MANUAL OF TRAUMATIC BRAIN INJURY
ASSESSMENT AND MANAGEMENT

Felise S. Zollman

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Manual of Traumatic Brain Injury
Manual of Traumatic Brain Injury
Assessment and Management

*Second Edition*

**Editor**

*Felise S. Zollman, MD, FAAN, FAAMA*
Assistant Professor
Department of Neurological Sciences
Rush University Medical Center
Chicago, Illinois
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Contributors

Amar Agha, MD
Consultant Endocrinologist
Department of Endocrinology and Diabetes Metabolism
Beaumont Hospital and RCSI Medical School
Dublin, Ireland

David N. Alexander, MD
Professor, Department of Neurology
University of California, Los Angeles;
Medical Director
California Rehabilitation Institute & UCLA’s Neurological Rehabilitation and Research Unit
Reed Neurological Research Center
Los Angeles, California

Lucy-Ann Behan, MD
Consultant Endocrinologist
Department of Endocrinology and Diabetes Metabolism
Tallaght Hospital and Trinity College Medical School
Dublin, Ireland

Erica Bellamkonda, MD
Consultant and Assistant Professor
Department of Physical Medicine and Rehabilitation
Mayo Clinic
Rochester, Minnesota

Laura M. Benson, PhD
Neuropsychology Service
Department of Psychiatry and Behavioral Sciences
NorthShore University HealthSystem
Evanston, Illinois

Debra E. Berens, PhD
Rehabilitation Consultant/Life Care Planner
Atlanta, Georgia

Saurabha Bhatnagar, MD
Instructor
Department of Physical Medicine and Rehabilitation
Harvard Medical School,
Massachusetts General Hospital,
and Spaulding Rehabilitation Hospital
Boston, Massachusetts

Ann S. Bines, MS, RN, CCRN
Nurse Manager
Brain Injury Medicine and Rehabilitation Program
Rehabilitation Institute of Chicago
Chicago, Illinois

Jennifer Bogner, PhD, ABPP
Vice-Chair of Research and Academic Affairs
Associate Professor
Department of Physical Medicine and Rehabilitation
The Ohio State University
Columbus, Ohio

Amy O. Bowles, MD
Deputy Chief, Department of Rehabilitation Medicine
Chief, Brain Injury Rehabilitation Service
Brooke Army Medical Center (BAMC)
San Antonio, Texas
Contributors

Matthew Breiding, PhD
Traumatic Brain Injury Team Lead
Division of Violence Prevention
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention
Atlanta, Georgia

Allen W. Brown, MD
Associate Professor of Physical Medicine and Rehabilitation
Mayo Clinic College of Medicine
Mayo Clinic
Rochester, Minnesota

Catherine Burress Kestner, PT, DPT, NCS
Physical Therapist
Outpatient Allied Health Rehabilitation Institute of Chicago
Chicago, Illinois

Stephen V. Cantrill, MD, FACEP
Department of Emergency Medicine
Denver Health Medical Center
Denver, Colorado;
Associate Professor
Department of Emergency Medicine
University of Colorado School of Medicine
Aurora, Colorado

Robert C. Cantu, MD, MA, FACS, FACSM
Chief, Neurosurgery Service
Chairman, Department of Surgery
Director, Service of Sports Medicine
Emerson Hospital
Concord, Massachusetts;
Clinical Professor
Department of Neurosurgery
Codirector
Center for the Study of Traumatic Encephalopathy
Boston University School of Medicine
Boston, Massachusetts

David X. Cifu, MD
Chairman and Herman J. Flax, MD Professor
Department of Physical Medicine and Rehabilitation
Founding Director, Center for Rehabilitation Sciences and Engineering
Virginia Commonwealth University
Richmond, Virginia

Aaron M. Cook, PharmD, BCPS
Clinical Coordinator-Neuroscience-Pulmonary/Critical Care
Associate Adjunct Professor, Pharmacy
Director, PGY1 Pharmacy Residency Program
University of Kentucky
Lexington, Kentucky

John D. Corrigan, PhD, ABPP
Director, Division of Rehabilitation Psychology
Professor, Department of Physical Medicine and Rehabilitation
The Ohio State University
Columbus, Ohio

Cassandra Cowie, BSc
Department of Research
University Health Network – Toronto Rehabilitation Institute
Toronto, Ontario, Canada

Marie Crandall, MD, MPH, FACS
Professor of Surgery
Director of Research, Department of Surgery
University of Florida College of Medicine
Jacksonville, Florida

Nora Cullen, MD, MSc
Associate Professor
University of Toronto
Toronto Rehabilitation Institute
Toronto, Ontario, Canada
Contributors  xiii

Cherina Cyborski, MD  
Chief of Rehabilitation Services  
NICOE/National Intrepid Center of Excellence  
Bethesda, Maryland

Kristen Dams-O’Connor, PhD  
Associate Professor, Rehabilitation Medicine  
Department of Rehabilitation  
Mount Sinai Hospital  
New York, New York

Deirdre R. Dawson, PhD  
Associate Professor  
Department of Occupational Science and Occupational Therapy, and Rehabilitation Sciences Institute  
University of Toronto;  
Senior Scientist  
Rotman Research Institute,  
Baycrest;  
Adjunct Scientist  
Toronto Rehabilitation Institute  
Toronto, Ontario, Canada

Ramon Diaz-Arrastia, MD, PhD  
Director of Clinical Research Center for Neuroscience and Regenerative Medicine  
Professor of Neurology  
Uniformed Services University of the Health Sciences  
Rockville, Maryland

Kan Ding, MD  
Assistant Professor  
Department of Neurology and Neurotherapeutics  
UT Southwestern Medical Center at Dallas  
Dallas, Texas

