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Today's Webinar is:

Acute Severe TBI: Lessons Learned and Prospects for Future Treatment

April 17, 2013, 1-2:30 p.m. EDT

Presenter

Dr. Don Marion, M.D., MSc

Senior Clinical Consultant, Clinical Affairs

Defense and Veterans Brain Injury Center (DVBIC)

Moderator

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Deputy Director, DVBIC

Continuing Education

This webinar has been approved for the following:

- 1.5 AMA PRA Category 1 Credits™
- 1.5 Credits by the American Psychological Association
- 1.5 Nursing contact hours as a co-provider with the American Nurses Credentialing Center
- 1.75 CE Contact hours for Physical Therapist and Assistant approved by the State of Illinois
- 1.75 CE Contact hours for Occupational Therapist and Assistant approved by the State of Illinois
- 1.5 CEHs for Social Work approved by the Missouri Division of Professional Registration Committee for Social Work

★ *Please note that DVBIC's awarding of continuing education credit is limited in scope to health care providers who actively provide psychological health and traumatic brain injury care to U.S. active-duty service members, reservists, National Guardsmen, military veterans and/or their families.*

★ *Only those who registered prior to 11:59 p.m. EDT on April 14, 2013 are eligible to receive CE credit.*

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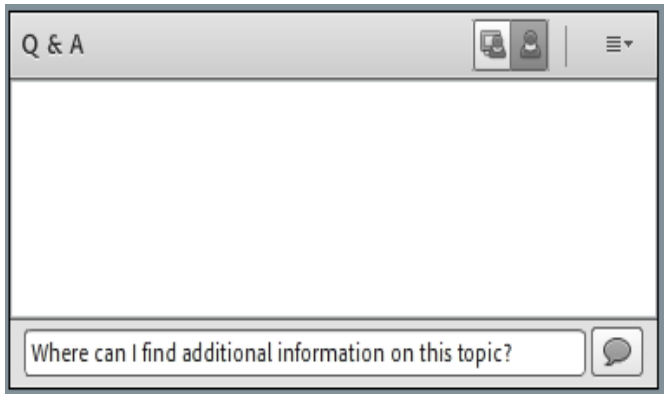

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Participant Passcode: DCOE

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- Throughout the webinar, you are welcome to submit questions via the Adobe Connect or Defense Connect Online question box located on the screen.

- The question box is monitored during the webinar, and questions will be forwarded to our presenter for response during the question-and-answer period.

- The presenter will respond to as many questions as time permits.

Webinar Topic Overview

Severe TBI occurs much less frequently than concussion (mild TBI) but typically results in long-term disability. Severe TBI is the most common cause of death and disability in those between the ages of one and 40 years. Among the estimated 1.7 million* people diagnosed with TBI each year, according to the Centers for Disease Control and Prevention (CDC), approximately 50,000 have severe injuries.

In this webinar, the speaker will define severe TBI and identify its causes and incidence in civilian and military populations. He will review the most commonly associated intracranial lesions and examine the focus of acute treatment of severe TBI. Finally, he will explore possible reasons for the limited success of current clinical trials and discuss recommendations for future trials.

*Or 3.5 million in 2009, as in Coronado VG, et. al., J of Safety Res. 43:299-307, 2012

Acute Severe TBI: Lessons Learned and Prospects for Future Treatment

Donald W. Marion, M.D., MSc

Senior Clinical Consultant, Clinical Affairs

DVBIC

Presenter

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Dr. Marion is an academic neurosurgeon who has focused on the clinical pathophysiology and treatment of TBI for more than 25 years. He was among the charter authors of the Brain Trauma Foundation's "Guidelines for the Management of Severe Traumatic Brain Injury" and published the first clinical report to show the benefit of therapeutic moderate hypothermia for TBI (The New England Journal of Medicine, 1997). He is the editor of a book entitled "Traumatic Brain Injury," and he has authored or co-authored more than 200 journal articles and book chapters, mostly related to TBI. Dr. Marion's previous positions have included professor and chair of the Department of Neurosurgery, The Boston University School of Medicine; professor and vice-chair, Department of Neurosurgery, The University of Pittsburgh School of Medicine; and director of the Brain Trauma Research Center at the University of Pittsburgh.

Disclaimer

The views expressed in this presentation are those of the author and do not reflect the official policy of the Department of Defense, Department of Veterans Affairs or the U. S. Government.

I do not have a relevant financial relationship to disclose, and I do not intend to discuss an off-label/investigative use of a commercial product.

Have Current Acute Care Practices Improved Outcomes for Patients with Severe TBI?

Outcomes in 1977

160 adults with severe closed head injuries

- Good Recovery: 36%
- Moderately Disabled: 24%
- Severely Disabled: 8%
- Vegetative: 2%
- Dead: 30%

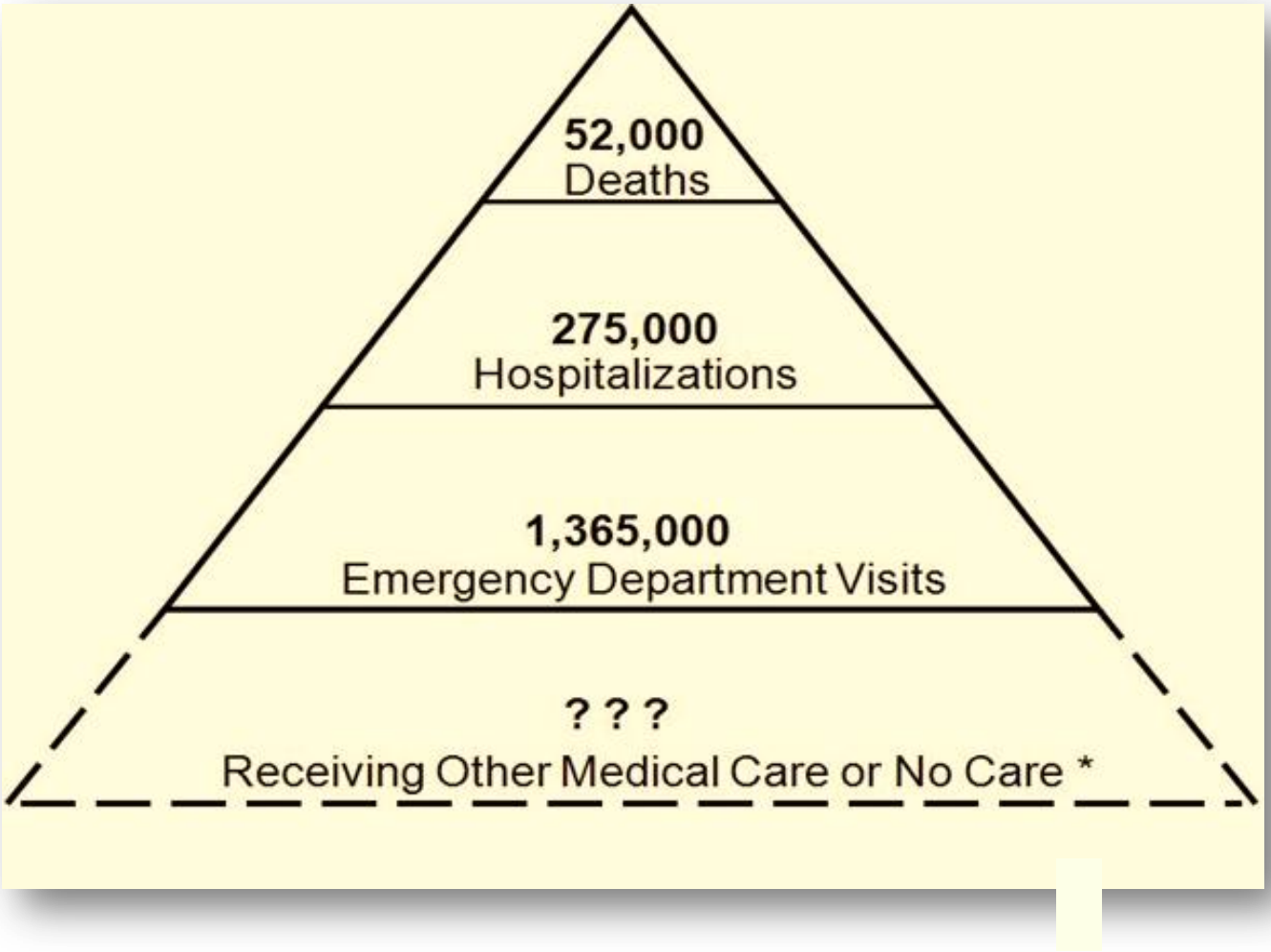
Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R. The outcome from severe head injury with early diagnosis and intensive management. J Neurosurg. 1977 Oct;47(4):491-502.

CDC Data

- In 2009 an estimated 3.5 million people sustained a traumatic brain injury (TBI).*
- TBI is a contributing factor to a third (30.5%) of all injury-related deaths in the United States.
- The annual cost is estimated to be $50 billion. **
- About 75% of TBIs that occur each year are concussions(mild TBI).

*Coronado VG, et. al., J of Safety Res. 43:299-307, 2012
**Zammit, Emerg Med Pract 2013 15:1-28

CDC: 2002-2006



Source: Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002 – 2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010. www.cdc.gov/TraumaticBrainInjury

