Adventures in Translational Research: From Bedside to Bench and Back Again

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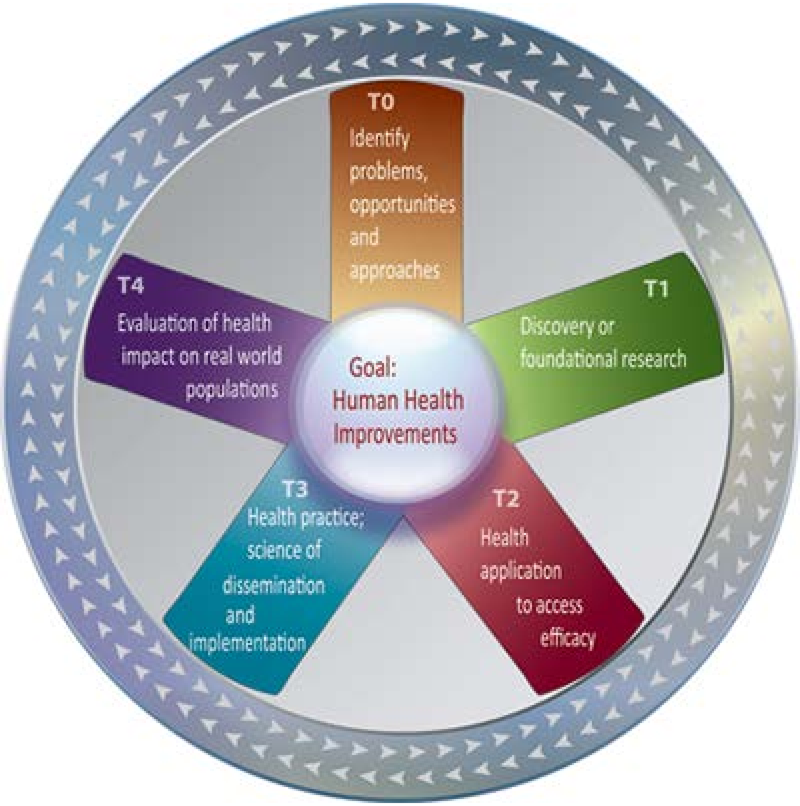
Precision Healthcare Requires Use of all Phases of Translational Research

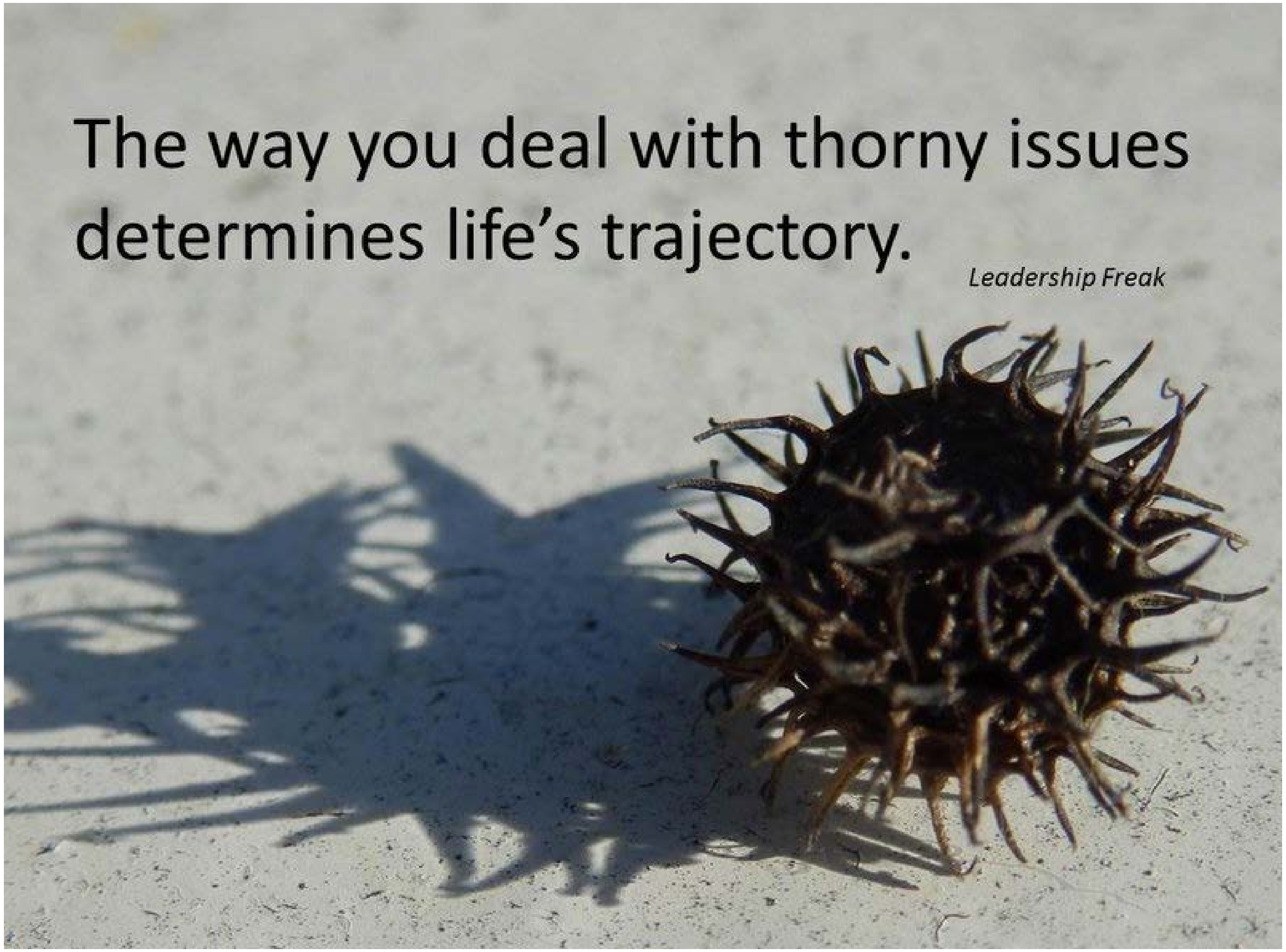


Translational Research Phases

(Khoury et al., 2007)

Research Phase	Definition	Type of Research
T_0	Identification of opportunities and approaches to health problem.	Basic research question
T_1	Discovery of candidate health application	Phase I and II clinical trials; observational studies
T_2	Health application to evidence-based practice guidelines	Phase III clinical trials; observational studies; evidence synthesis and guideline development
T_3	Practice guidelines to health practices	Dissemination research; implementation research; diffusion research; Phase IV clinical trials
T_4	Practice to population health impact	Outcomes research (includes many disciplines); population monitoring of morbidity, mortality, benefits, and risks studies

My research career



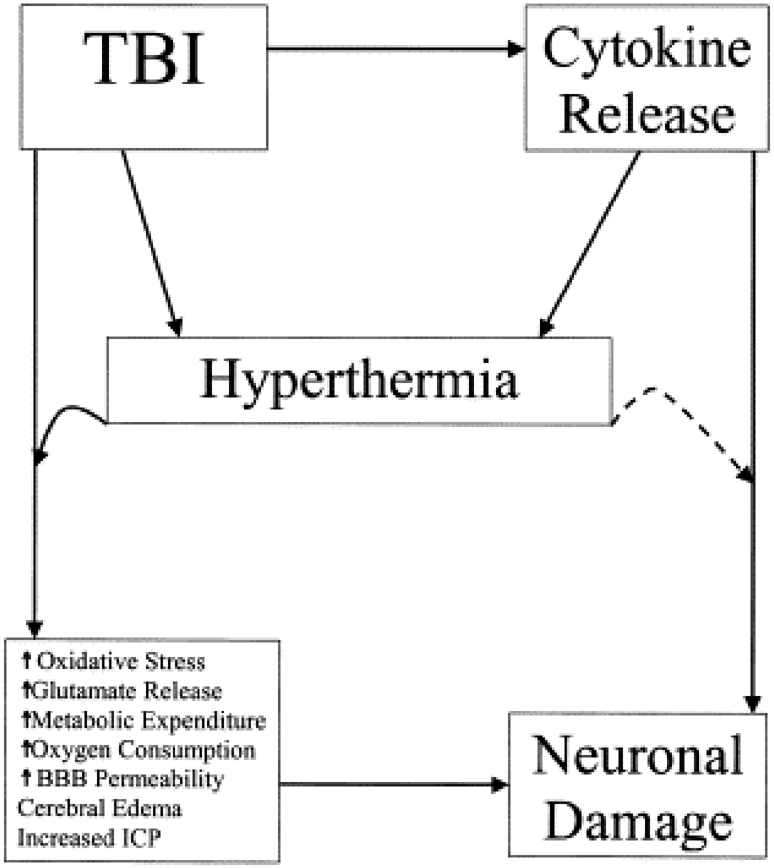
https://leadershipfreak.blog/2014/07/16/7-ways-to-push-through-thorny-issues/

