Prospective study of 305 consecutive patients with severe TBI studied to identify prognostic indicators; all ages.

Classification: Class I Study

Conclusions:

GCS	GOS 1
3	100%
4	80
5	68
6	51
7	27
8	22
9-15	15

Phuenpathom,[28] 1993

Description of Study: Retrospective study of 109 patients with acute subdural hematomas to determine outcome; all ages.

Classification: Class II Study

Conclusions:

	GOS
GCS	**1**
3	100%
4	90
5	63
6	33
7	22
8-15	

Wilberger,[34] 1990

Description of Study: Retrospective study of 101 adult patients with severe TBI who also had acute subdural hematomas.

Classification: Class III Study

Conclusions:

	GOS	
GCS	**1**	**4, 5**
3	90%	5%
4	76	10
5	62	18
6-7	51	44

Rivas,[29] 1988

Description of Study: Retrospective study of 66 patients with severe TBI who also had epidural hematomas; all ages.

Classification: Class III Study

Conclusions:

	GOS	
GCS Motor	**1**	**4, 5**
1	80%	20%
2-3	24	73
4-5	5	90

Colohan,[9] 1989

Description of Study: Prospective comparison of outcomes for 551 patients from New Delhi and 822 patients from Charlottesville with severe TBI; all ages.

Classification: Class II Study

Conclusions:

New Delhi

	GOS
GCS Motor	**1**
1	81.3%
2-4	40.9
5	4.8
6	0.2

Charlottesville

	GOS
GCS Motor	**1**
1	88.9%
2-4	56.2
5	12.5
6	0.4

Miller,[26] 1981

Description of Study: Prospective study of 225 patients with severe TBI to analyze factors related to outcome; all ages.

Classification: Class II Study

Conclusions:

	GOS	
GCS Motor	**1**	**4, 5**
3-4	71%	16%
5-7	30	59
8-15	13	79

Young,[35] 1981

Description of Study: Prospective study of outcomes at one year following severe TBI in 94 patients; all ages.

Classification: Class II Study

Conclusions:

	GOS	
GCS Motor	**1**	**4, 5**
3-4	90%	5%
5-7	33	49

VII. Evidentiary Table (continued)

Jaggi,[17] 1990

Description of Study: Prospective study of cerebral blood flow changes following severe TBI in 96 adults.

Classification: Class II Study

Conclusions:

	GOS	
GCS	1, 2	3-5
3-4	78.9%	21.2%
5-6	45.2	54.8
7-9	25.7	74.3

Gale,[12] 1983

Description of Study: Prospective study of outcomes in 142 adults with severe TBI.

Classification: Class III Study

Conclusions:

	GOS
GCS	1, 2
3-5	65%
6-7	20

Genneralli,[14] 1982

Description of Study: Retrospective multicenter study of 1,107 patients with severe TBI, GCS < 9 for 6 hours or more with onset of coma at any time within the first 48 hours of injury; GOS assessed at 3 months after injury.

Classification: Class III Study

Conclusions:

	GOS	
GCS Motor	1, 2	3-5
3-5	65%	34%
6-8	20	79

The type of intracranial lesion, particularly subdural hematoma, had a significant negative impact on outcomes for those with an initial GCS score of 3-5.

Genneralli,[13] 1994

Description of Study: A multicenter analysis of the Major Trauma Outcome Study database. The relationship between admission GCS score and mortality showed an exponential relationship with a marked increase in mortality in patients with GCS < 9.

Classification: Class III Study

VIIa. Description of the Studies According to Classification Criteria

First Author	Number of patients	Prospective	Time	When indicator was measured	What method	Who did it	Outcome measure	When	Blinded observer	Multi-variate statistics	What statistics
Fearnside[10]	315	Y	NR	6-48 hours after injury	GCS	NR	GOS	6 months	NR	Y	Logistic regression
Marshall[23]	746	Y	1984-1987	<48 hours of admission	GCS	NR	GOS	At discharge (32.5 days), last contact (674 days)	NR	Y	Conting table, Logistic regression
Narayan[27]	133	N	1976-1979	<6 hours of injury in 70%	GCS	Neurosurgeon	GOS	3, 6, 12 months	NR	Y	Logistic regression
Beca[1]	109	Y	1991-1992	NR	GCSm	NR	GOS	>6 months after injury	Y	NR	NR
Phuenpathom[28]	109	N	1986-1989	Immediately after admission and best score first 24 hours	GCS	NR	GOS injury	6 months after	NR	Y regression	Logistic
Wilberger[34]	101	N	1982-1987	NR	GCS	NR	GOS	NR	NR	NR	Chi Square t-test
Rivas[29]	161	N	1977-1986	On arrival	GCS	NR	GOS	>6 months after injury	NR	NR	Chi Square
Colohan[9]	551, 822	Y	1977-1979	On admission, time from injury variable	GCSm	NR	death	Within 2 years	NR	Y	Conting table, Mann-Whitney
Miller[26]	225	Y	1976-1980	6-24 hours after injury	GCS	House-staff	GOS	3, 6, 12 months for 60%, last contact for others	NR	NR	Chi Square

VIIa. Description of the Studies According to Classification Criteria (continued)

First Author	Number of patients	Prospective	Time	When indicator was measured	What method	Who did it	Outcome measure	When	Blinded observer	Multi-variate statistics	What statistics
Young[35]	170	Y	NR	During first week	GCS	NR	GOS	1 year	NR	Y	Multiple logistic regression
Jaggi[17]	96	Y	NR	< 96 hours	GCS	NR	GOS	6 months	Y	Y	2 way ANOVA, logistic regression
Gale[12]	451	Y	1980-1981	NR	GCS	NR	Death	NR	NR	NR	NR
Braakman[6]	305	Y	1973-1978	24 hours	GCS	NR	GOS	1, 3, 6, 12 months	NR	Y	Stepwise logistic regression
Gennarelli[13]	1,107	N	NR	Within 6-48 hours	GCS	NR	GOS	3 months	NR	N	NR
Gennarelli[14]	46,977	Y	1982-1989	On admission	GCS	NR	Death	in-hospital	NR	N	Exponential model

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AGE

I. Conclusions

A. Which feature of the parameter is supported by Class I evidence and has at least a 70% positive predictive value? There is an increasing probability of poor outcome with increasing age, in a stepwise manner.

B. Parameter measurement for prognosis:
    Age is not subject to observer measurement variability. Age should be obtained on admission, preferably with documentation.

II. Overview

The prognosis for recovery from trauma as one ages is a function not only of the aged brain, but the type of injury that occurs frequently in each age group. In addition, a decline in health as one ages may predispose the aged to systemic complications after head injury.

An examination of injury type with respect to age demonstrates an increasing proportion of injuries secondary to falls and pedestrian accidents with advancing age[2, 20, 24, 34, 42]. In this prospective study of the Traumatic Coma Data Bank (TCDB), motor-vehicle crashes were the cause of injury in 55% of patients ages 15–25, whereas only about 5% suffered falls. However, in the age range above 55, 45% suffered falls and only about 15% were in motor-vehicle crashes. However, falls as a mode of injury did not appear as an independent predictor of poor outcome. Old patients had a poor outcome compared to younger patients, regardless of the cause of injury.

In the TCDB study, a marked increase in pre-existing systemic disease was found with increasing age. There was a significantly increased percentage of poor outcomes (death and vegetative) in those patients with prior systemic disease in ages above 56 (86% vs 50%); however, this correlation was not found in younger age groups. In addition, multiple systemic injuries were less likely in the older age group thus emphasizing the role of the severity of brain injury in determining outcome.

The reaction of the aged brain to trauma may be apparent in the head computed tomography (CT) scans of patients. In the above TCDB study there was an age-related trend toward increasing intracranial hematomas with the largest intracerebral hematomas observed in the oldest groups. The chances of survival in patients with intracranial hematomas decrease with advancing age[2, 4, 9, 15, 29, 34, 39, 42, 43]. A significant correlation was noted in the TCDB study between a poor outcome and those patients who had intracerebral or extracerebral hematomas

greater than 15 cc, subarachnoid hemorrhage, midline shift, compressed cisterns, or shift, which all increased with age (except for compressed cisterns). Unfortunately there were too few older patients without mass lesion to critically evaluate the effect independent of age.

A multivariate logistic regression analysis was done of the TCDB to evaluate the independent effect of age on outcome from severe head injury. Age was found to be an independent predictor after other factors were excluded. One explanation for this is that the brain has a decreased capacity for repair as it ages. This has some support in that the proportion of survivors in Glasgow Outcome Scale scores of good recovery (GCS scores 5, 4, and 3) all declined with age.

III. Process

A MEDLINE search was performed between 1966 and 1995 exploring the following subjects: 1) age, 2) human head injury, and 3) prognosis. The search resulted in 44 references that were individually reviewed and classified.

IV. Scientific Foundation

In the last few decades, several authors have identified age as a strong prognostic indicator following injury to the brain[6, 14, 20, 22, 31, 41]. Most investigations have stressed that younger individuals do better than adults. A remarkably low mortality rate among children was noted as early as 1973.[20] Later studies described similar results, and revealed that a higher proportion of children achieved a lower incidence of mortality and better outcomes than adults.[1, 3, 5, 8, 17, 26]

There are discrepancies in the literature when defining the age point where prognosis significantly worsens. For example, there has been disagreement regarding the pediatric age group. One group of reports has indicated that outcome tends to be better in children under ten years of age[9, 13, 28, 44], while others report that children under five have a higher mortality rate[6, 18, 22, 25, 27, 32, 35, 36]. Several large pediatric head injury series have reported that children have a lower mortality than adults, while others report that the primary mortality rate does not differ between children and adults. Additionally, some investigations reported better outcomes below the age range of 40-50 years[6, 7, 12, 16, 19, 21, 36], while other studies reported outcome as a continuous function of age without threshold values [4, 10, 11, 17, 22, 26, 30, 31, 32, 37, 40]. These discrepancies appear to be related to variations in the definitions of age groups.

A prospective investigation of 372 TBI patients in the UK with a GCS score less than 13 or ISS greater than 16 and age above 14 years showed no prognostic effect of age to 50 years.[38] At this point, age became an independent predictor of mortality, and GCS and ISS added high mortality significance when individually added to this model.

A prospective study of age and outcome from the TCDB revealed that patients older than 60 had a significantly worse outcome. Six months after severe head injury, 92% were dead, vegetative, or severely disabled. Four Class I studies demonstrated a mortality of greater than 75% in severely brain injured patients older than 60.[5, 25, 31, 33] The critical age threshold for worsening prognosis appears to be above 60 in a review of Class I and II studies. However, this may be an artifact of the age grouping used by various authors in converting continuous data into categorical data.

The following chart summarizes the Class I papers with regard to age threshold and poor outcome:

First Author	Age Threshold	Poor Outcome	Age Range	Poor Outcome
Vollmer,[42] 1991	> 55	92% (GOS 1, 2, 3) 80% (GOS 1)	46-55	78% (GOS 1, 2, 3) 49% (GOS 1)
Braakman,[6] 1980	> 51 > 61	75% (GOS 1) 77% (GOS 1)	41-50	49% (GOS 1)
Teasdale,[40] 1979	> 60	87% (GOS 1, 2)	40-60	56% (GOS 1)
Narayan,[31] 1981	> 60	78%	41-60	57% (GOS 1, 2, 3) 46% (GOS 1)
Signorini,[38] 1999	≥ 50	Linear decline in probability of survival	14-49	No significant effect

V. Summary

Age is a strong factor influencing both mortality and morbidity. Despite some contradictions, most literature supports children faring better than adults who have severe brain injury. The significant influence of age on outcome is not explained by the increased frequency of systemic complications or intracerebral hematomas with age. Increasing age is a strong independent factor in prognosis with a significant increase in poor outcome above 60 years of age.

VI. Key Issues for Future Investigation

Future studies should record age as a continuous variable in their study designs. Furthermore, potentially confounding variables such as pre-existing medical conditions should be recorded and analyzed. The biology of the aging brain and its vulnerability to injury should be investigated.

VII. Evidentiary Table for Age and Outcome

Alberico,[1] 1987   + + + + -

Description of Study: Prospective analysis of a consecutive series of 330 severely head-injured pediatric and adult patients treated with the same protocol, by the same physicians and staff in the Intensive Care Unit. The pediatric patients had a significantly higher percentage of good outcomes than the adult patients. They also had a significantly lower mortality rate than the adult patients.

Classification: Class II Study

Conclusions:

	GOS	
Age	**1**	**5**
1-4 (N=6)	17%	17%
5-9 (N=18)	22	61
10-14 (N=20)	20	40
15-19 (N=56)	25	40
21-40	35	33
41-60	55	15
61-80	80	5

Amacher,[2] 1987   + - - + -

Description of Study: Retrospective analysis of 56 patients 80 or more years of age. Even if a significant proportion (60%) of old people may make a full recovery from head injury, the mortality rate is high even in those with good admissions.

Classification: Class III Study

Conclusions:

	GOS			
Age	**1**	**2**	**3**	**4 5**
≥ 80 (N=10)	80%	0%	10%	10%

Berger,[5] 1985   + + + + -

Description of Study: Retrospective analysis of a consecutive series of 37 children with severe head injury. The data confirm that morbidity and mortality are lower in children than in adults: 51% of these young patients had a good recovery or moderate disability after 6 months. The mortality rate of 33% is higher than in some reports but probably more closely approximates the death rate from these injuries.

Classification: Class II Study

Conclusions:

	GOS				
Age	**1**	**2**	**3**	**4**	**5**
0-5 (N=16)	26%	0%	12%	12%	50%
6-10 (N=7)	43	0	0	14	43
11-17 (N=14)	36	7	21	29	7

+, - refers to whether methodology parameters were met or not. (See description of studies and methodology section. Page 11)

VII. Evidentiary Table (continued)

Braakman,[6] 1980   + + + + +

Description of Study: Retrospective analysis of 305 consecutive head-injured Dutch patients. The relationship between age and mortality after 6 months shows an increasing mortality rate with increasing age.

Classification: Class I Study

Conclusions:

	GOS
Age	**1**
0-10 (N=40)	35%
11-20 (N=85)	33
21-30 (N=46)	37
31-40 (N=38)	44
41-50 (N=29)	55
51-60 (N=20)	75
61-70 (N=26)	77
≥70 (N=21)	100

Bricolo,[7] 1977   + - - + +

Description of Study: Retrospective analysis of 800 patients with severe head injuries with and without decerebrate rigidity. In patients of all ages without decerebrate rigidity, the mortality rate progressively increases with age whereas the mortality rate in decerebrate patients is constant and independent of age. Of the survivors, three-fourths of those with good recovery were under 40 years of age.

Classification: Class III Study

Conclusions:

	GOS
Age (N=800)	**1**
5	1%
10	4
20	8
30	15
40	22
50	29
60	35
70	45
80	55

VII. Evidentiary Table (continued)

Bruce,[8] 1978   + + - + -

Description of Study: Retrospective analysis of the outcome in 53 children following severe head injury. 90% of the patients made a good recovery or were moderately disabled, and 8% died or were left vegetative.

Classification: Class III Study

Conclusions:

	GOS		
Age	**1**	**2-3**	**4-5**
0-5 (N=21)	5%	5%	90%
6-10 (N=19)	5	5	90
10-17 (N=13)	8	0	92

Choi,[11] 1983   + + - + +

Description of Study: Retrospective analysis of 264 patients with severe head injury. A combination of the Glasgow Coma Scale score, oculocephalic response, and age can provide a simple but reliable prediction of outcome in severe head injury.

Classification: Class II Study

Conclusions: Age not assessed as an independent predictor of outcome.

Edna,[14] 1983   + - + + -

Description of Study: Prospective analysis including 1,120 head-injured patients between 1979 and 1980. In addition to the level of unconsciousness at admission, age, pupillary light reactions, intracranial hematoma, associated extracranial injuries, and skull fractures seem to be important for predicting the outcome.

Classification: Class III Study

Conclusions:

	GOS
Age	**1-2**
0-39 (N=38)	24%
≥ 40 (N=18)	33

Gordon,[16] 1995   + + - + +

Description of Study: Retrospective analysis of 2,298 head-injured patients. Outcome significantly correlates to age and type and severity of lesion. No table of age versus outcome in GCS less than or equal to 8.

Classification: Class II Study

VII. Evidentiary Table (continued)

Heiskanen,[19] 1970   + + - + -

Description of Study: Retrospective analysis of 204 patients with severe head injury. In patients over 60, no special or heroic methods of treatment are indicated, but in children and adolescents every effort should be made as long as there has not been respiratory arrest and cerebral death.

Classification: Class III Study

Conclusions:

	GOS
Age	**1**
0-20 (N=62)	32%
21-40 (N=62)	48
41-60 (N=53)	59
≥ 60 (N=27)	78

Jennett,[22] 1979   + + + + -

Description of Study: Retrospective analysis of the relationship between clinical features of brain dysfunction in the first week after severe head injury and outcome 6 months later for 1,000 patients. Depth of coma, pupil reactions, eye movements, motor response pattern, and patient's age proved to be the most reliable predictors of outcome.

Classification: Class II Study

Conclusions:

	GOS
Age	**1-2**
< 20 (N=320)	33%
20-39 (N=284)	47
40-59 (N=245)	56
> 60 (N=151)	87

Leurssen,[26] 1988   + - + + -

Description of Study: Prospective analysis of a series of 8,814 head-injured patients admitted to 41 hospitals in three separate metropolitan areas. The pediatric patients exhibited a significantly lower mortality rate compared to the adults indicating that age itself, even within the pediatric age range, is a major independent factor affecting the mortality rate in head-injured patients.

Classification: Class III Study

Conclusions:

	GOS
Age	**1**
0-14 (N=95)	28%
≥ 15 (N=681)	48

Miller,[30] 1981   + + + + -

Description of Study: Prospective analysis of 225 patients with severe head injury who were managed in a uniform way and analyzed to relate outcome to several clinical variables. Factors important in predicting a poor outcome include the presence of an intracranial hematoma, increasing age, abnormal motor responses, impaired or absent eye movements or pupillary reflexes, early hypotension, hypoxemia, or hypercarbia, and elevation of intracranial pressure over 20 mm Hg, despite artificial ventilation.