Craig DiTommaso, MD  
Assistant Professor and Director of Inpatient Rehabilitation  
Department of Physical Medicine and Rehabilitation  
Baylor College of Medicine  
Houston, Texas

Ana Durand-Sanchez, MD  
Assistant Professor  
Department of Physical Medicine and Rehabilitation  
Indiana University  
Indianapolis, Indiana

Blessen C. Eapen, MD  
Section Chief, Polytrauma Rehabilitation Center  
TBI/Polytrauma Fellowship Program Director  
South Texas Veterans Health Care System  
San Antonio, Texas

Elie P. Elovic, MD  
Director, Traumatic Brain Injury Program  
Renown Rehabilitation Hospital  
Renown Health  
Reno, Nevada

Jennifer Field  
J Field Foundation  
White Stone, Virginia

Jennifer Fleming, PhD  
Conjoint Associate Professor  
School of Health and Rehabilitation Sciences  
The University of Queensland;  
Occupational Therapy Department  
Princess Alexandra Hospital  
Brisbane, Australia

Brandon A. Francis, MD, MPH  
Fellow in Neurocritical Care  
Department of Neurology  
Northwestern University, Feinberg School of Medicine  
Chicago, Illinois

Julie Fuith-Costa, MS, CCC-SLP  
Clinical Manager  
Day Rehabilitation  
The Rehabilitation Institute of Chicago  
River Forest, Illinois

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Contributors

Joshua B. Gaither, MD
Associate Professor, Department of Emergency Medicine
University of Arizona College of Medicine
Tucson, Arizona

Deep S. Garg, MD
Traumatic Brain Injury/Polytrauma Fellow
Department of Physical Medicine and Rehabilitation
Audie L. Murphy VA Medical Center
San Antonio, Texas

Jason Georgekutty, DO
Traumatic Brain Injury/Polytrauma Fellow
Department of Physical Medicine and Rehabilitation
Audie L. Murphy VA Medical Center
San Antonio, Texas

Christopher Giza, MD
Departments of Pediatrics and Pediatric Neurology
Ronald Reagan UCLA Medical Center
UCLA Medical Center
Santa Monica, California

Gary Goldberg, MD
Medical Director, Polytrauma Transitional Rehabilitation Program
Hunter Holmes McGuire VA Medical Center;
Professor
Department of Physical Medicine and Rehabilitation
Medical College of Virginia
Virginia Commonwealth University Health System
Richmond, Virginia

Wayne A. Gordon, PhD
Professor, Rehabilitation Medicine
Associate Professor, Psychiatry
Department of Rehabilitation
Mount Sinai Hospital
New York, New York

Michael M. Green, DO
Assistant Professor, Physical Medicine and Rehabilitation
Department of Pediatrics/Physical Medicine and Rehabilitation
University of Utah School of Medicine
Salt Lake City, Utah

Arlene I. Greenspan, DrPH, MPH, PT
Associate Director for Science
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention
Atlanta, Georgia

Brian D. Greenwald, MD
Medical Director, JFK Johnson Rehabilitation Center for Head Injuries
Associate Medical Director,
JFK Johnson Rehabilitation Institute
Clinical Associate Professor
Rutgers Robert Wood Johnson Medical School
Edison, New Jersey

Christine Greiss, DO, FAAPMR
Clinical Assistant Professor
JFK Johnson Rehabilitation Institute
Department of Physical Medicine and Rehabilitation
Rutgers Robert Wood Johnson Medical School
Edison, New Jersey

Flora Hammond, MD
Covalt Professor of Physical Medicine and Rehabilitation
Chair, Indiana University Department of Physical Medicine and Rehabilitation
Chief of Medical Affairs, Rehabilitation Hospital of Indiana
Indianapolis, Indiana
Mark Harniss, PhD
Clinical Associate Professor
Department of Rehabilitation Medicine
School of Medicine
University of Washington
Seattle, Washington

Micelle J. Haydel, MD
Albert J. Lauro Endowed Professorship in Emergency Medicine
Clinical Professor of Medicine/Emergency Medicine
Director of Education, Emergency Medicine
Louisiana State University Health Sciences Center
New Orleans, Louisiana

Michael Henrie, DO
Assistant Professor
Department of Physical Medicine and Rehabilitation
University of Utah
Salt Lake City, Utah

Mary Alexis Iaccarino, MD
Brain Injury Medicine Fellow
Department of Physical Medicine and Rehabilitation
Harvard Medical School, Massachusetts General Hospital, and Spaulding Rehabilitation Hospital
Boston, Massachusetts

Grant L. Iverson, PhD
Professor
Department of Physical Medicine and Rehabilitation
Harvard Medical School
Charlestown, Massachusetts

Michael S. Jaffee, MD
Associate Professor
Department of Neurology
University of Virginia Health System
Charlottesville, Virginia

Carlos A. Jaramillo, MD, PhD
Staff Physician
Polytrauma Rehabilitation Center
South Texas Veterans Health Care System
San Antonio, Texas

Jonathan Jenness, OD
Senior Resident
Padula Institute of Vision Rehabilitation
Guilford, Connecticut

Kurt L. Johnson, PhD
Professor
Department of Rehabilitation Medicine
Nancy and Buster Alvord Endowed Professor in Multiple Sclerosis Research
School of Medicine
University of Washington
Seattle, Washington

Ricardo E. Jorge, MD
Professor
Menninger Department of Psychiatry and Behavioral Sciences
Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry
Baylor College of Medicine
Houston, Texas

Joanne Klevens, MD, MPH, PhD
Epidemiologist, Sexual Violence and Child Maltreatment Team
Research and Evaluation Branch
Division of Violence Prevention
Centers for Disease Control and Prevention
Atlanta, Georgia

