Journal of Neurotrauma

Editor-in-Chief

John T. Povlishock, Ph.D.
VCU Neuroscience Center
Virginia Commonwealth University
Medical College of Virginia Campus
1101 E. Marshall St.
P.O. Box 980709
Richmond, VA 23298-0709
(804) 828-9623
Fax: (804) 828-9477
E-mail: j.neurotrauma@verizon.net

Deputy Editor

M. Ross Bullock, M.D., Ph.D.
Department of Neurosurgery
Virginia Commonwealth University
Medical College of Virginia Campus
1200 E. Broad St.
P.O. Box 980631
Richmond, VA 23298-0631
(804) 828-9165
Fax: (804) 827-1693
E-mail: robulloc@hsc.vcu.edu

European Editor

Lars T. Hillered, M.D., Ph.D.
Department of Neuroscience, Neurosurgery
Uppsala University Hospital
SE-751 85 Uppsala
Sweden
46-18-611-4969
Fax: 46-18-558-617
E-mail: lars.hillered@neurokir.uu.se

Australasian Editor

Yoichi Katayama, M.D., Ph.D.
Department of Neurological Surgery
Nihon University School of Medicine
30-1 Oyaguchi-Kamimachi
Itabashi-ku, Tokyo 173-8610
Japan
81-3-3972-8111
Fax: 81-3-3554-0425
E-mail: ykatayam@med.nihon-u.ac.jp

Section Editors

Charles H. Tator, M.D., Ph.D.
Clinical Management of Spinal Cord Injury
Division of Neurosurgery
University of Toronto

Edward D. Hall, Ph.D.
Neuroprotective and Neurorestorative Pharmacology
Department of Anatomy and Neurobiology
University of Kentucky–College of Medicine

Douglas K. Anderson, Ph.D.
Reorganization and Repair
Department of Neuroscience
University of Florida, College of Medicine

David I. Graham, M.B., Ph.D.
Neuropathology
Department of Neuropathology
Institute of Neurological Sciences
Southern General Hospital

Yoichi Katayama, M.D., Ph.D.
Neurophysiology and Metabolism
Department of Neurological Surgery
Nihon University School of Medicine
Tokyo

Harvey Levin, Ph.D.
Neuropsychology and Behavior
Physical Medicine & Rehabilitation
Baylor College of Medicine

M. Ross Bullock, M.D., Ph.D.
Clinical Management of Brain Injury
Medical College of Virginia Campus of Virginia Commonwealth University
Richmond

John F. Ditunno, Jr., M.D.
Rehabilitation
Department of Rehabilitation Medicine
Thomas Jefferson University Hospital

Editorial Board

Andrew R. Blight, Ph.D.
ACORDA Therapeutics, Inc.
Hawthorne, NY

Peter C. Blumbergs, M.D.
Institute of Medical & Veterinary Science
Adelaide, SA

Jacqueline C. Bresnahan, Ph.D.
Ohio State University
Columbus

Pak H. Chan, Ph.D.
Stanford University Medical Center

Robert S. Clark, M.D.
Children's Hospital of Pittsburgh

Guy L. Clifton, M.D.
University of Texas Medical School
Houston

Douglas S. DeWitt, Ph.D.
University of Texas
Galveston

W. Dalton Dietrich, III, Ph.D.
University of Miami
School of Medicine

C. Edward Dixon, Ph.D.
University of Pittsburgh

Michael Fehlings, M.D., Ph.D.
Toronto Western Hospital

Fred H. Gage, Ph.D.
The Salk Institute

M. Sean Grady, M.D.
University of Pennsylvania

Ronald L. Hayes, Ph.D.
University of Florida
College of Medicine

David A. Hovda, Ph.D.
University of California School of Medicine
Los Angeles

Chung Y. Hsu, M.D., Ph.D.
Taipei Medical University
Taiwan

Claire E. Hulsebosch, Ph.D.
University of Texas Medical Branch
Galveston

John A. Jane, M.D., Ph.D.
University of Virginia
Charlottesville

Ji-yao Jiang, M.D., Ph.D.
Shanghai Jiaotong University School of Medicine
People's Republic of China

Patrick M. Kochanek, M.D.
Critical Care Medicine
Safar Center for Resuscitation Research
Pittsburgh

Morimichi Koshinaga, M.D., Ph.D.
Nihon University School of Medicine
Tokyo

Bruce G. Lyeth, Ph.D.
University of California
Davis

William L. Maxwell, Ph.D.
University of Glasgow

David F. Meaney, Ph.D.
University of Pennsylvania

R.J. Moulton, M.D.
St. Michael's Hospital
Toronto

J. Paul Muizelaar, M.D., Ph.D.
University of California at Davis

Linda Noble, Ph.D.
University of California
San Francisco

Claudia Robertson, M.D.
Baylor College of Medicine

Kathryn Saatman, Ph.D.
University of Kentucky

Bernhard A. Sabel, Ph.D.
Otto-von-Guericke University of Magdeburg
Germany

Stephen W. Scheff, Ph.D.
University of Kentucky
Lexington

Lisa Schnell, Ph.D.
University Zurich—Irchel

Esther Shohami, Ph.D.
The Hebrew University School of Pharmacy

Douglas Smith, M.D.
University of Pennsylvania School of Medicine

Joe E. Springer, Ph.D.
University of Kentucky Medical Center
Lexington

Oswald Steward, Ph.D.
University of California
Irvine

Robert Vink, Ph.D.
Adelaide University
Australia

Kevin K.W. Wang, Ph.D.
University of Florida

Stephen G. Waxman, M.D., Ph.D.
Yale University School of Medicine

Mary Ann Liebert, Inc. publishers

www.liebertpub.com

Guidelines for the Management of Severe Traumatic Brain Injury

3rd Edition

A Joint Project of the

Brain Trauma Foundation
Improving the Outcome of Brain Trauma Patients Worldwide

and

American Association of Neurological Surgeons (AANS)
Congress of Neurological Surgeons (CNS)
AANS/CNS Joint Section on Neurotrauma and Critical Care

Copyright © 2007 Brain Trauma Foundation, Inc. Copies are available through the Brain Trauma Foundation, 708 Third Avenue, Suite 1810, New York, NY 10017-4201, phone (212) 772-0608, fax (212) 772-0357. Website: www.braintrauma.org E-mail: btfinfo@braintrauma.org

Mary Ann Liebert, Inc. publishers

General Information

JOURNAL OF NEUROTRAUMA is a treatment-oriented journal reporting rigorously reviewed experimental and clinical studies, concentrating on neurochemical, neurophysiological, and neuropathological research on spinal cord injury, head trauma, peripheral neural injuries, and related neural injuries such as stroke.

JOURNAL OF NEUROTRAUMA (ISSN: 0897-7151) published (monthly) 12 times per year by Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor, New Rochelle, NY 10801-5215. Telephone: (914) 740-2100; fax: (914) 740-2101; e-mail: info@liebertpub.com Online: www.liebertpub.com **Postmaster:** Send address changes to *JOURNAL OF NEUROTRAUMA*. Subscription Department, Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor, New Rochelle, NY 10801-5215. Mailed in Canada under CPM #40026674.

Subscriptions should be addressed to the Publisher and are payable in advance. Rates for subscriptions are for a volume of 12 issues: USA print $1,241, International print $1,584, USA print and online $1,481, International print and online $1,832, and online only (worldwide) $1,169. Subscriptions begin with the first issue of the current volume. Bulk subscriptions available upon request from the Publisher. No cancellations/refunds can be honored after publication of a volume's first issue. No refunds/returns on single issue purchases.

JOURNAL OF NEUROTRAUMA is owned and published by Mary Ann Liebert, Inc. Copyright © 2007 by Mary Ann Liebert, Inc. Printed in the United States of America.

See Instructions for Authors page for information on manuscript submission or visit our web site: www.liebertpub.com

Business Communications should be addressed to the Publisher.

Advertising inquiries from within the United States or Canada should be addressed to Catherine Hiller, Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor, New Rochelle, NY 10801-5215, (914) 740-2100. For Europe/Outside the U.S., contact: Hilary Turnbull, imPRESS International Media Ltd., Carrington Kirk, Carrington, Midlothian EH 23 4LR, UK. Telephone: +44 (0)1875-825-700; fax: +44 (0)1875-825-701; e-mail: impress@impressmedia.com All advertisements are subject to approval by the Publisher. The acceptance of advertisements does not constitute an endorsement of the product or service advertised.

Reprints, except special orders of 100 or more, are available from the authors. For permission to photocopy for internal purposes 24 copies or less, please request permission and pay the appropriate fee by contacting the Customer Relations Dept. of the Copyright Clearance Center, Inc., 22 Rosewood Drive, Danvers, MA 01923, 978-750-8400, fax: 978-750-4470. If the number of copies of an article is 25 or higher, contact the Publisher directly for options.

Manuscripts should be directed to the Editor-in-Chief, John T. Povlishock, Ph.D., Journal of Neurotrauma, VCU Neuroscience Center, Virginia Commonwealth University, Medical College of Virginia Campus, 1101 East Marshall Street, Richmond, VA 23298, to the European Editor, Lars Hillered, M.D., Ph.D., Department of Neuroscience, Neurosurgery, Uppsala University Hospital, SE-751 85 Uppsala, Sweden, or the Australasian Editor, Yoichi Katayama, M.D., Ph.D., Department of Neurological Surgery, Nihon University School of Medicine, 30 Oyaguchi-Kamimachi, Itabashiku-Tokyo 173, Japan.

All papers, news, comments, opinions, findings, conclusions, or recommendations in *JOURNAL OF NEUROTRAUMA* are those of the author(s), and do not constitute opinions, findings, conclusions, or recommendations of the Journal, its publisher, and its editorial staff.

JOURNAL OF NEUROTRAUMA is a **Journal Club** selection.

JOURNAL OF NEUROTRAUMA* is indexed in *MEDLINE, BIOSIS Previews, Current Contents/Life Sciences, EMBASE/Excerpta Medica, and Science Citation Index–Expanded.

The paper on which *JOURNAL OF NEUROTRAUMA* is printed meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper). Printed on acid-free paper effective with Volume 14, Number 8, 1997.

Please visit us on the web: www.liebertpub.com

Guidelines for the Management of Severe Traumatic Brain Injury

A Joint project of the
Brain Trauma Foundation
American Association of Neurological Surgeons (AANS)
Congress of Neurological Surgeons (CNS)
AANS/CNS Joint Section on Neurotrauma and Critical Care

These guidelines are copyrighted by the Brain Trauma Foundation copyright ©2007. Copies are available through the Brain Trauma Foundation, 708 Third Avenue, Suite 1810, New York, NY 10017-4201, phone (212) 772-0608, fax (212) 772-0357. Website: www.braintrauma.org. E-mail: info@brain trauma.

Journal of Neurotrauma

(ISSN: 0897-7151)

VOLUME 24 SUPPLEMENT 1 2007

GUIDELINES FOR THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY

Acknowledgments

Editor's Commentary
M.R. Bullock and J.T. Povlishock

Introduction S-1

Methods S-3

I. Blood Pressure and Oxygenation S-7

II. Hyperosmolar Therapy S-14

III. Prophylactic Hypothermia S-21

IV. Infection Prophylaxis S-26

V. Deep Vein Thrombosis Prophylaxis S-32

VI. Indications for Intracranial Pressure Monitoring S-37

VII. Intracranial Pressure Monitoring Technology S-45

VIII. Intracranial Pressure Thresholds S-55

IX. Cerebral Perfusion Thresholds S-59

X. Brain Oxygen Monitoring and Thresholds S-65

XI. Anesthetics, Analgesics, and Sedatives S-71

XII. Nutrition S-77

XIII. Antiseizure Prophylaxis S-83

XIV. Hyperventilation S-87

XV. Steroids S-91

Appendix A. Changes in Quality Ratings from the 2nd Edition to the 3rd Edition S-96

(*continued*)

Appendix B. Electronic Literature Search Strategies (Database: Ovid MEDLINE) S-99

Appendix C. Criteria for Including a Study in which the Sample Includes TBI Patients and Patients with Other Pathologies or Pediatric Patients S-105

Appendix D. Electronic Literature Search Yield S-106

Appendix E. Evidence Table Template S-106

Instructions for Authors can be found on our website at **www.liebertpub.com**

Mary Ann Liebert, Inc. publishers

www.liebertpub.com

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
DOI: 10.1089/neu.2007.9999

Acknowledgments

THE BRAIN TRAUMA FOUNDATION gratefully acknowledges and would like to thank the following persons for their contributions to this or previous editions of the *Guidelines for the Management of Severe Traumatic Brain Injury*:

Susan Bratton, MD, MPH
M. Ross Bullock, MD, PhD
Nancy Carney, PhD
Randall M. Chesnut, MD
William Coplin, MD
Jamshid Ghajar, MD, PhD
Guy L. Clifton, MD
Flora F. McConnell Hammond, MD
Odette A. Harris, MD, MPH
Roger Härtl, MD
Andrew I. R. Maas, MD
Geoffrey T. Manley, MD, PhD
Donald W. Marion, MD
Raj K. Narayan, MD
Andrew Nemecek, MD
David W. Newell, MD
Lawrence H. Pitts, MD
Guy Rosenthal, MD
Michael J. Rosner, MD
Joost Schouten, MD
Franco Servadei, MD
Lori A. Shutter, MD, PT
Nino Stocchetti, MD
Shelly D. Timmons, MD, PhD
Jamie S. Ullman, MD
Walter Videtta, MD
Beverly C. Walters, MD
Jack E. Wilberger, MD
David W. Wright, MD

The Brain Trauma Foundation also gratefully acknowledges the following members of the Review Committee and the professional societies they represent:

P. David Adelson, MD, FACS, FAAP, *American Academy of Pediatrics, Congress of Neurological Surgeons*
Arthur Cooper, MD, *Committee on Accreditation of Educational Programs*
William Coplin, MD, *Neurocritical Care Society*
Mark Dearden, MD, *Leeds General Infirmary, U.K., European Brain Injury Consortium*
Thomas J. Esposito, MD, *American Association for the Surgery of Trauma*
Mary Fallat, MD, *American College of Surgeons Committee on Trauma*
Brahm Goldstein, MD, *American Academy of Pediatrics*
Andrew S. Jagoda, MD, *American College of Emergency Physicians*
Anthony Marmarou, PhD, *American Brain Injury Consortium*
Lawrence F. Marshall, MD, *American Board of Neurological Surgery*
Stephan Mayer, MD, *Neurocritical Care Society*
David Mendelow, MD, *European Brain Injury Consortium*
Robert E. O'Connor, MD, *National Association of EMS Physicians*
Thomas Scalea, MD, *American College of Surgeons Committee on Trauma*
Andreas Unterberg, MD, *European Brain Injury Consortium*
Alex B. Valadka, MD, *AANS/CNS Joint Section on Neurotrauma and Critical Care*
Walter Videtta, MD, *Latin American Brain Injury Consortium*
Beverly C. Walters, MD, *AANS/CNS Guidelines Committee*

ACKNOWLEDGMENTS

Finally, the Brain Trauma Foundation would also like to acknowledge and thank the following individuals for their contribution to the 3rd Edition of the *Guidelines for the Management of Severe Traumatic Brain Injury*:

Susan Carson, MPH, *Oregon Health & Science University*
Cynthia Davis-O'Reilly, BSc, *Brain Trauma Foundation Center for Guidelines Management*
Pamela Drexel, *Brain Trauma Foundation*
Rochelle Fu, PhD, *Oregon Health & Science University*
Susan Norris, MD, MPH, MSc, *Oregon Evidence-based Practice Center*
Michelle Pappas, BA, *Brain Trauma Foundation Center for Guidelines Management*
Kimberly Peterson, MS, *Oregon Health & Science University*
Adair Prall, MD, *South Denver Neurosurgery*
Patricia Raksin, MD, *Cook County Hospital*

Susan Carson, Rochelle Fu, Susan Norris, Kimberly Peterson, and Nancy Carney are staff or affiliates of the Oregon Evidence-Based Practice Center (EPC). The EPC's role in the development of these guidelines is described within this report. The Agency for Healthcare Research and Quality has not reviewed this report.

Disclaimer of Liability

THE INFORMATION CONTAINED in the *Guidelines for the Management of Severe Traumatic Brain Injury* reflects the current state of knowledge at the time of publication. The Brain Trauma Foundation (BTF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), and other collaborating organizations are not engaged in rendering professional medical services and assume no responsibility for patient outcomes resulting from application of these general recommendations in specific patient circumstances. Accordingly, the BTF, AANS, and CNS consider adherence to these clinical practice guidelines will not necessarily assure a successful medical outcome. The information contained in these guidelines reflects published scientific evidence at the time of completion of the guidelines and cannot anticipate subsequent findings and/or additional evidence, and therefore should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same result. Medical advice and decisions are appropriately made only by a competent and licensed physician who must make decisions in light of all the facts and circumstances in each individual and particular case and on the basis of availability of resources and expertise. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and are not a substitute for physician-patient consultation. Accordingly, the BTF, AANS, and CNS consider adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
DOI: 10.1089/neu.2007.9998

Editor's Commentary

The *Journal of Neurotrauma* is proud to publish a special issue dedicated to the new edition of the *Guidelines for the Management of Severe Traumatic Brain Injury*. Under the sponsorship of the Brain Trauma Foundation, these guidelines were first published in 1995, and the 2nd revised edition was published in 2000.[1] This 3rd edition is substantially different, with six new topics added for a total of 15 chapters.

The Brain Trauma Foundation has drawn together 22 experts for the authorship of these guidelines, including 15 emerging experts in the field, each of whom were trained in evidence-based medicine methodology. The Foundation established the Center for Guidelines Management, which worked in partnership with methodologists from the Oregon Evidence-based Practice Center to develop the 3rd Edition of these *Guidelines.* This group performed comprehensive electronic searches of all databases relevant to the neurotrauma literature, up to April 2006. They used criteria to assess the quality of the included literature that was based on the United States Preventive Services Taskforce, the National Health Services (UK) Centre for Reviews and Dissemination, and the Cochrane Collaboration.

Two independent members of the EPC staff reviewed each selected study and classified them as Class I, Class II, or Class III, with the aid of the neurotrauma expert panel. The literature lists and classifications were refined by consensus discussion, among the experts. The studies were limited to **human** studies in the **adult** age group (>17 years) in the **English** language, covering **traumatic brain injury** (TBI), and excluding editorials, expert opinion, and studies of fewer than 25 patients. The topics for review were selected based upon these criteria when there were sufficient published studies to formulate recommendations. Many more topics (such as decompressive craniotomy) were initially listed, but were eliminated, either because they were covered in other guideline documents, such as *Guidelines for the Surgical Management of Traumatic Brain Injury*[2] or because of insufficient data.

For hypothermia, the conflicting findings in over 15 clinical trials in TBI led the EPC group to implement it's own independent meta-analysis to assess the clinical trials in question.

As with the previous guidelines for TBI, the reader must be aware of the limitations and restricted scope of the guidelines. The guidelines reflect only what is contained in the existing human-based literature. They do not reflect pathomechanistic information from animal studies, nor *in vitro* or mathematical modeling studies.

Since the first *Guidelines for Management of Traumatic Brain Injury* were published in 1995, there have been several studies clearly demonstrating that TBI management in accordance with the *Guidelines* can achieve substantially better outcomes in terms of metrics such as mortality rate, functional outcome scores, length of hospital stay, and costs.[3,4] This has been shown in single Level I and II trauma centers in the United States, and in large population-based studies in Eastern Europe.[5] Previous editions of the guidelines have been translated into over 15 different languages, and applied in most European countries, several countries in South America, and in parts of China. In the United States, surveys conducted in 1995, 2000, and 2006 have shown that increasing numbers of severe TBI patients are being managed in accordance with the *Guidelines,* with ICP monitoring, for example, rising from 32% in 1995 to 78% in 2005. The influence of these *Guidelines* upon patient care has thus already been enormous; and taken together with the *Companion Guidelines* for pediatric TBI,[6] prehospital management of TBI,[7] management of penetrating TBI,[8] and surgical management of TBI,[2] these documents offer the possibility for uniformity of TBI care, and conformity with the best standards of clinical practice. Only in this way can we provide the best milieu for the conduct of clinical trials to evaluate putative new therapies, which are being brought forth for clinical trials.

As in all areas of clinical medicine, the optimal plan of management for an individual patient may not fall exactly within the recommendations of these guidelines. This is because all patients, and in particular, neurotrauma patients, have heterogeneous injuries, and optimal management depends on a synthesis of the established knowledge based upon *Guidelines,* and then applied to the clinical findings in the individual patient, and refined by the clinical judgment of the treating physician.

REFERENCES

1. Bullock R, Chestnut R, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2000;17:449–554.
2. Bullock R, Chestnut R, Ghajar J, et al. Guidelines for the surgical management of traumatic brain injury. Neurosurgery 2006;58:S2-1–S2-62.
3. Fakhry SM, Trask AL, Waller MA, et al. IRTC Neurotrauma Task Force: management of brain injured patients by an evidence-based medicine protocol improves outcomes and decreases hospital charges. J Trauma 2004;56:492–493.
4. Palmer S, Bader M, Qureshi A, et al. The impact of outcomes in a community hospital setting using the AANS Traumatic Brain Injury Guidelines. American Association of Neurological Surgeons. J Trauma 2001;50:657–664.
5. Vukic L, Negovetic D, Kovac D, et al. The effect of implementation of guidelines for the management of severe head injury on patient treatment and outcomes. Acta Neurochir 1999;141:102–1208.
6. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children and adolescents. Pediatr Crit Care Med 2003;4:S417–S491.
7. Gabriel EJ, Ghajar J, Jagoda A, Pons PT, Scalea T, Walters BC. *Guidelines for Pre-Hospital Management of Traumatic Brain Injury*. Brain Trauma Foundation: New York, 2000.
8. Guidelines for the management of penetrating brain injury. J Trauma 2001;51:S3–S6.

SURVEY REFERENCES

1. Ghajar J, Hariri RJ, Narayan RK et al. Crit. Care Med. 1995;23:560–567.
2. Hesdorffer DC, Ghajar J, Jacouo L. J Trauma 2002;52: 1202–1209.
3. Hesdorffer DC, and Ghajar J. Marked improvement in adherence to traumatic brain injury guidelines in United States trauma centers. J Trauma (in press).

—M. Ross Bullock, M.D., Ph.D.
Deputy Editor
—John T. Povlishock, Ph.D.
Editor-in-Chief

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-1–S-2
DOI: 10.1089/neu.2007.9997

Introduction

TRAUMATIC BRAIN INJURY (TBI) is a major cause of disability, death, and economic cost to our society. One of the central concepts that emerged from research is that all neurological damage from TBI does not occur at the moment of impact, but evolves over the ensuing hours and days. Furthermore, improved outcome results when these secondary, delayed insults, resulting in reduced cerebral perfusion to the injured brain, are prevented or respond to treatment. This is reflected in the progressive and significant reduction in severe TBI mortality from 50% to 35% to 25% and lower over the last 30 years, even when adjusted for injury severity, age and other admission prognostic parameters.[1] This trend in reduced mortality and improved outcomes from TBI has been subsequent to the use of evidence-based protocols that emphasize monitoring and maintaining adequate cerebral perfusion.[2,3]

In preparation for the revision of the 2nd edition of these Guidelines, a systematic review of the literature was conducted to assess the influence of the use of the Guidelines on mortality and morbidity from TBI. The results indicated that consistent application of ICU-based protocols improves outcomes, and reduces mortality and length of stay.[4–7]

This is the third edition of the evidence-based Guidelines for the Management of Severe Traumatic Brain Injury, following the first and second editions in 1995 and 2000.[8,9] These Guidelines address key topics useful for the management of severe TBI in adult patients with a Glasgow Coma Scale score of 3–8. The following are notable changes from the second edition:

- Six new topics were added and two topics were assigned to the pre-hospital Guidelines. This is not an exhaustive review of all TBI management but rather a focus on interventions that have an impact on outcome and have sufficient scientific data specific to TBI to warrant the development of new topics.
- The Levels of Recommendation were changed from "Standard, Guideline, and Option" to "Level I, Level II, and Level III," respectively. The previous language did not lend itself to clear operational definitions. Recommendation Levels I, II, and III, are derived from Class I, II, and III evidence, respectively.
- The classification of certain publications included in previous editions has been changed. Publications were classified both by design and quality (see Methods section and Appendix A).
- This is the first edition of these Guidelines for which a meta-analysis was conducted, for the topic of Prophylactic Hypothermia.

In 2004, the Brain Trauma Foundation (BTF) called a meeting of all the TBI Guidelines contributing authors for the purpose of formalizing a collaborative process of Guidelines updates, publication, and implementation shared by those with a stake in acute TBI care. A partnership of interested professional associations was formed to review, endorse and implement future editions of the Guidelines. The mission of this TBI Partnership is to improve the outcome of TBI through collaboration and the promotion of evidence-based medicine.

For these and future Guidelines projects, contributing authors agreed to establish a Center for Guidelines Management (Center), which would be responsible for generating new guidelines as well as updating those that exist. The participants endorsed the BTF proposal to establish the Center to be located at Oregon Health & Sciences University (OHSU). A collaboration was established between the Center and the Oregon Evidence-based Practice Center (EPC). The Oregon EPC conducts systematic reviews of various healthcare topics for federal and state agencies and private foundations. These reviews report the evidence from clinical research studies, and the quality of that evidence, for use by policy makers in decisions about guidelines and coverage issues. The collaboration made the expertise and personnel of the EPC available to the Center

The TBI partnership further agreed to adopt and explicitly adhere to a systematic process and set of criteria for reviewing, assessing, and synthesizing the scientific literature. The process and criteria (see Methods Section) are derived from work by the U.S. Preventive Services Task Force,[10] the National Health Service Centre for Reviews and Dissemination (U.K.),[11] and

the Cochrane Collaboration.[12] The goal was to establish a process for *Guidelines* development that was scientifically rigorous, consistent across all topics, and independent of the interests and biases of contributing authors.

The partnership also recommended appointing a Review Committee to consist of a small number of individuals who would serve as liaison between the guidelines development process and the key medical societies related to TBI. These representatives of neurosurgery, trauma, neurointensive care, pediatrics, emergency medicine, and prehospital care, as well as international organizations, are standing members of the Committee across all Guidelines updates. The current members of this Committee, listed at the front of this document, reviewed this edition of the Guidelines.

In order to continue to improve outcomes for TBI patients, it is necessary to generate strong research capable of answering key questions, and to assess, synthesize, and disseminate the findings of that research so that practitioners have access to evidence-based information. Therefore, this document should not only be used as a roadmap to improve treatment, but also as a template from which to generate high quality research for future use. The primary marker of the success of the 3rd edition of these *Guidelines* will be a sufficient body of Class I and II studies for Level I and II recommendations in the 4th edition.

The BTF maintains and revises several TBI Guidelines on an annual basis resulting in a 5-year cycle, approximately, for each Guideline:

- Guidelines for Prehospital Management of Traumatic Brain Injury
- Guidelines for the Management of Severe Traumatic Brain Injury
- Guidelines for the Surgical Management of Traumatic Brain Injury
- Prognosis of Severe Traumatic Brain Injury

These BTF Guidelines are developed and maintained in a collaborative agreement with the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS), and in collaboration with the AANS/CNS Joint Section on Neurotrauma and Critical Care, European Brain Injury Consortium, other stakeholders in TBI patient outcome.

REFERENCES

1. Lu J, Marmarou A, Choi S, et al. Mortality from traumatic brain injury. Acta Neurochir 2005[suppl];95:281–285.
2. Ghajar J, Hariri RJ, Narayan RK, et al. Survey of critical care management of comatose, head-injured patients in the United States. Crit Care Med 1995;23:560–567.
3. Hesdorffer D, Ghajar J, Iacono L. Predictors of compliance with the evidence-based guidelines for traumatic brain injury care: a survey of United States trauma centers. J Trauma 2002;52:1202–1209.
4. Fakhry SM, Trask AL, Waller MA, et al. IRTC Neurotrauma Task Force: Management of brain-injured patients by an evidence-based medicine protocol improves outcomes and decreases hospital charges. J Trauma 2004;56: 492–493.
5. Palmer S, Bader M, Qureshi A, et al. The impact on outcomes in a community hospital setting of using the AANS traumatic brain injury guidelines. American Association of Neurological Surgeons. J Trauma 2001;50:657–664.
6. Vitaz T, McIlvoy L, Raque G, et al. Development and implementation of a clinical pathway for severe traumatic brain injury. J Trauma 2001;51:369–375.
7. Vukic L, Negovetic D, Kovac D, et al. The effect of implementation of guidelines for the management of severe head injury on patient treatment and outcomes. Acta Neurochir 1999;141:1203–1208.
8. Bullock R, Chesnut R, Clifton G et al. Guidelines for the management of severe head injury. Brain Trauma Foundation, American Association of Neurological Surgeons Joint Section on Neurotrauma and Critical Care. J Neurotrauma 1996;13:641–734.
9. Bullock RM, Chesnut RM, Clifton GL et al. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2000;17:449–554.
10. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prevent Med 2001;20:21–35.
11. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). York, UK: NHS Centre for Reviews and Dissemination; 2001. 4 (2nd edition).
12. Mulrow CD, Oxman AD. How to conduct a Cochrane systematic review. Version 3.0.2. Paper presented at: Cochrane Collaboration, 1997; San Antonio, TX.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-3–S-6
DOI: 10.1089/neu.2007.9996

Methods

I. TOPIC REFINEMENT

The Brain Trauma Foundation (BTF) and BTF Center for Guidelines Management (Center) convened a virtual meeting of previous guideline authors and colleagues new to the project. This group agreed that separate guidelines should be provided for prehospital and prognosis topics. Thus, these were eliminated from the current update. They specified which previous topics would be maintained and agreed upon new topics to include. Previous topics which were updated are Blood Pressure and Oxygenation, Indications for Intracranial Pressure (ICP) Monitoring, ICP Treatment Threshold, ICP Monitoring Technology, Cerebral Perfusion Thresholds, Nutrition, Antiseizure Prophylaxis, Hyperventilation, and Steroids. New topics are Prophylactic Hypothermia, Brain Oxygen Monitoring and Thresholds, Infection Prophylaxis, and Deep Vein Thrombosis Prophylaxis. The previous topic of Mannitol was expanded to Hyperosmolar Therapy, and the previous topic of Barbiturates was expanded to Anesthetics, Analgesics, and Sedatives.

II. INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria

- Human subjects
- Traumatic brain injury
- English language
- Adults (age $\geq$ 18 years)
- In-hospital (e.g., no studies from the prehospital setting)
- $\geq$25 subjects
- Randomized controlled trials (RCTs), cohort studies, case-control studies, case series, databases, registries

Exclusion Criteria

- Sample contained $>$15% of pediatric patients or $>$15% of patients with pathologies other than TBI, and the data were not reported separately (see Appendix C)
- Wrong independent variable (e.g., the intervention was not specific to the topic)
- Wrong dependent variable (e.g., outcomes were not mortality or morbidity, or did not associate with clinical outcomes)
- Case studies, editorials, comments, letters

III. LITERATURE SEARCH AND RETRIEVAL

Center staff worked with a doctoral level research librarian to construct electronic search strategies for each topic (see Appendix B). For new topics, the literature was searched from 1966 to 2004, and for previous topics from 1996 to 2004. Strategies with the highest likelihood of capturing most of the targeted literature were used, which resulted in the acquisition of a large proportion of nonrelevant citations. Two authors were assigned to each topic, and a set of abstracts was sent to each. Blinded to each others' work, they read the abstracts and eliminated citations using the pre-determined inclusion/exclusion criteria.

Center staff compared the selections, and identified and resolved discrepancies either through consensus or through use of a third reviewer. A set of full-text publications was then sent to each author. Again blinded to each others' work, they read the publications and selected those that met the inclusion criteria.

Results of the electronic searches were supplemented by recommendations of peers and by reading reference lists of included studies. A second search was conducted from 2004 through April 2006 to capture any relevant Class I or II literature (see Quality Assessment section of this chapter) that might have been published since the first literature search in 2004. Relevant publications were added to those from the original search, constituting the final library of studies that were used as evidence in this document. The yield of literature from each phase of the search is presented in Appendix D.

IV. DATA ABSTRACTION AND SYNTHESIS

Two authors independently abstracted data from each publication using an evidence table template (see Appendix E). They compared results of their data abstraction and through consensus finalized the data tables. Due to methodological heterogeneity of studies within topics, and to the lack of literature of adequate quality, data were not combined quantitatively for all but one topic. The exception was Prophylactic Hypothermia, for which a meta-analysis was performed.

Authors drafted manuscripts for each topic. The entire team gathered for a 2-day work session to discuss the literature base and to achieve consensus on classification of evidence and level of recommendations. Some topics, while considered important, were eliminated due to lack of a literature base (e.g., At-Risk Non-Comatose Patient, Hyperacute Rehabilitation, ICP in the Elderly, and Decompressive Therapies). Manuscripts were revised. Virtual meetings were held with a subset of the co-authors to complete the editing and consensus processes. The final draft manuscript was circulated to the peer review panel.

V. QUALITY ASSESSMENT AND CLASSIFICATION OF EVIDENCE FOR TREATMENT TOPICS

In April of 2004, the Brain Trauma Foundation established a collaboration with the Evidence-Based Practice Center (EPC) from Oregon Health & Science University (OHSU). Center staff worked with two EPC epidemiologists to develop criteria and procedures for the quality assessment of the literature. Criteria for classification of evidence based on study design and quality are in Table 1, and are derived from criteria developed by the U.S. Preventive Services Task Force,[1] the National Health Service Centre for Reviews and Dissemination (U.K.),[2] and the Cochrane Collaboration.[3] These criteria were used to assess the literature for all topics except ICP Monitoring Technology. Quality criteria specific to technology assessment were used to assess the ICP Monitoring Technology topic.

Two investigators independently read the studies included in the Evidence Tables (both new studies and those maintained from the previous edition) and classified them as Class I, II, or III, based on the design and quality criteria in Table 1. Discrepancies were resolved through consensus, or through a third person's review.

Table 1. Criteria for Classification of Evidence

Class of evidence	*Study design*	*Quality criteria*
I	Good quality randomized controlled trial (RCT)	Adequate random assignment method Allocation concealment Groups similar at baseline Outcome assessors blinded Adequate sample size Intention-to-treat analysis Follow-up rate 85% No differential loss to follow-up Maintenance of comparable groups
II	Moderate quality RCT	Violation of one or more of the criteria for a good quality RCT[a]
II	Good quality cohort	Blind or independent assessment in a prospective study, or use of reliable[b] data in a retrospective study Non-biased selection Follow-up rate 85% Adequate sample size Statistical analysis of potential confounders[c]
II	Good quality case-control	Accurate ascertainment of cases Nonbiased selection of cases/controls with exclusion criteria applied equally to both Adequate response rate Appropriate attention to potential confounding variables
III	Poor quality RCT	Major violations of the criteria for a good or moderate quality RCT[a]

III	Moderate or poor quality cohort	Violation of one or more criteria for a good quality cohort[a]
III	Moderate or poor quality case-control	Violation of one or more criteria for a good quality case-control[a]
III	Case Series, Databases or Registries	

[a]Assessor needs to make a judgment about whether one or more violations are sufficient to downgrade the class of study, based upon the topic, the seriousness of the violation(s), their potential impact on the results, and other aspects of the study. Two or three violations do not necessarily constitute a major flaw. The assessor needs to make a coherent argument why the violation(s) either do, or do not, warrant a downgrade.

[b]Reliable data are concrete data such as mortality or re-operation.

[c]Publication authors must provide a description of important baseline characteristics, and control for those that are unequally distributed between treatment groups.

Class I Evidence is derived from randomized controlled trials. However, some may be poorly designed, lack sufficient patient numbers, or suffer from other methodological inadequacies that render them Class II or III.

Class II Evidence is derived from clinical studies in which data were collected prospectively, and retrospective analyses that were based on reliable data. Comparison of two or more groups must be clearly distinguished. Types of studies include observational, cohort, prevalence, and case control. Class II evidence may also be derived from flawed RCTs.

Class III Evidence is derived from prospectively collected data that is observational, and retrospectively collected data. Types of studies include case series, databases or registries, case reports, and expert opinion. Class III evidence may also be derived from flawed RCTs, cohort, or case-control studies.

VI. QUALITY ASSESSMENT AND CLASSIFICATION OF EVIDENCE FOR ICP MONITORING TECHNOLOGY

Quality criteria typically used for literature about technology assessment are presented in Table 2, and are derived from criteria developed by the U.S. Preventive Services Task Force.[1] As indicated in Table 2, a key criterion for establishing Class I evidence for technology assessment is the application of the device in patients with and without the disease. Thus, the ability to use these criteria in evaluating ICP monitoring technology is limited, in that it would not be ethical to test the monitors in people without probable elevated ICP. Criteria were applied when feasible to estimate the reliability of the findings from each study included for this topic; however, levels of recommendation were not applied.

Table 2. Quality Assessment of Diagnostic Studies

Criteria	
Screening test relevant, available, adequately described	
Study uses credible reference standard, performed regardless of test results	
Reference standard interpreted independently of screening test	
Handles indeterminate results in a reasonable manner	
Spectrum of patients included in the study	
Adequate sample size	
Administration of reliable screening test	
Class of evidence based on above criteria	
Class I:	Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.
Class II:	Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50–100 subjects) and with a "medium" spectrum of patients. A study may be Class II with fewer than 50 patients if it meets all of the other criteria for Class II.
Class III:	Has fatal flaw such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

VII. LEVEL OF RECOMMENDATION

Levels of recommendation are Level I, II, and III, derived from Class I, II, and III evidence, respectively. Level I recommendations are based on the strongest evidence for effectiveness, and represent principles of patient management that reflect a high degree of clinical certainty. Level II recommendations reflect a moderate degree of clinical certainty. For Level III recommendations, the degree of clinical certainty is not established.

To determine the recommendation level derived from a meta-analysis, three criteria are considered:

- Are all included studies of the same quality class?
- Are the findings of the studies in the same or contradictory directions?
- What are the results of analyses that examine potential confounding factors?

Thus, a meta-analysis containing only Class II studies may be used to make a Level III recommendation if the answers to the above questions render uncertainty in the confidence of the overall findings.

VIII. REFERENCES

1. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prevent Med 2001;20:21–35.
2. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). York, UK: NHS Centre for Reviews and Dissemination; 2001. 4 (2nd edition).
3. Mulrow CD, Oxman AD. How to conduct a Cochrane systematic review. Version 3.0.2. Paper presented at: Cochrane Collaboration, 1997; San Antonio, TX.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-7–S-13
DOI: 10.1089/neu.2007.9995

I. Blood Pressure and Oxygenation

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Blood pressure should be monitored and hypotension (systolic blood pressure < 90 mm Hg) avoided.

C. Level III

Oxygenation should be monitored and hypoxia ($PaO_2 < 60$ mm Hg or O_2 saturation $< 90\%$) avoided.