Traumatic Brain Injury

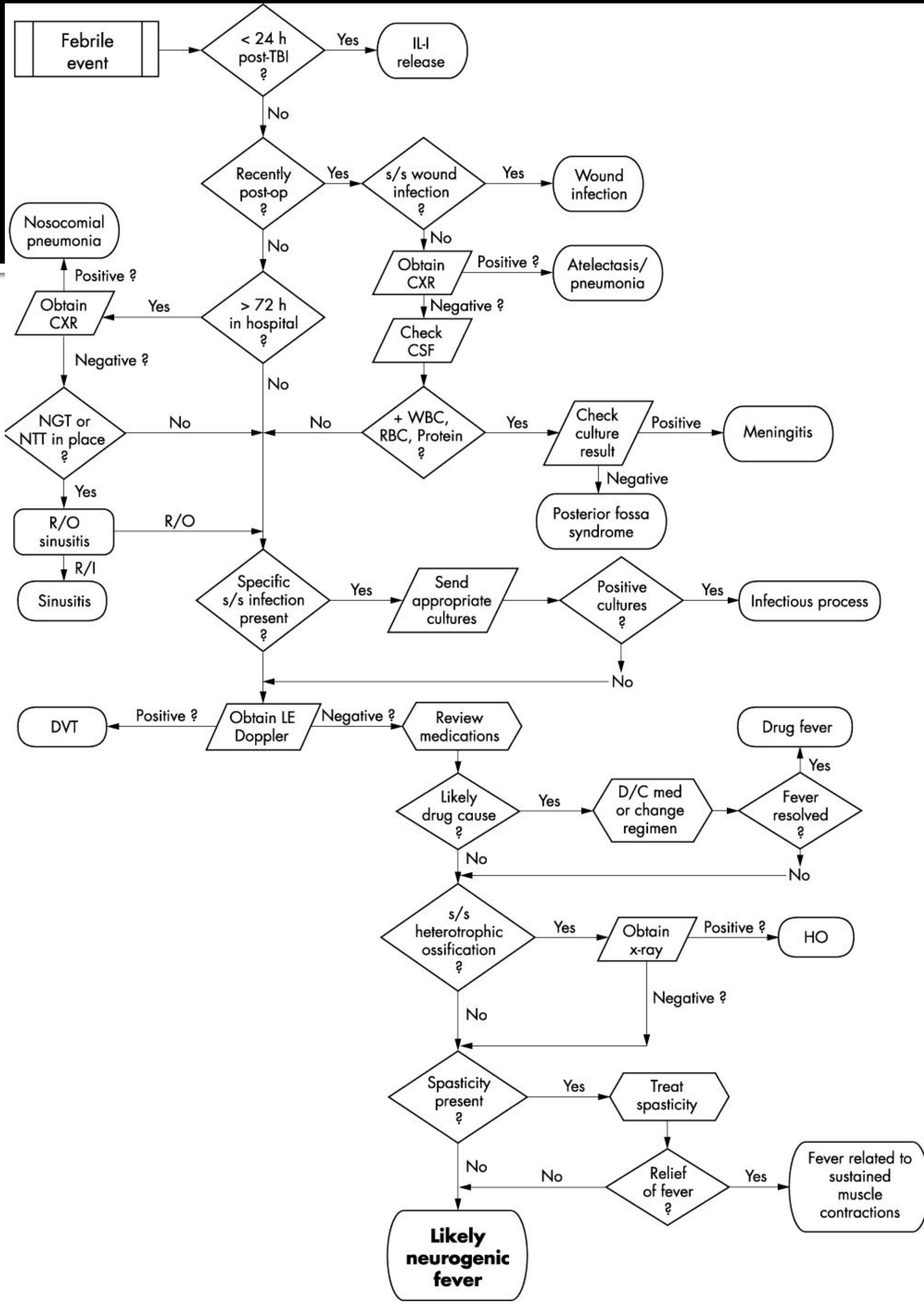
- Is leading cause of death and disability worldwide
  - In EU, more than 1M hospital admissions annually
  - In US, more than 2.5 M ED visits, hospitalization or death
- 5.3 million Americans are living with TBI-related disability (Guerro et al. in press)
- Secondary factors can negatively influence functional outcome

How do we better care for patients with neurogenic fever?

Potential Synergistic Effects of Hyperthermia Following TBI



- Increased cytokine release (Taupin et al., 1993; Toulmond & Rothwell, 1995)
- Increased glutamate release (Faden et al., 1989; Huang et al., 2001)
- Increased NO release (Alm et al., 2000; Sharma et al., 2000)
- Increased ICP (Hagerdal et al., 1975; Rossi et al., 2001)
- Increased metabolic expenditure (AANS, 2000; Clifton et al., 1986; Holtzclaw, 1992)
- Increased Neuronal Damage (Chatzipanteli et al., 2000; Dietrich et al., 1996; Whalen et al., 1997)



Starting at the Bedside: Developing a Hyperthermia Event Algorithm for TBI Patients

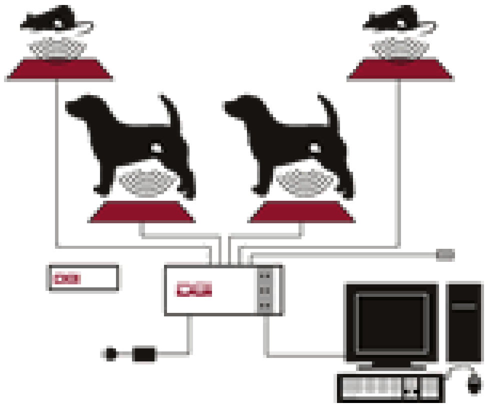
(Thompson, Pinto-Martin & Bullock, 2001)

To the Bench: Characterization of an Animal Model of PTH

- Would allow for clearer understanding of the sequela in order that future interventional studies may be undertaken and then translated to patient care
- Well characterized experimental model of lateral fluid-percussion brain injury (McIntosh et al., 1989) was utilized in the anesthetized rat as the basis for the characterization