Sunil Kothari, MD, MA
Assistant Professor
Department of Physical Medicine and Rehabilitation
Baylor College of Medicine
Houston, Texas
Contributors

Jason Krellman, PhD
Assistant Professor, Rehabilitation Medicine
Department of Rehabilitation Medicine
Mount Sinai Hospital
New York, New York

Richard D. Kunz, MD
Assistant Professor
Department of Physical Medicine and Rehabilitation
Virginia Commonwealth University
Richmond, Virginia

Rael T. Lange, PhD
Senior Scientist/Research Director
Defense and Veterans Brain Injury Center
Walter Reed National Military Medical Center
Bethesda, Maryland

Michelle C. LaPlaca, PhD
Associate Professor
Department of Biomedical Engineering
Georgia Technical Institute and Emory University
Atlanta, Georgia

Eric B. Larson, PhD
Assistant Professor
Department of Physical Medicine and Rehabilitation
Northwestern University, Feinberg School of Medicine
Chicago, Illinois

Jeffrey David Lewine, PhD
Professor of Translational Neuroscience
The Mind Research Network
Albuquerque, New Mexico

Lisa A. Lombard, MD
Medical Director, Rehabilitation Medicine
Hospital of Indiana;
Assistant Professor
Department of Physical Medicine and Rehabilitation
Indiana University School of Medicine
Indianapolis, Indiana

David F. Long, MD
Medical Director
Brain Injury Program
Bryn Mawr Rehabilitation Hospital
Malvern, Pennsylvania

Matthew B. Maas, MD
Assistant Professor of Neurology and Anesthesiology
Northwestern University, Feinberg School of Medicine
Chicago, Illinois

Barbara Magnuson Woodward, PharmD, CNSC
Nutrition Support Service, Coordinator
UK HealthCare – Pharmacy Services; Associate Professor (Adjunct Series)
Department of Pharmacy Practice and Science
University of Kentucky
College of Pharmacy
Lexington, Kentucky

James F. Malec, PhD, ABPP-CN, Rp
Professor and Research Director
Physical Medicine and Rehabilitation
Indiana University School of Medicine and Rehabilitation Hospital of Indiana
Indianapolis, Indiana
Contributors

Todd Masel, MD
Assistant Professor, Department of Neurology
Residency Program Director, Department of Neurology
University of Texas Medical Branch at Galveston
Galveston, Texas

Philip H. Montenigro, PhD
MD/PhD Candidate
Department of Anatomy and Neurobiology
Alzheimer’s Disease and Chronic Traumatic Encephalopathy Center
Boston University School of Medicine
Boston, Massachusetts

Phalgun Nori, MD
Staff Physician and Clinical Investigator
San Antonio Polytrauma Rehabilitation Center
South Texas Veterans Health Care System
San Antonio, Texas

David O. Okonkwo, MD, PhD
Professor of Neurological Surgery
Department of Neurological Surgery
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Kristine O’Phelan, MD
Associate Professor of Clinical Neurology
Director, Neurocritical Care
University of Miami, Miller School of Medicine
Miami, Florida

William V. Padula, OD, SFNAP, FAAO, FNORA
Associate Professor
Department of Neuro-Optometry
Salus University of Health Sciences College of Optometry
Elkins Park, Pennsylvania; Director
Padula Institute of Vision Rehabilitation
Guilford, Connecticut

David M. Panczykowski, MD
Resident Physician
Department of Neurological Surgery
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Sangeeta Patel Driver, MD, MPH
Attending Physician, Rehabilitation Institute of Chicago
Assistant Professor, Department of Physical Medicine and Rehabilitation Northwestern University, Feinberg School of Medicine
Chicago, Illinois

Vani Rao, MBBS, MD
Associate Professor
Director, Brain Injury Program
Director, Behavior Neurology and Neuropsychiatry Fellowship Program
Department of Psychiatry and Behavioral Science
Johns Hopkins Bayview Medical Center
Baltimore, Maryland

William A. Robbins, MD
TBI Polytrauma Fellow
Department of Physical Medicine and Rehabilitation
Hunter Holmes McGuire VA Medical Center
Richmond, Virginia
Contributors

Lisa Rosen, MS
Manager, LIFE Center
Rehabilitation Institute of Chicago
Chicago, Illinois

Joshua M. Rosenow, MD, FAANS, FACS
Director, Stereotactic and Functional Neurosurgery
Northwestern Memorial Healthcare
Northwestern Memorial Hospital;
Associate Professor of Neurosurgery, Neurology, and Physical Medicine and Rehabilitation
Northwestern University, Feinberg School of Medicine
Chicago, Illinois

Durga Roy, MD
Assistant Professor
Department of Psychiatry and Behavioral Science
Johns Hopkins University School of Medicine
Baltimore, Maryland

Angelle M. Sander, PhD
Associate Professor and Director, Division of Clinical Neuropsychology and Rehabilitation Psychology
Department of Physical Medicine and Rehabilitation
Baylor College of Medicine
Houston, Texas

Teresa A. Savage, PhD, RN
Clinical Assistant Professor
Department of Women, Children, and Family Health Science
University of Illinois at Chicago
Chicago, Illinois

Billie Schultz, MD
Assistant Professor of Physical Medicine and Rehabilitation
Mayo Clinic College of Medicine
Mayo Clinic
Rochester, Minnesota

Hazem Shahin, MD
Attending Physician, Rehabilitation Institute of Chicago
Assistant Professor, Department of Physical Medicine and Rehabilitation
Northwestern University, Feinberg School of Medicine
Chicago, Illinois

