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14. ABSTRACT

The Purpose of the proposal titled "Characterization and Application of a Large Animal Model of Penetrating Ballistic Brain Injury (PBBI)" is to develop a large animal model with military relevance. Of military casualties with moderate to severe traumatic brain injuries (TBI) 15-18% are due to penetrating mechanisms. Almost all (97%) of prospective clinical trials of TBI exclude patients with PBBI and no prospective clinical trials specifically focus on PBBI. A large animal model of PBBI will enable the initial assessment of products and procedures that were developed for blunt TBI to be assessed for safety and efficacy in a penetrating model. This project will characterize the profiles of PBBI's physiology and histopathology with increasing magnitudes of injury. The investigators hypothesize that in swine, PBBI will cause tissue damage, inflammation and coagulopathy, and that the extent of these changes will depend on the percent of cavitation related to brain volume. Animal use approvals have been obtained and initial studies have been completed in Yorkshire swine to develop the model and verify assays and antibodies. The project is on schedule and is currently undergoing further studies in the Sinclair swine.

15. SUBJECT TERMS
PENETRATING, TRAUMA, BALLISTIC, INJURY

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INTRODUCTION

The Purpose of the proposal titled "Characterization and Application of a Large Animal Model of Penetrating Ballistic Brain Injury (PBBI)" is to develop a large animal model with military relevance. Of military casualties with moderate to severe traumatic brain injuries (TBI) 15-18% are due to penetrating mechanisms. Almost all (97%) of prospective clinical trials of TBI exclude patients with PBBI and no prospective clinical trials specifically focus on PBBI. A large animal model of PBBI will enable the initial assessment of products and procedures that were developed for blunt TBI to be assessed for safety and efficacy in a penetrating model. This project will characterize the profiles of PBBI's physiology and histopathology with increasing magnitudes of injury. The investigators hypothesize that in swine, PBBI will cause tissue damage, inflammation and coagulopathy, and that the extent of these changes will depend on the percent of cavitation related to brain volume.

BODY

In Year 1, the Scope of Work for this project is:

- *Obtain animal use approval and modify personnel contracts*
- *Preliminary logistical and engineering studies in animals (6)*
- *Start the studies as to the extent of injury on brain damage and coagulation in the additional animals (24).*

Upon funding in March of 2011, an extensive review of clinical data pertaining to PBBI was conducted and organized into a review manuscript. (Santiago LA, Oh BC, Dash PK, Holcomb JB, Wade CE. A clinical comparison of penetrating and blunt traumatic brain injuries. *Brain Inj.* 2012; 26 (2): 107-25.) Instrumentation development and refinement occurred in coordination with WAIR from August to December 2011.

Animal use approval was obtained in July 2010 and renewed on October 21, 2010 ; all personnel and equipment were in place to begin studies immediately. The initial animal experiments were carried out in Yorkshire swine from October 2011 to February 2012 (Figs. 1-3). Antibodies were used to examine the histological consequences of PBBI (Fig. 4). A variable dose design was chosen (Fig. 3). The primary statistical test employed will be ANOVA with comparison between doses and, where appropriate, adjusted for repeated measures over time. It is noted that PBBI may cause dendritic and axonal disturbances, as well as changes in astrocyte localization/morphology reminiscent of glial scar formation (Fig. 4). Additional cadaver studies were conducted in Sinclair miniature swine.

As there were differences found between injury and control models, the next step is to initiate studies in Sinclair miniature swine at four injury levels. Four doses of cavitational injury will be: 0, 2.5, 5, and 7.5% of brain volume. These are adjusted from the preliminary findings. Further histological, coagulation and biochemical analysis will enable the development of a full characterization of the model and injury. In addition, computed tomography and diffuse tensor imaging will be used to complete the physiological analysis.

KEY RESEARCH ACCOMPLISHMENTS

- The large animal model was established and refined in Yorkshire swine (see Supporting Data below).
- Antibodies and assays were refined and established for the swine model and will not be used for all future experimental evaluations.
- A dose response was observed between the severity of cavitational injury and the assessment of histopathology and physiological damage.
- Experiments have begun on the Sinclair miniature model

REPORTABLE OUTCOMES

- Accepted publication of clinical review of PBBI (Manuscript is Appendix 1)
- Completed personnel contracts and training (Related CVs are Appendix 2)
- Received animal use approval (Appendix 3)
- Completed instrumentation development and refinement
- Completed preliminary studies in Yorkshire swine (see Supporting Data below)
- Initiated additional studies in Sinclair miniature swine

CONCLUSION

The experiments are on schedule to continue in the Sinclair model. The preliminary experiments does a "dose response" to injury and initial histology and pathology reports are providing more detail on the track of injury and the biologic responses. Markers and assays are validated for swine tissue, so future will move forward as planned in the original scope of work. This work is vital to the investigation of penetrating traumatic injuries. Upon the completion of these studies, a large animal model will be characterized an validated, so that it can be used to research future treatments and protocols.

Future Budget

As the project as developed, several adjustments have been made to the budget without changing the scope of work. Instead of finding a Neurosurgeon collaborator, we have enlisted the full time help of a postdoctoral fellow, Juan Malo. This did increase our overall personnel budget line for YR 1 (Total Personnel Cost YR 1), however, his expertise and dedication to the project allowed us to save on our supply and equipment expenditures (Total Supply and Equipment costs YR 1). One trip was charged at a cost of . And F&A Costs for YR 1 will be approximately . Bringing the total for Year 1 to which is under budget (Original YR 1 =). Any estimations are due to the fact that the year will close after this report has been submitted, but changes will be minimal.

Thus, based upon the experiments and needs of the project from Year 1, we have realigned our Year 2 budget (Appendix 4) as follows and request approval for our plan.

Personnel. The Salary Support will remain at current levels and be maintained through
2013 for all personnel except for Ms. Lisa Baer, the Research Manager, John R. Salsbury, Animal Surgeon and Anthony Moore, a Research Coordinator. Now that the models and protocols have been established, less oversight and work is needed from these personnel. Ms. Baer will be reduced from 50% to 30%, Mr. Salsbury will go form 30% to 25% and Mr. Moore will go from 50% to 25%. The other named personnel include:

- Dr. Charles Wade, PI, 10%
- Dr. John Holcomb, Co-I, 2%
- Dr. Pramod Dash, Co-I, 15%
- Juan Malo, Postdoctoral Fellow, 100%
- Nena Matijevic, Co-I, 2%

Equipment. No future equipment will be purchased

Travel. For Travel, is assigned for Year 2 to cover travel to DC for trainings and briefings or other relevant scientific conferences concerning this research project.

Supplies and Other Costs. For costs related to assays and biomarkers, is allocated for YR 2. And additional will be used for animal and surgical costs. Diffusion tensor imaging will also be completed in YR 2 and will require . Finally, the coagulation panel of Assays will costs per time point and we estimate that 14 time points will be used per animal for a total of this year.

Thus, will be used in YR 2 to complete this project. F&A costs are calculated at 53% and will come to . *For a TOTAL of.*

We will remain on budget, and should any further clarification or information be needed, please contact Xiang Fang (Xiang.Fang@uth.tmc.edu, 713-500-5428).

REFERENCES: Santiago LA, Oh BC, Dash PK, Holcomb JB, Wade CE. A clinical comparison of penetrating and blunt traumatic brain injuries. *Brain Inj.* 2012; 26 (2): 107-25.

APPENDICES

Appendix 1– Manuscript Proof

Appendix 2 – Added Personnel CV (Malo)

Appendix 3 – Animal Use Approval

Appendix 4 – Budget

SUPPORTING DATA

Figure 1. The cavitational injury is compared below. Our PBBI model is verified in Yorkshire swine. Our protocol can induce moderate to severe injury as evidenced above. We will use Sinclair miniature swine in future efforts.
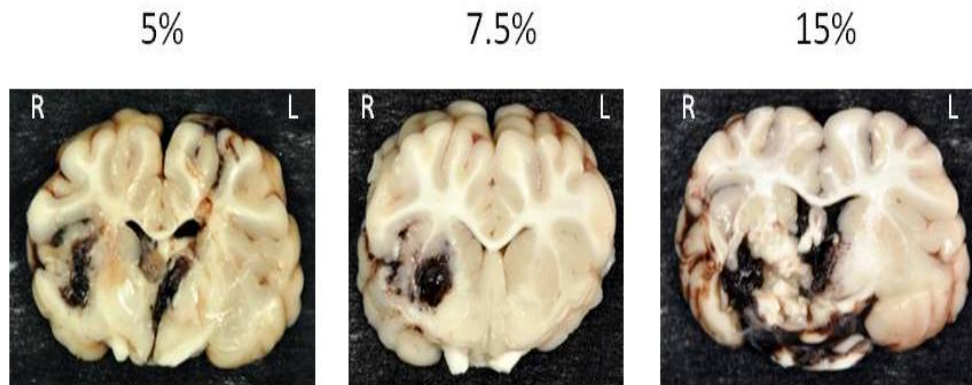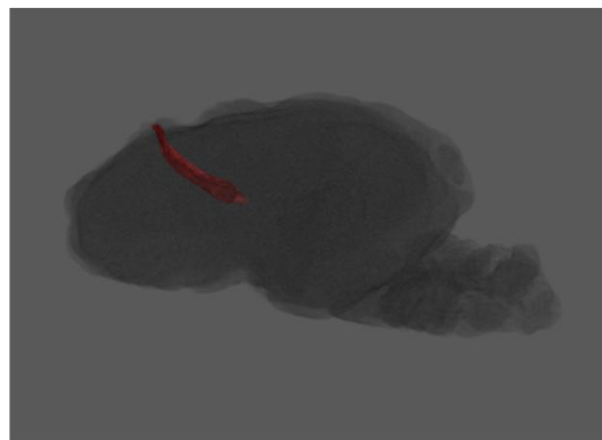

Figure 2. The track of the cavitational injury is shown below. The track is able to be assessed in order to ensure the correct percentage of cavitational injury is produced and in the correct region of the brain.

CT SCAN 7.5% CAVITATIONAL INJURY

- Injury Track volume: 117.6 mm3 (1.2%)
- Whole Brain volume: 98,655.7 mm3 (100%)
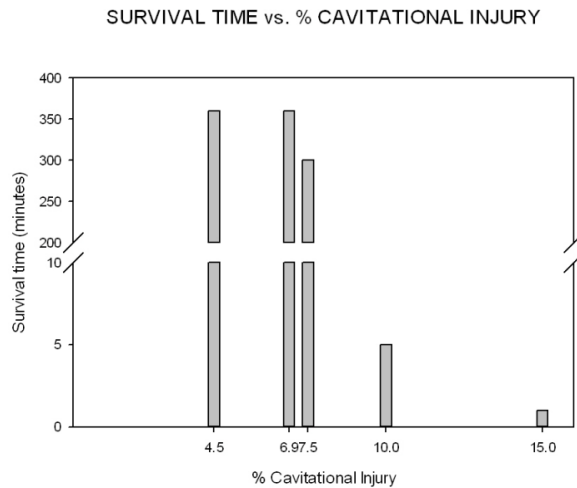
SURVIVAL TIME vs. % CAVITATIONAL INJURY

Figure 3. The level of cavitational injury is compared to the survival time of the animal model. An inverse relationship is observed between the severity of injury and the length of survival. The higher the percentage of cavitaitonal injury is to the brain volume, the shorter the survival time.