II. OVERVIEW

For ethical reasons, a prospective, controlled study concerning the effects of hypotension or hypoxia on outcome from severe traumatic brain injury (TBI) has never been done. Nevertheless, there is a growing body of evidence that secondary insults occur frequently and exert a powerful, adverse influence on outcomes from severe TBI. These effects appear to be more profound than those that result when hypoxic or hypotensive episodes of similar magnitude occur in trauma patients without neurologic involvement. Therefore, it is important to determine if there is evidence for specific threshold values for oxygenation and blood pressure support.

III. PROCESS

For this update, Medline was searched from 1996 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 17 potentially relevant studies, 3 were added to the existing table and used as evidence for this question (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Hypoxemia

In TBI patients, secondary brain injury may result from systemic hypotension and hypoxemia.[3,18] The effect of hypoxemia was demonstrated by the analysis of a large, prospectively collected data set from the Traumatic Coma Data Bank (TCDB).[2,11] Hypoxemia occurred in 22.4% of severe TBI patients and was significantly associated with increased morbidity and mortality.

In a helicopter transport study, which was not adjusted for confounding factors, 55% of TBI patients were hypoxemic prior to intubation.[18] 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 of $<60\%$, the mortality rate was 50% and all of the survivors were severely disabled.

In an inhospital study of 124 patients with TBI of varying degrees of severity, Jones et al. performed a subgroup analysis of 71 patients for whom there was data collection for eight different types of secondary insults (including hypoxemia and hypotension).[8] Duration of hypoxemia (defined as $SaO_2 \leq 90\%$; median duration ranging from 11.5 to 20 min) was found to be an independent predictor of mortality ($p = 0.024$) but not morbidity ("good" outcome [12-month GCS of good recovery and moderate disability] versus "bad" outcome [GCS of severe disability, vegetative survival, or death], $p = 0.1217$).

Hypotension

Both prehospital and inhospital hypotension have been shown to have a deleterious influence on outcome from severe TBI.[4] In the TCDB studies referenced above,[2,11] a single prehospital observation of hypotension (systolic blood pressure [SBP] <90 mm Hg) was among the five most powerful predictors of outcome. This was statistically independent of the other major predictors such as age, admission Glasgow Coma Scale (GCS) score, ad-

mission 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.[2] These data validate similar retrospectively analyzed Class III[5,6,7,9,12–17,19] reports published previously.

Several studies analyzed the association of inhospital hypotension with unfavorable outcomes. Manley et al. reported a non-significant trend toward increased mortality in patients with GCS < 13 experiencing a single inhospital event of hypotension (SBP ≤ 90) (relative risk 2.05, 95% CI 0.67–6.23).[10] The relative risk increased to 8.1 (95% CI 1.63–39.9) for those with two or more episodes. Thus repeated episodes of hypotension in the hospital may have a strong effect on mortality. Jones et al. found that in patients with episodes of in-hospital hypotension, increased total duration of hypotensive episodes was a significant predictor of both mortality ($p = 0.0064$) and morbidity ("Good" vs. "Bad" outcome, $p = 0.0118$).[8]

The question of the influence of hypoxia and hypotension on outcome has not been subject to manipulative investigation, as it is unethical to assign patients to experimental hypotension. Therefore the large, prospectively collected, observational data set from the TCDB is the best information on the subject that is available. This and other studies show a strong association between hypotension and poor outcomes. However, because of ethical considerations there is no Class I study of the effect of blood pressure resuscitation on outcome.

In a series of studies by Vassar et al.,[20–22] designed to determine the optimal choice of resuscitation fluid, correcting hypotension was associated with improved outcomes. One of these studies was a randomized, double-blind, multicenter trial comparing the efficacy of administering 250 mL of hypertonic saline versus normal saline as the initial resuscitation fluid in 194 hypotensive trauma patients; 144 of these patients (74%) had a severe TBI (defined as an abbreviated injury score [AIS] for the head of 4, 5, or 6). Hypertonic saline significantly increased blood pressure and decreased overall fluid requirements.

Resuscitation End-Points

The value of 90 mm Hg as a systolic pressure threshold for hypotension has been defined by blood pressure distributions for normal adults. Thus, this is more a statistical than a physiological finding. Given the influence of cerebral perfusion pressure (CPP) on outcome, it is possible that systolic pressures 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, but currently there are no data to support this. As such, 90 mm Hg should be considered a threshold to avoid; the actual values to target remain unclear.

V. SUMMARY

A significant proportion of TBI patients have hypoxemia or hypotension in the prehospital setting as well as inhospital. Hypotension or hypoxia increase morbidity and mortality from severe TBI. At present, the defining level of hypotension is unclear. Hypotension, defined as a single observation of an SBP of less than 90 mm Hg, must be avoided if possible, or rapidly corrected in severe TBI patients.[1,4] A similar situation applies to the definition of hypoxia as apnea cyanosis in the field, or a $PaO_2 < 60$ mm Hg. Clinical intuition suggests that correcting hypotension and hypoxia improves outcomes; however, clinical studies have failed to provide the supporting data.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

The major questions for resuscitating the severe TBI patient are as follows:

- The level of hypoxia and hypotension that correlates with poor outcome
- Treatment thresholds
- Optimal resuscitation protocols for hypoxia and hypotension
- The impact of correcting hypoxia and hypotension on outcome
- Specification of target values

VII. EVIDENCE TABLE

Evidence Table I. Blood Pressure and Oxygenation

Reference	*Description of study*	*Data class*	*Conclusion*
Chesnut et al., 1993[2]	A prospective study of 717 consecutive severe TBI patients admitted to four centers investigated the effect on outcome of hypotension (SBP <90 mm Hg) occurring from injury through resuscitation.	III	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 et al., 1995[3]	A prospective audit of 131 patients with severe TBI evaluating the early management of these patients in Northern Ireland.	III	27% of patients were hypoxemic on arrival to the ED.
Fearnside et al., 1993[4]	A prospective study of prehospital and inhospital predictors of outcome in 315 consecutive severe TBI patients admitted to a single trauma center.	III	Hypotension (SBP <90 mm Hg) was an independent predictor of increased morbidity and mortality.
Gentleman et al., 1992[5]	A retrospective study of 600 severe TBI patients in three cohorts evaluating the influence of hypotension on outcome and the effect of improved prehospital care in decreasing its incidence and negative impact.	III	Improving prehospital management decreased the incidence of hypotension but its impact on outcome in patients suffering hypotensive insults was maintained as a statistically significant, independent predictor of poor outcome. Management strategies that prevent or minimize hypotension in the prehospital phase improve outcome from severe TBI.
Hill et al., 1993[6]	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.	III	Improving the management of hypovolemic hypotension is a potential mechanism for improving the outcome from severe TBI.
Jeffreys et al., 1981[7]	A retrospective review of hospital records in 190 TBI patients who died after admission	III	Hypotension was one of the four most common avoidable factors correlated with death.
Kohi et al., 1984[9]	A retrospective evaluation of 67 severe TBI patients seen over a 6-month period were correlated with 6-month outcome.	III	Early hypotension increases the mortality and worsens the prognosis of survivors in severe TBI.

(*continued*)

Evidence Table I. Blood Pressure and Oxygenation (Cont'd)

Reference	*Description of study*	*Data class*	*Conclusion*
Marmarou et al., 1991[11]	From a prospectively collected database of 1,030 severe TBI patients; all 428 patients who met ICU monitoring criteria were analyzed for monitoring parameters that determined outcome and their threshold values.	III	The two most critical values were the proposition of hourly ICP readings greater than 20 mm Hg and the proportion of hourly SBP readings less than 80 mm Hg. The incidence of morbidity and mortality resulting from severe TBI is strongly related to ICP and hypotension measured during the course of ICP management.
Miller et al., 1982[12]	A prospective study of 225 severely head-injured patients regarding the influence of secondary insults on outcome.	III	Hypotension (SBP $<$ 95 mm Hg) was significantly associated with increased morbidity and mortality.
Miller et al., 1978[13]	One hundred consecutive severe TBI patients were prospectively studied regarding the influence of secondary insults on outcome. Seminal report relating early hypotension to increased morbidity and mortality. Influence of hypotension on outcome not analyzed independently from other associated factors.	III	Hypotension (SBP $<$ 95 mm Hg) associated with a non-significant trend toward worse outcome in entire cohort. This trend met statistical significance for patients without mass lesions. Hypotension is a predictor of increased morbidity and mortality from severe TBI.
Narayan et al., 1982[14]	Retrospective analysis of 207 consecutively admitted severe TBI patients. Management included aggressive attempts to control ICP using a threshold of 20 mm Hg.	III	ICP control using a threshold of 20 mm Hg as a part of an overall aggressive treatment approach to severe TBI associated with improved outcome.
Pietropaoli et al., 1992[15]	A retrospective review of the impact of hypotension (SBP 90 mm Hg) on 53 otherwise normotensive severe TBI patients who received early surgery (within 72 h of injury).	III	Early surgery with intraoperative hypotension was significantly correlated with increased mortality from severe TBI in a duration-dependent fashion. The mortality rate was 82% in the group with hypotension and 25% in the normotensive group ($p < 0.001$). The duration f intraoperative hypotension was inversely correlated with Glasgow Outcome Scale score using linear regression ($R = -0.30$, $p = 0.02$).
Rose et al., 1977[16]	A retrospective review of hospital and necropsy records of 116 TBI patients who were known to have talked before dying.	III	Hypotension is a major avoidable cause of increased mortality in patients with moderate TBI.
Seelig et al., 1986[17]	A study of all patients ($n = 160$) with an ICP of 30 mm Hg	III	Early hypotension was significantly correlated with

	during the first 72 h after injury from a prospectively collected database of severe TBI patients (n = 348).		increased incidence and severity of intracranial hypertension and increased mortality.
Stocchetti et al., 1996[18]	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.	III	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.
Vassar et al., 1990[20]	A randomized, double-blind, clinical trial of 106 patients over an 8-month period. Intracranial hemorrhage was present in 28 (26%) patients.	II	No beneficial or adverse effects of rapid infusion of 7.5% NaCl or 7.5% NaCl/6% dextran 70 were 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 et al., 1991[21]	A randomized, double-blind multicenter clinical trial of 166 hypotensive patients over a 44-month month period. Fifty-three of these patients (32%) had a severe TBI (defined as an AIS score for the head of 4, 5, or 6).	III	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
Vassar et al., 1993[22]	A randomized, double-blind multicenter trial comparing the efficacy of administering 250 mL of hypertonic saline versus 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 TBI (defined as an abbreviated injury score [AIS] for the head of 4, 5, or 6).	III	Raising the blood pressure in the hypotensive, severe TBI 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. Thee 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.
New studies			
Jones et al., 1994[8]	Prospective analysis of 124 patients ≥14 years old admitted to single center with a GCS ≤12, or >12 and Injury Severity Score ≥16, with clinical	III	Mortality is best predicted by durations of hypotensive (p = 0.0064), hypoxemia (p = 0.0244), and pyrexic (p = 0.0137) insults. Morbidity ("Good" vs. "Bad"

(*continued*)

Evidence Table I. Blood Pressure and Oxygenation (Cont'd)

Reference	*Description of study*	*Data class*	*Conclusion*
	indications for monitoring. Subgroup analysis performed on 71 patients for whom data existed for 8 potential secondary insults (ICP, hypotension, hypertension, CPP, hypoxemia, pyrexia, bradycardia, tachycardia) to identify predictors of morbidity/mortality		outcome) was predicted by hypotensive insults ($p = 0.0118$), and pupillary response on admission ($p = 0.0226$).
Manley et al., 2001[10]	Prospective cohort of 107 patients with GCS 13 admitted to a single center; primarily evaluating impact of hypoxic and hypotensive episodes during initial resuscitation on mortality. Impact of multiple episodes of hypoxia or hypotension analyzed.	III	Early inhospital hypotension but not hypoxia is associated with increased mortality. Odds ratio for mortality increases from 2.1 to 8.1 with repeated episodes of hypotension.
Struchen et al., 2001[19]	Cohort of 184 patients with severe TBI admitted to a single level I trauma center neurosurgical ICU who received continuous monitoring of ICP, MAP, CPP, and jugular venous saturation (SjO_2). Primary outcomes were GOS and Disability Rating Scale (DRS). Analysis included multiple regression model evaluating effect of physiologic variables on outcome.	III	Adjusting for age and emergency room GCS, ICP $>$ 25 mm Hg, MAP $<$ 80 mm Hg, CPP $<$ 60 mm Hg, and $SjO_2 < 50\%$ were associated with worse outcomes.

VIII. REFERENCES

1. American College of Surgeons. Advanced Trauma Life Support Instructor's Manual. Chicago, 1996.
2. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34:216–222.
3. Cooke RS, McNicholl BP, Byrnes DP. Early management of severe head injury in Northern Ireland. Injury; 1995; 26:395–397.
4. Fearnside MR, Cook RJ, McDougall P, et al. The Westmead Head Injury Project outcome in severe head injury. A comparative analysis of pre-hospital, clinical, and CT variables. Br J Neurosurg 1993;7:267–279.
5. Gentleman D. Causes and effects of systemic complications among severely head-injured patients transferred to a neurosurgical unit. Int Surg 1992;77:297–302.
6. Hill DA, Abraham KJ, West RH. Factors affecting outcome in the resuscitation of severely injured patients. Aust NZ J Surg 1993;63:604-609.
7. Jeffreys RV, Jones JJ. Avoidable factors contributing to the death of head injury patients in general hospitals in Mersey Region. Lancet 1981;2:459–461.
8. Jones PA, Andrews PJD, Midgely S, et al. Measuring the burden of secondary insults in head injured patients during intensive care. J Neurosurg Anesthesiol 1994;6: 4–14.
9. Kohi YM, Mendelow AD, Teasdale GM, et al. Extracranial insults and outcome in patients with acute head injury—relationship to the Glasgow Coma Scale. Injury 1984;16:25–29.
10. Manley G, Knudson M, Morabito D, et al. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. Arch Surg 2001;136:1118–1123.

11. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 1991;75:159–166.

12. Miller JD, Becker DP. Secondary insults to the injured brain. J R Coll Surg (Edinb) 1982;27:292–298.

13. Miller JD, Sweet RC, Narayan R, et al. Early insults to the injured brain. JAMA 1978;240:439–442.

14. Narayan R, Kishore P, Becker D, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with head injury. J Neurosurg 1982;56:650–659.

15. Pietropaoli JA, Rogers FB, Shackford SR, et al. The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. J Trauma 1992;33:403–407.

16. Rose J, Valtonen S, Jennett B. Avoidable factors contributing to death after head injury. Br Med J 1977;2:615–618.

17. Seelig JM, Klauber MR, Toole BM, et al. Increased ICP and systemic hypotension during the first 72 hours following severe head injury. In: Miller JD, Teasdale GM, Rowan JO, et al. (eds): Intracranial Pressure VI. Springer-Verlag, Berlin, 1986:675–679.

18. Stochetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. J Trauma 1996;40:764–767.

19. Struchen MA, Hannay HJ, Contant CF, et al. The relation between acute physiological variables and outcome on the Glasgow Outcome Scale and Disability Rating Scale following severe traumatic brain injury. J Neurotrauma 2001;18:115–125.

20. Vassar MJ, Perry CA, Holcroft JW. Analysis of potential risks associated with 7.5% sodium chloride resuscitation of traumatic shock. Arch Surg 1990;125:1309–1315.

21. Vassar MJ, Perry CA, Gannaway WL, et al. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. Arch Surg 1991;126:1065–1072.

22. Vassar MJ, Fischer RP, O'Brien PE, et al. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. The Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. Arch Surg 1993;128:1003–1011.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-14–S-20
DOI: 10.1089/neu.2007.9994

II. Hyperosmolar Therapy

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Mannitol is effective for control of raised intracranial pressure (ICP) at doses of 0.25 gm/kg to 1 g/kg body weight. Arterial hypotension (systolic blood pressure < 90 mm Hg) should be avoided.

C. Level III

Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes.

II. OVERVIEW

Hyperosmolar agents currently in clinical use for traumatic brain injury (TBI) are mannitol and hypertonic saline (HS) (Table 1).

Mannitol

Mannitol is widely used in the control of raised ICP following TBI. Its use is advocated in two circumstances. First, a single administration can have short term beneficial effects, during which further diagnostic procedures (e.g., CT scan) and interventions (e.g., evacuation of intracranial mass lesions) can be accomplished. Second, mannitol has been used as a prolonged therapy for raised ICP. There is, however, a lack of evidence to recommend repeated, regular administration of mannitol over several days. Although there are data regarding its basic mechanism of action, there are few human studies that validate different regimens of mannitol administration.

Hypertonic Saline

Current therapies used for ICP control (mannitol, barbiturates) bear the risk of further reducing perfusion to the brain either by lowering blood pressure and cerebral perfusion pressure (CPP) or by causing cerebral vasoconstriction (hyperventilation). Ideally, a therapeutic intervention should effectively reduce ICP while preserving or improving CPP.

The use of HS for ICP control was discovered from studies on "small volume resuscitation."[28,43,51,59] Hypertonic saline solutions were tested in poly-traumatized patients with hemorrhagic shock. The subgroup with accompanying TBI showed the greatest benefit in terms of survival and hemodynamic parameters were restored effectively.[59] The findings that HS may benefit patients with TBI while preserving or even improving hemodynamic parameters stimulated further research on the effects of HS solutions on increased intracranial pressure in patients with TBI[15,18,36,40,41,46,51] subarachnoid hemorrhage,[18,55,56] stroke,[50] and other pathologies.[14]

III. PROCESS

This chapter combines information from the previous guideline about mannitol with new information about hypertonic saline. For this topic, Medline was searched from 1966 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 42 potentially relevant studies, no new studies were added to the existing table for mannitol (Evidence Table I) and 2 were included as evidence for the use of hypertonic saline (Evidence Table II).

Three publications about mannitol were identified in the literature research[8,9,10] that were not included as evidence due to questions about the integrity of the trial data.[61]

IV. SCIENTIFIC FOUNDATION

Mannitol

Over the last three decades, mannitol has replaced other osmotic diuretics for the treatment of raised ICP.[2,4,7,12,19,20,26,30] Its beneficial effects on ICP, CPP,

CBF, and 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 in animal models.[7,31,34,35,37] There is still controversy regarding the exact mechanisms by which it exerts its beneficial effect, and it is possible that it has two distinct effects in the brain.[33]

1. One effect may be an immediate plasma expanding effect, which reduces the hematocrit, increases the deformability of erythrocytes, and thereby reduces blood viscosity, increases CBF, and increases cerebral oxygen delivery.[2,6,21,31,35,34,35,44] These rheological effects may 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).[30,33,34,44]
2. The osmotic effect of mannitol is delayed for 15–30 min while gradients are established between plasma and cells.[2] Its effects persist for a variable period of 90 min to 6 or more h, depending upon the clinical conditions.[4,6,27,30,57] Arterial hypotension, sepsis, nephrotoxic drugs, or preexisting renal disease place patients at increased risk for renal failure with hyperosmotic therapy.[4,13,26,31]

Relatively little is known regarding the risks of mannitol when given in combination with hypertonic saline, or when used for longer periods (>24 h). The last edition of these guidelines provided a Level III recommendation that intermittent boluses may be more effective than continuous infusion. However, recent analysis concluded that there are insufficient data to support one form of mannitol infusion over another.[42,46,48]

The administration of mannitol has become common practice in the management of TBI with suspected or actual raised intracranial pressure. In a randomized controlled trial (RCT) comparing mannitol with barbiturates for control of high ICP after TBI, mannitol was superior to barbiturates, improving CPP, ICP, and mortality.[49] However, the evidence from this study is Class III.

Hypertonic Saline

Mechanism of action. The principal effect on ICP is possibly due to osmotic mobilization of water across the intact blood–brain barrier (BBB) which reduces cerebral water content.[5,17,39,60] While not applicable as evidence, in an animal study HS was shown to decrease water content, mainly of non-traumatized brain tissue, due to an osmotic effect after building up a gradient across the intact blood brain barrier.[11] Effects on the microcirculation may also play an important role: HS dehydrates endothelial cells and erythrocytes which increases the diameter of the vessels and deformability of erythrocytes and leads to plasma volume expansion with improved blood flow.[22,25,29,39,49,52,53] HS also reduces leukocyte adhesion in the traumatized brain.[16]

Potential side effects. A rebound phenomenon as seen with mannitol has been reported after 3% saline administration for non-traumatic edema,[40] but not after human TBI even with multiple use.[16,18] Hypertonic saline infusion bears the risk of central pontine myelinolysis when given to patients with preexisting chronic hyponatremia.[24] Hyponatremia should be excluded before administration of HS. In healthy individuals with normonatremia, central pontine myelinolysis was not reported with doses of hypertonic saline given for ICP reduction. In the pediatric population sustained hypernatremia and hyperosmolarity were generally well tolerated as long as there were no other conditions present, such as hypovolemia which may result in acute renal failure.[23] Hypertonic saline also carries a risk of inducing or aggravating pulmonary edema in patients with underlying cardiac or pulmonary problems.[40]

Continuous infusion. Shackford et al. conducted a RCT with 34 adult patients with a GCS of 13 and less after TBI. The hypertonic saline group received 1.6% saline titrated to treat hemodynamic instability with systolic blood pressures of <90 mm Hg during their pre and inhospital phase for up to 5 days.[51] Maintenance fluid in these patients was normal saline. The other patient group received lactated Ringer's for hemodynamic instability and half normal saline as maintenance solution. The groups were not well matched and the HS group at baseline had higher ICPs and lower GCS scores. Despite these differences the ICP course was not different between groups. Outcome at discharge was also not different between groups. Serum sodium and osmolarity were higher in the HS group. Given the difference in study groups in terms of initial ICP and GCS, it is not possible to draw firm conclusions from this study. In addition, the concentration of HS tested (1.6%) was low compared to other trials.

In a retrospective study, Qureshi et al. reported the effects of a continuous 3% saline/acetate infusion in 36 patients with severe TBI compared to the continuous infusion of normal saline in 46 control patients.[41] The incidence of cerebral mass lesions and penetrating TBI was higher in the HS group and ICP was not monitored in all patients. Given the mismatch of patients between groups this study does not help to clarify the role of continuous infusion of HS after TBI.

More studies regarding continuous administration of HS have been done in children with severe TBI.[1] Three Class III studies showed beneficial effects of continuous

HS infusion on ICP in pediatric TBI patients.[23,38,54] Effective doses range between 0.1 and 1.0 mL/kg of body weight per hour, administered on a sliding scale. The choice of mannitol or hypertonic saline as first line hyperosmolar agent was left to the treating physician. The pediatric guidelines[1] currently recommend continuous infusion of 3% saline for control of increased ICP as a Level III recommendation.

Bolus administration for treatment of intracranial hypertension. Four case series have been published evaluating bolus infusion of between 7.2% and 10% saline in patients after TBI.[16,18,36,45] In a total of 32 patients, bolus infusion of HS reliably decreased ICP in all studies. HS effectively lowered ICP in patients that were refractory tomannitol.[16,18,45] Repeated administration of HS in the same patient was always followed by a reduction in ICP and a rebound phenomenon was not observed.[16,18] In a pilot RCT HS bolus infusion was compared to mannitol in nine patients, and HS was found to be equivalent or superior to mannitol for ICP reduction.[3] Taken together, these studies suggest that HS as a bolus infusion may be an effective adjuvant or alternative to mannitol in the treatment of intracranial hypertension. However, the case series design, and the small sample of the trial, do not allow for conclusions.

Table 1. Definition of Commonly Used Terms in the Treatment of Intracranial Hypertension with Hyperosmotic Solutions

Osmolarity	The osmotic concentration of a solution expressed as osmoles of solute per liter of solution
Osmolality	The osmotic concentration of a solution expressed as osmoles of solute per kg of solution. Osmolality (mOsm/kg) = ([Na] × 2) + (glucose/18) + (BUN/2.3) (Na^+ in mmol/L glucose and BUN in mg/dL)
Osmotic pressure	The pressure exerted by a solution necessary to prevent osmosis into that solution when it is separated from the pure solvent by a semipermeable membrane. Osmotic pressure (mmHg) = 19.3 × osmolality (mOsm/kg)
Oncotic pressure	A small portion of the total osmotic pressure that is due to the presence of large protein molecules
Hyperosmolarity	Increase in the osmolarity of a solution to above the normal plasma concentration
Hypertonicity	The ability of a hyperosmolar solution to redistribute fluid from the intra- to the extracellular compartment. Urea, for example, may be hyperosmotic but since it equilibrates rapidly across membranes it is not hypertonic (see Table 2: low BBB reflexion coefficient for urea)

V. SUMMARY

Mannitol is effective in reducing ICP in the management of traumatic intracranial hypertension. Current evidence is not strong enough to make recommendations on the use, concentration and method of administration of hypertonic saline for the treatment of traumatic intracranial hypertension.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

- An RCT is required to determine the relative benefit of hypertonic saline versus mannitol.
- Research is needed to determine the optimal administration and concentration for hypertonic saline.
- The use of a single high dose of mannitol needs to be validated, preferably in a multicenter trial, as well as for the entire severe TBI population.
- Studies are required to determine the efficacy of prolonged hypertonic therapy for raised ICP, especially with respect to the effect of this therapy in relation to outcome.

VII. EVIDENCE TABLES

Evidence Table I. Mannitol

Reference	*Description*	*Data class*	*Conclusion*
Becker and Vries, 1972[4]	The alleviation of increased ICP by chronic administration of osmotic agents. Retrospective analysis over an epoch of ICU care; patients not clearly identified.	III	Continuous infusion of Mannitol offers no advantage over bolus use. Mannitol, often causes renal failure when continued if serum osmolarity exceeds 320 mOSm.
Eisenberg et al., 1988[12]	High dose barbiturate control of elevated ICP in patients with severe TBI. A trial of barbiturates in patients who fail ICP control with conventional measures ($n = 73$) randomized patients).	II	Mannitol, hyperventilation, and CSF drainage were effective for ICP control in 78% of patients.
James et al., 1980[19]	Method for the control of ICP with hypertonic mannitol. Retrospective study based upon ICU usage patterns.	III	Effect becomes less after multiple doses, especially greater than 3–4 doses/24 h. Hyperventilation initially avoids risk of ICP "spike" in first minutes.
Marshall et al., 1978[27]	Mannitol dose requirements in TBI patients. Retrospective study.	III	1. An osmotic gradient of 10 mOSm or more is effective in lowering ICP. 2. Fast i.v. infusion of 0.5–1 g/kg is best; effect begins at 2 min, lasts 6–8 h or more. 3. Effect becomes less after multiple doses—esp. >3–4 doses/24 h 4. Hyperventilation initially avoids any risk of ICP "spike" in first minutes.
Mendelow et al., 1985[31]	Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human TBI. Retrospective analysis.	III	Mannitol consistently improved MAP, CPP, and CBF, and lowered ICP by 10–20 min after infusion; the effect was greater with diffuse injury, and in normal hemisphere. CBF increase was greatest when CPP was 50 mm Hg. (rheologic effect is important).
Miller et al., 1975[32]	Effect of mannitol and steroid therapy on intracranial volume-pressure relationships. Observations in an ICU TBI population, using, e.g., pressure/volume index as endpoint.	III	Brain compliance and V/P response improves rapidly after mannitol infusion; possibly a rheological effect.

(*continued*)

Evidence Table I. Mannitol (Cont'd)

Reference	*Description*	*Data class*	*Conclusion*
Muizelaar et al., 1984[33]	Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severe TBI patients.	III	Mannitol works best on ICP when autoregulation is intact; suggests rheologic effect is more important than osmotic effect.
Schwartz et al., 1984[49]	Randomized trial comparing mannitol with barbiturates for ICP control. Crossover permitted. Sequential analysis, $n = 59$.	III	Pentobarbital was not significantly better than mannitol. Mannitol group had better outcome mortality 41% vs. 77%. CPP much better with mannitol than barbiturates (75 vs. 45 mm Hg)

Evidence Table II. Hypertonic Saline

Reference	*Description*	*Data class*	*Conclusion*
Qureshi et al., 1999[41]	Retrospective analysis comparing continuous administration of 3% sodium chloride/acetate solution at 75–50 mL/h ($n = 30$) or 2% solution ($n = 6$) to NS maintenance in 82 TBI patients with GCS $\leq$ 8.	III	More penetrating TBI and mass lesions in HS group. HS group had a higher inhospital mortality. Patients treated with HS were more likely to receive barbiturate treatment.
Shackford et al., 1998[51]	Randomized controlled trial comparing 1.6% saline to lactated Ringer's for hemodynamic instability in pre and inhospital phase in 34 patients with TBI and GCS $\leq$ 13.	III	Baseline ICP higher and GCS lower in HS group. Despite this, HS effectively lowered ICP; ICP course was not different between groups. Cumulative fluid balance greater in LR group. Daily serum sodium, osmolarity and ICP interventions greater in HS group. GOS was not different between groups

VIII. REFERENCES

1. Adelson PD, Bratton SL, Carney NA, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Pediatr. Crit. Care Med. 2003;4.
2. Barry KG, Berman AR. Mannitol infusion. Part III. The acute effect of the intravenous infusion of mannitol on blood and plasma volume. N. Engl. J. Med. 1961;264: 1085–1088.
3. Battison C, Andrews PJ, Graham C, et al. Randomized, controlled trial of the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. Crit. Care Med. 2005;33: 196–202.
4. Becker DP, Vries JK. The alleviation of increased intracranial pressure by the chronic administration of osmotic agents. In: Intracranial Pressure M. Brock and H Dietz (eds), Springer: Berlin) 1972:309–315.
5. Berger S, Schurer L, Hartl R, et al. Reduction of post-traumatic intracranial hypertension by hypertonic/hyperoncotic saline/dextran and hypertonic mannitol. Neurosurgery 1999;37:98–107.
6. Brown FD, Johns L, Jafar JJ, et al. Detailed monitoring of the effects of mannitol following experimental head injury. J Neurosurg 1979;50:423–432.
7. Bullock R, Teasdale GM. Head injuries. In: ABC of Major Trauma. Skinner, O'Driscoll, and Erlam (eds), BMJ Medical Publisher: London, 1991.

8. Cruz J, Minoja G, Okuchi K. Improving clinical outcomes from acute subdural hematomas with the emergency preoperative administration of high doses of mannitol: a randomized trial. Neurosurgery 2001;49:864–871.

9. Cruz J, Minoja G, Okuchi K. Major clinical and physiological benefits of early high doses of mannitol for intraparenchymal temporal lobe hemorrhages with abnormal papillary widening: a randomized trial. Neurosurgery 2002;51:628–637.

10. Cruz J, Minoja G, Okuchi K, et al. Successful use of new high-dose mannitol treatment in patients with Glasgow Coma Scale scores of 3 and bilateral abnormal pupillary widening: a randomized trial. J. Neurosurg. 2004;100:376–383.

11. Cserr HF, De Pasquale M, Patlak CS. Regulation of brain water and electrolytes during acute hyperosmolality in rats. Am. J. Physiol. 1987;253:F522–529.

12. Eisenberg HM, Frankowski RF, Contant C, Marshall LM, Walker MD, and the Comprehensive Central Nervous System Trauma Centers. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J. Neurosurg. 1988;69:15–23.

13. Feig PU, McCurdy DK. The hypertonic state. N. Engl. J. Med. 1977;297:1449.

14. Gemma M, Cozzi S, Tommasino C, et al. 7.5% hypertonic saline versus 20% mannitol during elective supratentorial procedures. J. Neurosurg. Anesthesiol. 1997;9:329–334.

15. Hartl R, Ghajar J, Hochleuthner H, et al. Hypertonic/hyperoncotic saline reliably reduces ICP in severely head-injured patients with intracranial hypertension. Acta Neurochir. Suppl. (Wien) 1977;70:126–129.

16. Härtl R, Medary M, Ruge M, et al. Hypertonic/hyperoncotic saline attenuates microcirculatory disturbances after traumatic brain injury. J. Trauma 1977;42:S41–S47.

17. Härtl R, Schürer L, Goetz C, et al. The effect of hypertonic fluid resuscitation on brain edema in rabbits subjected to brain injury and hemorrhagic shock. Shock 1995;3: 274–279.

18. Horn P, Munch E, Vajkoczy P, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. Neurol. Res. 1999;21:758–764.

19. James HE. Methodology for the control of intracranial pressure with hypertonic mannitol. Acta Neurochir. 1980; 51:161–172.

20. Jennett B, Teasdale GM. Management of Head Injuries. FA Davis: Philadelphia, 1982.

21. Kassel NF, Baumann KW, Hitchon PW, et al. The effect of high dose mannitol on cerebral blood flow in dogs with normal intracranial pressure. Stroke 1982;13:59–61.

22. Kempski O, Obert C, Mainka T, et al. Small volume resuscitation as treatment of cerebral blood flow disturbances and increased ICP in trauma and ischemia. Acta Neurochir. Suppl. 1996;66:114–117.

23. Khanna S, Davis D, Peterson B, et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric traumatic brain injury. Crit. Care Med. 2000;28:1144–1151.

24. Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. Science 1981;211:1068–1070.

25. Kreimeier U, Bruckner UB, Messmer K. Improvement of nutritional blood flow using hypertonic-hyperoncotic solutions for primary treatment of hemorrhagic hypotension. Eur. Surg. Res. 1988;20:277–279.

26. Loughhead MG. Brain resuscitation and protection. Med. J. Aust. 1988;148:458–466.

27. Marshall LF, Smith RW, Rauscher LA. Mannitol dose requirements in brain injured patients. J. Neurosurg. 1978; 48:169–172.

28. Mattox KL, Maningas PA, Moore EE, et al. Prehospital hypertonic saline/dextran infusion for post-traumatic hypotension. The U.S.A. Multicenter Trial. Ann. Surg. 1991;213:482–491.

29. Mazzoni MC, Borgstrom P, Intaglietta M, et al. Capillary narrowing in hemorrhagic shock is rectified by hyperosmotic saline-dextran reinfusion. Circ. Shock 1990;31:407–418.

30. McGraw CP, Howard G. The effect of mannitol on increased intracranial pressure. Neurosurgury 1983;13: 269–271.

31. Mendellow AD, Teasdale GM, Russell T, et al. Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. J. Neurosurg. 1985;63: 43–48.

32. Miller JD, Leach PJ. Assessing the effects of mannitol and steroid therapy on intracranial volume/pressure relationships. J. Neurosurg. 1975;42:274–281.

33. Muizelaar JP, Lutz HA, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head injured patients. J. Neurosurg. 1984;61: 700–706.

34. Muizelaar JP, Vanderpoel HG, Li Z, et al. Pial arteriolar diameter and CO2 reactivity during prolonged hyperventilation in the rabbit. J. Neurosurg. 1988;69:923–927.

35. Muizelaar JP, Wei EP, Kontos HA, et al. Mannitol causes compensatory cerebral vasoconstriction and vasodilatation to blood viscosity changes. J. Neurosurg. 1983;59:822–828.

36. Munar F, Ferrer AM, de Nadal M, et al. Cerebral hemodynamic effects of 7.2% hypertonic saline in patients with head injury and raised intracranial pressure. J. Neurotrauma 2000;17:41–51.

37. Nath F, Galbraith S. The effect of mannitol on cerebral white matter water content. J. Neurosurg. 1986;65:41–43.

38. Peterson B, Khanna S, Fisher B, et al. Prolonged hypernatremia controls elevated intracranial pressure in head-in-

jured pediatric patients. Crit. Care Med. 2000;28:1136–1143.

39. Prough DS, Whitley JM, Taylor CL, et al. Regional cerebral blood flow following resuscitation from hemorrhagic shock with hypertonic saline. Influence of a subdural mass. Anesthesiology 1991;75:319–327.

40. Qureshi AI, Suarez JI, Bhardwaj A, et al. Use of hypertonic (3%) saline/acetate infusion in the treatment of cerebral edema: effect on intracranial pressure and lateral displacement of the brain. Crit. Care Med. 1998;26:440–446.

41. Qureshi AI, Suarez JI, Castro A, et al. Use of hypertonic saline/acetate infusion in treatment of cerebral edema in patients with head trauma: experience at a single center. J. Trauma 1999;47:659–665.

42. Roberts I, Schierhout G, Wakai A. Mannitol for acute traumatic brain injury. Cochrane Syst. Rev. 2003;2:CD001049.

43. Rocha e Silva M, Velasco IT, Nogueira da Silva RI, et al. Hyperosmotic sodium salts reverse severe hemorrhagic shock: other solutes do not. Am. J. Physiol. 1987;253: H751–H762.

44. Rosner MJ, Coley I. Cerebral perfusion pressure: a hemodynamic mechanism of mannitol and the pre-mannitol hemogram. Neurosurgery 1987;21:147–156.

45. Schatzmann C, Heissler HE, Konig K, Klinge-Xhemajli P, et al. Treatment of elevated intracranial pressure by infusions of 10% saline in severely head injured patients. Acta Neurochir. Suppl. (Wien) 1998;71:31–33.

46. Schierhout G, Roberts I. Mannitol for acute traumatic brain injury. Cochrane Database Syst. Rev. 2000;2: CD001208.

47. Schmoker JD, Zhuang J, Shackford SR. Hypertonic fluid resuscitation improves cerebral oxygen delivery and reduces intracranial pressure after hemorrhagic shock. J. Trauma 1991;31:1607–1613.

48. Schrot RJ, Muizelaar JP. Mannitol in acute traumatic brain injury. Lancet 2002;359:1633–1634.

49. Schwartz ML, Tator CH, Rowed DW, University of Toronto Head Injury Treatment Study. A prospective randomized comparison of pentobarbital and mannitol. Can. J. Neurol. Sci. 1984;11:434–440.

50. Schwarz S, Schwab S, Bertram M, et al. Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. Stroke 1998;29:1550–1555.

51. Shackford SR, Bourguignon PR, Wald SL, et al. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. J. Trauma 1998;44: 50–58.

52. Shackford SR, Schmoker JD, Zhuang J. The effect of hypertonic resuscitation on pial arteriolar tone after brain injury and shock. J. Trauma 1994;37:899-908.

53. Shackford SR, Zhuang J, Schmoker J. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. J. Neurosurg 1992;76:91–98.

54. Simma B, Burger R, Falk M, et al. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. Crit. Care Med. 1998;26:1265–1270.

55. Suarez JI, Qureshi AI, Bhardwaj A, et al. Treatment of refractory intracranial hypertension with 23.4% saline. Crit. Care Med. 1998;26:1118–1122.

56. Suarez JI, Qureshi AI, Parekh PD, et al. Administration of hypertonic (3%) sodium chloride/acetate in hyponatremic patients with symptomatic vasospasm following subarachnoid hemorrhage. J. Neurosurg. Anesthesiol. 1999;11:178–184.

57. Takagi H, Saito T, Kitahara T, et al. The mechanism of the ICP reducing effect of mannitol. In: Intracranial Pressure V. S. Ishii, H. Nagai, and N. Brock (eds), Springer: Berlin, 1983:729–733.

58. Vassar MJ, Perry CA, Gannaway WL, et al. 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. Arch. Surg. 1991;126:1065–1072.