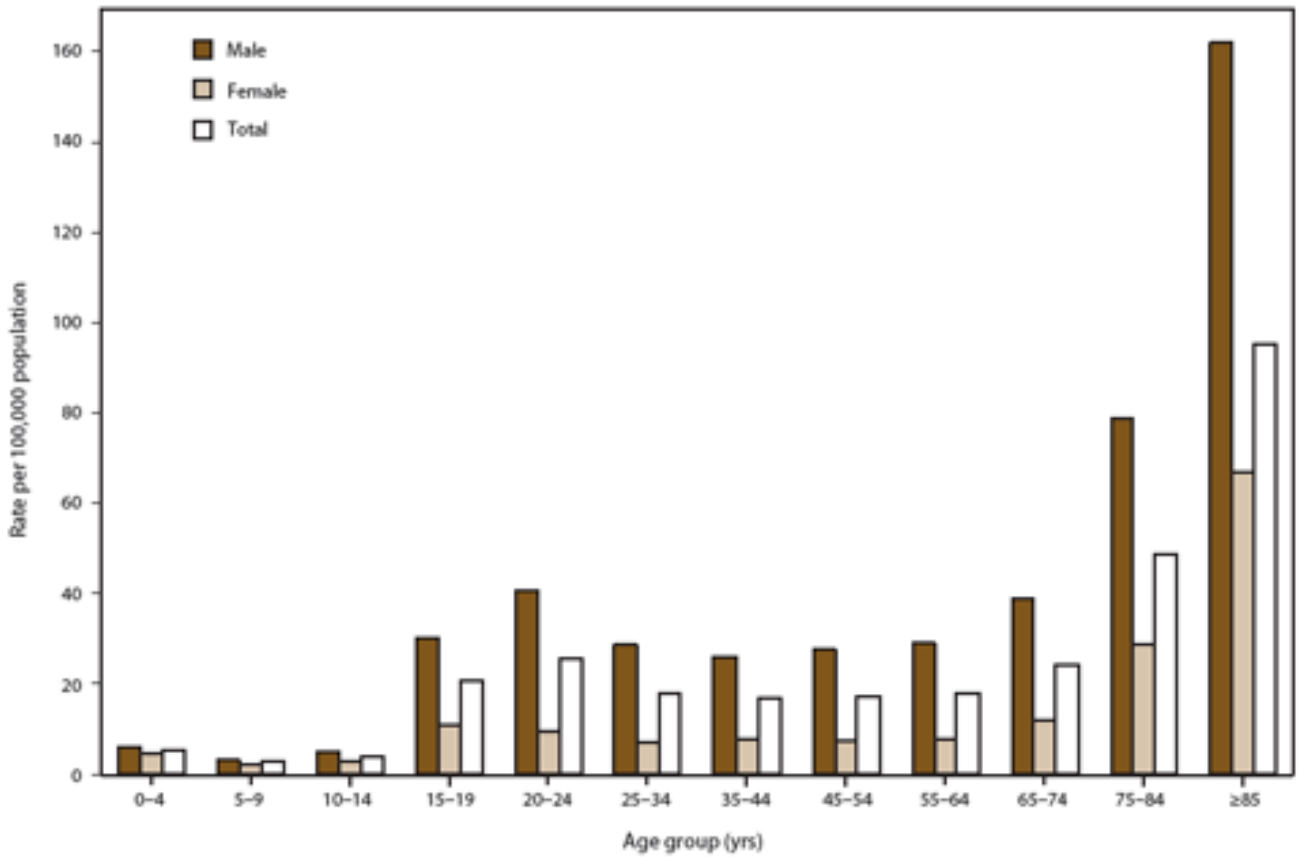
Annual Estimates of Emergency Department Visits, Hospitalizations, and Deaths

	2002	2003	2004	2005	2006
Emergency Department Visits	1,248,660	1,228,731	1,424,548	1,492,879	1,429,159
Hospitalizations	246,381	274,596	285,778	274,426	294,556
Deaths	50,566	50,736	51,164	52,860	52,365

From 2002 to 2006, the rate of emergency department visits for TBI increased by 13%, and for hospitalizations by 16%

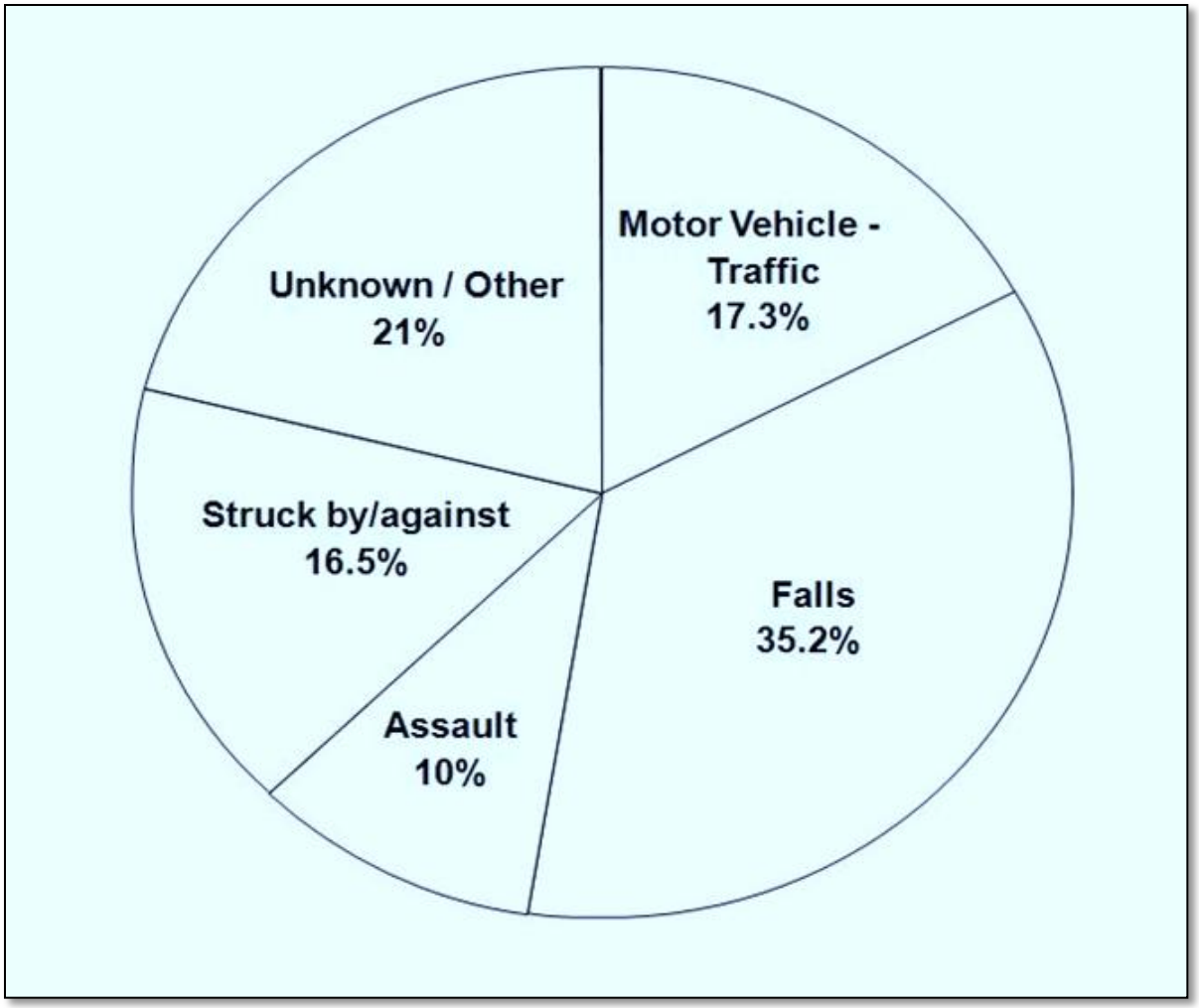
Source: Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002 – 2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.

Average Annual TBI Death Rates, 1997-2007 (CDC)



http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6005a1.htm?s_cid=ss6005a1_w