Classification: Class II Study

Conclusions:

	GOS		
Age	**1**	**2-3**	**4-5**
0-20	19%	11%	70%
21-40	34	10	56
41-60	44	12	44
61-90	71	23	6

($N_T = 225$)

Narayan,[31] 1981   + + + + +

Description of Study: Prospective analysis of 133 severely head-injured patients in predicting outcome. A combination of clinical data including age, GCS score, pupillary response, presence of surgical mass lesions, extra-ocular motility, and motor posturing predicts outcome with 82% accuracy, 43% with over 90% confidence.

Classification: Class I Study

Conclusions:

	GOS		
Age	**1**	**2, 3**	**4, 5**
0-20 (N=46)	17%	11%	72%
21-40 (N=50)	28	6	66
41-60 (N=28)	46	11	43
≥ 61 (N=9)	78	0	23

Overgaard,[32] 1973   + + + - +

Description of Study: Prospective analysis of 201 patients injured in road-traffic accidents in an attempt to ascertain clinical factors of prognostic significance after traumatic head injury. Increasing age and post-traumatic hypotension were both related to poor recovery, while major intracranial and extracranial surgical complications were associated with poor functional recovery and increased mortality, respectively.

Classification: Class II Study

VII. Evidentiary Table (continued)

Ruff, [36] 1993   + - - + +

Description of Study: Retrospective analysis of 335 severely head-injured patients with respect to outcome as a function of employment status or return to school. The three most potent predictors for returning to work or school are intactness of the patient's verbal intellectual power, speed of information processing, and age.

Classification: Class III Study

Signorini, [38] 1999   + + + + +

Description of Study: Prospective analysis of 372 consecutive TBI patients with a GCS score less than 13 or ISS greater than 16 and age greater than 14 years. Multiple logistic regression resulted in a predictive survival model using mortality at one year with 98% follow-up. No effect of age to 50 years, then age was significantly correlated to higher mortality, particularly if associated with a lower GCS score and higher ISS score.

Classification: Class I Study

Teasdale, [40] 1979   + + + + +

Description of Study: Retrospective analysis of 1,000 severely head-injured patients with respect to age and outcome. Age has an important influence on outcome after severe head injury and this is not explained solely by the increased frequency of intracranial complications in older patients. It is necessary to take age into account when considering the prognosis of an individual patient and also when comparing series of patients managed in different centers or treated in different ways.

Classification: Class I Study

Conclusions:

	GOS
Age	**1**
11-20	35%
21-30	39
31-40	45
41-50	55
51-60	66
61-70	77
71-80	85
81-90	95

VII. Evidentiary Table (continued)

Vollmer,[42] 1991   + + + + +

Description of Study: Prospective analysis of age and clinical outcome following traumatic coma, age 15 years or older. The effect of age and outcome following head injury is dependent on an alteration in the pathophysiological response of the aging central nervous system to severe trauma and not on an increased incidence of non-neurological complications or other clinical parameters.

Classification: Class II Study

Conclusions:

	GOS				
Age	**1**	**2**	**3**	**4**	**5**
15-25 (N=311)	31%	4%	16%	16%	33%
26-35 (N=151)	29	7	16	21	28
36-45 (N=83)	41	7	18	17	17
46-55 (N=45)	49	9	20	11	11
≥ 56 (N=71)	80	3	9	9	0

Evidentiary Table for Age and Outcome

First Author	Number of patients	Prospective	Time	When indicator was measured	What method	Who did it	Outcome measure	When	Blinded observer at outcome	Multi-variate statist. Y=yes ND=not done	What statistics
Alberico[1]	330	Y	1976-1984	On admission	Age	Neurosurg	GOS	3 months, 8 years	NR	ND	Descriptive
Amacher[2]	56	N	1981-1985	On admission	Age	NR	Excellent - poor grading	NR	NR	ND	Descriptive
Becker[4]	160	N	1972-1976	On admission	Age	Neurosurg	GOS	> 3 months	NR	ND	Chi Square
Berger[5]	37	Y	1972-1982	On admission	Age	NR	GOS	> 6 months	NR	ND	Descriptive
Braakman[6]	305	Y	1972-1978	On admission	Age	NR	GOS	6 months	NR	Y	Multivariant
Bricolo[7]	800	N	1973-1975	On admission	Age	Neurosurg	Motor pattern	< 48 months	NR	ND	Descriptive
Bruce[8]	53	N	1975-1977	On admission	Age	NR	GOS	6 months	NR	ND	Descriptive
Choi[11]	264	N	1976-1981	On admission	Age	NR	GOS	6 months	NR	Y	Logistic regression
Edna[14]	1,120	Y	1979-1988	On admission	Age	NR	GOS	At discharge	NR	ND	Chi Square
Gordon[16]	2,298	N	1968-1988	On admission	Age	NR	GOS	3, 6, 12 months	NR	ND	Chi Square
Heiskanen[19]	204	N	1962-1965	On admission	Age	NR	Death	3-5 years	NR	ND	Student's t-test
Jennett[22]	1,000	N	1968-1976	On admission	Age	NR	GOS	6 months	NR	ND	Descriptive
Luerssen[26]	8,814	N	1980-1981	On admission	Age	NR	Death	NR	NR	Y	Chi Square, Logistic regression analysis
Miller[30]	225	Y	1976-1980	On admission	Age	NR	GOS	3, 6, 12 months	NR	ND	Chi Square
Narayan[31]	133	Y	1976-1979	On admission	Age	NR	GOS	3, 6, 12 months	NR	Y	Logistic regression analysis
Overgaard[32]	201	Y	1968-1969	On admission	Age	NR	Neurol. func. examin.	24, 36 months	NR	ND	Chi Square
Ruff[36]	93	N	4 years	On admission	Age	NR	Employment, return to school	6, 12 months	NR	Y	Logistic regression analysis
Signorini[38]	372	Y	1989-1991	On admission	Age	NR	Death	12 months	NR	Y	Logistic regression analysis
Teasdale[40]	1,000	Y	1968-1976	On admission	Age	NR	GOS	6 months	NR	ND	Descriptive
Vollmer[42]	661	Y	1984-1987	On admission	Age	NR	GOS	6 months	NR	Y	Chi Square, Logistic regression analysis

NR=not recorded; GOS=Glasgow Outcome Scale; ND= not done

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PUPILLARY DIAMETER AND LIGHT REFLEX

I. Conclusions

A. Which feature of the parameter is supported by Class I evidence and has at least a 70% positive predictive value? Bilaterally absent pupillary light reflex.

B. Recommendations for parameter measurement for prognosis:
  1. How should it be measured?
     - A measurement difference of 1mm or more is defined as asymmetry.
     - A **fixed** pupil shows no response (< 1mm) to bright light.
     - A pupillary size of > 4mm is recommended as the measure for a **dilated** pupil.
     - The duration of pupillary dilation and fixation should be recorded.

       The following pupillary exam should be noted with L (left) or R (right) distinction and duration:
     - Evidence of direct orbital trauma
     - Asymmetrical response to light
     - Asymmetry at rest
     - Fixed pupil (one or both)
     - Dilated pupil (one or both)
     - Fixed and dilated pupils (one or both)
  2. When should it be measured?
     - After pulmonary and hemodynamic resuscitation
  3. Who should measure it?
     - Trained medical personnel

II. Overview

The parasympathetic, pupilloconstrictor, light reflex pathway mediated by the third cranial nerve is anatomically adjacent to brainstem areas controlling consciousness and the medial temporal lobe. Therefore, damage to the midbrain third nucleus or the efferent third nerve by temporal lobe compression produces dilation of the pupil. If the damage or compression is significant, the pupil will be unresponsive (fixed) to a light stimulus. This pupillary light reflex and the size of the pupil has traditionally been used as a clinical parameter in assessing transtentorial herniation and as a prognostic indicator. The pupillary light reflex and size

equality of pupils has a high interobserver reliability.[21] The use of the pupillary size and light reflex are, therefore, indirect measures of dysfunction to pathways subserving consciousness and, thus, an important clinical parameter in assessing outcome from traumatic coma. Direct orbital trauma can damage the third nerve leading to a dilated and/or a fixed pupil and be independent of intracranial hypertension. Direct oculomotor trauma should be excluded before pupillary reactivity or size is used as a prognostic indicator.

III. Search Process

A MEDLINE search for the period 1980-1995 was done using the key words "pupils," "pupils and prognosis," and "pupils and trauma." This resulted in the critical review of 19 articles.

IV. Scientific Foundation

The pupillary light reflex pathways are adjacent to brain structures essential for cognitive function and the temporal lobe. Increased intracranial pressure resulting in uncal herniation compresses the third cranial nerve resulting in a reduction in parasympathetic tone to the pupillary constrictor fibers and therefore results in a dilated pupil. Similarly, destruction of the third nerve parasympathetic brainstem pathway also results in a dilated and fixed to light pupil. Therefore, the pupillary light reflex is an indirect measure of herniation and brainstem injury. Generally, dilation and fixation of one pupil signifies herniation, whereas the appearance of bilaterally dilated and fixed pupils is consistent with irreversible brainstem injury in a fully resuscitated patient. A limitation in terms of prognosis is a dilated and nonreactive pupil due to direct orbital trauma without brainstem or intracranial third nerve compression. The "blown pupil" is important in the context of a decreased level of consciousness. This measurement of pupil function must be assessed for outcome with the level of consciousness or intracranial pathology.

Clinical studies investigating the prognostic weight of the pupillary light reflex have examined this parameter in a variety of methodologies. Few studies have rigorously measured the size and reaction of the pupil to light.[18] The vast majority label pupils as dilated without giving the size and do not state whether the pupils are fixed to light even though it is implied.

The incidence of pupillary abnormalities (%) within 24 hours, post-resuscitation, in patients with severe head injury is shown in the following table:

First Author	Both Reactive	One Reactive	One or Both Unreactive	Both Unreactive
Jennett,[8] 1976	78%	—%	—%	22%[†]
Jennett,[9] 1979	—	—	—	19*, 29, 32
Braakman,[4] 1980	62	12	—	26
Miller,[13] 1981	77	—	—	23
Narayan,[14] 1981	65	—	—	35
Heiden,[7] 1983	68	—	—	32
Van Dongen,[22] 1983	47	—	53	—
Levin,[10] 1990[††]	64	—	36	—
Marshall,[12] 1991	56	11	—	33
Average	65	12	—	28

*Represents % from Glasgow, Netherlands, and Los Angeles, respectively.
[†]Earlier series from Glasgow and Netherlands
[††]Traumatic Coma Data Bank (TCDB) study

On average 65% of patients with severe head injury have normally reactive pupils after resuscitation, 12% have one abnormal pupil, and 28% have bilateral pupillary nonreactivity.

There is significant interaction between pupillary reactivity and other early indicators of prognosis; Glasgow Coma Scale (GCS) score, [4] hypotension, [1] and CT basal cisterns, [22] as seen in the following table:

	GCS 3-5	GCS 6-7	SBP < 60	SBP 60-90	Cisterns Partly Open	Cisterns Closed
Unreactive Pupils (%)	56	20	65	53	15*	38*

*Includes bilateral and unilateral unreactive pupils

In reviewing large studies (> 200 patients), there was a strong association between bilaterally unreactive pupils and poor outcome as shown in the following table:

		% Vegetative/Dead (Glasgow Outcome Scale Score [GOS] 1, 2)		
First Author	# of Patients	Bilateral Reactive Pupils	Unilateral Unreactive	Bilateral Unreactive
Jennett,[8] 1976	600	42%	—%	95%
Braakman,[4] 1980	305	29	54	90
Heiden,[7] 1983	213	36	—	91
Marshall,[12] 1991	746	32	34	74
	Average	**35**	**44**	**88**

In two Class I studies, bilaterally absent pupil reaction had a greater than 70% positive predictive value for a poor outcome. In a prospective study of 133 patients with severe head injury, bilaterally absent pupillary light reflex was noted in 35%; a poor outcome (dead, vegetative, or severely disabled) was found in 70% of these patients.[14] Similarly, in a larger study of 305 patients with regard to prognostic features, bilaterally absent pupillary light reflex was associated with a 90% mortality (see Evidentiary Table).[4]

In large series, patients who had bilaterally reactive pupils made a significantly better outcome as seen below:

		% Good Recovery/Moderate Disability (GOS 4, 5)		
First Author	# of Patients	Bilateral Reactive Pupils	Unilateral Reactive	Bilateral Unreactive
Jennett,[8] 1976	600	50%	—%	5%
Heiden,[7] 1983	213	49	—	3
Levin,[10] 1990	259	53	17*	—
	Average	**51**		**4**

*One or both pupils unreactive.

The outcome from bilaterally unreactive pupils is influenced by the underlying pathology and timing of surgical evaluation of significant hematomas. In patients who are comatose from epidural hematomas, the mortality with bilateral fixed pupils is only 56% compared to an average of 88% in patients with subdural hematomas.[15, 16] In another study of patients who were operated on for epidural hematomas, with bilaterally fixed pupils, only 18% had a poor

outcome (GOS 1-2) compared to 64% poor outcome in those patients who were operated on for subdural hematomas and had bilaterally fixed pupils.[17,18] In this same study a delay of greater than three hours in evacuating a traumatic intracranial hematoma increased the chance of a poor outcome with bilateral fixed pupils from 40% to 63%.

In conclusion, pupil reactivity to light can prognosticate outcome. However, direct orbital trauma should be excluded as a causative agent, hypotension should be reversed prior to assessment of pupils, and repeat examination after evacuation of intracranial hematomas should be performed.

V.   Summary

The pupillary diameter and the pupilloconstrictor light reflex are the two parameters that have been studied extensively in relation to prognosis. Accurate measurement of pupil diameter or the constrictor response or the duration of the response has not been performed in studies on traumatic brain-injured individuals—for lack of a standardized measuring procedure. The following is recommended:

1. Pupillary light reflex for each eye should be used as a prognostic parameter.
2. The duration of pupillary dilation and fixation should be documented.
3. A pupillary size greater than 4 mm is recommended as the measure for a dilated pupil.[17]
4. A fixed pupil should be defined as no constrictor response to bright light.
5. Right or left distinction should be made when the pupils are asymmetric.
6. Hypotension and hypoxia should be corrected before assessing pupils for prognosis.
7. Direct orbital trauma should be excluded.
8. Pupils should be reassessed after surgical evacuation of intracranial hematomas.

VI.   Key Issues for Further Investigation

Future studies should dissect the prognostic value of each of the recommended measurements to discern the least number of pupillary size and light reflex measurements necessary to reliably prognosticate outcome. Also, a standardized method of measuring pupil size and reactivity to light would decrease interobserver variability.

VII.   Evidentiary Table

Andrews and Pitts,[2] 1991

Description of Study: Retrospective study of 153 consecutive patients presenting with transtentorial herniation—altered level of consciousness, anisocoria or pupillary unresponsiveness, and abnormal motor findings; age range 2-83 years.

Classification: Class III Study

Conclusions:

	GOS		
	1-3	**4**	**5**
One Pupil Fixed	72%	13%	15%
Both Pupils Fixed	96	4	0

Braakman,[4] 1980

Description of Study: Review of the International Databank with reference to 305 comatose head-injured patients' prognostic parameters measured with 24 hours of admission and (GOS) evaluated at 6 months.

Classification: Class I Study

Conclusions:

	GOS
	1
Both Pupils Reactive	29%
One Pupil Fixed	54
Both Pupils Fixed	**91 + PPV = 91%**

Choi,[5] 1988

Description of Study: A review of 523 severely head-injured patients analyzing significant prognostic parameters to predict outcome into four GOS categories.

Classification: Class III Study

Conclusions: Pupillary response to light was a significant ($p < .001$) factor in determining outcome.

Cordobes,[6] 1981

Description of Study: Retrospective analysis of 82 patients with regard to mortality before and after instituting a computed tomography (CT) scanner.

Classification: Class III Study

Conclusions:

	GOS
	1
One Pupil Fixed	18%
Both Pupils Fixed	100

Heiden,[7] 1983

Description of Study: Prospective study of 213 patients of all ages with severe head injury to identify favorable and unfavorable clinical factors.

Classification: Class II Study

Conclusions:

	GOS		
	1, 2	**3**	**4, 5**
Both Pupils Reactive	36%	15%	49%
Both Pupils Fixed	91	6	3

Jennett,[8] 1976

Description of Study: Prospective study in 600 severe head injury patients from Glasgow and the Netherlands.

Classification: Class II Study

Conclusions:

	GOS	
	1, 2	**4, 5**
Both Pupils Reactive	42%	50%
Both Pupils Fixed	95	5

Jennett,[9] 1979

Description of Study: Expanded patient enrollment from 1976 publication with 1,000 patients from Glasgow, Netherlands, and Los Angeles.

Classification: Class I Study

Conclusions:

	GOS	
	1, 2	**4, 5**
Both Pupils Reactive	39%	50%
Both Pupils Fixed	91	4

Levin,[10] 1990

Description of Study: Review of 300 survivors in the Traumatic Coma Data Bank prognostic factors in evaluating GOS at 1 year after injury; age range 16-70.

Classification: Class I Study

Conclusions:

	GOS			
	2	**3**	**4**	**5**
Both Pupils Reactive	4 %	14%	21%	61%
One or Both Fixed	15	38	20	27

Lobato,[11] 1988

Description of Study: Review of 64 consecutive comatose patients who were operated on for epidural hematomas; age range 1-72 years.

Classification: Class III Study

Conclusions:

	GOS			
	1	**3**	**4**	**5**
Both Pupils Reactive	13%	4%	39%	43%
One Pupil Fixed	11	4	44	41
Both Pupils Fixed	82	0	9	9

Marshall,[12] 1991

Description of Study: Prospective analysis of 746 patients in the Traumatic Coma Data Bank. Pupil status unknown in 106 of these patients.