59. Wade CE, Grady JJ, Kramer GC, et al. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. J. Trauma 1997;42:S61–S65.

60. Zornow MH. Hypertonic saline as a safe and efficacious treatment of intracranial hypertension. J. Neurosurg. Anesthesiol. 1996;8:175–177.

61. Roberts I, Smith R, Evans S. Doubts over head injury studies. BMJ 2007;334:392–394.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-21–S-25
DOI: 10.1089/neu.2007.9993

III. Prophylactic Hypothermia

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

There are insufficient data to support a Level II recommendation for this topic.

C. Level III

Pooled data indicate that prophylactic hypothermia is not significantly associated with decreased mortality when compared with normothermic controls. However, preliminary findings suggest that a greater decrease in mortality risk is observed when target temperatures are maintained for more than 48 h.

Prophylactic hypothermia is associated with significantly higher Glasgow Outcome Scale (GOS) scores when compared to scores for normothermic controls.

Comment Regarding Classification of Level of Evidence for Meta-Analyses

As stated in the Method Section of this guideline, to determine the recommendation level derived from a meta-analysis, three criteria are considered: (1) are all included studies of the same quality class, (2) are the findings of the studies in the same or contradictory directions, and (3) what are the results of sub-analyses that examine concerns about potential confounding factors? In this meta-analysis, although all included studies were Class II, the sub-analyses findings introduced sufficient concern about unknown influences to render the recommendation a Level III.

II. OVERVIEW

Although hypothermia is often induced prophylactically on admission and used for ICP elevation in the ICU in many trauma centers, the scientific literature has failed to consistently support its positive influence on mortality and morbidity. Four meta-analyses of hypothermia in patients with TBI have been published.[2,7,8,12] All analyses concluded that the evidence was insufficient to support routine use of hypothermia, and recommended further study to determine factors that might explain variation in results. Thus, for this topic a meta-analysis was conducted of induced prophylactic hypothermia that includes studies published subsequent to the last meta-analysis, using specific inclusion criteria designed to minimize heterogeneity. Only studies assessed to be Class II evidence or better were included. Also excluded was literature about induced hypothermia for ICP control because there were inconsistent inclusion criteria and outcome assessments across studies.

Study Selection Criteria

Selection criteria were as follows:

- Patients with TBI, age ≥14 years (studies that enrolled patients under age 14 were included if at least 85% of patients were ≥14 years)
- Hypothermia therapy used as prophylaxis, regardless of intracranial pressure (ICP) (studies in which hypothermia was used as treatment for uncontrollable ICP, and those that enrolled only patients with controlled ICP (e.g., <20 mm Hg), were excluded)
- Assessed all-cause mortality

Outcomes

All-cause mortality at the end of the follow-up period was the primary outcome evaluated. Secondary outcomes included favorable neurological status, defined as the proportion of patients that achieved a Glasgow Outcome Scale score (GOS) of 4 or 5 (good outcome) at the end of the follow-up period.

Statistical Methods

Only data from the moderate (Level II) to good (Level I) quality trials were used to calculate the pooled relative risk (RR) and 95% confidence intervals (CIs) for all-cause mortality and good neurological outcome using a random-effects model. Analyses were conducted using RevMan version 4.2 (Update Software). Statistical heterogeneity was calculated using the chi-squared test.

A priori particular aspects of hypothermia treatment were identified, and a sensitivity analysis was conducted

to examine their relationship to all-cause mortality. These aspects were as follows:

- Target cooling temperature (32–33°C or >33°C)
- Cooling duration (<48 h, 48 h, or >48 h)
- Rate of rewarming (1°C per hour, 1°C per day, or slower)

A *post hoc* analysis was conducted of the relationship between trial setting (single center vs. multicenter) and mortality.

III. PROCESS

Reference lists of the four previous good-quality systematic reviews[2,7,8,12] provided the basis for identification of all eligible randomized controlled trials from 1966 through September, 2002. Electronic databases included MEDLINE (OVID), EMBASE, Cochrane Library, Current Contents, EMBASE, CENTRAL, Science Citation Dissertation Abstract, AANS and CNS abstract center, and Specialist Trials Register for the Injuries Group. Searches included various combinations of MeSH (Medical Subject Headings) terms and text words for hypothermia, brain injury, craniocerebral trauma, and neurosurgery. A supplemental literature search was conducted of MEDLINE (2002 through April 2006) using the search strategy for this question (see Appendix B).

Of 29 potentially relevant trials, 13 met the inclusion criteria for this report.[1,3–6,9–11,13–17] Of those, six trials were assessed as Level II (moderate quality),[1,3,5,10,11,13] and seven as Level III (poor quality).[4,6,9,14–17] Only the moderate quality trials are included in the meta-analysis (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Primary Analysis

Overall, the risk of all-cause mortality for patients treated with hypothermia was not significantly different from that observed in the control groups (RR 0.76; 95% CI 0.50, 1.05; $p = 0.18$) (Fig. 1). However, hypothermia was associated with a 46% increased chance of good outcome, defined as a GOS score of 4 or 5 (RR 1.46; 95% CI 1.12, 1.92; $p = 0.006$) (Fig. 2).

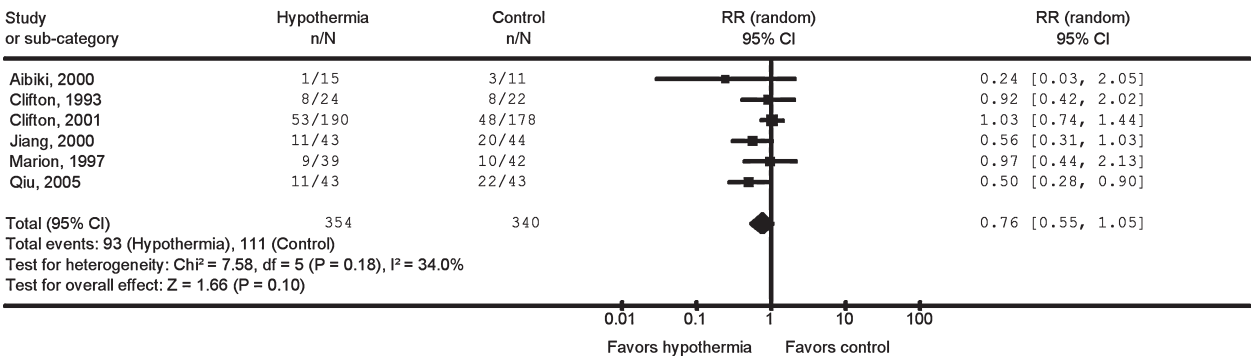

FIG. 1. All-cause mortality.

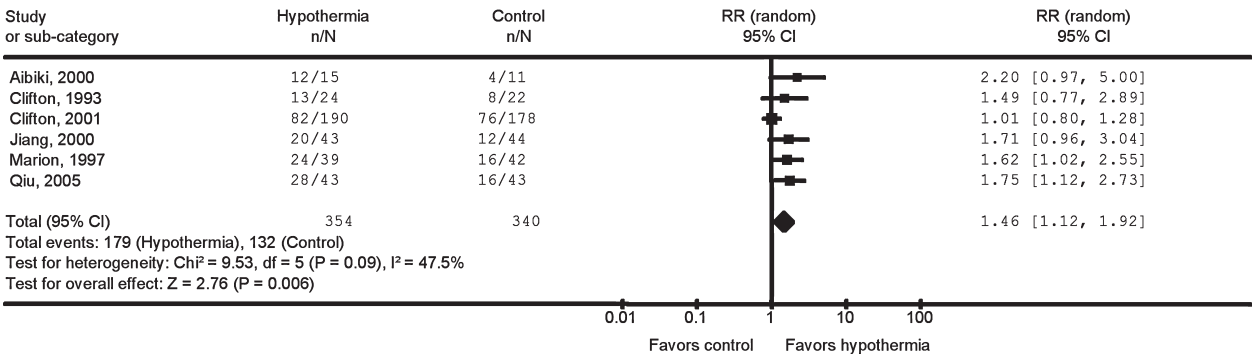

FIG. 2. Good neurological outcomes (GOS score 4 or 5).

Subgroup Analyses

Interpretation of results from subgroup analyses based on aspects of hypothermia treatment protocols is limited due to small sample sizes.

Mortality. Cooling duration was the only aspect of hypothermia treatment, specified a priori, that was possibly associated with decreased rates of death. Preliminary results suggest that there was a significantly lower risk of death when hypothermia was maintained for more than 48 h (RR 0.51; 95% CI 0.34, 0.78). Target cooling temperature and rate of rewarming did not influence mortality.

The *post hoc* analysis indicated an influence of study setting on mortality. One of the six trials, which was the largest trial ($n = 392$) was conducted at multiple centers. When removed from the analysis, hypothermia was associated with a significant decrease in mortality (RR 0.64; 95% CI 0.46, 0.89).

GOS. Target temperature was the only aspect of hypothermia treatment protocols that was possibly associated with improved outcomes. There was significantly greater chance of better outcomes with target temperature ranges of 32–33°C (RR 1.67; CI 1.18, 2.35) and 33–35°C (RR 1.75; CI 1.12, 2.73). Findings from subgroup analyses did not suggest any clear relationship between cooling duration or rate of rewarming and improved outcomes.

As with mortality, the *post hoc* analysis of study setting showed a higher chance of good outcomes from studies conducted in single centers (RR 1.70; CI 1.33, 2.17)

Potential Confounding Influence or Effect Modification of Temperature Management Protocol

A concern regarding interpretation of outcome, introduced in one RCT[3] and a recent systematic review,[8] is the interaction of the patient's baseline temperature at hospital admission with treatment group allocation. As illustrated in Table 1, at randomization, there are four potential patient categories: (a) hypothermic patient randomized to hypothermia; (b) hypothermic patient randomized to normothermia; (c) normothermic patient randomized to hypothermia; and (d) normothermic patient randomized to normothermia.

Table 1. Four Potential Categories for TBI Patients Randomized to Hypothermia or Normothermia

		Hypothermia	*Normothermia*
Condition at admission	Hypothermic	a	b
	Normothermic	c	d

There is potential for either a confounding influence or an effect modification (interaction) of warming hypothermic patients who are randomized to the normothermic group, or of having patients in the normothermic group become hypothermic during the observation period. Clifton et al.[3] addressed this question in part by conducting a subanalysis of 102 patients who were hypothermic at hospital admission, and finding a non-significant trend toward poor outcomes in the control group (Table 1, category b) compared to the treatment group (category a). Data in the studies included in this meta-analysis were insufficient to address this question. Thus, all results reported must be considered in light of the possibility that baseline temperature either confounds or interacts with outcome. Furthermore, there is the possibility that patients who are hypothermic on admission have a decreased brain temperature and may have a pseudo-lowering of the GCS independent of the level of TBI.

V. SUMMARY

Evidence from six moderate quality RCTs did not clearly demonstrate that hypothermia was associated with consistent and statistically significant reductions in all-cause mortality. However, patients treated with hypothermia were more likely to have favorable neurological outcomes, defined as GOS scores of 4 or 5. Preliminary findings suggest that hypothermia may have higher chances of reducing mortality when cooling is maintained for more than 48 hours. Interpretation of results from this and other subgroup analyses based on different aspects of the hypothermia treatment protocols were limited due to small sample sizes. Potential confounding and effect modifying factors that are not accounted for in the trials included in this analysis, such as patients' temperature at admission, limit these recommendations to Level III.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Although 13 RCTs of hypothermia meeting the inclusion criteria have been conducted, only six were included in the meta-analysis due to serious quality flaws in the remaining seven. Flaws, which are markers for improvement in future research, included the following:

- Inadequate or poorly described randomization or allocation concealment
- Inability to rule out confounding of treatment effects, due to differences in (or inadequately described) baseline prognostic factors
- No blinding of outcome assessors
- Inadequate management of missing outcome data

Improvements should also include use of independent event monitoring committees, larger sample sizes across multiple trauma centers, and increased standardization and reporting of control group temperature management protocols.

VII. EVIDENCE TABLES

Evidence Table I. Prophylactic Hypothermia

Reference	*Description of study*	*Data class*	*Conclusion*
Abiki et al., 2000[1]	Single-center RCT comparing effect of moderate hypothermia (3–4 days, 32–33°C) [n 15] vs. normothermia [n 11] on GOS at 6 months post-injury.	II	1 patient died in the hypothermia group (6.7%) vs. 3 in normothermi group (27.3%). Significantly better outcomes (good recovery to moderate disability on 6-month GOS) in hypothermia than normothermia group (80% vs. 36.4%, respectively; ($p = 0.04$).
Clifton et al., 1993[5]	Multi-center RCT comparing effect of hypothermia (2 days, 32 –33°C) [$n = 24$] vs. normothermia $n = 22$] on GOS at 3 months post-injury.	II	No significant difference in mortality between hypothermia and normothermia groups (35% and 36% respectively) or 3-month GOS (good recovery to moderate disability = 52.2% in hypothermia and 36.4% in normothermia groups). Significantly fewer seizures in hypothermia group ($p = 0.019$). No significant differences between groups on other complications.
Clifton et al., 1993[5]	Multi-center RCT comparing effect of hypothermia (2 days, 33°C) [$n = 199$] vs. normothermia $n = 193$] on GOS at 6 months post-injury.	II	No significant difference in mortality between hypothermia and normothermia groups (28% and 27% respectively) or 6-month GOS (severe disability, vegetative, or dead [combined] = 57% in both groups). Trend toward poor outcomes for patients hypothermic on arrival who were randomized to normothermia.
Jiang et al., 2000[10]	Single-center RCT comparing of effect of long-term (3–14 days) mild hypothermia (33–35°C) [$n = 43$] vs. normothermia [$n = 44$] on mortality and GOS at 1 year post-injury.	II	Significantly less hypothermia than normothermia group (25.6% vs. 45.5% respectivly). Significantly better outcomes (good recovery to moderate disability on 1-year GOS) in hypothermia than normothermia group (46.5% vs. 27.3%, respectively; $p < 0.05$). No significant difference

			between groups in complications.
Marion et al., 1997[11]	Single-center RCT comparing of effect of moderate hypothermia (24 h, 32–33°C) [$n = 40$] vs. normothermia [$n = 42$] on GOS at 3 and 6 months, and 1 = year	II	Significantly less recovery to moderate disability on 1-year GOS) in hypothermia than normothermia group (62% vs. 38%, respectively; $p = 0.05$).
Qiu et al., 2005[13]	Single-center RCT comparing effect of mild hypothermia (3–5 days, 33–35°C) [$n = 43$] vs. normothermia [$n = 43$] on mortality and GOS at 2 years post-injury.	II	Significantly less mortality in hypothermia than normothermia group (25.6% vs. 51.2%, respectively). Significantly better outcomes (good recovery or moderate disability on 2-year GOS) in hypothermia than normothermia group (65.1% vs. 37.2, respectivly; $p < 0.05$. Significantly more pulmonary infection in hypothermia than normothermia group (60.5% vs. 32.6%, respectively) and more thrombocytopenia in hypothermia than normothermia group (62.8% vs. 39.5%, respectively; $p < 0.05$).

VIII. REFERENCES

1. Aibiki M, Maekawa S, Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. Crit Care Med 2000;28:3902–3906.
2. Alderson P, Gadkary C, Signorini DF. Therapeutic hypothermia for head injury. Cochrane Database Syst Rev 2004;4:CD001048.
3. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 2001;344:556–563.
4. Clifton GL, Allen S, Berry J, et al. Systemic hypothermia in treatment of brain injury. J Neurotrauma 1992;9(Suppl 2):S487–S495.
5. Clifton GL, Allen S, Barrodale P, et al. A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 1993;10:263-271.
6. Gal R, Cundrle I, Zimova I, et al. Mild hypothermia therapy for patients with severe brain injury. Clin Neurol Neurosurg 2002;104:318–321.
7. Harris OA, Colford JM, Jr., Good MC, et al. The role of hypothermia in the management of severe brain injury: a meta-analysis. Arch Neurol 2002;59:1077–1083.
8. Henderson WR, Dhingra VK, Chittock DR, et al. Hypothermia in the management of traumatic brain injury. A systematic review and meta-analysis. Intensive Care Med 2003;29:1637–1644.
9. Hirayama T, Katayama Y, Kano T, et al. Impact of moderate hypothermia on therapies for intracranial pressure control in severe traumatic brain injury. Intracranial Pressure IX: 9th International Symposium held in Nagaya Japan. Springer-Verlag: New York, 1994:233–236.
10. Jiang J, Yu M, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. J Neurosurg. 2000;93: 546–549.
11. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 1997;336:540–546.
12. McIntyre LA, Fergusson DA, Hebert PC, et al. Prolonged therapeutic hypothermia after traumatic brain injury in adults: a systematic review. JAMA 2003;289:2992–2999.
13. Qiu W-S, Liu W-G, Shen H, et al. Therapeutic effect of mild hypothermia on severe traumatic head injury. Chin J Traumatol 2005;8:27–32.
14. Smrcka M, Vidlak M, Maca K, et al. The influence of mild hypothermia on ICP, CPP and outcome in patients with primary and secondary brain injury. Acta Neuochir Suppl 2005;95:273–275.
15. Yan Y, Tang W. Changes of evoked potentials and evaluation of mild hypothermia for treatment of severe brain injury. Chin J Traumatol 2001;4:8–13.
16. Zhi D, Zhang S, Lin X. Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. Surg Neurol 2003;59:381–385.
17. Zhu Y, Yao J, Lu S, et al. Study on changes of partial pressure of brain tissue oxygen and brain temperature in acute phase of severe head injury during mild hypothermia therapy. Chin J Traumatol 2003;6:152–155.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-26–S-31
DOI: 10.1089/neu.2007.9992

IV. Infection Prophylaxis

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Periprocedural antibiotics for intubation should be administered to reduce the incidence of pneumonia. However, it does not change length of stay or mortality.

Early tracheostomy should be performed to reduce mechanical ventilation days. However, it does not alter mortality or the rate of nosocomial pneumonia.

C. Level III

Routine ventricular catheter exchange or prophylactic antibiotic use for ventricular catheter placement is not recommended to reduce infection.

Early extubation in qualified patients can be done without increased risk of pneumonia.

II. OVERVIEW

In severe traumatic brain injury (TBI) patients, the incidence of infection is increased with mechanical ventilation and invasive monitoring techniques. Infections contribute to morbidity, mortality, and increased hospital length of stay.[7,11,21] For example, as many as 70% of mechanically ventilated patients can develop pneumonia,[21] and ICP monitoring infection rates can be as high as 27%.[14] While there is no current evidence that short-term use of ICP monitors leads to increased morbidity and mortality, health care costs can increase with device reinsertion and administration of antibiotics. Infection prophylaxis for TBI can be divided into several aspects of care, including external ventricular drainage (EVD) and other ICP monitoring devices, and prophylaxis to prevent nosocomial systemic infections.

III. PROCESS

For this new topic, Medline was searched from 1966 through April of 2006 (see Appendix B for search strategy). A second search was conducted using the key words tracheostomy and TBI. Results were supplemented with literature recommended by peers or identified from reference lists. Of 54 potentially relevant studies, 7 were included as evidence for this topic (Evidence Tables I and II).

IV. SCIENTIFIC FOUNDATION

Pressure Monitors

The incidence of infection for ICP devices is reported to be $<$1%–27%,[14] but this incidence also depends upon the method of ascertaining infection. Ventriculostomy colonization is easier to detect because of CSF sampling. Few studies have actually sent ICP devices for culture after usage. When ICP device bacterial colonization is compared, ventricular (by CSF culturing) has an average infection rate of 8% and parenchymal (by culturing the device tip) has an infection rate of 14%.[5] Several factors have been identified that may affect the risk of EVD infection: duration of monitoring; use of prophylactic parenteral antibiotics; presence of concurrent other systemic infections; presence of intraventricular or subarachnoid hemorrhage; open skull fracture, including basilar skull fractures with CSF leak; leakage around the ventriculostomy catheter; and flushing of the ventriculostomy tubing.[2,3,9,14–16,18,22,25,27]

In studies of patients with neurological processes other than or including TBI, contradictory results were found when analyzing infection risk factors for EVD. Mayhall et al.[16] published a sentinel, prospective, observational study of 172 patients with 213 ventriculostomies. The authors found that the cumulative infection risk increased if monitoring duration exceeded five days. However, no increased infection risk was noted if patients had multiple catheters, leading to the conclusion that routine, pro-

phylactic catheter exchanges at 5 days would potentially lower the overall infection rate. Winfield et al.[25] challenged the analysis of cumulative risk in terms of infection and catheter duration. In 184 monitors over a 12-year period, they found the daily infection rate to be less than 2% through the monitoring period. No correlation was noted between daily infection rate and monitoring duration. Age, hospital site of monitor placement, and diagnosis (trauma vs. non-trauma) had no effect on infection rate. The authors concluded that prophylactic catheter exchange was not substantiated.

In a cohort of 584 severe TBI patients, Holloway et al.[9] reevaluated the EVD infection rate and monitoring duration at the same institution as Mayhall.[25] The authors included patients from the multi-centered Traumatic Coma Data Bank. They found that the risk of EVD infections rose over the first 10 days, but, thereafter, decreased significantly. There was no difference in the infection rate in patients who had catheter exchange prior to or after 5-day intervals, concluding that routine catheter exchange offered no benefit. EVD infection was positively associated with systemic infection and ventricular hemorrhage.

Studies that included non-TBI patients support the findings discussed above. Park et al.[18] studied 595 patients with ventricular drains, 213 of which were catheterized for more than 10 days. The authors found a non-linear relationship between daily infection rates and monitoring duration, increasing over the first 4 days, reaching a plateau after day 4, and subsequently ranging between 1% and 2% regardless of catheter duration for catheters originally placed at the authors' institution. Twenty-two percent received prophylactic exchanges, which did not affect infection rates. Hospital site of insertion, age, and diagnosis (trauma vs. no trauma), again, had no effect. Wong, et al.[26] performed a randomized trial of routine catheter exchange on 103 patients, only 18 of whom had TBI. There was no significant difference in outcome or infection rate, the latter of which was slightly higher in the catheter exchange group. Indeed, the risk of infection has not been shown to exceed the risk of complications resulting from the catheter exchange procedure (5.6%).[17]

Prophylactic antibiotic use was also studied in ICP monitors.[1–3,19,20,24] Sundbarg et al.[24] analyzed 648 patients who underwent "prolonged" (greater than 24 h) ventricular drainage, 142 of which were severe TBI. None were given prophylactic antibiotics for the catheters, but 76% received antibiotics for systemic illnesses. The TBI patients had no positive CSF cultures but did have the highest rate of other infections among the cohorts studied.

Several studies, which included a substantial number of non-TBI patients, have addressed prophylactic antibiotic usage in patients with EVD. Aucoin et al.[2] showed no significant difference in infection rate between patients treated with and without procedural or peri-procedural antibiotics. However, patients receiving routine bacitracin flushes to maintain patency experienced significantly higher infection rate (18% vs. 5.7%). The lack of prophylactic antibiotic effect on infection rate was also found by others.[1,20]

Poon et al.[19] prospectively studied 228 patients, only 22 of whom had TBI, using peri-procedural Unasyn (Group 1) versus Unasyn/aztreonam (Group 2) for EVD monitoring duration (mean duration, 4 ± 3 days). Routine catheter exchanges were performed on most patients. Group 2 had a significantly lower infection rate than Group 1 (11% vs. 3%). It is not clear why a different regimen was used between the two groups, and no placebo group was used for this study. Group 1 had a higher incidence of extracranial infections (42% vs. 20%). However, the infections in the second group were diagnosed to be resistant staphylococcus and fungal infections.

A multi-centered, randomized controlled trial (RCT) by Zambramski et al.[27] studied the effects of antibiotic-impregnated (minocycline and rifampin) catheters on CSF infection rates and catheter colonization. Such catheters are designed to cover gram-positive pathogens, specifically, staphylococcal species. Among 288 patients (37 were TBI patients and not separately analyzed), there was a significant difference in infection rate in the impregnated versus non-impregnated catheters (1.3% vs. 9.4%). The colonization rate was also significantly different (17.9% vs. 36.7%) with all positive cultures sensitive to minocycline. However, some rifampin resistance was noted. Overall, the catheters were judged to be safe and effective in reducing infection rates.

Systemic Nosocomial Infections

Systemic infection rates increase with TBI severity and coexisting chest trauma.[8] In general, for trauma patients receiving prolonged (greater than 48 h) antibiotic prophylaxis, an increase in the incidence of resistant or gram-negative pneumonias was noted, with a higher incidence of antibiotic-related complications than those patients not receiving such prophylaxis.[10]

In the available studies of TBI patients, prophylactic antibiotics have not shown a reduction in nosocomial infections.[7,8] Goodpasture et al.[7] conducted a prospective trial on a small number of severe TBI patients. The authors reported an increased infection rate in patients not treated with prophylactic antibiotics for intubation compared to those who received antibiotics, the duration of which was not well defined. However, the former group was noted to have mild gram-positive infections, whereas the treated patients had a higher incidence of gram-negative infections, which were deemed more se-

vere. Furthermore, antibiotics did not alter the rate of bacterial colonization of the respiratory tract and was associated with an earlier appearance of gram-negative organisms.

Sirvent et al.[21] conducted a RCT of 100 critically ill patients, 86% of whom had severe TBI, evenly divided into a treatment group of cefuroxime 1.5 g for two doses within 6 h after intubation and a control group not given antibiotics after endotracheal intubation. There was a statistically significant decrease in the incidence of pneumonia in the treated group (23% vs. 64%, $p = 0.016$), but no difference in mortality.

Liberati et al.[13] did a meta-analysis of 36 randomized trials for respiratory tract infection prophylaxis in 6922 adult intensive care patients, mostly without TBI. They studied a combination of topical and systemic antibiotics to reduce infection and mortality. Topical antibiotics were usually a mixture of antibiotics applied enterally and/or as a paste or gel applied to the mouth or oropharynx. Only topical antibiotic usage reduced the infection rate.

Early tracheostomy has been proposed to decrease the incidence of pneumonias in critically ill patients.[12] Recent randomized trials,[14,23] though small in numbers, found no differences in pneumonia rates or mortality in severe TBI patients undergoing early tracheostomy (<1 week). As an alternative to tracheostomy, Hsieh et al.[11] found that extubation of severe TBI patients, as long as they satisfied respiratory criteria and possessed an intact gag and cough reflex, did not result in increased incidence of pneumonia. In a later study by the same group, including patients with other neurological conditions, a delay in extubation was associated with an increased incidence of pneumonia, whereas extubation itself was not.[6]

V. SUMMARY

Good clinical practice recommends that ventriculostomies and other ICP monitors should be placed under sterile conditions to closed drainage systems, minimizing manipulation and flushing. There is no support for routine catheter exchanges as a means of preventing CSF infections.

There is no support for use of prolonged antibiotics for systemic prophylaxis in intubated TBI patients, given the risk of selecting for resistant organisms. However, a single study supports the use of a short course of antibiotics at the time of intubation to reduce the incidence of pneumonia. Early tracheostomy or extubation in severe TBI patients have not been shown to alter the rates of pneumonia, but the former may reduce the duration of mechanical ventilation.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

There is a lack of RCTs with sufficient numbers of TBI patients to study the effect of prophylactic antibiotics for external ventricular drains and other ICP devices. Due to the preponderance of Class III evidence and continued clinical uncertainty, such trials, including those with antibiotic impregnated catheters, would be both ethical and useful.

VII. EVIDENCE TABLES

Evidence Table I. Intracranial Pressure Monitoring and External Ventricular Drains

Reference	*Description of study*	*Data class*	*Conclusion*
Holloway et al., 1996[9]	Retrospective analysis of 584 severe TBI patients from the Medical College of Virginia Neurocore Data Bank and the multicenter Traumatic Coma Data Bank. Authors evaluated the effect of catheter exchange on the incidence of infection.	III	Sixty-one patients were found to have ventriculostomy-related infection. Overall, the infection rate rose over the first 10 days of catheterization, thereafter dropping off to near zero. There was no difference in infection rates between groups based on length of catheterization: <5 days (13%) versus >5 days (18%). Catheter exchange, either within or greater than 5 days, had no effect on infection rate.

Sundbarg et al., 1996[9]	Retrospective analysis of 648 patients undergoing ventricular catheter placement for ICP monitoring and "prolonged drainage," 142 of whom had severe TBI. None were given prophylactic antibiotics, but a high percentage (76%) received antibiotics for other systemic illnesses.	III	The TBI patients had no incidence of definitive CSF infection and a 3.7% rate of positive CSF cultures deemed contaminants.

Evidence Table II. Systemic Nosocomial Infections

Reference	*Description of study*	*Data class*	*Conclusion*
Bouderka et al., 2004[4]	Randomized trial of 62 patients with severe TBI, who, on the fifth hospital day, were randomized to early tracheostomies (Group 1, n = 31) or prolonged intubation (Group 2, n = 31).	II	There was no difference in the rate of mortality or pneumonia between the groups. Early tracheostomy group showed a decrease in the number of overall mechanical ventilation days, and mechanical ventilation days after the diagnosis of pneumonia. ICU days were not reduced.
Goodpasture et al., 1977[7]	Prospective study of 28 patients with severe TBI; 16 (Group 1) were given prophylactic antibiotics for endotracheal intubation. A subsequent cohort of 12 TBI patients (Group 2) were not given prophylactic antibiotics.	III	An increased respiratory tract infection rate was noted in Group 2, but usually with Gram positive organisms. Antibiotic prophylaxis did not alter the rate of bacterial colonization and was associated with an earlier appearance of Gram negative organisms, the infections of which were more severe.
Hsieh et al., 1992[11]	Retrospective review of 109 severe TBI patients on mechanical ventilation for 24 h h. Extubation was performed when patients met respiratory criteria for extubation and possessed an intact cough and gag reflex.	III	Forty-one percent of the patients developed pneumonia, which increased the duration of intubation and ventilation, and hospital/ICU length of stay, but not mortality. Extubation was not significantly associated with an increased risk of pneumonia.
Sirvent et al., 1997[21]	RCT of 100 mechanically ventilated ICU patients (86% of which were severe TBI) assigned to a treatment group (n= 50, 43 TBI) of cefuroxime 1.5 grams IV for two doses or no treatment group (n = 50, 43 TBI) after endotracheal intubation.	II	The overall incidence of pneumonia was 37%, 24% in Group 1, and 50% in the control group. The difference was statistically significant. There was no difference in mortality. A short course of prophylactic cefuroxime was effective in decreasing the incidence of nosocomial pneumonia in mechanically ventilated patients.

Sugerman et al., 1997[23]	Multicenter RCT (with crossover) of early tracheostomy in critically ill patients receiving intubation and mechanical ventilation. Of the 127 patients, 67 had severe TBI. Thirty-five were randomized to the tracheostomy group on days 3–5 and 32 to continued endotracheal intubation. Twenty-five of the latter underwent late (days 10–14) tracheostomy.	II	There was no difference in rate of pneumonia or death in TBI patients undergoing early tracheostomy.

VIII. REFERENCES

1. Alleyene CH, Mahmood H, Zambramski J. The efficacy and cost of prophylactic and periprocedural antibiotics in patients with external ventricular drains. Neurosurgery 2000;47:1124–1129.
2. Aucoin PJ, Kotilainen HR, Gantz NM. Intracranial pressure monitors: epidemiologic study of risk factors and infections. Am J Med 1986;80:369–376.
3. Blomstedt GC. Results of trimethoprim-sulfamethoxazole prophylaxis in ventriculostomy and shunting procedures. J Neurosurg 1985;62:694–697.
4. Bouderka MA, Fakhir B, Bouaggad A, et al. Early tracheostomy versus prolonged endotracheal intubation in severe head injury. J Trauma 2004;57:251–254.
5. Brain Trauma Foundation, American Association of Neurological Surgeons. Recommendations for intracranial pressure monitoring technology. In: Management and Prognosis of Severe Traumatic Brain Injury. Brain Trauma Foundation: New York, 2000:75–90.
6. Coplin WM, Pierson DJ, Cooley KD et al. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med 2000;161: 1530–1536.
7. Goodpasture HC, Romig DA, Voth DW. A prospective study of tracheobronchial bacterial flora in acutely brain-injured patients with and without antibiotic prophylaxis. J Neurosurg 1977;47:228–235.
8. Helling TS, Evans LL, Fowler DL, et al. Infectious complications in patients with severe head injury. J Trauma 1988;28:1575–1577.
9. Holloway KL, Barnes T, Choi S. Ventriculostomy infections: the effect of monitoring duration and catheter exchange in 584 patients. J Neurosurg 1996;85:419–424.
10. Hoth JJ, Franklin GA, Stassen NA, et al. Prophylactic antibiotics adversely affect nosocomial pneumonia in trauma patients. J Trauma 2003;55:249–254.
11. Hsieh AH-H, Bishop MJ, Kublis PS, et al. Pneumonia following closed head injury. Am Rev Respir Dis 1995; 146:290–294.
12. Kluger Y, Paul DB, Lucke J, et al. Early tracheostomy in trauma patients. Eur J Emerg Med 1996;3:95–101.
13. Liberati A, D'Amico R, Pifferi, et al. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev 2004;1:CD000022.
14. Lozier AP, Sciacca RR, Romanoli M, et al. Ventriculostomy-related infection: a critical review of the literature. Neurosurgery 2002;51:170–182.
15. Lyke KE, Obasanjo OO, Williams MA, et al. Ventriculitis complicating use of intraventricular catheters in adult neurosurgical patients. Clin Infect Dis 2001;33:2028–2033.
16. Mayhall CG, Archer NH, Lamb VA, et al. Ventriculostomy-related infections. A prospective epidemiologic study. N Engl J Med 1984;310:553–559.
17. Paramore CG, Turner DA. Relative risks of ventriculostomy infection and morbidity. Acta Neurochir (Wien) 1994;127:79–84.
18. Park P, Garton HJL, Kocan MJ, et al. Risk of infection with prolonged ventricular catheterization. Neurosurgery 2004;55:594–601.
19. Poon WS, Wai S. CSF antibiotic prophylaxis for neurosurgical patients with ventriculostomy: a randomised study. Acta Neurochir Suppl 1998;71:146–148.
20. Rebuck JA, Murry KR, Rhoney DH, et al. Infection related to intracranial pressure monitors in adults: analysis of risk factors and antibiotic prophylaxis. J Neurol Neurosurg Psychiatry 2000;69:381–384.
21. Sirvent JM, Torres A, Mustafa E, et al. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. Am J Respir Crit Care Med 1997;155:1729–1734.
22. Stenager E, Gerner-Smidt P, Kock-Jensen C. Ventriculostomy-related infections—an epidemiological study. Acta Neurochir (Wien) 1986;83:20–23.
23. Sugerman HJ, Wolfe L, Pasquale MD, et al. Multicenter,

randomized, prospective trial of early tracheostomy. J Trauma 1997;43:741–747.

24. Sundbarg G, Nordstrom C-H, Soderstrom S. Complication due to prolonged ventricular fluid pressure recording. Br. J Neurosurg 1988;2:485–495.
25. Winfield JA, Rosenthal P, Kanter R, et al. Duration of Intracranial pressure monitoring does not predict daily risk of infections complications. Neurosurgery 1993;33:424–431.
26. Wong GKC, Poon WS, Wai S, et al. Failure of regular external ventricular drain exchange to reduce cerebrospinal fluid infection: result of a randomised controlled trial. J Neurol Neurosurg Psychiatry 2002;73:759–761.
27. Zambramski JM, Whiting D, Darouiche RO, et al. Efficacy of antimicrobial-impregnated external ventricular drain catheters: a prospective, randomized, controlled trial. Neurosurgery 2003;98:725–730.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-32–S-36
DOI: 10.1089/neu.2007.9991

V. Deep Vein Thrombosis Prophylaxis

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

There are insufficient data to support Level II recommendation for this topic.

C. Level III

Graduated compression stockings or intermittent pneumatic compression (IPC) stockings are recommended, unless lower extremity injuries prevent their use. Use should be continued until patients are ambulatory.

Low molecular weight heparin (LMWH) or low dose unfractionated heparin should be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage.

There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis (DVT).

II. OVERVIEW

Patients with severe TBI are at significant risk of developing venous thromboembolic events (VTEs) with their accompanying morbidity and mortality. In a review of data from the National Trauma Databank, Knudson et al. found TBI (AIS $\geq$ 3) to be a high risk factor for VTE (odds ratio 2.59).[9] The risk of developing deep venous thrombosis (DVT) in the absence of prophylaxis was estimated to be 20% after severe TBI.[6]

Rates of DVT vary depending on the methods used for detection. Clear distinctions need to be made between clinically evident DVTs and those detected by laboratory investigations (Duplex scanning, venography, radiolabeled fibrinogen scans) in asymptomatic patients. Most DVTs diagnosed by screening tests are confined to the calf, are clinically silent, and remain so without adverse consequences.[3] However thrombi involving the proximal leg veins are more likely to produce symptoms and result in a pulmonary embolus (PE). A review of the Pennsylvania Trauma Outcomes Study by Page et al, found an incidence of PE of 0.38% in TBI patients during their acute hospital stay.[12]

PE is known to be associated with high rates of morbidity and mortality in hospitalized patients. Treatment of PE in neurosurgical patients is often complicated by uncertainty regarding the safety of anticoagulation among patients who have recently undergone craniotomy or suffered intracranial hemorrhage from trauma. Furthermore, a high proportion of patients who develop DVTs have residual venous abnormalities: persistent occlusion and/or venous incompetence, leg swelling, discomfort, or ulcers that diminish quality of life. All these manifestations of VTEs, make prevention critical.

Options for prevention of VTE in neurosurgical patients include both mechanical (graduated compression stockings, intermittent pneumatic compression stockings), and pharmacological (low-dose heparin, and low-molecular-weight heparin) therapies. Intuitively, mechanical therapies carry less associated risk. A study by Davidson et al. did not find any change in mean arterial pressure, intracranial pressure, or central venous pressure in TBI patients receiving ICP monitoring with the initiation of sequential pneumatic compression devices.[4] However, lower extremity injuries may prevent or limit their use in some trauma patients and the devices may limit physical therapy and progressive ambulation. Risks associated with the use of LMWH and low-dose heparin include both intracranial and systemic bleeding, the effects of which may range from minor morbidity to death. Any decision regarding the use of these anti-VTE therapies must weigh efficacy against harm from the proposed intervention.

III. PROCESS

For this new topic, Medline was searched from 1966 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 37 potentially relevant studies, 5 were included as evidence for this topic (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Mechanical Interventions

In 1986, Black et al. published a prospective cohort study of 523 patients, of whom 89 had TBI, all treated with intermittent pneumatic compression stockings.[2] Rates of clinically apparent DVT and PE were determined. The incidence of VTE in the entire study group with intracranial disorders was 3.8%, with no cases of VTE detected in patients with TBI.