Figure 4. Immunoflouresce was used to classify the injury on a Yorkshire swine with a 6.9% caviational injury. Uninjured sections (Left) are compared to injured sections (Right). MAP2 (microtubule-associated protein 2) identifies the structure of the dendritic strution of the hippocampus. The white arrow indicated a disruption in the staining, suggesting damage. Glial fibrillary acidic protein (GFAP) and Amyloid precursor protein (APP) staining both show an increase in expression with injury. The increase in GFAP indicates glial activation and the increase in APP suggests increased axonal damage.

6.9% CAVITATIONAL INJURY LEVEL
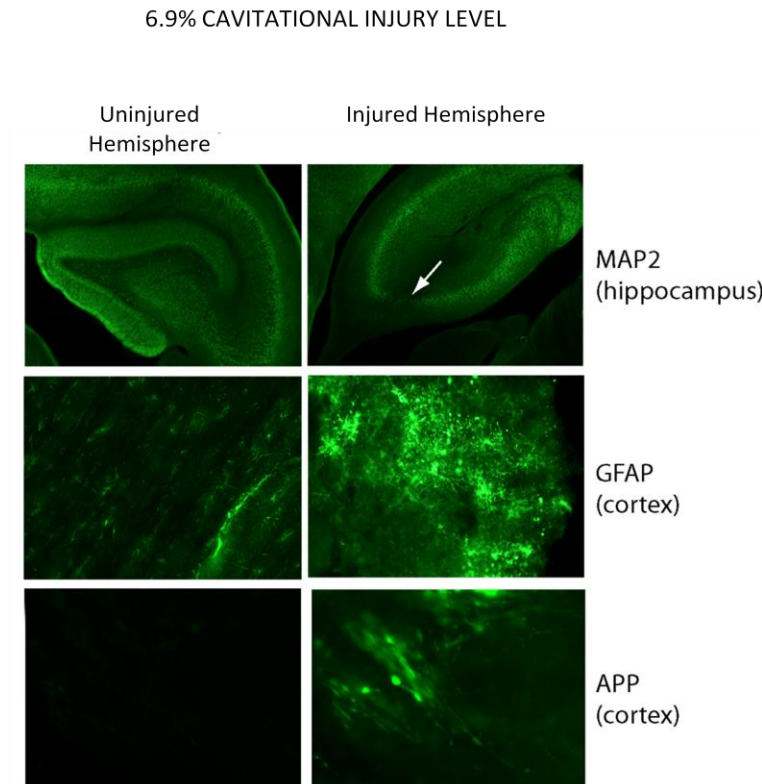
Appendix 1

REVIEW

A clinical comparison of penetrating and blunt traumatic brain injuries

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Abstract

Background: Traumatic brain injury (TBI) is a leading cause of injury death and long-term disability in the USA. It commonly results from blunt (closed) or penetrating trauma. The majority of civilian TBI is caused by falls or motor vehicle collisions, whereas military TBI mainly results from explosions. Although penetrating injuries are less common than closed injuries in the civilian population, they are far more lethal. Unfortunately, the pathophysiologic differences between penetrating and closed TBI remain poorly understood due to the lack of studies on the subject. Many studies on the prognostic factors of mortality and functional outcome after TBI exclude penetrating brain injuries from their series because they are believed to have a different pathophysiology.
Methods: 125 Articles regarding brain injury were reviewed and summarized for this report.
Results: Despite the absence of a clear delineation between penetrating and blunt TBI, the current guidelines for penetrating TBI suggest defaulting to management strategies used for closed TBI with limited supportive evidence. Thus, injuries that appear to have different pathophysiologies and outcomes are managed equally and perhaps not optimally.
Conclusion: In view of the incomplete understanding of the impact of mechanism of injury on TBI outcomes, as demonstrated in the current review, new research studies are required to improve evidence-based TBI guidelines tailored especially for penetrating injuries.

Keywords: *Trauma, head trauma, adult brain injury, epidemiology, human studies*

Introduction

Traumatic brain injury (TBI) is most commonly caused by two mechanisms of injury, blunt and penetrating trauma. In blunt TBI, a concussive mechanical force is imparted to the head through direct contact with a blunt object, an inert broad surface or a rapidly expanding fluid wave. Such a force produces a rapid acceleration and/or deceleration of the head, which may result in scalp lacerations, depressed skull fractures, diffuse brain swelling and intracranial haematomas. Alternatively, penetrating TBI results when a moving projectile or a sharp inanimate object fractures the cranium, perforates the meninges, lacerates and crushes the brain parenchyma along its trajectory and exposes the cranial vault to the external environment. Penetrating TBI differs fundamentally from blunt TBI in that the dura mater is perforated by trauma. This clinical difference may be explained by the distinct kinetics of two different mechanisms of injury. Unlike a blunt object (e.g. car steering wheel or baseball bat), which presents a relatively large contact area to the surface of the head, a projectile (e.g. bullet or shrapnel) presents a small contact area

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that allows high-pressure tissue penetration. Despite their mechanistic differences, closed and penetrating TBIs may share common pathologic features in humans.

In the late 19th century, Horsley reported hypotension, respiratory depression and increased intracranial pressure (ICP) in two different canine models, one for concussion and another for penetrating ballistic brain injury [1–3]. He attributed these pathologic effects to Duret's 'choc cephalorachidien', a mechanism by which the respiratory and vagal centres of the medulla oblongata were compressed by the displacement of the brain and the crushing effect of the cerebrospinal fluid via the ventricular system. Despite the similarities observed in these experiments, ballistics studies [2, 4–7] from the same period described injury characteristics unique to penetrating TBI. Tissues were disrupted by projectiles in a variety of ways, including the deformation of projectiles after skull collision, the creation of secondary projectiles from bullet or bone fragments, the formation of a permanent cavity after crushing of the soft tissues and the powerful expansion of a temporary cavity [4].

Now, more than a century later, the lack of studies on the pathophysiology of penetrating TBI and the exclusion of penetrating injuries from a large TBI series [8–17] has rendered the clinician unable to estimate the effect of many clinical features of penetrating TBI outcomes. Currently, no prospective multi-centre study has evaluated the independent effect of hypotension on penetrating TBI mortality using multivariate regression modelling, even though several single-centre retrospective studies have shown that hypotension has a frequency of 10–50% [18–21] and that it correlates with increased mortality. In addition, the frequency and clinical characteristics of intracranial hypertension in penetrating TBI remain poorly understood because few of these patients (13–24%) actually receive ICP monitoring [18, 19]. Similarly, the patterns of intracranial injury in penetrating TBI are not fully characterized, since only 59–70% of patients arriving alive to the hospital are evaluated with a head computed tomography (CT) scan [18, 22]. Of note, the literature often attributes such an inconsistent use of ICP monitoring and CT scanning to the patient's expectant death, brain death or the assumption that metallic fragments will preclude a radiological diagnosis due to imaging artifacts. Nevertheless, a formal evaluation of the criteria used for ordering these tests is currently lacking and should be further investigated. It is also important to elucidate whether clinical features such as hypotension, hypoxia, hypocapnia, coagulopathy and intoxication affect the patient's level of consciousness on admission, steering the clinician away from further

evaluation with ICP monitoring and CT scanning. Thus, a comprehensive evaluation of the prognostic value of the aforementioned clinical features could help to improve knowledge of the pathophysiology of penetrating TBI, allowing the clinician to identify potentially survivable injuries in a timely manner.

The main purpose of this review article is to describe the epidemiology, mortality risk factors and long-term outcomes of TBI. A comparison between closed and penetrating brain injuries is also made whenever the evidence allows it. The epidemiology of military TBI is also discussed with an emphasis on the causes of TBI in the recent Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). Finally, a summary and description of the current guidelines for the management of TBI are also presented.

Epidemiology

Traumatic brain injury is a leading cause of injury death and long-term disability in the US. An estimated 1.7 million people sustain a TBI annually, resulting in 1.365 million emergency department (ED) visits, 275 000 hospitalizations and 52 000 deaths [23]. The age-adjusted, annual incidence of TBI-related death is 17.4 persons per 100 000 population, accounting for 30.5% of all injury deaths. Civilian TBI results most commonly from blunt (closed) trauma (88–95%) rather than penetrating trauma (5–12%) [24–28]. Falls and firearms are the main external causes of closed and penetrating TBI, respectively [23, 29–31]. TBIs resulting from falls and motor vehicle-traffic collisions account for the majority of TBI-related, emergency department visits (58%) and hospitalizations (70%) [23]. Overall, it is evident that TBI has a significant impact on healthcare and creates substantial financial burdens for the survivors.

Penetrating injuries are a major aetiology of TBI and a significant cause of injury death [32]. Even though falls account for 18.8% of TBI-related deaths, they only comprise 11.5% of all-cause injury deaths and have a case fatality rate (CFR) of less than 1% [33]. In contrast, penetrating TBIs due to gunshot wounds (GSW) are the leading cause of TBI-related death at 40% (Table I) [34, 35], comprise 15% all-cause injury deaths and have a CFR of 61% [36, 37]. It is also important to note that the CFR of penetrating TBI varies widely according to intentionality. Intentionally self-inflicted injuries have a CFR of 83.1%, whereas assaultive, unintentional and legal intervention injuries have much lower CFRs, namely 41.5%, 22.6% and 16.6%, respectively [37]. The high lethality of self-inflicted penetrating TBI should be of great concern to public health authorities, law

Table I. Annualized rate of TBI-related death in the US (1989–1998), by major external cause [35].

Cause	Rate per 100 000 population (% Total)
Falls	2.1 (10)
Firearms	8.1 (40)
MVT collision	7.0 (35)
Other/unspecified	3.0 (15)
Total	20.2 (100)

enforcement agencies and society in general, because most penetrating injuries are suicidal in nature (47%) [37]. In view of the presented statistics, it is evident that penetrating injuries are far more lethal than blunt injuries.

Penetrating TBI poses a great challenge to regional health systems since the window of opportunity for managing this disease is relatively short. In a study by Siccardi et al. [38], 72% of patients with penetrating injuries died at the scene, while 92% died within 3 hours of injury. Similarly, Cavaliere et al. [39] demonstrated that 88% of patients succumbed within 3 hours of injury. Most recently, Murano et al. [40] reported that 34% of patients were either dead-on-arrival or died during their initial ED evaluation, accounting for 50% of the deaths in their series. Furthermore, an exhaustive review of the literature published prior to 2002 showed that the overall mortality rate of patients with penetrating TBI admitted to neurosurgical centres was 40–79% and that 81–85% of all deaths occurred within 48 hours of admission [18, 19, 41].

The causes of military TBI differ substantially from that of civilian TBI. While the prevailing sources of civilian TBI are falls and motor vehicle-traffic collisions (MVC), the main cause of TBI in the recent conflicts of Iraq and Afghanistan are explosions [42, 43]. Explosions are of great epidemiological importance since they are responsible for 61% of severe TBIs in combat operations [44]. They are capable of inflicting considerable bodily damage through various mechanisms of injury, such as direct exposure to the air pressure wave (primary), impact from objects being propelled by the blast (secondary), being expelled from the explosion site and hitting a stationary object (tertiary) or exposure to hot gases or flames that burn (quaternary) [45–48]. Illustrating the gravity of blasts, Owens et al. [42] reported that 79% of combat casualties (excluding soldiers killed-in-action, KIA) were caused by blasts, whereas 19% resulted from MVCs, and 2% resulted from GSWs. The authors also related that 88% of head and neck wounds were caused by explosions, while 8% resulted from MVCs and 4% from GSWs. In addition to the high proportion of blast-related

casualties, Kelly et al. [49] reported on the increased lethality of blast-related injuries over time. A study that compared two metachronous cohorts of fatally wounded soldiers correlated an increase in the number of killed soldiers per month (35 vs 71) with an increase in the percentage of deaths caused by explosions (56% vs 76%). The authors attributed the mortality rise to the enemy's increased use and/or enhanced lethality of explosive devices.