Classification: Class II Study

Conclusions:

	GOS
	1, 2
Both Pupils Reactive At All Times	10%
One Pupil Fixed	47
Both Pupils Fixed	82

VII.   Evidentiary Table (continued)

Miller,[13] 1981

Description of Study: A prospective study of 225 consecutive severe head injury patients in regard to outcome. 41% and 10% of the surgical and nonsurgical cases, respectively, had bilateral fixed pupils; age range 2-89.

Classification: Class III Study

Conclusions:

	GOS		
	1	2, 3	4, 5
Surgical: Both Pupils Fixed	77%	12%	11%
Nonsurgical: Both Pupils Fixed	71	11	18

Narayan,[14] 1981

Description of Study: A study of 133 consecutive patients with severe head injury; age range 0-61+ years.

Classification: Class I Study

Conclusions:

	GOS		
	1	2-3	4-5
Both Pupils Reactive	16%	8%	76%
Both Pupils Unreactive	61	9	30
positive productive value (PPV) = 70%			

Phonprasert,[15] 1980

Description of Study: An analysis of 138 consecutive patients who were operated on for epidural hematomas with regard to factors influencing mortality; age range 3 to 71 years.

Classification: Class III Study

Conclusions:

	GOS
	1
One Pupil Fixed	15%
Both Pupils Fixed	56

Phuenpathom,[16] 1993

Description of Study: A retrospective outcome prediction study of 109 consecutive with a GCS score of 3-15 who presented with an acute subdural hematoma. 83 patients had clot removal. Age range was 6 months to 79 years old.

Classification: Class III Study

Conclusions:

	GOS
	1
Both Pupils Reactive	16%
One Pupil Fixed	48
Both Pupils Fixed	88

Rivas,[17] 1988

Description of Study: A series of 161 consecutive patients with a GCS score of 3-15 were operated on for epidural hematomas with regard to prognostic factors; age range 3 days to 78 years old.

Classification: Class II Study

Conclusions:

	GOS			
	1	3	4	5
One Pupil Fixed	14%	4%	43%	39%
Both Pupils Fixed	82	0	9	9

Sakas,[18] 1995

Description of Study: One-year outcome analysis of 40 consecutive patients who underwent craniotomy for traumatic hematoma at various times after developing bilaterally fixed and dilated pupils (> 4 mm); age range 6-75 years old.

Classification: Class II Study

Conclusions:

	GOS		
	1, 2	3	4, 5
Patients Operated On Within Three Hours of Both Pupils Fixed	40%	30%	30%
Patients Operated On After Three Hours of Both Pupils Fixed	63	12	25
Patients Operated On for Epidural Hematomas and Both Pupils Fixed	18	27	55
Patients Operated On for Subdural Hematomas and Both Pupils Fixed	64	23	13

VII.   Evidentiary Table (continued)

Stone,[19] 1983

Description of Study: Review of 206 patients who were operated on for acute subdural hematomas; age range 3-88 years old.

Classification: Class III Study

Conclusions:

	GOS
	4, 5
One Pupil Fixed	25%
Both Pupils Fixed	25

Suddaby,[20] 1987

Description of Study: Review of 49 cases of civilian gunshot wounds to the brain with a GCS score of 3-15; age range 8-92 years old.

Classification: Class III Study

Conclusions:

	GOS	
	1-3	**4, 5**
Both Pupils Reactive	28%	72%
Both Pupils Fixed	100	0

Wilberger,[23] 1991

Description of Study: Review of 115 severely head injured patients (GCS ≤ 7) with subdural hematoma analyzing morbidity, mortality, and operative timing.

Classification: Class III Study

Conclusions:

	GOS
	1
Both Pupils Fixed	88%

VIIa. Description of the Studies According to the Classification Criteria

First Author	Number of Patients	Prospective/ Retrospective	Time	When indicator was measured	What method	Who did it	Outcome measure	When	Blinded	Multivariate observer	What Statistics
Andrews[2]	153	R	1981-88	Admission exam	Physical	NR	GOS	1-37 months	No	No	Chi Square
Braakman[4]	305	R	1973-78	Best pupillary response within 24 hours of admission	Physical exam	NR	GOS	6 months	NR	Yes	Independence Model
Choi[5]	523	R	1976-86	In ER	Physical exam	ER staff	GOS	6 months	NR	Yes	Location model discriminant analysis
Cordobes[6]	82	R	1973-80	Just before operation	Physical exam	NR	GOS	NR	NR	No	Chi Square
Heiden[7]	213	P	NR	24 hours post-injury	Physical exam	NR	GOS	1 year	No	No	Mantel-Haenzel (similar to Chi Square)
Jennett[8]	600	P	1968-76	Within 24 hours post-injury	Physical exam	NR	GOS	6 months	No	No	Chi Square
Jennett[9]	1,000	P	1968-76	Within 24 hours post-injury	Physical exam	NR	GOS	6 months	No	No	Chi Square
Levin[10]	300	P	1984-87	First post-resuscitation pupillary reactivity and lowest post-resuscitation pupillary reactivity	Physical exam	Neurosurgeon	GOS (263 points) and complete neuro-psych. assessment (127 points)	1 year	NR	Yes	Logistic and linear regression
Lobato[11]	64	R	1977-86	At operation	Physical exam	NR	GOS	6 months	NR	No	Chi Square
Marshall[12]	640	P	1984-87	Post-resuscitation	Physical exam	NR	GOS	Last contact	NR	Yes	Chi Square
Miller[13]	225	P	1976-80	Admission, mean delay 3 hrs. s/p injury/or at time of deterioration	Physical exam	Authors	GOS	3,6,12 months	NR	No	Chi Square
Narayan[14]	133	P	1976-79	Admission	Physical exam	NR	GOS	3,6,12 months	NR	Yes	Logistic regression

NR=not reported

VIIa. Description of the Studies According to the Classification Criteria (continued)

First Author	# of Patients	Prospective/ Retrospective	Time	When indicator was measured	What method	Who did it	Outcome measure	When	Blinded	Multivariate observer	What Statistics
Phonprasert[15]	138	P	1971-78	NR	NR	NR	Mortality	NR	NR	No	Chi Square
Phuenpathom[16]	109	R	1/86- 12/89	Admission and 24 hour post-admission	Referral notes/ patient records	NR	GOS	6 months	No	Yes	Logistic regression
Rivas[17]	161	P	1977-86	Admission	Physical exam	NR	GOS— good recovery,	6 months	No	No	Chi Square
Sakas[18]	40	P & R	1985-88	Admission	Physical exam, CT findings, chart review	Authors, residents & nurses	GOS	6 months and 1 year post-op	NR	No	Chi Square
Stone[19]	206	R	1/69 - 6/81	Pre-operative	Visual inspection /chart review	NR	GOS— Functional recovery	6 months	No	No	Chi Square
Suddaby[20]	49	R	1975-85	Admission	Chart review	Authors	GOS	Discharge	No	NR	NR
Wilberger[23]	101	R	1982-87	Early operative at time of operation/ Intervention < 4 hours	NR	NR	GOS— Functional recovery	18 months	No	No	Chi Square/ Student paired or pooled t-test post-trauma

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HYPOTENSION

I. Conclusions

  A. Which feature of the parameter is supported by Class I evidence and has at least a 70% positive predictive value (PPV)? A systolic blood pressure less than 90 mm Hg was found to have a 67% PPV for poor outcome and, when combined with hypoxia, a 79% PPV.
  B. Parameter measurement:
    1. How should it be measured?
        Systolic and diastolic blood pressure should be measured using the most accurate system available under the circumstances. Monitoring by arterial line, when free of signal artifact, provides data that is both accurate and continuous and is the method of choice. Methods that do not determine the mean arterial pressure are less valuable.
    2. When should it be measured?
        Blood pressures should be measured as frequently as possible. The incidence and duration of hypotension (systolic blood pressure < 90 mm Hg) should be documented by direct blood pressure values.
    3. Who should measure it?
        Blood pressure should be measured by trained medical personnel.

II. Overview

Secondary brain insults are defined as post-traumatic insults to the brain arising from extracranial sources and intracranial hypertension. They are generally ischemic and include hypotension, hypoxia, anemia, infection, etc. There is a growing body of evidence that secondary insults to the injured brain are common and can powerfully influence recovery. The most detrimental and best studied of these is hypotension. Because hypotension is amenable to therapeutic manipulation, an understanding of its influence on prognosis is useful for both prediction of outcome at present and optimization of recovery in the future.

III. Process

A MEDLINE search back to 1966 was undertaken using the following key words: "head injury or brain injury" and "secondary insult or hypotension" and "outcome or prognosis" and "human subject." This produced 70 references that were individually reviewed for design, content, and relevance. The results of this review were then incorporated into analysis presented here.

IV. Scientific Foundation

In the scientific literature published to date, the definition of hypotension has been accepted from the literature on systemic insults. Despite the necessity for redefining this term in the brain injury literature, for the purposes of clarity in the following discussion, this entity is defined as:

- Hypotension = Systolic blood pressure < 90 mm Hg

The major secondary brain insults that have been studied with respect to their influence on outcome from severe brain injury are hypotension and hypoxia. Seminal studies by Miller, et al., established the importance of these secondary insults as outcome determinants, but did not study their independence with respect to other predictive factors.[6,7]

The largest and most definitive study of the influence of secondary brain insults on outcome comes from a Class I analysis of a large (717 patients), prospectively collected data set from the Traumatic Coma Data Bank (TCDB).[2] Hypotension was defined as a single measurement of a systolic blood pressure less than 90 mm Hg. The occurrence of one or more episodes of hypotension during the period from injury through resuscitation or during the shorter period of resuscitation only was associated with a doubling of mortality and a marked increase in morbidity (see Evidentiary Table).[2] Hypotension was found to be a statistically significant predictor of outcome and statistically independent of other major predictors of outcome, including age, hypoxia, and the presence or absence of severe trauma to one or more extracranial organ systems. When the influence of hypotension on outcome was controlled separately, the statistical significance of severe trauma to one or more extracranial organ systems as a predictor of outcome was eliminated, suggesting that the influence of systemic multiple trauma on the outcome of severe head injury patients is primarily mediated through hypotension.

The analysis of outcome from severe head injury in the TCDB revealed that the five most powerful predictors occurring from injury through resuscitation were age, intracranial (computed tomographic) diagnosis, pupillary reactivity, post-resuscitation Glasgow Coma Scale (GCS) score, and presence or absence of hypotension. Notably, of these five major predictors, only the occurrence and severity of hypotension is amenable to medical manipulation.

The analysis of a smaller, prospectively collected database from Australia corroborated the above findings.[4] This study found early and late hypotension to be statistically significant, independent predictors of outcome, both for mortality and for dichotomized quality of outcome (good or moderate-to-severe deficits versus vegetative survival or death). In this study, hypotension was again the only predictor amenable to medical modification.

Further support of the strong association between early hypotension and outcome comes from a study of the influence of various resuscitation fluids on the outcome of hypotensive multiple system trauma patients.[12] The subgroup of patients with severe head injuries had an overall mortality of 74%, with those being treated using conventional means of resuscitation having an 88% mortality rate.

A Class II report has recently extended the above findings to the pediatric population (age less than 17 years).[10] In this study, both hypoxia and hypotension had deleterious influences on outcome with hypotension being significantly more powerful in independently determining recovery. In this study, an episode of hypotension appeared to eliminate the generally more favorable outcome afforded by youth.

Although the above studies firmly establish an association between secondary brain insults (particularly hypotension) and outcome, they do not address the issue of whether preventing or treating such insults during this period improves recovery. With respect to secondary insults in general (hypotension, hypoxia, hypercapnia, and anemia), a recent Class III study addressed the ability of on-site, physician-directed resuscitation to decrease the incidence of secondary brain insults and improve outcome.[1] Patients whose secondary brain insults were reversed in the field had a 42% decrease in the frequency of poor outcomes (death, vegetative survival, or severe deficits) at three-month follow-up. Unfortunately, this study did not control for many confounding factors. Nevertheless, it does suggest that patients with secondary brain insults that respond to treatment have improved outcome when compared to those that are refractory to correction.

With respect to hypotension in particular, Class II results from a recent Class I study strongly suggest that reversing or preventing hypotension in the field improves outcome. A recent prospective, randomized, placebo-controlled, multicenter trial examined the efficacy of administering 250 cc's of hypertonic (7.5%) saline versus normal saline as the initial resuscitation fluid in hypotensive, multiple-trauma patients. For the group as a whole, there was no statistically significant difference in outcome between the two groups. The hypertonic saline group did have improved blood pressure responses, decreased overall fluid requirements, and a trend toward improvement in survival. A retrospective, subgroup analysis of those patients with severe head injury, however, revealed that those patients in this group that received hypertonic saline as their initial bolus had a statistically significant improvement in survival measured at the time of discharge.[12] Although such a retrospective, subgroup analysis renders this a Class II result from a Class I study, it strongly suggests that the correction of hypotension in the field improves outcome from severe head injury.

The occurrence of early secondary brain insults also appears to be correlated with the subsequent appearance of other factors that are strongly associated with prognosis. In particular, early systemic hypotension appears to exacerbate the subsequent development of intracranial hypertension in terms of both frequency of occurrence and magnitude.[5, 8, 11] Unfortunately, at present, data regarding the strength of these associations and their independent utility as prognostic indicators are unavailable.

The improvement in outcome from severe head injury that would result if hypotension was eliminated as a secondary insult has been modelled.[3] The interaction of secondary brain insults occurring during the early (injury through resuscitation) and late (intensive care unit) periods was evaluated in 493 patients from the TCDB who survived at least nine hours in the intensive care unit. Although the definitions of early and late insults used in this study were somewhat different from previous TCDB investigations, the frequency of secondary insults remained high, with early hypotension occurring in 14% of patients and late hypotension in 32%. Of note, late hypotension was the only hypotensive insult in 24%. The percent outcome of vegetative survival or death was 17% for patients without hypotensive episodes, 47% for those with early hypotension, 66% for those with late hypotension, and 77% for those with both insults. Both early and late hypotension were significant, independent predictors of outcome in these patients, controlling for age, sex, mechanism of injury, GCS score, and intracranial diagnosis. Logistic regression modeling revealed that early hypotension was responsible for a 15-fold excess mortality and late hypotension for an 11-fold excess mortality, these two factors individually being the two most responsible for excess risk of any analyzed variables.

The influence on outcome of iatrogenic hypotensive episodes was reported in a Class III study that examined the influence of intraoperative hypotension on outcome in patients with severe head injury who had not otherwise been hypotensive.[9] All procedures were performed within 72 hours of admission. Patients with intraoperative hypotension had significantly worse neurologic outcomes than those without. Additionally, outcome was inversely correlated with duration of intraoperative hypotension. This study suggests that the potential benefits of therapeutic procedures can be reversed if there is concomitant hypotension. Therefore, the performance of these procedures either has to be predicated on strict avoidance of hypotensive episodes or consideration be given to delaying them.

V.   Summary

Hypotension, occurring at any time from injury through the acute intensive care course, has been found to be a primary predictor of outcome from severe head injury for the health care delivery systems within which prognostic variables have been best studied. Hypotension *is* repeatedly found to be one of the five most powerful predictors of outcome and is generally the only one of these five that is amenable to therapeutic modification. A single recording of a hypotensive episode is generally associated with a doubling of mortality and a marked increase in morbidity from a given head injury. The estimated reduction in unfavorable outcome that would result from the elimination of hypotensive secondary brain insults is profound.

VI. Key Issues for Future Investigation

Although the impact on outcome of hypotension as a secondary brain insult is well established, there are only very preliminary studies on how it can be eliminated or minimized, on what the effective mechanisms are for doing so, and on what the specific influences are on outcome of such protocols. There is also little known as to the "critical values" of magnitude and duration for hypotension following brain injury. Future investigations must prospectively collect accurate and frequent physiologic data on the occurrence of hypotension (systolic blood pressure < 90 mm Hg) as well as the actual blood pressure values throughout resuscitation. Critical physiologic threshold values and the efficacy of various therapeutic manipulations in decreasing secondary brain insults and improving outcome must be derived from such data using statistical methods that control for factor-factor interactions as well as the magnitude of effect attributable to individual factors. Given the magnitude of influence on outcome attributed to secondary insults in predictive models, investigations into their prevention or elimination might well represent the area of early brain injury treatment with the greatest potential for improving outcome.

VII. Evidentiary Table for Resuscitation of Blood Pressure and Oxygenation

Carrel,[1] 1994

Description of Study: Retrospective study of 51 consecutive patients with non-penetrating severe head injury treated with physician-directed aggressive advanced traumatic life support in the field. They assessed the effect of secondary insults on 3-month outcome. The secondary insults studied were anemia (hematocrit $\leq 30\%$), hypotension (systolic arterial pressure ≤ 95 mm Hg), hypercapnia ($PaCO_2 \geq 45$ mm Hg), and hypoxemia ($PaO_2 \leq 65$ mm Hg).

Classification: Class III Study

Conclusions:

	GOS 1, 2, 3	GOS 4, 5
No Secondary Insults	42%	58%
Secondary Insults	72	28

Chesnut,[2] 1993

Description of Study: A prospective study of 717 severe head injury patients admitted consecutively to four centers investigated the effect on outcome of hypotension (systolic blood pressure [SBP] < 90 mm Hg) occurring from injury through resuscitation.

Classification: Class I Study

Conclusions:

	GOS 1	GOS 2, 3	GOS 4, 5
Neither	27%	19%	54%
Hypoxia	28	22	50
Hypotension	50% + PPV=67%	17	33
Both	57% + PPV=79%	22	20

Chesnut,[3] 1993

Description of Study: A prospective study of 717 severe head injury patients admitted consecutively to four centers investigated the effect on outcome of hypotension (SBP < 90 mm Hg) occurring from injury through resuscitation (early hypotension; N = 717) or in the Intensive Care Unit (ICU) (late hypotension; N = 493).

Classification: Class I Study

Conclusions:

	GOS 1, 2	Relative Risk of Mortality
No Hypotension	17%	
Early Hypotension	47	15-fold (p < 0.001)
Late Hypotension	66	11-fold (p < 0.001)
Early & Late Hypotension	77	

Fearnside,[4] 1993

Description of Study: A prospective study of 315 severe head injury patients admitted consecutively to a single center investigated prehospital and in-hospital predictors of outcome.