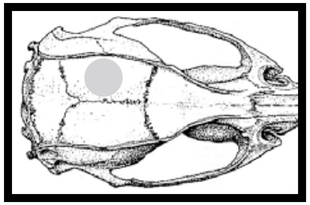
Materials/Methods

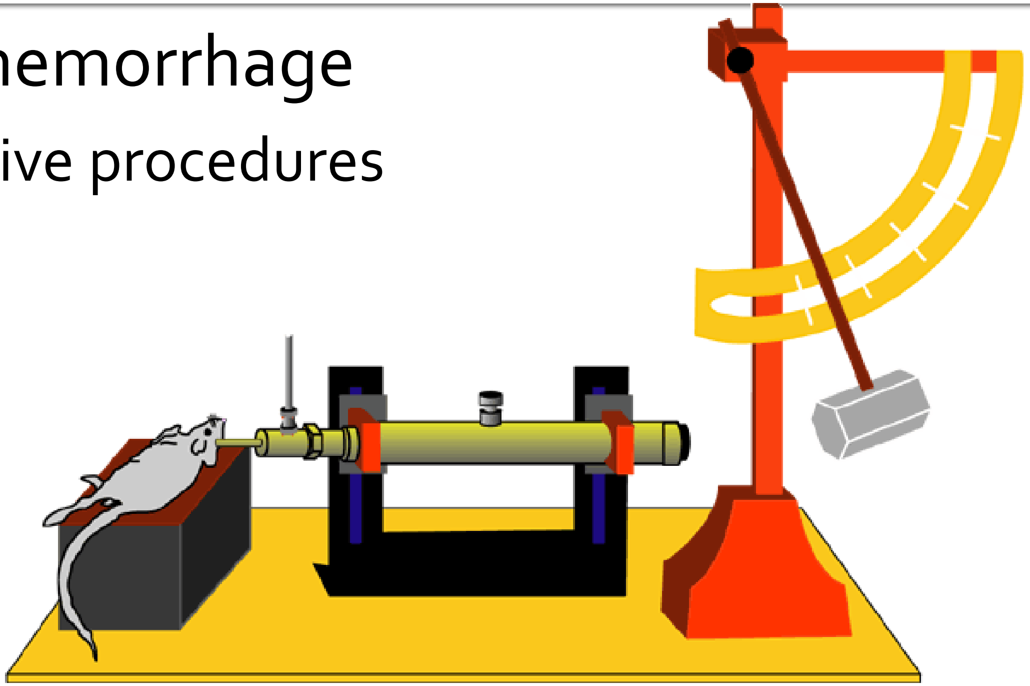
- Sprague-Dawley Rats underwent intraperitoneal thermistor implantation (Data Sciences).
- Baseline T patterns established
- 7 days later, animals were re-anesthetized and subjected to severe lateral FPI
- Physiologic normothermia maintained
- Animals monitored via telemetry for temperature measurements for 7 days
- Behavioral testing at 48H/7D
- Sacrificed at 7D for histology



Fluid Percussion Model

- Focal contusion and hemorrhage
  - No ventilation or invasive procedures required for survival

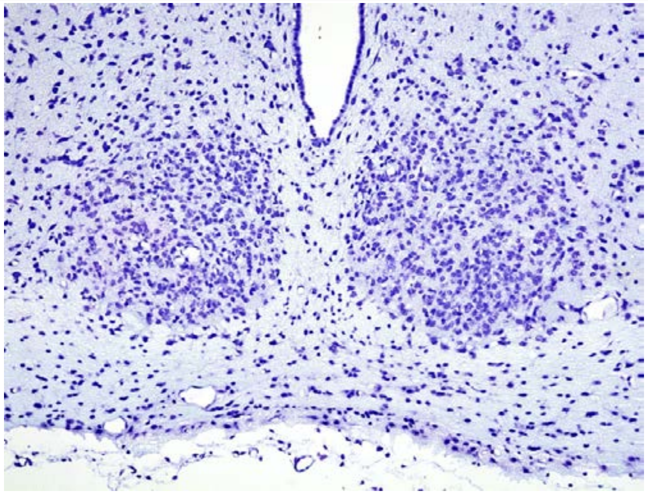


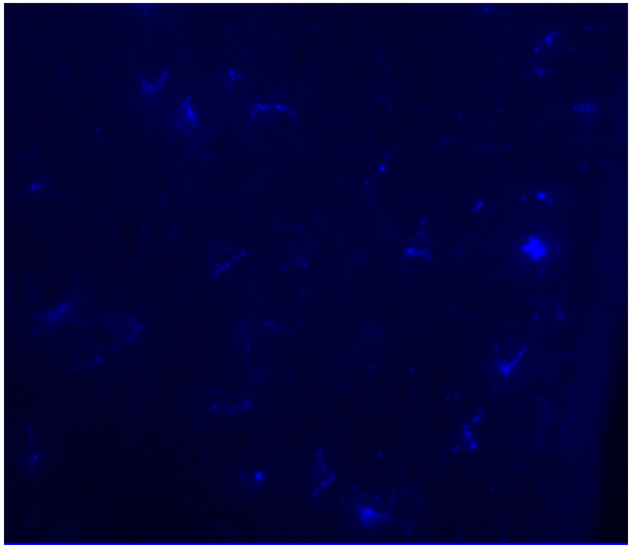


- Models morphologic, cerebrovascular, metabolic, receptor and behavioral changes of human TBI

(for review see Thompson, Lifshitz et al 2005)

Histology and Immunohistochemistry



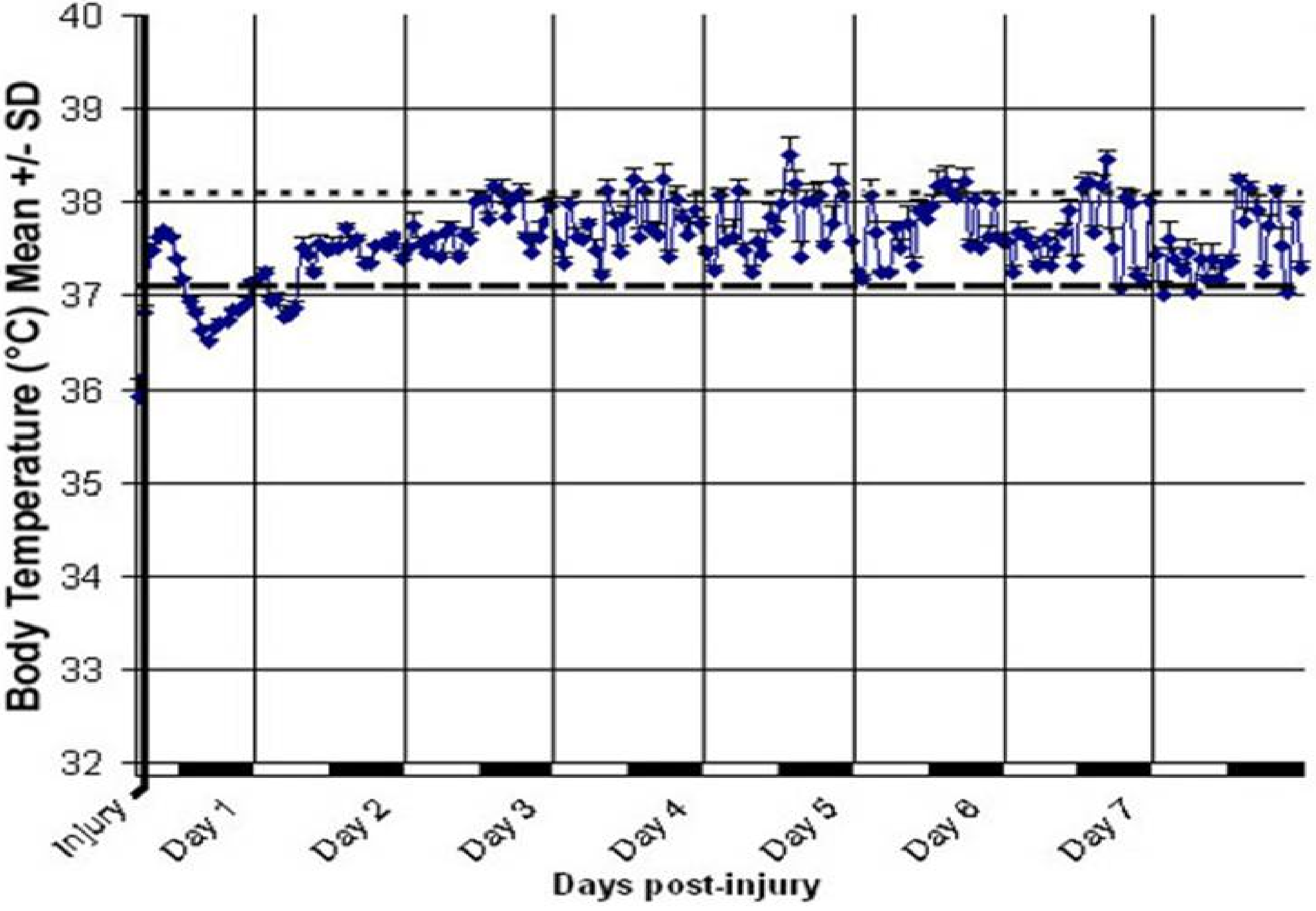


Nissl Staining for Cell counts

Triple labelling protocol used to identify:

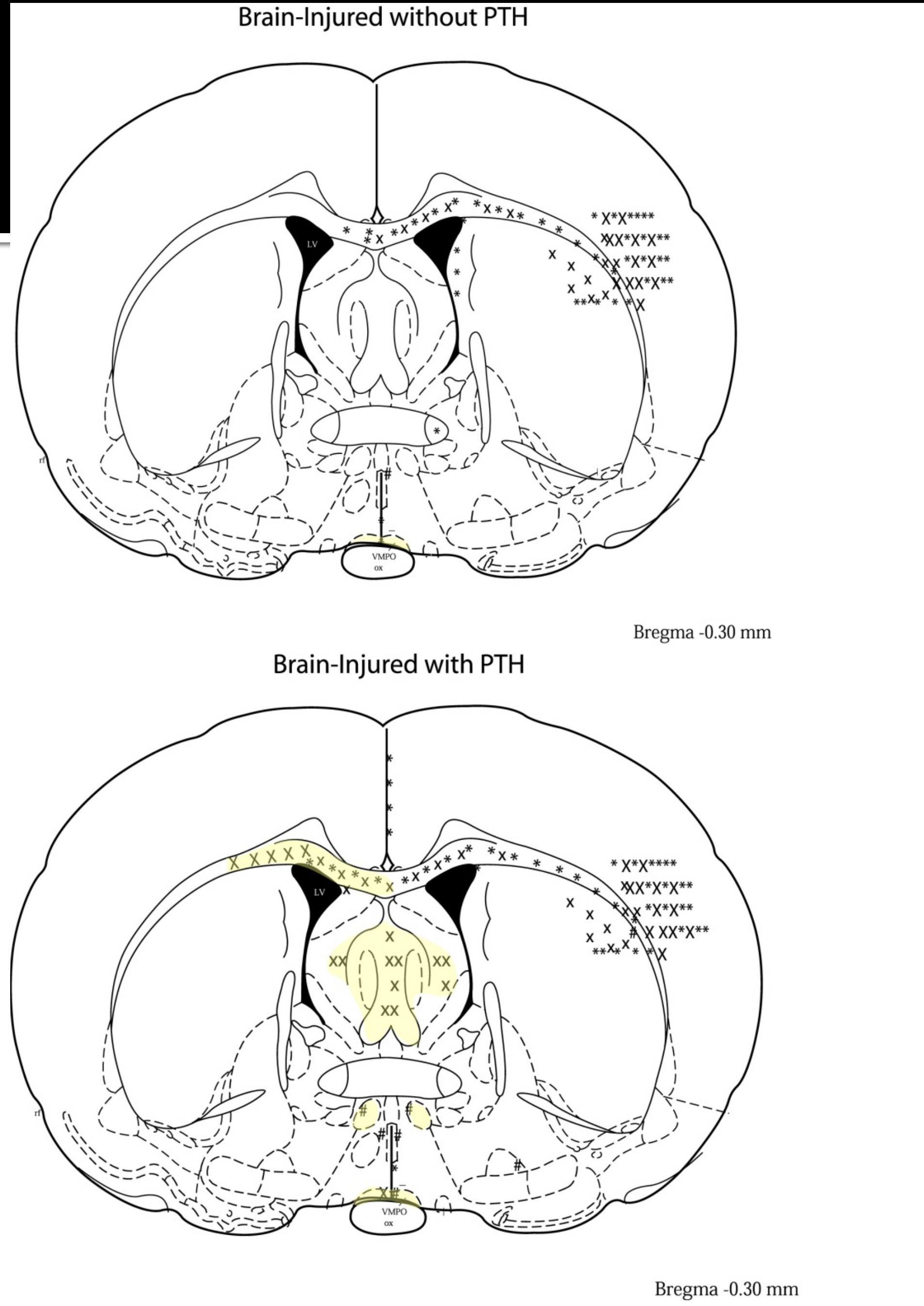
- IL-1B (R&D) (green)
- GFAP (Sigma) (blue): reactive astrocytes
- ED-1 (Serotec) (red): microglia/macrophages

Pattern 2: PTH



Histograms Developed

(Thompson et al., JCBFM 2005)



Facilitators and Barriers

- Understood clinical condition well-(validity)
- Used to working collaboratively in multidisciplinary environment
- Steep learning curve for many techniques (but doable)
- Required significant input of resources (human and capital)

Back to Bedside-T2

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Fever Management Practices of Neuroscience Nurses: National and Regional Perspectives

Hilaire J. Thompson, Catherine J. Kirkness, Pamela H. Mitchell, Deborah J. Webb

Abstract: Neuroscience patients with fever may have worse outcomes than those who are afebrile. However, neuroscience nurses who encounter this common problem face a translational gap between patient-outcomes research and bedside practice because there is no current evidence-based standard of care for fever management of the neurologically vulnerable patient. The aim of this study was to determine if there are trends in national practices for fever and hyperthermia management of the neurologically vulnerable patient. A 15-item mailed questionnaire was used to determine national and regional trends in fever and hyperthermia management and decision making by neuroscience nurses. Members of the American Association of Neuroscience Nurses were surveyed (N = 1,225) and returned 328 usable surveys. Fewer than 20% of respondents reported having an explicit fever management protocol in place for neurologic patients, and 12.5% reported having a nonspecific patient protocol available for fever management. Several clear and consistent patterns in interventions for fever and hyperthermia management were seen nationally, including acetaminophen administration at a dose of 650 mg every 4 hours, ice packs, water cooling blankets, and tepid bathing. However, regional differences were seen in intervention choices and initial temperature to treat.

JAN JOURNAL OF ADVANCED NURSING

ORIGINAL RESEARCH

Clinical management of fever by nurses: doing what works

Hilaire J. Thompson & Sarah H. Kagan

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THOMPSON H.J. & KAGAN S.H. (2011) Clinical management of fever by nurses: doing what works. *Journal of Advanced Nursing* 67(2), 359–370.
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Abstract

Aims. The specific aims were to (1) define fever from the nurse's perspective; (2) describe fever management decision-making by nurses and (3) describe barriers to evidence-based practice across various settings.

Background. Publication of practice guidelines, which address fever management, has not yielded improvements in nursing care. This may be related to differences in ways nurses define and approach fever.

Method. The collective case study approach was used to guide the process of data collection and analysis. Data were collected during 2006–7. Transcripts were coded using the constant comparative method until themes were identified. Cross-case comparison was conducted. The nursing process was used as an analytical filter for refinement and presentation of the findings.

Findings. Nurses across settings defined fever as a (single) elevated temperature that exceeded some established protocol. Regardless of practice setting, interventions chosen by nurses were frequently based on trial and error or individual conventions – 'what works'– rather than evidence-based practice. Some nurses' accounts indicated use of interventions that were clearly contraindicated by the literature. Participants working on dedicated neuroscience units articulated specific differences in patient care more than those working on mixed units.

Conclusions. By defining a set temperature for intervention, protocols may serve as a barrier to critical clinical judgment. We recommend that protocols be developed in an interdisciplinary manner to foster local adaptation of best practices. This could further best practice by encouraging individual nurses to think of protocols not as a recipe, but rather as a guide when individualizing patient care. There is value of specialty knowledge in narrowing the translational gap, offering institutions evidence for planning and structuring the organization of care.

Intensive and Critical Care Nursing (2007) 23, 91–96

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ORIGINAL ARTICLE

Intensive care unit management of fever following traumatic brain injury

Hilaire J. Thompson[a,*], Catherine J. Kirkness[a], Pamela H. Mitchell[b]

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KEYWORDS
Head injury;
Hyperthermia;
Normothermia;
Clinical decision making;
Evidence-based practice