Unfortunately, the incidence of TBI in the recent OIF and OEF conflicts is not clearly ascertained in the literature, presumably because many cases of mild closed TBI are not detected post-injury and because the bodily distribution of wounds for all combat casualties (e.g. Wounded In Action, Died Of Wounds and KIA) is not reported [42, 50]. Additionally, no study to date reports the number of soldiers with brain injuries per number of servicemen present or, alternatively, per combat unit of time. Despite the lack of a reliable estimate of incidence, several studies do provide an estimate of TBI frequency in military casualties. In a study of combat wounds sustained by 1566 combatants in OIF and OEF (2001–2005), Owens et al. [42] reported that the proportion of head wounds was 8%. They also observed that the proportion of head and neck wounds in these conflicts was higher than that observed in World War II, the Korean war and the Vietnam war (30% vs 16–21%), mainly due to a reduction of thoracic wounds achieved with the use of military personal armour systems [51]. Belmont et al. [50] reported an added increase in the proportion of head and neck wounds (36.2%) during the surge portion of OIF (2003), mainly as a consequence of explosions, and this is consistent with Kelly et al.'s [49] observations.

In regard to the causative mechanisms of military TBI, Wade [44] conducted a preliminary analysis of 5547 combat casualties with documented TBIs and observed 17.4% penetrating injuries, 61.4% blunt injuries and 21.1% primary injuries (e.g. those that were neither classified as penetrating nor blunt). Notably, the frequency of these injury types varies considerably with clinical setting. For instance, Bell et al. [52] studied a population of 408 medically evacuated patients from OIF (2003–2008) who received neurosurgical evaluations at the Walter Reed Medical Center and found that the majority of TBIs (56%) were caused by penetrating trauma. Consistent with other combat wound studies, the authors also reported that explosions caused 71% of penetrating TBIs and 47% of closed TBIs. These data are in sharp contrast with those presented by Warden et al. [53] in a study of 433 veterans diagnosed with TBI at the Defense and Veteran Brain Injury Center (2003–2005). While most TBIs evaluated by the Walter Reed Medical Center's

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neurosurgical service resulted from penetrating trauma (56%), most of those evaluated by the Defense and Veteran Brain Injury Center resulted from blunt trauma (88%). This disparity is largely explained by patient selection biases (e.g. neurosurgical unit or neurology clinic).

Mortality risk factors

Several prognostic factors are used to predict TBI mortality in the acute phase. The most commonly used indicators are the Glasgow Coma Scale (GCS) score [54–56], the pupillary light reflex reaction [19, 41, 57] and CT scan findings [58]. In addition, missile track and mechanism of injury also play a significant role in mortality prediction from TBI. Table II provides a summary of prognostic factors associated with increased acute mortality, some of which are further discussed below.

GCS score

The GCS score is used to assess the patient's level of consciousness on admission or post-resuscitation, with values ranging from 3–15. Using this scale, TBI severity may be classified as mild, moderate or severe if the GCS score falls in the ranges of 13–15, 9–12 or 3–8, respectively. According to Demetriades et al. [24], as many as 70% of TBI cases resulting from both blunt or penetrating trauma are classified as mild (GCS 13–15). Alternatively, the penetrating TBI literature tends to classify injury severity as severe or non-severe on the basis of a GCS ≤ 8 or a GCS > 8, respectively. This choice of dichotomy does not appear to improve the positive predictive value of either group, especially since the probability of death prior to any neurologic evaluation may be as high as 70% [38]. However, regardless of the patient selection bias (e.g. patients admitted alive to the neurosurgical unit), a GCS ≤ 8 still confers a significant mortality to patients with penetrating TBIs, ranging from 51–94% [40, 59]. In the case of a subset of severely injured patients, namely those with GCS 3–5, the prognosis is uniformly poor with a mortality of 87–97%. Such devastating outcomes are of great epidemiological significance given that the majority of civilians with penetrating TBIs (53–81%) fall in this GCS category. This is not the case in military series, where only 10–34% of patients with

Table II. Prognostic factors of increased acute mortality in patients with traumatic brain injury.

Factor	References
Demographics	
Advanced age	[15, 24, 35, 68, Wardlaw, J.M. et al. 2002; DuBose, J.J. et al. 2008]
Male gender	(Faul, M. et al. 2006)
Suicidal intent	[37]
Injury-related	
Penetrating trauma	[24, 25, 28, 68, DuBose, J.J. et al. 2008]
GCS ≤ 8, and particularly GCS 3–5	[24, 67, DuBose, J.J. et al. 2008; Young, B. et al. 1981]
Pupillary light reflex abnormalities	[19, 50, 59, 64, 71, Wardlaw, J.M. et al. 2002; Petridis, A.K. et al. 2010]
High Injury Severity Score (ISS)	(DuBose, J.J. et al. 2008)
Increased intracranial pressure (ICP)	(Petridis, A.K. et al. 2010)
Head CT scan	
Subdural haematoma	[16]
Subarachnoid haemorrhage	[66, Wardlaw, J.M. et al. 2002]
Midline shift > 3 mm	[66]
Intraventricular haemorrhage	
Compression or obliteration of mesencephalic cisterns	[66, Toutant, S.M. et al. 1984] [59, 67, Erdogan, E. et al. 2004; Solmaz, I. et al. 2009]
Missile Track[a]	
Bihemispheric vs unihemispheric	[18, 20, 38, 39, Grahm, T.W. et al. 1990; Nagib, M.G. et al. 1986; Jacobs, D.G. et al. 1995]
Multilobar vs unilobar	[21, 38, 61, Nagib, M.G. et al. 1986; Levi, L. et al. 1990]
Ventricular involvement vs none	[57, 61]
Type III-IV diffuse injury as determined by Marshall CT scan classification[b]	[64]
Systemic	
Hypotension	[18, 24, DuBose, J.J. et al. 2008; Kaufmann, H.H. et al. 1983]
Coagulopathy	[67]

[a]In the specific case of penetrating brain injuries.
[b]According to the Marshall CT scan classification, type III diffuse injuries have compressed cisterns and midline shift of 0–5 mm, while type IV injuries have midline shift > 5 mm. Both injury types exclude the presence of a high- or mixed density lesion > 25 mL, otherwise it is considered a mass lesion.

penetrating TBI present to the hospital with GCS 3–5. Besides, the mortality rate of servicemen with brain injuries in this GCS group is 58–69% compared to a rate of 90% in civilians with a similar level of consciousness [60, 61]. Many factors may account for this disparity, including the soldier's young age and optimal physical condition, the use of helmets in the military and the early death of some servicemen due to polytrauma [42]. Whether military or civilian, the use of GCS score is widely accepted by clinicians since the published literature demonstrates a strong correlation with outcome.

Pupillary light reflex

Pupillary light reflex reaction may be affected by TBI as a result of third cranial nerve compression against the clivus or the free edge of the tentorium [62] or as consequence of upper midbrain damage, particularly at the junction of the optic nerve and the pretectal nucleus [63]. Eye trauma and drug intoxication may also alter pupillary appearance, so it is necessary to rule out these setiologies prior to formulating a management plan for TBI based on the ophthalmic exam. Following TBI, pupillary reaction is normal in 50–61% patients, unequal in 9–23% and fixed dilated in 27–47% [50, 59]. According to Kaufman et al. [19], penetrating TBI mortality varies drastically according to pupillary appearance. If both pupils react, 79% of patients survive; if one pupil reacts, 50% survive; and if neither pupil reacts, only 1% survive. A similar trend is also observed in closed TBI. In a study of 748 severe TBI patients (GCS $\leq$ 8), which excluded penetrating injuries, Martins et al. [64] demonstrated that the mortality risk of patients with only one reactive pupil was 2.65-times that of patients with bilateral reactive pupils. This risk increased to 11.52-times when both pupils were unreactive. Given the grim prognosis of mydriasis, the current consensus among neurosurgeons is to manage these patients non-operatively. According to a national survey conducted by Kaufman et al. [65], 77% of neurosurgeons elected not to operate on patients with bilateral dilated pupils, whereas 72% chose to operate on those with only one dilated pupil. Nevertheless, no study of penetrating TBI to date has compared the outcomes of patients who are surgically-treated and exhibited pupillary abnormalities on admission with those of historical controls treated non-operatively. Therefore, further research is needed to determine the validity of papillary light reflex as a TBI prognostic indicator and to rule out any survival benefit attributable to surgery in patients with TBI with mydraisis.

Computed tomography (CT) scanning

With the advent of CT, intracranial injuries can be promptly characterized after TBI. Injuries may be classified as 'focal' if the CT scan reveals a space-occupying, 'mass lesion', such as an epidural or subdural haematoma, or as 'diffuse' if the CT scan fails to demonstrate a mass lesion, but coma persists for more than six hours. In a multi-centre study of 1107 patients who suffered severe closed TBIs (GCS $\leq$ 8), Genarelli et al. [16] reported mortality rates of 48% and 32% for focal and diffuse injuries, respectively. Subdural haematoma was the most common focal lesion (51%) in this series, and it was also the deadliest form of injury, with a mortality rate of 61%. In another study of 753 patients with a closed TBI from the NIH Traumatic Coma Data Bank, Eisenberg et al. [66] reported that patients with compressed mesencephalic cisterns were 3-times more likely to die than those with normal cisterns. Univariate analysis indicated that the mortality risk also doubled in the presence of mass lesion, midline shift >3 mm or subarachnoid haemorrhage. Unfortunately, the lack of studies on the use of CT scanning in penetrating TBI leaves clinicians with a poor understanding of how different intracranial injuries impact survival in this group of patients.

New research is warranted for the radiographic characterization of penetrating brain injuries and their corresponding management. Although it is arguable that the presence of metallic fragments makes CT scan interpretation difficult after ballistic injuries due to x-ray artifacts, it is important to discern if this imaging modality is invariably useless to clinicians or if it aids in the diagnosis of certain surgically treatable injuries. In addition, the prognostic value of CT needs to be evaluated in the light of other diagnostic criteria. For instance, mortality was better predicted by the combined analysis of CT scan features and GCS score than by either variable alone [25]. In Gennarelli et al.'s [25] previously mentioned study, the mortality associated with subdural haematoma increased considerably as GCS scores decreased. Patients with GCS 6–8 had a mortality of 36%, while those with GCS 3–5 had a mortality of 74%. A similar GCS effect was also observed in diffuse injuries, where GCS 6–8 and GCS 3–5 had mortality of 13% and 51%, respectively [16]. Therefore, while CT scanning remains a valuable diagnostic tool in TBI, its full potential may only be reached with further research.

