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Abstract: .

Traumatic brain injury – integrated approaches to improving clinical care and research

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Executive summary

A concerted effort to tackle the vast global health problem posed by Traumatic Brain Injury (TBI) is long overdue. TBI is a public health problem of huge, but insufficiently recognized, proportions. Globally, TBI is the leading cause of mortality in young adults and represents a major cause of death and disability across all ages, with the substantial burden of disability and death occurring in low- and middle-income countries. This Commission for *The Lancet Neurology* has the overall goals of providing information and expert recommendations to a broad audience of policy makers, funders, and patient representatives, as well as health care professionals and researchers, about deficiencies in current and past approaches, key requirements, and new paths for progress in TBI clinical care and research.

The epidemiology of TBI is changing: In high income countries (HICs), TBI is increasing in the elderly, due to falls while in low and middle-income countries (LMICs), the burden of TBI from road traffic incidents is increasing. Variations in data collection and reporting contribute to reported differences between regions and countries. Accurate epidemiologic monitoring and robust health economic data collection are important for informing health care policy and prevention programs, and require improvement. Highly developed and coordinated systems of care are crucial for management of patients with TBI. However, in practice, implementation of such frameworks is highly variable, and disconnects exist in the chain of care. Optimization of systems of care should be high on the policy agenda and could yield substantial gains.

TBI is a complex disease, with a lack of strong evidence to support treatment guidelines and recommendations. Most multicenter clinical trials of medical and surgical interventions have failed to show efficacy, despite promising preclinical results. At the bedside, treatment strategies are generally based on guidelines that promote a “one size fits all approach” and are insufficiently targeted to the needs of individual patients. Attempts to individualise treatment are hampered by the diversity of the disease, and the use of relatively simplistic methods for characterising initial severity and quantifying late outcome. Multidimensional approaches are essential to address these challenges. Further, we have failed to appreciate the risk of long-term disabling sequelae in patients with relatively mild injuries.

Prognostic models can help clinicians provide reliable information to patients and relatives, and facilitate comparative audit of care between centers and countries. There is an urgent need for further development, validation and implementation of prognostic models in TBI, particularly for less severe TBI. Advances in genomics, blood biomarkers, advanced MR imaging, and

pathophysiological monitoring, combined with informatics to integrate data from multiple sources, offer new research avenues to improve disease characterisation and monitoring of disease evolution. These tools could also aid understanding of mechanisms and prognosis, and facilitate targeted treatment strategies for individual patients.

This multitude of challenges in TBI - encompassing systems of care, clinical management, and research strategy - demand novel approaches to the generation of new evidence and its implementation in clinical practice. Comparative effectiveness research offers opportunities to capitalise on the diversity of TBI and systems of care, and assess therapies in real world conditions. The global challenges posed by TBI demand global collaborations and a change in research culture to endorse broad data sharing.

This Commission covers key topics that are critical to meet the global burden of TBI and reduce its effects on individuals and society. These include: epidemiology (section 1); health economics (section 2); prevention (section 3); systems of care (section 4); clinical management (section 5); better characterization of TBI for precision medicine (section 6); characterizing outcome (section 7); prognosis in TBI: linking initial severity to outcome (section 8); and new directions for acquiring and implementing evidence (section 9). Panel 1 summarises key messages from the Commission and provides recommendations to advance clinical care and research in TBI.

There is a need to raise awareness regarding the scale of the challenges posed by TBI. If we are to tackle the individual and societal burden of TBI, these efforts need to go beyond a clinical audience and address the public, politicians, and other stakeholders. We need to develop and implement policies for better prevention and systems of care. We also need a commitment to long-term investment in TBI research across a range of disciplines, so that we can determine best practice and facilitate individualized management strategies. A combination of innovative research methods and global collaboration stands the best chance of achieving these aims, and ensuring that progress in basic and clinical research is effectively translated into clinical practice and public health policy.

Panel 1

Key messages	Recommendations	Read more
Worldwide, TBI is the leading cause of injury-related death and disability, and a huge burden to patients and families.	Concerted efforts are required to address the vast global health problem posed by TBI. Policies aimed at reducing the burden and impact of TBI should focus on prevention, improving access to care and stimulating clinical research to improve treatment standards.	Part 1, 3, 4, 9
In LMICs, the incidence of TBIs due to traffic incidents is increasing, whilst in HICs TBI increasingly affecting elderly patients, mostly due to falls. Methodological variations, however, confound comparisons of epidemiologic patterns of TBI between regions, countries and continents.	An international consensus is required on definitions and improved standardisation of epidemiological monitoring of TBI by health-care professionals and governmental agencies, to allow accurate measurement of incidence, prevalence, and mortality, and comparison of rates of access to community, hospital and institutional care.	Part 1.5, 1.6, 4.5
Traumatic Brain Injury may represent an important modifiable risk factor for epilepsy, stroke and late-life neurodegenerative disease.	Studies are needed, both in children and adults, to better understand links between all severities of TBI and an increased risk of epilepsy, stroke and neurodegenerative disorders.	Part 1.4
Traumatic Brain Injury results in substantial health care and societal costs.	More effective TBI prevention is vital, and could deliver cost savings that help fund improved access to health care and research for TBI.	Part 2
Any risk of an early second injury after even a mild TBI should be avoided.	Professional sporting organisations should set an example for children and amateurs by removing any player with a suspected concussion from play immediately.	Part 3.4
Access to health care is often inconsistent between centres, regions,	Health care policies should improve access to acute- and post-acute care	Part 4