Classification: Class I Study

Conclusions:

	GOS 1
No Hypotension	27%
Hypotension	42

Miller,[6] 1982

Description of Study: 225 severe head injury patients were prospectively studied with respect to the influence of secondary insults on outcome. The predictive independence of hypotension in comparison to other associated factors, however, was not investigated.

Classification: Class II Study

Conclusions:

	GOS 1	GOS 2, 3	GOS 4, 5
Neither	24%	12%	64%
Hypoxia*	50	9	41
Hypotension*†	53	12	35
Anaemia*	52	9	38

*Secondary insults not mutually exclusive.

†Hypotension = systolic blood pressure < 95 mm Hg

VII. Evidentiary Table (continued)

Miller,[7] 1978

Description of Study: 100 consecutive severe head injury patients were prospectively studied with respect to the influence of secondary insults on outcome (report of first 100 patients in subsequent report of 225 patients [*vide supra*]). Hypotension (SBP < 95 mm Hg) associated with a trend (not statistically significant) toward worse outcome in entire cohort; trend met statistical significance for patients without mass lesions. Influence of hypotension on outcome not analyzed independently from other associated factors.

Classification: Class III Study

Conclusions:

	GOS 1, 3	GOS 4, 5
Patients with Mass Lesions		
No Insults	50%	50%
Systemic Insults*	75	25
Patients without Mass Lesions†		
No Insults	12	88
Systemic Insults*	36	64
*Systemic insults = hypoxia, hypotension, anaemia, hypercarbia		
†Statistically significant		

Pietropaoli,[9] 1992

Description of Study: Retrospective review of the impact of intraoperative hypotension (SBP < 90 mm Hg) on 53 otherwise normotensive severe head injury patients who required early surgery (within 72 hours of injury).

Classification: Class III Study

Conclusions:

Intraoperative Hypotension	GOS 1	GOS 2, 3	GOS 4, 5
No	25%	17%	58%
Yes	82	2	6
The inverse correlation of intraoperative hypotension with outcome was duration dependent.			

VII. Evidentiary Table (continued)

Pigula,[10] 1993

Description of Study: 58 children (< 17 years old) with severe head injuries were prospectively studied for the effect of hypotension (SBP < 90 mm Hg) on outcome.

Classification: Class II Study

Conclusions:

	Mortality	
	Children	**Adults**
No Hypotension or Hypoxia	16%	42%
Hypotension or Hypoxia	67	66

Vassar,[12] 1993

Description of Study: Prospective, randomized, controlled, multicenter trial comparing the efficacy of administering 250 ml of hypertonic saline with or without dextran 70 vs normal saline as the initial resuscitation fluid in facilitating the resuscitation and improving the outcome of hypotensive trauma patients. In this trial, the hypertonic saline group had significantly improved blood pressure responses and decreased overall fluid requirements. Although there was an associated improvement in survival for the overall group, it did not reach statistical significance. Post-hoc analysis of the severe head injury group (Class II analysis) revealed that the hypertonic saline group had a statistically significant improvement in survival-to-discharge vs that predicted by the Major Trauma Outcome Study (MTOS).*

Classification: Class II Study

Conclusions:

	LR	**HS**	**HS-6%**	**HS-12%**
Predicted GOS 1 (MTOS)	86%	87%	84%	86%
Actual GOS 1	88	66	73	70
P (Actual vs Predicted)	NS	< .001	< .05	< .005

Abbreviations:
LR=Lactated Ringer's
HS=Hypertonic (7.5%) saline
HS-6%=Hypertonic saline with 6% dextran 70
HS-12%=Hypertonic saline with 12% dextran 70
NS=Not significant

* This study was a prospective, randomized, placebo-controlled trial for hypotensive trauma victims in general. The analysis with respect to severe head injury patients was post-hoc so that, although data collection was prospective, randomization of the subgroup was not in a strict sense. Therefore, with respect to the group of severe head injury patients, this is a Class II study. See text for details.

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CT SCAN FEATURES

I. Conclusions

A. Which feature of the parameter is supported by Class I and strong Class II evidence and has at least a 70% positive predictive value (PPV) in severe head injury?
   a. Presence of abnormalities on initial computed tomography (CT) examination
   b. CT classification
   c. Compressed or absent basal cisterns
   d. Traumatic subarachnoid hemorrhage (tSAH):
      - Blood in the basal cisterns
      - Extensive tSAH

B. Parameter measurement:
   1. How should it be measured?
      - Compressed or absent basal cisterns measured at the midbrain level.
      - tSAH should be noted in the basal cisterns or over the convexity.
      - Midline shift should be measured at the level of the septum pellucidum.
   2. When should it be measured?
      - Within 12 hours of injury
      - The full extent of intracranial pathology, however, may not be disclosed on early CT examination.
   3. Who should measure it?
      - A neuroradiologist or other qualified physician, experienced in reading CT-scans of the brain

II. Overview

The classical clinical features with prognostic significance in patients with severe traumatic brain injury (TBI) include age, Glasgow Coma Scale (GCS) score, pupil reactivity, brainstem reflexes, and the presence of post-traumatic hypotension. Many patients today arrive in the hospital already intubated, paralyzed, and ventilated. An accurate estimation of the GCS score and changes in the GCS score in the initial hours after trauma are therefore often difficult to obtain. In a recent survey on patients with severe and moderate head injury, conducted by the European Brain Injury Consortium, the full GCS score was only testable in 56% of patients on admission to neurosurgery (Murray, et al.,[2] 1998). Prognostic features based on the results of technical examinations are therefore needed. CT scanning is routinely performed in all patients

with severe TBI and provides information with important therapeutic implications for operative intervention or indications for intracranial pressure (ICP) monitoring, and may provide information concerning prognostic significance.

III. Search Process

A MEDLINE search from 1976 through mid-1998 was undertaken using the following key words: "head injury," "computerized tomography," "prognosis," and "outcome". A search on "head injury," "CT scan," and "prognosis" resulted in 27 articles, and a search on "head injury," "CT scan," and "outcome" in 55 articles. Only English-language literature and papers reporting on adult head injury were reviewed. In total, 31 manuscripts relevant to the prognostic value of the CT scan in the acute stage of adult head injury were identified. Individual CT characteristics found to be particularly relevant in terms of prognosis were:

a.   Status of basal cisterns
b.   tSAH
c.   Presence and degree of midline shift
d.   Presence and type of intracranial lesions

These subheadings, including "intraventricular hemorrhage," "intracranial lesions," "normal CT," "epidural hematoma," and "subdural hematoma" were then subjected to a second search, combining these with "head injury," "brain injury," "prognosis," and "outcome." This search yielded an additional 18 manuscripts. Cross referencing and expertise available amongst authors added an additional 14 manuscripts.

IV. Scientific Foundation

Topics analyzed for prognostic significance were:
   A.   Abnormalities on CT
   B.   CT classification
   C.   Individual CT characteristics:
      ▪   Status of basal cisterns
      ▪   tSAH
      ▪   Midline shift
      ▪   Presence or absence of intracranial mass lesions

If data permitted, the prognostic value of each feature was analyzed with respect to the Glasgow Outcome Scale (GOS)[1], dichotomized into unfavorable (dead, vegetative, severe, disabled) and favorable outcome (moderate disability/good recovery). If such analysis was not possible on data reported, features were related to mortality.

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A. Abnormal CT Scan

Description of parameter: Any abnormality noted on CT examination, consistent with TBI.

Reliability of Scoring

No reports concerning the intraobserver reliability in scoring presence or absence of abnormalities on CT examination after head injury are reported. The incidence of occurrence of abnormalities on CT varies in two reports of the Traumatic Coma Data Bank (TCDB). In the initial report by Eisenberg, et al. (1990), describing the CT scan in 753 patients, a normal CT was observed in 45 patients[2]; in the subsequent report by Marshall, et al. (1991), despite a slightly lower number of patients reported in the study (746) an incidence of 52 cases is described. Whether this discrepancy is caused by observer variation or due to methodological inconsistencies is unclear.

Incidence of Abnormal CT

The reported incidence of abnormalities on CT scan in patients with severe traumatic brain injury (TBI) varies between 68%-94%. Data are summarized in Table 1.

Table 1 — Incidence of Abnormal CT Scans in Severe TBI Patients

First Author	Study Population	Incidence of Abnormal CT	
Sweet,[10] 1978	140 patients GCS ≤ 8	114/140	81.5%
Narayan,[8] 1981	133 severely head-injured patients	91/133	68.5
Holliday,[4] 1982	160 patients with closed head injury who had a CT scan within 24 hours of admission, in whom ICP was monitored	143/160	89
Van Dongen,[11] 1983	GCS ≤ 8	102/116	88
Lobato,[5] 1986	GCS ≤ 8	402/448	90
Eisenberg,[2] 1990	GCS ≤ 8 within 48 hours	708/753	94
Marshall,[6] 1991	GCS ≤ 8 Traumatic Coma Data Bank	694/746	93
Selladurai,[9] 1992	GCS ≤ 8	101/109	93
Fearnside,[3] 1993	GCS ≤ 8	275/315	87
European Nimodipine trial,[1] 1994	GCS ≤ 8	754/819	92
EBIC survey,[7] 1998	GCS ≤ 12	862/983	87

Prognostic Value

Class I and Class II studies show presence of abnormalities on CT to have a positive predictive value of 77%-78% with respect to unfavorable outcome in series of patients with severe head injury as defined by a GCS score of 8 or less. However, both studies already have an incidence just over 70% of unfavorable outcome in the overall population. The predictive value of presence of abnormalities on initial CT examination is therefore limited. The negative predictive value, that is, the relation between absence of abnormalities and favorable outcome, is of much greater importance and significance. Prognosis in patients without abnormalities on

initial CT examination is better than in the overall population of patients with severe head injury. Favorable outcomes are reported by Narayan, et al. (1981), Van Dongen, et al. (1983), Holliday, et al. (1982), and Lobato, et al. (1986), in 76%-83% of patients with a normal CT scan on admission.[4,5,6,11] Marshall, et al. (1991), in the report on the TCDB find 62% favorable outcome in patients with a normal CT scan on admission (diffuse injury I).[6] This lower percentage with respect to the other series reported is probably caused by the earlier determination of outcome (e.g., on discharge). Lobato, et al. (1986), however, showed that in approximately one-third of the patients with an initial normal CT scan new lesions may develop on subsequent CT examination. In these patients, ICP can be raised in up to 75% of cases. Patients developing such new lesions had a slightly less favorable outcome than when CT scan remained normal (65% vs 76%). Admission GCS score was not related to outcome in patients without abnormalities.[5] Holliday, et al. (1982), show the occurrence of raised ICP requiring treatment in 41% of patients with a normal CT scan on admission. In 85% of these patients there was severe concomitant pulmonary injury and/or post-traumatic hypotension.[4]

Conclusions

- Initial CT examination demonstrates abnormalities in approximately 90% of patients with severe head injury.
- Prognosis in patients with severe head injury with demonstrable pathology on initial CT examination is less favorable than when CT is normal.
- In patients with a normal CT on admission, outcome is primarily related to concomitant extracranial injuries.
- The absence of abnormalities on CT at admission does not preclude the occurrence of raised ICP, and significant new lesions may develop in 40% of patients.

Evidentiary Table — Abnormal CT and Outcome
Holliday,[4] 1982

Years of Study: 1976-1980

Description of Study: Study on predictive value of normal CT scan in head injury. Seventeen patients out of a series of 160 with severe head injury (GCS < 9) and ICP monitoring showing a normal CT.

Classification: Class III Study

Conclusions: Seven of 17 patients with a normal CT scan showed elevated ICP over 25 mm Hg. Six of these patients had major pulmonary injury. Overall outcome was good. In only 3 patients was the outcome unfavorable and this was due to extracranial pathology.

Evidentiary Table — Abnormal CT and Outcome

Van Dongen,[11] 1983

Years of Study: 1977-1979

Description of Study: Prospective, consecutive series examining prognostic value of CT in 121 patients with severe head injury.

Classification: Class I Study

Conclusions: Normal CT scan was noted in 14 patients (12%). Outcome in this small group was favorable (78.5%).

Outcome at 1 Year:	GOS 1, 2, 3	GOS 4, 5
Normal Scan	3%	11%
Abnormal Scan	76	1
PPV*: 78%		
*Positive predictive value		

Lobato,[5] 1986

Years of Study: 1977-1985

Description of Study: Forty-six patients out of a total series of 448 severe head injury with GCS score of 8 or less for at least 6 hours after injury showing no abnormalities on CT.

Classification: Class II Study

Conclusions: No abnormalities were noted in 10.2% of patients with severe head injury. Absence of abnormalities showed a PPV of 76% to favorable outcome. Twenty-four of the 46 patients with a normal CT scan on admission developed new lesions on subsequent examinations. 71% of these patients had a raised ICP. A moderate degree of raised ICP was only seen in 4 patients (8.5%) when the CT remained normal. Outcome was more unfavorable when new lesions developed.

Outcome at 6 Months:	Unfavorable	Favorable
GCS 3-4	4	11
GCS 5-8	7	24

Marshall,[6] 1991

Years of Study: 1984-1987

Description of Study: Prospective study of 746 patients with severe head injury.

Classification: Class II Study

Conclusions: Incidence of normal CT scan in this prospective series was 6.9%. There was favorable outcome on discharge in 61% of these patients.

Outcome at Discharge:	Unfavorable	Favorable
Normal CT Scan	20	32
(Diffuse Injury I		
Abnormal CT Scan	522	155
PPV: 77%		

Evidence for Classification

First Author	> 25	GOS 6 Months	Prospective	Indicator 24 hours	Statistics	Class
Lobato[5]	+	+	+	+	-	II
Holliday[4]	-	-	-	+	-	III
Van Dongen[11]	+	+	+	+	+	I
Marshall[6]	+	-	+	+	-	II

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B.   CT Classification of Head Injury and Its Prognostic Significance

Conventional classification of CT findings in severely head-injured patients differentiates between focal (extradural and subdural hematomas, as well as intracerebral hematomas and space occupying contusions) and diffuse head injuries (Gennarelli, et al., 1982).[3] Diffuse injuries according to this classification are defined by the absence of mass lesions, although small contusions without mass effect may be present. In terms of outcome, patients with diffuse injuries were found to have an intermediate prognosis when compared to patients with epidural

or subdural hematomas. While acute subdural hematomas with low GCS scores had a high mortality, diffuse injuries with higher GCS scores showed a low mortality and a high incidence of good recovery.

In practice, some confusion exists between this category of patients with diffuse lesions and the more neuropathologically oriented entity of diffuse axonal injury (DAI). DAI is based primarily on neuropathological hallmarks, characterized by wide-spread tearing of axones and/or small blood vessels. Radiologic criteria for diagnosis of DAI are small hemorrhagic lesions at the cortico-medullary junction, in the corpus collosum, in the midbrain, and in the brain stem, sometimes in conjunction with some intraventricular bleeding. DAI can sometimes be superimposed by generalized brain swelling (Adams, et al., 1982; Zimmerman, et al., 1978).

Lobato, et al. (1983), have expanded on the anatomical patterns of the conventional CT classification, outlining eight categories of injury, mainly subdividing patients with focal lesions (Table 1). This classification was shown to have a stronger predictive value than the conventional categorization. Outcome was significantly better in extradural hematoma without concomitant brain swelling, simple brain contusion, generalized swelling, and in the absence of lesions.

Table 1
Classification of CT Lesions and Outcome (Lobato,[4] 1983)

CT Findings	Number of Patients	Unfavorable Outcome (%)
No Lesions	28	32%
Extracerebral Hematoma	19	15
Extracerebral Hematoma and Swelling	27	100
Bilateral Swelling	42	12
Single Brain Contusion	45	22
Multiple Unilateral Contusion	32	84
Multiple Bilateral Contusion	42	54
Diffuse Axonal Injury	43	86

Marshall, et al. (1991), in the publication on the Traumatic Coma Data Bank, propose a new classification in which the category of diffuse injury is further expanded, taking into account signs of raised ICP (i.e., compressed or absent basal cisterns), midline shift, and the presence of mass lesions (Table 2).

Table 2
CT Classification TCDB

Category	Definition
Diffuse Injury I (no visible pathology)	No visible intracranial pathology seen on CT scan.
Diffuse Injury II	Cisterns are present with midline shift 0-5 mm and/or lesions densities present, no high or mixed density lesion > 25 cc, may include bone fragments and foreign bodies.
Diffuse Injury III (swelling)	Cisterns compressed or absent with midline shift 0-5 mm, no high or mixed density lesion > 25 cc.
Diffuse Injury IV (shift)	Midline shift > 5 mm, no high or mixed density lesion > 25 cc.
Evacuated Mass Lesion	Any lesion surgically evacuated.
Non-Evacuated Mass Lesion	High or mixed density lesion > 25 cc, not surgically evacuated.

The frequency of occurrence of the various CT categories according to this classification in three large series of head injury patients is shown in Table 3.

Table 3
Incidence of CT Categories in Head Injury (Marshall,[5] 1991)

	TCDB n = 746		European Nimodipine Trial n = 819		EBIC Survey n = 983	
Diffuse Injury I	52	7%	69	8.4%	121	12%
Diffuse Injury II	177	23.7	270	32.9	273	28
Diffuse Injury III (swelling)	153	20.5	89	10.9	101	10
Diffuse Injury IV (shift)	32	4.2	31	3.8	21	2
Evacuated Mass Lesion	276	37	314	38.3	467	48
Non-Evacuated Mass Lesion	36	4.8	36	4.4		

A clear correlation between CT classification and outcome was shown on analysis of the TCDB (Table 4).