Missile track

In the case of penetrating TBI, the missile track has important prognostic value as demonstrated by various studies (Table II). In a meta-analysis of the

effect of missile track characteristics on mortality, Polin et al. [67] reported that 86.9% of patients with bihemispheric injuries died vs 58.2% of those with unihemispheric injuries. Similarly, injuries with ventricular involvement had a mortality of 86.3%, whereas those with no involvement had a mortality of 68%. Further, a comprehensive review of penetrating TBIs reported that the risk of dying from multilobar injuries was 3–84-times that of unilobar injuries [59]. Unfortunately, even though most recent studies document missile track characteristics and disclose the percentage of patients undergoing surgery, they fail to document the procedures performed and the primary diagnosis that motivated the intervention. As a consequence, the frequency of and the mortality risk associated with concomitant mass lesions (which may have been surgically evacuated) are poorly understood. What is certain is that the probability of death due to penetrating TBI appears to increase with larger volumes of tissue damage, mainly due to extensive necrosis, oedema, prolonged ischemia and increased ICP.

Mechanism of injury

Although few studies have compared the early outcomes of penetrating and closed TBI, the existing literature points to a greater severity and mortality in cases of penetrating trauma. Gennarelli et al. [25] studied 59 713 patients with TBIs (1982–1989) with and without extracranial injuries and found that the mortality of patients with a penetrating TBI was at least 4-times greater than that of patients with closed TBI after adjusting for injury severity. Also in this series, only 39.8% of patients with a penetrating TBI were discharged from the hospital in comparison to 73.8% of patients with all-cause TBIs. Peek-Asa et al. [28] analysed 795 patients with moderate-to-severe TBIs (1992–1996) and reported a higher CFR for penetrating TBI than for closed TBI, namely 56.4% vs 21.0%, while controlling for age, gender, GCS score and multiple trauma. Of note, firearms accounted for 93.6% of all penetrating brain injuries in this series and it was the external cause associated with the highest CFR at 58.3%. Besides, the CFRs of penetrating and blunt injuries in the GCS 3–5 group were 90.4% and 57.0%, respectively. Demetriades et al. [24, 68] studied 7764 patients without hypotension or major extra-cranial injuries and confirmed that the prognostic value of GCS on mortality rate changed with age and mechanism of injury. Mortality was significantly higher in penetrating injuries than in blunt ones, namely 42% vs 9%. In addition, a penetrating mechanism of injury was more likely to be associated with GCS ≤ 8. Similar results were obtained by

Valadka et al. [69] in a study of patients admitted to the ICU with gunshot and non-gunshot TBIs. A rapid progression to death occurred in 71% of the patients with gunshot TBIs, in comparison to 17% of the patients with non-gunshot TBIs; thus confirming the higher lethality of gunshot wounds over other mechanisms of injury.

Surgical intervention

In regards to the surgical management of patients with severe brain-injuries, the decision to operate on these patients is influenced by a myriad of factors. However, the GCS score appears to weigh heavily on this decision, as more than half of those patients with a GCS 3–5 are managed non-operatively in Kaufman et al.'s [65] survey. Although the prevailing consensus is to elevate depressed skull fractures, provide superficial debridement, evacuate mass lesions and provide watertight dural closure with or without autologous tissue, these surgical procedures are less likely to be offered to patients with low GCS scores. In fact, most neurosurgeons consider them futile, especially in the presence of pupillary non-reactivity, ventricular penetration, subarachnoid haemorrhage or bihemispheric injury [67, 70, 71].

Despite such pessimistic claims of futility in the literature, Levy et al. [72] are able to show, in a study of penetrating TBIs, a significant difference in survival between operative and non-operative patients with GCS 3–5 (38% vs 0.7%). Unfortunately, the majority of survivors experience severe disability or remain in a persistent vegetative state. The authors conclude that patients with GCS 3–5 are not likely to benefit from surgery given their poor functional outcomes. However, it is not clear from the study methodology whether endotracheal intubation may have under-estimated the admission GCS scores, thereby enrolling patients with less severe injuries into the series. In spite of the survival improvement obtained from surgery, the decision to operate on potentially salvageable patients transcends the surgeon's comprehensive evaluation of the mortality risk factors. Other aspects such as patient quality-of-life, access to rehabilitation services and the emotional and financial burden of caregivers need to be considered as well [73, 74].

It should be noted that the futility of surgical intervention, as it relates to long-term functional outcomes, continues to be challenged. In a meta-analysis of 1422 civilians with severe TBI (mostly from closed injuries) by Danish et al. [75], it is reported that decompressive craniectomy is able to achieve a 6-month post-operative mortality rate of 28% and a mean quality-of-life value of 60%, which corresponds roughly to a level of moderate disability.

According to the authors, the latter finding contends the common understanding that hemicraniectomy shifts the outcome from death to a persistent vegetative state or severe disability.

In the military setting, early decompressive craniectomy is likewise advocated for patients with severe brain injuries, especially prior to air transporting servicemen with severe TBIs from combat hospitals (Level III) in Iraq and Afghanistan to definitive care medical centres (Level V) in the US [76]. Nevertheless, the effect of this surgical modality on long-term outcomes is not clearly ascertained in the military literature. In a retrospective study of 408 severe TBIs from OIF and OEF, of which 82% resulted from penetrating injuries, Bell et al. [77] reported that craniectomized patients (23.5%) experienced worse outcomes than did non-craniectomized patients (76.4%) at 6 months and 1 year post-injury. However, the authors attribute this outcome difference to the selection of more severely-injured patients to undergo surgery. In view of the incomplete knowledge about the use of decompressive craniectomy in servicemen with brain injuries, a control trial should be considered by the military authorities to validate its efficacy on long-term outcomes.

Long-term outcome

Post-acute morbidity

Most studies fail to distinguish between the post-acute morbidity of blunt TBI and that of penetrating TBI. An exception is a study by Black et al. [78], where penetrating TBI was associated with greater morbidity and lower functional outcome than blunt TBI was. The post-acute complications of 317 patients from the Traumatic Brain Injury Model Systems of Care (1988–1999) were analysed and patients with penetrating injuries suffered higher rates of respiratory failure, pneumonitis/pneumonia, skull fracture, cerebrospinal fluid leak and hypotonia than did those patients with blunt injuries. Injury severity was also found to be an independent predictor of medical complications. In view of the scarcity of information regarding the post-acute morbidity of penetrating TBI, new research is necessary in order to expedite the identification of high-risk patients.

Survival

Life expectancy is reduced by 4–7 years in TBI survivors [79–81]. This grim reality is supported by several large retrospective studies. In a cohort of 3679 patients with TBIs from South Carolina (1999–2001), Selassie et al. [82] report that 8.4% of patients died within 15 months of hospital discharge and that 17% of deaths were directly related to their TBIs. Harrison-Felix et al. [79, 81] studied two populations of patients with TBIs admitted to rehabilitation units, namely 1678 persons from a single institution over the course of four decades (1961–2002) and 2178 persons from the TBI Model Systems National Database (1988–2001) [81], and reported that the likelihood of death at 1 year post-injury was 1.5–2-times that of the general population after adjusting for age, gender and race. Further, a study by Baguley et al. [83] that considered 476 patients with TBIs admitted to an Australian rehabilitation service (1986–1996) estimated a 10-year, post-injury mortality rate of 3.7–8.3% vs an expected mortality rate of 0.6–3.0% in the general population. However, most injuries in this cohort were caused by closed head trauma (97%), with only a small number of penetrating brain injuries being recorded.

Although these retrospective studies confirmed the detrimental effect of TBI on post-hospitalization mortality, they did not analyse the effect of mechanism of injury (e.g. penetrating vs blunt trauma) on this end-point, presumably because penetrating brain injuries are often under-represented in civilian TBI series or because the trauma registries did not query the mechanism of injury [26]. For these reasons, the mortality of penetrating TBI in the post-acute period remains largely unknown in the civilian population and requires further study.

On the contrary, survival is better reported in the military population given the higher frequency of penetrating injuries in soldiers as compared to civilians. A study of 1127 Vietnam soldiers who sustained penetrating TBIs and remained alive for at least 1 week after injury [84] reported a 15-year mortality rate of 8%, with 50% of the deaths occurring within 1 year post-injury. Of note, the latter figure is higher than the all-cause mortality rate of 2.6% estimated by the Centers for Disease Control from a sample of 9324 Vietnam veterans at a mean follow-up of 13.7 years [85]. Thus, this infers that penetrating TBI confers an added long-term mortality risk to those individuals who suffer it vs those who do not.

Several prognostic factors are associated with an increased post-acute mortality in patients with TBIs (Table III). Interestingly, GCS score appears not to be predictive of acute mortality at one year post-injury [81, 86]. According to Colantonio el al. [87], who evaluated 2721 patients from the Ontario Trauma Registry (1993–1995), the relative risk (RR) of death after 1 year post-injury decreased with advancing age (as raw death rates inevitably increased for older age groups) and increased in the presence of comorbidities (RR 1.27–2.08) and

Table III. Prognostic factors of increased post-acute mortality in patients with traumatic brain injury.

Factor		References
Pre-injury	Advanced age	[64, 81, 82, 87]
	Male gender	[82]
	Presence of comorbities	[82, 87]
	Presence of a psychiatric condition	[87]
	Medicare/government medical insurance	[82]
	Low income	[80]
	Unemployment	[81]
	Less education[a]	[79, 81]
	Earlier year of injury[b]	[79]
Injury-related	High Injury Severity Score (ISS)[c]	[87]
	Marshall CT classification (Type III-IV worse prognosis than Type I)[d]	[64]
Post-injury	Longer duration of unconsciousness	[79]
	Longer hospitalization[e]	[79]
	Discharge to a place other than home (e.g. rehabilitation hospital or long-term care facility)	[79]
	Greater disability at rehabilitation discharge (e.g. vegetative state vs good recovery, moderate or severe disability)	[79, 81]

[a]Harrison-Felix et al. [79]. College degree holders have one third the mortality risk of those persons without a high school degree.
[b]Harrison-Felix et al. [79]. 3% decrease in mortality risk for each calendar year sooner.
[c]Colantonio et al. [87]. Association reported, but data not shown.
[d]According to the Marshall CT scan classification, type III diffuse injuries have compressed cisterns and midline shift of 0–5 mm, while type IV injuries have midline shift > 5 mm. Both injury types exclude the presence of a high- or mixed density lesion > 25 mL, otherwise it is considered a mass lesion. On the other hand, type I injuries have no evidence of intracranial pathology.
[e]Harrison-Felix et al. [79]. 5% increase in mortality risk for each additional day of hospitalization.

psychiatric illness or after discharge to a location other than home (RR 1.87). Harrison-Felix et al. [79] reported that male (RR 3.13), unemployment at the time of injury, less education at rehabilitation admission, longer hospitalization and longer duration of unconsciousness and remaining in a vegetative state at discharge (RR 2.903) were all associated with an increased risk of death at 1 year post-injury after adjusting for age. Furthermore, the authors related that age was an independent risk factor for death, with an 8% risk increase for each additional year of age at injury. The latter finding was consistent with a study by Selassie et al. [82], where individuals aged ≥ 75 years at the time of injury were 3–4-times more likely to die within 15 months post-discharge than those aged 35–74. Moreover, it is worth noting that recent TBI studies have not considered the confounding effect that early withdrawal of life support may have on post-acute mortality rates, even though this effect has long been recognized in critical care studies [88]. In this sense, future investigations should clearly distinguish those deaths attributed to the withholding of life support from those related to disease refractoriness.