CDC 2002-2006: Causes of TBI



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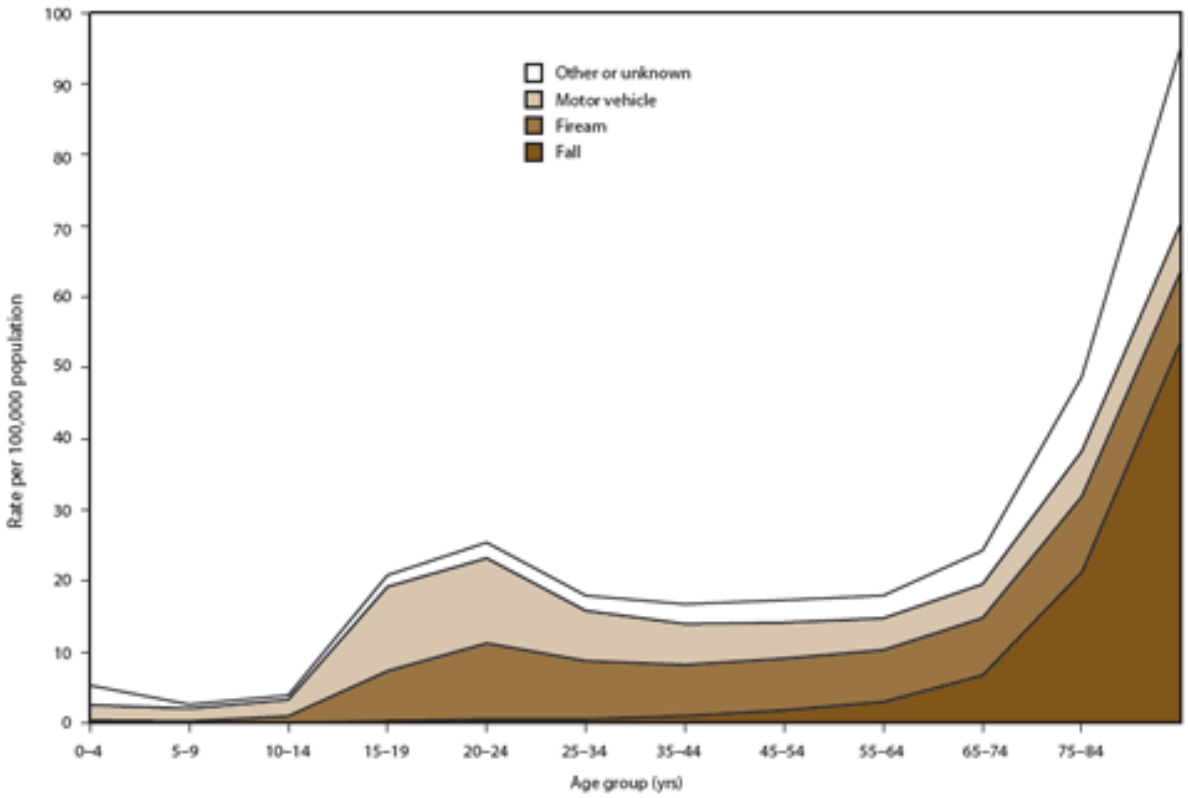
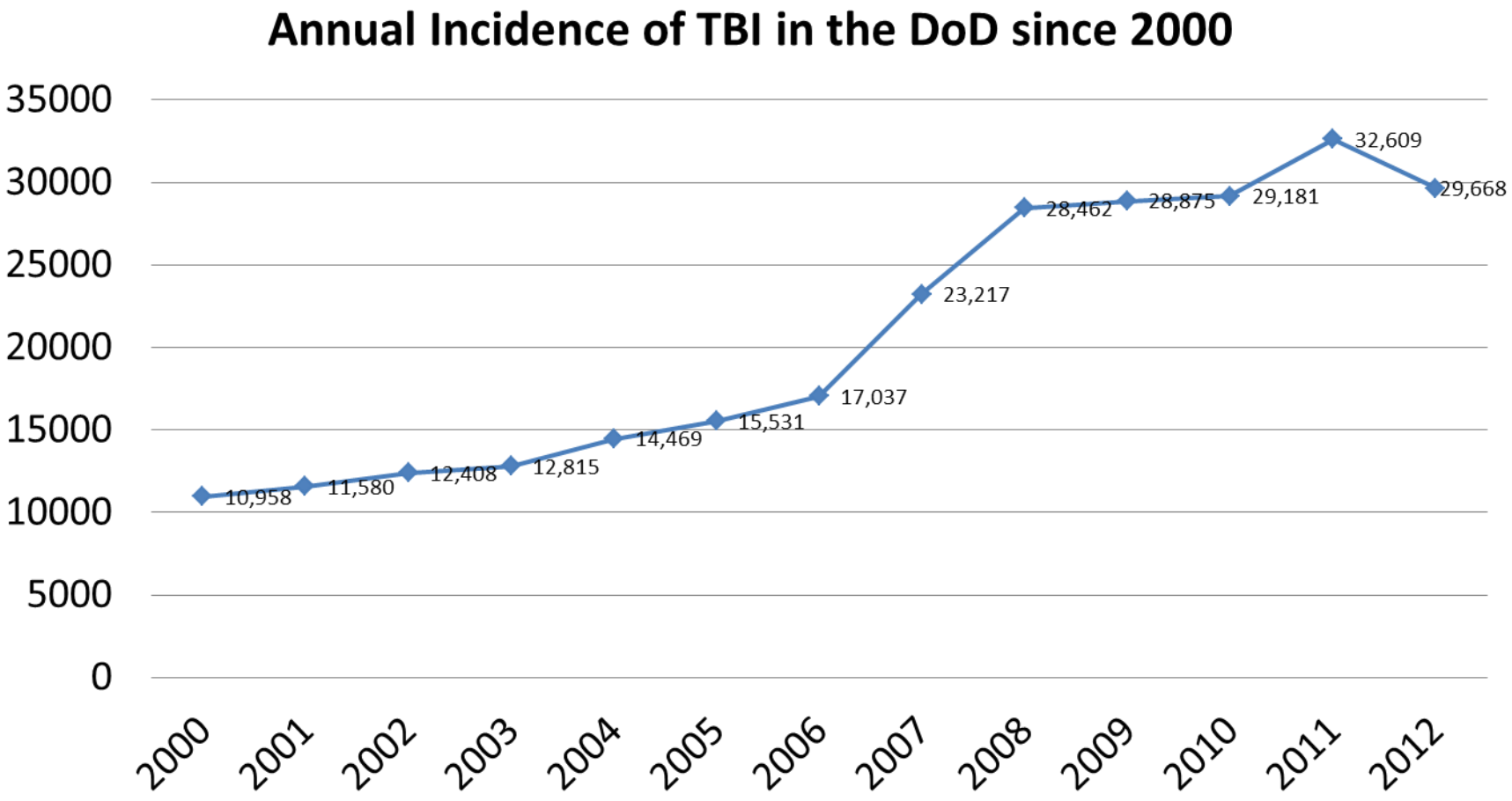
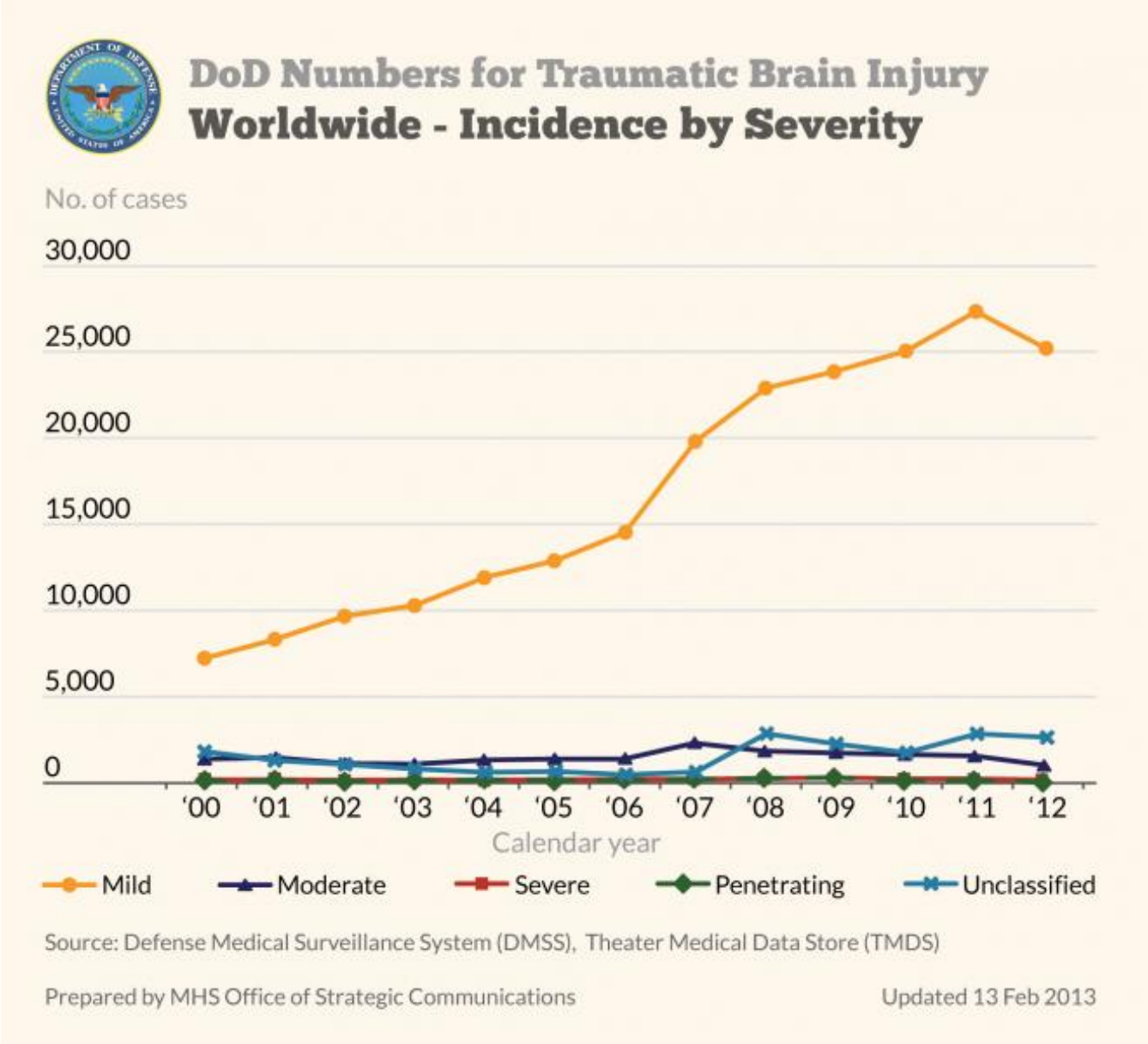


http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6005a1.htm?s_cid=ss6005a1_w

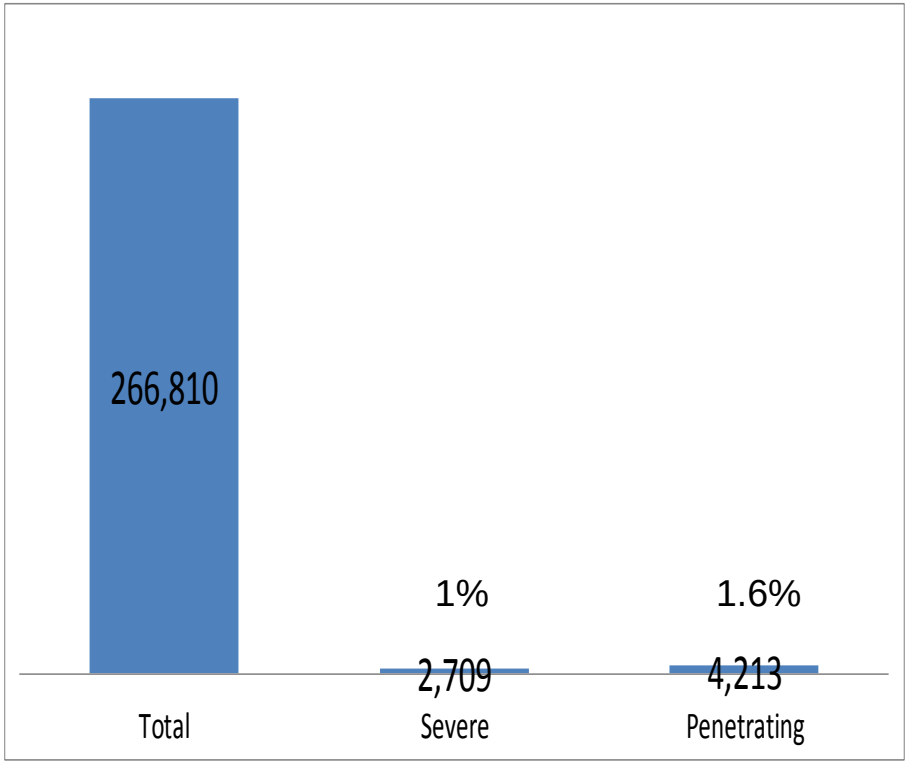
TBI in the Department of Defense (DoD)



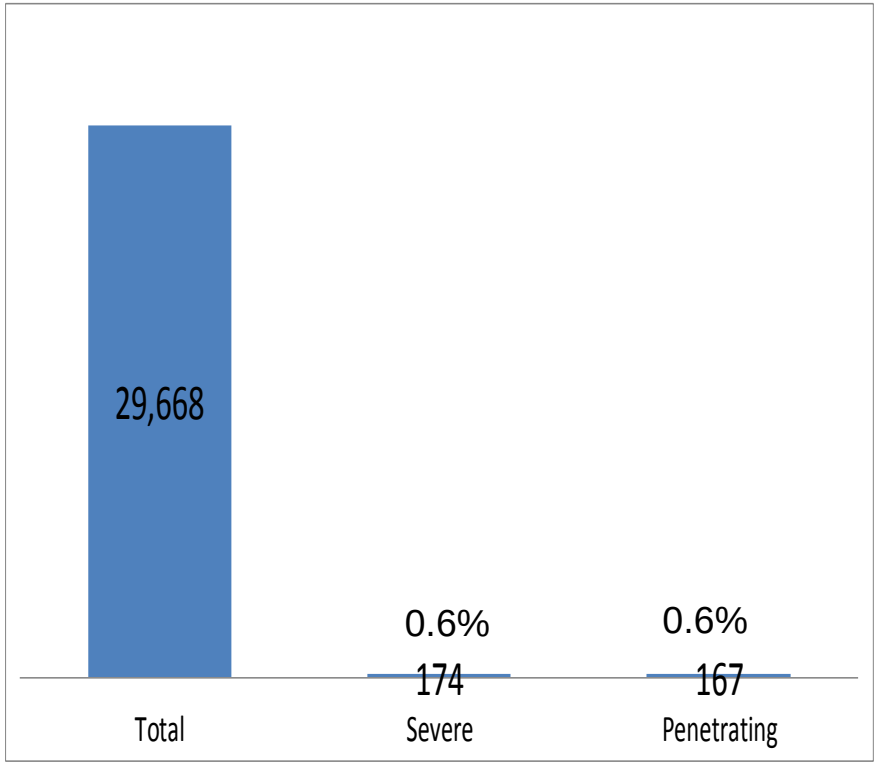
Source: DVBIC.org


DoD Numbers for Traumatic Brain Injury
Worldwide - Incidence by Severity
No. of cases
30,000
25,000
20,000
15,000
10,000
5,000
0
'00
'01
'02
'03
'04
'05
'06
'07
'08
'09
'10
'11
'12
Calendar year
Mild
Moderate
Severe
Penetrating
Unclassified
Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS)
Prepared by MHS Office of Strategic Communications
Updated 13 Feb 2013