Table 4
CT Classification and Outcome on Discharge (Marshall,[5] 1991)

	Number of Patients	Unfavorable Outcome (D, VS, SD)	Favorable Outcome (MD + GR)
Diffuse Injury I	52	38%	62%
Diffuse Injury II	177	65	35
Diffuse Injury III	153	84	16
Diffuse Injury IV	32	94	6
Evacuated Mass Lesion	276	77	23
Non-Evacuated Mass Lesion	36	89	11

Walder, et al. (1995), have compared the predictive value of the TCDB classification to the worst applicable severity code from the Abbreviated Injury Score (AIS). A high correlation was found between AIS and outcome at six months, the TCDB classification and outcome as well as between GCS score and outcome. The predictive power for favorable outcome was shown to be greater for the AIS score than for the TCDB classification (Table 5), with a PPV of 95% toward favorable outcome in the AIS scores 0-3. Conversely an AIS score of 5 was shown to have a PPV of 71% toward the outcome categories dead or vegetative.

Table 5
Predictive Power of AIS, TCDB, CT Classification, and GCS score (Walder[7], 1995)

	Statistical Value of Prediction Sensitivity	Specificity	Positive Predictive Value	Likelihood Ratio	Percentage Correct Predictions
AIS 0-3	40%	98%	95%	25:1	73%
TCDB					
Classification I-IV	51	86	75	3:6:1	66
GCS score 6-8	57	69	59	1:9:1	64

Conclusions
- A strong correlation exists between the worst intracranial AIS severity code of the initial CT in severe head injury and outcome at six months.
- The TCDB CT classification is strongly correlated to outcome.

Recommendations for Further Research
- Investigation of interobserver reliability in classifying severe head injury according to CT scan.
- There should be further investigation concerning predictive power of the intracranial AIS severity code of the initial CT.

Evidentiary Table — CT Classification and Outcome

Gennarelli,[3] 1982

Description: Retrospective analysis of 1,107 patients with severe head injury from seven centers analyzing outcome and type of CT lesion.

Classification: Class III Study

Conclusions: Differentiation of focal versus diffuse injuries being split into two categories of severity: marked heterogeneity of outcome; type of lesion as important on outcome as GCS score. Rank order of prognosis: subdural hematoma < diffuse injuries < extradural hematoma.

Lobato,[4] 1983

Years of Study: 1977-1982

Description: Study of a consecutive series of 277 severely head-injured patients.

Classification: Class II/III Study

Conclusions: Patients with pure extracerebral hematoma, single brain contusion, generalized brain swelling, and normal CT scans had a significantly better outcome than patients developing acute hemispheric swelling after operation for a large extracerebral hematoma or patients with multiple brain contusion, either unilateral or bilateral, and patients with DAI.

Marshall,[5] 1991

Years of Study: 1984-1987

Description: Prospective study of a consecutive series of 746 severely head- injured patients in four centers (TCDB).

Classification: Class II Study

Conclusions: CT classification has clear prognostic value.

Walder,[7] 1995

Years of Study: 1986-1988

Description: Prospective series of 109 severely head injured patients (GCS ≤ 8) evaluating predictive value of worst applicable intracranial severity score from the AIS and CT classification according to the TCDB.

Classification: Class I Study

Conclusions: The AIS based on initial CT scan provides useful prognostic information in patients with severe head injury. The predictive value of an AIS 0-3 for favorable outcome is higher than the TCDB classification.

Evidence for Classification

Author	> 25 patients	GOS/ mortality 6 months	Prospective	Indicator within 24 hours	Statistics	Class
Gennarelli[3]	+	-	-		-	III
Lobato[4]	+	+	+	-	-	II/III
Marshall[5]	+	-	+	+	-	II
Walder[7]	+	+	+	+	+	I

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C. Individual CT Scan Characteristics

Definition of parameter: Although the status of the basal cisterns is one of the best studied CT parameters of prognostic significance, it remains ill defined. Most studies concerning the state of the basal cisterns focus on the perimesencephalic cisterns. Authors describe absent, compressed, or open cisterns. Only two authors give definitions of the parameter studied.[11, 15]

- Partial obliteration: Cisterns visible as hypodense slits, usually in one hemisphere.
- Complete obliteration: Cisterns no longer visible as CSF (cerebrospinal fluid) spaces.

Liu, et al. (1995), suggest adding aspects concerning density and deformation of the brain stem in a grading system to the basal cisterns. They describe a good correlation between their proposed grading scale (Grades 0-5) and outcome.[9]

Reliability of Scoring Basal Cisterns

No interobserver variation studies have been reported concerning the reliability of scoring of the basal cisterns.

Incidence

An overview of the incidence of compressed or absent basal cisterns in reported series of patients with severe head injury is shown in Table 1.

Table 1
Incidence of Compressed or Absent Basal Cisterns

First Author	Patient Population	Incidence	
Van Dongen,[15] 1983	GCS ≤ 8	80/116	68.9%
Teasdale,[12] 1984	diffuse head injury in coma	19/37	51
Toutant,[14] 1984	GCS ≤ 8	118/218	54
Cordobes,[4] 1986	78 patients with diffuse axonal injury	59/78	76
Colquhoun,[3] 1989	comatose head injury	49/60	81.6
Eisenberg,[5] 1990	GCS ≤ 8 within 48 hours	413/753	58
Selladurai,[11] 1992	GCS ≤ 8	74/109	67.8
European Nimodipine Trial[1]	GCS ≤ 8	472/819	57.6

Association with Other Prognostic Indicators

Two studies describe a strong association between status of the basal cisterns and pupil reactivity.[12,15] Other authors report an association with the GCS score[2,14] and with the presence of focal lesions[2] or with a history of early hypoxic or hypotensive insults.[5]

Table 2
Pupil Reactivity and Status of Basal Cisterns

Status of Cisterns	Pupil Reactivity	
	One or Both Reacting	Neither Reacting
Cisterns Present	17%	1%
Cisterns Absent	12	7

(Teasdale,[12] 1984)

Status of Cisterns	Pupil Reactivity	
	Both Reacting	One or None
Partially or Completely Open	40%	17%
Completely Obliterated	14	44

(Van Dongen,[15] 1983)

1. Status of Basal Cisterns and Other CT Indicators of Raised ICP

Compression or absence of the basal cisterns on CT scan is considered one of the indicators of raised intracranial pressure (ICP).[7,10,13] Other signs of raised ICP include obliteration of the third ventricle and the presence of small ventricles, often considered indicative of diffuse brain swelling in the absence of midline shift. Some authors combine the status of the third ventricle and that of the basal cisterns in evaluating prognostic significance. Teasdale, et al. report that

the third ventricle usually becomes obliterated before the basal cisterns.[13] In the study by Lang, et al. (1994), on 118 patients with diffuse traumatic brain swelling, however, no direct relation was seen between the status of the third ventricle and that of the basal cisterns. When the third ventricle was not visible the basal cisterns remained present in more than half of the patients.[8]

The assessment of the lateral ventricles as being "slitlike" is debatable and in the absence of knowledge of the pretraumatic size of the ventricles it is difficult to attach too much importance to the size of the ventricles. Especially in children the size of the lateral ventricles may normally be small.[15] The main CT parameters indicating raised ICP, therefore, are the status of the third ventricle and that of the basal cisterns. This is confirmed by two Class II studies[5,12] and one Class III study.[3]

Prognostic Value

One Class I,[15] four Class II, [4,5,11,12] and various Class III studies[2,3,14,16] describe an association between compression or absence of basal cisterns and unfavorable outcome. Van Dongen, et al. (1983), in a series of 116 comatose head injured patients in whom CT was performed, showed a 97% positive predictive value for unfavorable outcome when the cisterns were completely obliterated.[15] In a stepwise forward selection of features using the multinominal independence model, the state of the basal cisterns together with lesions of the brain parenchyma emerge as a powerful combination of predictors. Sharp predictions based on these two variables could be made in 30% of cases, all predictions related to the probability of death. The predictive performance of a set of four common CT combinations, using the state of the basal cisterns as the basic discriminative feature was remarkable, allowing predictions in 63% of cases of which 93% were accurate. However, when combining a set of CT features with clinical features including pupil reactivity, best motor response, and age, the state of the basal cisterns was not selected as a discriminating parameter. This was caused by overlap in prognostic information in relation to the pupil reactivity.

In the preliminary report on CT features in the national pilot TCDB, the ominous value of compressed or absent basal cisterns in severe head injury was further demonstrated.[14] Mortality rate when cisterns were absent was 77%; 39% when cisterns were compressed; and only 22% when cisterns were open. A relatively greater importance of cisterns in the risk of poor outcome was shown among patients with a GCS score of 6 to 8. These data were confirmed in the report by Eisenberg, et al. (1990), on the initial CT findings from the NIH TCDB.[5] In this study the risk of dying in severely head-injured patients was increased twofold if the mesencephalic cisterns were compressed or obliterated. The risk of elevated ICP for those patients with abnormal cisterns was increased threefold compared to patients with normal cisterns. The value of the status of the basal cisterns as an indicator for presence of increased ICP has been confirmed in many other studies. Cordobes, et al. (1986), in a small study of 78 patients with post-traumatic diffuse axonal injury, showed increased ICP to be present in 50% of the patients with CT scan evidence of ventriculocisternal collapse and this phenomenon was also associated with an unfavorable outcome.[4] Similar conclusions were drawn by Colquhoun, et al. (1989), and Teasdale, et al. (1984).[3,12]

Yanaka, et al. (1993), in a retrospective study on 170 patients with acute subdural hematoma also show in these patients a positive predictive value of 77% to unfavorable outcome in the presence of compressed basal cisterns.[16]

Conclusions

- Compressed or absent basal cisterns indicate a threefold risk of raised ICP.
- Status of basal cisterns is related to outcome.
- Mortality is increased two- to threefold in the presence of compressed or absent basal cisterns.
- Strong association exists between the status of the basal cisterns and pupil reactivity.
- Some association of the status of the basal cisterns is reported with GCS score, presence of focal lesions, or early hypoxic and hypotensive insults.

Recommendation for Future Research

- Define and test better definition of open, partially compressed, or absent basal cisterns.
- Determine of observer reliability.
- Need to further investigate the independent value of the status of basal cisterns as predictive parameter.
- Need to further investigate the relative value of status of basal cisterns and compression of third ventricle as indicator of raised ICP and CT-predictor.

Evidentiary Table: Basal Cisterns and Outcome

Van Dongen,[15] 1983

Years of Study: 1977-1979

Description: Prospective consecutive series examining prognostic value of CT in 121 patients with severe head injury.

Classification: Class I Study

Conclusions: Status of the basal cisterns was shown to be a powerful prognostic indicator, but is strongly related to pupil reactivity. Based on status of the basal cisterns and the presence or absence of lesions in the brain parenchyma, sharp predictions were possible in 30% of cases. Adding CT features to clinical features increased the rate of sharp predictions from 48% to 62%.

Outcome 12 Months:

	Unfavorable	Favorable
Open Cisterns	12	19
Compressed Cisterns	10	11
Absent Cisterns	57	2

PPV = 84% (67/80)

Evidentiary Table: Basal Cisterns and Outcome (continued)

Teasdale,[12] 1984

Description: Prospective analysis of 37 patients with severe diffuse injury.

Classification: Class II Study

Conclusions: Compression of third ventricle and basal cisterns closely correlated with increased ICP and worse prognosis. Association between pupil reactivity and status of the basal cisterns.

Status Basal Cisterns/Third Ventricle:

	Unfavorable Outcome	Favorable Outcome
Present	9	9
Absent	15	4

Toutant,[14]1984

Years of Study: 1981-1982

Description: Prospective study of 218 patients with severe head injury (GCS < 8) from the pilot phase of the National Traumatic Coma Data Bank analyzing prognostic importance of basal cisterns.

Classification: Class III Study

Conclusions: Mortality was doubled when basal cisterns were compressed and increased threefold when absent. Prognostic value remained strong after adjusting for GCS score. Status of the cisterns was more important in patients with higher GCS scores.

	Unfavorable Outcome	Favorable Outcome
Open Cisterns (n = 82)	44	56
Compressed Cisterns (n = 70)	64	46
Absent Cisterns (n = 48)	85	15

Cordobes,[4] 1986

Years of Study: 1977-1984

Description: Selected series of 78 patients with diffuse axonal injury.

Classification: Class II Study

Conclusions: Collapsed or absent basal cisterns present in 59 out of 78 (75%) patients. Compression or absence of basal cisterns is correlated to unfavorable outcome

Outcome at 6 Months:

	Unfavorable	Favorable
Open Cisterns	12	7
Compressed Cisterns	20	7
Absent Cisterns	29	
PPV = 87%		

Evidentiary Table: Basal Cisterns and Outcome (continued)

Colquhoun,[3] 1989

Years of Study: 1985-1986

Description: Retrospective study on prognostic significance of third ventricle and basal cisterns in 60 patients whose CT scan showed evidence of primary brain injury.

Classification: Class III Study

Conclusions: Compression and obliteration of the third ventricle and basal cisterns were shown to have a close correlation with raised ICP and poor prognosis.

Outcome at 6 Months:

	Unfavorable	Favorable
Normal Third Ventricle and Basal Cisterns	2	9
One or Both Compressed	10	8
One or Both Absent	26	5

Eisenberg,[5] 1990

Years of Study: 1984-1987

Description: CT features studied in National Traumatic Coma Data Bank.

Classification: Class II Study

Conclusions: Compressed cisterns were noted in 58% of patients. Abnormal cisterns indicate a threefold risk of abnormal ICP and a threefold increase in mortality. An association exists between diffuse swelling as defined by abnormal cisterns and/or small ventricles and early hypoxia/hypotension.

Selladurai,[11] 1992

Years of Study: 1989-1991

Description: Prospective consecutive series of 109 patients with severe head injury studied within 48 hours of injury.

Classification: Class II Study

Conclusions: Status of basal cisterns strongly correlated to outcome. Complete obliteration of basal cisterns doubles unfavorable outcome (34% to 81%)

Outcome at 6 Months:

	Unfavorable	Favorable
Patent Basal Cisterns	13	22
Partial Obliteration	16	10
Complete Obliteration	38	10
PPV = 73%		

Evidentiary Table: Basal Cisterns and Outcome (continued)

Athiappan,[2] 1993

Years of Study: 1990-1992

Description: Study of 107 patients with moderate and severe head injury (GCS < 11). CT examination within 24 hours.

Classification: Class III Study

Conclusions: Obliteration of basal cisterns increases mortality threefold (27% to 76%). Correlation between status of the basal cisterns and type of pathology and GCS score.

Outcome at 3 Months:

	Dead	**Alive**
Normal Cisterns	17	45
Obliterated Cisterns	35	10

Yanaka,[16] 1993

Years of Study: 1985-1992

Description: Retrospective study of 170 patients with acute subdural hematoma, identifying clinical and radiologic prognostic variables.

Classification: Class III Study

Conclusions: Obliteration of cisterns indicates a poorer prognosis. Rating of prognostic effectiveness:
1. Pupils
2. Obliteration ambient cistern
3. Midline shift
4. Age
5. GCS score

Prognostic equations including the status of the ambient cisterns were formulated; association existed between the status of the basal cisterns and presence of contusions.

Status of Basal Cisterns:

	Poor Outcome	**Functional Outcome (3 Month)**
Basal Cisterns Open	12	63
Basal Cisterns Compressed	73	22
PPV = 77%		

Evidentiary Table: Basal Cisterns and Outcome (continued)

Liu,[10] 1995

Years of Study: 1985-1987

Description: Retrospective study on 334 consecutive cases of head injury evaluating grading system of status of basal cisterns and brainstem changes versus outcome.

Classification: Class III Study

Conclusions: Good correlation between proposed grading system and outcome.

Outcome 12 Months:

	Unfavorable	Favorable
Grade 0	9	25
Grade 1	6	7
Grade 2	6	8
Grade 3	17	8
Grade 4	4	1
Grade 5	48	4

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2. Traumatic Subarachnoid Hemorrhage

Definition of parameter: presence of blood in the subarachnoid space, either over the convexity or in the basal cisterns.

Reliability of Scoring

No formal investigation has been performed concerning the reliability of scoring this parameter. In the European Nimodipine trial a difference of opinion concerning the presence or absence of traumatic subarachnoid hemorrhage (tSAH) was reported between the review committee and investigators in "a number of cases." In the paper by Harders, et al. (1996), on treatment of tSAH with Nimodipine, in patients of varying clinical severity the review committee could not confirm the presence of subarachnoid blood on the initial CT scan in 26 of the 123 patients (21%) included in the study.[7] Kakarieka (1997) in his monograph on tSAH concludes that the CT findings of tSAH do not have a high reliability.[8] This conclusion is supported by El Tabou, et al. (1995).[16] Greene, et al. (1995), however, although not directly reporting results, describe in the presence of tSAH a 94% interobserver reliability in grading the degree of tSAH.[6]

Incidence and Grading

An overview of the reported incidence of tSAH in patients with head injury of varying severity is shown in Table 1.

Table 1

Incidence of Subarachnoid Hemorrhage

First Author	Patient Population	Incidence tSAH		Remarks
Eisenberg,[3] 1990	GCS ≤ 8 (within 48 hours n = 753		40 %	No absolute numbers reported
Selladurai,[15] 1992	GCS ≤ 8	32/109	29.4	
Vollmer,[19] 1991	GCS ≤ 8	237/588	40	TCDB
Kakarieka,[10] 1994	Severe head injury in adults (GCS ≤ 8)	268/819	33	Population European Nimodipine Trial
Lang,[11] 1994	Head injury with diffuse brain swelling (children and adults)	46/118	39	tSAH + intraventricular hemorrhage
Gaetani,[6] 1995	Head injury GCS 3-15	148/515	28.7	
Greene,[7] 1995	GCS 3-15 GCS 3-9	355/3157 178/704	11 26.6	Higher incidence of tSAH in more severe injuries
Taneda,[18] 1996	Head injury GCS 3-15	130/883	14.7	
Murray,[13] 1998	EBIC* survey GCS 3-12	385/953	40	EBIC Survey
Marshall,[12] 1998	GCS 4-12	568/1067	53	International Tirilazad Trial

*EBIC = European Brain Injury Consortium

A few investigations have been performed concerning the degree and localization of blood in the subarachnoid space. Most investigators studying the influence of the extent of SAH use the grading system proposed by Fisher et al. for patients with spontaneous SAH. Greene, et al. propose a different grading system, specific for trauma patients (Table 2).