Functional outcomes

Traumatic brain injury may result in long-term physical, cognitive, emotional and occupational disabilities. In 2003, the estimated incidence of TBI-related disability in the USA was 125 000 cases,

accounting for 43.3% of all TBI hospitalizations [89]. Meanwhile, the estimated prevalence of disabled TBI survivors was 3.2 million in 2005 [90]. Unfortunately, the burden of disability posed by TBI often alters the living status of patients, making them highly dependent on others. This is evident from a prospective study of patients with severe TBIs [91] which demonstrated that more patients lived in a supervised setting at 2–5 years post-injury than did pre-injury (20% vs 2%). Similarly, another group studied a population of 208 patients with severe brain-injuries and found that 40% experienced poor community integration at a mean 3.5-year follow-up [92]. According to the authors, very few 'poorly integrated' patients performed home tasks alone, including planning social events (14%), managing finances (27%), grocery shopping (14%), meal preparation (20%), child care (26%) and housework (17%). Although the latter studies suggest that the ability to care for one's self is profoundly affected by the long-term impairments of TBI, they do not make a distinction between the outcomes of blunt and penetrating injuries.

Unfortunately, there is paucity of studies on the chronic morbidity of penetrating TBI. This drawback is quite evident from civilian studies where investigators either fail to classify TBIs by mechanism of injury or exclude penetrating injuries from the final outcome analysis. An exception to this analytical approach is notable in a study by Valadka et al. [69] from Houston. Data from 63 gunshot-

wound brain injuries and 402 non-gunshot-wound brain injuries demonstrated that mechanism of injury did not have a significant effect on the 3-month outcomes of patients admitted to the neurological ICU. The likelihood of good recovery or severe disability did not differ in patients with blunt or penetrating brain injuries. This study used an inclusion/exclusion criterion to create two comparable groups with similar demographics and injury severity. The groups also utilized the same management protocols for treating all patients, eliminating the more severely injured patients; thus, a lack of significant difference among group outcomes resulted.

Unlike civilian studies, military studies have proposed comprehensive methodologies to assess the long-term outcomes of penetrating TBI, including level of independent functioning, motor performance and communication ability, among others. This is the case of the Vietnam Head Injury Study conducted by Sweeney and Smutok [93] in 1983, where 700 combat veterans who suffered a penetrating TBI were evaluated by a multidisciplinary research team at an average of 14 years post-injury. A preliminary report of the data collected from the first 160 subjects revealed 15% self-care dependence, 28% motor abnormalities (e.g. hemiplegia, monoplegia, involuntary movement disorder, triplegia) and 2.5% non-ambulatory status. These observations must be interpreted with caution since they are only representative of 14% of the subjects included in the Vietnam Head Injury Registry. To the best of the authors' knowledge, the final results of this study were never published as originally proposed in the methodology section, including a comparison between injured and non-injured Vietnam veterans matched for age, date of service and scores in cognitive testing. In view of the scarce knowledge about the long-term outcomes after penetrating TBI in both the civilian and military populations, new research studies are urgently needed to better characterize the chronic morbidity experienced by these patients, so that new screening initiatives may be developed accordingly.

Functional outcome assessment scores

Several clinical measures are used to evaluate the long-term functional outcomes of moderate-to-severe TBI. These include the Glasgow Outcome Scale (GOS) [94], the Disability Rating Scale (DRS) [95, 96], the Rancho Los Amigos Levels of Cognitive Functioning Scale (LCFS) [97], the Sydney Psychosocial Reintegration Scale (SPRS) [98] and the cognitive and motor components of the Functional Independence Measure (FIM^{TM})

[91, 99]. Although GOS has been widely used in research studies for its simplicity, it is a broad predictor of outcome that lacks specificity for functional categories. DRS, LCFS, SPRS and FIM^{TM}, on the other hand, are more comprehensive than GOS in that they further assess the patient's functional status, psychosocial adjustment, communication and cognitive ability for independent living with a much higher sensitivity and inter-rater reliability than GOS does [94, 95, 99–103]. Although the GCS score is a strong predictor of mortality in the acute phase of TBI [104], its usefulness as a predictor of functional outcome, as determined by the GOS score, is still uncertain [105–107].

Nevertheless, several investigators have attempted to ascertain the relationship between injury severity scores and TBI functional outcomes. Zafonte et al. [86] reported in a study of 501 patients with TBIs (1988–1993) that the GCS score had a significant low-to-moderate correlation with the cognitive FIM^{TM} and LCFS scores. Similarly, Cowen et al. [108] observed that patients with severe TBI (GCS 3–7) had lower motor and cognitive FIM^{TM} scores on admission and discharge, longer rehabilitation length of stay (LOS) and higher costs of acute hospitalization than patients with mild brain injuries (GCS 13–15). Importantly, this study showed rehabilitation improved the motor and cognitive FIM^{TM} scores in all injury severity groups. The authors also observed that a longer rehabilitation LOS was associated with higher gains in FIM^{TM} scores, while a longer acute hospitalization LOS was associated with lower scores on admission to rehabilitation, presumably due to increased injury severity and medical complications. Similar improvements in functional outcome were observed by Zafonte et al. [109] in a prospective cohort of 27 survivors of gunshot wounds to the brain with initial GCS ≤ 8 and by DeGuise et al. [91] in a cohort of 88 survivors from all-cause TBIs with initial GCS ≤ 8. Furthermore, Harrison-Felix et al. [81] found that greater disability at rehabilitation discharge, as determined by the DRS score, was strongly predictive of death after 1 year post-injury. Similarly, in a 13-year follow-up study of 69 patients admitted to a rehabilitation service and classified as 'dependent on discharge' (FIM score ≤ 54), Baguley et al. [83] reported that the cohort of deceased patients had lower FIM^{TM} scores at discharge than did the cohort of survivors, even though the FIM^{TM} scores of both cohorts were comparable on admission. Therefore, outcome measures not only categorize the degree of disability, but also predict post-acute mortality.

Traumatic brain injury clinical trials

Although recent clinical trials have studied the effects of several therapies on severe TBI, most of these studies have excluded penetrating brain injuries. For instance, the ProTECT study [110] compared intravenous progesterone vs placebo in patients with a closed TBI with GCS 4–10 and found a modest improvement in functional outcomes for those patients with moderate injuries. It would be important to elucidate if patients with penetrating TBIs, with comparable GCS scores, could benefit from progesterone as well. Rockswold et al. [111] found that hyperbaric hyperoxia increased cerebral blood flow, improved cerebral metabolic rate of oxygen and reduced cerebrospinal fluid lactate concentrations in patients with a closed TBI to a greater extent than did normobaric hyperoxia or control standard care. It would be valuable to know if hyperbaric oxygen could improve the cerebral metabolism of patients with penetrating TBIs in the same way. The effects of other therapies such as pre-hospital hypertonic fluid resuscitation, intensive insulin therapy, selective or systemic hypothermia, early enteral feedings and neuroprotective agents (i.e. amantadine, dexanabinol, nimodipine, THAM) have only been studied in patients with a closed TBI [112–121]. Thus, it is warranted to investigate these therapies in patients with penetrating TBIs to determine their safety and efficacy. Most importantly, these separate studies are imperative, as it must not be assumed that patients with penetrating TBIs will respond to a given therapy in the same manner patients with a closed TBI do, especially since the pathophysiologic differences of these two mechanisms of injury remain largely unknown.

Guidelines for the management of severe traumatic brain injury

In 1995, the Brain Trauma Foundation (BTF) and the American Association of Neurological Surgeons (AANS) proposed new evidence-based guidelines for the management of severe TBI [122, 123]. However, the scope of this project did not include penetrating brain injuries. Consequently, in 2001, the American Association for the Surgery of Trauma published a comprehensive review of the prognosis and management of penetrating brain injuries that was intended to complement the preceding guidelines. This project was named 'Guidelines for the Management of Penetrating Brain Injuries' [124]. Table IV summarizes the findings of this project by listing those prognostic factors that have been correlated to an increased acute mortality after penetrating injuries. Notice that the correlations are mostly supported by Class III observational

studies containing at least 25 subjects. Typically, such studies gather consecutive data in a designated period of time and correlate patient entry characteristics (e.g. age, GCS score) to well-defined outcomes (e.g. mortality, GOS). A higher level of evidence reliability, namely Class I or II, may be attained if the study design is prospective (rather than retrospective) and if the effect of confounding variables (e.g. age, pre-injury co-morbidity) on outcomes is adjusted for using robust statistical methods.

A review of Tables II and VI reveals many common prognostic factors of early death, including $GCS \leq 8$, increased ICP, pupillary light reflex abnormalities and intracranial mass lesions. Importantly, it should not be assumed that a particular factor has an equivalent effect on the acute mortality of penetrating and blunt brain injuries. New studies are needed to elucidate the frequency of risk factors by mechanism of injury, especially the frequency of intracranial lesions (e.g. subdural haematoma, subarachnoid haemorrhage, cisternal effacement). Once brain injuries are properly characterized, it may be possible to identify those risk factors that confer the highest mortality after penetrating and blunt injuries, respectively. Moreover, the authors of the penetrating TBI guidelines identified a set of prognostic factors that were also associated with poor functional outcomes, mainly as determined by low GOS (Table V). Knowledge of these factors may be important in determining which patient populations are likely to benefit from specific novel therapies.

Three major TBI guideline projects have been undertaken in the US and Europe (Table VI) and the approach and scope of each project is quite different. In the case of the 'Guidelines for the Management of Severe Traumatic Brain Injury' [123], sponsored by the BTF and AANS, the authors base their recommendations on a systematic review of clinical studies and cautiously refrain from elevating a particular diagnostic, therapeutic or prophylactic measure to the stature of 'guideline' in view of the fact that the majority of supporting studies are observational (Class III). Nevertheless, recommendations are still issued on a broad range of management strategies as long as consensus exists about their safety and clinical efficacy. For example, even though the effect of mannitol infusion on TBI acute mortality remains unknown and ethical tenets preclude a randomized control trial to prove a survival benefit attributable to this therapy, the use of mannitol is recommended because its efficacy for lowering ICP has been widely documented.

In the case of the 'Guidelines for the Management of Penetrating Brain Injury' [124], the authors address management strategies not considered in

Table IV. Prognostic factors of increased acute mortality in penetrating brain injury; correlations supported by class III studies unless stated otherwise.*

Factor	References
Neurologic measures	
GCS score ≤ 8	[19, 40, 60, 61, Grahm, T.W. et al. 1990, Levi, L. et al. 1990b, Mancuso, P. et al. 1988, Nagib, M.G. et al. 1986, Petridis, A.K. et al. 2010]
Bilateral non-reactive pupils	[19, 41, 57 Petridis, A.K. et al. 2010]
High intracranial pressure (Class II)	[18,19]
Cisternal effacement	[18]
Wound characteristics[a]	
Missile track	
Bihemispheric vs unihemispheric	[19, 38, 39, 40, 57, Grahm, T.W. et al. 1990, Nagib, M.G. et al. 1986, Clark, W.C. et al. 1986, Jacobs, D.G. et al. 1995]
Multilobar vs unilobar	[21, 38, 39, 61, 104, Levi, L. et al. 1990a, Nagib, M.G. et al. 1986, Petridis, A.K. et al. 2010, Shoung, H.M. et al. 1985]
Ventricular penetration	[40, 57, 61, Levi, L. et al. 1990a, Petridis, A.K. et al. 2010, Clark, W.C. et al. 1986]
Presence of intracranial haemorrhage or mass lesions	
Mass lesions/contusions (Class I)	[57]
Intraventricular haemorrhage	[19, 57, Nagib, M.G. et al. 1986]
Subarachnoid haemorrhage	[19]
Intracranial haematomas (e.g. epidural, subdural and intracranial)	
Systemic measures	
Hypotension	[18–21, 24, 40, 41, Stoffel, M. et al. 2009]
Hypertension	[41, Stoffel, M. et al. 2009]
Respiratory distress	[20, 40, Jacobs, D.G. et al. 1995]
Coagulopathy[b]	[57]
Intent of injury	
Civilian setting: Suicidal intent vs assaultive or accidental intents	[19,38,39, Grahm, T.W. et al. 1990, Nagib, M.G. et al. 1986, Jacobs, D.G. et al. 1995]
Cause of injury	
Military setting: Gunshot vs shrapnel wounds	[61]
Demographics (correlation less supported by Class III studies)	
Age[c]	[19, 38, Hernesniemi, J. 1979]

*Derived from Part II: Prognosis in penetrating brain injury [59]. Several studies published after 2001 were also included in this table [22,40, Petridis, A.K. et al. 2010, Glapa, M. et al. 2009].
[a]As determined by head CT scan and/or autopsy.
[b]Shaffrey et al. [57] Coagulopathy increases mortality at low GCS scores, but its effect decreases as GCS scores increase.
[c]The effect of age on acute mortality after penetrating TBI is less clear, presumably because penetrating injuries affect young individuals more often than they do old individuals and the statistical analysis sometimes fails to reach significance.