Tracy Shannon, PsyD
Clinical Assistant Professor
Division of Rehabilitation Psychology
Department of Physical Medicine and Rehabilitation
The Ohio State University Wexner Medical Center
Columbus, Ohio

Daniel Shrey, MD
Assistant Clinical Professor
Department of Neurology
Children’s Hospital of Orange County; Department of Pediatrics
University of California–Irvine, School of Medicine
Irvine, California

Noah D. Silverberg, PhD
Clinical Assistant Professor
Division of Physical Medicine and Rehabilitation
University of British Columbia and GF Strong Rehab Centre
Vancouver, British Columbia Canada

Daniella C. Sisniega, BS
MD Student
Boston University School of Medicine
Boston, Massachusetts

Caroline Sizer, MD
Traumatic Brain Injury/Polytrauma Fellow Physician
Department of Physical Medicine and Rehabilitation
Hunter Holmes McGuire VA Medical Center
Richmond, Virginia
Jerry J. Sweet, PhD, ABPP
Director, Neuropsychology Service
Head, Psychology Division
Vice Chair, Department of Psychiatry and Behavioral Sciences
NorthShore University HealthSystem
Evanston, Illinois

Eric S. Swirsky, JD, MA
Director of Graduate Studies
Clinical Assistant Professor
College of Applied Health Sciences
Department of Biomedical and Health Information Sciences
University of Illinois at Chicago
Chicago, Illinois

Christina Taggart, BA, MA
Department of Research
University Health Network – Toronto Rehabilitation Institute
Toronto, Ontario, Canada

Sharief Taraman, MD
Pediatric Neurology and Medical Informatics
Director, Multi-Disciplinary Concussion Clinic
Assistant Division Chief, Neurology
CHOC Children’s Specialists
Health Sciences Assistant Clinical Professor
Department of Pediatrics
University of California–Irvine, School of Medicine
Irvine, California

Theodore Tsaousides, PhD
Assistant Professor
Department of Rehabilitation Medicine
Icahn School of Medicine at Mount Sinai
New York, New York

William C. Walker, MD
Ernst and Helga Prosser Professor
Department of Physical Medicine and Rehabilitation
Virginia Commonwealth University
Richmond, Virginia

Thomas K. Watanabe, MD
Clinical Director, Drucker Brain Injury Center
Department of Physical Medicine and Rehabilitation
MossRehab/Einstein Healthcare Network
Elkins Park, Pennsylvania

Roger O. Weed, PhD
Professor Emeritus
Georgia State University
Atlanta, Georgia

Elizabeth Wojciechowski, PhD, PMH-CNS-BC
Education Program Manager, LIFE Center
Rehabilitation Institute of Chicago
Chicago, Illinois

Cindy Zadikoff, MD, MSc
Associate Professor
Northwestern University, Feinberg School of Medicine
Chicago, Illinois

Ross Zafonte, DO
Earle P. and Ida S. Charlton Professor and Chairman
Department of Physical Medicine and Rehabilitation
Harvard Medical School, Massachusetts General Hospital, and Spaulding Rehabilitation Hospital
Boston, Massachusetts
Contributors

Nathan D. Zasler, MD, FAAPMR, FAADEP, DAAPM, CBIST
Professor, Department of Physical Medicine and Rehabilitation
Virginia Commonwealth University
Richmond, Virginia;
Associate Professor, Adjunct
Department of Physical Medicine and Rehabilitation
University of Virginia
Charlottesville, Virginia

Felise S. Zollman, MD, FAAN, FAAMA
Assistant Professor
Department of Neurological Sciences
Rush University Medical Center
Chicago, Illinois
Preface

The first edition of the Manual of Traumatic Brain Injury Management, published in 2011, was designed to fill a unique niche: to provide relevant clinical information about management of traumatic brain injury (TBI) in a succinct, readily accessible format while at the same time offering readers specific electronic and print recommendations on each topic for those who wished to delve deeper. This second edition serves to update chapter content on the basis of knowledge developed in this rapidly growing field since publication of the first edition, and to further refine the approach to delivery of content. Every chapter has been revised to reflect our knowledge base as of 2016, from clinical content to additional reading recommendations. For many topics, content was comprehensively overhauled (e.g., expanded discussion of injury prevention and chronic traumatic encephalopathy). Several new chapters have also been added, including anoxia complicating TBI, screening for emotional distress in TBI patients, assistive technology in TBI, and management of chronic behavioral disturbances. Each chapter now includes a Key Points section, intended to focus the reader’s attention on the most critical content within.

This edition is divided into five parts. Part I, Core Concepts, acquaints the reader with the basic essentials needed to provide a context for clinical decision-making. Part II, Mild Traumatic Brain Injury, offers a comprehensive treatment of this topic, including natural history, initial management, postconcussion syndrome, and sport concussion. Part III, Moderate to Severe Traumatic Brain Injury, covers prehospital and intensive care management, rehabilitation care, community reintegration, and management of selected associated impairments, including cognitive and behavioral impairments, challenges with sexuality, and decision-making capacity. A chapter on prognosis in TBI provides an evidence-based, concise approach to understanding postinjury outcomes. Part IV, Complications and Long-Term Sequelae, covers a variety of topics from posttraumatic epilepsy and hydrocephalus to chronic cognitive, behavioral, and motor impairments, including spasticity and movement disorders. Part V, Special Considerations and Traumatic Brain Injury Resources, addresses selected populations based on age (pediatrics and geriatrics) or injury environment (military, workers’ compensation), as well as return to work, complementary and alternative treatment modalities, and ethical and medicolegal issues associated with TBI, and offers a unique perspective on life after TBI from a patient’s perspective.