Table 2

Grading Systens for Subarachnoid Hemorrhage

Fisher	Greene
Grading of SAH:	Proposed grading system for scoring tSAH:
Group 1: no blood	Grade 1: thin (≤ 5 mm)
Group 2: layer < 1 mm thick	Grade 2: thick (> 5 mm)
Group 3: layer > 1 mm thick	Grade 3: thin (≤ 5 mm) with mass lesion
Group 4: ventricular involvement	Grade 4: thick (> 5 mm) with mass lesion

There is no consistent reporting on the location of subarachnoid blood after trauma. Some authors describe the location in various basal cisterns, in the fissures, on the tentorium, or over the convexity,[10] others only differentiate between the presence of blood in basal cisterns, over the convexity, or a combination of the two.[6] The most frequent location is over the convexity, followed by the fissures and basal cisterns. Location of tSAH in the Sylvian fissure has been reported to be indicative of the development of local contusions.[16]

Associations with Other Lesions and/or Prognostic Variables

Patients with tSAH have a higher incidence of contusions, acute subdural hematomas, intraventricular hemorrhage, and increased ICP signs. Kakarieka reports contusions as associated lesions in 77% of patients with tSAH and acute subdural hematoma in 44% of patients. Gaetani, et al. (1995), report an association of contusions or other intracranial lesions in 63% of patients.[6] Both Gaetani, et al. (1995), and Greene, et al. (1995), report an association between admission GCS score and CT grade of tSAH.[6, 7]

Traumatic SAH as Prognostic Variable

There is Class I evidence supporting a 72% PPV for unfavorable outcome in patients with CT scans showing tSAH in the suprasellar or ambient cisterns. A 78% PPV of an unfavorable outcome is associated with Fisher's Grade 4 tSAH.

Although attention was already called to the presence of SAH in severely head-injured patients as an important risk factor in the Japanese literature in 1983,[14] it is only recently that this aspect has gained attention in the international literature. Takaneka, et al. (1990), described the poor prognostic significance of the presence of tSAH, especially in the perimesencephalic region in a limited series of 30 patients with severe shearing injuries.[17] Among 17 patients with tSAH there were 11 cases with perimesencephalic hemorrhage of which 10 died. Selladurai, et al. (1992), in a consecutive series of 109 patients with severe head injury also report a significant correlation between the presence of CT visible subarachnoid blood and poor outcome (p = 0.002).[15] The presence of tSAH is correlated to the occurrence of secondary deterioration[11]; degree and location of tSAH have been reported to be an indication of delayed ischemic symptoms, caused by vasospasm (Table 3).

Table 3
tSAH and Delayed Ischemia: Relation Between Degree of tSAH and Occurrence of Delayed Ischemia (Taneda,[18] 1996)

Degree of tSAH	Number	Delayed Ischemia	
		yes	no
small (< 1 mm)	101	3	98
extensive (> 1 mm)	29	7	22
	130	10	120

In the population of the U.S. Traumatic Coma Data Bank an incidence of tSAH of 40% was reported. A twofold increase in the risk of dying was noted in the group with subarachnoid blood. The presence of subarachnoid blood also appeared to predict an abnormal ICP and the predictive value of tSAH was shown to be additive to other CT scan parameters, such as the presence of abnormal cisterns, mass lesion, and midline shift. Eisenberg, et al., showed CT scan parameters to be of greater prognostic significance than clinical variables, such as age and post-resuscitation GCS score, when employing a predictive model including CT scan features and clinical variables.[3] Traumatic SAH rated second to effacement of the basal cisterns. The calculated odds ratios were 2.13 for tSAH, versus 1.03 for age and 0.71 for post-resuscitation GCS score. Upon analyzing the relative predictive value of CT parameters alone, tSAH also rated second to effacement of the basal cisterns. In the report on the European trial on Nimodipine in severe head injury, a trend toward a favorable effect in the Nimodipine-treated

group was seen in patients exhibiting tSAH (1994). The clinical significance of the finding of subarachnoid blood on the CT scan in this series has been further analyzed and reported by Kakarieka, et al. (1994).[9] The outcome of patients with traumatic SAH was significantly worse than that of patients whose first CT scan did not show subarachnoid blood. The outcome was unfavorable in 60% of tSAH patients compared to 30% in patients without SAH (p < 0.01). Logistic regression analysis showed the presence of subarachnoid blood to be one of the most important factors of independent prognostic significance (odds ratio 0.29). The presence of tSAH was shown to have a PPV of 60% for an unfavorable outcome. When differentiated to the location of tSAH, the presence of blood in the various basal cisterns demonstrated a PPV of 69% to 72% and blood over the convexity had a PPV of 61% (Table 4). Gaetani, et al. (1995) also show the presence of tSAH in the basal cisterns to be more indicative of unfavorable outcome than tSAH over the convexity.[6]

A larger extent of SAH is related to poorer outcome.[8,9,18] Kakarieka shows in Fisher's Grade 3 a PPV of 62% and in Fisher's Grade 4 a PPV of 79% toward unfavorable outcome (Table 5); Harder's study (1996) shows a PPV of 78% to unfavorable outcome in Fisher's Grades 3 and 4. The independent predictive value of tSAH has also been found by Greene, et al. (1995), with a 78% PPV for the presence of tSAH and poor outcome in patients with severe head injury.[7] However, in patients with mild and moderate head injury the adverse influence of tSAH on outcome was much less pronounced. In patients with acute subdural hematomas, Domenicucci, et al. (1998), report a PPV of 86% to mortality in the presence of tSAH.[2]

Table 4
Distribution of tSAH and Outcome (Kakarieka,[9] 1997)

Distribution of tSAH	Unfavorable	Favorable	PPV
No tSAH	87	193	31%
Convexity	56	38	60
Interhemispheric Fissure	38	17	69
Lateral Sylvian Fissure	46	22	68
Suprasellar Cisterns	21	8	72
Ambient Cisterns	26	10	72
Quadrigeminal Cisterns	9	4	69

(n= 409)

Table 5
Relation Between Degree of tSAH and Outcome (Kakarieka,[9] 1997)

Fisher Grade	Unfavorable	Favorable
1	87	193
2	23	26
3	29	18
4	26	7

(n= 409)

Conclusions

- tSAH is a frequent occurrence in severe head injury (26%-53%).
- Most frequent location is over the convexity.
- Mortality is increased twofold in the presence of tSAH.
- Presence of blood in the basal cisterns carries a PPV to unfavorable outcome of approximately 70%.
- Extent of tSAH is related to outcome.
- tSAH is a significant independent prognostic indicator.

Recommendations for Future Research

- There should be further development of a grading system for tSAH, specific to head injury
- There should be observer reliability studies using grading systems
- There should be identification of the relative prognostic value of grading and location of tSAH

Evidentiary Table: Traumatic Subarachnoid Hemorrhage and Outcome

Shigemori,[16] 1990

Year of Study: Unknown

Description: Study of 20 patients with tSAH; GCS scores 3-15.

Classification: Class III Study

Conclusions: Most frequent location is the Sylvian fissure; this location may be indicative of development of local contusions. Extensive hemorrhage in basal cisterns indicates a poorer outcome.

Takaneka,[17] 1990

Year of Study: Unknown

Description: Retrospective study on 30 patients with shearing injury.

Classification: Class III Study

Conclusions: Presence of tSAH indicates a poor prognosis.

Outcome	Unfavorable	Favorable
tSAH+	16	1
tSAH-	4	9

Evidentiary Table: Traumatic Subarachnoid Hemorrhage and Outcome (continued)

Eisenberg,[3] 1990

Years of Study: 1984-1987

Description: Prospective consecutive series of 753 patients with non-penetrating severe head injury from the NIH Traumatic Coma Data Bank in whom admission CT examination was performed.

Classification: Class II Study

Conclusions: tSAH occurs in 29 of 753 (39%). Mortality increases by twofold in presence of tSAH (26% to 55%). Presence of tSAH is predictive of raised ICP. The presence of tSAH has independent predictive value.

Selladurai,[15] 1992

Years of Study: 1989-1991

Description: Prospective consecutive series of 109 patients with severe head injury studied within 48 hours of injury.

Classification: Class III Study

Conclusions: Presence of CT visible subarachnoid blood correlates with a poor outcome ($p \leq 0.0002$). Mortality increased twofold in the presence of tSAH.

Outcome 6 Months	Unfavorable	Favorable
tSAH +	29	3
tSAH -	38	39

Lang,[11] 1994

Years of Study: 1978-1982

Description: Selected, prospective series of 118 patients (59 adults and 59 children), secondarily referred with diffuse brain swelling as defined by absent basal cisterns or absent third ventricle without a shift of more than 6 mm.

Classification: Class III Study

Conclusions: tSAH or intraventricular hemorrhage occurred in 46 of the 118 cases and is significantly correlated to the occurrence of secondary deterioration.

Evidentiary Table: Traumatic Subarachnoid Hemorrhage and Outcome (continued)

Kakarieka,[10] 1994

Years of Study: 1989-1991

Description: Population consisted of patients with severe, non-penetrating head injury enrolled in the randomized, prospective, double-blind study on the effect of Nimodipine in severe head injury. Prognostic evaluation on basis of 414 placebo-treated patients.

Classification: Class I Study

Conclusions: Incidence of tSAH was 33% and adversely influenced outcome. Unfavorable outcome in the presence of tSAH was doubled (30% to 60%). Logistic regression analysis showed tSAH to be one of the most important prognostic factors. The number of hypotensive episodes was higher in patients with tSAH.

Outcome at 6 Months	Unfavorable	Favorable
tSAH+	87	58
tSAH-	81	188

Gaetani,[6] 1995

Years of Study: 1992-1994

Description: Retrospective series of 148 patients with head injury of varying degrees (mild, moderate, and severe) with demonstrated presence of subarachnoid blood on CT examination. Evaluation of clinical significance of degree and extent of SAH was according to Fisher's grade.

Classification: Class III Study

Conclusions: Degree of tSAH is significantly related to GCS score on admission and to outcome. Distribution of tSAH is also of prognostic significance. Patients with blood both over the convexity and in the basal cisterns have worse outcomes.

Outcome at 6 Months

Distribution of tSAH	Unfavorable	Favorable
Spaces Over Convexity	37	54
Basal Cisterns	17	19
Mixed	17	4

Evidentiary Table: Traumatic Subarachnoid Hemorrhage and Outcome (continued)

Greene,[7] 1995

Years of Study: 1988-1991

Description: Retrospective cohort study of 252 patients with head injury of variable degrees showing CT evidence of tSAH.

Classification: Class III Study

Conclusions: Degree of SAH as defined by proposed grading system is related to admission GCS score and outcome at discharge. Stepwise regression analysis confirmed the independent predictive value of the presence of tSAH.

CT Grade of tSAH

	Outcome at Discharge Severe Head Injury GCS 3-9		Outcome at Discharge Mild and Moderate GCS 10-12	
	Unfavorable	Favorable	Unfavorable	Favorable
Grade 1	11	7	1	34
Grade 2	8	3	0	6
Grade 3	45	16	7	35
Grade 4	48	6	4	21

PPV = 78% (112/144)

Harders,[8] 1996

Year of Study: 1994

Description: Prospective, randomized trial on the effect of Nimodipine in 61 patients with tSAH of varying severity (n = 61).

Classification: Class II Study

Conclusions: Most frequent location of blood in the subarachnoid space is over the convexity (67%); less frequently in the basal cisterns (40%). Some relationship between the presence of subarachnoid blood and contusions or acute subdural hematoma. The amount of blood as graded by the Fisher system was related to poorer outcome.

Relation Between Degree of tSAH and Outcome:
Outcome at 6 Months:

Fisher Grade	Unfavorable	Favorable
1	0	14
2	6	13
3	15	6
4	7	0

Evidentiary Table: Traumatic Subarachnoid Hemorrhage and Outcome (continued)

Taneda,[18] 1996

Years of Study: 10-year period

Description: Prospective study of 130 patients with head injury of varying severity (mild, moderate, severe) with CT evidence of subarachnoid blood on admission.

Classification: Class III Study

Conclusions: Ten patients in this series developed delayed ischemic symptoms. The degree and location of tSAH was a predictive indicator of delayed ischemic symptoms. In the patients with symptoms of delayed ischemia, vasospasm was angiographically proven. Mortality was significantly higher in the presence of more subarachnoid blood.

tSAH	Number	Outcome at 3 Months	
		Dead	Alive
Small (< 1 mm)	101	27	74
Extensive (> 1 mm)	29	17	12

Domenicucci,[2] 1998

Years of Study: 1993 and 1994

Description: Retrospective study of 31 patients with severe head injury and ASDH. Analysis of subarachnoid spaces and shift.

Classification: Class III Study

Conclusions: Overall mortality was 68%; in the presence of tSAH; 86%.

Outcome at 6 Months

	Dead	Alive
Absence of tSAH or Undetectable Subarachnoid Space	9	8
tSAH+	12	2

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Table 2
Description of Studies

First Author	> 25 patients	GOS/ Mortality 6 Months	Prospective	Indicator Measured within 24 Hours	Statistics	Class
Lang,[11] 1994	+	-	+	?	-	III
Eisenberg,[3] 1990	+	-	+	+	+	II
Selladurai,[15] 1992	+	+	+	-	-	III
Gaetani,[6] 1995	+	+	-	+?	-	III
Taneda,[18] 1996	+	-	+	+	-	III
Shigemori,[15] 1990	-	-	-	+	-	III
Greene,[7] 1995	+	-	-	+	+	III
Harders,[8] 1996	+	+	+	+	-	II
Kakarieka,[10] 1994	+	+	+	+	+	I
Takaneka,[17] 1990	+	-	-	+	-	III
Domenicucci,[2] 1998	+	-	-	+	-	III

3. Midline shift

Definition of Parameter: The presence of midline shift is defined as the absolute distance (in mm) that midline structures of the brain are displaced in respect to the midline determined by averaging the distance between the inner tables of the skull. Most authors describe the degree of displacement of the septum pellucidum relative to the midline. Ross, et al. (1989) further examined shift of the pineal gland and of the aquaduct.[10]

Reliability of Scoring Midline Shift

No formal observer reliability studies concerning the scoring of midline shift were found. It is remarkable that in three manuscripts authors quantify the degree of midline shift down to .1 mm.[5,6,16] At the same time, Young states that two observers would agree down to the limit of 1 mm.[5]

The degree of midline shift and quantification of this is highly variable in the various reports. An overview of the various classifications, as mentioned by the different authors, is given in Table 1.

Table 1
Variable Classification of Shift Between Authors

First Author	Classification of shift
Kotwica and Brzezinski,[5] 1993	< 1.5 mm, 1.5-3 mm, ≥ 3 mm
Young,[16] 1981	< 4.1 mm, ≥ 4.1 mm
Lobato,[8] 1991	≤ 5 mm, 6-15 mm, ≥ 15 mm
Quattrochi,[9] 1991	Absent / Present
Lipper,[6] 1985	< 3.8 mm, ≥ 3.8 mm
Fearnside,[4] 1993	< 5 mm, 5-10 mm, >10 mm
Selladurai,[12] 1992	< 5 mm, 5-10 mm. > 10 mm
Eisenberg,[3] 1990	≤ 3 mm, > 3 mm
Vollmer,[19] 1991	≤ 5 mm, > 5 mm

Incidence

Midline shift is a relatively frequent occurrence in series of patients with severe head injury. An overview of the reported incidence is shown in Table 2.

Table 2
Incidence of Midline Shift

First Author	Patient Population	Incidence		Remarks
Young,[16] 1981	170 head-injured patients with focal neurological deficit or unconsciousness for 6 hours	69/170 25/170	40.6% 14.7	All shift Shift ≥ 4.1 mm
Lipper,[6] 1985	128 patients with severe head injury	46/128	36	Shift ≥ 3.8 mm
Eisenberg,[3] 1990	GCS ≤ 8 within 48 hours	255/753	34	Shift ≥ 3 mm
Lobato,[8] 1991	211 patients who talk and deteriorate	89/211 46/211	42.2 21.8	Shift 6-15 mm Shift > 15 mm
Quattrocchi,[9] 1991	56 patients with intracranial hematoma and 19 patients with normal CT	28/75	37.3	
Selladurai,[12] 1992	109 patients with severe head injury	27/109 17/109	24.7 15.6	Shift 5-10 Shift > 10 mm
Athiappan,[1] 1993	107 patients with moderate and severe head injury	35/107	32.7	
Kotwica,[5] 1993	200 adult patients with acute subdural hematoma	96/200 63/200	48 31.5	Shift 1.5-3 mm Shift ≥ 3 mm
Vollmer,[14] 1991	661 patients with severe head injury (GCS ≤ 8) in whom CT was available	176/597	29	Shift > 5 mm

Association with Other Prognostic Variables

A few studies describe the relative importance of the degree of midline shift in respect to other prognostic CT variables. A relation to the presence or absence of focal lesions[5] and the GCS score[16] is described. Athiappan, et al. (1993), found the prognostic value of midline shift more important in patients with single contusions or intracerebral hematoma than for those with multiple lesions and extraaxial or subdural hematoma.[1] They conclude that the presence of midline shift is better correlated with the type of pathology and GCS score, rather than that the degree of midline shift can be taken alone.