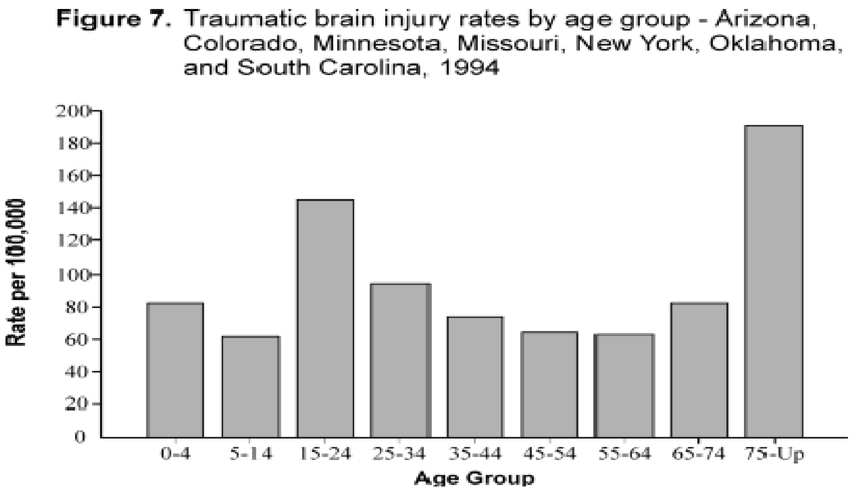
Summary Fever, in the presence of traumatic brain injury (TBI), is associated with worsened neurologic outcomes. Studies prior to the publication of management guidelines revealed an undertreatment of fever in patients with neurologic insults. Presently the adult TBI guidelines state that maintenance of normothermia should be a standard of care therefore improvement in management of fever in these patients would be expected. The specific aims of the study were to: (1) determine the incidence of fever ($T \geq 38.5\,^{\circ}C$) in a population of critically ill patients with TBI; (2) describe what interventions were recorded by intensive care unit (ICU) nurses in managing fever; (3) ascertain the rate of adherence with published normothermia

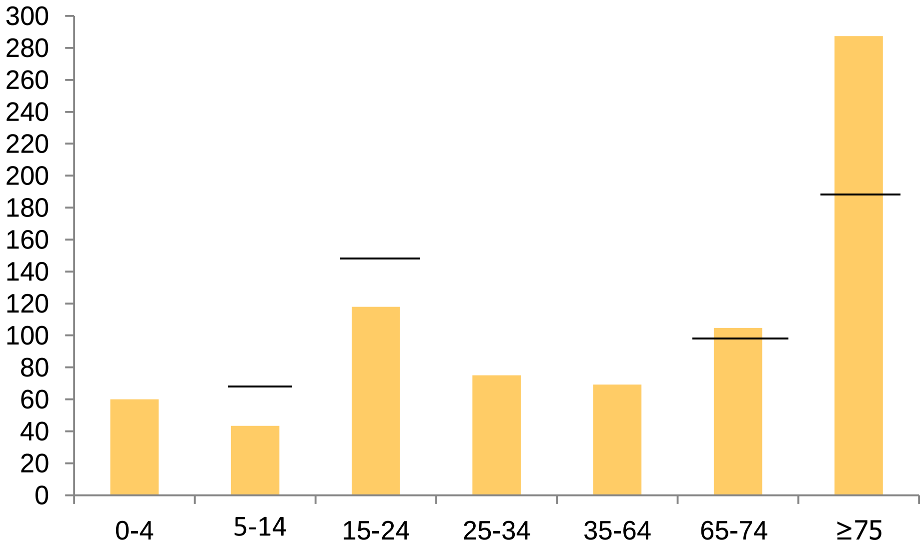
What can we do to improve outcomes for older adults following TBI?

Traumatic Brain Injury in Older Adults

- >25% of all TBIs in the US occur among adults 65 and older
- More than 75% of these are considered "mild" head injuries Frieden et al. (2015) TBI in the US: ED Visits Hospitalizations and Deaths
- Age-adjusted rates of TBI in older adults significantly higher than the general population
  - Highest rates of death and hospitalization
  - In 2014, more than 25% of US TBI related deaths and hospitalizations were in persons 65+ though only 13% of population CDC, MMWR (2017)

Comparing Rates of Hospitalization from TBI 1994 and 2003





CDC Report to Congress 1999; MMWR, March 2, 2007 / 56(08);167-170

Traumatic Brain Injury in Older Adults: Epidemiology, Outcomes, and Future Implications

Hilaire J. Thompson, PhD,[*] Wayne C. McCormick, MD, MPH,[†] and Sarah H. Kagan, PhD[‡]

Traumatic brain injury (TBI) is a significant problem in older adults. In persons aged 65 and older, TBI is responsible for more than 80,000 emergency department visits each year; three-quarters of these visits result in hospitalization as a result of the injury. Adults aged 75 and older have the highest rates of TBI-related hospitalization and death. Falls are the leading cause of TBI for older adults (51%), and motor vehicle traffic crashes are second (9%). Older age is known to negatively influence outcome after TBI. Although geriatric and neurotrauma investigators have identified the prognostic significance of preadmission functional ability, comorbidities, sex, and other factors such as cerebral perfusion pressure on recovery after illness or injury, these variables remain understudied in older adults with TBI. In the absence of good clinical data, predicting outcomes and providing care in the older adult population with TBI remains problematic. To address this significant public health issue, a refocusing of research efforts on this population is justified to prevent TBI in the older adult and to discern unique care requirements to facilitate best patient outcomes. J Am Geriatr Soc 54:1590–1595, 2006.

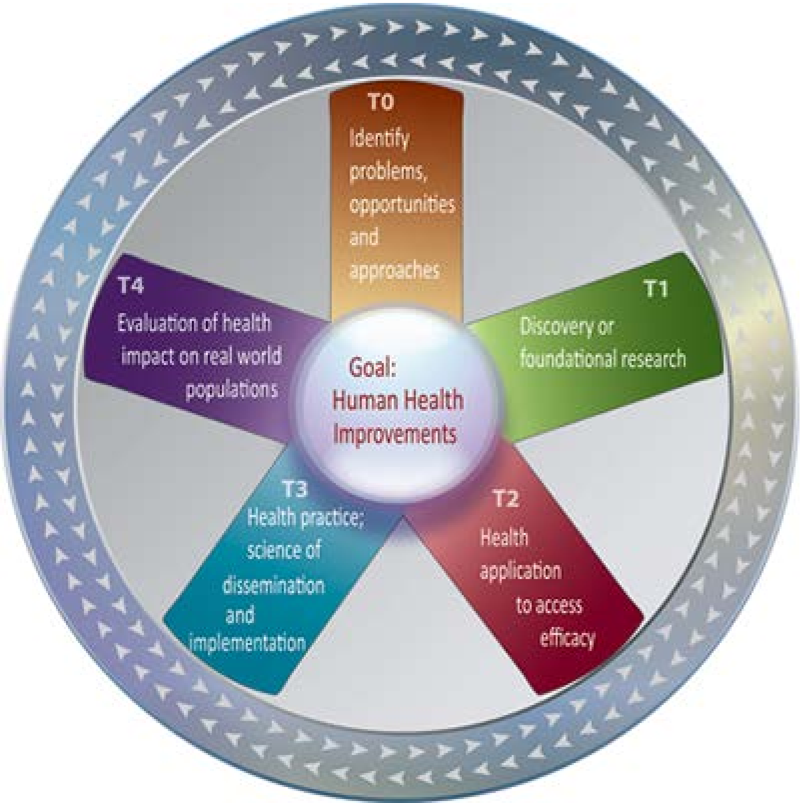
Key words: traumatic brain injury; head injury; geriatric; trauma; injury; epidemiology; outcomes; functional status

ity,[5] the presence of comorbidities,[6,7] sex,[8] and other factors such as cerebral perfusion pressure (CPP)[9] on recovery after illness or injury, these variables remain understudied in older adults with TBI. The relative neglect of these variables in neuroscience research may partially explain why predicting outcomes and providing care in the older adult population with TBI remains so problematic. The current "one size fits all" approach to management of adults with TBI often neglects the special issues of the older adult. This review addresses the epidemiology of TBI in older adults and factors affecting patient outcomes, focusing on the implications of the current state of knowledge and identifying areas for future research and clinical inquiry.