The content of this book can be digested at several levels of complexity: as a succinct introduction to TBI, reliant on the Key Points provided in each chapter; as a concise but thorough chapter by chapter treatment of each topic relevant to TBI; or as a springboard to more comprehensive learning based on the directed additional resource recommendations of each chapter author. There is truly something meaningful in the pages which follow for everyone interested in understanding the management of traumatic brain injury.
PART I

Core Concepts
Traumatic brain injury (TBI) has a broad spectrum of severity, pathology, physiology, and sequela. This chapter will present pertinent definitions, nomenclature, and concepts relevant to the discussion of TBI.

**PRIMARY VERSUS SECONDARY INJURY**

The distinction is somewhat arbitrary and the specific combination and magnitude of secondary injury is to a great extent determined by the nature of the primary injury. This description is useful, however, in order to aid clinicians in identifying potential preventable or reversible causes of secondary brain injury. (See Chapter 2 for further details.)

- **Primary injury**—the physiological or anatomical insult, often but not exclusively the result of direct trauma to head. The primary injury may be associated with structural changes resulting from mechanical forces initially applied during injury. These forces may cause tissue distortion, shearing, and vascular injury as well as destabilization of cell membranes and frank membrane destruction.

- **Secondary injury**—systemic or local changes, which increase tissue damage. Many secondary insults result directly from the primary injury and some are caused by discreet systemic or local phenomena. Secondary injury mechanisms include generation of free radicals, excitotoxicity, disturbance of ionic homeostasis, disruption of the blood–brain barrier, generation of nitric oxide, lipid peroxidation, mitochondrial dysfunction and energy failure, inflammation, secondary hemorrhage, axonal disruption, apoptotic cell death, and ischemia. Ischemia may be due to microvascular changes, systemic hypotension or hypoxia, or elevated intracranial pressure.

**CLASSIFICATION OF TBI BY MECHANISM**

This classification is useful because injuries produced by different mechanisms are distinct in their pathophysiologies and natural courses.

- **Closed/blunt force**—injury caused by direct force to head, acceleration–deceleration, or rotational forces. Common causes include falls, assaults, and motor vehicle collisions.
I. Core Concepts

- **Blast injury**—injury caused by overpressure waves generated from high-grade explosives. A large amount of thermal, mechanical, and electromagnetic energy is transferred to the brain. Energy can come directly through the cranium or be transmitted indirectly through oscillating pressures in fluid-filled large blood vessels. This may cause damage to the blood–brain barrier or gray–white matter junction, and can cause cerebral edema, axonal injury, apoptosis, and tissue degeneration.

- **Penetrating injury**—injury induced by an object that penetrates the cranial vault. Common causes include gunshot wounds, shrapnel, and knife wounds.

**CLINICAL CLASSIFICATION OF TBI**

The Glasgow Coma Scale (GCS) [1] (Table 1.1) is central to clinical classification of TBI. Clinical/injury severity classification is the most commonly used classification system in the clinical care of patients with TBI as well as in clinical neurotrauma research. (See Chapter 3 for further discussion of this topic.)

- **Mild TBI (MTBI)**—GCS 13 to 15, the majority of patients with cranial trauma fall in this group. Patients are awake, and may be confused but can communicate and follow commands.

- **Moderate TBI**—GCS 9 to 12, these patients are generally drowsy to obtunded but not comatose. They can open their eyes and localize painful stimuli. They are at high risk of clinical deterioration and must be monitored carefully.

- **Severe TBI**—GCS 3 to 8, these patients are obtunded to comatose, they do not follow commands and may exhibit decerebrate or decorticate posturing. They have significant structural and metabolic brain dysfunction and are at high risk of secondary brain injury and deterioration.

**TABLE 1.1  Glasgow Coma Scale**

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous 4</td>
<td>Oriented 5</td>
<td>Obeys commands 6</td>
</tr>
<tr>
<td>To speech 3</td>
<td>Confused conversation 4</td>
<td>Localizes pain 5</td>
</tr>
<tr>
<td>To pain 2</td>
<td>Inappropriate words 3</td>
<td>Withdrawal 4</td>
</tr>
<tr>
<td>None 1</td>
<td>Incomprehensible sounds 2</td>
<td>Abnormal flexion (decorticate) 3</td>
</tr>
<tr>
<td></td>
<td>None 1</td>
<td>Extension (decerebrate) 2</td>
</tr>
</tbody>
</table>

**STRUCTURALLY BASED DESCRIPTIONS OF TBI**

Structural descriptions incorporate information from imaging studies. They often aide in selection of patients who may benefit from a specific therapy such as surgical evacuation of a hematoma.
• **Epidural hematoma (EDH)** (Figure 1.1)—an extradural collection of blood. It is often associated with a skull fracture and typically has an arterial origin. Margins of the hematoma do not cross the skull suture lines and often appear convex on imaging studies. If an EDH is evacuated in a timely fashion to reverse mass effect or if the hematoma is small in size, patient outcomes are usually good.

• **Subdural hematoma (SDH)** (Figure 1.2)—a collection of blood in the subdural space. SDHs may be chronic or acute, and are caused by venous bleeding from cortical bridging veins. Bleeding may extend over the entire hemisphere. Acute SDHs are significantly associated with seizures. Acute SDHs are also associated with significant alteration of cerebral blood flow and metabolism of the underlying hemisphere and generally have a worse outcome than EDHs.

![Figure 1.1 Epidural hematoma.](image1)

![Figure 1.2 Subdural hematoma.](image2)
6  I. Core Concepts

- **Traumatic axonal injury** (TAI, also referred to as diffuse axonal injury [DAI])—injury to axonal connections triggered by inertial forces, predominantly acceleration–deceleration, with subsequent structural and metabolic consequences of mechanical deformation.