Prognostic Value of Midline Shift

Class I and Class II evidence demonstrate the prognostic significance of both presence or absence as well as degree of midline shift in patients with severe head injury[3, 4, 6, 14]; Class II evidence supports the greatest prognostic value of brain shift in patients with GCS scores 5-7.[16] In the study by Fearnside, et al. (1993), midline shift and other CT parameters were third in strength (after age and motor score) in a logistic regression analysis of the relative importance of prognostic variables.[4] Lobato, et al. (1991), showed in patients with secondary deterioration to coma that the degree of midline shift rates third after GCS score and highest mean ICP.[8]

Other authors, however, have not been able to show such prognostic significance; Selladurai, et al. (1992), describing a poor outcome in the majority of patients with a midline shift greater than 10 mm, could not show overall statistical significance in the total population of 109 patients with severe head injury.[12] The limited prognostic value of midline shift in this study could in part be explained by the presence of diffuse axonal injury and bilateral hemorrhagic lesions in the significant proportion of patients with midline shift less than 10 mm. In patients comatose due to acute epidural hematoma, Seelig, et al. (1984), found no correlation between the degree of midline shift and outcome.[11]

In patients with subdural hematoma some authors report a good correlation between midline shift and outcome, others a less evident relation: Kotwica and Brzezinski showed 42% favorable outcomes and a mortality of 39% when the shift was below 1.5 cm, and a 76% mortality when shift exceeded 3 cm.[5] Yanaka reports a mean midline shift of 2.9 mm in those patients with a functional recovery and 12.8 mm in those with a poor outcome.[15] Lobato, et al. (1991), only found a relation at extreme values of shift comparing a midline shift less than 4 mm versus a shift of more than 12 mm.[8] The outcome in the intermediate values did not differ. Domenicucci, et al. (1998), describe slightly larger average shift in patients dying with acute subdural hematoma than in survivors, but these results are not statistically significant.[2] Zumkeller, et al. (1996), also reporting on acute subdural hematomata, describe a decrease in survival density curves at shifts greater than 12 mm, but 50% survival occurs at a shift of 20 mm. A PPV of 70% to mortality can be calculated at a shift of approximately 23-24 mm.[17]

In the initial report on the Traumatic Coma Data Bank (TCDB),[3] a midline shift of 3 mm or more was noted in 34% of patients. In contrast to other studies they find a midline shift, regardless of the underlying pathology, a very strong predictor of abnormal ICP. The risk of dying was proportional to the degree of midline shift. From the published best fit curve between degree of midline shift and outcome, it can be inferred that a PPV of 70% for mortality can be calculated at a midline shift of 1.5 cm or more. This is in agreement with the PPV of 68% to fatal outcome reported by Lobato, et al. (1991), when the shift exceeds 1.5 cm.[8] From the data presented by Vollmer, et al. (1991), on a more definitive analysis of the TCDB, including six-month outcome, a PPV of 78% for poor outcome, as defined by the Glasgow Outcome Scale (GOS) categories dead and vegetative, can be calculated in the presence of a shift of 5 mm or greater in patients over 45 years of age. The relation between shift and poor outcome is, however, more evident in younger patients, in whom poor outcome is doubled. Because of the better, age-dependent prognosis in these patients, the PPV of this parameter at ages below 45 is only 53%.[14] Young, et al. (1981), however, report a PPV of 68% versus unfavorable outcome already at shifts of more than 4.1 mm.[16]

Quattrocchi, et al. (1991), in a retrospective study of 75 consecutive patients with head injury, also found a prognostic significance of the presence or absence of midline shift on the admission CT. The presence of midline shift was associated with a poor outcome in 50% of cases, whereas the absence of midline shift was associated with a poor outcome in only 14% of cases (p < 0.05). Significant predictive factors for poor outcome in this study were the presence of intracranial hemorrhage (34%), intracranial hemorrhage with midline shift (61%), and midline shift out of proportion to the extent of intracranial hemorrhage (88%).[9]

Conclusions

- Presence of midline shift is inversely related to prognosis; however, interaction with the presence of intracranial lesions and other CT parameters exists.
- Class I evidence shows a PPV of 78% to poor outcome in the presence of shift greater than 5 mm in patients over 45 years of age.
- Class II evidence shows a PPV of 70% to unfavorable outcome at midline shift greater than 1.5 cm.
- Presence of midline shift is indicative of increased intracranial pressure. The degree of midline shift has not been well studied and authors report widely differing values.
- The value of shift seems less important than other CT parameters, because the degree of shift is also influenced by the location of intracerebral lesions and the presence of bilateral abnormalities. Moreover, the presence and degree of midline shift as seen on the admission CT scan can be significantly altered on subsequent investigations, following the evacuation of mass lesions.

Recommendations for Future Research

- Further observer reliability studies.
- Further uniform classification of degree of shift.
- Further investigations concerning association with other prognostic variables.
- Further investigation of independent predictive value of midline shift as CT predictor.

Evidentiary Table: Midline Shift and Outcome

Domenicucci,[2] 1998

Years of Study: 1993-1994

Description: Retrospective study of 31 patients with severe head injury and acute subdural hematoma; analysis of subarachnoid spaces and shift.

Classification: Class III Study

Conclusions: Average shift higher in patients dying (10.7 mm) than in survivors (8.9 mm), but no significant difference.

Eisenberg,[3] 1990

Years of Study: 1984-1987

Description: Prospective study of early head CT in 753 patients with severe head injury. Analysis of shift at the level of the septum pellucidum and mortality examined as one subset.

Classification: Class II Study

Conclusions: At 1.5 cm shift or greater there was a 70% or higher percent of patients dying. Other parameters such as basal cisterns, mass lesions, tSAH, and ICP were examined.

Evidentiary Table: Midline Shift and Outcome (continued)

Fearnside,[4] 1993

Years of Study: Study duration 2-year period

Description: Prospective series of 315 consecutive patients with a GCS score less than 8 or deterioration to this level within 48 hours of injury. Analysis of prognostic significance of clinical and CT variables; outcome 6 months after injury.

Classification: Class II Study

Conclusions: CT parameters with predictive value concerning mortality were: cerebral edema, compressed/absent basal cisterns, shift, and presence of intraventricular hemorrhage. Cerebral edema was considered present in three of the following four variables:
1. Loss of grey/white matter differentiation
2. Compressed ventricles
3. Effaced sulci
4. Effaced or compressed perimesencephalic cisterns.

Degrees of shift defined were as follows: none, less than 5 mm, 5-10 mm, and greater than 15 mm. Logistic regression analysis concerning clinical and CT variables showed predictors of mortality to be: 1) age, 2) motor score, and 3) any of the 3 CT parameters. Predictors of disability in survivors were different: 1) hypotension, 2) abnormal motor response, 3) tSAH, and 4) intracerebral contusion or hemorrhage.

Kotwica and Brzezinski,[5] 1993

Years of Study: 1982-1990

Description: Consecutive series of 200 adult patients operated on for acute subdural hematoma with a GCS score less than 10 prior to operation. Analysis of relationship between age, GCS score, operative timing, concomitant presence of focal lesions, shift, and outcome at 3 months.

Classification: Class III Study

Conclusions: Significant correlation between midline shift, presence of contusions, and outcome.

Outcome at 3 Months

Shift	Unfavorable	Favorable
< 1.5	24	17
1.5-3	72	24
> 3	58	5

Evidentiary Table: Midline Shift and Outcome (continued)

Lipper,[6] 1985

Year of Study: Unknown

Description: Retrospective analysis of CT findings in 128 patients with head injury as defined by not obeying commands and unable to formulate formal words.

Classification: Class II Study

Conclusions: Number of slices on which a lesion was seen under presence of shift were related to outcome. Favorable outcome was seen in 80% of patients with a normal CT scan.

Relation Between Shift and Outcome (3 Months or 1 Year)

Shift	Unfavorable	Favorable
shift < 3.8 mm	25	57
shift ≥ 3.8 mm	29	17

Lobato,[7] 1988

Years of Study: 1977-1986

Description: Retrospective analysis of 64 consecutive cases of patients in comas with epidural hematoma.

Classification: Class III Study

Conclusions: Significant correlation between outcome and mechanism of injury, interval between trauma and surgery, motor score before operation, hematoma CT density and hematoma volume. 57% of patients had one or more associated intracranial lesions.

Lobato,[8] 1991

Years of Study: 1977-1989

Description: 211 patients with secondary deterioration to coma out of a series of 838 head-injured patients. Analysis of cause of deterioration and prognostic indicators. Time of outcome determination not reported.

Classification: Class III Study

Conclusions: 80.5% of the 211 patients showing secondary deterioration were shown to have a focal mass lesion. In 52.3% of these patients it was an intracerebral mass lesion. Multivariate regression analysis showed prognostic values of the following parameters:1) GCS, 2) highest mean ICP, 3) degree of midline shift, 4) type of lesion, and 5) age.

Relation between Midline Shift and Outcome:

Midline Shift	Fatal	Functional
≤ 5 mm	14	62
6-15 mm	23	66
> 15 mm	31	15

Evidentiary Table: Midline Shift and Outcome (continued)

Quattrocchi,[9] 1991

Year of Study: 1987

Description: Retrospective study of 56 patients with head injury (GCS 3-12) with intracranial hematoma. Data were compared to a randomly selected series of 19 patients with normal CT scans. Purpose of the study was to determine specific CT criteria for predicting outcome. GOS score determined at 6 months and 1 year.

Classification: Class III Study

Conclusions: Significant factors for poor outcome were intracranial hemorrhage, intracranial hemorrhage plus shift, and shift out of proportion to intracranial hemorrhage.

Relationship Between Presence and Absence of Shift and Outcome:

Shift	Unfavorable	Favorable
shift -	4	24
shift +	14	14

Relationship Between Degree of Shift and Outcome:

Shift	Unfavorable	Favorable
shift = mass	8	12
shift > mass	7	1
PPV ≥ 70% for mortality		

Ross,[10] 1989

Year of Study: No year of study reported.

Description: Prospective blinded trial on 46 patients with acute post-traumatic intracerebral hematoma; the relation between the degree of midline shift, GCS score and outcome at 3 months was investigated. The study included 19 patients with acute subdural hematoma, 14 with intracerebral hematoma, and 13 with epidural hematoma.

Classification: Class III Study

Conclusions: Significant relation between level of consciousness and lateral pineal or septal shift. Significant correlation between outcome (3 months) and septal shift, but not between outcome and pineal or aqueductal shift. No difference in shift between patients with acute subdural hematoma, epidural hematoma, or intracerebral hematoma.

Relation Between GCS, Shift, and Outcome:

	Outcome at 3 Months	Lateral Pineal Shift	Lateral Septal Shift
GCS 3-5	Poor	6.8 mm	12.6 mm
	Alert	6.0	10.5
GCS 6-8	Poor	8.2	13.4
	Alert	5.2	9.4

Evidentiary Table: Midline Shift and Outcome (continued)

Seelig,[11] 1984

Years of Study: 1980-1982

Description: Prospective series of 51 patients, comatose with epidural hematoma. Study population formed part of the pilot National Traumatic Coma Data Bank (581 patients). Analysis of clinical and CT variables.

Classification: Class III Study

Conclusions: Motor score before operation was most powerful predictor. No relationship between presence or absence of contusions, location of contusion, and midline shift to outcome. Time of outcome determination and tables not given in manuscript.

Servadei,[13] 1988

Years of Study: 1980-1986

Description: Out of 158 patients examined in CT era with epidural hematoma, 87 were comatose. Separate analysis of these patients. Study of changing characteristics in connection with increased availability of CT scanners.

Classification: Class III Study

Vollmer,[14] 1991

Year of Study: 1984-1987

Description: Prospective study on 661 patients from the Traumatic Coma Data Bank in whom CT examination was performed.

Classification: Class I Study

Conclusions: Primary focus of this report is on the relationship between age and outcome. Older patients had a greater frequency of shift greater than 5 mm than younger patient groups. Shift of midline, ventricular asymmetry, and effacement of the mesencephalic cisterns was closely correlated with higher rates of poor outcome (vegetative or dead).

	Age ≤ 45		Age > 45	
	Dead/Veg	SD/M/GR	Dead/Veg	SD/M/GR
Shift > 5 mm	67	59	39	11
Shift ≤ 5 mm	97	275	32	17
	PPV: 53%		PPV: 78%	

Evidentiary Table: Midline Shift and Outcome (continued)

Young,[16] 1981

Year of Study: Unknown

Description: Prospective series of 170 patients with head injury; severity defined as major neurological deficits and/or unconsciousness at 6 hours after injury. Study population includes patients with missile wounds. Analysis of predictive value of GCS score, age, and shift. Data are related to 1-year outcome. The value of shift as measured on CT scan was separately studied in 69 patients with GCS scores 5-7.

Classification: Class II Study

Conclusions: In patients with a GCS score less than 5 or greater than 7, there was a high predictive value of GCS score. Strong relationship between presence or absence of shift more than 4.1 mm and outcome. However, outcome prediction was not significantly improved when adding data concerning shift to the GCS score. Adding shift to GCS score later than 24 hours after admission, however, did improve predictive value.

Relation Between Midline Shift and Outcome at 1 Year:

Midline shift	Unfavorable	Favorable
< 4.1 mm	17	27
≥ 4.1 mm	17	8

Zumkeller,[17] 1996

Years of Study: 10-year period

Description: Retrospective study of 174 patients with isolated severe head injury and unilateral acute subdural hematoma; analysis of shift and hematoma thickness.

Classification: Class III Study

Conclusions: Survival density decreases markedly at shift greater than 12 mm. Survival rate of 50% at shift is 20 mm. Shift exceeding hematoma thickness is unfavorable sign.

Description of Studies

First Author	> 25	GOS 6 Month	Prospective	Indicator < 24 Hours	Statistics	Class
Ross[10]	+	-	+	+	-	III
Seelig[11]	+	-	+	+	-	III
Kotwica[5]	+	-	+	+	-	III
Young[16]	+	+	+	+	+/-	II
Lobato,[8] 1991	+	?	+	-	+	III
Lobato,[7] 1988	+	+	-	+	-	III
Fearnside[4]	+	+	+	-	+	II
Quattrocchi[9]	+	+	-	-	-	III
Lipper[6]	+	+	-	?	+	II
Servadei[13]	+	+	-	+	-	III
Eisenberg[3]	+	-	+	+	+	II
Domenicucci[2]	+	-	-	+	-	III
Zumkeller[17]	+	-	-	+	-	III
Vollmer[14]	+	+	+	+	+	I

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4. Intracranial Lesions

Intracranial lesions are differentiated into extracerebral and intracerebral lesions; extracerebral lesions in the acute phase after head injury consist of epidural and acute subdural hematomas. Identifying such lesions is important for purposes of management, but at the same time allows quantifying severity of primary damage by determining number of lesions, type of lesions, their sizes, location, and mass effect.

Definitions: *Epidural hematoma:* high/or mixed density blood collection, between dura and skull. Acute subdural hematoma: high/or mixed density blood collection in the subdural or "intradural" space. *Parenchymal lesions:* Intraparenchymal lesions are ill defined in the literature and definitions inconsistently applied. Intraparenchymal lesions may be differentiated in low-density, mixed-density, and high-density lesions. High-density lesions may be small, located in the subcortical white matter, basal ganglia or brain stem and then form part of so-called "diffuse axonal injury."[49] Other lesions, of variable density, may be larger and cause mass effect. There is no sharp demarcation between contusions of a hemorrhagic nature and intracerebral hematoma.

Reliability of Scoring

No observer reliability studies concerning the scoring of intracranial lesions were found.

Incidence of Intercranial Lesions

First Author	Sweet,[43] 1978; n = 140	Kobayashi,[17] 1983; n = 138	Gennarelli,[10] 1982; n = 107	Marshall,[22] 1991; n = 746 evacuated lesions	European Nimodipine Trial,[1] 1994; n = 819
Epidural Hematoma	5 (25%)	23 (16%)	96 (9%)	45 (6%)	134 (16%)
Acute Subdural Hematoma	32 (23%)	45 (33%)	319 (29%)	159 (21%)	248 (30%)
Contusions	32 (23%)	33 (38%)	134 (12%)		501 (61%)
Contusions (mass lesion)			71 (6%)		96 (12%)
Intracerebral Hemorrhage		32 (23%)	71 (9.5%)		70 (8.5%)

Association with Other Lesions and/or Prognostic Variables

Intracerebral lesions occur frequently in patients with epidural hematoma.[11, 14, 15, 19, 21, 29, 36] In patients with acute subdural hematoma, intracerebral lesions are common.[8, 18, 46, 48] Haselsberger, et al. (1988), demonstrated that patients with "pure" epidural hematomas had a good outcome in 70% of cases as compared to 44% of those with associated intracerebral lesions.[11]

Jamjoom, et al. (1992), compared two series of patients with epidural hematoma with and without intracerebral lesions and showed with statistical significance that patients with intracerebral lesions were older, had more falls as mechanism of injury, had a lower GCS score at the time of treatment, and presented with more extracranial injuries.[14] The correlation between age and outcome in patients with epidural hematoma can be explained in part by the incidence of associated intracerebral lesions. Only 20% of patients aged 20 or younger had associated intracerebral lesions, whereas such lesions were present in 80% of patients over the age of 60. In patients with acute subdural hematomas, the presence of associated intracerebral lesions is negatively related to outcome. Kotwica and Brzezinski (1993) describe a mortality of 85% for an acute subdural hematoma with an associated unilateral contusion, and 17% when no such lesion exists.[18] In the study by Wilberger, et al. (1991), patients with acute subdural hematomas had a mortality rate of 72% when associated with contusions versus 52% of those without contusions.[46]

This difference was related to the highest postoperative increased ICP. Seelig, et al. (1981), as well as Domenicucci, et al.(1998), however, showed no significant difference in outcome for patients with acute subdural hematoma with and without associated contusions.[8, 32] Similarly, Seelig, et al. (1984), and Servadei, et al. (1988), could not confirm the relationship between intracerebral associated lesions and outcome in patients with epidural hematoma.[33, 35] Hemorrhagic contusions occur more frequently in the elderly, where falls are the common most cause of head injury. Intraparenchymal hemorrhage is more frequent in patients with alcohol use.[7, 31]

Predictive Value

The analysis of the predictive value of the presence or absence of intracranial lesions in patients with severe head injury is complicated by the fact that many studies reporting on such lesions include patients with injuries of less severity (i.e., GCS > 8). Time to operation and widely varying indications for operation, particularly concerning intracranial lesions, are factors possibly influencing treatment results and prognosis. The mortality of comatose patients with epidural hematoma is lower than in patients with acute subdural hematoma (Table 1). A higher percentage of favorable outcome is described in patients with severe head injury and an epidural hematoma, and a lower percentage of favorable outcome in patients with acute subdural hematoma is described in comparison to patients with diffuse lesions.[10] Class II evidence shows a PPV of 77% for unfavorable outcome in severely head-injured patients in whom mass lesions were present and evacuated, and a PPV of 89% when mass lesions were not evacuated.[22] Class I evidence shows a PPV of 67% to unfavorable outcome in the presence of a combination of high-density intracerebral and extracerebral lesions.[24] Other Class I evidence shows a PPV of 79% to poor outcome (dead/vegetative) in the presence of lesions greater than 15 ml in patients over 45 years of age.[45]