TBI in the DoD: 2000-2012

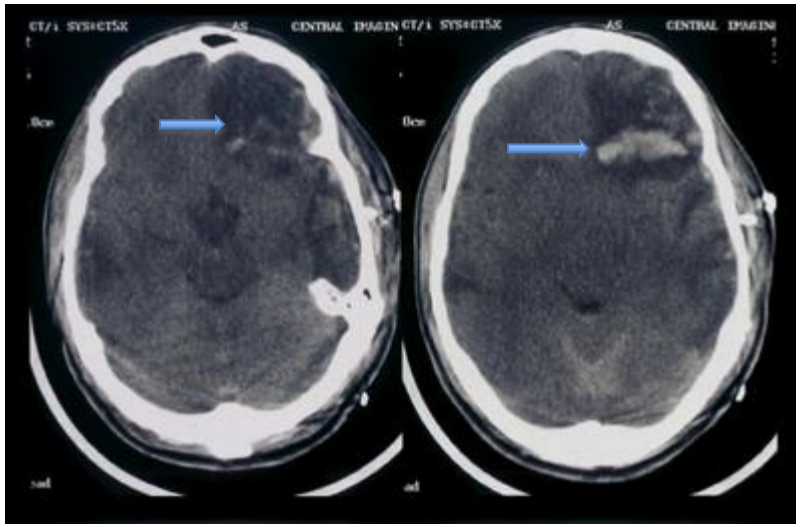


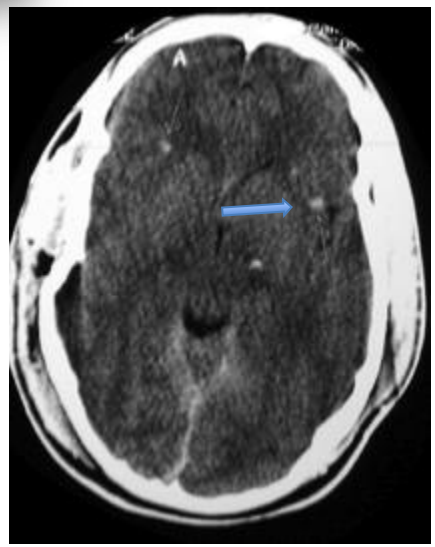
TBI in the DoD: 2012

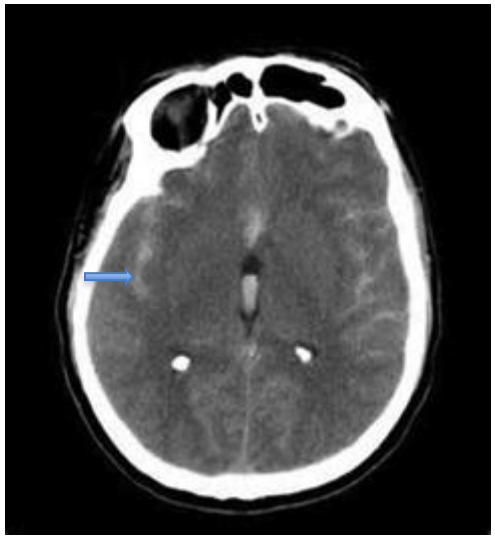


Source: DVBIC.org

Common Intracranial Lesions







(images courtesy of Donald Marion, M.D.: personal cases)

Blast Injury - Mechanism

Primary	Secondary	Tertiary	Quaternary

• Blast overpressure
  • Eardrum rupture and middle ear damage
  • Blast lung
  • TBI from blast alone
  • Abdominal hemorrhage and perforation
  • Eye rupture
	• Material striking the person
	  • Penetrating ballistic (fragmentation) or blunt injuries
	  • Eye penetration
	  • Closed and open brain injury
		• Body Displacement
		  • Victim thrown into stationary objects
			• Any injury or disease not due to other mechanisms
			  • Burns
			  • Toxic inhalation
			  • Crush injuries
			  • Radiation exposure

Poly-mechanism:
Blast with resultant motor vehicle collision

Secondary Brain Injury

Impact

0-6 hrs

-ischemia
-breakdown of BBB
-disruption of autoregulatory mechanisms

7-36 hrs

-high extracellular levels of:
EAA's
cytokines
free radicals
-cellular inflammatory response
-regional hyperthermia
-unpredictable effects of standard therapy

1-7 days

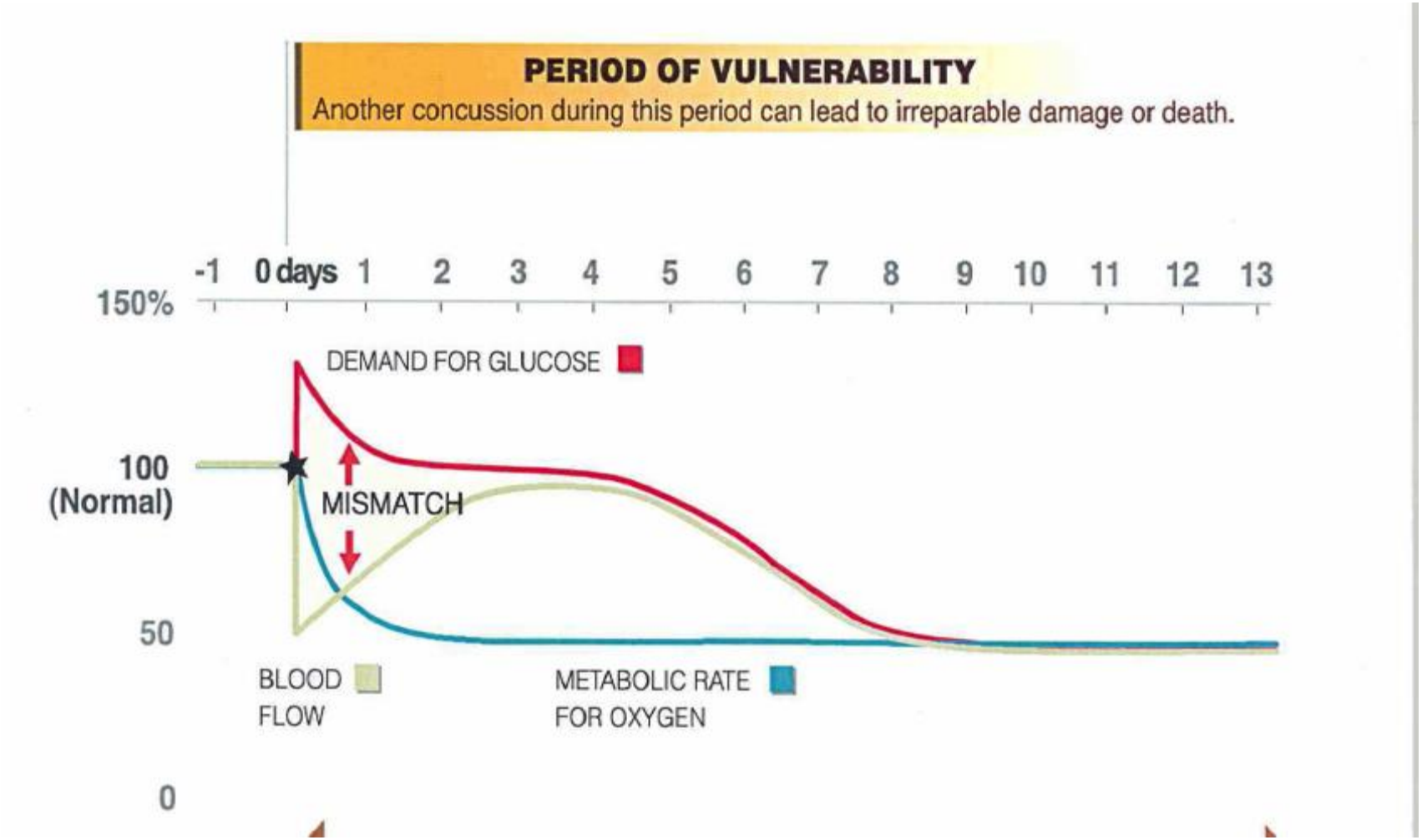
-cytotoxic edema
-vasogenic edema
-hyperemia

-intracranial hypertension
-cell death
-brain death

Basic Assumptions

- Ischemia is common early after injury
- There is significant regional heterogeneity of post-traumatic physiologic and metabolic abnormalities
- Secondary brain injury occurs for several days after injury

Neurometabolic Changes in Concussion



 Hovda et al, 1998

Goals for Acute Care

Provide an optimal environment for recovery of damaged tissue

- enhance or preserve perfusion to ischemic tissue
- avoid therapy that has the potential to limit regional perfusion