- **Traumatic subarachnoid hemorrhage (TSAH or SAH)** (Figure 1.3)—hemorrhage in the subarachnoid space that is not associated with significant mass effect. It often accompanies other types of traumatic hemorrhage. The presence of TSAH has been associated with an increased risk of an unfavorable 6-month outcome in patients with moderate to severe TBI [2].

- **Intraventricular hemorrhage (IVH)**—bleeding into the ventricular system after trauma. It may be associated with acute hydrocephalous and is a risk factor for development of delayed hydrocephalous. IVH is typically seen in conjunction with TSAH.

- **Contusion** (Figure 1.4)—parenchymal hemorrhage, typically in frontal or temporal lobes. Contusions may be “coup” or “contre coup.”
  - **Coup injury**—results from direct transmission of force to brain tissue underlying the region of impact.
  - **Contre coup injury**—results from the indirect forces acting in a region contralateral to the region of impact.

- **Skull fractures**—skull fractures may occur after trauma because of blunt or penetrating injury. They may involve the convexity or the skull base and may be open or closed depending on the presence of an overlying scalp laceration. Large depressed skull fractures may need to be surgically elevated. Depressed skull fractures are associated with an increased risk of seizures [3].
1. Traumatic Brain Injury: Definitions and Nomenclature

**CONCUSSION**

This term is generally used to refer to an altered mental state occurring after trauma, which may or may not include brief loss of consciousness. Symptoms reflect a functional disturbance rather than structural injury. There are several diagnostic tools that can be used to aid in identifying those with concussion after head injury. Several of these are listed in Table 1.2; however, they are not meant to be used to “rule out” concussion. Please refer to the AAN 2013 guideline on the management of concussion in sports [4]. (See also Chapter 6 for a more detailed discussion of concussion vs. MTBI.)

**TABLE 1.2 Commonly Used Tools to Identify Those Individuals With Concussion After Sport-Related Head Trauma**

<table>
<thead>
<tr>
<th>PCS: Post concussive symptom scale</th>
<th>GSC: Graded symptom checklist</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAC: Standardized assessment of concussion</td>
<td>Neuropsychological testing</td>
</tr>
<tr>
<td>BESS: Balance error scoring system</td>
<td>SOT: Sensory organization test</td>
</tr>
</tbody>
</table>


**POSTTRAUMATIC AMNESIA**

Posttraumatic amnesia (PTA) is the impaired recall of events surrounding the injury. Retrograde PTA involves impaired recollection of events immediately preceding the injury and anterograde PTA is a deficit in forming new memories after the injury [5].
I. Core Concepts

POSTCONCUSSION DISORDER

Also known as postconcussion syndrome, this term refers to postconcussive symptoms that persist for 3 or more months postinjury. Symptoms are quite variable and are not unique to this diagnosis [6]. (See Table 1.3.) (See Chapters 15–17 for further discussion of this topic.)

<table>
<thead>
<tr>
<th>TABLE 1.3 Symptoms of Post concussion Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, dizziness, drowsiness</td>
</tr>
<tr>
<td>Excess sleep, fatigue, feel “in a fog”</td>
</tr>
<tr>
<td>Feel “slowed down,” headache, irritability</td>
</tr>
<tr>
<td>Memory problems, nausea, nervousness</td>
</tr>
<tr>
<td>Numbness/tingling, poor balance, poor concentration</td>
</tr>
<tr>
<td>Ringing in ears, sadness, sensitivity to light</td>
</tr>
<tr>
<td>Sensitivity to noise, trouble falling asleep, vomiting</td>
</tr>
</tbody>
</table>


SECOND-IMPACT SYNDROME

A second MTBI occurring while an individual remains symptomatic from the first MTBI may cause the “second-impact syndrome.” This rare phenomenon involves acute cerebrovascular congestion and loss of cerebrovascular autoregulation resulting in malignant brain swelling, which is life threatening [7]. (See Chapter 11 for further discussion of this topic.)

RECOVERY AND SEQUELAE

Definitions

- **Diaschisis**—dysfunction in an area of the brain that is remote from an area with structural damage but is connected to the damaged area via neuronal pathways.
- **Neuroprotection**—therapies or management strategies that prevent or limit secondary injury and lead to improved survival of neurons, microglia, or the supporting microvasculature.
- **Neuroplasticity**—changes in brain structure (neuronal and glial connectivity) and function due to experience. This is a major mechanism for recovery of function after traumatic injury.
- **Gliosis**—formation of a dense network of glial cells in areas of brain injury that do not contribute to functional recovery. This can occur after trauma, stroke, or demyelination.
- **Atrophy**—loss of neurons and glia and their connections. This can occur after TBI and is usually related to the severity of the initial injury.
ADDITIONAL READING

**Electronic Reference**
Brain Trauma Foundation Website. http://www.braintrauma.org

**Textbook/Chapter**

**Journal Articles**

**REFERENCES**

Essential Concepts in TBI Biomechanics and Neuropathology

Michelle C. LaPlaca

GENERAL PRINCIPLES

Traumatic Brain Injury as a Continuum

Traumatic brain injury (TBI) can be defined as transient or persistent brain dysfunction, occurring as the result of head movement and/or collision between the head and an object or surface that causes suprathreshold loading to the brain. TBI occurs as a continuum of events, from the traumatic insult to the primary injury to secondary injury to the clinical outcome. Biomechanics plays a critical role in understanding the TBI continuum.