A number of studies have assessed the efficacy of mechanical interventions in preventing DVT in neurosurgical patients. The first such report by Skillman et al. in 1978 enrolled 95 patients randomized to treatment with intermittent pneumatic compression stockings and no treatment.[13] Patients were screened for DVT with daily radiolabeled fibrinogen scans, and those with positive scans underwent venography to confirm the diagnosis. The authors found an 8.5% incidence of DVT in the treatment group compared with a rate of 25% in untreated controls ($p < 0.05$). However, no data regarding patients specifically with TBI were presented. In 1989, Turpie et al. reported the results of a randomized study in 239 neurosurgical patients of whom 57 had TBI.[14] Radiolabeled fibrinogen scanning or impedence plethysmography was used to screen for DVT, with venography performed if either test was abnormal. Patients were randomized to graduated compression stockings, graduated compression stockings plus IPC, or no treatment, with DVT rates of 8.8%, 9%, and 16%, respectively. Ten deaths were reported in the group treated with compression stockings alone, none thought to be due to VTE. One case of PE was found on post-mortem examination in this group, but cause of death was attributed to massive cerebral edema. In each of the two other groups, four deaths were reported, none attributed to VTE.

The demonstrated efficacy of mechanical measures to prevent DVT in neurosurgical, multisystem trauma, and TBI patients, along with the minimal side effects, lead us to recommend their use in all patients with severe TBI. However, because of the lack of Class II data specific to TBI on this topic, the recommendation must be made at Level III. Obviously, the use of graduated compression and IPC stockings may be limited by lower extremity injuries.

Pharmacological Interventions

In 2002, Kim et al. reported a case series of 64 patients admitted to a Level I trauma center with severe TBI.[7] DVT prophylaxis consisted of 5000 units of subcutaneous heparin given twice daily. For analysis patients were grouped according to time of prophylaxis initiation: less than or greater than 72 h following admission. No differences in rates of DVT, PE, or death were found between groups. However, the small sample size and retrospective nature of the study preclude any conclusions regarding efficacy or safety of early versus late prophylaxis with low-dose heparin after TBI. Also in 2002, Norwood et al. conducted a prospective study of 150 patients with TBI treated with enoxaparin 30 mg twice daily beginning 24 h after arrival to the emergency department.[10] The rate of clinically evident DVT was 4%. Notably, during this study the protocol for initiation of enoxaparin therapy was changed to 24 h following any neurosurgical intervention, after two of 22 patients (9.1%) who underwent craniotomy, developed post-operative bleeding while receiving surgical evacuation. The rate of bleeding complications in patients treated non-operatively was 3%. The rate of Doppler-detected DVT reported by Norwood was lower compared to historical controls; however, there was a higher incidence of bleeding complications with early initiation of enoxaparin therapy.

In 2003, Kleindienst et al. reported a case series of 940 neurosurgical patients, including 344 patients with TBI who were treated with compression stockings and certoparin 18 mg once daily within 24 h of admission or surgery.[8] Prophylaxis with certoparin was initiated in TBI patients only when a head CT within 24 h of admission or surgery did not show any progression of intracranial bleeding. Patients did not receive certoparin if they were chronically treated with oral anti-coagulant or anti-platelet therapy, or had abnormal coagulation studies, platelet aggregation test, or platelet count below 100,000/mL on admission. Among patients in whom DVT was suspected on clinical grounds, the diagnosis was confirmed with Duplex sonography or venography. Among the 280 TBI patients who received certoparin, none were diagnosed with VTE. However, nine study patients (3.2%) with TBI had progressive intracranial hematoma, eight of whom received re-operation. Four of the nine TBI patients with an expanding intracranial hematoma received certoparin prior to the screening CT scan. Nevertheless, the observed rate of patients with expanding intracranial hematoma receiving reoperation in this retrospective series again raises concern for harm.

In 2003, Gerlach et al. reported a prospective cohort study of 2,823 patients undergoing intracranial surgeries who were treated with nadroparin (0.3 mL/day) and compression stockings within 24 h of surgery.[5] This study included 231 patients with TBI (81 subdural hematomas, 47 epidural hematomas, 42 cranial fractures, and 61 decompressive craniectomies). No clinically apparent VTE was reported among patients with these lesions. However, DVT was identified in one patient undergoing surgical reconstruction of the basal frontal cranial region after severe TBI and in another after evacuation of a chronic subdural hematoma. The rate of clinically significant post-opera-

tive hematomas in patients undergoing evacuation of acute subdural hematomas was 2.5%, 0% in patients with epidural hematomas, and 1.6% following decompressive craniectomy. This study raises the possibility that different TBI pathologies have different risks from prophylaxis with LMWH. However, subset analysis is limited by both small sample size and lack of a control group.

Though studies regarding pharmacologic DVT prophylaxis in patients with severe TBI along with studies from elective neurosurgical patients suggest that low-dose heparin or LMWH is efficacious in reducing the risk of VTE, the available data show a trend toward increased risk of intracranial bleeding. Case studies suggest that pharmacologic prophylaxis should not be initiated peri-operatively, but when it is safe to begin such therapy in patients with severe TBI remains poorly defined. Moreover, no recommendations regarding drug choice or optimal dosing in neurosurgical patients can be made based on current evidence.

Mechanical versus Pharmacological Interventions

Several studies have compared the efficacy and complication rates of LMWH or low-dose heparin in preventing DVT in patients undergoing elective neurosurgical procedures against treatment with mechanical prophylaxis. Agnelli et al. compared enoxaparin (40 mg once daily) begun 24 h post-operatively with compression stockings alone in patients undergoing elective cranial or spinal surgery.[1] Lower rates of DVT were found in patients receiving enoxaparin in comparison to those treated with graduated compression stockings alone (17% vs. 32%, $p = 0.004$). Lower rates of proximal DVT (5% vs. 13%, $p = 0.04$) were also seen. No significantly increased risk of major (3% vs. 3%) or minor (9% vs. 5%) bleeding complications was noted between groups. Similarly, Nurmohamed et al. found non-significant lower rates of proximal DVT or pulmonary embolism (6.9% vs. 11.5%, $p = 0.065$) in patients treated with nadroparin and graduated compression stockings, compared to those treated with graduated compression stockings alone.[11] However, a trend towards a higher rate of major bleeding complications (2.5% vs. 0.8%, $p = 0.087$) was found in nadroparin-treated patients. These studies suggest that DVT prophylaxis with pharmacological agents is more efficacious than mechanical measures alone in preventing DVT in neurosurgical patients. However, any attempt to extrapolate data from elective neurosurgical patients to patients with TBI must be viewed with caution, as the later frequently have intracranial hemorrhages at risk of expansion.

V. SUMMARY

Level III evidence supports the use of graduated compression or IPC stockings placed for DVT prophylaxis for patients with severe TBI, unless lower extremity injuries prevent their use. Level III evidence supports the use of prophylaxis with low-dose heparin or LMWH for prevention of DVT in patients with severe TBI. However, no reliable data can support a recommendation regarding when it is safe to begin pharmacological prophylaxis. Moreover, no recommendations can be made regarding medication choice or optimal dosing regimen for patients with severe TBI, based on the current evidence.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

A randomized controlled trial (RCT) of mechanical prophylaxis alone versus with the addition of pharmacological prophylaxis of DVT in patients with severe TBI is needed. Such a study should specifically address the issue of when it is safe to begin pharmacological therapy, ideal agent, and dosing regimen in the patient with traumatic intracranial bleeding.

Whether the risks of pharmacological DVT prophylaxis are greater in specific traumatic intracranial lesions (contusions, subdural hematomas), than in others (small traumatic subarachnoid hemorrhage) needs to be explored. In addition, the indications, risks, and benefits of vena cava filters in severe TBI patients requires investigation.

VII. EVIDENCE TABLE

Evidence Table I. Deep Vein Thrombosis Prophylaxis

Reference	*Description of study*	*Data class*	*Conclusion*
Black et al., 1986[2]	Prospective, observational study of 523 neurosurgical patients including 89 TBI patients treated with external pneumatic calf compression.	III	Overall, rates of DVT were 3.8% in intracranial disorders and 0% in patients with TBI. Use of external pneumatic calf compression may be associated with low rates of DVT in TBI patients.

Gerlach et al., 2003[5]	Prospective observational study of 2,823 patients undergoing intracranial surgery including 231 patients with TBI (81 acute subdural hematomas, 47epidural hematomas, 42 cranial fractures, 61 decompressive craniectomies) treated with compression stockings plus nadroparin 0.3 mL/day within 24 h of surgery.	III	No clinically apparent VTE was identified in patients with subdural hematomas, epidural hematomas, decompressive craniectomies, or cranial fracture. Early initiation of nadroparin after TBI may be associated with lower rates of DVT compared with historical controls; however, increased incidence of intracranial bleeding may occur. Different TBI pathologies may be associated with different rates of post-operative bleeding.
Kim et al., 2002[7]	Retrospective study of 64 patients with severe TBI admitted to a Level I trauma center. Patients were divided into those in whom prophylaxis with 5000 units of subcutaneous heparin was begun less than or greater than 72 h after admission.	III	No significant difference between patients begun on heparin prophylaxis early or late after admission for TBI. Rates of DVT were 4% in those whom heparin prophylaxis was begun less than 72 h after admission and 6% in those whom prophylaxis was initiated after 72 h. (Study was underpowered to detect efficacy of intervention or complication rates from intervention.)
Kleindienst et al., 2003[10]	Retrospective analysis of 940 neurosurgical patients including 344 patients with TBI treated with compression stockings and certoparin 18 mg/day within 24 h of admission or surgery whenever a control CT scan did not show progression of an intracranial hematoma.	III	No TBI patients were diagnosed with DVT. Nine TBI patients (3.2%) had progression of intracranial hematomas, eight of whom received re-operation. Early initiation of certoparin after TBI may be associated with lower rates of DVT compared with historical controls; however, increased incidence of intracranial bleeding may occur.
Norwood et al., 2002[7]	Prospective, observational study of 150 TBI patients treated with enoxaparin 30 mg twice daily for DVT prophylaxis beginning 24 h after arrival to the emergency department. Observed rate of DVT was 2%. (Study protocol was changed to initiation of enoxaparin at 24 h after any surgical intervention rather than arrival to ED after two of 24 (8%) of patients developed post-operative bleeding and received repeat craniotomy.)	III	The rate of hematoma progression on CT after initiation of enoxaparin was 4% Early initiation of enoxaparin after TBI may be associated with lower rates of DVT compared with historical controls; however, increased incidence of intracranial bleeding may occur.

VIII. REFERENCES

1. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stocking compared with compression stocking alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med 1998;339:80–85.
2. Black PM, Baker MF, Snook CP. Experience with external pneumatic calf compression in neurology and neurosurgery. Neurosurgery 1986;18:440–444.
3. Buller HR, Agnelli, Hull RD et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:401S–428S.
4. Davidson JE, Williams DC, Hoffman. Effect of intermittent pneumatic leg compression on intracranial pressure in brain-injured patients. Crit Care Med 1993;21: 224–227.
5. Gerlach R, Scheuer T, Beck J et al. Risk of postoperative hemorrhage intracranial surgery after early nadroparin ad-

ministration: results of a prospective study. Neurosurgery 2003;53:1028–1034.

6. Kaufman HH, Satterwhite T, McConnell BJ, et al. Deep vein thrombosis and pulmonary embolism in head-injured patients. Angiology 1983;34:627–638.
7. Kim J, Gearhart MM, Zurick A, et al. Preliminary report on the safety of heparin for deep venous thrombosis prophylaxis after severe head injury. J Trauma 2002;53: 38–42.
8. Kleindienst A, Harvey HB, Mater, E et al. Early antithrombotic prophylaxis with low molecular weight heparin in neurosurgery. Acta Neurochir (Wein) 2003;145: 1085–1090.
9. Knudson MM, Ikossi DG, Khaw L, et al. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg 2004;240:490–496.
10. Norwood SH, McAuley CE, Berne JD, et al. Prospective evaluation of the safety of enoxaparin prophylaxis for venous thromboembolism in patients with intracranial hemorrhagic injuries. Arch Surg 2002;137:696–701.
11. Nurmohamed MT, van Riel AM, Henkens CM, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. Thromb Haemost 1996;75:233–238.
12. Page RB, Spott MA, Krishnamurthy S, et al. Head injury and pulmonary embolism: a retrospective report based on the Pennsylvania Trauma Outcomes study. Neurosurgery 2004;54:143–148.
13. Skillman JJ, Collins RE, Coe NP, et al. Prevention of deep vein thrombosis in neurosurgical patients: a controlled, randomized trial of external pneumatic compression boots. Surgery 1978;83:354–358.
14. Turpie AG, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent compression with control. Arch Intern Med 1989;149: 679–681.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-37–S-44
DOI: 10.1089/neu.2007.9990

VI. Indications for Intracranial Pressure Monitoring

I. RECOMMENDATIONS

A. Level I

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

B. Level II

Intracranial pressure (ICP) should be monitored in all salvageable patients with a severe traumatic brain injury (TBI; Glasgow Coma Scale [GCS] score of 3–8 after resuscitation) and an abnormal computed tomography (CT) scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns.

C. Level III

ICP monitoring is indicated in patients with severe TBI 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, or systolic blood pressure (BP) $<$ 90 mm Hg.

II. OVERVIEW

It is now clear that only part of the damage to the brain during TBI 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 TBI by using intensive managemenst protocols.[2,20,22,28] 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 setting, which includes monitoring ICP.

The main objective of intensive monitoring is to maintain adequate cerebral perfusion and oxygenation and avoid secondary injury while the brain recovers. Cerebral perfusion is reduced and poorer outcomes are associated with systemic hypotension[6] and intracranial hypertension (ICH).[18,33] Cerebral perfusion pressure (CPP), an indirect measure of cerebral perfusion, incorporates mean arterial blood pressure (MAP) and ICP parameters. CPP values below 50 are associated with poor outcome (see CPP topic). The only way to reliably determine CPP and cerebral hypoperfusion is to continuously monitor ICP and blood pressure.[4,5,23,31]

As with any invasive monitoring device, ICP monitoring has direct costs, uses medical personnel resources for insertion, maintenance, troubleshooting, and treatment, and has associated risks (see ICP Technology topic). These must be outweighed by the benefits or usefulness of ICP monitoring which can be captured in selecting patients that are at risk for ICH. This would also minimize the risks of prophylactic treatment of ICH in the absence of ICP monitoring.

There are three key questions addressing the utility of ICP monitoring in TBI patients:

1. Which patients are at risk for ICH?
2. Are ICP data useful?
3. Does ICP monitoring and treatment improve outcomes?

III. PROCESS

For this update, Medline was searched from 1996 through July of 2004 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 36 potentially relevant studies, 12 were added to the existing table and used as evidence for this question (Evidence Tables I, II, and III).

IV. SCIENTIFIC FOUNDATION

Which Patients Are at Risk for ICH?

The correlation between ICH and poor outcome in patients with severe TBI has been demonstrated in several studies.[2,17,18,22,25] Comatose (GCS $<$ 9) TBI patients

constitute the group at highest risk for ICH.[18,26] Admission CT scans are variable predictors of ICH in severe TBI patients as evidenced in the following studies:

In 1982, Narayan et al. reported a prospectively studied series of patients with severe TBI and found that, in comatose TBI patients with an abnormal CT scan, the incidence of ICH was 53–63%.[26] In contrast, patients with a normal CT scan at admission had a relatively low incidence of ICH (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 systolic BP $<$ 90 mm Hg), their risk of ICH was similar to that of patients with abnormal CT scans.

Others also have found a relatively low incidence of ICH in severe TBI patients with a normal CT scan. In 1986, Lobato et al. studied 46 patients with severe TBI who had completely normal CT scans during days 1–7 after injury.[16] They reported "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, since 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, in a prospective multicenter study of 753 severe TBI patients, Eisenberg et al. found that a patient whose admission CT scan does not show a mass lesion, midline shift, or abnormal cisterns has a 10–15% chance of developing ICH.[9]

In 1998, Poca et al. correlated the Marshall CT classification of admission CT scans in severe TBI patients with incidence of ICH and found that three out of 94 patients had diffuse injury I (no visible intracranial pathology on CT).[29] These patients had ICP less than 20 mm Hg; however, one patient had an evolution of the CT to diffuse injury II, demonstrating one out of three severe TBI patients with a normal admission CT evolved into new intracranial lesions.

In 2004, Miller et al. conducted a retrospective review of 82 patients with severe TBI without surgical mass lesions.[23] They did not correlate CT characteristics of midline shift, basal cisterns, ventricular effacement, sulci compression, and gray/white matter contrast with initial ICP, although there was a correlation with later high ICP values.

Lee et al. (1998) studied the relationship of isolated diffuse axonal injury (DAI) to ICH in 36 out of 660 severe TBI patients.[15] Patients were mildly hyperventilated and maximal hourly ICP values were recorded showing 90% of all the readings below 20 mm Hg. Ten patients had all ICP readings below 20 mm Hg, and the remainder had readings above 20 mm Hg, with four having readings above 40 mm Hg (which were associated with fever). Four patients died and discharge outcome was correlated with severity of DAI.

In summary, there is a markedly lower incidence of ICH in severe TBI patients with completely normal admission and follow up CT scans that do not have associated admission parameters.26 Abnormal CT scans are variable predictors of ICH except in CT scans showing severe intracranial pathology.

Are ICP Data Useful?

ICP data can be used to predict outcome and worsening intracranial pathology, calculate and manage CPP, allow therapeutic CSF drainage with ventricular ICP monitoring and restrict potentially deleterious ICP reduction therapies. ICP is a robust predictor of outcome from TBI and threshold values for treatment are recommended based on this evidence[18,20,22,25] (see ICP Threshold topic).

ICP monitoring can be the first indicator of worsening intracranial pathology and surgical mass lesions. Servadei et al. (2002) studied 110 consecutive patients with traumatic subarachnoid hemorrhage, of which 31 had severe TBI and ICP monitoring.[34] ICP monitoring was the first indicator of evolving lesions in 20% of the severe TBI group, four out of five of whom received an operation.

CPP management cannot be done without measuring ICP and MABP. CPP levels are used for therapeutic intervention that targets both MABP and ICP (see CPP topic).

Prophylactic treatment of ICP without ICP monitoring is not without risk. Prolonged hyperventilation worsens outcome[24] and significantly reduces cerebral blood flow based on jugular venous oxygen saturation monitoring.[11,35] Prophylactic paralysis increases pneumonia and ICU stay.[13] Barbiturates have a significant risk of hypotension and prophylactic administration is not recommended.[30] Mannitol has a variable ICP response in both extent of ICP decrease and duration.[19,21]

In summary, ICP data are useful for prognosis and in guiding therapy.

Does ICP Monitoring and Treatment Improve Outcome?

A randomized trial of ICP monitoring with and without treatment is unlikely to be carried out. Similarly, a trial for treating or not treating systemic hypotension is not likely. Both hypotension and raised ICP are the leading causes of death in severe TBI, and are treated if either is suspected, regardless of whether ICP or blood

pressure is monitored. The question remains, does ICH reflect an irreversible, evolving pathology sustained at the time of injury? The question can be answered partially by examining the outcome of those patients that respond to therapies that lower ICP.

Eisenberg et al. (1988) reported in a multi-center study of the use of pentobarbital to treat patients with ICP elevations refractory to all other therapy.[8] In their study, patients whose ICP could be controlled had a much better outcome than those in whom it could not be controlled.

Saul and Ducker[32] prospectively studied 127 severe TBI patients who were treated with mannitol and CSF drainage for an ICP 20–25 mm Hg, and were compared to a similar group of 106 patients treated at a lower ICP of 15 mm Hg. They found a significant reduction in mortality in the lower ICP threshold treatment group.

Howells et al. found that patients who respond to CPP treatment which incorporated ICP had better outcomes.[12] They studied 64 patients treated according to a CPP directed protocol (CPP $>$ 70 and ICP $<$ 25 mm Hg). Patients with intact pressure autoregulation who responded to the CPP protocol by decreasing ICP had a significantly better outcome compared to those patients who responded by increasing ICP (pressure passive autoregulation). It may be that patients with intact pressure autoregulation would have tolerated high ICP and low CPP without a change in outcome, but determining this would have required a "do not treat" arm of the study.

Decompressive craniectomy for ICH is associated with better outcomes in those patients that have a decrease in ICP. Aarabi et al. studied 50 consecutive severe TBI patients, 40 of whom had intractable ICH and underwent decompressive craniectomy, leading to a significantly lowered ICP from a mean of 24 to 14 mm Hg.[1] For the 30-day survivors of the original sample (n = 39), good outcome (Glasgow Outcome Scale score [GOS] of 4 or 5) occurred in 51.3%. Similar results were reported by Timofeev et al. in 49 severe TBI patients with ICH that underwent decompressive craniectomy.[36]

Does ICP monitoring per se make a difference in outcome? Cremer et al. reported a retrospective analysis of severe TBI patients managed at two different trauma centers who differed in the use of ICP monitoring.[7] One center with 122 patients that did not monitor ICP but used ICP lowering treatment (82% sedatives and paralytics, 25% mannitol, 22% hyperventilation and 2% ventricular drainage) was compared to another with 211 patients that used ICP monitoring in 67% of severe TBI patients and treated ICP significantly more except for hyperventilation and ventricular drainage which was equally used in both centers. There was no difference in mortality or 12-month GOS. However, differences between the groups in the sample render the findings minimally useful. More than twice the patients in the ICP monitoring center had hypotension on admission compared to the center that did not monitor ICP, which also had a significant number of patients transferred from other hospitals.

Protocols that incorporate ICP monitoring and other advanced monitoring have demonstrated improved outcomes when compared to earlier time periods without a protocol.[27,10,28] In addition the frequency of ICP monitoring in trauma centers has been reported to be associated with improved outcomes.[3,14]

In summary, patients who do not have ICH or who respond to ICP-lowering therapies have a lower mortality than those who have intractable ICH. There are no data on patients with untreated ICH compared to treated ICH and little data on the outcome of patients that respond to ICP lowering therapies.[30]

V. SUMMARY

There is evidence to support the use of ICP monitoring in severe TBI patients at risk for ICH. ICP cannot be reliably predicted by CT scan alone. ICP data are useful in predicting outcome and guiding therapy, and there is an improvement in outcomes in those patients who respond to ICP lowering therapies. The limited data on improvement in outcome in those patients that respond to ICP lowering treatment warrants ICP monitoring to treat this group of patients. Not monitoring ICP while treating for elevated ICP can be deleterious and result in a poor outcome.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

A randomized clinical trial (RCT) of ICP monitoring, with and without treatment, would be extremely useful in establishing the value of ICH treatment, but it is unlikely considering that most TBI experts consider ICP or CPP parameters to be the primary basis for ICU management decisions in the care of the severe TBI patient. Further studies on sequential normal CT scans in severe TBI patients and the incidence of ICH and evolving lesions would be useful to identify a group that may not require ICP monitoring and treatment.

VII. EVIDENCE TABLES

Evidence Table I. Which Patients Are at High Risk for ICH?

Reference	*Description of study*	*Data class*	*Conclusion*
Eisenberg et al., 1990[9]	Prospective multicenter study in which authors examined the CT scans of 753 patients with severe TBI who were treated in a consistent fashion.	III	"Severe TBI 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."
Lobato et al., 1986[16]	Study of 46 severe TBI patients who had normal CT scans days 1 through 7 post-injury.	III	"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 one-third of patients with a normal admission scan developed new pathology within the first few days of the injury.
Marmarou et al., 1991[18]	A study of 428 severe TBI patients describing the relationship between raised ICP (>20 mm Hg), hypotension and outcome.	III	The proportion of ICP measurements >20 mm Hg was highly significant in explaining outcome ($p < 0.0001$). As ICP increased, favorable outcomes became less likely while worse outcomes became more likely. The next most significant factor in predicting outcome was the proportion of mean BP measurements <80 mm Hg. Patients with a GCS < 8 are at high risk of developing ICH.
Miller et al., 1981[22]	Series of 225 prospective, consecutive patients with severe TBI managed by a uniform and intensive protocol in an effort to relate outcome to several clinical variables.	III	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.
Narayan et al., 1982[26]	207 consecutive patients with severe TBI who underwent ICP monitoring were analyzed to determine the efficacy and need of ICP monitoring.	III	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 two of three adverse features (age >40 years, uni- or bilateral posturing, or systolic BP < 90 mm Hg), the incidence of ICH was 60%. Patients with a GCS ≤8 are at high risk for developing ICH, especially if their CT scan is abnormal.

New studies

Lee et al., 1998[15]	ICP and CPP data reviewed in 36 severe TBI patients with clinical and radiological evidence of diffuse axonal injury.	III	Of 2,698 hourly peak ICP recordings, 905 were 20 mm Hg.
Miller et al., 2004[23]	82 severe TBI patients were retrospectively analyzed regarding initial CT findings relative to ICP.	III	CT findings regarding gray/white differentiation, transfalcine herniation, size of ventricles, and basilar cistern sulci are associated with, but not predictive of, intracranial hypertension.
Poca et al., 1998[29]	Patterns of ICP elevations were correlated with CT diagnostic categories in 94 patients with severe TBI.	III	Intracranial hypertension correlated with injury patterns identified on CT. Diffuse injury type I had no ICP elevations, whereas the incidence for type II was 27.6%, type III was 63.2%, and type IV was 100%. One of three patients with no CT pathology evolved new intracranial lesions.

Evidence Table II. Are ICP Data Useful?

Reference	*Description of study*	*Data class*	*Conclusion*
Narayan et al., 1981[25]	Clinical signs, MEPs, CT scans, and ICP data were prospectively recorded and analyzed in 133 severe TBI patients to ascertain their accuracy and relative value, either individually or in various combinations, in predicting one of two categories of outcome.	III	ICP $>$ 20 mm Hg that treatment was associated with a significantly poorer prognosis (36% Good or Moderate Disability on the GOS) than if the ICP was $<$20 mm Hg (80% Good Recovery or Moderate Disability).
New study			
Servadei et al., 2002[34]	ICP ranges assessed in patients with traumatic subarachnoid hemorrhage to determine if there were any identifiable changes predictive of worsening CT findings.	III	ICP monitoring was the first indicator of evolving lesions in 20% of patients. However, in 40% of patients, CT worsening was not associated with ICP elevations, thus ICP monitoring alone may be inadequate to follow CT abnormalities.

Evidence Table III. Does ICP Monitoring Improve Outcome?

Reference	*Description of study*	*Data class*	*Conclusion*
Eisenberg et al., 1988[8]	In a multicenter study, 73 Patients with severe TBI and elevated ICP were randomized to receive either a regimen that included high-dose pentobarbital or one that was similar but did not include pentobarbital.	II	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

(*continued*)

Evidence Table III. Does ICP Monitoring Improve Outcome? (Cont'd)

Reference	*Description of study*	*Data class*	*Conclusion*
			1 month, 925 of the patients who responded to treatment survived and 83% who did not respond had died.
Saul et al., 1982[32]	Prospective study of 127 severe TBI patients who were treated with mannitol and CSF drainage for ICP > 20–25 mm Hg and 106 patients who were treated similarly except at a lower ICP level (>15 mm Hg).	III	Mortality was 46% in the patients treated for ICP > 20–25 mm Hg and 28% in the 106 patients treated at an ICP level of >15 mm Hg.
New studies			
Aarabi et al., 2006[1]	Prospective observational study of 50 severe TBI patients, 40 with intractable ICH whose ICP was measured before decompressive craniectomy.	III	Of the subgroup of 40 whose ICP had been measured before decompression, the mean ICP deceased after decompression from 23.9 to 14.4 mm Hg ($p < 0.001$). Of the 30-day survivors of the total original group of 50 ($n = 39$), 51.3% had a GOS score of 4 or 5.
Cremer et al., 2005[7]	Retrospective study with prospective outcome data collection comparing mortality and 12 month GOS in severe TBI patients treated in two hospitals, one with ICP monitoring ($n = 211$) and the other without ($n = 122$).	III	No significant difference in mortality or GOS at 12 months. Baseline differences between groups in hypotension on admission and number of patients transferred from other hospitals.
Fakhry et al., 2004[10]	Retrospective comparison of mortality and outcomes for severe TBI patients in three groups: (1) before the use of guidelines-based protocol (1991–1994, $n = 219$); (2) after initiation of the protocol with low compliance (1995–1996, $n = 188$; (3) after initiation of the protocol with high compliance (1997–2000, $n = 423$).	III	Significant decrease in mortality between patients from 1991–1996 and those from 1997–2000 (4.55, ($p = 0.047$). Significantly more patients with GOS scores of 4 or 5 in the 1997–2000 cohort (61.5%) than in the 1995–1996 (50.3%) or 1991–1994 (43.3%) cohorts ($p < 0.001$).
Howells et al., 2005[12]	Prospective comparison of outcomes for severe TBI patients treated in two hospitals, one using an ICP-oriented protocol (ICP < 20 mm Hg, CPP > 60 mm Hg, $n = 67$) and the other using a CPP-oriented protocol (CPP at least 70 mm Hg, ICP below 25 mm Hg as a secondary target, $n = 64$).	III	Among the 64 patients treated with the CPP-oriented protocol, those with intact pressure autoregulation who responded to the CPP protocol by decreasing ICP had a significantly better outcome compared to those patients who responded by increasing ICP.
Lane et al., 2000[14]	Retrospective review of the Ontario Trauma Registry evaluating 541 severely TBI patients with ICP monitoring.	III	When severity of injury was controlled for, ICP monitoring was associated with improved survival.
Palmer et al., 2001[27]	Prospective and retrospective cohort at a single level I trauma center comparing mortality and outcomes for patients treated before ($n = 37$)	II	Mortality at 6 months was significantly reduced from 43 to 16% with the protocol. ICU days remained the same and hospital costs

	and after ($n = 56$) implementation of a protocol based on the Brain Trauma Foundation guidelines.		were increased. GOS scores of 4 or 5 increased from 27% in the pre-guidelines group to 69.6% in the post-guidelines group (odds ratio = 9.13, $p = 0.005$).
Patel et al., 2002[28]	Comparative retrospective review of severe TBI patients from two time periods, pre (1991–1993) and post (1994–1997) establishment of a dedicated Neurosciences Critical Care Unit (NCCU).	III	53 patients treatead in the pre-establishment group had 59% ICP monitoring. 129 patients in the post-establishment group had 96% ICP monitoring. Significantly better outcomes were found in the post-establishment group.
Timofeev et al., 2006[36]	Retrospective analysis of outcomes for severe TBI patients ($n = 49$) treated for intractable ICH with decompressive craniectomy.	III	Of 27 patients for whom pre- and post-surgical ICP was measured, mean ICP decreased from 25 ± 6 mm Hg to 16 ± 6 mm Hg ($p < 0.01$). Of the entire sample, 61.2% had a good recovery or moderate disability score on the GOS.

VIII. REFERENCES

1. Aarabi B, Hesdorffer D, Ahn, E, et al. Outcome following decompressive craniectomy for malignant swelling due to severe head injury. J Neurosurg 2006;104:469–479.
2. Becker DP, Miller JD, Ward JD, et al. The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 1977;47:491–502.
3. Bulger E, Nathens A, Rivara F et al. Management of severe head injury: institutional variations in care and effect on outcome. Crit Care Med 2002;30:1870–1876.
4. Chambers IR, Treadwell L, Mendelow AD. The cause and incidence of secondary insults in severely head-injured adults and children. Br J Neurosurg 2000;14:424–431.
5. Chambers IR, Treadwell L, Mendelow AD. Determination of threshold levels of cerebral perfusion pressure and intracranial pressure in severe head injury by using receiver-operating characteristic curves: an observational study in 291 patients. J Neurosurg 2001;94:412–416.
6. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34:216–222.
7. Cremer O, van Dijk G, van Wensen E, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome alter severe head injury. Crit Care Med 2005;33:2207–2213.
8. Eisenberg HM, Frankowski RF, Contant CF, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 1988;69: 15–23.
9. Eisenberg HM, Gary HE, Jr., Aldrich EF, et al. Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. J Neurosurg 1990;73:688–698.
10. Fakhry S, Trask A, Waller M et al. Management of brain-injured patients by evidence-based medicine protocol improves outcomes and decreases hospital charges. J Trauma 2004;56:492–500.
11. Gopinath SP, Robertson CS, Contant CF, et al. Jugular venous desaturation and outcome after head injury. J Neurol Neurosurg Psychiatry 1994;57:717–723.
12. Howells T, Elf K, Jones P et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. J Neurosurg 2005;102:311–317.
13. Hsiang JK, Chesnut RM, Crisp CB, et al. Early, routine paralysis for intracranial pressure control in severe head injury: is it necessary? Crit Care Med 1994;22:1471–1476.
14. Lane PL, Skoretz TG, Doig G, et al. Intracranial pressure monitoring and outcomes after traumatic brain injury. Can J Surg 2000;43:442–448.
15. Lee TT, Galarza M, Villanueva PA. Diffuse axonal injury (DAI) is not associated with elevated intracranial pressure (ICP). Acta Neurochir (Wien) 1998;140:41–46.
16. Lobato RD, Sarabia R, Rivas JJ, et al. Normal computerized tomography scans in severe head injury. Prognostic and clinical management implications. J Neurosurg 1986;65:784–789.
17. Lundberg N, Troupp H, Lorin H. Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. J Neurosurg 1965;22:581–590.
18. Marmarou A, Anderson RL, Ward JD. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 1991;75:s59-s66.
19. Marshall LF, Smith RW, Rauscher LA, et al. Mannitol dose requirements in brain-injured patients. J Neurosurg 1978; 48:169–172.

20. Marshall LF, Smith RW, Shapiro HM. The outcome with aggressive treatment in severe head injuries. Part I: the significance of intracranial pressure monitoring. J Neurosurg 1979;50:20–25.

21. Mendelow AD, Teasdale GM, Russell T, et al. Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. J Neurosurg 1985;63:43–48.

22. Miller JD, Butterworth JF, Gudeman SK, et al. Further experience in the management of severe head injury. J Neurosurg 1981;54:289–299.

23. Miller MT, Pasquale M, Kurek S, et al. Initial head computed tomographic scan characteristics have a linear relationship with initial intracranial pressure after trauma. J Trauma 2004;56:967–972.

24. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991;75:731–739.

25. Narayan RK, Greenberg RP, Miller JD, et al. Improved confidence of outcome prediction in severe head injury. A comparative analysis of the clinical examination, multimodality evoked potentials, CT scanning, and intracranial pressure. J Neurosurg 1981;54:751–762.

26. Narayan RK, Kishore PR, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. J Neurosurg 1982;56: 650–659.

27. Palmer S, Bader M, Qureshi A et al. The impact of outcomes in a community hospital setting of using the AANS traumatic brain injury guidelines. J Trauma 2001;50(4):657–662.

28. Patel HC, Menon DK, Tebbs S, et al. Specialist neurocritical care and outcome from head injury. Intensive Care Med 2002;28:547–553.

29. Poca MA, Sahuquillo J, Baguena M, et al. Incidence of intracranial hypertension after severe head injury: a prospective study using the Traumatic Coma Data Bank classification. Acta Neurochir Suppl 1998;71:27–30.

30. Roberts I. Barbiturates for acute traumatic brain injury. The Cochrane Library, Volume 4, 2005.

31. Rosner MJ, Daughton S. Cerebral perfusion pressure management in head injury. J Trauma 1990;30:933–940.

32. Saul TG, Ducker TB. Effect of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. J Neurosurg 1982;56:498–503.

33. Schoon P, Benito ML, Orlandi G, et al. Incidence of intracranial hypertension related to jugular bulb oxygen saturation disturbances in severe traumatic brain injury patients. Acta Neurochir Suppl 2002;81:285–287.

34. Servadei F, Antonelli V, Giuliani G, et al. Evolving lesions in traumatic subarachnoid hemorrhage: prospective study of 110 patients with emphasis on the role of ICP monitoring. Acta Neurochir Suppl 2002;81:81–82.

35. Sheinberg M, Kanter MJ, Robertson CS, et al. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. J Neurosurg 1992;76:212–217.

36. Timofeev I, Kirkpatrick P, Corteen E, et al. Decompressive craniectomy in traumatic brain injury: outcome following protocol-driven therapy. Acta Neurochir (Suppl) 2006;96:11–16.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-45–S-54
DOI: 10.1089/neu.2007.9989

VII. Intracranial Pressure Monitoring Technology

I. CONCLUSIONS

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 can be recalibrated *in situ*. ICP transduction via fiberoptic or micro strain gauge devices placed in ventricular catheters provide similar benefits, but at a higher cost.

Parenchymal ICP monitors cannot be recalibrated during monitoring. Parenchimal ICP monitors, using micro strain pressure transducers, have negligible drift. The measurement drift is independent of the duration of monitoring.

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

II. OVERVIEW

In patients for whom ICP monitoring is indicated, a decision must be made about what type of monitoring device to use. The optimal ICP monitoring device is one that is accurate, reliable, cost effective, and causes minimal patient morbidity.

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.[2] The purpose of this standard is to provide labeling, safety, and performance requirements, and to test methods that will help assure a reasonable level of safety and effectiveness of devices intended for use in the measurement of ICP. According to the AAMI 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, 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. There is evidence that external strain gauge transducers are accurate.1 They 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.

Micro 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.

III. PROCESS

For this update, Medline was searched from 1996 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 39 potentially relevant studies, 7 were added to the existing tables and used as evidence for this question (see Evidence Tables I and II).

IV. SCIENTIFIC FOUNDATION

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

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

A. ICP Monitoring Device Accuracy and Reliability

As specified in the Methods section of this document, the strongest evidence for the accuracy and reliability of ICP monitors would be derived from well designed studies that compare simultaneous readings from the moni-

tor being tested to those of an established reference standard and that, among other things, would include large samples of broad-spectrum patients. The ventricular fluid coupled ICP monitor is the established reference standard for measuring ICP.[17] Fourteen publications were identified that simultaneously compared the ventricular monitor to other monitors in a total of 273 patients with TBI (see Evidence Table I).[5–7,10,15,19,20,24,27,28,31,32,34,36] Location of pressure transduction devices varied across studies. Sample sizes for the individual studies ranged from five to 51 patients. Due to changes in technology, only more current publications were considered relevant.

Four studies compared readings from the reference monitor to those of parenchymal strain gauge catheter tip pressure transducer device.[15,27,28,36] Of those, two were published since 1995,[15,36] one of which indicated that readings from the parenchymal strain gauge device varied within 2 mm Hg from those of the reference standard.

In four studies that compared readings from the reference monitor to those of parenchymal fiberoptic catheter tip pressure transduction devices,[10,24,32,34] only one was published since 1995,[34] and reported a strong correlation between initial parenchymal and ventricular measurement.