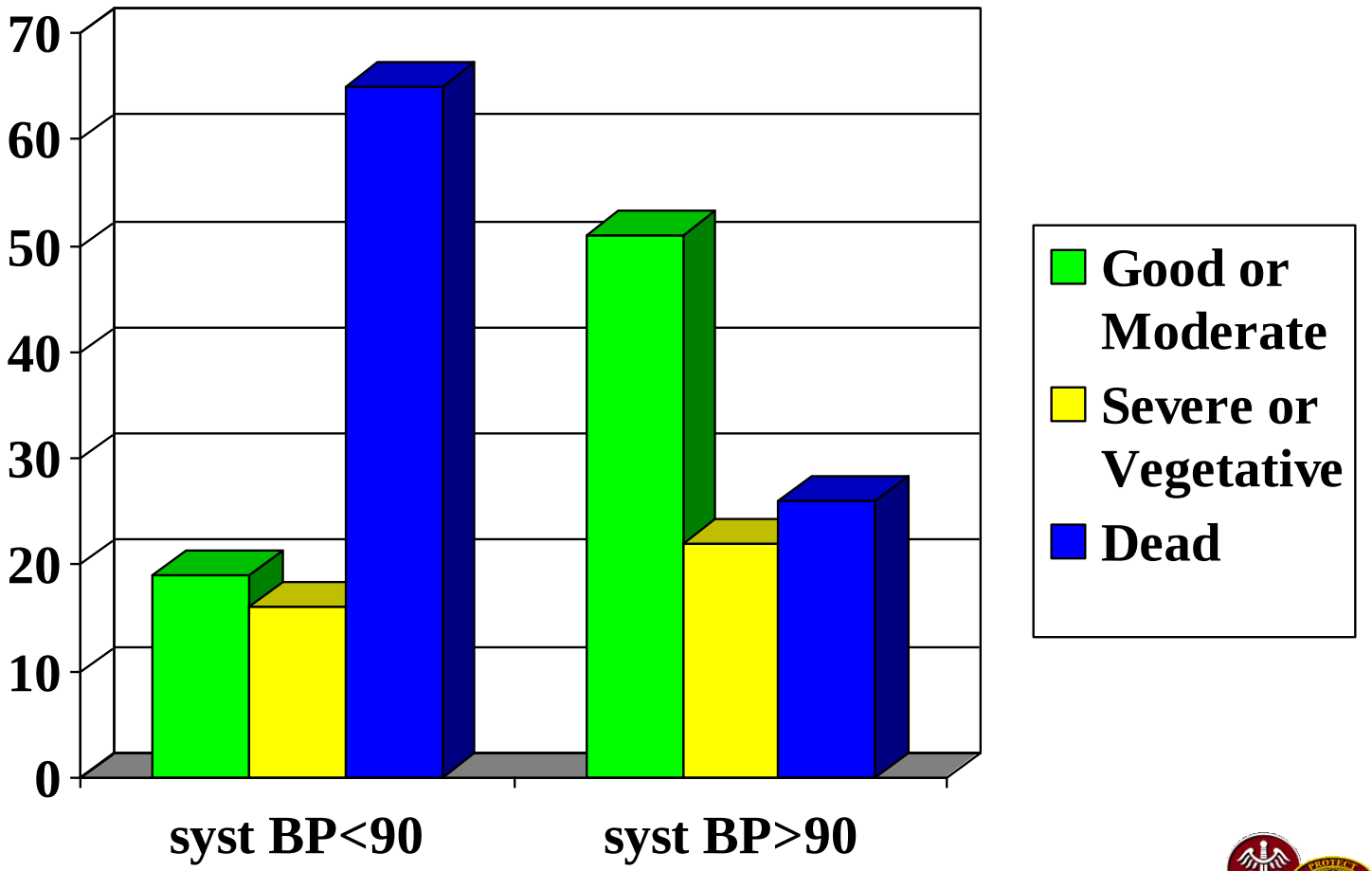
Pre-Hospital

- Rapid resuscitation of blood pressure, oxygenation
  - organized trauma systems, with neurosurgical input
  - early intubation of comatose patients

- Transfer to a facility with immediate neurosurgical availability

Hypotension and TBI

699 Patients in Traumatic Coma Data Bank



Emergency Department

- Advanced Trauma Life Support practices
- Trauma team led by fellowship-trained trauma surgeon
- Immediate availability of OR
- Surgical priorities
  - laparotomy, thoracotomy prior to CT of head
  - fixation of long bone fractures?

Indications for Craniotomy

- Large mass lesion with associated neurologic compromise
- Threat of uncal herniation
- Intractable intracranial pressure (ICP)

Monitoring Techniques

Technique	Necessary	Practical	Can be used to direct therapy
Intracranial pressure monitor	Yes	Yes	Yes
Blood pressure monitor	Yes	Yes	Yes
Central venous pressure monitor	Yes	Yes	Yes
Pulmonary artery pressure monitor	Maybe	Yes	Yes
Transcranial Doppler	No	Yes	Maybe
Cerebral blood flow monitor	No	Yes	Maybe
Jugular vein oxygen monitor	No	Yes	Maybe
Brain tissue pO2 monitor	No	Maybe	No
Microdialysis	No	Maybe	No

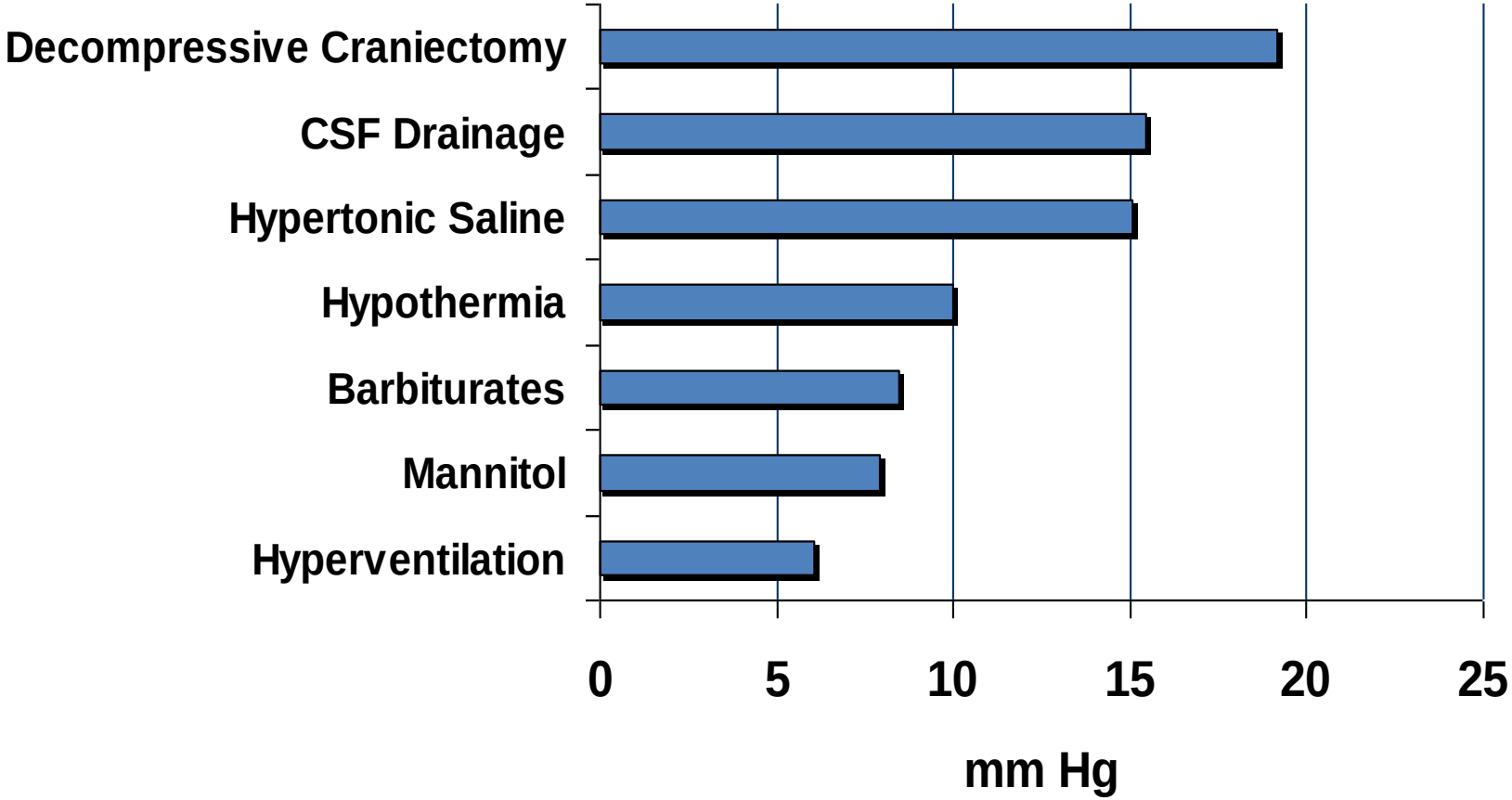
Indications for ICP monitoring

- GCS<9, not following commands
- Mass lesion or contusion on CT
- Prolonged hypoxia, hypotension

ICP Management

- Stepwise vs directed therapy
- Paralysis/sedation: a reasonable first step?
- CSF drainage
- Mannitol
- Barbiturates
- Decompressive craniectomy

Mean ICP Change for Various Therapies *before and after therapy*

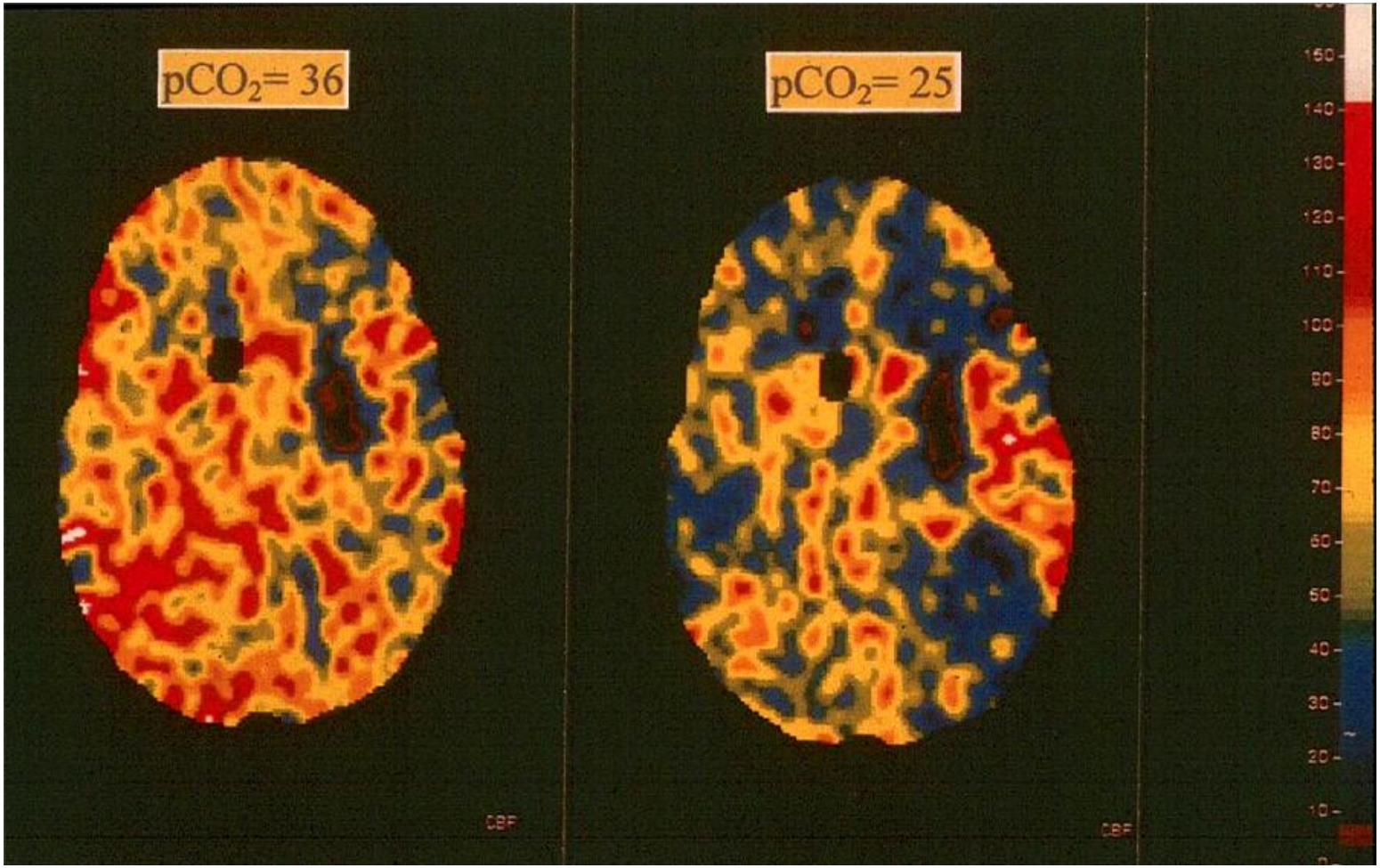


Schreckinger M, Marion DW. Contemporary management of traumatic intracranial hypertension: is there a role for therapeutic hypothermia? Neurocrit Care. 2009 Dec;11(3):427-36.