Table V. Prognostic factors of poor functional outcomes in penetrating head injury.*

	References
Correlation supported by Class III studies	
Demographics:	
Age	(Hernesniemi, J. 1979)
Intent of injury	
Suicidal intent vs assaultive or accidental intents	(Grahm, T.W. et al. 1990, Nagib, M.G. et al. 1986, Jacobs, D.G. et al. 1995, Hernesniemi, J. 1979)
Neurologic measures:	
GCS score ≤ 8 vs GCS score > 8	[20–22, Nagib, M.G. et al. 1986]
Bilateral non-reactive pupils	[21]
Wound characteristics-missile track	
Bihemispheric vs unihemispheric	[20, Grahm, T.W. et al. 1990, Clark, W.C. et al. 1986, Lillard, P.L. 1978]
Ventricular penetration	(Clark, W.C. et al. 1986)

*Derived from Part II: Prognosis in penetrating brain injury [59]. Several studies published after 2001 were also included in this table [22, 40, (Glapa, M. et al. 2009, Petridis, A.K. et al. 2010].
‡As determined by head CT scan and/or autopsy.

Table VI. Current recommendations for the management of traumatic brain injury.[a]

Diagnostic, therapeutic or prophylactic strategy	Guidelines for the Management of Severe Traumatic Brain Injury (GMSTBI) [123][b]	Guidelines for the Management of Penetrating Brain Injury [124]	EBIC – Guidelines for the Management of Severe Head Injuries in Adults [125][c]
Blood pressure	• Avoid SBP < 90 mmHg (II)	• Defaults to GMSTBI	• MAP > 90 mmHg • Give IV fluids to maintain normovolemia and normal blood chemistries
Oxygenation	• Avoid PaO$_2$ < 60 mmHg or SaO2 90% (III) • Avoid jugular venous saturation < 50% or brain tissue oxygen tension < 15 mmHg (III)	• Defaults to GMSTBI	• SaO$_2$ > 95% • PaO$_2$ > 100 mmHg • PaCO$_2$ 30–35 mmHg
Hyperventilation	• Prophylactic hyperventilation to achieve a pCO$_2$ of 25 mmHg not recommended (II) • Avoid use of hyperventilation in the first 24 hours post-injury when cerebral blood flow is usually compromised (III)	• Defaults to GMSTBI	• Mild-to-moderate hyperventilation to achieve a PaCO$_2$ 30–35 mmHg • If osmotherapy fails, more intensive hyperventilation (PaCO$_2$ < 30 mmHg), preferably with monitoring of cerebral oxygenation (e.g. jugular oximetry)
Neuroimaging	• No recommendation issued, but its common use implied in the text	• CT scan strongly recommended for the identification of intracranial lesions (III) • Angiography recommended for suspected vascular injuries (III) • Routine MRI not recommended for acute management, especially if the wound contains metallic fragments	• No recommendation emitted, but its common use implied in the text
ICP monitoring	• Indicated for ICP > 20 mmHg (II) • Indicated for patients with GCS 3–8 after resuscitation and an abnormal CT scan (II) • Indicated for severe TBI patients with a normal CT scan if age > 40, unilateral or bilateral motor posturing or SBP < 90 mmHg are present (III)	• Early ICP monitoring recommended when unable to assess neurologic status, when need to evacuate a mass lesion is unclear or when imaging suggests increased ICP (e.g. cisternal compression, midline shift) (III)	• Indicated for ICP > 20–25 mmHg
CPP	• Avoid CPP < 50 mmHg (III) • Avoid aggressive attempts to maintain CPP > 70 mmHg with fluids and pressors because of the risk of adult respiratory distress syndrome (ARDS) (II)	• Defaults to GMSTBI	• CPP 60–70 mmHg • Volume expansion and inotropes or vasopressors when blood pressure is insufficient to maintain CPP in normovolemic patient, CVP monitoring necessary
Hyperosmolar therapy	• Mannitol is effective for the control of ICP at doses 0.25–1 g/Kg (II) • Restrict use of mannitol prior to ICP monitoring in patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes (III)	• Defaults to GMSTBI	• Mannitol bolus infusions to control elevated ICP, while keeping serum osmolarity < 315 • Furosemide (Lasix) when osmotherapy is insufficient • Glycerol or sorbitol not advocated as osmotherapeutic agents
Anaesthetics	• Propofol recommended for the control of ICP. High-dose propofol may cause significant morbidity (II) • High dose barbiturates recommended to control elevated ICP refractory to medical or surgical treatment (II)	• Defaults to GMSTBI	• Not considered, therefore no recommendation issued

Prophylactic hypothermia	Hypothermia for > 48 hours may decrease mortality, but the evidence is unclear. However, GOS scores improve significantly in hypothermia-treated patients compared with those not treated (III)	Defaults to GMSTBI	Not considered, therefore no recommendation issued
Anti-seizure prophylaxis	One-week therapy indicated for the prevention of early post-traumatic seizures (II). Avoid the prophylactic use of phenytoin and valproate for the prevention of late seizures (II)	One-week therapy indicated for the prevention of early post-traumatic seizures (I, II)	No recommendation issued. Authors advise the presence of an anaesthetist with anticonvulsants accessible during patient transport
Antibiotic prophylaxis	Peri-procedural antibiotics for intubation to reduce the risk of pneumonia (II). Routine exchange of ventricular catheter or prophylactic antibiotic use for ventricular catheter placement not recommended (III)	Broad-spectrum antibiotics recommended (III)	Not considered, therefore no recommendation issued
Surgery	Not considered, therefore no recommendation issued	Local wound closure when scalp not devitalized and intracranial pathology is ruled out (III); For more extensive wounds, surgical debridement with watertight dural closure (III); Surgical debridement of missile track not generally recommended (III)	Non-operative management for: (a) Closed depressed skull fracture without a mass effect (b) Small haemorrhagic contusions or intracerebral lesions. Operative management for: (a) Open, compound, depressed compound fracture that causes a mass effect (b) Clinical deterioration (c) > 1 cm thick extracerebral clot, > 25–30 mL intracerebral haematoma (d) Midline shift > 5 mm (e) Enlargement of contralateral ventricle (f) Obliteration of basal cisterns/third ventricle (g) Raised or increasing ICP
Vascular injuries	Not considered, therefore no recommendation issued	CT angiography or conventional angiography recommended for the identification of traumatic intracranial aneurysms (TICA) or arteriovenous fistulas	Not considered, therefore no recommendation issued
CSF leaks	Not considered, therefore no recommendation issued	Surgical repair indicated when CSF leaks fail to close spontaneously or fail CSF diversion	Not considered, therefore no recommendation issued
DVT prophylaxis	Graduated compression stockings or intermittent pneumatic stockings are recommended (III)	Defaults to GMSTBI	Not considered, therefore no recommendation issued
Nutrition	Patients should attain full caloric replacement by day 7 post-injury (II)	Defaults to GMSTBI	Not considered, therefore no recommendation issued
Steroids	Steroid use not recommended	Defaults to GMSTBI	Not considered, therefore no recommendation issued

[a] The class of evidence is shown in parentheses whenever disclosed.
[b] These guidelines did not consider penetrating brain injuries.
[c] Maas et al. [125]. This work provided guidelines for the management of TBI based on practice consensus. Its purpose was not to examine the evidence systematically.
SBP, systolic blood pressure; MAP, mean arterial pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; DVT, deep vein thrombosis.

the preceding guidelines, namely the use of neuro-imaging for the characterization of missile track and intracranial lesions, the use of angiography for the detection of vascular injuries and the surgical management of entry wounds and CSF leaks. These guidelines default to those used for closed TBI whenever there is insufficient data to support a particular strategy for penetrating TBI. New research studies are necessary to support the use of ICP monitoring, hyperosmolar therapy, anaesthetic use, hypothermia and hyperventilation in patients with penetrating injuries.

In the 'Guidelines for the Management of Severe Head Injuries in Adults' [125], sponsored by the European Brain Injury Consortium (EBIC), the authors formulate recommendations based on practice consensus rather than a systematic review of the literature. Unlike their US counterparts, they emphasize the need to maintain a homeostatic milieu by keeping mean arterial pressures above 90 mmHg and arterial blood gases within specific ranges. In addition, the authors advocate the aggressive use of resuscitation fluids, inotropes/vasopressors, diuretics and intensive hyperventilation ($PaCO_2 < 30$ mmHg) in order to ensure a cerebral perfusion pressure of 60–70 mmHg. They do acknowledge that the use of these measures remains controversial and that central venous pressure monitoring and jugular oximetry may be necessary to ensure normovolemia and to avoid increased cerebral oxygen extraction, respectively. Furthermore, the EBIC guidelines propose a set of criteria for non-operative and operative management. Nevertheless, a distinction is not made between the surgical management of penetrating and blunt brain injuries. Further research is also needed to elucidate the current surgical management of TBI by mechanism of injury.

Summary

Traumatic brain injury is a leading cause of injury death and long-term disability in the US. Several prognostic factors are associated with increased post-acute mortality in survivors of TBIs, including advanced age, male gender, pre-injury co-morbidity, long duration of unconsciousness, long hospitalization and persistent vegetative state at discharge. Of note, these prognostic factors have been identified in civilian studies that either exclude or under-represent patients with penetrating injuries. Therefore, the effect of mechanism of injury on long-term outcomes is not well known. For this reason, new research is warranted to identify those clinical factors which are most predictive of post-acute mortality after penetrating TBI.

The pathophysiologic differences between penetrating and closed TBI also remain poorly understood due to the lack of studies on this subject. Despite the absence of a clear delineation between injury types, the current guidelines for the management of penetrating TBI recommend defaulting to strategies used in closed TBI. Thus, diseases that appear to have different pathophysiologies and outcomes are often managed equally and perhaps not optimally. This is the case of ICP monitoring and hyperosmolar therapy, two management strategies that have been validated in closed TBI, but not in penetrating TBI. For this reason, new research studies are needed to improve and expand evidence-based TBI guidelines tailored specifically to penetrating TBI. In addition, future clinical studies (especially those funded by the US Department of Defense) on the efficacy of neuroprotective agents should avoid excluding patients with penetrating injuries from their series, since a therapeutic benefit may be inadvertently overlooked for this group.