Precision of parenchymal ICP monitors has also been assessed by comparing the measurement value at the time of ICP monitor removal with zero atmosphere (degree of difference = drift).[1,3,12,15,18,21,29,30,38] Data from eight studies published since 1995 are presented in Evidence Table II. Of these, two publications report accuracy for the micro strain gauge transducer[12,15] and six for the fiberoptic.[3,18,21,29,30,38] However, the literature on fiberoptic transducers is outdated, as there were significant improvements for the fiberoptic transducer in the manufacturing and testing processes in 1999 (manufacturer correspondence), and studies were conducted with data collection from populations treated before the improvements were made. In 153 separate parenchymal ICP probe measurements there were less than 1% of readings above or below 5 mm Hg, when compared to zero atmosphere, at the time of the ICP device removal.[12,15]

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. The potential risks of catheter misplacement, infection, hemorrhage and obstruction have led to alternative intracranial sites for ICP monitoring.

The following statements regarding ICP monitor location are derived from the primarily Class III evidence included in this review:

- Ventricular pressure measurement is the reference standard for ICP monitoring.[2,5–7,10,12,15,16,18,19–21,27,28,31,32,33,36,40,41]
- ICP measurement by parenchymal micro strain gauge[15,36] pressure transduction is similar to ventricular ICP. Some investigators have found that subdural and parenchymal fiberoptic catheter tip pressure monitoring did not always correlate well with ventricular ICP (note that currently available fiberoptic transducers have not been the subject of a clinical publication).[18,21,29,30,34,38]
- Fluid coupled epidural devices or subarachnoid bolts[2,4,8,16,19,20,40] and pneumatic epidural devices[7,31,33] are less accurate than ventricular ICP monitors. Significant differences in readings have been demonstrated between ICP devices placed in the parenchyma versus the subdural space.[13]

C. Complications

ICP monitoring complications include infection (see Infection Prophylaxis topic), hemorrhage, malfunction, obstruction, or malposition. While the current literature suggests these complications generally do not produce long term morbidity in patients, they can cause inaccurate ICP readings, and they can increase costs by requiring replacement of the monitor.

i. Hemorrhage. 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 in terms of morbidity. There were eight publications on ventriculostomy associated hematomas[9,14,21,22,23,26,37,39] reporting an average incidence of 1.1% versus an article on subarachnoid bolts (no hematomas), subdural catheters (no hematomas),[23] and micro strain gauge devices (three hematomas in 28 patients, 11%).[15] There have been no publications on the complication rate of an improved fiberoptic transducer in populations studied since 1999. Significant hematomas receiving surgical evacuation occurred in 0.5% of patients in published reports with more than 200 patients receiving ICP monitoring.[22,26,34]

ii. Malfunction. Malfunction or obstruction in fluid coupled ventricular catheters, subarachnoid bolts, or subdural catheters has been reported as 6.3%, 16%, and 10.5% respectively.[2,3,23] In reports of ventricular catheter malposition, 3% of patients needed operative revision.[25,26,35] There have been no publications on the complication rate of an improved fiberoptic transducer in pop-

ulations studied since 1999. Malfunctions of micro strain gauge devices are reported as 0%.[12,15]

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 below summarizes each type of ICP monitor by the parameters discussed above.

D. Cost

Estimated costs of the various ICP devices are presented in Tables 1 and 2. The non-disposable hardware that need to be purchased with fiberoptic and strain gauge catheter tip ICP devices range in cost from $6,000 to $10,000 per bed. ICP transduction with an external strain gauge costs $208 versus an average of $545 for micro strain gauge or fiberoptic transducers.

Table 1. Cost (2005) of ICP Monitoring Devices

Device location	*Method of pressure transduction*	*Product description and catalog number*	*Estimated 2005 cost (in dollars)*	*Reusable display monitor and/or calibration device (in dollars)*
Ventricular	FC external strain gauge	Generic:		
		Ventricular catheter	$75	
		External drainage bag	$80	
		Abbott Transpac IV transducer	$53	
	FC micro strain gauge catheter tip	Codman:		
		External CSF drainage bag	$197	
		Microsensor ventricular Kit	$600	$6,600
		Monitor		
	FC fiberoptic	Integra Neuroscience:		
		External CSF drainage bag	$80	
		Microventricular pressure monitoring kit	$450	
		Multiparametric MPM-1		$10,000[a]
	Pneumatic	Speigelberg	n/a	n/a
Parenchymal	Micro strain gauge	Codman:		
		Microsensor ventricular kit	$600	
		Monitor		$6,600
	Fiberoptic	Integra Neuroscience:		
		Microventricular pressure monitoring kit	$450	
		Multiparametric MPM-1		$10,000[a]
	Pneumatic	Speigelberg	n/a	n/a
Subarachnoic	FC external strain gauge	Generic:		
		Ventricular catheter	$75	
		Abbott Transpac IV transducer	$53	
Subdural	Micro strain gauge	Codman:		
		Microsensor ventricular kit	$600	
		Monitor		$6,600
	Fiberoptic	Integra Neuroscience:		
		Microventricular pressure monitoring kit	$450	
		Multiparametric MPM-1		$10,000[a]
	FC external strain gauge	Generic:		
		Abbott Transpac IV transducer	$53	
Epidural	FC external strain gauge	Generic:		
		Abbott Transpac IV transducer	$53	
	Pneumatic	Speigelberg	n/a	n/a

[a]Multiparametric monitor for temperature and oxygen as well as ICP.
FC, fluid coupled.
n/a, data not available.

V. RANKING OF ICP MONITORING TECHNOLOGY

ICP monitoring devices were ranked based on their accuracy, reliability, and cost, as follows:

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

Table 2. Ranking for ICP Monitoring Technologies

Device location		*Method of pressure transduction*	*Accuracy*	*Recalibration*	*Estimated 2005 cost (in dollars)*
Ventricular	1	FC external strain gauge	+	+	$208
	2	FC micro strain gauge	+	+	$600
	3	FC fiberoptic	n/a	+	$450
Parenchymal	4	Micro strain gauge	+	−	$600
	5	Fiberoptic	n/a	−	$450
Subarachnoic	6	FC external strain gauge	−	+	$53
Subdural	7	Micro strain gauge	−	−	$600
	8	Fiberoptic	n/a	−	$450
	9	FC external strain gauge	−	+	$53
Epidural	10	FC external strain gauge	−	+	85
		Pneumatic	−	+	n/a

[a]There were significant improvements in the manufacturing and testing processes in 1999, which have not been the subject of a clinical publication.

FC, fluid coupled.

n/a, data not available.

VI. SUMMARY

In patients who receive ICP monitoring, a ventricular catheter connected to an external strain gauge transducer is the most accurate and cost effective method of monitoring ICP. Clinically significant infections or hemorrhage associated with ICP devices causing patient morbidity are rare and should not deter the decision to monitor ICP.

Parenchymal transducer devices measure ICP similar to ventricular ICP pressure but have the potential for measurement differences 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 FUTURE 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 receive ICP monitoring.
- It is unclear if a difference in pressure between ventricular and parenchymal ICP is normal. Studies measuring ventricular and parenchymal ICP simultaneously report both positive and negative differences. However, these studies are difficult to interpret if the ICP device was inaccurate. A study of parenchymal and ventricular ICP measurements using an accurate transducer device is needed.
- Research is needed to answer the question, does parenchymal monitoring in or near a contusion site provide ICP data that improves ICP management, and subsequent outcome, compared to other sites of ICP monitoring?
- Further improvement in ICP monitoring technology should focus on developing multiparametric ICP devices that can provide simultaneous measurement of ventricular CSF drainage, parenchymal ICP, and other advanced monitoring parameters. This would allow *in situ* recalibration and give accurate ICP measurements in case of transient fluid obstruction.

VIII. EVIDENCE TABLES

Evidence Table I. ICP Monitoring Device Accuracy and Reliability

Reference	*Description of study*	*Conclusion*
Artru et al., 1992[1]	A prospective study of parenchymal fiberoptic catheter tip ICP monitors in 100 patients	Daily baseline drift of 0.3 mm Hg
Barlow et al., 1985[2]	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	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 et al., 1997[3]	A prospective study of 101 fiberoptic pressure transducers (52 subdural and 42 ventricular) in 86 patients.	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 et al., 1995[4]	Comparison of an epidural ICP monitor and a parenchymal fiberoptic catheter tip ICP monitor in 10 severe head injury patients.	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 et al., 1993[6]	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.	60% of the ICP readings with the fiberoptic device were within 2 mm Hg of the ventricular fluid coupled ICP readings.
Chambers et al., 1990[5]	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.	54% and 74% of the fiberoptic subdural and fiberoptic ventricular ICP readings respectively were with 5 mm Hg of the ventricular fluid coupled ICP measurements.
Czech et al., 1993[7]	Comparison of simultaneous ICP recordings in 15 patients using a ventricular flid coupled ICP monitoring system and an epidural pneumatic ICP monitoring device.	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 et al., 1984[8]	Assessment of ICP measurement accuracy in a subarachnoid/subdural fluid coupled bolt device using an infusion test in 18 patients	Device read ICP accurately accordin to infusion test 48% of the time.
Gambardella et al., 1992[10]	Comparison of a parenchymal fiberoptic catheter tip pressure transduction device to ventricular fluid coupled ICP readings in 18 adults patients.	55% of parenchymal fiberoptic ICP readings were 5 mm Hg higher or lower than ventricular ICP measurements.
Gopinath et al., 1995[12]	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.	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.

(*continued*)

Evidence Table I. ICP Monitoring Device Accuracy and Reliability (Cont'd)

Reference	*Description of study*	*Conclusion*
Gray et al., 1996[13]	Comparison of ICP readings in 15 patients using catheter tip strain gauge devices simultaneously in parenchymal and subdural locations.	ICP measurement differences of >4 mm Hg were noted in 30% of the readings. Daily baseline drift of 0.3 mm Hg in parenchymal location.
Mendelow et al., 1983[19]	Simultaneous recordings of ICP using two types of subdural fluid coupled bolt devices and a ventricular catheter fluid coupled system in 31 patients.	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 et al., 1988[20]	Simultaneous recordings of ICP using a subdural/subarachnoid fluid coupled catheter and a ventricular fluid coupled catheter in 31 patients.	The difference between the ICP readings was −0.12 mm Hg with a standard deviation of 5.29 mm Hg.
Ostrup et al., 1987[24]	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.	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.
Piek et al., 1990[27]	In a series of 100 patiens, 13 had simultaneous ICP recordings from a parenchymal strain gauge catheter tip pressure transducer device and a ventricular fluid coupled catheter.	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 et al., 1987[28]	Simultaneous recordings of ICP using a parenchymal strain gauge catheter tip pressure transducer device and a ventricular fluid coupled catheter in seven patients.	Parenchymal ICP was 4–12 mm Hg lower than ventricular ICP but parallel changes in pressure were noted.
Powell et al., 1985[31]	Simultaneous recordings of ICP using an epidural pneumatic pressure transducer and a ventricular fluid coupled catheter in 17 patients.	Marked differences in pressure up to 30 mm Hg were recorded.
Schickner et al., 1992[32]	Comparison of ICP readings between a parenchymal fiberoptic catheter tip pressure transducer device and ventricular fluid coupled catheter in 10 patients.	66% of the parenchymal fiberoptic measurements exceeded ventricular ICP and 21% were lower. Absolute pressure differences of up to 40 mm Hg were recorded.
Schwartz et al., 1992[33]	Comparison of ICP readings between an epidural pneumatic pressure transducer device and a subdural strain gauge, subdural fiberoptic or ventricular fluid coupled catheter 6 patients.	ICP readings from the epidural device correlated with the other device readings in only one case.
Shapiro et al., 1996[34]	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.	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 et al., 1982[40]	Comparison of ICP measurements between two subarachnoid fluid coupled pressure transducers in the same patient. Twenty patients were studied, four of them had unilateral mass lesions	More than 50% of patients demonstrated significant differences in ICP. Patients harboring intracranial mass lesions showing clear differences.
New studies		
Koskinen et al., 2005[15]	A prospective study in 28 patients with parenchymal micro strain gauge ICP transducer and in 22 patients with parenchymal microstrain gauge ICP transducers and concurrent ventriculostomies.	Only 21% of the probes showed zero drift greater than ±2 mm Hg when removed. 22% of the probes read more than ±2 mm Hg compared to ventricular CSF pressure readings. Three hematomas (nonoperable) and no significant infections (probes were not cultured).
Martinez-Manas et al., 2000[18]	Prospective study done in 1997 of 101 patients (71% TBI) all patients had GCS < 9 who had 108 consecutive fiberoptic ICP monitors placed (63% parenchymal, 28% subdural and the rest intraventricular.	Probe tips were sent for culture and 13.2% were positive. Intracranial hematoma occurred near the probe placement in 4%. 89% of the probes showed a positive or negative drift after removal (range −24 to +35 mm Hg which was not correlated with duration of monitoring.
Munch et al., 1998[21]	Parenchymal ($n = 104$) and ventricular ($n = 32$) fiberoptic transduced ICP devices were placed. Accuracy of expected ICP was assessed by neurological exam and CT scan. 118 patients studied prospectively over an 18-month period. Fiberobtics (104) and ventrics (32) placed. Reliability assessed by neuro exam and CT, complications assessed	85% of the ICP devices were deemed reliable. Complications included 18.1% needed replacement due to failure. 23.5% were dislocated. Only one positive CSF culture noted.
Piper et al., 2001[329]	Zero drift characteristics of 34 parenchymal fiberoptic probes studied in 50 patients with a 4-day mean duration of ICP monitoring (range 1–12 days)	50% of the parenchymal probes had measurements greater than ±3 mm Hg after removal when compared to zero drift. There was no correlation with the duration of monitoring.
Poca et al., 2002[30]	163 patients who had 187 fiberoptic parenchymal bolts placed prospectively and studied over a three year period. all patients had TBI and GCS < 9. Mean duration of monitoring was 5 ± 2.2 days.	89% of probes showed drift (−12 to +7 mm Hg) when removed and 17% had positive culture of the probe tip. 10% sensor mal function and 2.8% hematoma rate (nonoperable) was reported.
Signorini et al., 1998[36]	10 patients (8 TBI) had placement of micro strain gauge parenchymal ICP monitor and comparisons with fiberoptic parenchymal monitors (5) and intraventricular fluid coupled monitors (5) were performed.	A difference of 9 mm Hg was noted between the two parenchymal monitors. Following removal, 33% of the micro strain gauge monitor readings and 50% of the fiberoptic monitor readings were greater than ±2 mm Hg from zero drift, respectively.

(*continued*)

Evidence Table I. ICP Monitoring Device Accuracy and Reliability (Cont'd)

Reference	*Description of study*	*Conclusion*
Stendel R et al., 2003[38]	Prospective comparison testing of the Neurovent ICP and fiberoptic parenchymal probes in 148 patients (72% TBI) of whom an early group of 50 patients received fiberoptic probes and then 98 had Neurovent parenchymal monitors placed.	Hematomas were noted in 2% and 1% of fiberoptic (C) and Neurovent (N) probes respectively. Technical problems in the following: dislocation 14% (C) and 2% (N), damage 6% (C) and 5% (N), Error 8% (C) and 0% (N) and drift 3.5 mm + 3.1 (C) and 1.7 mm + 1.36 (N) were reported.

Evidence Table II. Comparison to Zero Drift in Parenchymal ICP Pressure Devices[a]

Author	*Year of study*	*TBI patients%*	*Number of probes*	*Parenchymal transducer type*	*Percentage difference from > ± 2 mm Hg*	*Percentage difference from > ± 5 mm Hg*	*Range (mm Hg)*
Koskinen et al., 2005[15]	1996–2004	NA	128	Micro strain gauge	20%	1%	−5, +4
Gopinath et al., 1995[12]	N/A	72%	25	Micro strain gauge	11%	0%	−2, +2
Stendel et al., 2003[38]	2000	72%	50	Fiberoptic[b]	46%	36%	0, +12
Poca et al., 2002[3]	1993–1996	100%	126	Fiberoptic[b]	51%	24%	−12, +7
Piper et al., 2001[29]	NA	NA	40	Fiberoptic[b]	50%	NA	−13, +22
Martinez et al., 2000[18]	1997	71%	108	Fiberoptic[b]	74%	52%	−24, +35
Munch et al., 1998[21]	1993–1998	83%	95	Fiberoptic[b]	45%	26%	−5, +12
Bavetta et al., 1997[3]	NA	NA	83	Fiberoptic (60% subdural and 40% parenchymal)[b]	65%	23%	−12, +14

[a]Studies found no association between measurement differences and the duration of monitoring. Fiberoptic and micro strain gauge parenchymal ICP devices are listed by manufacturer on Table 4. All studies are from after 1990.

[b]There were significant improvements in the manufacturing and testing processes in 1999, which have not been the subject of a clinical publication.

IX. REFERENCES

1. Artru F, Terrier A, Gibert I, et al. [Monitoring of intracranial pressure with intraparenchymal fiberoptic transducer. Technical aspects and clinical reliability]. Ann Fr Anesth Reanim 1992;11:424–429.
2. Barlow P, Mendelow AD, Lawrence AE, et al. Clinical evaluation of two methods of subdural pressure monitoring. J Neurosurg 1985;63:578–582.
3. Bavetta S, Sutcliffe JC, Sparrow OC, et al. A prospective comparison of fiber-optic and fluid-filled single lumen bolt subdural pressure transducers in ventilated neurosurgical patients. Br J Neurosurg 1996;10:279–284.
4. Bruder N, N'Zoghe P, Graziani N, et al. A comparison of extradural and intraparenchymatous intracranial pressures in head-injured patients. Intensive Care Med 1995;21: 850–852.
5. Chambers IR, Mendelow AD, Sinar EJ, et al. A clinical

evaluation of the Camino subdural screw and ventricular monitoring kits. Neurosurgery 1990;26:421–423.

6. Chambers KR, Kane PJ, Choksey MS, et al. An evaluation of the camino ventricular bolt system in clinical practice. Neurosurgery 1993;33:866–868.
7. Czech T, Korn A, Reinprecht A, et al. Clinical evaluation of a new epidural pressure monitor. Acta Neurochir (Wien) 1993;125:169–172.
8. Dearden NM, McDowall DG, Gibson RM. Assessment of Leeds device for monitoring intracranial pressure. J Neurosurg 1984;60:123–129.
9. Friedman WA, Vries JK. Percutaneous tunnel ventriculostomy. Summary of 100 procedures. J Neurosurg 1980; 53:662–665.
10. Gambardella G, d'Avella D, Tomasello F. Monitoring of brain tissue pressure with a fiberoptic device. Neurosurgery 1992;31:918–921.
11. Gardner RM. Accuracy and reliability of disposable pressure transducers coupled with modern pressure monitors. Crit Care Med 1996;24:879–882.
12. Gopinath SP, Robertson CS, Contant CF, et al. Clinical evaluation of a miniature strain-gauge transducer for monitoring intracranial pressure. Neurosurgery 1995;36: 1137–1140.
13. Gray WP, Palmer JD, Gill J, et al. A clinical study of parenchymal and subdural miniature strain-gauge transducers for monitoring intracranial pressure. Neurosurgery 1996;39:927–931.
14. Guyot LL, Dowling C, Diaz FG, Michael DB. Cerebral monitoring devices: analysis of complications. Acta Neurochir Suppl 1998;71:47–49.
15. Koskinen LO, Olivecrona M. Clinical experience with the intraparenchymal intracranial pressure monitoring Codman MicroSensor system. Neurosurgery 2005;56:693–698.
16. Kosteljanetz M, Borgesen SE, Stjernholm P, et al. Clinical evaluation of a simple epidural pressure sensor. Acta Neurochir (Wien) 1986;83:108–111.
17. Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Scand 1960;36(Suppl 149):1–193.
18. Martínez-Mañas RM, Santamarta D, de Campos JM, et al. Camino intracranial pressure monitor: prospective study of accuracy and complications. J Neurol Neurosurg Psychiatry 2000;69:82–86.
19. Mendelow AD, Rowan JO, Murray L, et al. A clinical comparison of subdural screw pressure measurements with ventricular pressure. J Neurosurg 1983;58:45–50.
20. Mollman HD, Rockswold GL, Ford SE. A clinical comparison of subarachnoid catheters to ventriculostomy and subarachnoid bolts: a prospective study. J Neurosurg 1988;68:737–741.
21. Münch E, Weigel R, Schmiedek P, Schürer L. The Camino intracranial pressure device in clinical practice: reliability, handling characteristics and complications. Acta Neurochir (Wien) 1998;140:1113–1119.
22. Narayan R, Kishore PRS, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? J Neurosurgery 1982;56:650–659.
23. North B, Reilly P. comparison among three methods of intracranial pressure recording. Neurosurgery 1986;18:730.
24. Ostrup RC, Luerssen TG, Marshall LF, et al. Continuous monitoring of intracranial pressure with a miniaturized fiberoptic device. J Neurosurg 1987;67:206–209.
25. Pang D, Grabb PA. Accurate placement of coronal ventricular catheter using stereotactic coordinate-guided freehand passage. Technical note. J Neurosurg 1994;80:750–755.
26. Paramore CG, Turner DA. Relative risks of ventriculostomy infection and morbidity. Acta Neurochir (Wien) 1994;127:79–84.
27. Piek J, Bock WJ. Continuous monitoring of cerebral tissue pressure in neurosurgical practice—experiences with 100 patients. Intensive Care Med 1990;16:184–188.
28. Piek J, Kosub B, Kuch F, et al. A practical technique for continuous monitoring of cerebral tissue pressure in neurosurgical patients. Preliminary results. Acta Neurochir (Wien) 1987;87:144–149.
29. Piper I, Barnes A, Smith D, et al. The Camino intracranial pressure sensor: is it optimal technology? An internal audit with a review of current intracranial pressure monitoring technologies. Neurosurgery 2001;49:1158–1164.
30. Poca MA, Sahuquillo J, Arribas M, et al. Fiberoptic intraparenchymal brain pressure monitoring with the Camino V420 monitor: reflections on our experience in 163 severely head-injured patients. J Neurotrauma 2002;19:439–448.
31. Powell MP, Crockard HA. Behavior of an extradural pressure monitor in clinical use. Comparison of extradural with intraventricular pressure in patients with acute and chronically raised intracranial pressure. J Neurosurg 1985;63: 745–749.
32. Schickner DJ, Young RF. Intracranial pressure monitoring: fiberoptic monitor compared with the ventricular catheter. Surg Neurol 1992;37:251–254.
33. Schwarz N, Matuschka H, Meznik A. [The Spiegelberg device for epidural registration of the ICP]. Unfallchirurg 1992;95:113–117.
34. Shapiro S, Bowman R, Surg CJ. The fiberoptic intraparenchymal cerebral pressure monitor in 244 patients. Neurology 1996;45:278–282.
35. Shults WT, Hamby S, Corbett JJ, et al. Neuro-ophthalmic complications of intracranial catheters. Neurosurgery 1993.33:135–138.

36. Signorini DF, Shad A, Piper IR, et al. A clinical evaluation of the Codman MicroSensor for intracranial pressure monitoring. Br J Neurosurg 1998;12:223–227.

37. Stangl AP, Meyer B, Zentner J, et al. Continuous external CSF drainage—a perpetual problem in neurosurgery. Surg Neurol 1998;50:77–82.

38. Stendel R, Heidenreich J, Schilling A, et al. Clinical evaluation of a new intracranial pressure monitoring device. Acta Neurochir (Wien) 2003;145:185–193.

39. Sundbarg G, Nordstrom CH, Soderstrom S. Complications due to prolonged ventricular fluid pressure recording. Br J. Neurosurg 1988;2:485–495.

40. Weaver DD, Winn HR, Jane JA. Differential intracranial pressure in patients with unilateral mass lesions. J. Neurosurg 1982;56:660–665.

41. Yablon JS, Lantner HJ, McCormack TM, et al. Clinical experience with a fiberoptic intracranial pressure monitor. J Clin Monit 1993;9:171–175.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-55–S-58
DOI: 10.1089/neu.2007.9988

VIII. Intracranial Pressure Thresholds

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Treatment should be initiated with intracranial pressure (ICP) thresholds above 20 mm Hg.

C. Level III

A combination of ICP values, and clinical and brain CT findings, should be used to determine the need for treatment.

II. OVERVIEW

Quantitative guidelines are needed for ICP management. The impact of ICP on outcome from severe traumatic brain injury (TBI) appears to lie in its role in determining cerebral perfusion pressure (CPP), and as an indicator of mass effect. Since 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

For this update, Medline was searched from 1996 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 10 potentially relevant studies, 3 were added to the existing table and used as evidence for this question (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

There remain no large randomized trials that directly 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 mmHg steps against outcome in a logistic regression model, and found 20 mm Hg to have the optimal predictive value.4

These values are in keeping with small, non-controlled reports suggesting a range of 15–25 mm Hg.[5,7,9,10] The report by Saul and Ducker changed the ICP threshold from 25 to 15 mm Hg in two sequentially treated groups of patients and found an associated decrease in mortality from 46% to 28%.[9] 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. Shreiber et al. assessed prospectively collected data from 233 patients regarding the impact on survival for multiple predictive parameters. They found an ICP $\geq$ 15 mm Hg was one of five independent risk factors associated with death.[10]

The study by Eisenberg et al. is the only prospective, double-blind, placebo-controlled study demonstrating improved outcome attributable to lowering ICP.[3] 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 (for details, see Anesthetics, Analgesics, and Sedatives chapter), and they did not stratify outcome by threshold.

A small prospective trial reported 27 patients assigned to ICP treatment groups of 20 or 25 mm Hg. Identical treatment protocols were used, including maintenance of CPP at $>$70 and SjO_2 at $>$54%. The 6-month GOS found no difference between groups.[8]

Patients can herniate at intracranial pressures less than 20–25 mm Hg. The likelihood of herniation depends on the location of an intracranial mass lesion.[1,6] In the report by Marshall et al., pupillary abnormalities occurred with ICP values as low as 18 mm Hg.[6] Therefore, at all points, any chosen threshold must be closely and repeatedly corroborated with the clinical exam and CT imaging in an individual patient.

The intracranial pressure at which patients begin to show signs of neurological deterioration can also occasionally be greater than 20–25 mm Hg. There is some evidence that ICPs higher than 20 mm Hg may be tolerated in patients that have minimal or no signs of brain injury on their CT scans.[2]

V. SUMMARY

Current data support 20–25 mm Hg as an upper threshold above which treatment to lower ICP should generally be initiated.[3,4,7–9]

VI. KEY ISSUES FOR FUTURE INVESTIGATION

The critical value of ICP and its interaction with CPP and other measures (e.g., SjO_2, $PbtO_2$, CBF) is a major unanswered question. As the importance of other parameters is recognized and the ability is improved to safely maintain adequate intracranial parameters somewhat independently of ICP, the issue of an absolute value for ICP may become less important. ICP may be most closely related to the risk of herniation, which seems to vary between and within patients over the course of therapy. Two potentially important steps toward identifying more concrete treatment thresholds for ICP are to:

- Develop a method to estimate "herniation pressure"
- Determine the critical values for other parameters

VII. EVIDENCE TABLE

Evidence Table I. Intracranial Pressure Thresholds

Reference	*Description of study*	*Data class*	*Conclusion*
Andrews et al., 1988[1]	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.	III	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. Factors other than ICP (such as location of mass lesion) must be considered in guiding treatment.
Eisenberg et al., 1988[3]	Prospective, multicenter study wherein 73 severe TBI 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.	II	The outcome for study patients whose ICP could be kept below 20 mmHg using either regimen was significantly better than those whose ICP could not be controlled.
Marmarou et al., 1991[4]	From a prospectively collected database of 1,030 severe TBI patients, all 428 patients who met ICU monitoring criteria were analyzed for monitoring parameters that determined outcome and their threshold values.	III	Using logistic regression, the threshold value of 20 mm Hg was found to best correlate with outcome at 6 months. The proportion of hourly ICP reading greater then 20 mm Hg was a significant independent determinant of outcome. The four centers used ICP treatment thresholds of 20–25 mm Hg. The degree to which this confounds the regression statistics is unclear. The incidence of morbidity and mortality resulting from severe TBI is strongly related to ICP control wherein 20 mm Hg is the most predictive threshold.

Marshall et al., 1979[5]	Retrospective review of 100 consecutively admitted severe TBI patients	III	Patients managed with a regimen including ICP monitoring using a threshold of 15 mm Hg had improved outcome compared to published reports using less ICP-intensive therapy.
Narayan et al., 1982[7]	Retrospective analysis of the courses of 207 consecutively admitted severe TBI patients. Management included aggressive attempts to control ICP using a threshold of 20 mm Hg.	III	Outcome was significantly correlated with the ability to control ICP. ICP control using a threshold of 20 mm Hg as a part of an overall aggressive treatment approach to severe TBI associated with improved outcome.
Saul et al., 1982[9]	A series of 127 severe TBI 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.	III	The 46% mortality in the first group was significantly greater then the 28% mortality in the second group. Suggests an increase in mortality if ICP maintained above a threshold of 15–25 mm Hg.
New studies			
Chambers et al., 2001[2]	Prospective series of 207 adult patients with ICP and CPP monitoring were analyzed using ROC curves to determine if there were significant thresholds for the determination of outcome.	III	The sensitivity for ICP rose for values >10 mm Hg, but it was only 61% at 30 mm Hg. ICP cut off value for all patients was 35 mm Hg, but ranged from 22 to 36 mm Hg for different CT classifications. It may be inappropriate to set a single target ICP, as higher values may be tolerated in certain CT classifications.
Ratanalert et al., 2004[8]	Prospective trial of 27 patients, grouped into ICP treatment thresholds of 20 or 25 mm Hg. Treatment protocols were similar between groups with CPP kept as >70 and SjO_2 at >54%.	III	No difference in outcome between ICP thresholds of 20 or 25 mm Hg.
Schreiber et al., 2002[10]	233 patients with ICP monitoring were analyzed from a prospectively collected database of 368 patients. Potentially predictive parameters were analyzed to determine their impact on survival.	III	An opening ICP of 15 mm Hg was identified as one of five risk factors associated with higher mortality.

VIII. REFERENCES

1. Andrews BT, Chiles BW, Olsen WL, et al. The effect of intracerebral hematoma location on the risk of brain-stem compression and on clinical outcome. J Neurosurg 1988; 69:518–522.
2. Chambers IR, Treadwell L, Mendelow AD. Determination of threshold levels of cerebral perfusion pressure and intracranial pressure in severe head injury by using receiver-operating characteristic curves: an observational study in 291 patients. J Neurosurg 2001;94:412–416.
3. Eisenberg H, Frankowski R, Contant C, et al. High-dose

barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 1988;69:15–23.

4. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 1991;75:S159–S166.
5. Marshall L, Smith R, Shapiro H. The outcome with aggressive treatment in severe head injuries. Part I. The significance of intracranial pressure monitoring. J Neurosurg 1979;50:20–25.
6. Marshall LF, Barba D, Toole BM, et al. The oval pupil: clinical significance and relationship to intracranial hypertension. J Neurosurg 1983;58:566–568.
7. Narayan R, Kishore P, Becker D, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with head injury. J Neurosurg 1982;56:650–659.
8. Ratanalert SN, Phuenpathom N, Saeheng S, et al. ICP threshold in CPP management of severe head injury patients. Surg Neurol 2004;61:429–435.
9. Saul TG, Ducker TB. Effects of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. J Neurosurg 1982;56:498–503.
10. Schreiber MA, Aoki N, Scott B, et al. Determination of mortality in patients with severe blunt head injury. Arch Surg 2002;137:285–290.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-59–S-64
DOI: 10.1089/neu.2007.9987

IX. Cerebral Perfusion Thresholds

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Aggressive attempts to maintain cerebral perfusion pressure (CPP) above 70 mm Hg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome (ARDS).

C. Level III

CPP of <50 mm Hg should be avoided.

The CPP value to target lies within the range of 50–70 mm Hg. Patients with intact pressure autoregulation tolerate higher CPP values.

Ancillary monitoring of cerebral parameters that include blood flow, oxygenation, or metabolism facilitates CPP management.

II. OVERVIEW

There is a substantial body of evidence that systemic hypotension independently increases the morbidity and mortality from TBI, both clinical[10,14,24,26] and histological.[15,29] CPP has been used as an index of the input pressure determining cerebral blood flow and therefore perfusion. CPP is defined as the MAP minus the ICP. It has long proven its value as a perfusion parameter in physiological studies.[16,18,32] Its clinical use as a monitoring parameter burgeoned in the late 1980s[28] in parallel with the concept that induced hypertension may improve outcome. Until this period, it was the practice to avoid systemic hypertension as it was felt to contribute to intracranial hypertension.[22]

Rosner and Daughton proposed a management strategy based primarily on CPP management, stressing the maintenance of CPP at >70 mm Hg and often at much higher levels.[28] This approach provided outcomes that were superior to an unadjusted control group from the Traumatic Coma Data Bank where ICP management was the primary therapeutic goal. Subsequently, CPP management became widely practiced, despite misgivings that the primary issue might be avoidance of cerebral hypotension rather than benefit from CPP elevation per se.[10,13] The question of what is the optimal CPP to maintain after TBI remains unanswered.

III. PROCESS

For this update, Medline was searched from 1996 through April 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 48 potentially relevant studies, six were added to the existing table and used as evidence for this question (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Is Low CPP Harmful?

This question suffers from lack of an adequate, generalizable definition of low CPP. The individual parameters of CPP (blood pressure and ICP) have been shown to be critically related to outcome from TBI. Systemic hypotension is highly associated with poor outcome.[6,10,14,24,26] As well, elevated ICP predicts increased mortality and less recovery.[2,6,21]

Low cerebral blood flow per se is associated with poor outcome. However, the reliability of CPP in this regard remains less well defined. When physiological indices (rather than clinical outcomes) are used as dependent variables, there is evidence that low CPP is associated with unfavorable physiological values. Within the range of autoregulation, low CPP is associated with increased ICP through compensatory vasodilation in response to decreased perfusion pressure.[3,4] Looking at SjO_2 and transcranial Doppler pulsatility index values, Chan et al. found that these parameters appeared to stabilize at CPP

values of 60–70 mm Hg, suggesting that this range might represent the lower end of cerebral pressure autoregulation.[7,8] It has also been demonstrated that decreased CPP values associate with levels of brain tissue O_2 saturation ($PbrO_2$) and jugular venous oxygen saturation that correlate with unfavorable outcomes, and that raising the CPP above 60 mm Hg may avoid cerebral O_2 desaturation.[20,27] Sahuquillo et al. studied PbO_2 values as a function of CPP in severe TBI patients and did not find that low PbO_2 values were predictable with low CPPs ranging from 48 to 70 mm Hg. They also found that raising CPP did not increase oxygen availability in the majority of cases.[30] Cerebral microdialysis studies suggest that, although the normal brain may be more resistant to low CPP, the injured brain may show signs of ischemia if the CPP trends below 50 mm Hg, without significantly benefiting from various elevations above this threshold.[25] These studies suggest that there is a physiologic threshold for CPP of 50–60 mm Hg, below which cerebral ischemia may occur.

When CPP per se is evaluated in terms of human clinical outcome, low CPP is frequently found to correlate with poor outcome. Clifton et al. retrospectively analyzed data on CPP within the dataset from 392 patients in the randomized controlled trial of therapeutic hypothermia for severe TBI.[11] When they analyzed individual predictive variables separately, they found CPP of <60 mm Hg to be associated with an increased proportion of patients with poor outcome. They found similar associations for intracranial pressure >25 mm Hg, mean arterial pressure <70 mm Hg, and fluid balance lower than -594 mL. When these variables were combined into a stepwise logistic regression model, however, CPP fell out, although the other three variables remained within the group of most powerful variables in determining outcome.

Juul et al. retrospectively analyzed the data on ICP and CPP within the dataset of 427 patients in the international, multicenter, randomized, double-blind trial of the *N*-methyl-D-aspartate antagonist Selfotel.[19] They found that a CPP of <60 mm Hg was associated with worse outcome, however this relationship is confounded by high ICP which independently associates with poor outcome.

Andrews et al. prospectively studied 124 severe TBI patients for the purpose of determining predictive variables.[1] They employed on-line collection of physiologic variables, which allowed them to detect and grade a number of secondary insults, including low CPP. Using decision tree analysis, they found that CPP was predictive of outcome when insults were severe and, in common with systemic hypotensive insults of moderate or severe intensity, was more predictive of outcome than ICP. Systemic hypotension per se was consistently important as a predictor of unfavorable outcome in all analyses.

These studies support CPP as a valuable monitoring parameter in managing patients with severe TBI. They suggest that there is a critical threshold for CPP that, in aggregate, appears to lie between 50 and 60 mm Hg. They do not support substituting CPP for monitoring and management of either of its constituent parameters (MAP and ICP).

Is Elevating CPP above a "Critical Threshold" Beneficial or Detrimental?

Early proponents of CPP management reported improved outcomes for severe TBI patients whose CPPs were higher during their treatment course. McGraw developed a model using retrospective data analysis that proposed that patients with a CPP of >80 mm Hg had better outcomes than those with a lower CPP.[23] The same group subsequently reported a 100% mortality for patients for whom $\geq 33\%$ of their CPP course was <60 mm Hg.[9] Both of these studies, however, were retrospective data analyses without risk adjustment on patients managed using ICP-targeted therapy.

Rosner and Daughton prospectively studied 34 patients managed with CPP of >70 mm Hg.[28] When they compared their outcomes to those from the Traumatic Coma Data Bank, they described an increase in good or moderately impaired outcomes and a decrease in mortality, which they attributed to the elevation of CPP. However, there was no adjustment for differences between the two populations. One subsequent analysis suggested that the outcome differences disappeared if there was adjustment for the incidence of in-ICU hypotension (presumably rare in patients undergoing CPP elevation).[10]

With respect to ICP or intracranial hypertension, elevating CPP by up to 30 mm Hg does not appear to be associated with intracranial hypertension in patients with patently intact pressure autoregulation.[3,5] In patients with impaired autoregulation, the ICP response to such CPP elevation is less predictable, sometimes slightly decreasing,[3] while others see mostly a small elevation, albeit some patients demonstrate more profound ICP responses.[5] In these papers, MAP elevation was generally initiated at CPP values of >60 mm Hg. Increased intracranial hemorrhage has not been generally reported as a complication, even in reports where CPP was greatly augmented.[23,27,28]

Subsequent reports call into question whether there is any marginal gain by maintaining the CPP at an elevated level. Robertson et al. reported a randomized controlled trial of CPP therapy versus ICP therapy.[27] In the CPP

therapy group, CPP was kept at >70 mm Hg; in the ICP therapy group, CPP was kept at >50 mm Hg, and ICP was specifically kept at ≤20 mm Hg. They found no significant difference in outcome between the two groups. However, the risk of ARDS was five times greater among patients in the CPP-targeted group and associated with a more frequent use of epinephrine and a higher dose of dopamine. One perceived benefit of the CPP-based protocol was fewer episodes of jugular venous desaturation, which logistic regression modeling suggested was attributed to less hyperventilation in the CPP group. They also noted, however, that the expected influence on outcome of such desaturations was probably minimized because all episodes in both groups were rapidly corrected.