Hyperventilation

- Prophylactic hyperventilation not indicated
- Used for acute neurologic deterioration
- Effect on extracellular intermediates of secondary injury negligible

Effect of Hyperventilaton on Xenon-CT Cerebral Blood Flow



(Images courtesy of Dr. Donald Marion)

Decompressive Craniectomy

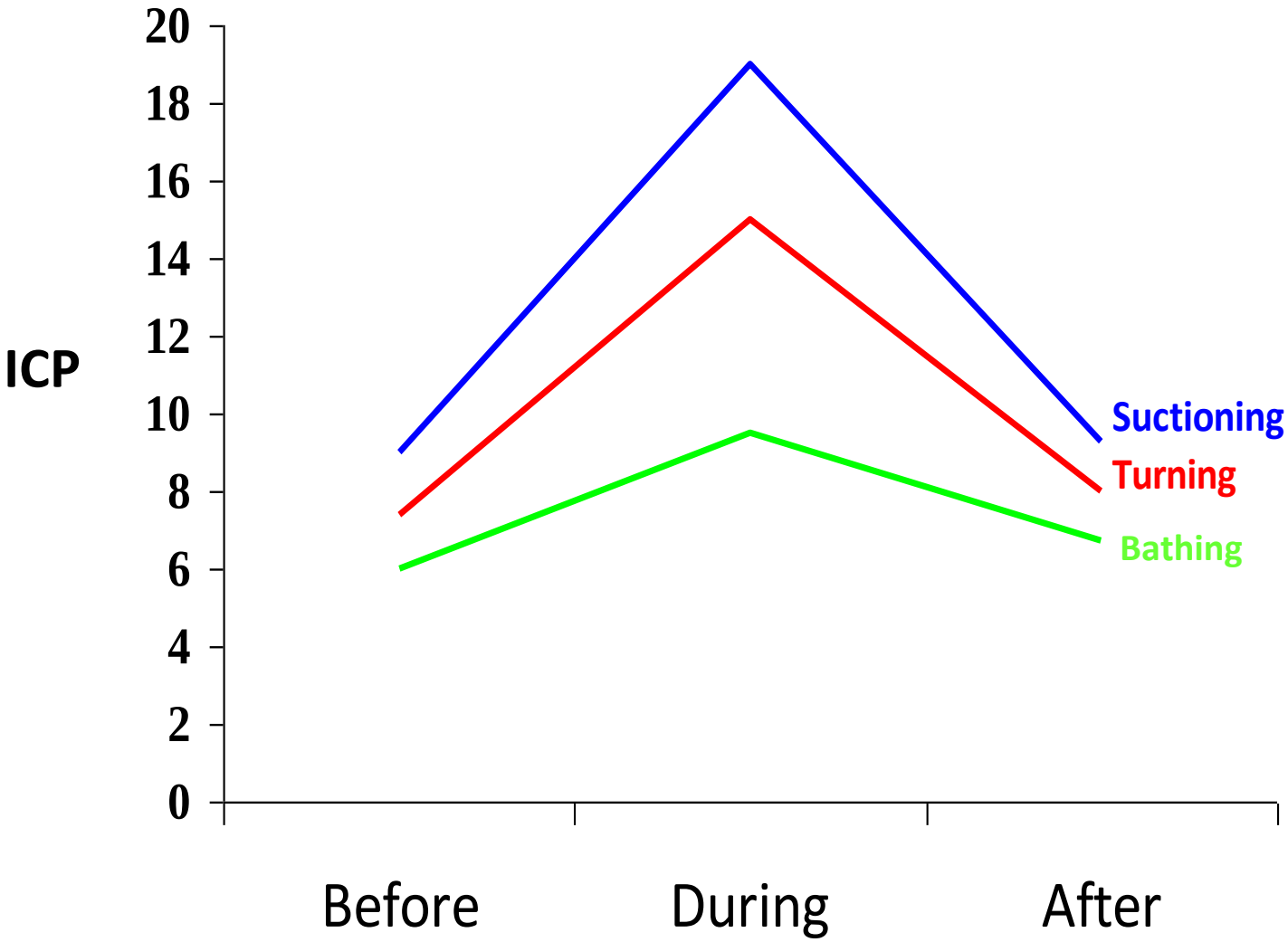
- Penetrating Injury
  - superficial debridement routine
  - embraced by DoD
    - Bell, et al., Neurosurg Focus, 2010
    - Ragel, et al., Neurosurg Focus, 2010

- Closed TBI
  - predictable reduction of ICP
  - worse outcomes?
    - Cooper, et al., NEJM, 2011: 2 fold greater risk of unfavorable 6 month outcome compared with standard treatment (PRCT, 155 civilian adults)

ICP vs Cerebral Perfusion Pressure (CPP)

- If pressure autoregulation is intact, CPP of 60 mmHg may be an appropriate threshold
- If “pressure passive,” CPP as low as 50 mmHg may be acceptable
- Aggressive treatment of CPP with fluids may lead to increased pulmonary complications

Nursing Activities and ICP



 Rising (1993) Journal of Neuroscience Nursing, 25(5)

Family Contact and ICP

Presence, touch and voice of family/significant others...

- Does not significantly increase ICP
- Has been demonstrated to decrease ICP

Bruya (1981) Journal of Neuroscience Nursing, 13; Hendrickson (1987) Journal of Neuroscience Nursing, 19(1); Mitchell (1985) Nursing Administration Quarterly, 9(4); Treolar (1991) Journal of Neuroscience Nursing, 23(5)

Significance of Hyperthermia

- Hyperthermia (39°C) superimposed on transient ischemia: 10-fold increase in ischemic neurons, significant increase in calpain activation and spectrin degradation *
- Hyperthermia occuring 24 hours after transient ischemia: significant increase in the number of ischemic neurons in selectively vulnerable brain regions **

** rodent ischemia model; Morimoto, et al., Brain Res 746:43, 1997*
***rodent ischemia model; Baena, et al., Neurol 48:768, 1997*

Correlation of Brain and Body Temperatures

- Comparison of continuously monitored brain, bladder and rectal temps in eight TBI patients
- Results:
  - brain temp usually higher
  - brain-bladder temps: 0.32 to 1.9^{o}C
  - brain-rectal temps: 0.1 to 2°C
  - differences greatest with temps above 38°C

Henker, Brown, Marion; Neurosurgery 42:1071, 1998

Blood Pressure

- Assure normal intravascular volume
  - central venous pressure
  - pulmonary artery pressure
- Optimal fluids
  - normal saline or Lactated Ringers solution
  - colloid
  - hypertonic saline
- Optimal pressors

What Fluid to Use?

- Experimental studies suggest that hypertonic saline or colloid improves outcomes, lessens edema

  large volume resuscitation with LR or NS more likely to cause edema than colloid or WB

- Clinical studies provocative but inconclusive
  - numbers too small?
  - multicenter PRCT appears to be warranted

Timing of Repair of Extremity Fractures

- Early repair = early mobilization
- Is this tolerated by the severely injured brain?

Intraoperative Hypotension and TBI

- Intraoperative hypotension:
  - → 82% mortality
- No intraoperative hypotension:
  - → 25% mortality

(53 TBI patients who required surgery within 72 hours of injury)

Pietropaoli et al, J Trauma, 1992

Joint Theater Trauma Systems (JTTS) Recommendations for acute care of service members are consistent with these principles

JTTS Recommendations

MANAGEMENT OF PATIENTS WITH SEVERE HEAD TRAUMA				
Original Release/Approval		3 Mar 2005	Note: This CPG requires an annual review.	
Reviewed:	Dec 11	Approved:	6 Mar 2012	
Supersedes:	Management of Patients with Severe Head Trauma 13 Feb 2009			
☐ Minor Changes *(or)*		☐ **Changes are substantial and require a thorough reading of this CPG** *(or)*		
☒ Significant Changes:		PI monitoring plan added		

JTTS Recommendations

Address life-threatening injuries and begin resuscitation using ATLS protocols

- Normal saline is the preferred crystalloid solution for resuscitation of patients who do not require massive transfusion
- Blood products are preferred over albumin and Hespan if colloids are necessary
- Consider recombinant Factor VIIa for life threatening intracranial bleeding
- **Normoventilation with a goal PaCO2 of 35-40 should be maintained**
- Antibiotics are unnecessary for isolated closed head injuries. Casualties with open head injuries should receive one gram (children 50 mg/kg) Cefazolin (Ancef) IV on admission and then every 8 hours until wounds are closed
- **Do not use steroids**. Steroids provide no benefit to head injured patients and have been proven to worsen outcomes in patients with severe head injury

JTTS Recommendations

- Manage hypotension and hypoxemia
  - keep SBP > 90 mm Hg
  - keep SaO2 > 93%
- Document serial neurological examinations.
  - GCS
  - pupil size and reactivity
  - presence of gross unilateral weakness, paraplegia, or quadriplegia
- Neurosurgeons at Level III facilities should give strong consideration to placing ICP monitors or Ventriculostomy catheters in patients prior to Critical Care Air Transport Team (CCATT) movement out of theater when these patients are at risk for developing increased intracranial pressure and/or when their neurologic exam may be difficult to follow during transport.

JTTS Recommendations

- If possible, for casualties transferring to Level III facilities with neurosurgical capability, avoid medications that cause long-lasting sedation or paralysis. Neurosurgeons at these sites will examine the casualty upon arrival. **However, at no time should medication selection override the need to safely transport the casualty.**
  - Vecuronium is preferred for paralysis
  - Propofol is preferred for sedation
  - **<u>Intermittent administration of narcotics is preferred over continuous infusions</u>**

JTTS Recommendations

- If treatment for intracranial hypertension is needed prior to transfer: (asymmetric motor posturing, unilateral or bilateral fixed, dilated pupil, decreasing level of consciousness)
  - initiate 3% Saline Protocol
  - optimize pO2/pCO2 (pO2 > 80 mm Hg, pCO2 35-40 mm Hg)
  - avoid/rapidly treat hypotension
  - elevate head of bed (may keep patient flat in the setting of suspected spine injury and use reverse Trendelenburg position
  - Patients with moderate head injury who deteriorate and those with severe head injury should receive 250ml bolus of 3% saline and then infusion of 3% saline at 50-100ml/hr for resuscitation en route to the Level III center. If further deterioration occurs or if the patient shows signs of herniation (pupillary dilation, hypertension and bradycardia, progression to decerebrate posturing) consider using Mannitol 1g/kg bolus IV, followed by 0.25g/kg rapid IV push q4hrs.
- Note: Do not use Mannitol in hypotensive or under-resuscitated casualties.