Table 1
Mortality Reported in Series of Patients with Epidural or Acute Subdural Hematoma

Epidural Hematoma First Author	% Mortality	Acute Subdural Hematoma First Author	% Mortality
Phonprasert,[25] 1980	24%	Seelig,[32] 1981	57%
Cordobes,[4] 1981	26	Gennarelli,[10] 1982 (GCS 3-5)	74
Gennarelli,[10] 1982 (GCS 3-5)	36	Gennarelli,[10] 1982 (GCS 6-8)	36
Gennarelli,[10] 1982 (GCS 6-8)	9	Klun,[16] 1984	79
Bricolo,[2] 1984	14	Stone,[42] 1986	59
Seelig,[33] 1984	41	Stening,[40] 1986	76
Reale,[28] 1984	27	Haselsberger,[11] 1988	57
Dan,[6] 1986	59	Marshall,[22] 1991	50
Haselsberger,[11] 1988	38	Wilberger,[46] 1991	66
Lobato,[21] 1988	28	Phuenpathom,[26] 1993	74
Servadei,[34] 1988	27	Hatashita,[12] 1993	55
Marshall,[22] 1991	18	Kotwica,[18] 1993	55

No correlation is found between hematoma localization and outcome in patients with epidural hematoma.[19, 21, 29, 35] Hematoma volume in epidural hematoma,[21, 29, 35] subdural hematoma,[13, 42, 48, 50] as well as in intraparenchymal lesions correlates well with outcome.[20]

Lobato, et al. (1988), show poor outcomes in only 20% of patients with epidural clots less than 150 cc versus 58% when the clot volume is greater than 150 cc.[21] Yanaka, et al. (1993), shows in patients with acute subdural hematoma that the mean hematoma volume was 31 cc for patients with functional recovery and 104 cc for those patients with an unfavorable outcome.[48] Stone, et al. (1983), demonstrates that patients with an acute subdural hematoma volume of less than 100 cc had a mortality rate of 51% and those with hematoma over 100 cc had a 79% mortality. Zumkeller,

et al. (1996), on analysis of patients comatose with an acute subdural hematoma, found a 50% survival rate at a hematoma thickness of 18 mm or less. A PPV toward mortality of 70% can be inferred to occur at a hematoma thicknesses of approximately 23 mm. A PPV of 75% for mortality was demonstrated when midline shift exceeded hematoma thickness by more than 5 mm.[50] Lipper, et al. (1985), in a retrospective analysis of 128 patients with severe head injury, developed a prognostic equation based on the number of slices of the CT scan on which hemorrhagic lesions were visible. The equation allowed accurate prediction in 69% of cases. The model was less accurate in extra-axial lesions.[20] The presence of visible subarachnoid spaces without signs of tSAH has been shown to be indicative of favorable outcome in patients with acute subdural hematoma.

In patients with intraparenchymal lesions, the presence of multiple lesions is associated with a poorer outcome. Sweet, et al. (1978), describe in 52 patients with bilateral lesions an association between high-density lesions, higher ICP, and worse prognosis.[43] Patients with low-density lesions and small ventricles, however, generally show lower ICPs and a better prognosis. Chocksey, et al. (1993), in a retospective study of 202 patients, describe a direct relationship between the number of intracerebral lesions and outcome. In patients with a single hematoma, 58% have a favorable outcome, in patients with two clots, 20%, while no patients with three or more hematomas have a favorable outcome.[3] Quattrocchi, et al. (1991), describe worse outcome when intracranial hemorrhage is associated with midline shift and especially when the midline shift is out of proportion to the extent of intracranial hemorrhage, 88% of the patients in this group showing a poor outcome.[27] Cordobes, et al. (1986), presenting results on 78 patients with diffuse axonal injury show a poorer outcome when intraparenchymal hemorrhage is associated with intraventricular hemorrhage or global brain swelling.[5] In the series reported from the Traumatic Coma Data Bank, 71 patients were operated on for an intracerebral hematoma. Nineteen (26.8%) died, while unfavorable outcome on discharge came to a total of 52 (74%).[22] Eide and Tysnes (1992), describe a poorer outcome at three months in patients with multifocal contusions when compared to those with focal contusions.[9]

CT examination yields by definition momentary information. When determining prognostic significance of lesions on the CT scan, the time elapsed between injury and CT examination must be taken into account. Various authors have addressed the issue of changes on CT appearance over time. Kobayashi, et al. (1983), describing a series of 138 patients, noted new lesions developing in 60 patients. In these patients outcome was favorable in only 12, while a favorable outcome was seen in 60 of the 78 patients not developing a new lesion.[17] Sweet, et al. (1978), in a series of 143 patients, show that 13 of the initial 75 patients with unilateral lesions on admission develop controlateral lesions during the first week.[43] Tseng (1992) describes 32 patients with delayed traumatic intracerebral hematoma. This delayed hemorrhage was found after a time interval varying from 7 hours to 10 days. Seventy-five percent of these patients had a favorable outcome; poor prognosis was associated with an earlier occurrence, larger hematoma, low GCS score, clinical deterioration, and obliteration of the supra chiasmatic cistern. In the majority of these patients, contusions were present on the initial CT scan. The delayed lesion was diagnosed between 12 hours and 6 days after trauma.[44] Soloniuk, et al. (1986), describe 35 patients with delayed traumatic intracerebral hematoma. In 20% of these patients, the diagnosis was made within 3 hours, in 6% between 3 and 6 hours, in 29% between 6 and 24 hours, and in 46% more than 24 hours after injury. Half of these patients were not comatose at the time of admission.[37] Yamaki, et al. (1990), shows the development of traumatic

intracranial hematoma from brain contusions in 48 patients. In 56% of these patients, the lesion developed within 6 hours, in 81% within 12 hours, and in all patients within 24 hours after injury. Stein, et al. (1992), describe new lesions developing on the CT scan in 123 patients out of a series of 253 patients with head injury. Coagulation disturbances were present in the majority (55%) of these patients.[39] In a recent study by Servadei, et al. (1995), 37 patients are described, from a series of 412, developing new lesions within a 12-hour period from time of admission. In 22 patients, these hematomas evolved toward surgical removal. Lesions most prone to enlarge were epidural hematomas and intracerebral hemorrhages.[35]

When describing outcome results and prognosis in patients with demonstrable lesions on the CT scan, it may be worthwhile to include results of subsequent CT examinations and to report the "full extent" of such lesions, i.e., the "worst CT" in addition to the initial CT scan results.

Conclusions
- Extracerebral and intracerebral lesions occur frequently in comatose patients with head injury.
- Presence of mass lesions has a PPV of 78% to unfavorable outcome (Class II).
- Presence of mass lesions in patients over 45 years of age carries a PPV of 79% to poor outcome as defined by the categories dead and vegetative.
- Mortality is higher in acute subdural hematoma than in extradural hematoma.
- Outcome is more favorable in patients with severe head injury and an epidural hematoma and less favorable in acute subdural hematoma in comparison to patients with diffuse injuries.
- Hematoma volume is correlated to outcome.
- Intraparenchymal lesions are ill defined.

Recommendations for Future Research
- There is a need for improved definition for intraparenchymal lesions.
- A more detailed recording of surgical indications is required in future studies. Standardized reporting of indications for surgery (clinical, such as occurrence of deterioration, CT, results of ICP monitoring), time to operation, and involving lesions are a prerequisite for comparison of different series and determination of prognostic value. Also reasons for not operating, i.e., poor prognosis or local "conservative" policy, should be explicitly stated.

Evidentiary Table: Intracranial Lesions and Outcome

Eide and Tysnes,[9] 1992

Years of Study: 1984-1989

Description: Evaluation of outcome in 143 patients admitted with cerebral contusions, defined as non-homogeneous area of low- and high-attenuation values.

Classification: Class III Study

Conclusions: Outcome at 3 months was poorer in patients with multifocal contusions than in focal contusions. Longer-term evaluation did show increased occurrence of post-traumatic mental disturbances, also in patients with focal contusions.

Outcome in Patients with Brain Contusion

	Unfavorable	Favorable
Focal Contusion	0	57
Multifocal Unilateral	17	19
Multifocal Bilateral	31	19

Gennarelli,[10] 1982

Description: Retrospective analysis of 1,107 patients with severe head injury from seven centers analyzing outcome and type of CT lesion.

Classification: Class III Study

Conclusions: Differentiation of focal versus diffuse injuries being split into two categories of severity: market heterogeneity of outcome; type of lesion as important on outcome as GCS score. Rank order of prognosis: subdural hematoma < diffuse injuries < extradural hematoma.

	Number of patients	Unfavorable	Favorable
Diffuse Injury	487	48%	52%
Focal Injury	620	67	33
Epidural Hematoma	96	37	63
Acute Subdural Hematoma	319	77	22
Other Focal Lesions		61	39

Evidentiary Table: Intracranial Lesions and Outcome (continued)

Kobayashi,[17] 1983

Years of Study: 1977-1981

Description: Analysis of serial CT scans performed in 138 patients with severe head injury.

Classification: Class III Study

Conclusions: New findings were visible on follow-up CTs in 91 of the 138 patients. Significant correlation was demonstrated between favorable outcome and absence of new lesions, and between poor outcome and development of new lesions.

Relationship Between Progression of Lesions and Outcome

	Unfavorable	Favorable
No New Lesion	18	60
New Lesions	48	12

Lipper,[20] 1985

Year of Study: Not Reported

Description: Retrospective analysis on 128 randomly selected patients with severe head injury. Evaluation of predictive significance of extent of hemorrhagic lesions. Outcome determinations at 3 months and 1 year.

Classification: Class II Study

Conclusions: Based on the number of slices (each 1 cm thick) of the CT scan on which hemorrhagic lesions were visible. A prognostic equation was developed, providing accurate prediction in 69.7% of cases. Model is less accurate in extra-axonal lesions.

Relationship Between Extent of Lesion and Outcome

Number of Slices with Hemorrhagic Lesions	Unfavorable	Favorable
None	14	55
1 or 2	3	5
3 or 4	12	12
5 or 6	15	9
7 or 8	2	1

Lobato,[21] 1988

Year of Study: Not Reported

Description: Analysis of 55 patients out of a series of 520 patients with severe head injury, showing post-traumatic hemispheric swelling.

Classification: Class III Study

Conclusions: Highest mortality (87%) in this category of patients with severe head injury. Strong association with the presence of acute subdural hematoma (85%) or epidural hematoma (9%). Also relation to arterial hypotension and/or hypoxia on admission.

Evidentiary Table: Intracranial Lesions and Outcome (continued)

Marshall,[22] 1991

Description: Prospective study of a consecutive series of 746 severely head injured patients in four centers Traumatic Coma Data Bank (TCDB).

Classification: Class II Study

Conclusions: Outcome more unfavorable in patients with evacuated or non-evacuated mass lesions. Presence of mass lesions carries a PPV of 78% to unfavorable outcome.

Outcome at Discharge

	Unfavorable	Favorable
Diffuse Injury	294	120
Evacuated Mass Lesion	213	63
Non-Evacuated Mass Lesion	32	4

Miller,[23] 1979

Year of Study: Not Reported

Description: Study of 74 patients with severe head injury (GCS ≤ 9) investigating relationship between CT scan, GCS score, and ICP versus outcome. Patients with epidural hematoma or subdural hematoma were excluded.

Classification: Class III Study

Conclusions: In the presence of high-density intraparenchymal lesions there was a 50% change of raised ICP and a strong correlation with poor outcome. In patients with cerebral contusion, admission GCS score was unrelated to outcome.

Focal Lesions and Increased ICP

	ICP Normal	ICP Raised
CT Normal/Diffuse Swelling	34	7
CT Contusion or Mixed Lesions	14	19

(n = 74)

Relationship Between CT Scan, Coma Scale, and Outcome

GCS score on Admission	CT Normal/ Diffuse Swelling		CT Contusion or Mixed Lesion	
	Unfavorable	Favorable	Unfavorable	Favorable
3-4	3	0	8	1
5-7	3	18	8	8
8-10	9	15	3	4
11	9	2	1	0

Evidentiary Table: Intracranial Lesions and Outcome (continued)

Narayan,[24] 1981

Years of Study: 1976-1979

Description: Evaluation of prognostic parameters including CT scan in a consecutive series of 133 patients with severe head injury.

Classification: Class I/II Study

Conclusions: Concerning CT data, the presence of high-density lesions was the best, but not a very good prognostic indicator allowing 64% correct predictions. CT was less accurate than clinical predictors. In combination with clinical parameters, adding the CT scan improved confidence of prediction. CT was not selected on regression analysis for best prognosticators.

Relationship Between Presence of Intracerebral Lesions and Outcome

Intracerebral Lesion	None	Unfavorable	Favorable
Normal/Low Density	59	22%	78%
High Density Lesions	74	54	46

Quattrocchi,[27] 1991

Year of Study: 1987

Description: Retrospective study on 75 patients (data fully available in 56) with intracranial hemorrhage of varying severity.

Classification: Class III Study

Conclusions: Predictive features for poor outcome with a presence of intracranial hemorrhage (34%), combination of intracranial hemorrhage and shift and shift out of proportion to intracranial hemorrhage (88% mortality).

Relationship Between Intracranial Hemorrhage, Shift, and Outcome

	Dead	Alive
No ICH	1	18
ICH	14	42
Ich Plus Shift	11	17
Shift Out of Proportion to Intracranial Hemorrhage	6	2

Evidentiary Table: Intracranial Lesions and Outcome (continued)

Rudnik,[30] 1992

Years of Study: 1980-1986

Description: Evaluation of prognostic value of clinical and CT parameters in 146 patients with severe head injury (GCS ≤ 8).

Classification: Class III Study

Conclusions: GCS had the greatest prognostic significance, followed by degree of intracranial mass lesions. Isolated subdural hematoma or epidural hematoma were indicative of a good prognosis; the combination with multiple contusions or intracerebral hemorrhage indicated a poor prognosis.

Seelig,[33] 1984

Years of Study: 1980-1982

Description: Description of treatment results in 51% operated on for epidural hematoma in comatose condition; part of 581 patients in a national pilot Traumatic Coma Data Bank.

Classification: Class III Study

Conclusions: Overall mortality 41%, in 50% of the cases association with intracerebral contusions. Motor score before operation was the most powerful prognostic indicator.

Servadei,[35] 1995

Years of Study: 1990-1994

Description: Retrospective review of 37 patients out of a series of 412 showing changing lesions within 12 hours of admission.

Classification: Class III Study

Conclusions: Of the 37 patients showing changes, 15 cases evolved toward reabsorption and in 22 cases lesion size increased. Indications for control CT detecting these lesions were a raising ICP in 5 patients, clinical deterioration in 10, and scheduled controlled CT in 13 patients.

Stein,[38] 1993

Years of Study: 1986-1989

Description: Retrospective review of 337 patients with moderate and severe head injury, who had follow-up CT within 72 hours.

Classification: Class III Study

Conclusions: 149 patients (44.5%) showed new lesions. Highly significant association between appearance of delayed insults and severity of initial injury, hypotension, pulmonary injury, coagulopathy or subdural hematoma on initial CT. Appearance of new lesions was strongly related to outcome and was shown to be of independent predictive value.

Evidentiary Table: Intracranial Lesions and Outcome (continued)

Sweet,[43] 1978

Years of Study: 1976-1977

Description: Analysis of serial CT in 140 head-injured patients evaluating progression of lesion and relationship between intraparenchymal abnormalities and outcome.

Classification: Class III Study

Conclusions: Admission CT showed unilateral lesions in 75 patients and 39 bilateral lesions. Subsequent CT during the first week showed progression in 13 of the unilateral lesions, totaling 52 bilateral lesions. Bilateral increased density lesions were associated with a poorer motor score, a higher ICP, and worse outcome.

Type of Lesion versus Outcome

CT lesion	Unfavorable	Favorable
Normal	5	21
Unilateral	21	41
Bilateral Swelling	8	21
Bilateral Hypodense	17	6

Tseng,[44] 1992

Years of Study: 1987-1989

Description: Report on 32 patients with delayed traumatic intracranial hematoma (DTICH).

Classification: Class III Study

Conclusions: Incidence of DTICH was 5.9% of patients admitted with neurological signs or abnormal CT scan. Reason for control CT scan was clinical deterioration in 10 patients and failure to recover in 22 patients.

Vollmer,[45] 1991

Description: Prospective analysis of 661 patients aged 15 years and older in realation to clinical outcome.

Classification: Class II Study

Conclusions: The proportion of patients with intracranial hematomas increases with age. Analysis based on the presence and evacuation of a large lesion showed that the increasing age was associated with poorer outcome in each subgroup.

	Age < 45		Age > 45	
	Dead/Veg	SD/M/GR	Dead/Veg	SD/M/GR
Lesion ≥ 15 ml	55	65	57	15
No lesion or lesion < 15	122	292	31	16
	PPV: 46%		PPV: -79%	

SD= severe disability; M=moderate disability; GR=good recovery

Description of Studies

First Author	>25	GOS 6 Month	Prospective	Indicator within 24 Hours	Statistics	Class
Lobato[21]	+	?	-	+	-	III
Lipper[20]	+	+	-	+	+	II
Eide[9]	+	-	-	+	-	III
Kobayashi[17]	+	-	-	-	-	III
Seelig[33]	+	-	+	+	-	III
Tseng[44]	+	-	-	-	-	III
Sweet[43]	+	+	+	-	-	III
Stein[38]	+	?	-	-	-	III
Servadei[35]	+	?	-	+	-	III
Quattrocchi[27]	+	+	-	+	-	III
Miller[23]	+	+	-	+	-	III
Narayan[24]	+	+	+	+?	+	I/II
Rudnik[30]	+	?	?	?	+	III
Gennarelli[10]	+	-	-		-	III
Marshall[22]	+	-	+	+	-	II

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