- **Traumatic insult**: The external cause is categorized by the mechanism (e.g., motor vehicle collision) and the intent (e.g., unintentional) [1]. Traumatic loading typically occurs on the order of milliseconds to seconds.
- **Primary injury**: The immediate (milliseconds to seconds) result of the associated traumatic event. This is the mechanical response to the insult.
- **Secondary injury**: The cascade of changing biochemical and molecular events (seconds to weeks) that results from the primary injury.
- **Injury outcome (weeks to years)**: Consequences of the primary and secondary injury, combined with recovery and repair of the brain. The ability to heal will depend on many factors, including metabolic state and endogenous repair capacity of the brain. The cell and tissue level events in the brain can manifest as sensory, motor, cognitive, behavioral, affective, systemic, and/or somatic conditions.

Confounding Factors in the TBI Response

The TBI response is the result of numerous interrelated processes that have inherent heterogeneity and complexity across time scales (the continuum) and system levels (subcellular [nano], cellular [micro], tissue/organ [meso], and systemic/organism [macro]).

Secondary injury mechanisms that mediate TBI pathologies are variable due to:

- Heterogeneity in traumatic insults and individual responses
- Complexity of interactions among cellular signaling pathways
- Constantly changing cellular activities and systemic adaptations [2]
- Periods of hyperactivity and hypoactivity
Types and Sources of Heterogeneity

TBI is extremely heterogeneous due to its nature [3]. Heterogeneity stems from the variation in the inherent nature of a system and/or in the response to a changing state.

A. Preinjury heterogeneity (innate, premorbid):
   1. Innate heterogeneity (nonchangeable): individual characteristics such as sex, age, stature, genetic variation, and neuroanatomic and musculoskeletal variations
   2. Premorbid factors (potentially changeable): individual preexisting medical conditions or disease (e.g., previous head injury exposure, cardiovascular disease); health state at time of injury (e.g., hydration, nutritional status, recent sleep pattern, stress state)

B. Event heterogeneity (biomechanics, environmental):
   1. Biomechanics of the causative event: magnitude and direction of force and acceleration, surface area of impact (i.e., force distribution), loading duration
   2. Environmental heterogeneity at the time of the event: temperature, humidity, head protection, impact surface, degree of anticipation

C. Peri-injury heterogeneity (early injury response, clinical intervention):
   1. Primary injury or biomechanical response: dependent on tissue mechanical properties, tissue orientation, loading direction
   2. Early secondary injury: complex cell signaling cascades dependent on type and number of cells affected, intrinsic cellular characteristics
   3. Clinical intervention: variations in the time window to care and prehospital protocols

D. Postinjury heterogeneity (secondary injury, repair capacity, clinical management):
   1. Secondary injury: overlapping signaling cascades, systemic influence
   2. Repair capacity: innate and premorbid factors superimposed with the injury response and ability to stably repair (i.e., neuroplasticity)

BIOMECHANICS AND PRIMARY INJURY

The event biomechanics (traumatic insult and resulting head movement) and the mechanical response (primary injury to the brain) are linked. For a TBI to occur, the traumatic load to the head must be transduced to the brain tissue. Force transduction to the tissue and cells is not well understood because each loading event and individual is unique. Details of the biomechanical conditions around a traumatic insult are typically not known.

Event Biomechanics: Load → Dynamic Head Response → Transduction to Brain → Brain Response
I. Core Concepts

- **Loading conditions**: The forces, rates, and other parameters of the traumatic insult. Load is usually a combination of impact and inertial forces:
  - **Impact load**: Force resulting from a moving person striking a mass or obstruction, or a moving object or obstruction striking a person. The collision transfers energy and produces contact phenomenon (*focal injury*).
  - **Inertial or impulsive load**: Load resulting when a person is put in motion by an applied force. Unless there is rigid support, the head will rotate, with the neck as a pivot. *Diffuse injury* may result from the inertial load (especially high angular acceleration) and from the brain movement upon deceleration.
  - **Penetrating load (e.g., bullet)**: It has high velocity and energy transfer over a small impact area.
  - **Loading rate is important**: Slowly applied force will result in lower stress than rapidly applied force.

The force produced by loading and subsequent head movement (acceleration pattern) will be transduced to the brain tissue and the cell components.

- **Acceleration** = velocity / time of the head can be angular or linear (usually a combination). An impact will cause the head to accelerate, then decelerate.
- **Force = mass × acceleration**. The lower the mass, the higher the acceleration must be to keep the force constant.
- Protective gear and safety measures aim to distribute and dissipate force.

The biomechanical response is a function of material properties and cell orientation and will dictate the primary injury.

- Material properties across brain regions vary [5]. The brain is a relatively soft tissue. Cell orientation and tissue composition (e.g., blood vessels, white matter tracts) contribute to differences in properties and overall tissue response.
- More force + softer tissue = more strain; suprathreshold force will deform tissue to the point of damage. Deformation (or strain) can be tensile (stretch), compressive, and/or shear (*note*: the brain is especially vulnerable to shear strain).
- Higher strain rate is more damaging than lower strain rate.
- Structural failure of the brain includes microtears, macrotears, compression, tension and/or shearing within and between brain regions, damage of vascular structures (resulting in bleeding) (meso and macroscale).
- Insults to the neural cells will, in turn, depend on mechanical response of the cells (strain and strain rate). Primary damage may manifest in neurons, glial cells, and vascular cells as axonal stretching, membrane disruption, ion imbalance, interruption in normal conduction and synaptic transmission, and glial damage (nano and microscale).