If a single-institution study is unable to reach the desired statistical power due to a small number of penetrating injuries, then a multi-centre study should be considered to elucidate any outcome differences. In the case of penetrating TBI, there is also paucity of studies addressing the frequency of hypotension, hypoxia, coagulopathy and increased ICP and the independent effects of these pathologic features on acute mortality. Unfortunately, the inconsistent use of CT scanning and ICP monitoring after penetrating TBI raises questions about the criteria used for operative vs non-operative management, the frequency and therapeutic control of ICPs and the adequacy of cerebral oxygen delivery in this group of patients. Therefore, a prospective, multi-centre study of closed and penetrating TBI with access to pre-hospital data (e.g. vital signs, oxygen saturation, end tidal CO_2, procedures performed) is warranted to elucidate mechanism-specific risk factors associated with increased mortality.

Penetrating trauma, $GCS \leq 8$, pupillary light reflex abnormalities, elevated ICP and certain CT scan characteristics (Table II) are highly predictive of acute mortality after TBI. In patients with a closed TBI, the presence of subdural haematoma, subarachnoid haemorrhage, intraventricular haemorrhage or cisternal effacement increases the risk of early death substantially. Meanwhile, in patients with penetrating TBIs, missile tracks involving both hemispheres, multiple lobes or the ventricular system are associated with an increased mortality. Despite these facts, the frequency and the mortality risk associated with concomitant mass lesions after penetrating TBI are still poorly understood, and it is not known whether surgical evacuation of mass lesions provides a survival benefit to patients with

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penetrating TBIs with GCS ≤ 8. Given that ethical tenets would preclude a control trial in humans, an animal model may help elucidate the effect of surgery on this group's survival.

In view of the heavy burden of disability and the enormous financial losses imposed by TBI, it is better to prevent this disease from occurring than to face its devastating sequelae. However, if ever confronted with a patient with a TBI, the clinician should be able to manage this disease based on evidence-based guidelines tailored specifically to the mechanism of injury at hand. To this end, new research studies are needed to elucidate the pathophysiologic differences between penetrating and blunt TBI, a knowledge which would then aid in the development of new diagnostic and therapeutic strategies.

Acknowledgements

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Appendix 2

Juan Sebastian Malo

Permanent Mailing Address
Antonio Malo 1-81
Cuenca 361, ECU

Preferred Phone: 440-864-6879
Juan_Malo@meei.harvard.edu

Medical Education

Universidad de Cuenca, Ecuador 10/2001 - 07/2007   M.D: 08/2007

Medical School Honors / Awards

- Second Place, IV National Basic Science Contest, March 2003.
 - Second Place, Provincial Basic Science Contest, January 2003.
 - Award for Academic excellence, Honorable Faculty Council, May 2002.
- Second Place, III National Basic Science Contest, April 2002.
- First Place, Provincial Basic Science Contest, December 2001.

Examinations

USMLE Step 2 CS (Clinical Skills)   06/2008. Passed
USMLE Step 2 CK (Clinical Knowledge)   02/2009: 210
USMLE Step 1   05/2008: 215

Work Experience

11/2009 - 01/2010

Ministry of Public Health, Ecuador
Rural physician
Served as rural physician at Batallon de Selva #64 (Military Base). Provided medical care for the community, military staff and their families.

Volunteer Experience

08/2010 – Present

Latin American Initiative/Harvard Medical School
Admissions Committee Member

04/ 2010

HUGS Foundation/Department of Genetics HMS, Ecuador
Physician and translator
Recruited patients and families, collected blood and tissue samples for the genetic study of Microtia at HMS Seidman Laboratory. Assisted during surgical procedures for stage 1 through 4 of reconstructive microtia surgeries. Also served as a translator for patients and families during pre and postoperative screenings, rounds, recovery room and other settings.

09/ 2009

Medical Missions for Children (MMFC), Ecuador
Physician and translator
Assisted during reconstructive surgical procedures of cleft lip and palate, and served as a translator for patients and families during pre and postoperative screenings, rounds, recovery room and other settings.

08/ 2009

HUGS Foundation, Microtia Mission, Ecuador
Physician and translator
Assisted during surgical procedures for stage 1 through 4 of reconstructive microtia surgeries. Also served as a translator for patients and families during pre and postoperative screenings, rounds, recovery room and other settings.

06/ 2009 - 07/2009

Mount Sinai Hospital, New York
Observer
Attended and participated at morning and afternoon rounds, team meetings and at the department of surgery weekly M&M conferences. Followed cases during the pre, peri and post operative periods, observing procedures in the operating room as well as in the inpatient and outpatient settings.

03/ 2009 - 05/2009

Homero Castanier Hospital, Ecuador
Surgical second assistant
Assisted in procedures at the division of Thoracic surgery.

07/ 2008 - 09/2008

Cleveland Clinic Foundation, Ohio
Observer
Observed procedures in both the Surgery and Anesthesia departments, inside and out the Operating room, attended and participated in rounds.

09/ 2005 - 03/2006

University's Communitarian Extension, U. of Cuenca, Ecuador
Caravan leader
Organized and coordinated the activities to be assigned to the different brigades. Delivered direct medical care to patients, under the supervision of a professor assigned by the school.

07/ 2005 - 06/2006

Student Association, School of Medicine, U. Cuenca, Ecuador
President
Performed duties as the students' representative at the Faculty Council, Academic Reform Committee and other entities as required. Some of my obligations consisted of being in charge of coordinating different scientific, cultural and social activities, as well as organizing and working at the Medical Caravans traveling to underserved communities in the southern region of Ecuador. Was president and editor of the school magazine "Pulso".

07/ 2005

II People's Health Assembly, Ecuador
Translator and guide
Acted as guide and translator for international physicians and students participants of the "Health in the hands of the People" open house.

10/ 2004 - 05/2005

Pediatric Club, School of Medicine, U. of Cuenca, Ecuador
Vice-President
My responsibilities were to be in charge of coordinating and participating in activities such as scheduling weekly visits to the mothers and kids to check on their progress and needs during hospitalization, also special visits with "hospital clowns", for the children of the Pediatrics Department at the University Hospital. Also, coordinating social and cultural activities for the

acquisition of medical supplies for the Department.

12/ 2002 - 01/2003

University's Communitarian Extension, U. of Cuenca, Ecuador
Brigade member
Gave preventive medicine workshops and lectures to families, and to children at the local school.
Checked and recorded vital signs as part of the physical examination during consults.

07/ 2002 - 06/2003

Student Association, School of Medicine, U. Cuenca, Ecuador
Pro-Secretary
In charge of coordinating activities and looking out for the well being of first year students.

Research Experience

01/2010 - Present

Harvard Medical School, MEEI, Massachusetts
Research Fellow, Tessa Hadlock, MD
Study the effects of various pharmacologic, mechanical, and electrical interventions on facial
nerve regeneration, using a rodent facial nerve model. Explore the effects of passive assistance
therapy and sensory protection on nerve regeneration in the face. This experimental paradigm
involves rodent microsurgery, animal conditioning and testing, data analysis, and manuscript
preparation. Also involved in clinical research data acquisition and analysis in the Facial Nerve
Center.

04/2009 - 06/2009

Cinterandes Foundation, Ecuador
Research Assistant, Edgar Rodas, MD, FACS
Involved in two projects creating the data base of the mobile surgical unit: Operative experience
with Inguinal and Femoral Hernias; Incidence of Inguinal Hernia concomitant with
cryptorchidism.

01/2004 - 06/2004

Meditac-NASA Telehealth/VCU/Cinterandes Foundation, Ecuador
Telemedicine operator, Edgar Rodas, MD, FACS
Data collection of networked telemedicine presurgical screening for telemedicine test beds.
Running telemedicine conferences with national and international telemedicine stations.

Publications

Peer Reviewed Journal Articles/Abstracts

Hadlock TA, Malo JS, Henstrom DK. Free Gracilis Transfer for Smile in Children: The MEEI Experience in Excursion and Quality of Life Changes. Archives of Facial Plastic Surgery. Publication Status: Accepted.

Henstrom DK, Malo JS, Cheney ML, Hadlock TA. Platsymectomy: An Effective Intervention for Facial Synkinesis and Hypertonicity. Archives of Facial Plastic Surgery. Publication Status: Accepted.

Oral Presentation

Heaton, J., Knox, C., Malo, J., Hadlock, T. (2011, April). A System for Delivering Mechanical Stimulation to the Rat Whisker Pad during Facial Nerve Regeneration.
Oral Presentation presented at: 5th International IEEE EMBS Conference on Neural Engineering; Cancun, Mexico.

Henstrom, D., Malo, J., Cheney M., Hadlock T. (2010, September). Platsymectomy: An Effective Intervention for Facial Synkinesis and Hypertonicity.
Oral Presentation presented at: AAFPRS Annual Meeting; Boston, MA.

Rodas, E., Malo, J. (2009, May). Herniorrafia Convencional. Oral Presentation presented at: XXXIII National Surgery Congress; Cuenca, Ecuador.

Hobbies & Interests
Sports: Tennis, basketball and running. Outdoor activities: hiking and camping. Passionate about travel and learning about new cultures.

Language Fluency (Other than English)
I was born and raised in Cuenca, Ecuador; Spanish is my first language.

Other Awards/Accomplishments
- First Place, University Provincial Basketball Championship. 2002, 2004, 2005.
- First Place, Long Jump, University Provincial Track and Field Championship. 2002-2006.
- First Place, Long Jump, South American Track and Field Grand Prix. Cuenca, Ecuador, 2004.
- Goodwill Ambassador, Ministry of Tourism of Ecuador. Quito, Ecuador, 2000.

Appendix 3

ANIMAL WELFARE COMMITTEE

6410 Fannin Street
UPB 1100
Houston Tx, 77030

713-500-7944
Fax 713-500-7951

APPROVAL – ANIMAL PROTOCOL

October 21, 2010

HSC-AWC-10-154- "Characterization and Application of a Large Animal Model of Penetrating Ballistic Brain Injury (PBBI)"

PI: Charles Wade, PhD

SPECIES: Swine

NUMBER OF ANIMALS APPROVED TO ORDER: 30

FUNDING AGENCY: DOD (W23RYX0168N601)

PROVISIONS: *NONE*

APPROVED: At a Convened Meeting

APPROVAL DATE: September 24, 2010   EXPIRATION DATE: September 30, 2011

CHAIRPERSON: Cynthia Chappell, Ph.D.

Approval is given to initiate this protocol for the use of animals, contingent upon compliance with any other provisions.

REVISIONS REQUIRED BY THE AWC – If the AWC requires that revisions be made to a protocol which has already been submitted for funding, the PI must submit the revisions to the funding agency as soon as the revised protocol/materials have been approved by the AWC.

CHANGES – Revisions must be submitted for review and approval prior to implementation. Minor changes, e.g. dosing regimens, methods of euthanasia, anesthesia, surgery, etc. may be submitted in memo from. If changes are extensive, OR INVOLVE ANOTHER SPECIES, A NEW SET OF ANIMAL protocol Review Forms must be submitted.