In their analysis of the data from the international, multicenter, randomized, double-blind Selfotel trial, Juul et al. did not find a benefit of maintaining CPP greater than 60 mm Hg.[19]

There is a growing body of clinical evidence that elevating the CPP above the threshold for ischemia may not be beneficial and may indeed have detrimental cerebral and systemic effects. Cruz et al. reported a prospectively collected dataset with one group of patients managed based on jugular venous saturation and CPP, and another group managed under a CPP-based protocol, targeting a CPP of >70 mm Hg.[13] The patients were characterized by having CT evidence of diffuse swelling either on admission or following craniotomy for clot evacuation. The patients were well matched in terms of demographic and injury variables. However, there was no adjustment for other confounding variables (e.g., no adjustment was done to control for specific management variables that covaried with the two treatment philosophies). Mortality in the cohort managed according to jugular venous saturation was 9% versus 30% in the CPP group. This study strongly suggests that CPP-based therapy may not be optimal in all patient groups and that it should be possible to match management strategies to patient characteristics.

Howells et al. compared two separate prospective databases of severe TBI patients managed via two differing philosophies allowed quantitative comparison of outcomes using ICP-guided protocols versus CPP-guided protocols.[17] Their general results supported using CPP as an important index in directing targeted therapy. They noted that a CPP of >60 mm Hg appeared to be too high in some patients. They reported that CPP-based management appeared more efficacious in patients with more intact autoregulation. Patients with less intact autoregulation, however, appeared to do less well if their CPP exceeded 60 mm Hg.

Steiner et al. used an on-line method of measuring cerebral pressure autoregulation and estimated the CPP at which autoregulation appeared most robust in 60% of their patient group.[31] The more closely the mean CPP at which individual patients were maintained approximated the CPP at which their autoregulation was optimal, the more likely that patient was to have a favorable outcome. In addition to the hazard of too low CPP, they specifically stated that maintaining the CPP at levels that are too high may have a negative influence on outcome.

There also appear to be serious detrimental systemic effects of elevating CPP. Analyzing data from their randomized controlled trial (RCT) on ICP-based management versus CPP-based management, Contant et al. reported a highly significant association (fivefold increase in risk) between CPP-based therapy and ARDS.[12] Associated medical maneuvers included increased administration of epinephrine and dopamine. Patients who developed ARDS had a higher average ICP and received more treatment to manage intracranial hypertension. They were 2.5 times more likely to develop refractory intracranial hypertension and this group was two times more likely to be vegetative or dead at 6-month follow-up. In this trial, it was felt that any potential benefits of a focus on elevating CPP was obviated by such systemic complications.[27]

V. SUMMARY

It is important to differentiate physiologic thresholds representing potential injury from clinical thresholds to treat. Much of the definition of the former can come from simple physiologic monitoring; the latter requires clinical evidence from controlled trials using outcome as their dependant variable. With respect to CPP, it appears that the critical threshold for ischemia generally lies in the realm of 50–60 mm Hg and can be further delineated in individual patients by ancillary monitoring.

At this time, it is not possible to posit an optimal level of CPP to target to improve outcome in terms of avoiding clinical episodes of ischemia and minimizing the cerebral vascular contributions to ICP instability. It is becoming increasingly apparent that elevating the CPP via pressors and volume expansion is associated with serious systemic toxicity, may be incongruent with frequently encountered intracranial conditions, and is not clearly associated with any benefit in terms of general outcome. Based on a purely pragmatic analysis of the randomized, controlled hypothermia trial, Clifton et al. noted that a CPP target threshold should be set approximately 10 mm Hg above what is determined to be a critical threshold in order to avoid dips below the critical

level.[11] In combination with the studies presented above, this would suggest a general threshold in the realm of 60 mm Hg, with further fine-tuning in individual patients based on monitoring of cerebral oxygenation and metabolism and assessment of the status of pressure autoregulation. Such fine-tuning would be indicated in patients not readily responding to basic treatment or with systemic contraindications to increased CPP manipulation. Routinely using pressors and volume expansion to maintain CPP at >70 mm Hg is not supported based on systemic complications.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Minimally invasive, efficient, and accurate methods of determining and following the relationships between CPP and autoregulation and between CPP and ischemia in individual patients are needed. There is a need for randomized trials of the influence on outcome of basing optimal CPP on ischemia monitoring (e.g., jugular venous saturation or $PtiO_2$) or on the quantitative indices of pressure autoregulation.

VII. EVIDENCE TABLE

Evidence Table I. Cerebral Perfusion Thresholds

Reference	*Study description*	*Data class*	*Conclusion*
Changaris et al., 1987[9]	Retrospective analysis of the relationship between 1-year outcomes and initial CPP in 136 patients with severe TBI.	III	All patients with CPP of <60 mm Hg on the second post-injury day died; more patients had a good outcome than died when CPP was >80 mm Hg.
Cruz, 1998[13]	Prospective observational study of 6-month outcomes in adults with severe TBI characterized by brain swelling where 178 were treated according to cerebral oxygen extraction and CPP and 175 were treated with management of CPP alone.	III	Mortality in the cohort managed according to jugular venous saturation was 9% versus 30% in the CPP group.
McGraw, 1989[23]	Retrospective analysis of the relationship between 1-year outcomes and initial CPP in 221 patients with severe TBI.	III	The likelihood of good outcomes was significantly higher and of death significantly lower if CPP was >80 mm Hg.
Robertson et al., 1999[27]	RCT comparing the influence of CPP- versus ICP-targeted management on 6-month outcome in 189 adults with severe TBI.	II	No difference in outcome. ICP group had more jugular desaturations but these were rapidly managed. CPP group had more systemic complications. ARDS was five times greater in the CBF-targeted group ($p = 0.007$).
Rosner and Daughton, 1990[28]	Prospective study of outcomes in 34 TBI patients who were managed by actively keeping CPP above 70 mm Hg.	III	The mortality rate was 21%, and good recovery rate was 68%.

New studies

Andrews et al., 2002[1]	Prospective analysis of the influence of quantitative data on secondary insults on 1 year outcome for 69 adults with mild, moderate and severe TBI.	III	Low CPP and hypotension were powerful predictors of death and poor outcome.
Clifton et al., 2002[11]	Retrospective review of 393 patients from the multicenter randomized hypothermia trial, comparing 60 month outcome with ICP, MAP, CPP, and fluid balance.	III	Poor outcome was associated with CPP of <60 mm Hg. No benefit to maintaining CPP > 70 mm Hg.
Contant et al., 2001[12]	Retrospective analysis of the factors related to the occurrence of ARDS in the 189 adults with severe TBI from the RCT comparing CPP- with ICP-targeted.	III	Five-fold increase in risk of ARDS in CPP group strongly related to use of pressors.
Howells et al., 2005[17]	Prospective observation of 6-month outcome for 131 severe TBI adults who received either ICP (Lund) or CPP-targeted acute care.	III	Patients with intact autoregulation had better outcomes with CPP elevation. Patients with defective autoregulation had better outcomes with ICP targeted acute care and lower CPPs of 50–60 mm Hg.
Juul et al., 2000[19]	Retrospective review of the 427 adult patients in the Selfotel RCT of the influence of ICP and CPP on neurological deterioration and 6 month outcome.	III	CPPs greater than 60 mm Hg had no significant influence on outcome.
Steiner et al., 2002[31]	Prospective observation of CPP and outcome at 6 months for 114 adults with moderate or severe TBI.	III	Optimal CPP for each patient was calculated based on the pressure reactivity index. Patients whose mean CPP varied above or below the optimal CPP were less likely to have a favorable outcome.

VIII. REFERENCES

1. Andrews PJ, Sleeman DH, Statham PF, et al. Predicting recovery in patients suffering from traumatic brain injury by using admission variables and physiological data: a comparison between decision tree analysis and logistic regression. J Neurosurg 2002;97:326–336.
2. Becker DP, Miller JD, Ward JD, et al. The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 1977;47:491–502.
3. Bouma GJ, Muizelaar JP. Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation. J Neurosurg 1990;73:368–374.
4. Bouma GJ, Muizelaar JP, Bandoh K, et al. Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow. Journal of Neurosurg 1992;77:15–19.
5. Bruce DA, Langfitt TW, Miller JD, et al. Regional cerebral blood flow, intracranial pressure, and brain metabolism in comatose patients. J Neurosurg 1973;38:131–144.
6. Bullock R, Chesnut RM, Clifton G, et al. Guidelines for the management of severe head injury. Brain Trauma Foundation. J Neurotrauma 2000;17:451–553.
7. Chan KH, Dearden NM, Miller JD, et al. Multimodality monitoring as a guide to treatment of intracranial hypertension after severe brain injury. Neurosurgery 1993;32:547–552.

8. Chan KH, Miller JD, Dearden NM, et al. The effect of changes in cerebral perfusion pressure upon middle cerebral artery blood flow velocity and jugular bulb venous oxygen saturation after severe brain injury. J Neurosurg 1992;77:55–61.
9. Changaris DG, McGraw CP, Richardson JD, et al. Correlation of cerebral perfusion pressure and Glasgow Coma Scale to outcome. J Trauma 1987;27:1007–1013.
10. Chesnut RM. Avoidance of hypotension: condition sine qua non of successful severe head-injury management. J Trauma 1997;42:S4–S9.
11. Clifton GL, Miller ER, Choi SC, et al. Fluid thresholds and outcome from severe brain injury. Crit Care Med 2002; 30:739–745.
12. Contant CF, Valadka AB, Gopinath SP, et al. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg 2001;95: 560–568.
13. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. Crit Care Med 1998;26:344–351.
14. Fearnside MR, Cook RJ, McDougall P, et al. The Westmead Head Injury Project. Physical and social outcomes following severe head injury. Br J Neurosurg 1993;7: 643–650.
15. Graham DI, Adams JH, Doyle D: Ischaemic brain damage in fatal non-missile head injuries. J Neurol Sci 1978;39: 213–234.
16. Hekmatpanah J. Cerebral circulation and perfusion in experimental increased intracranial pressure. J Neurosurg 1970;32:21–29.
17. Howells T, Elf K, Jones PA, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. J Neurosurg 2005;102:311–317.
18. Jennett WB, Harper AM, Miller JD, et al. Relation between cerebral blood-flow and cerebral perfusion pressure. Br J Surg 1970;57:390.
19. Juul N, Morris GF, Marshall SB, et al. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. J Neurosurg 2000;92:1–6.
20. Kiening KL, Hartl R, Unterberg AW, et al. Brain tissue pO2-monitoring in comatose patients: implications for therapy. Neurol Res 1997;19:233–240.
21. Marshall LF, Smith RW, Shapiro HM. The outcome with aggressive treatment in severe head injuries. Part I: the significance of intracranial pressure monitoring. J Neurosurg 1979;50:20–25.
22. Marshall WJ, Jackson JL, Langfitt TW. Brain swelling caused by trauma and arterial hypertension. Hemodynamic aspects. Arch Neurol 1969;21:545–553.
23. McGraw CP. A cerebral perfusion pressure greater that 80 mm Hg is more beneficial. In: Hoff JT, Betz AL (eds): ICP VII. Springer-Verlag: Berlin, 1989:839–841.
24. Miller JD, Becker DP. Secondary insults to the injured brain. J R Coll Surg (Edinb) 1982;27:292–298.
25. Nordstrom CH, Reinstrup P, Xu W, et al. Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. Anesthesiology 2003;98:809–814.
26. Pietropaoli JA, Rogers FB, Shackford SR, et al. The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. J Trauma 1992;33: 403–407.
27. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med 1999;27:2086–2095.
28. Rosner MJ, Daughton S. Cerebral perfusion pressure management in head injury. J Trauma 1990;30:933-940.
29. Ross DT, Graham DI, Adams JH. Selective loss of neurons from the thalamic reticular nucleus following severe human head injury. J Neurotrauma 1993;10:151–165.
30. Sahuquillo J, Amoros S, Santos A, et al. Does an increase in cerebral perfusion pressure always mean a better oxygenated brain? A study in head-injured patients. Acta Neurochir Suppl 2000;76:457–462.
31. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med 2002; 30:733–738.
32. Zwetnow NN. Effects of increased cerebrospinal fluid pressure on the blood flow and on the energy metabolism of the brain. An experimental study. Acta Physiol Scand Suppl 1970;339:1–31.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-65–S-70
DOI: 10.1089/neu.2007.9986

X. Brain Oxygen Monitoring and Thresholds

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

There are insufficient data to support a Level II recommendation for this topic.

C. Level III

Jugular venous saturation (<50%) or brain tissue oxygen tension (<15 mm Hg) are treatment thresholds.

Jugular venous saturation or brain tissue oxygen monitoring measure cerebral oxygenation.

II. OVERVIEW

Intracranial pressure (ICP) monitoring is routinely used for patients with severe TBI. ICP is influenced by several factors that affect the pressure-volume relationship. However, monitoring ICP gives only limited information regarding other factors known to be important to the pathophysiology of TBI, such as cerebral blood flow and metabolism. The development of additional monitoring systems to provide information regarding cerebral blood flow and metabolism has been a long-standing aim in neurocritical care.

Therapy following severe TBI is directed towards preventing secondary brain injury. Achieving this objective relies on assuring the delivery of an adequate supply of oxygen and metabolic substrate to the brain. Delivery of oxygen to the brain is a function of the oxygen content of the blood and the cerebral blood flow (CBF). Delivery of glucose and other metabolic substrates to the brain also depends on CBF. Kety and Schmidt pioneered methods to measure CBF in experimental animals and humans.[4] Their methods are still used today, and have served as the scientific basis for many of the technologies used to measure CBF, including Xe-CT, positron emission tomography (PET) studies of CBF, and others. While these technologies have made important contributions to our current understanding of pathophysiology in severe TBI, none are in common clinical use. In part, this is due to expense, expertise requirements, and patient transport necessary to perform these studies. In addition, the intermittent nature of the measurements has also limited their clinical utility. Also, any measurement of flow must be interpreted in the context of possible alterations of cerebral metabolism in the injured brain.

In recent years, methods to continuously monitor measures of adequate cerebral perfusion have been developed. Broadly, these monitoring systems seek either to measure CBF directly (thermal diffusion probes, trans-cranial Doppler), to measure adequate delivery of oxygen (jugular venous saturation monitors, brain tissue oxygen monitors, near-infrared spectroscopy), or to assess the metabolic state of the brain (cerebral microdialysis). A full discussion of all these technologies is beyond the scope of this topic. We have focused our analysis only on those monitoring systems which to date have yielded sufficient clinical experience to relate the data to outcomes in patients with TBI, namely jugular and brain tissue oxygen monitoring.

III. PROCESS

For this new topic, Medline was searched from 1966 through the April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 217 potentially relevant studies, 12 were included as evidence for this topic (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Jugular Venous Saturation Monitoring

A number of studies have assessed the role of jugular venous saturation monitoring in patients with severe TBI. In 1993, Robertson reported a prospective case series of 116 patients with severe TBI.[6] Seventy-six episodes of

desaturation ($SjO_2 < 50\%$) were confirmed in 46 patients. In patients without desaturation episodes, mortality was 18%. Patients with one or multiple desaturation episodes had mortality rates of 46% and 71%, respectively. A further study by Robertson et al., in 1995 included 177 patients with severe TBI (Glasgow Coma Scale Score [GCS] ≤ 8) and demonstrated that 39% of monitored patients had at least one episode of desaturation.[7] The causes of desaturation were about equally divided between systemic (hypotension, hypoxia, hypocarbia, anemia) and cerebral (elevated ICP, vasospasm) etiologies. Good recovery or moderate disability occurred in 44% of patients with no episodes of desaturation, 30% of patients with one episode, and 15% of patients with multiple episodes of desaturation. Mortality was found to be higher in patients with one or multiple episodes (37% and 69%), as opposed to no episodes of desaturation (21%).

Episodes of desaturation may be more common early after injury. In 1995, Schneider et al. reported a prospective case series of 54 patients of whom 28 suffered severe TBI.[8] Episodes of desaturation were frequent in the first 48 h after injury in non-survivors, while patients who survived typically had episodes of desaturation 3–5 days after injury.

High SjO_2 values have also been associated with poor outcome. In 1999, Cormio et al. reported a retrospective series of 450 patients who underwent jugular venous saturation monitoring.[2] Patients with mean $SjO_2 > 75\%$ were found to have significantly higher cerebral blood flow measured intermittently by the Kety-Schmidt nitrous oxide method. High SjO_2 occurs with hyperemia or after infarction, as non-viable tissue does not extract oxygen. In addition, this group was found to have significantly worse outcome measured by Glasgow Outcome Scale Score (GOS) at 6 months post-injury, compared with patients whose mean SjO_2 was 56–74%.

SjO_2 values alone may not provide the best critical threshold indicator of prognosis. In a consecutive study of 229 comatose TBI patients, arterio-jugular difference of oxygen content ($AJDO_2$) in addition to SjO_2 was obtained every 12 h, and the measurements correlated with 6-month outcome.[10] SjO_2 measurements below 55% were recorded in 4.6% with the majority due to profound hyperventilation or CPP < 60. Higher mean $AJDO_2$ (4.3 vol %) was found to be associated with a good outcome and it was an independent predictor of outcome. The authors postulate that a low SjO_2 may indicate low oxygen delivery but $AJDO_2$ represents oxygen extraction by the brain. In either case, the missing variable is cerebral blood flow, which is needed to calculate the cerebral metabolic rate for brain oxygen consumption.

The association of low and high SjO_2 with poor outcome still leaves open the question of whether treatment directed at restoring normal jugular venous saturation improves outcome. In 1998, Cruz reported a prospective controlled, but non-randomized and non-blinded study of 353 patients with severe TBI and diffuse brain swelling on CT.[3] The control group ($n = 175$) underwent monitoring and management of cerebral perfusion pressure alone, while the experimental group ($n = 178$) underwent monitoring and management of arteriovenous oxygen difference ($AVDO_2$) as well as cerebral perfusion pressure. At 6 months post-injury, the authors found improved GOS in the experimental group. However, the lack of randomization and the non-blinded nature of the study raise concern regarding possible selection and treatment bias. In 1997, Le Roux et al. reported a prospective case series of 32 patients with severe TBI treated for worsening $AVDO_2$ with either mannitol or craniotomy, and found that patients with limited improvement in $AVDO_2$ following treatment had increased incidence of delayed cerebral infarction and worse outcome at 6 months post-injury.[5]

Brain Tissue Oxygen Monitoring

Several studies investigated the relationship between outcome and brain tissue oxygen tension ($P_{br}O_2$). In 1998, Valadka et al. reported a prospective case series of 34 patients with severe TBI and found that the likelihood of death increased with increasing duration of time of $P_{br}O_2$ less that 15 mm Hg.[12] Additionally, their data suggest that the occurrence of any $P_{br}O_2$ less than or equal to 6 mm Hg, regardless of its duration, is associated with an increased chance of death. Bardt et al. also reported in 1998 a prospective case series of 35 patients with severe TBI and found that $P_{br}O_2$ values less than 10 mm Hg for more than 30 min had considerably higher rates of mortality (56% vs. 9%).1 Likewise, rates of favorable outcome (GOS 4–5) were lower (22% vs. 73%) in this group. In 2000, van den Brink et al. reported a prospective case series of 101 patients and found that initial $P_{br}O_2$ values less than 10 mm Hg lasting for more than 30 min were associated with increased mortality and worse outcomes.[13] In this study both depth and duration of low $P_{br}O_2$ correlated with mortality. A 50% risk of death was associated with $P_{br}O_2$ values less than 15 mm Hg lasting 4 h or longer.

The association of low $P_{br}O_2$ values with poor outcome raises the question of whether treatment directed at improving $P_{br}O_2$ improves outcome. Studies have explored the relationship of oxygen-directed therapy on both metabolic and clinical outcome parameters. In 2004, Tolias et

al. studied 52 patients with severe TBI treated with an F_iO_2 of 1.0 beginning within 6 h of admission and compared these to a cohort of 112 matched historical controls.11 They measured ICP and used microdialysis to study brain metabolites. They found an increase in brain glucose, and a decrease in brain glutamate, lactate, lactate/glucose, and lactate/pyruvate ratio in the group treated with an F_iO_2 of 1.0. They also noted a decrease in ICP without change in CPP in the patient group treated with oxygen-directed therapy. While suggesting improved metabolic patterns in patients placed on an F_iO_2 of 1.0 soon after injury, definitive conclusions regarding treatment cannot be drawn from this study which used historical controls and found a nonsignificant improvement in outcome in the treatment group. In 2005, Stieffel et al. reported a series of 53 patients with severe TBI treated with both standard ICP and CPP treatment goals (ICP $<$ 20 mm Hg, CPP $>$ 60 mm Hg) and the addition of an oxygen-directed therapy protocol aimed at maintaining $P_{br}O_2$ greater than 25 mm Hg.[9] They compared mortality and outcome at discharge with historical controls, finding a significant decrease in mortality (44% to 25%) in those treated with an oxygen-directed therapy protocol. Limitations of this study, including the reliance on historical controls which had significant mortality by today's standards and the lack of any medium or long-term outcome measures, limits the possibility of drawing definitive recommendations regarding therapy in severe TBI patients.

V. SUMMARY

Evidence supports a Level III recommendation for use of jugular venous saturation and brain tissue oxygen monitoring, in addition to standard intracranial pressure monitors, in the management of patients with severe TBI. However, the accuracy of jugular venous saturation and brain tissue oxygen monitoring was not evaluated in this guideline. Current evidence suggests that episodes of desaturation ($SjO_2 < 50$–55%) are associated with worse outcomes, and high extraction ($AJVO_2$) are associated with good outcome. Low values of $P_{br}O_2$ ($<$10–15 mm Hg) and the extent of their duration (greater than 30 min) are associated with high rates of mortality.

Though many technologies including cerebral microdialysis, thermal diffusion probes, transcranial Doppler, near-infrared spectroscopy, and others hold promise in advancing the care of severe TBI patients, there is currently insufficient evidence to determine whether the information they provide is useful for patient management or prognosis.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

While the establishment of critical thresholds for SjO_2, $AJDO_2$, and $P_{br}O_2$ are important milestones, future investigations need to explore what specific therapeutic strategies can prevent these thresholds from being crossed and whether this intervention improves outcome. If treatment preventing desaturation events or low $P_{br}O_2$ is shown to improve outcome in patients with severe TBI, the use of these monitoring systems will mark an important advance in the care of TBI patients.

For SjO_2 monitors, issues of reliability need to be addressed and may require technological improvements. For brain tissue oxygen monitors, studies are needed to address issues of probe placement with respect to the location of the injury (most injured vs. least injured hemisphere; pericontusional vs. relatively uninjured brain).

VII. EVIDENCE TABLE

Evidence Table I. Brain Oxygen Monitoring and Thresholds

Reference	*Study description*	*Data class*	*Conclusion*
Bardt et al., 1998[1]	Prospective, observational study of 35 severe TBI (GCS $\leq$ 8) patients who underwent monitoring of brain tissue oxygen. Outcome was assessed by GOS at 6 months post-injury.	III	Time spent with a $PbrO_2 < 10$ was related to outcome as follows: Patients ($n = 12$) with $PbrO_2 < 10$ mm Hg for $<$30 min had rates of: Favorable outcome: 73% Unfavorable outcome: 18% Death: 9%

(*continued*)

Evidence Table I. Brain Oxygen Monitoring and Thresholds (Cont'd)

Reference	*Study description*	*Data class*	*Conclusion*
			Patients (n = 23) with $PbrO_2$ < 10 mm Hg for >30 min had rates of: Favorable outcome: 22% Unfavorable outcome: 22% Death: 56% Low $PbrO_2$ values and the duration of time spent with low$PbrO_2$ are associated with mortality.
Cornio et al., 1998[1]	Retrospective analysis of 450 TBI patients who underwent jugular venous saturation monitoring in which the relationship of elevated SjO_2 to GOS at 3 or 6 months was studied. The relationship of SjO_2 to CBF measured by Kety-Schmidt method was also studied.	III	Patients in group with mean $SjVO_2$ > 75% had significantly higher CBF. Patients in group with mean SjO_2 > 75% had significantly worse outcomes (death or vegetative state in 49% and severe disability in 26%) compared with those with mean SjO_2 of 74–56%. High SjO_2 values may be associated with poor outcomes.
Cruz, 1998[3]	Prospective, controlled but non-randomized and non-blinded study of 353 TBI patients undergoing continuous jugular bulb saturation and cerebral extraction of oxygen ($AVDO_2$) monitoring, in which GOS at 6 months was compared between patients who underwent monitoring and those who did not.	III	Outcome at 6 months by GOS improved in patients who underwent SjO_2 and $AVDO_2$ monitoring. Monitoring SjO_2 may improve outcome in severe TBI. However, caution must be utilized in interpreting the results of this study as the non-randomized, non-blinded nature of the study may introduce treatment bias.
Le Roux et al., 1997[5]	Prospective, observational study of 32 TBI patients with GCS ≤ 8 who underwent jugular bulb oxygen and $AVDO_2$ monitoring, in which the incidence of delayed cerebral infarction and GOS at 6 months post-injury was assessed.	III	A limited improvement in elevated $AVDO_2$ after treatment (craniotomy or mannitol administration) was significantly associated with delayed cerebral infarction and unfavorable outcome. Lack of response of SjO_2 to treatment measures may be associated with poor outcome in severe TBI.
Robertson, 1993[6]	Prospective, observational study of SjO_2 monitoring in 116 TBI patiens (100 with closed head injury and 16 with penetrating head injury) in which desaturation episodes (SjO_2 < 50%) were monitored and correlated to GOS at 3 months post-injury.	III	The number of episodes of desaturation were found to be associated with mortality as follows: no desaturation episodes: mortality 18% 1 desaturation episode: mortality 46% multiple desaturation episodes: mortality 71%. Episodes of desaturation are related to mortality and GOS at 3 months
Robertson et al., 1995[7]	Prospective, observational study of continuous SjO_2 monitoring during first 5–10 days after injury in 177 TBI patients with GCS ≤ 8 in	III	Causes of desaturation are about equally divided between systemic and cerebral causes. 39% of patients had at least one episode of desaturation (112 episodes in 69 patients)

	which episodes of desaturation ($SjO_2 <= 50\%$) were correlated with GOS at 3 months post-injury.		Systemic causes (hypotension, hypoxia, hypocarbia, anemia) were responsible for 51 episodes, while cerebral causes (elevated ICP, vasospasm) were responsible for 54 episodes. The number of desaturation episodes were related to outcome as follows: Good recovery/moderate disability No episodes: 44% One episode: 30% Multiple episodes: 15% Severe disability/vegetative state No episodes: 35% One episode: 33% Multiple episodes: 15% Death No episodes: 21% One episode: 37% Multiple episodes: 69% Episodes of desaturation are common and are relataed to mortality and GOS at 3 months.
Schneider et al., 1995[8]	Prospective case series of 54 patients (28 severe TBI)	III	Episodes of desaturation frequent in the first 48 h after injury in non-survivors; survivors typically had episodes of desaturation 3–5 days after injury.
Stiefel et al., 2005[9]	Prospective study of 53 severe TBI patients from before brain and after ($n = 28$).	III	Significantly higher mortality in control (44% vs. treatment group (25%; $p < 0.05$).
Stocchetti et al., 2004[10]	Prospective observational study of 229 severe TBI patients measuring $AJDO_2$ and SjO2 every 12 h	III	At 6 months post-injury, favorable outcomes group had significantly higher mean $AJDO_2$ (4.3 vol %; SD 0.9) than severe disability/vegetative group (3.8 vol %; SD 1.3) or group that died (3.6 vol %; SD 1; $p = 0.001$). $AJDO_2$ was a significant and independent predictor of outcome.
Tolias et al., 2004[11]	Prospective study of 52 severe TBI patients treated with an F_iO_2 of 1.0 beginning within 6 h of admission, compared to 112 matched historical controls who did not receive the treatment.	III	No significant difference between groups on GOS scores at 3 and 6 months.
Valadka et al., 1998[12]	Prospective, observational study of 34 TBI patients who underwent monitoring of brain tissue oxygen. Outcome was assessed by GOS at 3 months post-injury.	III	The likelihood of death increased with increasing duration of time below $PbrO_2$ of 15 mm Hg or with occurrence of any value below 6 mm Hg. Low $PbrO_2$ values and the duration of time spent with low $PbrO_2$ are associated with mortality.
Van den Brink et al., 2000[13]	Prospective, observational study of 101 severe TBI (GCS ≤ 8) who underwent monitoring of brain tissue oxygen. Outcome was assessed by GOS at 6 months post-injury.	III	Patients with initially low values (<10 mm Hg) of $PbrO_2$ for more than 30 min had higher rates of mortality and worse outcomes than those whose $PbrO_2$ values were low for less than 30 min. Time spent with a low $PbrO_2$ was related to outcome as follows:

(*continued*)

Evidence Table I. Brain Oxygen Monitoring and Thresholds (Cont'd)

Reference	*Study description*	*Data class*	*Conclusion*
			$PbrO_2 < 5$ mm Hg of 30 min duration was associated with a 50% risk of death. $PbrO_2 < 10$ mm Hg of 1 h 45 min duration was associated with a 50% risk of death. $PbrO_2 < 15$ mm Hg of 4 h duration was associated with a 50% risk of death. Low $PbrO_2$ values and the duration of time spent with low PbO_2 are associated with mortality. A 50% risk of death was associated with a $PbrO_2$ less than 15 mm Hg lasting longer than 4 h.

VIII. REFERENCES

1. Bardt TF, Unterberg AW, Hartl R, et al. Monitoring of brain tissue PO_2 in traumatic brain injury: effect of cerebral hypoxia on outcome. Acta Neurochir Suppl 1998;71: 153–156.
2. Cormio M, Valadka AB, Robertson CS. Elevated jugular venous oxygen saturation after severe head injury. J Neurosurg 1999;90:9–15.
3. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. Crit Care Med 1998;26: 344–351.
4. Kety SS, Schmidt CF. The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am J Physiol 1945;143:53–56.
5. Le Roux PD, Newell DW, Lam AM, et al. Cerebral arteriovenous oxygen difference: a predictor of cerebral infarction and outcome in patients with severe head injury. J Neurosurg 1997;87:1–8.
6. Robertson CS. Desaturation episodes after severe head injury: influence on outcome. Acta Neurochir (Wien) Suppl 1993;59:98–101.
7. Robertson CS, Gopinath SP, Goodman JC, et al. $SjvO_2$ monitoring in head-injured patients. J Neurotrauma 1995; 12:891–896.
8. Schneider GH, von Helden A, Lanksch WR, et al. Continuous monitoring of jugular bulb oxygen saturation in comatose patients—therapeutic implications. Acta Neurochir (Wien) 1995;134:71–75.
9. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. J Neurosurg 2005;103:805–811.
10. Stocchetti N, Canavesi K, Magnoni S, et al. Arterio-jugular difference of oxygen content and outcome after head injury. Anesth Analg 2004;99:230–234.
11. Tolias CM, Reinert M, Seiler R, et al. Normobaric hyperoxia-–induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. J Neurosurg 2004;101:435–444.
12. Valadka AB, Gopinath SP, Contant CF, et al. Relationship of brain tissue PO_2 to outcome after severe head injury. Crit Care Med 1998;26:1576–1581.
13. van den Brink WA, van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. Neurosurgery 2000;46:868–878.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-71–S-76
DOI: 10.1089/neu.2007.9985

XI. Anesthetics, Analgesics, and Sedatives

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Prophylactic administration of barbiturates to induce burst suppression EEG is not recommended.

High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.

Propofol is recommended for the control of ICP, but not for improvement in mortality or 6 month outcome. High-dose propofol can produce significant morbidity.

II. OVERVIEW

Sedatives and Analgesics

A variety of pharmacological agents have been advocated to treat pain and agitation in the traumatic brain injury (TBI) patient. It is felt beneficial to minimize painful or noxious stimuli as well as agitation as they may potentially contribute to elevations in ICP, raises in blood pressure, body temperature elevations and resistance to controlled ventilation. Until recently the primary concern over the utilization of these agents has been related to their tendency to obscure the neurologic exam, with a secondary concern over potential adverse hemodymanic effects.

In the previous edition of these guidelines,[2] little information was provided regarding analgesic and sedation utilization in severe TBI. It was noted that there have been relatively few outcome studies and therefore "decisions about . . . use . . . and the choice of agents are left to the practitioner to make based on individual circumstances."

Barbiturates

Since the 1930s, high-dose barbiturates have been known to lower ICP.[10] However their well known risks and complications, as well as the ongoing controversy over their ultimate benefits, have limited their use to the most extreme of clinical situations. Both cerebral protective and ICP-lowering effects have been attributed to barbiturates: alterations in vascular tone and resistance, suppression of metabolism, inhibition of free radical-mediated lipid peroxidation and inhibition of excitotoxicity.[5,9,12] The most important effect may relate to coupling of cerebral blood flow (CBF) to regional metabolic demands such that the lower the metabolic requirements, the less the CBF and related cerebral blood volume with subsequent beneficial effects on ICP and global cerebral perfusion.

A number of barbiturates have been studied, with the most information available on pentobarbital. All 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 is known, however, about the potential complications 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) they can affect long-term ICP control when other medical and surgical therapies have failed, and (2) absolute ICP control improves ultimate neurologic outcome.

III. PROCESS

This chapter combines information from the previous guideline about barbiturates with new information about sedatives and analgesics. Medline was searched from 1966 through April of 2006 (see Appendix B for search strategy). Results were supplemented with literature recommended by peers or identified from reference lists. Of 92 potentially relevant studies, one new study was included as evidence and added to the existing table (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Sedatives and Analgesics

Only one study fulfilling the predetermined inclusion criteria for this topic provides an evidence base for recommendations about sedatives and analgesics. In 1999, Kelly et al.[13] conducted a double-blind, randomized controlled trial (RCT) comparing multiple endpoints for patients who received either propofol or morphine sulfate.

Propofol has become a widely used neuro-sedative as this sedative-hypnotic anesthetic agent has a rapid onset and short duration of action. In addition, propofol has been shown to depress cerebral metabolism and oxygen consumption and thus has a putative neuroprotective effect. Several studies found no statistically or clinically acute significant changes in MAP or ICP with propofol infusions, but they suggest that ICP might decrease slightly (mean, 2.1 mm Hg) after several hours of dosing.[8,18]

The primary end-point of the trial by Kelly et al.[12] was determining drug safety, but they also evaluated clinically relevant end-points, including ICP control, CPP, therapeutic intensity level (TIL) for ICP/CPP control, 6-month neurological outcome and treatment-related adverse events. Sixty-five patients with a GCS of 3–12 were randomized to receive either morphine sulfate (average infusion rate of 1.3 $\pm$ 0.7 mg/hour) or propofol (average infusion rate of 55 $\pm$ 42 mcg/kg/min). Twenty-three patients were excluded for various reasons from the efficacy analysis, leaving 23 in the propofol and 19 in the morphine group. Daily mean ICP and CPP were similar between the two groups; however, on day 3 ICP was lower in the propofol group ($p < 0.05$), and the TIL overall was higher in the morphine group.

There were no significant differences between groups in mortality or GOS. A favorable neurological outcome based on the GOS occurred in 52.5% of propofol treated patients compared to 47.4% of those receiving morphine, with mortality rates of 17.4% and 21.1%, respectively. In a post hoc, analysis, authors compared outcomes for patients receiving "high-dose" (total dose of >100 mg/kg for >48 h) versus "low-dose" propofol. While there were no significant differences in ICP/CPP between these groups, there was a significant difference in neurological outcome: high-dose favorable outcome 70% versus low-dose 38.5% ($p < 0.05$).

Significant concerns have subsequently arisen regarding the safety of high dose propofol infusions. Propofol Infusion Syndrome was first identified in children, but can occur in adults as well. Common clinical features include hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, and renal failure resulting in death. Thus extreme caution must be taken when using doses greater than 5 mg/kg/h or when usage of any dose exceeds 48 h in critically ill adults.[11]

The following section contains information about sedatives and analgesics from small studies that do not provide an evidence base for recommendations.

The most widely used narcotic in the acute setting has been morphine sulfate. Limited studies suggest a high level of analgesic efficacy and safety in this setting, however it provides minimal if any sedation and tachyphylaxis is extremely common, thus leading to continuous need for dose escalation and a prolonged period of "withdrawal" when therapy is discontinued. At least one study demonstrated a significant rebound increase in CBF and ICP with pharmacologic reversal of morphine.

The rapidly metabolized synthetic narcotics, fentanyl and sufentanyl, have become increasingly popular because of their brief duration of action. However, multiple studies have shown a mild but definite elevation in ICP with their utilization.[1,20] deNadal et al. showed a significant fall in mean arterial pressure (MAP) and rise in ICP ($p < 0.05$) lasting for up to 1 h after a single bolus dose of fentanyl (2 mcg/kg) in 30 severe TBI patients. Patients with preserved autoregulation experienced the largest elevations in ICP.[6]

One study suggested that the slow, titrated administration of fentanyl and sufentanyl may minimize ICP elevations.[14] Thus utilization of the synthetic narcotics should be undertaken with caution in potentially hemodynamically unstable patients and those with poor intracranial compliance. No studies were found examining the effects of continuous use of these agents on ICP or hemodynamics. Tachyphylaxis and withdrawal symptoms may occur after prolonged use of these agents.

Traditionally, benzodiazepines have been avoided in the TBI population because of their neuro-depressant effects and their long duration of action. However, Midazolam has gained wide popularity in neurosurgical intensive care units, especially to control agitation associated with mechanical ventilation. Papazian et al. studied 12 patients with GCS < 6 with a 0.15 mg/kg midazolam bolus. All had a baseline ICP of <18 mm Hg. Up to a 50% decrease in MAP ($p < 0.0001$) was observed with 33% of patients with a significant and sustained elevation in ICP, and a similar percentage with a sustained drop in cerebral perfusion pressure (CPP) below 50 mm Hg ($p < 0.0001$).[17] Nevertheless, caution must be exercised when using this agent as well. A test bolus of 2 mg can be used to ascertain efficacy and systemic response before initiating a continuous infusion. If necessary, midazolam can be reversed with flumazenil.

Barbiturates

There have been three randomized controlled trials of barbiturate therapy in severe TBI.

Prophylactic use of barbiturates. Two RCTs examined early, prophylactic administration and neither demonstrated significant clinical benefit. 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 fared much worse.[21] Patients with ICPs of >25 mm Hg for more than 15 min were randomly assigned to a pentobarbital or mannitol treatment group. In patients who underwent evacuation of mass lesions, mortalities were 40% and 43%, respectively. However, in patients with diffuse injury, there was 77% mortality in those on pentobarbital compared to 41% receiving mannitol. Additionally, these authors noted significant decrements in CPP in the pentobarbital group.

In 1985, Ward et al. reported results of an RCT of pentobarbital in 53 consecutive TBI patients who had an acute intradural hematoma or whose best motor response was abnormal flexion or extension.[22] There was no significant difference in 1-year GOS outcomes between treated patients and controls, while six in each group died from uncontrollable ICP. The undesirable side effect of hypotension (SBP < 80 mm Hg) occurred in 54% of the barbiturate-treated patients compared to 7% in the control group ($p < 0.001$).