JTTS Recommendations

Antiepileptic medications for seizure prophylaxis

- Consider for all patients with intracranial hemorrhage, penetrating brain injury, and seizure activity following the injury, or a GCS < 9
- Phenytoin or fosphenytoin are the preferred parenteral (IV or IM) medications
- Discontinue after seven days if there is no penetrating brain injury, no prior seizure history, and no development of seizures following the injury

Critical Care Air Transport Team *(CCATT)*

- Pilot program initiated in May 1994 at the 59th Medical Wing, Wilford Hall
- Formally approved and adopted into USAF Aeromedical Evacuation System: June 1996
- Currently there are 92 CCATT teams (reserve and AD)
  - 60 active duty team allocations are assigned to 11 different bases across seven major commands
- Transported more than 4,000 patients on ventilators with no significant or life-threatening complications in flight
- Air Mobility Command
  - Scott AFB, Illinois: Lead command responsible for aeromedical evacuation; responsible for providing daily oversight, management, and coordination of all CCATT activities

CCATT Transport: A Challenging Environment

- Long Distances
  - Baghdad to Germany 2,500 Miles
  - Germany to Wash, DC 4,000 Miles
  - Germany to San Antonio 6,000 Miles
- Cargo Aircraft: Austere Conditions
  - Temperature, noise, vibration, lighting, power
- "Stabilized" Patients: Injuries in Evolution
  - initial resuscitation performed
  - airway secure
  - shock treated, may be ongoing
  - surgical bleeding stopped
  - fractures stabilized

Occurrence of Secondary Insults with CCATT

Fifty-three percent of the patients had at least one documented episode of a secondary insult

- Hyperthermia was the most common secondary insult and was associated with severity of injury
- Hypoxia occurred most frequently within the area of responsibility, but was rare during CCATT flights, suggesting that concerns for altitude-induced hypoxia may not be a major factor in the decision when to move a patient

Dukes SF, Bridges E, Johantgen M. Occurrence of secondary insults of traumatic brain injury in patients transported by critical care air transport teams from Iraq/Afghanistan: 2003-2006. Mil Med. 2013 Jan;178(1):11-7. (Retrospective cohort study; 63 combat casualties with severe isolated traumatic brain injury transported by the U.S. Air Force Critical Care Air Transport Teams (CCATT) from 2003 through 2006. Data were obtained from the Wartime Critical Care Air Transport Database, which describes the patient's physiological state and care as they are transported across the continuum of care from the area of responsibility (Iraq/Afghanistan) to Germany and the United States.)

Effect of Guideline Management on Outcome of Patients with Traumatic Brain Injury

Group	GOS = 1 Died	GOS = 2 and 3 Severe Disability	GOS = 4 and 5 Good Outcome
Pre-TBI Guidelines	16 (43.24%)	11 (29.73%)	10 (27.03%)
Post-TBI Guidelines	9 (16.07%)	8 (14.29%)	39 (69.64%)
Total	25 (26.88%)	19 (20.43%)	49 (52.69%)

9.13 times higher odds ratio of good outcome relative to odds of a poor outcome or death compared to pre-guidelines group

Palmer S, Bader MK, Qureshi A, Palmer J, Shaver T, Borzatta M, Stalcup C. The impact on outcomes in a community hospital setting of using the AANS traumatic brain injury guidelines. Americans Associations for Neurologic Surgeons. J Trauma. 2001 Apr;50(4):657-64.

Protocol Driven Acute Care

- Meta-analysis of 13 studies, random effects model, that looked at management protocol (MP) driven acute care versus usual care for adult intensive care unit (ICU) patients with acute severe TBI, and assessed six-month neurologic outcome
- Use of MPs was associated with a favorable neurologic outcome (GOS 4 or 5) at six months (odds ratio [OR] 3.84) but not 12 months
- Use of MPs was associated with reduced mortality at hospital discharge and six months (OR 0.72 and 0.33, respectively), but not 12 months

English SW, et al. Protocol management of severe traumatic brain injury in intensive care units: a systematic review. Neurocrit Care. 2013 Feb;18(1):131-42

Clinical Research – What Is On the Horizon?

Therapeutic Moderate Hypothermia?

Source	Setting	N	Depth/Duration of Cooling	F/U	Good Outcome		P value
					Hypothermia	Normothermia	
Shiozaki, 1993	Single Hospital	33	34° C/48 hrs	6 mos	38%	6%	>0.05
Clifton, 1993	Single Hospital	46	32-33° C/48 hrs	3 mos	52%	36%	>0.29
Marion, 1997	Single Hospital	82	32-33° C/24 hrs	6 mos	56%	33%	=0.05
Jiang, 2000	Single Hospital	87	33-35° C/3-14 days	1 year	46.5%	27%	<0.05
Gal, 2002	Single Hospital	30	34° C/72 hrs	6 mos	87%	47%	=0.08
Zhi, 2003	Single Hospital	396	32-35° C/1-7 days	6 mos	62%	38%	<0.05
Qiu, 2005	Single Hospital	86	33-35° C/3-5 days	2 years	65%	37%	<0.05
Qiu, 2007	Single Hospital unilateral crani.	80	33-35° C/4 days	1 year	70%	48%	<0.05
Zhao, 2011	Single Hospital	81	32-33° C/72 hrs	3 mos	75%	51.2%	=.038
Shiozaki, 2001	11 Hospitals	91	34° C/48 hrs	3 mos	46%	59%	>0.99
Clifton, 2001	11 Hospitals	392	33° C/48 hrs	6 mos	43%	43%	=0.99
Hutchison, 2008	17 Hospitals	225 Peds	33° C/24 hrs	6 mos	69%	78%	=0.14
Clifton, 2010	6 Hospitals	97	34° C/48 hrs	6 mos	40%	44%	=0.67

 Summary Table courtesy of Dr. Donald Marion

Effect of Hypothermia on ICP: PRCTs

Study	Target Temperature	N	Mean ICP: H (mm Hg)	Mean ICP: N (mm Hg)	Difference (mm Hg)
Shiozaki, 1993	34	33	~15	~25.4	10.4
Smrcka, 2005	34	38	10.81	18.88	8.07
Liu, 2006	33-35	45	27.75	33.08	5.33
Qiu, 2007	33-35	80	23.56	25.45	1.89
Marion, 1997	32-33	82	15.4	19.7	4.3
Jiang, 2000	33-35	87	18.9	28.13	9.23
Clifton, 2001	33	392	15.65	17.4	1.75
Zhi, 2003	32-33	396	16.7	22.7	6
Biswas, 2002	32-34	21 (P)	9.5	12	2.5
Adelson, 2005	32-33	35 (P)	14.86	17.48	2.62
				Mean (±Std. Dev.)	**5.2 (3.16)**

Therapeutic Moderate Hypothermia

- 12 studies with 1327 participants selected for analysis
  - Analysis followed recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the QUOROM (quality of reporting of meta-analyses) statement
- Results: lower mortality (RR 0.73, 95% CI 0.62-0.85) and more common good neurologic outcome (RR 1.52, 95% CI 1.28-1.80)
  - Only short-term cooling studies analyzed: neither mortality (RR 0.98, 95% CI 0.75-1.30) nor neurologic outcome (RR 1.31, 95% CI 0.94-1.83) were improved.
  - 8 studies of long-term or goal-directed cooling: mortality reduced (RR 0.62, 95% CI 0.51-0.76) and good neurologic outcome was more common (RR 1.68, 95% CI 1.44-1.96)
- Conclusion: The best available evidence supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI to decrease mortality and improve rates of good neurologic recovery
  - Should be commenced as soon as possible after injury regardless of initial ICP, or before ICP is measured
  - Most studies report using a temperature of 32 degrees -34 degrees C.
  - The maximal benefit occurs with a long-term or goal-directed cooling protocol, in which cooling is continued for at least 72 hours and/or until stable normalization of intracranial pressure for at least 24 hours is achieved

Fox JL, et al. Prophylactic hypothermia for traumatic brain injury: a quantitative systematic review. CJEM. 2010 Jul;12(4):355-64. Review.

Decompressive Craniectomy

- *Guerra, et al, J Neurosurg 90:187, 1999*
  - 57 patients, most under age 30
  - best results if done > 48 hours after injury
    - slowly increasing ICP
  - Results: GOS 4,5: 58%

- *Polin, et al, Neurosurg 41:84, 1997*
  - 35 patients, bicoronal with dural patch for intractable ICP (no barbs, CSF drainage of cooling)
  - Results: GOS 4,5: 37%

- *Kunze, et al, Acta Neurochir Suppl(Wien) 71:16, 1998*
  - 28 patients, mean age 22
  - only after refractory to medical management
  - Results: GOS 4,5: 56%

Decompressive Craniectomy (DECRA) Trial

- Decompressive craniectomy did NOT improve functional outcomes at six months after injury when compared to a group randomly assigned to receive non-surgical second tier ICP therapy
  - PRCT of 155 adults with severe TBI and medically refractory ICH
  - 51 (70%) of those who underwent decompressive craniectomy died, were in a vegetative state, or had severe disabilities six months after injury
  - only 42 (51%) of the "standard-care" group had such unfavorable outcomes

- This was despite an immediate and sustained reduction of ICP by approximately 25% in the craniectomy group compared to the standard care group

Cooper DJ, et al. Decompressive Craniectomy in Diffuse Traumatic Brain Injury. N Engl J Med. 2011 Mar 25.

Progesterone

- Severe TBI patients were divided to three groups (placebo, progesterone, progesterone-vitamin D), each with 20 people, and enrolled April-Sept, 2011

- After three months, they were reassessed for GCS and GOS

- Findings: The recovery rate in the group receiving progesterone and vitamin D together was significantly higher than that of progesterone group, which was in turn higher than that of placebo group

Aminmansour B, et al. Comparison of the administration of progesterone versus progesterone and vitamin D in improvement of outcomes in patients with traumatic brain injury: A randomized clinical trial with placebo group. Adv Biomed Res. 2012;1:58. doi: 10.4103/2277-9175.100176. Epub 2012 Aug 28.

Benefit of O_2 Supplementation Is Not Clear

Effect of Supplemental Oxygen

- Patients with high PaO2 levels (average of 200 mmHg or more) had significantly higher mortality and lower discharge GCS scores than patients with a normal PaO2
  - patients with low PaO2 levels also had increased mortality
- Hyperoxia-induced oxygen-free radical toxicity with or without vasoconstriction may have been a factor
- (1,547 consecutive adults with severe TBI who survived more than 12 hours after hospital admission; PaO2 levels were measured within the first 24 hours and correlated with outcomes at discharge.)