The use of animals in research and any subsequent changes in the animal protocol must be approved by the AWC. Locations for the housing and manipulation of animals are contingent upon the health status of the animals, facility barrier level, containment level, and the availability of space. While appropriate housing of all animals is managed by CLAMC, housing decisions for the IMM are made in consultation with the **IMM Vivarium Committee**. The locations for AWC-approved animal manipulations outside of the barrier but within IMM facility must be endorsed by the IMM Vivarium committee since such activities may compromise the integrity of the barrier.

GRANT RENEWALS/SUBMISSION TO ANOTHER FUNDING AGENCY – If the protocol involving animals is identical to an approved protocol, send a memo to that effect to the AWC office, which also gives the Animal Protocol Review Number and title of the approved, protocol, and the name of any new title/funding agency. Include the first page of the new grant, the abstract, and the section describing the animal work (Section 2.F for NIH grants).

ANIMAL PROTOCOL REVIEW NUMBER – Animals purchased with the number listed above may be used only for the protocol(s) approved under this number.

PLEASE NOTE- It is your responsibility to ensure that all personnel working with animals are adequately trained. If individuals on your projects require training, contact Dr. Chris Smith x7732 to discuss training options.

ACURO Animal Use Appendix for Research Involving Animals
ABBREVIATED VERSION

NOTE: ACURO will ONLY review protocols that have been approved by your IACUC.
*****Animal work MAY NOT be initiated until the awardee receives ACURO approval.*****
*****Animal work initiated before receipt of ACURO approval will not be funded.*****

DoD-funded institutions using animals in research, product development, testing and education projects must provide electronic copies of the following documents to their DoD program manager for DoD US Army Medical Research and Materiel Command (USAMRMC) Animal Care and Use Review Office (ACURO) review and approval:

   a. a copy of their **IACUC-approved protocol(s)** (ACURO will ONLY review **approved** protocols)
   b. a copy of all IACUC-approved protocol amendments or modifications
   (**major** changes must be reviewed and approved by ACURO **PRIOR** to implementation)
   c. a copy of this completed Appendix and associated documents for each IACUC-approved protocol.

This requirement also applies to all subcontractors using animals in support of DoD-funded projects or programs.

The DoD policies and requirements for the use of animals in DoD-funded research, development, testing and evaluation are described in DoD Directive 3216.1, dated April 17, 1995 and Army Regulation 40-33, *The Care and Use of Laboratory Animals in DOD Programs*, dated February 16, 2005. These requirements may differ from those of other funding agencies. Specific information requested in the following animal use Appendix is derived from requirements in the Animal Welfare Regulations (AWRs), the *Guide for the Care and Use of Laboratory Animals*, and other applicable Federal regulations and DoD directives. Use of the Appendix is intended to meet the requirements of these documents.

Questions concerning animal use and review should be directed to the USAMRMC ACURO:

Phone: 301-619-6694
Fax: 301-619-4165
Email: acuro@amedd.army.mil
Mail: U.S. Army Medical Research and Materiel Command
             ATTN: MCMR-RPA
             504 Scott Street
             Fort Detrick, MD 21702-5012

~~~~~~

Each section of this Appendix must be completed. Begin typing responses after the colon ("：") for each section to ensure your typing is not within the hidden text. It is important that you carefully **read the instructions** for each paragraph to ensure you provide a comprehensive response. The additional instructions and written explanations provided for individual paragraphs are red, *italicized,* and coded as hidden text. To view the instructions and/or examples for each section, select the "**Show/Hide ¶**" button on your tool bar (the button itself appears as the ¶ symbol). To print the hidden text, select "Print" on the drop down file menu. Under the "Options" button, select "Hidden text" under the "Include with document" section. Please <u>do not</u> submit copies with the hidden text printed out to ACURO.

There are no space limitations for the responses.

It is essential that only animal studies or procedures documented in an IACUC–approved protocol or amendment to the protocol be performed at your facility. Additionally, Principal Investigators or other delegated research personnel should keep accurate records and be able to provide an audit trail of all animal use that correlates to their approved protocol. ACURO will collect this information for end-of-year DoD animal use reports.

X	Yes		No	All animal studies described in the attached IACUC-approved protocol are funded by this DOD award/contract. If no, 🛑 ! You must use the **full version** of the Animal Use Appendix.

1. Administrative Data: (Provide Attending Vet, IACUC, and Research Office info for the work site.)

Awardee / PI Name:	Charles E. Wade PhD		
Awardee / PI Email:	Charles.E.Wade@uth.tmc.edu	**Phone:**	713-500-5391
Study PI Name:	Charles E. Wade PhD		
Study PI Email:	Charles.E.Wade@uth.tmc.edu	**Phone:**	713-500-5391
Animal Research Site (RS):	The University of Texas Health Science Center at Houston		
RS Attending Veterinarian:	Christopher Smith, DVM		
Attending Vet Email:	Christopher.S.Smith@uth.tmc.edu	**Phone:**	713-500-7732
RS IACUC Point of Contact (POC):	Cynthia Edmonds		
IACUC POC Email:	Cynthia.L.Edmonds@uth.tmc.edu	**Phone:**	713-500-7936
RS Research/Grants Office Point of Contact (POC):	Jodi.Ogden@uth.tmc.edu		
Research Office POC Email:	Osp@uth.tmc.edu	**Phone:**	713-500-3968
Animal Protocol Title:	Characterization and Application of a Large Animal Model of PBBI		

2. Total Number of Animals Used (by Species)/ USDA Pain/Distress Category :

SPECIES	TOTAL NUMBER	HIGHEST USDA PAIN/DISTRESS CATEGORY
Swine	30	D

USDA Pain/Distress Category Definitions:

Column B: Animals being bred, and animals being held for use in research, testing, teaching, experiments or surgery but not yet used for those purposes. This would include breeders (unless surgery, genotyping, or some other manipulation was involved) and ALL offspring produced on this protocol that were NOT subjected to any manipulations such as genotyping and NOT used for experimental purposes.

Column C: List the number of animals that will experience no more than slight or momentary pain or distress as a result of experimental manipulations or procedures on this protocol. Examples of procedures or manipulations that would require an animal to be placed in Column C are those involving not more than slight or momentary pain or distress in a human being to which that procedure is applied, such as injections or other minor procedures.

*Column D: List the number of animals that will potentially experience more than momentary or slight pain or distress that **WILL** be alleviated through the use of anesthetics and/or analgesics. General anesthetics given for surgical procedures or the use of analgesics or anti-inflammatory agents to relieve pain are examples of this category.*

Column E: List the number of animals that will experience more than momentary or slight pain or distress that will NOT be alleviated or relieved with anesthetics or analgesics. Examples include research procedures or manipulations in which alleviation of pain or distress are contraindicated for a scientifically justifiable reason such as the experimental results are likely to be confounded if drugs relieving pain or distress were administered.

3. Literature Search for Unnecessary Duplication: This search is required for all animal use proposals. <u>Note the specific database requirements in subparagraph a.</u>

    a. Literature Source(s) Searched:
http://www.ntis.gov/products/fedrip.aspxhttp://projectreporter.nih.gov/reporter.cfm

X	Biomedical Research Database (**REQUIRED**) http://brd.dtic.mil/

AND one of the following

	Federal Research in Progress (FEDRIP) http://www.ntis.gov/products/fedrip.aspx

or

X	Research Portfolio Online Reporting Tool Expenditures and Results (RePORTER) http://projectreporter.nih.gov/reporter.cfm

    b. Date of Search:
Both database searches were performed on 31 January 2011.
    c. Period of Search:
BRD: 1998-2008; RePORTER: 1986-2010
    d. Key Words and/or Search Strategy:
Penetrating, brain, injury, swine
    e. Results of Search:
The literature search revealed several projects that used the rat as a model for PBBI. While the concepts and knowledge presented in these studies are relevant, they do not overlap with the studies proposed herein. A large animal model is needed to determine the impact of PBBI in a clinically relevant way.

****Questions 5-8 refer to the Research Site and RS Principal Investigator.****

Information and/or documents required in questions 5-7 may be provided directly to ACURO by the RS Principal Investigator. If the RS Principal Investigator prefers that ACURO staff contact the institution to obtain this information and/or documents, the RS PI must specifically request this action in writing. The RS PI should send this written request via email to acuro@amedd.army.mil.

4. Institutional Animal Care and Use Committee(s) (IACUC) Approval(s):

Institutional Animal Use Protocol Number: HSC-AWC-10-154

IACUC approval date: 21 OCT 2010   Protocol expiration date: 30 SEPT 2011

5. Institutional Accreditation / Assurances:

    a. Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) Accreditation (do NOT provide AAALAC correspondence):

[X] Yes [ ] No   Animal work is being performed at an AAALAC International-accredited facility.

b. Public Health Service Animal Welfare Assurance Statement:

[ ] Yes [X] No   Animal work is being performed at a PHS-assured facility.

c. Non-accredited, Unassured Facilities: If neither 7.a. nor 7.b. above apply to the facility where animal work is being performed, submit a statement signed by the Institutional Official that states the care and use of animals will be conducted in accordance with the National Research Council's 1996 *Guide for the Care and Use of Laboratory Animals* and applicable Federal and DoD regulations.

d. Overseas / Foreign Country Animal Work:

[ ] Yes [X] No   Animal work will be performed outside the United States.

If "Yes," please contact ACURO (see contact information on cover page) for additional requirements.

e. Site Visits

[ ] Yes [X] No   Animal work involves at least one of the following species: dogs, cats, nonhuman primates, marine mammals. If yes, provide a planned start date for work in these species.

6. Research Site Principal Investigator Assurances:

The law specifically requires several written assurances from the P.I. Please read and sign the assurances as indicated (this page may be photocopied and signed).

As the Principal Investigator on this protocol, I acknowledge my responsibilities and provide assurances for the following:

A. Painful Procedures: I assure that discomfort and injury to animals will be limited to that which is unavoidable in the conduct of scientifically valuable research and that analgesic, anesthetic, and/or tranquilizing drugs will be used where indicated and appropriate to minimize pain and/or distress to animals.

B. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC and the U.S. Army Medical Research and Materiel Command **Animal Care and Use Review Office** (ACURO) prior to its implementation.

C. Duplication of Effort: I have made a reasonable, good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

D. Statistical Assurance: I assure that I have consulted with a qualified individual who evaluated the experimental design with respect to the statistical analysis, and that the minimum number of animals needed for scientific validity will be used.
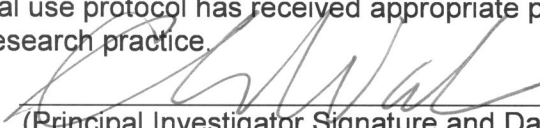
E. Training: I verify that the personnel performing the animal procedures/manipulations/observations described in this protocol are technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the procedures/manipulations.

F. Responsibility: I acknowledge the inherent moral, ethical and administrative obligations associated with the performance of this animal use protocol, and I assure that all individuals associated with this project will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to implement animal use alternatives where feasible, and conduct humane and lawful research.

G. Scientific Review: This proposed animal use protocol has received appropriate peer scientific review, and is consistent with good scientific research practice.

Charles E. Wade, PhD   2-1-2011
_____   _____
(Principal Investigator Printed Name)   (Principal Investigator Signature and Date)

NOTE: In accordance with Army Regulation 40-33, the USAMRMC Animal Care and Use Review Officer (or designee thereof) will conduct a site visit to all sites using nonhuman primates, dogs, cats or marine mammals in the proposal, or where a site visit is deemed warranted.