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 a GCS of 4–8.[7] ICP control 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 therapy at specific "ICP treatment failure" levels. There were 36 controls and 32 study patients, although 32 of the controls ultimately crossed-over and received barbiturates. 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 1 month compared to 17% for non-responders. Of all deaths, 80% were due to refractory ICP. At 6 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 any outcome other than mortality cannot be conclusively determined. Additionally, when one compares the non-crossover control patients ($n = 10$) with the patients initially randomized to barbiturates, the effect on mortality was lost: 100% versus 97.7% survival.

Prerandomization cardiac "complications" were evaluated and appeared to have an important interaction with barbiturate therapy and outcome. In those patients with prerandomization hypotension, control of ICP with either barbiturate or conventional treatment had a similar chance of success (24% vs. 29%).

It must be borne in mind that all of the RCTs of barbiturate therapy were undertaken when prolonged prophylactic hyperventilation, fluid restriction and steroids were considered the best available medical therapies for severe TBI.

Systematic review of barbiturate RCTs. In 1999 and 2004, the Cochrane Injuries Group undertook a systematic review of the three barbiturate RCTs.[19] In all three trials, death was an outcome measure and the pooled relative risk for death was 1.09 (95% CI 0.81–1.47). In the two studies utilizing the GOS, the pooled relative risk for adverse neurologic outcome was 1.15 (95% CI 0.81–1.64). In the two studies examining the effect on ICP, the relative risk for refractory ICP with barbiturate therapy was 0.81 (95% CI 0.62–1.06). In the two studies examining the occurrence of hypotension, there was a substantial increase of occurrence of hypotension in barbiturate treated patients (RR = 1.80, 95% CI 1.19–2.70).

The Cochrane group thus concluded: "There is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome. Barbiturate therapy results in a fall in blood pressure in one of four treated patients. The hypotensive effect of barbiturate therapy will offset any ICP lowering effect on cerebral perfusion pressure"

Therapeutic Regimens

Sedatives and analgesics. Table 1 provides general dosing guidelines if the option to utilize these agents is exercised.

Table 1. Dosing Regimens for Analgesics and Sedatives

Morphine sulfate	4 mg/hr continuous infusion Titrate as needed Reverse with narcan
Midazolam	2 mg test dose 2–4 mg/h continuous infusion Reverse with flumazenil
Fentanyl	2 mcg/kg test dose 2–5 mcg/kg/h continuous infusion
Sufentanyl	10–30 mcg test bolus 0.05–2 mcg/kg continuous infusion
Propofol	0.5 mg/kg test bolus 20–75 mcg/kg/min continuous infusion (not to exceed 5 mg/kg/hr)

Barbiturates. A number of therapeutic regimens using pentobarbital have been applied, all requiring a loading dose followed by a maintenance infusion. The Eisenberg RCT7 used the following protocol:

Loading dose 10 mg/kg over 30 min; 5 mg/kg every hour × 3 doses
Maintenance 1 mg/kg/h

Even though a goal of therapy is to establish serum pentobarbital levels in the range of 3–4 mg%, available pharmacologic 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 CBF occur when burst suppression is induced.

V. SUMMARY

Analgesics and sedatives are a common management strategy for ICP control, although there is no evidence to support their efficacy in this regard and they have not been shown to positively affect outcome. When utilized, attention must be paid to potential undesirable side effects that might contribute to secondary injury.

High dose barbiturate therapy can result in control of ICP when all other medical and surgical treatments have failed. However it has shown no clear benefit in improving outcome. The potential complications of this form of therapy mandate that its use be limited to critical care providers; that patients be hemodynamically stable before its introduction; and that appropriate, continuous systemic monitoring be available to avoid or treat any hemodynamic instability. Utilization of barbiturates for the prophylactic treatment of ICP is not indicated.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

More studies are needed to identify certain subsets of patients who might respond favorably to analgesic-sedative and/or barbiturate treatment, and to identify alternative agents, drug combinations, and dosing regimens.[14] Continuous dosing regimens must be further refined to determine affect on outcome.

More research should be added to current studies of the novel sedative-anesthetic dexmedetomidine and its effects in patients with severe TBI.[3] They should attempt to identify subsets of patients who might respond favorably or unfavorably to barbiturate treatment. For example, Cruz et al. suggested that certain patients may develop oligemic hypoxia if given barbiturates.[4] Lobato et al., based on their experience with 55 patients, suggested that barbiturates increase the odds of survival in the setting of post-traumatic unilateral hemispheric swelling.[15] And Nordstrom et al. demonstrated a correlation in 19 patients between cerebral vasoreactivity and the beneficial effects of barbiturate therapy on outcome.[16]

The effects of barbiturate-mediated ICP control on the quality of survival after severe TBI remain, for the most part, unknown. Further studies are required to adequately address outcomes utilizing the GOS, Disability Rating Scale, Functional Independence Measures, and neuropsychological testing.

Finally, additional studies examining the comparative clinical efficacy of different barbiturates or combinations of barbiturates are warranted.

VII. EVIDENCE TABLES

Evidence Table I. Anesthetics, Analgesics, and Sedatives

Reference	*Study description*	*Data class*	*Conclusion*
Eisenberg et al., 1988[7]	RCT of pentobarbital for medically refractory ICP in 37 patients with 36 controls. Crossover design allowed 32 of the 36 controls to receive pentobarbital.	II	The likelihood of survival for those patients whose ICP responded to barbiturate therapy was 92% compared to 17% for non-responders. In those patients with pre-randomized hypotension, barbiturates provided no benefit.

Schwartz et al., 1984[21]	RCT of prophylactic pentobarbital ($n = 28$) versus mannitol ($n = 31$) therapy for ICP elevations >25 mm Hg. Patients stratified based on presence/absence of intracranial hematoma.	III	Pentobarbital provided no benefits in mortality or ICP control for patients with intracranial mass lesions. In patients with diffuse injury, there was no benefit to ICP control, and significantly higher group ($p = 0.03$).
Ward et al., 1985[22]	RCT of pentobarbital vs. standard treatment in 53 patients with risk factors for elevated ICP.	II	No significant difference in mortality at 1 year BOS found between treatment groups. Hypotension (SBP < 80 mm Hg) occurred in 54% of pentobarbital-treated patients compared to 7% of controls ($p < 0.001$).
New study			
Kelly et al., 1999[13]	RCT of propofol versus morphine sulfate to determine drug safety in severe TBI patients. Secondary endpoints included ICP control, CPP, TIL, and 6-month GOS.	II	In 42 patients (23 propofol, 19 morphine sulfate), ICP and TIL were lower on day 3 ($p < 0.05$) in atients receiving propofol. There was no effect on mortality or GOS outcomes. In a post-hoc analysis of high- versus low-dose propofol patients, GOS favorable outcome was 70% versus 38.5%, respectively ($p < 0.05$).

VIII. REFERENCES

1. Albanese J, Durbec G, Viviand X, et al. Sufentanyl increases intracranial pressure in patients with head trauma. Anesthesiology 1993;74:493–497.
2. Bullock RM, Chesnut RM, Clifton RL, et al. Management and prognosis of severe traumatic brain injury. J Neurotrauma 2000;17:453–627.
3. Changani S, Papadokos P. The use of dexmedetomidine for sedation in patients with traumatic brain injury. Anesthesiology Suppl 2002;B20.
4. Cruz J. Adverse effects of pentobarbital on cerebral venous oxygenation of comatose patients with acute traumatic brain swelling: relationship to outcome. J Neurosurg 1996; 85:758–761.
5. Demopoulous HB, Flamm ES, Pietronigro DD, et al. The free radical pathology and the microcirculation in the major central nervous system trauma. Acta Physiol Scand Suppl 1980;492:91–119.
6. deNadal M, Ausina A, Sahuquillo J. Effects on intracranial pressure of fentanyl in severe head injury patients. Acta Neurochir 1998;71:10–12.
7. Eisenberg HM, Frankowski RF, Contant CF, et al. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 1988;69: 15–23.
8. Farling PA, Johnston JR, Coppel DL. Propofol infusion for sedation of patients with head injury in intensive care. Anesthesiology 1989;44:222–226.
9. Goodman JC, Valadka AB, Gopinath SP, et al. Lactate and excitatory amino acids measured by microdialysis are decreased by pentobarbital coma in head-injured patients. J Neurotrauma 1996;13:549–556.
10. Horsley JS. The intracranial pressure during barbital narcosis. Lancet 1937;1:141–143.
11. Kang TF. Propofol infusion syndrome in critically ill patients. Ann Pharmacother 2002;36:1453–1456.
12. Kassell NF, Hitchon PW, Gerk MK, et al. Alterations in cerebral blood flow, oxygen metabolism, and electrical activity produced by high-dose thiopental. Neurosurgery 1980;7:598–603.
13. Kelly PF, Goodale DB, Williams J, et al. Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial. J Neurosurg 1999;90:1042–1057.
14. Laver KK, Connolly LA, Schmeling WT. Opioid sedation does not alter intracranial pressure in head-injured patients. Can J Anaesthesiol 1997;44:929–933.
15. Lobato RD, Sarabia R, Cordobes C, et al. Posttraumatic cerebral hemispheric swelling. Analysis of 55 cases studied by CT. J Neurosurg 1988;68:417–423.

16. Nordstrom GH, Messseter K, Sundberg B, et al. Cerebral blood flow, vasoreactivity and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. J Neurosurg 1988;68:424–431.

17. Papazian L, Albanese J, Thirium X. Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. Br J Anesthesiol 1993;71:267–271.

18. Pinaud M, Lelausque J-N, Chetanneau, A, et al. Effects of propofol on cerebral hemodynamics and metabolism in patients with brain trauma. Anesthesiology 1990;73: 404–409.

19. Roberts I. Barbiturates for acute traumatic brain injury. The Cochrane Library, Volume 4, 2005.

20. Sperry RT, Bailey PL, Reichman MV. Fentanyl and sufentanyl increase intracranial pressure in head trauma patients. Anesthesiology 1992;77:416–420.

21. Schwartz M, Tator C, Towed D, et al. The University of Toronto head injury treatment study: a prospective, randomized comparison of pentobarbital and mannitol. Can J Neurol Sci 1984;11:434–440.

22. Ward JD, Becker DP, Miller JD, et al. Failure of prophylactic barbiturate coma in the treatment of severe head injury. J Neurosurg 1985;62:383–388.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-77–S-82
DOI: 10.1089/neu.2006.9984

XII. Nutrition

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Patients should be fed to attain full caloric replacement by day 7 post-injury.

II. OVERVIEW

There are still few studies specifically addressing the impact of nutrition on traumatic brain injury (TBI) outcome. The effects of TBI on metabolism and nitrogen wasting have been studied most thoroughly. Prior to the 1980s, there were occasional case reports of hypermetabolism in TBI. The general attitude toward nutritional replacement was based on the assumption that, due to coma, metabolic requirements were reduced. However, over the last 25 years, numerous studies have documented hypermetabolism and nitrogen wasting in TBI patients. Data measuring metabolic expenditure in rested comatose patients with isolated TBI yielded a mean increase of approximately 140% of the expected metabolic expenditure with variations from 120% to 250% of that expected. These findings were consistent whether corticosteroids were used or not.[5,20] Since the 2000 guidelines, two Class II studies have been conducted.[19,24]

III. PROCESS

For this update, Medline was searched from 1996 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 33 potentially relevant studies, 4 were added to the existing tables and used as evidence for this question (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Metabolism and Energy Expenditure and Caloric Intake

Researchers found that, in TBI 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 2 weeks after injury, energy expenditure seems to rise regardless of neurological course.

Nitrogen balance is an important measure of the adequacy of caloric intake and metabolism. The acceptable amount of nitrogen loss has not been quantified and has not been subjected to Class I studies relating it to global outcome. Randomized controlled trials (RCTs) measuring nitrogen balance or the degree of nitrogen loss as a surrogate of outcome have been performed,[3,6,10] but because they do not measure patient outcomes, they are not included as evidence for this topic. However, data from these studies suggest that at a high range of nitrogen intake ($>$17 g/day), less than 50% of administered nitrogen is retained after TBI. Therefore, the level of nitrogen intake that generally results in $<$10 g nitrogen loss per day is 15–17 g N/day or 0.3–0.5 g N/kg/day. 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 $>$15% protein calories.

Two studies evaluated the relationship of caloric intake to patient outcomes.[17,22] One Class II study found that the consequence of severe undernutrition for a 2-week period after injury was a significantly greater mortality rate as compared to full replacement of measured calories by 7 days.[17] A subsequent Class III study found no difference in morbidity at 6 months with full replacement at 3 versus 9 days.[22]

Timing of Feeding after Injury

To achieve full caloric replacement by 7 days, nutritional replacement is usually begun no later than 72 h after injury. One Class II study demonstrated fewer infective and overall complications by starting feeding (jejunal and/or gastric) at a rate that met the estimated energy and nitrogen requirements starting on day 1 after injury.[19] The study also showed that these patients had a higher percentage of energy and nitrogen requirements met by the end of the first week. There was a trend towards improvement at 3 months but no difference in outcome at 6 months as measured by the Glasgow Outcome Scale (GOS) score. There is evidence to suggest that 2–3 days are required to gradually increase feedings to full replacement whether feeding is by jejunal or gastric route.[8,22] Intravenous hyperalimentation is also started at levels below resting metabolism expenditure and advanced over 3 days. Whichever method is used, feedings are usually begun within 72 h of injury in order to achieve full nutritional support.

Formulations for Feeding

There have been no published studies comparing different specific formulations for parenteral or enteral nutrition in the setting of human TBI. Except for the protein content, the appropriate combination of the core components of nutritional support (carbohydrates, lipids, and proteins) are based on the critical care literature. As discussed above, the recommended amount of protein in enteral and parenteral formulations should make up about 15% of the total calories. The use of branch chain amino acids has not been studied in TBI. There is evidence in critical care literature that branch chain amino acids improve outcome in septic patients.[7] Glutamine supplementation may also be beneficial by decreasing the infection rate, but it has yet to be adequately studied in TBI patients. Immune enhancing and immune modulating diets containing glutamine, arginine, omega-3 fatty acids, and nucleotides have been studied in the critical care and surgical settings but not in TBI patients specifically.[11,15,16]

Method of Feeding

There are three options for the method of early feeding: gastric, jejunal, and parenteral. Some reports indicate that jejunal and parenteral replacement produce better nitrogen retention than gastric feeding.[8,9,21,22] Gastric alimentation has been used by some investigators.[22] Others have found altered gastric emptying or lower esophageal sphincter dysfunction to complicate gastric feeding.[16] One study reported better tolerance of enteral feeding with jejunal rather than gastric administration.[12] In studies of both gastric and jejunal administration, it has been possible to achieve full caloric feeding in most patients by 7 days after injury.[8,12,22]

Percutaneous endoscopic gastrostomy is well tolerated in TBI patients, but there is the concern that early intragastric feeding may pose the risk of formation of residual, delayed gastric emptying, and aspiration pneumonia. However, one Class III found 111/114 (97%) patients tolerated intragastric feeding (started at an initial rate of 25 mL/h and increased by 25 mL/h every 12 h until target was reached) without complication.[13] Another Class III study demonstrated better feeding tolerance with continuous compared to bolus feeding and were able to meet 75% of nutritional goals faster.[18] In this study, the authors also identified other significant independent predictors of feeding intolerance (use of sucralfate, propofol, pentabarbitol and days of mechanical ventilation, older age, admission diagnosis of either intracerebral hemorrhage or ischemic stroke). Use of prokinetic agents failed to improve tolerance to gastric feeding. There was no difference in clinical outcome (GOS, ICU, and hospital length of stay) with continuous versus bolus feeding.

Jejunal feeding by gastrojejunostomy avoids gastric intolerance found in gastric feeding and the use of intravenous catheters required in total parenteral nutrition. Jejunal alimentation by endoscopic or fluroscopic, not blind, placement has practical advantages over gastric feeding. A higher percentage of patients tolerate jejunal better than gastric feeding early after injury (first 72 h) with less risk of aspiration.[8,16] Increasingly, parenteral nutrition is started early after injury until either gastric feedings are tolerated or a jejunal feeding tube can be placed.[1,17]

The risk of infection has not been shown to be increased with parenteral nutrition as compared to enteral nutrition in TBI patients.[1,21] The primary advantage of parenteral nutrition is that it is well tolerated. While in laboratory animals, parenteral nutrition may aggravate brain swelling, the available evidence does not indicate this is a clinical problem.[21] No clearly superior method of feeding has been demonstrated either in terms of nitrogen retention, complications, or outcome.

Glycemic Control

Hyperglycemia has been shown to aggravate hypoxic ischemic brain injury in an extensive body of experimental literature with animals. One such study of cortical contusion injury in rats found hyperglycemia to exacerbate cortical contusion injury with superimposed ischemia.[2] In two Class III human studies, hyperglycemia has been associated with worsened outcome.[14,23]

Vitamins, Minerals, and Supplements

Zinc is the only supplement studied in detail in a TBI population. One small pilot Class II study reported a better 24-h peak GCS motor score at two time points after injury (days 15 and 21) with zinc supplementation.[24] There was also a significant improvement in two visceral protein levels (serum prealbumin, retinol binding protein) and a trend towards lower mortality.

V. SUMMARY

Data show that starved TBI patients lose sufficient nitrogen to reduce weight by 15% per week; 100–140% replacement of Resting Metabolism Expenditure with 15–20% nitrogen calories reduces nitrogen loss. Data in non-TBI injured patients show that a 30% weight loss increased mortality rate. The data 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 7 days improves outcome. Based on the level of nitrogen wasting documented in TBI patients and the nitrogen sparing effect of feeding, it is a Level II recommendation that full nutritional replacement be instituted by day 7 post-injury.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Studies are needed to determine if specific nutritional formulations and the addition of vitamins and other supplements can improve outcome of TBI patients. There is still some debate with regards to the timing of feeding, rate of the achievement of target caloric intake and method of delivery that could be answered by well designed clinical trials.

VII. EVIDENCE TABLE

Evidence Table I. Nutrition

Reference	*Study description*	*Data class*	*Conclusion*
Borzotta et al., 1994[1]	Energy expenditure (MREE) and nitrogen excretion (UNN) measured in patients with severe TBI randomized to early parenteral (TPN, $n = 21$) or jejunal (ENT, $n = 17$) feeding with identical formulations.	III	Either TPN or ENT support is equally effective when prescribed according to individual measurements of MREE and nitrogen excretion. 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) g N/day. Equal effectiveness in meeting nutritional goals. Infection rates and hospital costs similar.
Clifton et al., 1986[4]	A nomogram was presented for estimation of RME at bedside of comatose, TBI patients based on 312 days of measurement of energy expenditure in 57 patients.	III	No predictors for N excretion were found. The authors recommend use of a nomogram to estimate RME and measurement of nitrogen excretion to guide feeding.
Grahm et al., 1989[8]	Thirty-two TBI patients were randomized to nasojejunal or gastric feeding. Nitrogen balance in the nasojejunal group was −4.3 vs. −11.8 g/day in the gastric feeding group.	III	Nasojejunal feeding permitted increased caloric intake and improved nitrogen balance.

(*continued*)

Evidence Table I. Nutrition (Cont'd)

Reference	*Study description*	*Data class*	*Conclusion*
Hadley et al., 1986[9]	Forty-five acute TBI patients were randomized into two groups comparing the efficacy of TPN and enteral nutrition.	III	TPN patients had significantly higher mean daily N intakes ($p < 0.01$) and mean daily N losses ($p < 0.001$) than naso-gastrically fed patients; however, nitrogen balance was not improved. Patients with TBI who are fed larger nitrogen loads have exaggerated nitrogen losses.
Kirby et al., 1991[12]	Twenty-seven patients with severe TBI underwent feeding with percutaneous endoscopic gastrojejunostomy.	III	Average nitrogen balance was −5.7 g/day. The reduction in N loss by this technique appeared equal or superior to gastric or TPN.
Lam et al., 1991[14]	The clinical course of 169 patients with moderate or severe TBI was retrospectively reviewed and outcome correlated with serum glucose.	III	Among the more severely injured patients (GCS < 8), a serum glucose level greater than 200 mg/chl postoperatively was associated with a significantly worse outcome.
Rapp et al., 1983[17]	Thirty-eight TBI patients were randomly assigned to receive total parenteral nutrition (TPN) or standard enteral nutrition (SEN). Mean intake for the TPN group was 1750 calories and 10.2 g/day of N for the first 18 days. The TPN group got full nutritional replacement within 7 days of injury. The SEN group achieved 1600 calories replacement by 14 days after injury. For the SEN group mean intake in the same period was 685 calories and 4.0 g/day of N.	II	There were 8 deaths in the enteral nutrition group and none in the parenteral nutrition group in the first 18 days ($p < 0.001$). Early feeding reduced mortality from TBI.
Young et al., 1989[23]	Serum glucose levels were followed in 59 consecutive TBI patients for up to 18 days after injury and correlated with outcome.	III	The patients with the highest peak admission 24-h glucose levels had the worst 18-day neurological outcome.
Young et al., 1987[22]	Fifty-one TBI patients with admission GCS 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 N).	III	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, 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.

Young et al., 1987[21]	Ninety-six patients with severe TBI were randomly assigned to TPN or enteral nutrition. The incidence of increased ICP was measured in both groups for a period of 18 days.	III	There was no difference in rate of increased ICP between groups.
New studies			
Klodell et al., 1987[21]	Prospective observational study of 118 moderate to severe TBI patients provided percutaneous endoscopic gastrostomy (PEG) and intragastric feeding.	III	Intragastric feeding was tolerated in 111 of 114 patients. Five patients aspirated.
Rhoney et al., 1987[21]	Retrospective cohort study of 152 severe TBI subjects comparing bolus versus continuous gastric feeding.	III	Feeding intolerance was greater in bolus groups. Continuous group reached 75% goals earlier, trend towards less infection in continuous feeding. No difference in outcome (hosp/ICU stay, GOS, death)
Taylor et al., 1987[21]	RCT of TBI patients receiving mechanical ventilation comparing accelerated enteral feeding versus standard feeding.	II	There was a trend toward better GOS at 3 months in the accelerated feeding cohort, but no difference at 6 months. Accelerated feeding met goals faster in first week and there were less infections.
Young et al., 1996[24]	RCT of severe TBI comparing supplemental Zinc cover and above normal formulations	II	Nonsignificant trend toward higher mortality in control (n = 26) 26 versus treatment (n = 12; p = 0.09). Albumin, prealb, RBP were significantly higher in treatment group., GCS did not differ significantly.

MREE, metabolic resting energy expenditure; N, nitrogen; RME, resting metabolic expenditure; g, grams; TPN, total parenteral nutrition.

VIII. REFERENCES

1. Borzotta AP, Pennings J, Papasadero B, et al. Enteral versus parenteral nutrition after severe closed head injury. J Trauma 1994;37:459–468.
2. Cherian L, Goodman JC, Robertson CS. Hyperglycemia increases brain injury caused by secondary ischemia after cortical impact injury in rats. Crit Care Med 1997;25: 1378–1383.
3. Clifton GL, Robertson CS, Contant CF. Enteral hyperalimentation in head injury. J Neurosurg 1985;62:186–193.
4. Clifton GL, Robertson CS, Choi SC. Assessment of nutritional requirements of head-injured patients. J Neurosurg 1986;64:895–901.
5. Deutschman CS, Konstantinides FN, Raup S. Physiological and metabolic response to isolated closed-head injury. Part 1: Basal metabolic state: correlations of metabolic and physiological parameters with fasting and stressed controls. J Neurosurg 1986;64:89–98.
6. Dominioni L, Trocki O, Mochizuki H, et al. Prevention of severe postburn hypermetabolism and catabolism by immediate intragastric feeding. J Burn Care Rehabil 1984;5: 106–112.
7. Garcia-de-Lorenzo AC, Ortiz-Leyba M, Planas JC, et al. Parenteral administration of different amounts of branch-chain amino acids inseptic patients: clinical and metabolic aspects. Crit Care Med 1997;25:418–424.
8. Grahm TW, Zadrozny DB, Harrington T. The benefits of early jejunal hyperalimentation in the head-injured patient. Neurosurgery 1989;25:729–735.
9. Hadley MN, Grahm TW, Harrington T, et al. Nutritional support and neurotrauma: a critical review of early nutrition in forty-five acute head injury patients. Neurosurgery 1986;19:367–373.
10. Hausmann, D, Mosebach KO, Caspari R, et al. Combined enteral-parenteral nutrition versus total parenteral nutrition in brain-injured patients. A comparative study. Intensive Care Med 1985;11:80–84.

11. Huckleberry Y. Nutritional support and the surgical patient. Am J Health System Pharm 2004;61:671–4.

12. Kirby DF, Clifton GL, Turner H, et al. Early enteral nutrition after brain injury by percutaneous endoscopic gastrojejunostomy. JPEN 1991;15:298–302.

13. Klodell CT, Carroll M, Carrillo EH, et al. Routine intragastric feeding following traumatic brain injury is safe and well tolerated. Am J Surg 2000;179:168–171.

14. Lam AM, Winn HR, Cullen BF, et al. Hyperglycemia and neurological outcome in patients with head injury. J Neurosurg 1991;75:545–551.

15. Montejo JC, Zarazaga A, Lopez-Martinez J, et al. Immunonutrition in the intensive care unit. A systematic review and consensus statement. Clin Nutr 2003;22:221–233.

16. Ott L, Annis K, Hatton J, et al. Postpyloric enteral feeding costs for patients with severe head injury: blind placement, endoscopy, and PEG/J versus TPN. J Neurotrauma 1999; 16:233–242.

17. Rapp RP, Young B, Twyman D, et al. The favorable effect of early parenteral feeding on survival in head-injured patients. J Neurosurg 1983;58:906–912.

18. Rhoney DH, Parker D, Formea CM Jr, et al. Tolerability of bolus versus continuous gastric feeding in brain-injured patients. Neurol Res 2002;24:613–620.

19. Taylor SJ, Fettes SB, Jewkes C, et al. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 1999;27:2525–2531.

20. Young B, Ott L, Norton J, et al. Metabolic and nutritional sequelae in the non-steroid treated head injury patient. Neurosurgery 1985;17:784–791.

21. Young B, Ott L, Haack D, et al. Effect of total parenteral nutrition upon intracranial pressure in severe head injury. J Neurosurg, 1987;67:76–80.

22. Young B, Ott L, Twyman D, et al. The effect of nutritional support on outcome from severe head injury. J Neurosurg 1987;67:668–676.

23. Young B, Ott L, Dempsey R, et al. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. Ann Surg 1989;210:466–473.

24. Young B, Ott L, Kasarskis E, et al. Zinc supplementation is associated with improved neurologic recovery rate and visceral protein levels of patients with severe closed head injury. J Neurotrauma 1996;13:25–34.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-83–S-86
DOI: 10.1089/neu.2007.9983

XIII. Antiseizure Prophylaxis

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Prophylactic use of phenytoin or valproate is not recommended for preventing late posttraumatic seizures (PTS).

Anticonvulsants are indicated to decrease the incidence of early PTS (within 7 days of injury). However, early PTS is not associated with worse outcomes.

II. OVERVIEW

PTSs are classified as early, occurring within 7 days of injury, or late, occurring after 7 days following injury.[8,11] It is desirable to prevent both early and late PTS. However, it is also desirable to avoid neurobehavioral and other side effects of medications, particularly if they are ineffective in preventing seizures.

Prophylaxis for PTS refers to the practice of administering anticonvulsants to patients following traumatic brain injury (TBI) to prevent the occurrence of seizures. The rationale for routine seizure prophylaxis is that there is a relatively high incidence of PTS in TBI patients, and there are potential benefits to preventing seizures following TBI.[8,11]

The incidence of seizures following penetrating injuries is about 50% in patients followed for 15 years.[8] In civilian TBI studies that followed high-risk patients up to 36 months, the incidence of early PTS varied between 4% and 25%, and the incidence of late PTS varied between 9% and 42% in untreated patients.[8,2,5] 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.[8,11] Experimental studies have supported the idea that initial seizures may initiate kindling, which then may generate a permanent seizure focus.

Early retrospective studies indicated that phenytoin was effective for the prevention of PTS.[10,12] A practice survey among U.S. neurosurgeons in 1973 indicated that 60% used seizure prophylaxis for TBI patients.[6] On the other hand, anticonvulsants have been associated with adverse side effects including rashes, Stevens-Johnson syndrome, hematologic abnormalities, ataxia, and neurobehavioral side effects.[8,11,2] Certain risk factors have been identified that place TBI patients at increased risk for developing PTS.[9,11] These risk factors include the following:

Glasgow Coma Scale (GCS) Score < 10
Cortical contusion
Depressed skull fracture
Subdural hematoma
Epidural hematoma
Intracerebral hematoma
Penetrating head wound
Seizure within 24 h of injury

It is therefore important to evaluate the efficacy and overall benefit, as well as potential harms, of anticonvulsants used for the prevention of PTS.

III. PROCESS

For this update, Medline was searched from 1996 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 10 potentially relevant studies, one was added to the existing table and used as evidence for this question (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

Temkin et al. reported the results of a large randomized, double-blind, placebo-controlled trial of 404 patients evaluating the effect of phenytoin on early and late PTS.[9] 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 PTS in the treated group from 14.2% to 3.6% ($p < 0.001$). There was no significant reduction in the incidence of late PTS in the treated group. The survival curves for the placebo and active treatment groups showed no significant difference.

A secondary analysis was performed on the data from this trial to determine if treatment for early PTS was associated with significant drug related adverse side effects.[3] The occurrence of adverse drug effects during the first 2 weeks of treatment was low and not significantly different between the treated and placebo groups. Hypersensitivity reactions occurred in 0.6% of the phenytoin group versus 0% of the placebo group ($p = 1.0$) during week 1, and 2.5% of the phenytoin group versus 0% of the placebo group ($p = 0.12$) for the first 2 weeks of treatment. Mortality was also similar in both groups. The results of the study indicate that the incidence of early posttraumatic seizures can be effectively reduced by prophylactic administration of phenytoin for 1 or 2 weeks without a significant increase in serious drug related side effects.

In another secondary analysis of the same trial, Dikmen et al. found significantly impaired performance on neuropsychologic tests at 1 month after injury in severe TBI patients maintained on phenytoin. However, the difference was not apparent at 1 year following injury.[1]

An additional randomized, double-blind study evaluated the effect of valproate to reduce the incidence of early and late posttraumatic seizures.[7] The trial compared phenytoin to valproate for the prevention of early PTS, and valproate to placebo for the prevention of late PTS. The incidence of early PTS was similar in patients treated with either valproate or phenytoin. The incidence of late PTS was similar in patients treated with phenytoin for 1 week and then placebo, or patients treated with valproate for either 1 month then placebo, or with valproate for 6 months. There was a trend toward higher mortality in patients treated with valproate.

Young et al. conducted a randomized, double-blind study of 244 TBI patients and reported that phenytoin was not effective in preventing early or late PTS.[13] The incidence of early PTS was low in the placebo and treatment groups, however, which may have influenced the lack of protective effect of treatment on early PTS. No patient with a phenytoin plasma concentration of 12 mcg/ml or higher had a seizure however, and therefore, the possibility remained that higher levels may have been more effective in preventing late PTS. Methodological flaws in this study render the evidence Class III and limit inferences.

Manaka conducted a randomized, double-blind study of 126 patients receiving placebo or phenobarbital for the prevention of late PTS.[4] There was no significant reduction in late PTS in the active treatment group. This study provided Class III evidence.

The studies that form the evidence base for this topic indicate that anticonvulsants administered prophylactically reduce the incidence of early PTS but do not significantly reduce the incidence of late PTS. All of these studies classified seizures based on clinically recognized episodes. Currently there is no evidence on outcome in patients with non-convulsive seizures with or without prophylaxis. In addition, the available evidence does not indicate that prevention of PTS improves outcome.

V. SUMMARY

The majority of studies do not support the use of the prophylactic anticonvulsants evaluated thus far for the prevention of late PTS. Routine seizure prophylaxis later than 1 week following TBI is, therefore, not recommended. If late PTS occurs, patients should be managed in accordance with standard approaches to patients with new onset seizures. Phenytoin has been shown to reduce the incidence of early PTS. Valproate may also have a comparable effect to phenytoin on reducing early PTS but may also be associated with a higher mortality.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Additional studies are needed to determine if reduction in early PTS has an effect on outcome. Such studies should utilize continuous EEG monitoring to identify seizures. Future trials should investigate incidence of PTS in patients treated with neuroprotective agents that have antiepileptic activity, such as magnesium sulphate and other NMDA receptor antagonists.

VII. EVIDENCE TABLE

Evidence Table I. Antiseizure Prophylaxis

Reference	*Description of study*	*Data class*	*Conclusion*
Manaka et al., 1992[4]	Randomized, double-blind study of 126 patients receiving placebo or phenobarbital for effect on late PTS. Treatment was started 1 month following TBI.	III	No significant effect of phenobarbital on late PTS.
Temkin et al., 1990[9]	Randomized, double-blind study of 404 patients receiving placebo vs. phenytoin for the prevention of early and late PTS. Patients were followed for 24 months.	II	Significant reduction in early PTS by phenytoin and no significant effect in preventing late PTS.
Temkin et al., 1999[7]	Randomized, double-blind parallel group clinical trial of 380 patients at high risk for post-traumatic seizures assigned to either 1 week of phenytoin, 1 month of valproate, or 6 months of valproate.	II	Similar rates of early PTS in patients treated with either valproate or phenytoin. No significant difference in late PTS in patients treated with either phenytoin for 1 week, or valproate for either 1 month or 6 months.
Young et al., 1983[13]	Randomized, double-blind study of 244 patients receiving placebo vs. phenytoin for the prevention of early and late PTS.	III	No significant effect of phenytoin on early or late PTS.
New Study			
Dikmen et al., 1991[1]	Sub-group analysis (*n* 244) of double-blind RCT of 404 patients receiving placebo vs. phenytoin for the prevention of early and late PTS. Patients were evaluated at 1, 12, and 24 months using neuropsychologic and psychosocial measures.	II	No significant effect in the moderate TBI group at 1 month, and in moderate and severe TBI groups at 1 year.

VIII. REFERENCES

1. Dikmen SS, Temkin NR, Miller B, et al. Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. JAMA 1991;265:1271–1277.
2. Glotzner FL, Haubitz I, Miltner F, et al. Anfallsprophylaze mit carbamazepin nach schweren schadelhirnverletzungen. Neurochir Stuttg 1983;26:66–79.
3. Haltiner AM, Newell DW, Temkin NR, et al. Side effects and mortality associated with use of phenytoin for early posttraumatic seizure prophylaxis. J Neurosurg 1999;91: 588–592.
4. Manaka S. Cooperative prospective study on posttraumatic epilepsy: risk factors and the effect of prophylactic anticonvulsant. Jpn J Psychiatry Neurol 1992;46: 311–315.

5. Pechadre JC, Lauxerois M, Colnet G, et al. Prevention de l'epelepsie posttraumatique tardive par phenytoine dans les traumatismes carniens graves: suivi durant 2 ans. Presse Med 1991;20:841–845.
6. Rapport RL, Penry JK. A survey of attitudes toward the pharmacologic prophylaxis of posttraumatic epilepsy. J Neurosurg 1973;38:159–166.
7. Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. J Neurosurg 1999;91:593–600.
8. Temkin NR, Dikmen SS, Winn HR. Posttraumatic seizures. In: Eisenberg HM, Aldrich EF (eds). Management of Head Injury. W.B. Saunders: Philadelphia, 1991:425–435.
9. Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323:497–502.
10. Wohns RNW, Wyler AR. Prophylactic phenytoin in severe head injuries. J Neurosurg 1979;51:507–509.
11. Yablon SA: Posttraumatic seizures. Arch Phys Med Rehabil 1993;74:983–1001.
12. Young B, Rapp RP, Brooks W, et al. Post-traumatic epilepsy prophylaxis. Epilepsia 1979;20:671–681.
13. Young B, Rapp RP, Norton JA, et al. Failure of prophylactically administered phenytoin to prevent late posttraumatic seizures. J Neurosurg 1983;58:236–241.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-87–S-90
DOI: 10.1089/neu.2007.9982

XIV. Hyperventilation

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

Prophylactic hyperventilation (PaCO2 of 25 mm Hg or less) is not recommended.

C. Level III

Hyperventilation is recommended as a temporizing measure for the reduction of elevated intracranial pressure (ICP).

Hyperventilation should be avoided during the first 24 hours after injury when cerebral blood flow (CBF) is often critically reduced.

If hyperventilation is used, jugular venous oxygen saturation (SjO_2) or brain tissue oxygen tension ($PbrO_2$) measurements are recommended to monitor oxygen delivery.

II. OVERVIEW

Aggressive hyperventilation (arterial $PaCO_2 < 25$ mm Hg) has been a cornerstone in the management of severe traumatic brain injury (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,[15] and high or uncontrolled ICP is one of the most common causes of death and neurologic disability after TBI.[1,13,18] Therefore, the assumption has been made that hyperventilation benefits all patients with severe TBI. As recent as 1995, a survey found that hyperventilation was being used by 83% of U.S. trauma centers.[6]

However, hyperventilation reduces ICP by causing cerebral vasoconstriction and a subsequent reduction in CBF.[20] 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,[2,3,5,11,12,16,21,23,24] 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.[7,8,22] A randomized study found significantly poorer outcomes at 3 and 6 months when prophylactic hyperventilation was used, as compared to when it was not.[17] 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

For this update, Medline was searched from 1996 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 23 potentially relevant studies, 2 were added to the existing tables and used as evidence for this question (Evidence Tables I, II, and III).

IV. SCIENTIFIC FOUNDATION

CBF Following TBI

Three studies provide Class III evidence that CBF can be dangerously low soon after severe TBI (Evidence Table I).[2,12,26] Two measured CBF with xenon-CT/CBF method during the first 5 days following severe TBI in a total of 67 patients. In one, CBF measurements obtained during the first 24 h after injury were less than 18 mL/100 g/min in 31.4% of patients.[2] In the second, the mean CBF during the first few hours after injury was 27 mL/100g/min.[12]

The third study measured CBF with a thermodiffusion blood flow probe, again during the first 5 days post-injury, in 37 severe TBI patients.[26] Twelve patients had a CBF less than 18 mL/100g/min up to 48 h post-injury.

$PaCO_2$/CBF Reactivity and Cerebral Oxygen Utilization

Three Class III studies provide the evidence base for this topic (Evidence Table II).[10,19,25] Results associating

hyperventilation with SjO_2 and $PbrO_2$ values in a total of 102 patients are equivocal. One study showed no consistent positive or negative change in SjO_2 or $PbrO_2$ values.[10] A second study associated hyperventilation with a reduction of $PaCO_2$ and subsequent decrease in SjO_2 from 73% to 67%, but the SjO_2 values never dropped below 55%.[19] The third reported hyperventilation to be the second most common identifiable cause of jugular venous oxygen desaturation in a sample of 33 patients.[25]

Studies on regional CBF show significant variation in reduction in CBF following TBI. Two studies indicated lowest flows in brain tissue surrounding contusions or underlying subdural hematomas, and in patients with severe diffuse injuries.[12,23] Similarly, a third found that CO_2 vasoresponsivity was most abnormal in contusions and subdural hematomas.[14] Considering that CO_2 vasoresponsivity could range from almost absent to three times normal in these patients, there could be a dangerous reduction in CBF to brain tissue surrounding contusions or underlying subdural clots following hyperventilation. (Note only one of these three studies[12] had adequate design and sample to be included as evidence.)