*Injury threshold*: The insult level at which structural and functional compromise or failure takes place; described using injury tolerance criteria. Development of tolerance criteria requires understanding of the relationship among *traumatic insult*, *mechanical response* of the brain tissue, and the resulting *injury cascades* and *neuropathology*. 
SECONDARY INJURY

Primary structural damage (membranes and cell processes, intercellular connections) initiates and exacerbates secondary injury. The following general categories of secondary injury processes are interrelated:

A. Neurochemical and electrochemical imbalances (ions, neurotransmitters, cell signaling)
   1. Disruption of ion homeostasis (Ca$^{2+}$/Na$^+$ influx) [6], ion channel dysfunction [7], leading to membrane potential changes, high energy demand, and mitochondrial overload.
   2. Excess excitatory neurotransmitter release (e.g., glutamate); overactivation of glutamate receptors, leading to excitotoxicity [8].
   3. Aberrant cell signaling: ion channel dysfunction, abnormal G-protein activation, and subsequent second messenger pathways, leading to abnormal action at downstream targets [9].
   4. Electrophysiological abnormalities such as hyperexcitability, leading to network disturbances [10].

B. Impaired brain metabolism (oxygen and glucose availability and use)
   2. Fluctuation in metabolic demand and glucose metabolism [12,13].
   3. Impaired mitochondrial function, diminished glucose substrates, leading to reduced cellular respiration and less adenosine triphosphate (ATP) production, increases in CO$_2$ (hypercapnia), H$^+$ (acidosis).

C. Biomolecular degradation (enzyme activation, free radical attack)
   1. Proteases attack cytoskeleton (e.g., calpain [14]), lipases upset lipid metabolism (e.g., phospholipase A$_2$), endonucleases initiate nucleic acid damage.
   2. Free radical production (reactive oxygen species [ROS]; reactive nitrogen species [RNS]). Increase in hydroxyl radicals causes lipid peroxidation and compounds degradative processes [15].
   3. Secondary membrane damage (e.g., lipid peroxidation) impairs transport and signaling, as well as stability of membrane phospholipids [16].

D. Axonal damage and diffuse axonal injury (DAI) [17,18]
   1. Axons are stretched during the traumatic insult, causing transient axolemmal permeability.
   2. Both unmyelinated and myelinated axons are affected.
   3. Cytoskeletal damage impairs axonal transport, leading to axonal swelling.
   4. Oligodendrocyte damage may contribute to myelin degradation, further affecting white matter tracts and network function.

E. Vascular dysfunction (permeability, hemorrhage, reactivity) [19]
   1. Blood–brain barrier (BBB) disruption causes infiltration of blood-borne proteins, cells [20].
   2. Vascular leakage and microbleeding cause brain toxicity, hypoxia, coagulation, and hematoma formation.
   3. Uncoupling of cerebral blood flow and metabolism, hyperemia, uncontrolled cerebral perfusion pressure, vasospasm, contribute to edema, and raised intracranial pressure.
I. Core Concepts

F. Inflammation (central and peripheral contribution) [21,22]
   1. Acute inflammatory response (release of cytokines, histamines, arachidonic acid, bradykinin, nitric oxide) can become chronic/degenerative.
   2. Activation of microglia (increase in pro-inflammatory cytokines: e.g., IL-1-β, IL-6, TNF-α) [23].
   3. Pro-inflammatory and anti-inflammatory processes both contribute to the overall response [24].

G. Cerebral edema [25]
   1. Cerebral edema can occur when osmolality changes, resulting in fluid movement from one compartment to another.
   2. Underlying causes are increased intravascular hydrostatic pressure (vasogenic edema), increased interstitial fluid pressure due to blood pressure and protein leakage/abnormal oncotic pressures (interstitial edema), and cellular swelling due to ionic imbalance and osmosis (cytotoxic edema).

H. Cell death and cytotoxicity [26]
   1. Apoptosis: unscheduled “programmed” cell death; portions of cell death pathways are activated by the insult.
   2. Necrosis: traditionally distinct from apoptosis; likely one of many death pathways; features are end stage; enzymatically driven; exacerbated by inflammation.
   3. Autophagy: cell death through phagocytic processes [27].

IMPLICATIONS FOR THE FUTURE: DIAGNOSIS AND TREATMENT

Improved understanding of TBI requires both experimental and clinical data collection across the continuum. Complex data analytics and systems approaches are required for successful bidirectional translation. TBI heterogeneity may necessitate personalized diagnostic and treatment strategies.

Mechanistic Diagnostics

- Blood and cerebrospinal fluid (CSF) biomarkers are promising diagnostic aids, will likely require use of a panel of biomarkers [28,29].
- Biomarkers can unveil cellular injury mechanisms and be correlated with symptoms to increase understanding of TBI pathology.

Secondary Injury Mitigation

- Clinical symptoms are caused by numerous changing secondary injury cascades, necessitating frequent evaluation of clinical management strategies.
- It is difficult to narrow down dominant secondary injury pathways at the cell level as they relate to clinically significant features and injury mitigation.
- Combination therapeutics: Neuroprotection strategies will likely need to target multiple pathways [30–32], for example, glucose metabolism, inflammation, antioxidant protection, and axonal stabilization.
2. Essential Concepts in TBI Biomechanics and Neuropathology

KEY POINTS

- The full spectrum of TBI (from biomechanics to outcome) is complex and heterogeneous across both time scales and system levels.
- Biomechanics can provide important information about human tolerance to TBI, improving preventative and safety interventions.
- The traumatic insult initiates the propagation of secondary injury cascades, which manifest as physiologic and neurologic symptoms.
- Clinical outcome is a function of primary and secondary injury responses, as well as endogenous repair capability and intervention measures.

ADDITIONAL READING

Websites
http://www.nhtsa.gov/Research/Biomechanics+&+Trauma/Brain+Injury+Research

Textbooks/Chapters

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Agoston DV. Bench-to-bedside and bedside back to the bench; seeking a better understanding of the acute pathophysiological process in severe traumatic brain injury. Front Neurol. 2015;6(47):1–6.

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