EPIDEMIOLOGY

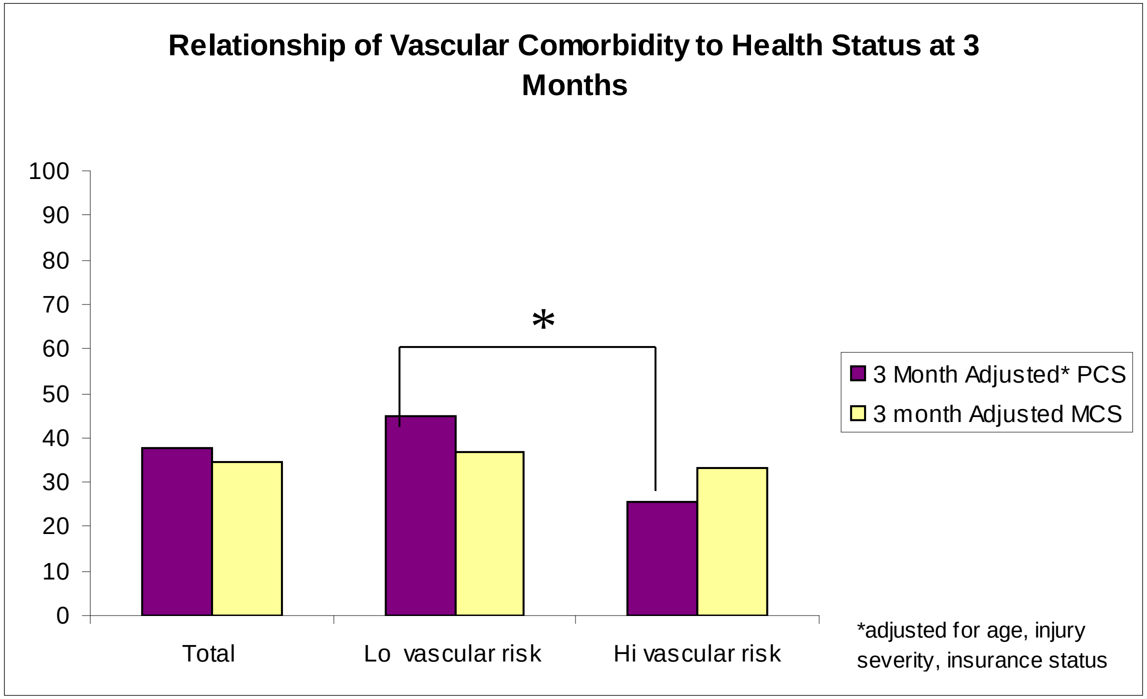
In persons aged 65 and older, TBI is responsible for more than 80,000 emergency department visits each year, approximately three-quarters of which result in hospitalization.[10] The age-adjusted rate of hospitalization for nonfatal TBI in the general population is 60.6 per 100,000 population;[11] for adults aged 65 and older, this rate more than doubles—to 155.9.[12]

Falls are the leading cause of TBI for older adults (51%), and motor vehicle crashes (MVCs) (pedestrian or



What is the effect of co-morbidity?

Decreased function in patients with vascular comorbidies



Thompson et al. 2007 J Neurotrauma

Comorbidity in Trauma Patients: the MoRT Study

- Individual comorbidities are prevalent in trauma patients
- Presence not predictive of mortality at discharge
- At 1 year, prediction improves, suggesting contributes more to mortality in the post-acute phase, offering an opportunity for improvement in care

Development and Validation of the Mortality Risk for Trauma Comorbidity Index

Hilaire J. Thompson, PhD, RN, FAAN, Frederick P. Rivara, MD, MPH,† Avery Nathens, MD, PhD, FACS,‡ Jin Wang, PhD,§ Gregory J. Jurkovich, MD, FACS,¶ and Ellen J. Mackenzie, PhD‖*

Objective: The aim of this study was to develop and validate a comorbidity index to predict the risk of mortality associated with chronic health conditions following a traumatic injury.

Summary Background Data: Currently available comorbidity adjustment tools do not account for certain chronic conditions, which may influence outcome following traumatic injury or they have not been fully validated for trauma. Controlling for comorbidity in trauma patients is becoming increasingly important as the population ages and elderly patients are more active, as well as to adjust for bias in trauma mortality studies.

Methods: Cohort study using data from the National Study on the Costs and Outcome of Trauma. Subject pool (N = 4644/Weighted Number = 14,069) was randomly divided in half; the first half of subjects was used to derive the risk scale, the second to validate the instrument. To construct the Mortality Risk Score for Trauma (MoRT), univariate analysis and odds ratios were performed to determine relative risk of mortality at hospital discharge comparing those persons with a comorbid condition to those without. Conditions significantly associated with mortality ($P < 0.05$) were included in the multivariate model. The variables in the final model were used to build the MoRT. The predictive ability of the MoRT and the Charlson Comorbidity Index (CCI) for discharge and 1-year mortality were estimated using the c-statistic in the validation sample.

Results: Six comorbidity factors were independently associated with the risk of mortality and formed the basis for the MoRT: severe liver disease, myocardial infarction, cerebrovascular disease, cardiac arrhythmias, dementia, and depression. The MoRT had a similar overall discrimination as the CCI for mortality at hospital discharge in injured adults (c-statistic: 0.56 vs. 0.56) although neither by itself performed well. The addition of age and gender improved the predictive ability of the MoRT (0.59; 95% CI: 0.56, 0.62) and the CCI (0.59; 0.56, 0.62). Similar results were seen at 1-year postinjury. The further addition of Injury Severity Score significantly improved the predictive ability of the MoRT (0.77, 95% CI: 0.74, 0.79) and the CCI (0.77, 95% CI: 0.75, 0.80).

Conclusions: The MoRTs primary advantage over current instruments is its parsimony, containing only 6 items. In the present study, the comorbid conditions found to be predictive of mortality had some overlap with the CCI, but this study identified 2 novel predictors: cardiac arrhythmias and depression. Inclusion and reporting of these items within trauma registries would therefore be an important step to allow further validation and use of the MoRT.

(*Ann Surg* 2010;252: 370–375)

The issue of comorbidity in traumatic injury is becoming increasingly important with the "graying" of the population, as in the United States, approximately 80% of all persons aged ≥65 years have at least 1 chronic condition, and 50% have at least 2.[1] The age-adjusted prevalence of diabetes, which increased 43% in the United States during 1997–2005 from 3.7% to 5.3%,[2] is a clear example of the potential synergy of preexisting health conditions in traumatic injury. There is an association between diabetes and risk for injury and an association between glucose regulation and outcome, including mortality following injury.[3–6] Additionally in adults, resuscitation efforts following a traumatic injury are frequently made more complex because of the high incidence of comorbid conditions, such as diabetes and hypertension, which may affect the responsiveness and perfusion needs of the vasculature. The presence of comorbid health conditions may be associated with difficulty diagnosing new conditions or adverse responses to therapeutic interventions,[7] which may result in complications.

Trauma patients with certain comorbid health conditions have been shown to be at higher risk for development of secondary complications (eg, pneumonia), lengthened overall hospital stay, and increased mortality.[8,9] In comparative effectiveness studies of trauma, it is therefore important to control for comorbidity to reduce the treatment bias resulting from conditions other than the injury itself[10] and to avoid inappropriate assignment of disease burden to injury.[11] Currently available comorbidity adjustment tools, such as

Are we obtaining accurate history?

- 15.3% of subjects had no data recorded regarding medical history in records (Thompson et al., 2012)
- 81% of patients with a documented history had at least 1 pre-injury condition
- absence of history and usual medications may delay or complicate diagnosis and treatment in older trauma patients(Norris, et al., 2008).

What is the role of provider in geriatric TBI outcomes?

Evaluation of the effect of intensity of care on mortality after traumatic brain injury

Hilaire J. Thompson, PhD, RN; Frederick P. Rivara, MD, MPH; Gregory J. Jurkovich, MD; Jin Wang, PhD; Avery B. Nathens, MD, PhD; Ellen J. MacKenzie, PhD

Objectives: To evaluate the effect of age on intensity of care provided to traumatically brain-injured adults and to determine the influence of intensity of care on mortality at discharge and 12 months postinjury, controlling for injury severity.

Design: Cohort study using the National Study on the Costs and Outcomes of Trauma (NSCOT) database. Risk ratio and Poisson regression analyses were performed using data weighted according to the population of eligible patients.

Setting and Patients: A total of 18 level 1 and 51 level 2 non-trauma centers located in 14 states in the United States and 1,776 adults aged 25–84 yrs with a diagnosis of traumatic brain injury.

Measurements: Injury severity was determined by the motor component of the Glasgow Coma Scale score, the Injury Severity Score, pupillary reactivity, and presence of midline shift. Factors evaluated as contributing to intensity of care included: admission to the intensive care unit, mechanical ventilation, placement of an intracranial pressure monitor, placement of a jugular bulb catheter, placement of a pulmonary artery catheter, critical care consultation, the number of specialty care consultations, mannitol use, treatment with barbiturate coma, decompressive craniectomy, number of nonneurosurgical procedures performed, the presence of a do-not-resuscitate order, and withdrawal of therapy.