Two studies, not included in the evidence base for this topic, associated hyperventilation-induced reduction in CBF with a significant increase in oxygen extraction fraction (OEF), but they did not find a significant relationship between hyperventilation and change in the cerebral metabolic rate of oxygen (CMRO2).[4,9]

Effect of Hyperventilation on Outcome

One Class II randomized controlled trial (RCT) of 113 patients (Evidence Table III) used a stratified, randomized design to compare outcomes of severe TBI patients provided normal ventilation ($PaCO_2$ 35 $\pm$ 2 mm Hg; n = 41; control group), hyperventilation ($PaCO_2$ 25 $\pm$ 2 mm Hg; n = 36), or hyperventilation with tromethamine (THAM; n = 36).[17] One benefit of hyperventilation is considered to be minimization of cerebrospinal fluid (CSF) acidosis. However, the effect on CSF pH may not be sustained due to a loss of $HCO3^-$ buffer. THAM treatment was introduced to test the hypothesis that it would reverse the effects of the loss of buffer.

Patients were stratified based on the motor component of the Glasgow Coma Scale (GCS) score (1–3 and 4–5). The Glasgow Outcome Scale (GOS) score was used to assess patient outcomes at 3, 6, and 12 months. For patients with a motor GCS of 4–5, the 3- and 6-month GOS scores were significantly lower in the hyperventilated patients than in the control or THAM groups. However, the effect was not sustained at 12 months. Also, the effect was not observed in patients with the lower motor GCS, minimizing the sample size for the control, hyperventilation, and THAM groups to 21, 17, and 21, respectively. The absence of a power analysis renders uncertainty about the adequacy of the sample size. For these reasons, the recommendation that hyperventilation be avoided is Level II.

V. SUMMARY

In the absence of trials that evaluate the direct effect of hyperventilation on patient outcomes, we have constructed a causal pathway to link hyperventilation with intermediate endpoints known to be associated with outcome. Independent of hyperventilation, CBF can drop dangerously low in the first hours following severe TBI. The introduction of hyperventilation could further decrease CBF, contributing to the likelihood of ischemia. The relationship between hyperventilation and metabolism, as well as cerebral oxygen extraction, is less clear. The one study that evaluated patient outcomes strongly suggests that hyperventilation be avoided for certain patient subgroups.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

The causal link between hyperventilation and intermediate endpoints, and the subsequent relationship between those endpoints and patient outcomes, needs to be clearly specified. Further RCTs need to be conducted in the following areas:

- How does short-term hyperventilation affect outcome?
- The effect of moderate hyperventilation in specific subgroups of patients.
- Critical levels of $PaCO_2$/CBF and outcome.

VII. EVIDENCE TABLES

Evidence Table I. CBF Early after Severe TBI

Reference	*Study description*	*Data class*	*Conclusion*
Bouma et al., 1992[2]	Measurement of CBF with xenon-CT/CBF method during first 5 days after severe TBI in 35 adults.	III	CBF measurements obtained during the first 24 h after injury were less than 18 mL/100 g/min in 31.4% of patients.
Marion et al., 1991[12]	Measurement of CBF with xenon-CT/CBF method during first 5 days after severe TBI in 32 adults.	III	The mean CBF during the first few hours after injury was 27 mL/100 g/min; CBF always lowest during the first 12–24 h after injury.
Sioutos et al., 1995[26]	Measurement of CBF with thermodiffusion blood flow probe during first 5 days after severe TBI in 37 adults.	III	33% of patients had a CBF less than 28 mL/100 g/min during the first 24–48 h after injury.

Evidence Table II. Effect of Hyperventilation on Cerebral Oxygen Extraction

Reference	*Study description*	*Data class*	*Conclusion*
Sheinberg et al., 1992[25]	Results of SjO_2 monitoring of 33 adults with severe TBI during first 5 days after injury	III	Hyperventilation was the second most common identifiable cause for jugular venous oxygen desaturations.
New Studies			
Imberti et al., 2002[10]	Study of the effect of hyperventilation of SjO_2 and $PbrO_2$ values in 36 adults with severe TBI.	III	Hyperventilation ($paCO_2$ from 36 to 29 mm Hg) for 20 min did not result in consistent positive or negative changes in the SjO_2 or $PbrO_2$ values.
Oertel et al., 2002[19]	Study of the effect of hyperventilation of SjO_2 values in 33 adults with severe TBI.	III	A reduction of the $paCO_2$ from 35 to 27 mm Hg led to a decrease in the SjO_2 from 73% to 67%; in no case did it result in an SjO_2 of less than 55%.

Evidence Table III. Effect of Hyperventilation on Outcome

Reference	*Study description*	*Data class*	*Conclusion*
Muizelaar et al., 1991[17]	Sub-analysis of an RCT of THAM in which 77 adults and children with severe TBI were enrolled.	II	Patients with an initial GCS motor score of 4–5 that were hyperventilated to a $paCO_2$ of 25 mm Hg during the first 5 days after injury had significantly worse outcomes 6 months after injury than did those kept at a $paCO_2$ of 35 mm Hg.

VIII. REFERENCES

1. Becker DP, Miller JD, Ward JD, et al. The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg 1977;47:491–502.
2. Bouma GJ, Muizelaar JP, Stringer WA, et al. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg 1992;77:360–368.
3. Cruz J. Low clinical ischemic threshold for cerebral blood flow in severe acute brain trauma. Case report. J Neurosurg 1994;80:143–147.
4. Diringer MN, Videen TO, Yundt K, et al. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. J Neurosurg 2002;96: 103–108.
5. Fieschi C, Battistini N, Beduschi A, et al. Regional cerebral blood flow and intraventricular pressure in acute head injuries. J Neurol Neurosurg Psychiatry 1974;37:1378–1388.
6. Ghajar J, Hariri RJ, Narayan RK, et al. Survey of critical care management of comatose, head-injured patients in the United States. Crit Care Med 1995;23:560–567.
7. Graham DI, Adams JH. Ischaemic brain damage in fatal head injuries. Lancet 1971;1:265–266.
8. Graham DI, Lawrence AE, Adams JH, et al. Brain damage in fatal non-missile head injury without high intracranial pressure. J Clin Pathol 1988;41:34–37.
9. Hutchinson PJ, Gupta AK, Fryer TF, et al. Correlation between cerebral blood flow, substrate delivery, and metabolism in head injury: a combined microdialysis and triple oxygen positron emission tomography study. J Cereb Blood Flow Metab 2002;22:735–745.
10. Imberti R, Bellinzona G, Langer M. Cerebral tissue PO_2 and $SjvO_2$ changes during moderate hyperventilation in patients with severe traumatic brain injury. J Neurosurg 2002;96:97–102.
11. Jaggi JL, Obrist WD, Gennarelli TA, et al. Relationship of early cerebral blood flow and metabolism to outcome in acute head injury. J Neurosurg 1990;72:176–182.
12. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg 1991;74:407–414.
13. Marshall LF, Smith RW, Shapiro HM. The outcome with aggressive treatment in severe head injuries. I. The significance of intracranial pressure monitoring. J Neurosurg 1979;50:20–25.
14. McLaughlin MR, Marion DW. Cerebral blood flow and vasoresponsivity within and around cerebral contusions. J Neurosurg 1996;85:871–876.
15. Miller JD, Becker DP, Ward JD, et al. Significance of intracranial hypertension in severe head injury. J Neurosurg 1977;47:503–510.
16. Muizelaar JP, Marmarou A, DeSalles AA, et al. Cerebral blood flow and metabolism in severely head-injured children. Part 1: Relationship with GCS score, outcome, ICP, and PVI. J Neurosurg 1989;71:63–71.
17. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991;75:731–739.
18. Narayan RK, Kishore PRS, Becker DP, et al. Intracranial pressure: to monitor or not to monitor. J Neurosurg 1982;56:650–659.
19. Oertel M, Kelly DF, Lee JH, et al. Efficacy of hyperventilation, blood pressure elevation, and metabolic suppression therapy in controlling intracranial pressure after head injury. J Neurosurg 2002;97:1045–1053.
20. Raichle ME, Plum F. Hyperventilation and cerebral blood flow. Stroke 1972;3:566–575.
21. Robertson CS, Clifton GL, Grossman RG, et al. Alterations in cerebral availability of metabolic substrates after severe head injury. J Trauma 1988;28:1523–1532.
22. Ross DT, Graham DI, Adams JH. Selective loss of neurons from the thalamic reticular nucleus following severe human head injury. J Neurotrauma 1993;10:151–165.
23. Salvant JB, Jr., Muizelaar JP. Changes in cerebral blood flow and metabolism related to the presence of subdural hematoma. Neurosurgery 1993;33:387–393.
24. Schroder ML, Muizelaar JP, Kuta AJ. Documented reversal of global ischemia immediately after removal of an acute subdural hematoma. Neurosurgery 1994;80:324–327.
25. Sheinberg M, Kanter MJ, Robertson CS, et al. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. J Neurosurg 1992;76:212–217.
26. Sioutos PJ, Orozco JA, Carter LP, et al. Continuous regional cerebral cortical blood flow monitoring in head-injured patients. Neurosurgery 1995;36:943–949.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-91–S-95
DOI: 10.1089/neu.2007.9981

XV. Steroids

I. RECOMMENDATIONS

A. Level I

The use of steroids is not recommended for improving outcome or reducing intracranial pressure (ICP). In patients with moderate or severe traumatic brain injury (TBI), high-dose methylprednisolone is associated with increased mortality and is contraindicated.

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 brain edema,20 reduction of cerebrospinal fluid production,[26] 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] Renauldin et al. in 1973 reported a beneficial effect of high-dose glucocorticoids in patients with brain tumors 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 TBI. In 1976 Gobiet et al. compared low- and high-dose Decadron to a previous control group of severe TBI patients and reported it to be of benefit in the high-dose group.[12] Also in 1976, Faupel et al. performed a double blind trial and reported a favorable dose-related effect on mortality in TBI patients using glucocorticoid treatment.[8] Subsequently, six major studies of glucocorticoid in severe TBI were conducted that evaluated clinical outcome, ICP, or both. None of these studies showed a substantial benefit of glucocorticoid therapy in these patients.[2,5,6,11,14,24] Trials in TBI patients have been completed using the synthetic glucocorticoid, triamcinolone,[13] the 21-aminosteroid tirilazad,[7,19] a trial using ultra-high-dose dexamethasone,[10] and a trial using high-dose methylprednisolone.[23] None of these trials has indicated an overall beneficial effect of steroids on outcome, and one trial was halted before completion when an interim analysis showed increased mortality with steroid administration. Moreover, a meta-analysis of trials of steroids in TBI revealed no overall beneficial effect on outcome.[1]

III. PROCESS

For this update, Medline was searched from 1996 through April of 2006 (see Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 14 potentially relevant studies, 2 were added to the existing table and used as evidence for this question (Evidence Table I).

IV. SCIENTIFIC FOUNDATION

In 1979, Cooper et al. reported a prospective, double-blind study of dexamethasone in patients with severe TBI.[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. The results showed no difference in outcome, ICP, or serial neurologic examinations among the groups.

Saul et al. reported a randomized clinical trial in 100 patients.[24] One group received methylprednisolone 5 mg/kg/day versus a control group that received no drug. There was no statistically significant difference in outcome between the treated and non-treated groups at 6 months. A subgroup analysis indicated that, in patients who improved during the first 3 days after TBI, the

steroid-treated group had better outcomes than the placebo group.

Gianotta et al. reported a double blind clinical trial of 88 patients comparing placebo; low-dose methylprednisolone 1.5 mg/kg loading, followed by a tapering dose; and high-dose methylprednisolone 30 mg/kg loading, followed by a tapering dose.[11] 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 with the low dose and placebo groups combined.

Gaab et al. reported the results of a randomized double-blind multicenter trial of the efficacy and safety of ultra-high-dose dexamethasone in patients with moderate and severe TBI.[10] The trial enrolled 300 patients, randomized to placebo or dexamethasone: 500 mg within 3 h of injury, followed by 200 mg after 3 h, then 200 mg every 6 h for eight doses for a total dexamethasone dose of 2.3 g, given within 51 h. 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 advantage of having a large number of patients who were treated early following injury and with very high doses of medication.

Marshall et al.1998[19] reported the results of a large randomized controlled trial (RCT) of the synthetic 21-amino steroid, tirilazad mesylate, on outcome for patients with severe TBI[19] 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 trial enrolled 1,170 patients; no overall benefit on outcome in TBI patients was detected. The same outcome was demonstrated in a similar trial conducted in Europe and Australia that included non-trauma patients.[18]

More recently, Watson et al., using an existing prospective database, conducted a retrospective comparison of occurrence of first late seizures between TBI patients (GCS $\leq$ 10) who received glucocorticoids (n = 125) and those who did not (n = 279).[25] The treatment group was further divided into those who received the treatment within 24 h of injury (n = 105) and those who received it between days 2 and 7 post-injury. Patients were followed for 2 years. Authors used multivariate analysis to control for seizure risk and injury severity. They found a 74% increase in risk of developing first late seizures for patients who received glucocorticoids within 24 h of injury over those who did not (p = 0.04; hazard ratio = 1.74; CI 1.01–2.98). There was no significant difference between groups in the development of second late seizures, or in mortality. However, the evidence is Level III due to lack of information about GCS, hypotension, and hypoxia in the different groups, as well as to the possibility of bias in the selection of patients who received the treatment.

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

The CRASH (Corticosteroid Randomization After Significant Head Injury) trial collaborators in 2004 reported the results of an international RCT of methylprednisolone in patients with TBI.[23] 10,008 patients from 239 hospitals in 49 countries were randomized to receive either 2 g IV methylprednisolone followed by 0.4 mg/h for 48 h, or placebo. Inclusion criteria were age 16 years or greater, GCS 14 or less, and admission to hospital within 8 h of injury. Exclusion criteria included any patient with clear indications or contraindications for corticosteroids as interpreted by the referring or admitting physicians. The study was halted by the data monitoring committee, after approximately 5 years and 2 months of enrollment, when interim analysis showed a deleterious effect of methylprednisolone. Specifically, 2-week mortality in the steroid group was 21% versus 18% in controls, with a 1.18 relative risk of death in the steroid group (95% CI 1.09–1.27, p = 0.0001). This increase in risk was no different when patients were adjusted for the presence of extracranial injuries. The authors stated that the cause of the increase in mortality was unclear, but was not due to infections or gastrointestinal bleeding.

V. SUMMARY

The majority of available evidence indicates that steroids do not improve outcome or lower ICP in severe TBI. There is strong evidence that steroids are deleterious; thus their use is not recommended for TBI.

VI. KEY ISSUES FOR FUTURE INVESTIGATION

Currently, there is little enthusiasm for re-examining the use of existing formulations of steroids for treatment of patients with TBI. If new compounds with different mechanisms of actions are discovered, further study may be justified.

VII. EVIDENCE TABLE

Evidence Table I. Steroids

Reference	*Study description*	*Data class*	*Conclusion*
Cooper et al., 1979[5]	Prospective, double-blind study of 97 patients with severe TBI, 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.	III	No significant difference was seen in 6-month outcome, serial neurological exams, or ICP.
Faupel et al., 1976[8]	Prospective, double-blind trial of dexamethasone vs placebo in 95 patients with severe TBI.	III	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, respectively.
Gaab et al., 1994[10]	Randomized, double-blind, multicenter trial of ultra-highdose dexamethasone in 300 patients with moderate and severe TBI, randomized to placebo or dexamethasone: 500 mg within 3 h of injury, followed by 200 mg after 3 h then 200 mg every 6 h for 8 doses for a total dexamethasone dose of 2.3 g, given within 51 h.	III	No significant difference in 12-month outcome or in time to improvement to GCS score $\geq$8 in treatment group compared with placebo.
Giannotta et al., 1984[11]	Prospective, double-blind study of 88 patients with severe TBI. Patients randomized to placebo, low-dose methylprednisolone (30 mg/kg/day) or high-dose methylprednisolone (100 mg/kg/day).	III	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.
Marshall et al., 1984[19]	RCT of the effect of synthetic 21-amino steroid, tirilizad mesylate for severe TBI.	II	No overall benefit on outcome was detected.
Saul et al., 1981[24]	Prospective, double-blind study of 100 patients with severe TBI, randomized to	II	No significant difference in outcome at 6 months. In a subgroup analysis, in patients

(*continued*)

Evidence Table I. Steroids (Cont'd)

Reference	*Study description*	*Data class*	*Conclusion*
	placebo or methylprednisolone 5 mg/kg/day.		who improved during the first 3 days after TBI, the steroid-treated group had better outcomes than the placebo group.
New studies			
Roberts et al., 2004[23]	Multicenter RCT of IV methylprednisolone (2 g IV load + 0.4 g/h × 48 h) vs. placebo in 10,008 patients with GCS < 14 within 8 h of injury, on mortality at 14 days	I	The study was halted after approximately 62 months, prior to reaching full enrollment, when the Data Monitoring Committee's interim analysis showed clear deleterious effect of treatment on survival. The deleterious effect of steroids was not different across groups stratified by injury severity. Dead: Treatment 21.1% Placebo 17.9% RR = 1.18; 95% CI 1.09–1.27, $p = 0.0001$
Watson et al., 2004[25]	Prospective cohort of 404 patients. Baseline differences between groups (more dural penetration by surgery and more nonreactive pupils in treatment group).	III	Patients who received glucocorticoids within 24 h had a 74% increase in risk of first late seizures ($p = 0.04$).

VIII. REFERENCES

1. Alderson P, Roberts I. Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials. Br Med J 1997;314:1855–1859.
2. Braakman R, Schouten HJA, Blaauw-van DM, et al. Megadose steroids in severe head injury. J Neurosurg 1983;58: 326–330.
3. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the National Acute Spinal Cord Injury Study. J Neurosurg 1985; 63:704–713.
4. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med 1990;322:1405–1411.
5. Cooper PR, Moody S, Clark WK, et al. Dexamethasone and severe head injury. A prospective double-blind study. J Neurosurg 1979;51:307–316.
6. Dearden NM, Gibson JS, McDowall DG, et al. Effect of high-dose dexamethasone on outcome from severe head injury. J Neurosurg 1986;64:81–88.
7. Doppenberg EMR, Bullock R. Clinical neuro-protection trials in severe traumatic brain injury: Lessons from previous studies. J Neurotrauma 1997;14:71–80.
8. Faupel G, Reulen HJ, Muller D, et al. Double-blind study on the effects of steroids on severe closed head injury. In: Pappius HM, Feindel W (eds), Dynamics of Brain Edema. Springer-Verlag: New York, 1976:337–343.
9. French LA, Galicich JH. The use of steroids for control of cerebral edema. Clin Neurosurg 1964;10:212–223.
10. Gaab MR, Trost HA, Alcantara A, et al. "Ultrahigh" dexamethasone in acute brain injury. Results from a prospective randomized double-blind multicenter trial (GUDHIS). German Ultrahigh Dexamethasone Head Injury Study Group. Zentralblatt Neurochirurgie 1994;55:135–143.
11. Giannotta SL, Weiss MH, Apuzzo MLJ, et al. High-dose glucocorticoids in the management of severe head injury. Neurosurgery 1984;15:497–501.

12. Gobiet W, Bock WJ, Liesgang J, et al. Treatment of acute cerebral edema with high dose of dexamethasone. In: Beks JWF, Bosch DA, Brock M (eds), Intracranial Pressure III. Springer-Verlag: New York, 1976:231–235.
13. Grumme T, Baethmann A, Kolodziejczyk D, et al. Treatment of patients with severe head injury by triamcinolone: a prospective, controlled multicenter clinical trial of 396 cases. Res Exp Med 1995;195:217–229.
14. Gudeman SK, Miller JD, Becker DP. Failure of high-dose steroid therapy to influence intracranial pressure in patients with severe head injury. J Neurosurg 1979;51:301–306.
15. Hall ED. The neuroprotective pharmacology of methylprednisolone. J Neurosurg 1992;76:13–22.
16. Hall ED, Wolf DL, Braughler JM: Effects of a single large dose of methylprednisolone sodium succinate on experimental posttraumatic spinal cord ischemia. Dose-response and time-action analysis. J Neurosurg 1984;61:124–130.
17. Hall ED, Yonkers PA, McCall JM, et al. Effects of the 21-aminosteroid U74006F on experimental head injury in mice. J Neurosurg 1988;68:456–461.
18. Kassell NF, Haley EC. Randomized, doubleblind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand. J Neurosurg 1996; 84:221–228.
19. Marshall LF, Maas AL, Marshall SB, et al. A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. J Neurosurg 1998;89:519–525.
20. Maxwell RE, Long DM, French LA. The effects of glucosteroids on experimental cold-induced brain edema: gross morphological alterations and vascular permeability changes. J Neurosurg 1971;34:477–487.
21. Pappius HM, McCann WP. Effects of steroids on cerebral edema in cats. Arch Neurol 1969;20:207–216.
22. Renaudin J, Fewer D, Wilson CB, et al. Dose dependency of Decadron in patients with partially excised brain tumors. J Neurosurg 1973;39:302–305.
23. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10,008 adults with clinically significant head injury (MRC CRASH trial): randomized placebo controlled trial. Lancet 2004;364:1321–1328.
24. Saul TG, Ducker TB, Salcman M, et al. Steroids in severe head injury. A prospective randomized clinical trial. J Neurosurg 1981;54:596–600.
25. Watson NF, Barber JK, Doherty MJ, et al. Does glucocorticoid administration prevent late seizures after head injury? Epilepsia 2004;45:690–694.
26. Weiss MH, Nulsen FE. The effect of glucocorticoids on CSF in dogs. J Neurosurg 1970;32:452–458.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-96–S-98
DOI: 10.1089/neu.2007.9980

Appendix A
Changes in Quality Ratings from the 2nd Edition to the 3rd Edition

Topic and reference	*2nd ed. 2000*	*3rd ed. 2000*	*Reason for change*
Blood pressure and oxygenation			
Chesnut 93	II	III	Descriptive
Fearnside 93	II	III	Descriptive
Marmarou 91	II	III	Descriptive
Miller 78	II	III	Descriptive
Miller 82	II	III	Case series
Seelig 86	II	III	Descriptive
ICP thresholds			
Marmarou 91	II	III	Descriptive
Cerebral perfusion thresholds			
Cruz 98	II	III	Patient selection procedures not reported. No power calculation reported. Can't rule out that the results were confounded by baseline characteristics because no analysis to control for confounding factors was reported. Outcome assessment not blinded.
Robertson 99	I	II	Randomization and allocation concealment methods were inadequate and failure was evidenced by baseline differences. However, they adjusted for demographic characteristics, and the disadvantage for ICP in the primary outcome remained. The concern is that there may be additional unknown differences at baseline that were not adjusted for.
Rosner 90	II	III	Descriptive
Mannitol			
Schwartz 84	I	III	Allocation concealment was inadequate (sealed envelopes can be manipulated). Differential loss to follow-up and maintenance of comparable groups not reported. Inadequate follow-up rate. Blinding not reported. Results of power calculation not reported. It was unclear if groups were similar at baseline. No intent-to-treat analysis (excluded 15.7% of patients who departed from the study protocol).
Barbiturates			
Eisenberg 88	I	II	Adequate allocation concealment. Adequate follow-up and maintenance of comparable groups. Method of

Topic and reference	*2nd ed. 2000*	*3rd ed. 2000*	*Reason for change*
			randomization not reported; blinding not reported; baseline differences between groups; post-randomization exclusions that were unequally distributed; lack of an intent-to-treat analysis; inadequately powered.
Schwartz 84	I	III	Allocation concealment was inadequate (sealed envelopes can be manipulated). Differential loss to follow-up and maintenance of comparable groups not reported. Inadequate follow-up rate. Blinding not reported. Results of power calculation not reported. It was unclear if groups were similar at baseline. No intent-to-treat analysis (excluded 15.7% of patients who departed from the study protocol).
Ward 85	I	II	Methods of randomization and allocation concealment were not reported. It was unclear if the outcome assessors were blinded.
Steroids			
Cooper 79	I	III	Randomization method not reported, groups at baseline not reported, 78% of patients included in the analysis. No intent-to-treat analysis. Data analysis not specified.
Faupel 76	I	III	Blinding not reported, randomization method not reported, groups at baseline not reported, inadequate analysis. Inadequate sample size; no power analysis. No intent-to-treat analysis.
Gaab 94	I	III	Randomization method not reported, baseline differences not reported. Allocation concealment not specified. Potential selection bias. High attrition; no intent-to-treat analysis.
Giannotta 84	I	III	Randomization method not reported, baseline difference in age, no power analysis. Inadequate data analysis.
Marshall 98	I	II	Study was blinded. Sample size adequate. No differential loss to follow-up. Randomization method not reported, allocation concealment not reported. Baseline differences between groups. Lack of intent-to-treat analysis. High loss to follow-up.
Saul 81	I	II	Randomization method not reported, allocation concealment not reported, no power analysis. Blinding not specified. However, no attrition or loss to follow-up.
Anti-seizure prophylaxis			
Manaka 92	I	III	Blinding not reported, randomization method not reported, inadequate allocation concealment, no power analysis, No intent to treat analysis
Temkin 90	I	II	Can't rule out that results were biased by high loss to follow-up.
Temkin 99	I	II	Can't rule out that results were biased by high loss to follow-up.
Young 83	I	III	No power analysis, eligibility criteria not reported, no intent-to-treat analysis, inadequate analysis method, high attrition.

(*continued*)

APPENDIX A. CHANGES IN QUALITY RATINGS FROM 2ND TO 3RD EDITION

Topic and reference	*2nd ed. 2000*	*3rd ed. 2000*	*Reason for change*
Nutrition			
Borzotta 94	I	III	Method of allocation concealment not reported. Outcome assessors not blinded. No power analysis reported. No intent-to-treat analysis. Inadequate analysis methods.
Clifton 86	II	III	Prospective observational
Grahm 89	I	III	Descriptive
Hadley 86	I	III	Allocation concealment not reported. Blinding not reported, randomization method not adequate, no power calculation, inadequate analysis method. No intent-to-treat analysis.
Kirby 91	II	III	Observational
Lam 91	II	III	Retrospective descriptive
Ott 99	II	III	Retrospective descriptive
Rapp 83	I	II	Randomization method not reported. No power calculation. Baseline differences in mean peak temp between groups. However, adequate analysis methods.
Young 89	II	III	Observational
Young 87a	I	III	Randomization method not reported. Allocation concealment not reported. Blinding not reported. No power analysis. High loss to follow-up. No intent-to-treat analysis.
Young 87b	I	III	No power analysis, randomization method not reported, allocation concealment not reported, no intent-to-treat analysis.
Indications for ICP monitoring			
Eisenberg 88	I	II	Adequate allocation concealment. Adequate follow-up and maintenance of comparable groups. Method of randomization not reported; blinding not reported; baseline differences between groups; post-randomization exclusions that were unequally distributed; lack of an intent-to-treat analysis; inadequately powered.
Eisenberg 90	I	III	Descriptive
Lobato 86	II	III	Case series
Marmarou 91	II	III	Descriptive
Marshall 79	II	III	Case series
Miller 81	II	III	Case series
Narayan 82	II	III	Case series
Narayan 81	II	III	Descriptive
Saul 82	II	III	Analysis methods not reported. Hypotension confounded outcomes.
Hyperventilation			
Bouma 92	II	III	Descriptive
Marion 91	II	III	Descriptive
Sioutos 95	II	III	Descriptive
Sheinberg 92	II	III	Descriptive

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
Pp. S-99–S-104
DOI: 10.1089/neu.2007.9979

Appendix B
Electronic Literature Search Strategies
(Database: Ovid MEDLINE)

Blood pressure and oxygenation

1 exp Craniocerebral Trauma/
2 hypoxia.mp.
3 hypotension.mp.
4 2 or 3
5 1 and 2
6 limit 5 to human
7 (field or pre-hospital).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8 (treatment or management or resuscitation).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
9 1 and 7 and 8
10 6 or 9
11 limit 10 to yr=1998–2004

Hyperosmolar therapy

1 exp Brain Injuries/
2 ((brain$ or cerebr$) adj3 (trauma$ or injur$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 1 or 2
4 hyperosmol$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 "Osmolar Concentration"/
6 saline.mp. or exp Sodium Chloride/
7 (hyperton$ adj3 saline).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8 5 and 6
9 4 or 7 or 8
10 3 and 9
11 3 and (4 or 5)

Prophylactic hypothermia

1 exp Brain Injuries/
2 hypertherm$.mp.
3 hypotherm$.mp.
4 ((brain or cerebr$) adj3 temperature$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 2 or 3 or 4
6 1 and (2 or 3)
7 1 and 6
8 limit 7 to human
9 limit 8 to english language
10 8 not 9
11 limit 10 to abstracts
12 9 or 11

13 exp "OUTCOME AND PROCESS ASSESSMENT (HEALTH CARE)"/
14 12 and 13
15 limit 12 to clinical trial
16 14 or 15

Infection prophylaxis
1 exp Craniocerebral Trauma/
2 exp Central Nervous System Infections/
3 exp Craniocerebral Trauma/co
4 exp Central Nervous System Infections/pc
5 2 and 3
6 1 and 4
7 5 or 6
8 1 and 2
9 exp Anti-Infective Agents/
10 exp Antibiotic Prophylaxis/
11 9 or 10
12 8 and 11
13 exp Catheterization/
14 exp Catheters, Indwelling/
15 exp VENTRICULOSTOMY/ or exp Cerebrospinal Fluid Shunts/
16 exp Monitoring, Physiologic/ and exp Intracranial Pressure/
17 13 or 14 or 15 or 16
18 8 and 17
19 2 and 11 and 17
20 7 or 12 or 18 or 19
21 limit 20 to human
22 limit 21 to english language
23 21 not 22
24 limit 23 to abstracts
25 22 or 24

Deep vein thrombosis prophylaxis
1 Venous Thrombosis/pc [Prevention & Control]
2 exp ANTICOAGULANTS/
3 Venous Thrombosis/
4 2 and 3
5 1 or 4
6 exp Craniocerebral Trauma/
7 5 and 6
8 Neurosurgery/
9 exp Neurosurgical Procedures/
10 exp Brain/su [Surgery]
11 8 or 9 or 10
12 5 and 11
13 7 or 12
14 exp brain/
15 5 and 14
16 13 or 15
17 Thrombophlebitis/ or Venous Thrombosis/ or Thrombosis/
18 pc.fs.
19 17 and 18
20 12 and 19

21 19 and 14
22 17 and 2
23 22 and 6
24 22 and 14
25 22 and 11
26 11 and 19
27 20 or 21 or 23 or 24 or 25 or 26
28 16 or 27

Indications for ICP monitoring
1 exp Craniocerebral Trauma/
2 exp Intracranial Pressure/
3 exp Intracranial Hypertension/
4 1 and 2
5 1 and 3
6 exp Intracranial Pressure/ and exp Monitoring, Physiologic/
7 1 and 6
8 limit 7 to yr=1998–2004

ICP monitoring technology
1 intracranial pressure$.mp.
2 monitor.mp.
3 1 and 2
4 limit 3 to yr=1998–2004

ICP thresholds
1 (intracranial hypertension or icp or intracranial pressure).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
2 head injur$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 (treatment or management or resuscitation).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4 (threshold or level).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5 1 and 2 and 3 and 4
6 limit 5 to human

Cerebral perfusion thresholds
1 exp Brain Injuries/
2 cerebral perfusion pressure.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 1 and 2
4 from 3 keep 1-233

Brain oxygen monitoring thresholds
1 exp Craniocerebral Trauma/
2 exp Craniocerebral Trauma/bl, mi, cf, pa, pp, ra, en, ri, us, ur, me [Blood, Microbiology, Cerebrospinal Fluid, Pathology, Physiopathology, Radiography, Enzymology, Radionuclide Imaging, Ultrasonography, Urine, Metabolism]
3 exp Monitoring, Physiologic/
4 1 and 3
5 OXYGEN/
6 1 and 5
7 limit 6 to human
8 3 and 7
9 2 and 5

10 9 not 8
11 limit 10 to human
12 Microdialysis/
13 1 and 12
14 monitor$.mp.
15 1 and 5 and 14
16 4 or 13 or 15
17 limit 16 to human
18 17 or 7
19 exp Oxygen Consumption/
20 1 and 19
21 limit 20 to human
22 18 or 21
23 limit 22 to "all adult (19 plus years)"
24 limit 23 to (case reports or letter)
25 23 not 24

Anesthetics

1 exp Craniocerebral Trauma/
2 exp Intracranial Pressure/
3 exp Intracranial Hypertension/
4 exp Intracranial Hypotension/
5 2 or 3 or 4
6 exp ANESTHETICS/
7 exp BARBITURATES/
8 exp PROPOFOL/
9 exp ETOMIDATE/
10 thiopentol.mp.
11 exp PENTOBARBITAL/
12 6 or 7 or 8 or 9 or 10 or 11
13 exp ANESTHESIA/
14 12 or 13
15 1 and 5 and 14
16 propofol infusion syndrome.mp.
17 15 or 16
18 limit 17 to human
19 limit 18 to english language
20 limit 18 to abstracts

Analgesics

1 exp ANALGESICS/
2 exp "Hypnotics and Sedatives"/
3 propofol.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4 exp phenothiazines/
5 exp central nervous system depressants/
6 1 or 2 or 3 or 4 or 5
7 exp Craniocerebral Trauma/
8 exp "SEVERITY OF ILLNESS INDEX"/ or exp INJURY SEVERITY SCORE/ or exp TRAUMA SEVERITY INDICES/
9 (severe or severity).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
10 exp Intensive Care Units/ or exp Critical Care/
11 8 or 9 or 10
12 6 and 7 and 11

13 limit 12 to (human and english language)

Barbiturates

1 exp Craniocerebral Trauma/
2 exp BARBITURATES/
3 etomidate.mp.
4 pentobarbital.mp.
5 thiopental.mp.
6 2 or 3 or 4 or 5
7 1 and 6
8 exp Intracranial Hypertension/dt [Drug Therapy]
9 6 and 8
10 7 or 9
11 limit 10 to yr=1998–2004

Nutrition

1 exp Craniocerebral Trauma/
2 exp nutrition/
3 1 and 2
4 exp Nutrition Therapy/
5 1 and 4
6 exp Energy Metabolism/
7 1 and 6
8 nutritional requirements/
9 1 and 8
10 exp nutrition assessment/
11 1 and 10
12 exp Craniocerebral Trauma/dh [Diet Therapy]
13 exp Dietary Supplements/
14 1 and 13
15 exp Craniocerebral Trauma/me [Metabolism]
16 (diet$ or nutrit$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
17 15 and 16
18 7 and 16
19 exp feeding methods/
20 1 and 19
21 exp vitamins/
22 1 and 21
23 3 or 5 or 9 or 11 or 12 or 14 or 17 or 18 or 20 or 22
24 limit 23 to human
25 limit 24 to english language
26 24 not 25
27 limit 26 to abstracts
28 25 or 27

Filters (second search for deep vein thrombosis prophylaxis)

1 venous thrombosis.mp. or exp Venous Thrombosis/
2 Vena Cava Filters/ or vena caval filters.mp.
3 greenfield filter$.mp.
4 (vena cava$ adj filter$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5 2 or 3 or 4
6 prevent$.mp.
7 prophyla$.mp.

8 pc.fs.
9 6 or 7 or 8
10 exp Blood Coagulation/ or exp Blood Coagulation Disorders/
11 hypocoag$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12 10 or 11
13 1 and 5 and 9 and 12

Antiseizure prophylaxis
1 seizure$.mp.
2 head injur$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3 1 and 2
4 limit 3 to yr=1998–2004

Hyperventilation
1 exp Craniocerebral Trauma/
2 exp ISCHEMIA/
3 exp Jugular Veins/
4 exp Regional Blood Flow/
5 exp PERFUSION/
6 exp HYPERVENTILATION/
7 2 or 3 or 4 or 5 or 6
8 1 and 7
9 limit 8 to yr=1998–2004

Steroids
1 exp Craniocerebral Trauma/
2 exp STEROIDS/
3 1 and 2)
4 limit 3 to yr=1998–2004

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
P. S-105
DOI: 10.1089/neu.2007.9978

Appendix C
Criteria for Including a Study in which the Sample Includes TBI Patients and Patients with Other Pathologies or Pediatric Patients

If:

- the sample for a study includes patients with TBI as well as patients with other pathologies, or pediatric patients,
- and the data are not reported separately,
- and there is an effect of the study,

then it cannot be known if the effect existed for the adult TBI group, or if it was large in the non-TBI or pediatric group, and non-existent in the adult TBI group. Therefore, there is limited confidence that the intervention had an effect for the adult TBI group.

Therefore, the following is required to include a study as evidence for a guideline topic:

1. Sample size $\geq$ 25 patients.
2. 85% or more of the patients are TBI, or adults.
3. Such a study could never be used to support a Level I recommendation.
4. Such a study can only support up to a Level II recommendation, and cannot be used to support a Level II recommendation if it is the only Class II study available.
5. If the study does not report the percent of patients with TBI or the percent of pediatric patients, it cannot be used as evidence at any level.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
P. S-106
DOI: 10.1089/neu.2007.9977

Appendix D
Electronic Literature Search Yield

Topic	*Search results*	*Abstracts read*	*Publicaions read*	*2nd edition studies included*	*New studies included*
Blood Pressure and oxygenation	366	171	17	18	3
Hyperosmolar therapy	364	205	42	9	2
Prophylactic hypothermia	88	71	29	[a]	6
Infection prophylaxis	957	216	54	[a]	7
Deep vein thrombosis prophylaxis	155	64	37	[a]	5
Indications for ICP monitoring	241	182	36	6	10
ICP monitoring technology	187	113	39	21	7
ICP treatment threshold	107	70	10	6	3
Cerebral perfusion pressure	297	209	48	5	6
Brain oxygen monitoring and treatment	807	607	217	[a]	12
Anesthetics, analgesics, and sedatives	773	397	92	3	1
Nutrition	179	87	33	11	4
Anti-seizure prophylaxis	186	53	10	4	1
Hyperventilation	772	302	23	5	2
Steroids	281	62	14	6	2

[a]New topic in 3rd edition.

JOURNAL OF NEUROTRAUMA
Volume 24, Supplement 1, 2007
© Brain Trauma Foundation
P. S-106
DOI: 10.1089/neu.2007.9976

Appendix E
Evidence Table Template

Source	*Study design*	*Setting/ population*	*Sample*	*Intervention*	*Co-interventions*	*Confounding variables*	*Length of follow-up*	*Measures*	*Analysis*	*Results*	*Caveats*	*Level of evidence*