Brenner M, et al. Association between early hyperoxia and worse outcomes after traumatic brain injury. Arch Surg. 2012 Nov 1;147(11):1042-6.

Supplemental pO_2

- PaO2 between 250 and 486 mm Hg during the first 72 hours after injury was associated with improved all-cause survival in patients with severe TBI, independent of hypocarbia or hypercarbia.

(193 patients, 44±18 yr; 77% male; admission Glasgow Coma Scale score 4±2)

Asher SR, et al. Survival Advantage and PaO2 Threshold in Severe Traumatic Brain Injury. J Neurosurg Anesthesiol. 2013 Apr;25(2):168-73.

Cochrane Reviews (2012)

- **HBOT:** In people with traumatic brain injury, while the addition of HBOT may reduce the risk of death and improve the final GCS, there is little evidence that the survivors have a good outcome. The routine application of HBOT to these patients cannot be justified from this review. 7 studies, 571 patients: 285 HBOT, 286 controls *

- **Progesterone:** Current clinical evidence from three small RCTs indicates progesterone may improve the neurologic outcome of patients suffering TBI. This evidence is still insufficient and further multicentre randomised controlled trials are required. 3 studies, 315 people **
- **Barbiturates:** 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 in four patients. This hypotensive effect will offset any ICP lowering effect on cerebral perfusion pressure. ***

*Bennett MH, Trytko B, Jonker B. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database Syst Rev. 2012 Dec 12
** Ma J, Huang S, Qin S, You C. Progesterone for acute traumatic brain injury. Cochrane Database Syst Rev. 2012 Oct 17
*** Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Cochrane Database Syst Rev. 2012 Dec 12

Fish Oil

- Omega-3 Fatty Acids
  - Docosahexaenoic acid (DHA)
  - Eicosapentaenoic acid (EPA)
- Direct evidence on the effect of omega-3 poly-unsaturated fatty acids (PUFA) on the incidence or severity of dementia is lacking. The available trials showed no benefit of omega-3 PUFA supplementation on cognitive function in cognitively healthy older people.

Hasadsri L, Wang BH, Lee JV, Erdman JW, Llano DA, Barbey AK, Wszalek T, Sharrock MF, Wang H. OMEGA-3 FATTY ACIDS FOR TREATMENT OF TRAUMATIC BRAIN INJURY. J Neurotrauma. 2013 Jan 30. [Epub ahead of print]
Sydenham E, Dangour AD, Lim WS. Omega 3 fatty acid for the prevention of cognitive decline and dementia. Cochrane Database Syst Rev. 2012 Jun 13

Vagal Nerve Stimulation

- Vagal Nerve Stimulation
  - decreased seizure frequency and severity
  - enhanced mood
  - reduced daytime sleepiness
  - increased slow wave sleep
  - improved cognition
  - improved memory
  - improved quality of life
- In rats, early stimulation of the vagus nerve accelerates the rate and extent of behavioral and cognitive recovery after fluid percussion brain injury in rats

Shi C, Flanagan SR, Samadani U. Vagus nerve stimulation to augment recovery from severe traumatic brain injury impeding consciousness: a prospective pilot clinical trial. Neurol Res. 2013 Apr;35(3):263-76.

Outcomes for Severe TBI

Biomarkers

- Biomarkers with the greatest predictive value for poor outcome at 72 hours: serum S-100B on admission, as well as plasma D-dimer and serum S-100B at 24 hours.*
  - Multimarker analysis indicated no substantial improvement in prediction accuracy over the best single predictors during this time frame

- CSF S100b profiles can reliably predict 6 month GOS and DRS, and mean and peak serum S100b can predict acute mortality, following severe TBI**

*Defazio MV, et al. The Potential Utility of Blood-Derived Biochemical Markers as Indicators of Early Clinical Trends After Severe Traumatic Brain Injury. World Neurosurg. 2013 Jan 8. retrospective series of 44 patients with severe TBI

**Goyal A, et al. S100b as a Prognostic Biomarker in Outcome Prediction for Patients with Severe TBI. J Neurotrauma. 2012 Nov 29. [Epub ahead of print]) N=138 patients with CSF samples, and 80 with serum samples; all adults with severe TBI

Biomarkers

Serum levels of ubiquitin carboxyl-terminal esterase L1 (UCH-L1) were the only independent predictor of death at discharge, but both UCH-L1 and glial fibrillary acidic protein (GFAP) levels strongly predicted death at six months post-injury.

(multivariate logistic regression; 81 patients with severe TBI recruited from four trauma centers)

Mondello S, et al. Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study. Crit Care. 2011 Jun 24;15(3):R156.

Influence of volume of cases on outcomes

- After controlling for severity, demographics, and insurance status, highest-volume centers demonstrated a 9% lower mortality risk ($p < 0.001$). High volume (>40 patients per quarter) is associated with improved severe TBI patient survival and, probably, improved quality of life.
- Lower-volume hospitals discharged a significantly larger proportion of TBI patients to skilled nursing facilities and fewer patients to home or rehabilitation facilities ($p < 0.01$).

(Analysis based on two high-volume hospitals that consistently treated more TBI patients (>40 patients per quarter), four that treated less than 40 patients per quarter, and one that transitioned to high-volume midway through the study period.)

Tepas JJ 3rd, Pracht EE, Orban BL, Flint LM. High-volume trauma centers have better outcomes treating traumatic brain injury. J Trauma Acute Care Surg. 2013 Jan;74(1):143-7; discussion 147-8.

Outcomes: Trauma Center Designation

- Level I trauma centers have better outcomes than lower-level centers in patients with specific injuries associated with high mortality and poor functional outcomes

- The volume of major trauma admissions does not influence outcome in either level I or II centers

(Mortality, intensive care unit stay, and severe disability at discharge for 12,254 patients were compared among level I and II trauma centers and between centers within the same level designation but different volumes of severe trauma (<240 vs > or =240 trauma admissions with ISS >15 per year). The outcomes were adjusted for age (<65 > or =65), gender, mechanism of injury, hypotension on admission, and ISS (< or =25 and >25))

Demetriades D, et al. The effect of trauma center designation and trauma volume on outcome in specific severe injuries. Ann Surg. 2005 Oct;242(4):512-7

Mortality Rates in the Military Have Improved

- Afghanistan/Iraq Killed-to-Injured ratio: 1-to-8 (1-to-2.5 in Vietnam)

- Combat related mortality: seven fold decrease
  - Vietnam: 1,704/100,000
  - Afghanistan/Iraq: 212-262/100,000

- Mortality was significantly better among military casualties overall (7.7% vs. 21.0%; $p<0.001$) compared with matched National Trauma Databank counterparts

(JTTR review of 604 patients meeting study criteria, with a mean age of 25.7 years. Glasgow Coma Scale was ≤8 in 27.8%, and 98.0% were men. Hypotension at presentation was noted in 5.5%. Blast (61.9%) and gunshot wound (19.5%) mechanisms accounted for the majority of combat injuries.)

DuBose JJ, et al. Isolated severe traumatic brain injuries sustained during combat operations: demographics, mortality outcomes, and lessons to be learned from contrasts to civilian counterparts. J Trauma. 2011 Jan;70(1):11-6

Cost of Care for Severe TBI

- When all costs are considered, aggressive care is significantly less costly than routine care ($1,264,000 ± $118,000 vs $1,361,000 ± $107,000) for the average 20 year old
- Aggressive care remains significantly less costly until age 80, at which age it costs more than routine care
- Comfort care for severe TBI is associated with poor outcomes and high costs, and should be reserved for situations in which aggressive approaches have failed or testing suggests such treatment is futile

(A decision-analytical model was used to determine whether aggressive treatment of severe traumatic brain injury (TBI), including invasive intracranial monitoring and decompressive craniectomy, is cost-effective. Comparison of use of Brain Trauma Foundation Guidelines vs not.)

Whitmore RG, et al. Is aggressive treatment of traumatic brain injury cost-effective? J Neurosurg. 2012 May;116(5):1106-13. doi: 10.3171/2012.1.JNS11962. Epub 2012 Mar 6.

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The views expressed in this presentation are those of the moderator and do not reflect the official policy of the Department of Defense, Department of Veterans Affairs or the U. S. Government.

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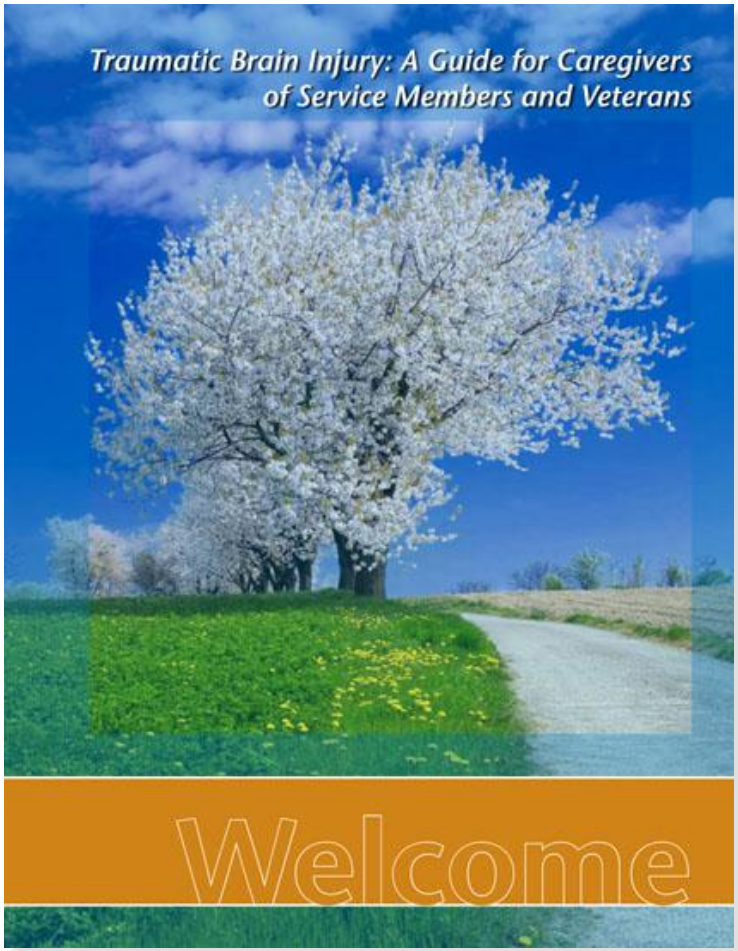
Family Caregiver Guide



Source of information and support for caregivers of service members and veterans with moderate to severe TBI

To request a Guide: DVBIC.org

OR

Download files of the Guide and view additional interactive educational tools: www.traumaticbraininjuryatoz.org

Questions?

Question-and-Answer Session

- Submit questions via the Adobe Connect or Defense Connect Online question box located on the screen.

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- We will respond to as many questions as time permits.

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