Main Results: Controlling for injury-related factors, sex, and comorbidity, as age increased, the overall likelihood of receiving various interventions decreased. After controlling for injury severity, sex, and comorbidity, factors associated with higher risk of in-hospital death were: being aged 75–84 yrs (relative risk [RR] 1.32, 95% confidence interval [CI] 1.13, 1.55), pulmonary artery catheter use (RR 1.56, 95% CI 1.30, 1.86), intubation (RR 4.17, 95% CI 2.28, 7.61), the presence of a do-not-resuscitate order (RR 3.21, 95% CI 2.21, 4.65), and withdrawal of therapy (RR 2.33, 95% CI 1.69, 3.23). In contrast, a higher number of specialty care consultations (surgical consults: RR 0.63, 95% CI 0.54, 0.74; medical consults: RR 0.87, 95% CI 0.79, 0.95; and other consults: RR 0.43, 95% CI 0.26, 0.69) were associated with decreased risk of death. The results were similar for factors associated with death at 12 months, with the exception that the number of medical consultations was not significant, whereas the number of nonneurosurgical procedures performed was associated with lower risk of death (RR 0.96, 95% CI 0.92, 0.99), as was obtaining critical care consultation services (RR 0.84, 95% CI 0.71, 1.0).

Conclusions: There is a lower intensity of care provided to older adults with traumatic brain injury. Although the specific contributions of specialists to patient management are unknown, their consultation was associated with decreased risk of in-hospital death and death within 12 months. It is important that careproviders have an increased awareness of the potential contribution of multidisciplinary clinical decision making to patient outcomes in older traumatically brain-injured patients. (Crit Care Med 2008; 36:282–290)

KEY WORDS: head injury; critical care consultation; specialty care consultation; pulmonary artery catheter; older adult

Unadjusted Distribution of Intensity of Care to TBI Patients

	25-54 years	55-64 years	65-74 years	75-84 years	
Care Provided	%	%	%	%	P
Designated Trauma Center					
Yes	79.3	76.9	71.5	53.1	<0.0001*
No	20.7	23.1	28.5	46.9	
Intracranial Pressure Monitoring					0.002*
Yes	16.8	13.5	9.2	8.1	
No	83.2	86.5	90.8	91.9	
Critical care consult					0.11
Yes	20.8	28.9	17.9	18.9	
No	79.2	71.1	82.1	81.1	

JOURNAL OF NEUROTRAUMA 29:1864–1871 (July 1, 2012)

DOI: 10.1089/neu.2011.2284

Utilization and Costs of Health Care after Geriatric Traumatic Brain Injury

Hilaire J. Thompson,[1,2] Sharada Weir,[3] Frederick P. Rivara,[2] Jin Wang,[2] Sean D. Sullivan,[4] David Salkever,[5] and Ellen J. MacKenzie[6]

Abstract

Despite the growing number of older adults experiencing traumatic brain injury (TBI), little information exists regarding their utilization and cost of health care services. Identifying patterns in the type of care received and determining their costs is an important first step toward understanding the return on investment and potential areas for improvement. We performed a health care utilization and cost analysis using the National Study on the Costs and Outcomes of Trauma (NSCOT) dataset. Subjects were persons 55–84 years of age with TBI treated in 69 U.S. hospitals located in 14 states ($n=414$, weighted $n=1038$). Health outcomes, health care utilization, and 1-year costs of care following TBI in 2005 U.S. dollars were estimated from hospital bills, patient surveys, medical records, and Medicare claims data. The subjects were further analyzed in three subgroups (55–64, 65–74, and 75–84 years of age). Unadjusted cost models were built, followed by a second set of models adjusting for demographic and pre-injury health status. Those in the oldest category (75–84 years) had significantly higher numbers of re-hospitalizations, home health care visits, and hours per week of unpaid care, and significantly lower numbers of physician and mental health professional visits than younger age groups (age 55–64 and 65–74 years). Significant age related differences were seen in all health outcomes tested at 12 months post-injury except for incidence of depressive symptoms. One-year total treatment costs did not differ significantly across age categories for brain-injured older adults in either the unadjusted or adjusted models. The unadjusted total mean 1-year cost of care was $77,872 in persons aged 55–64 years, $76,903 in persons aged 65–74 years, and $72,733 in persons aged 75–84 years. There were significant differences in cost drivers among the age groups. In the unadjusted model index hospitalization costs and inpatient rehabilitation costs were significantly lower in the oldest age category, while outpatient care costs and nursing home stays were lower in the younger age categories. In the adjusted model, in addition to these cost drivers, re-hospitalization costs were significantly higher among those 75–84 years of age, and receipt of informal care from friends and family was significantly different, being lowest among those aged 65–74 years, and highest among those aged 75–84 years. Identifying variations in care that these patients are receiving and determining the costs versus benefits is an important next step in understanding potential areas for improvement.

Health Care Utilization

Variable	Age 55-64	Age 65-74	Age 75-84	p-value
Number of re-hospitalizations or nursing home stays	0.23(1.31)	0.28(1.16)	0.55(1.55)	0.03[#,$]
Number of physician visits related to injury	2.4(10.2)	1.9(4.2)	0.9(2.8)	0.002[#,$]
Number of mental health professional visits	0.81(5.46)	0.18(1.47)	0.06(0.65)	0.04[#]
Receipt of paid home health care: # weeks receiving home health	0.08(0.94)	0.26(1.41)	0.66(2.04)	<0.0001[#,$]
Receipt of care from friends or family: average number of hours on unpaid care/week	1.5(6.6)	2.2(7.6)	3.5(10.1)	0.02[#,$]

What is the role of biology?

Inflammation, Aging and TBI

- **Inflammation** is one of the primary responses to **TBI**
- **Aging** associated with chronic low-level pro-inflammatory state
- ↑in cytokines associated with conditions of aging are related to ↑increased morbidity and mortality

10 Most Prevalent Symptoms Endorsed at 1-week Post-injury by Older and Younger Adults Post-TBI

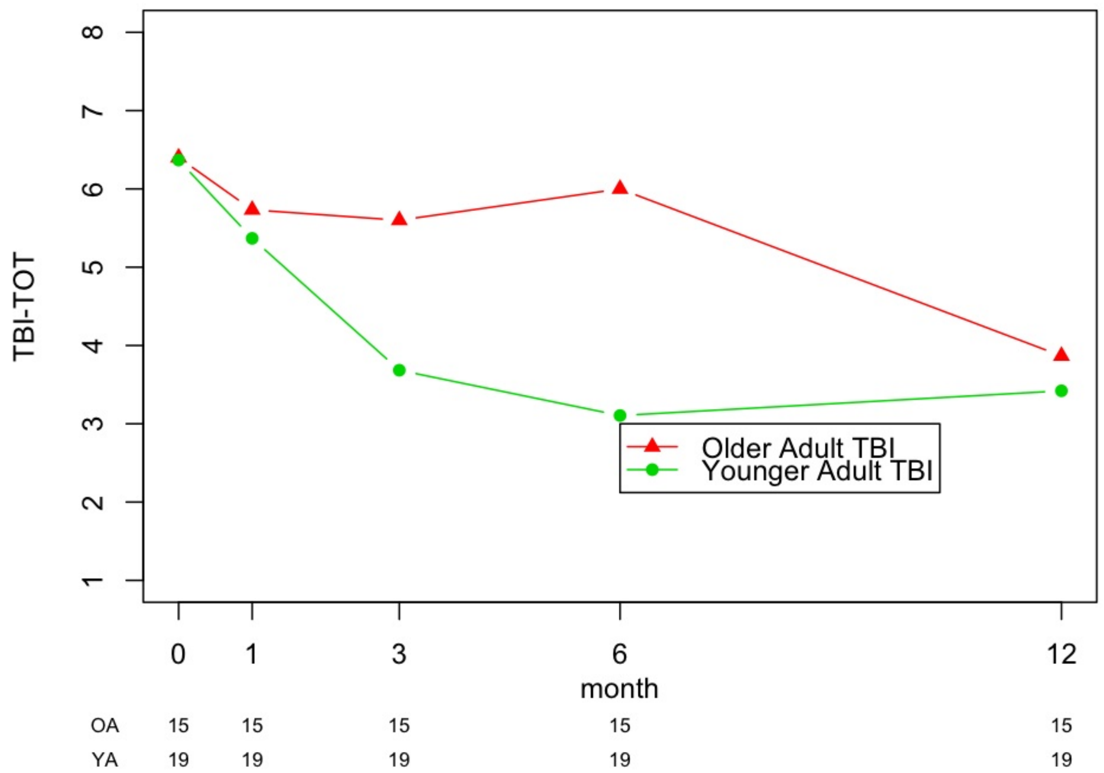
YOUNGER-PREVALENT SYMPTOMS

1. **Headache** (58%)
   Balance
3. Irritability (53%)
4. Fatigue (47%)
5. Dizziness (47%)
6. **Anxiety** (42%)
   Trouble concentrating
   Blurry vision
   Trouble sleeping
   Taste

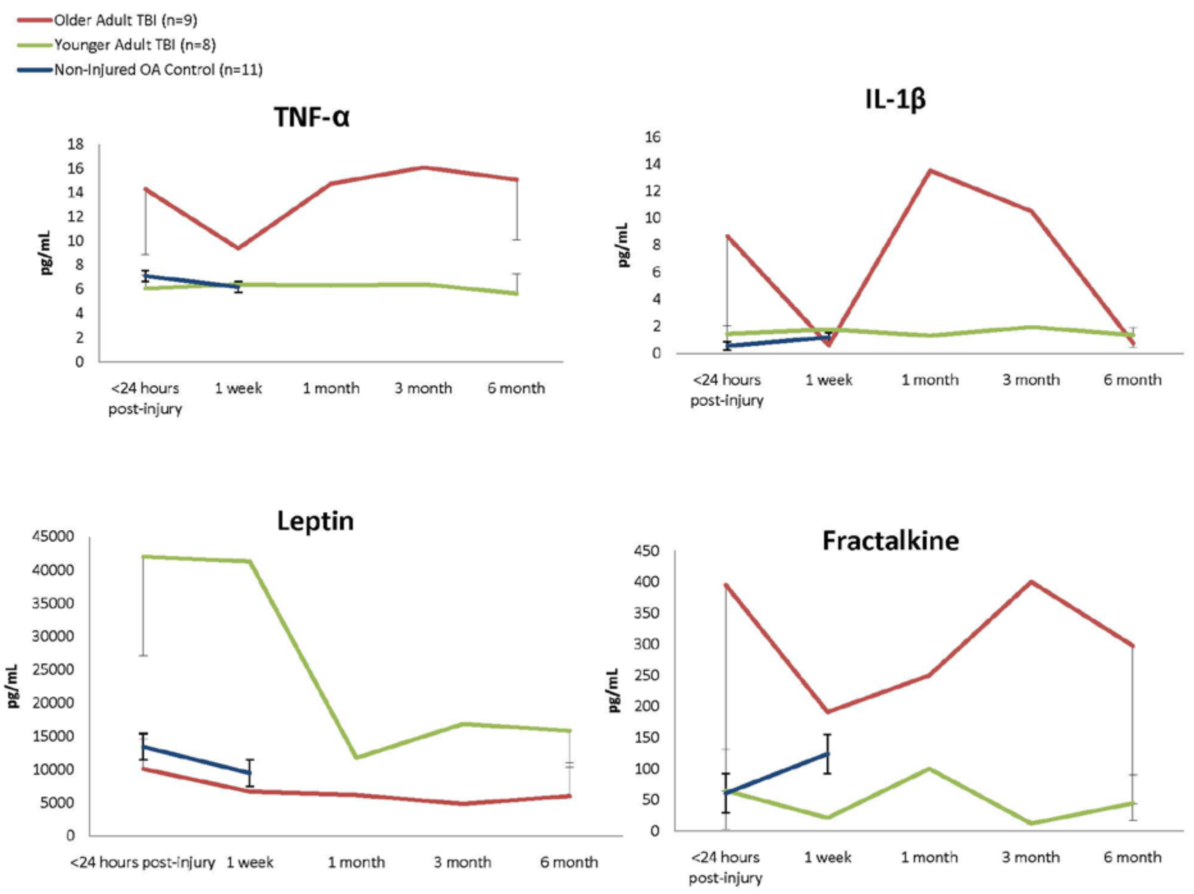
OLDER-PREVALENT SYMPTOMS

1. Balance (73%)
2. Fatigue (67%)
3. Dizziness (60%)
4. Trouble sleeping (53%)
5. **Memory difficulties** (47%)
   Irritability
7. Blurry vision (40%)
   Trouble concentrating
9. **Bothered by light** (33%)
   Taste

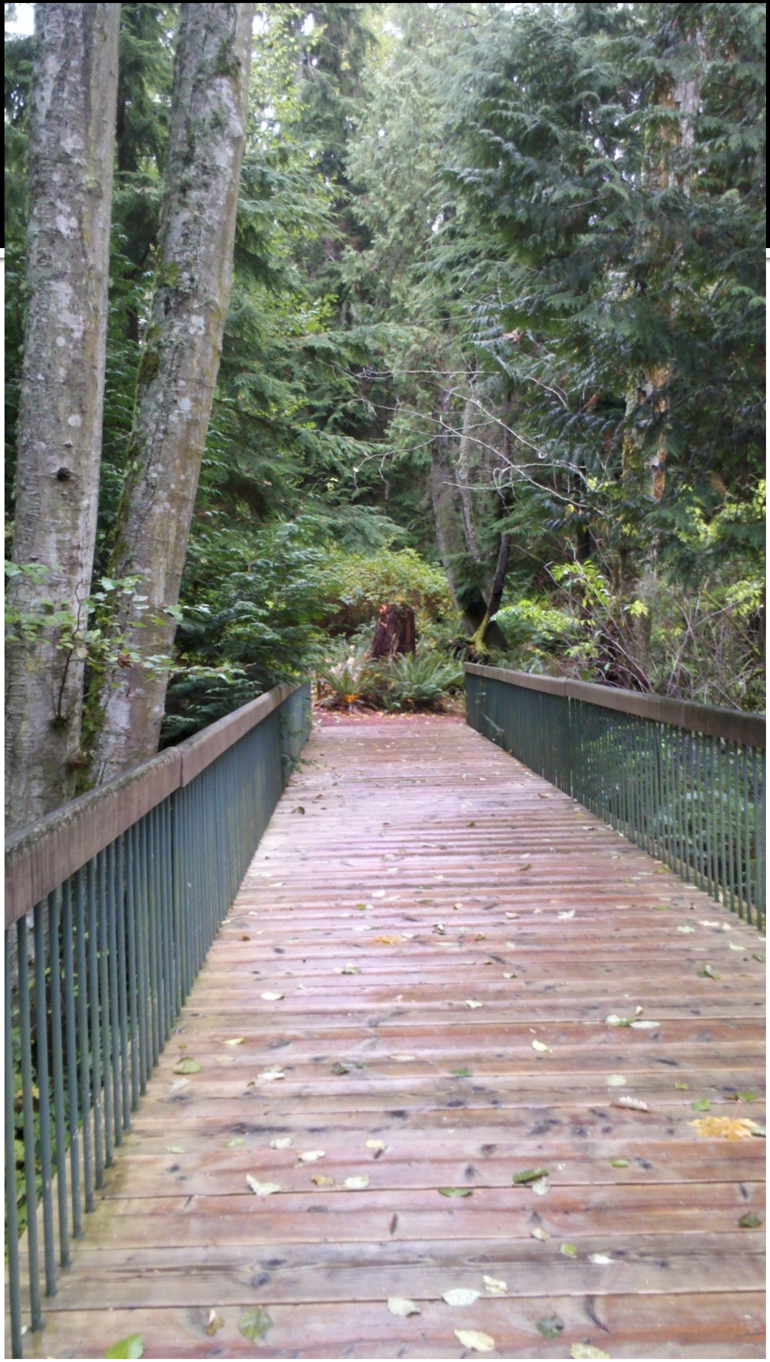
Total number of symptoms (HISC)



Inflammatory Markers



The Path Forward



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