and countries, especially with regard to acute and post-acute care.	to reduce the impact on patients, families, and society.	
Evidence underpinning guidelines for medical and surgical interventions and rehabilitation for TBI is weak.	Increased funding is needed to develop robust evidence to inform medical, surgical and rehabilitation interventions and improve outcomes for patients with TBI.	Part 5
There is a need to improve the diagnosis and classification of patients with TBI, and to better target current and new therapies to the needs of individual patients.	Funding bodies should implement targeted funding calls for research that improves the precision of diagnosis, classification and characterisation of TBI using multi-domain approaches.	Part 6
Trauma affects the brain in complex ways, which impact multiple outcome domains.	Implement targeted funding calls to facilitate the development and validation of multidimensional outcome constructs that quantify the overall burden of disability from TBI.	Part 7
No validated quality indicators for TBI exist. A validated set of quality indicators is essential for benchmarking quality of care	Funding bodies should stimulate the development of quality indicators for TBI which should represent a mix between structure, process and outcome indicators	Part 8
Substantial between-centre variability in treatment and outcome in TBI offers unique opportunities for comparative effectiveness research (CER) to provide stronger evidence.	Fund CER to identify best practices and to improve the level of evidence for systems of care, and diagnostic and therapeutic interventions.	Part 9
Coordinated research efforts on a global basis are required to address TBI.	A commitment of governmental and non-governmental funding bodies, as well as industrial partners is desired to facilitate global collaborations and legacy research.	Part 9

Introduction

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force.[1] It varies in severity from mild TBI (which includes concussion) to moderate and severe TBI. Severe TBI carries a high mortality rate, estimated at 30-40% in observational studies on unselected populations.[2] Survivors experience a substantial burden of physical, psychiatric, emotional, and cognitive disabilities, which disrupt the life of individuals and families, and pose huge costs to society. Such disabilities are not restricted to more severe cases, but also occur frequently after moderate or mild TBI.

TBI is a growing public health problem of substantial proportions. Over 50 million TBIs occur internationally each year.[3] The epidemiology of TBI is changing: in high income countries (HIC), TBI incidence is rising in the elderly, while in low and middle income countries (LMIC), the burden of TBI from road traffic incidents is increasing. Across all ages, TBI represents 30 to 40% of all-injury related deaths, and neurological injury is expected to remain the most important cause of disability from neurological disease (2–3 times higher than that for Alzheimer disease or cerebrovascular disorders) till 2030.[4] TBI costs the international economy approximately US $400 billion annually (which, given an estimated Standardized Gross World Product (SGWP) of $73·7 trillion[5], represents approximately 0·5% of the entire annual global output.

The wide variations in clinical manifestations of TBI are attributable to the complexity of the brain, and to the pattern and extent of damage, which depends on type, intensity, direction and duration of the external forces that cause TBI. In traffic related injuries, acceleration-deceleration forces can result in immediate shearing of connecting nerve fibres, or trigger progressive loss of connectivity over time. Forces generated by a fall or blow to the head more often cause bruises (contusions). Individuals may react very differently to similar injury forces. Conceptually, it is important to distinguish between the primary damage, inflicted at the time of injury, and secondary damage, which evolves over hours, days, weeks, or months, or even over a lifetime in some cases. Secondary damage is substantially driven by host responses to the primary injury. As a bruised ankle may swell following injury, so may the brain. The difference is that the brain is contained within the rigid skull, and any swelling results in increased pressure within the skull. This increased pressure, in turn, can lead to life threatening shifts of brain structures or make it more difficult for blood to flow through the brain, resulting in ischaemia and deprivation of oxygen to the brain. TBI is best viewed as a collection of different disease processes (figure 1), with different clinical patterns and outcomes, each requiring different approaches to diagnosis and management.

TBI may also impose a long-term risk for neurodegenerative disorders[6,7], stroke[8,9], Parkinsonism[10,11,12], epilepsy[13] and an increased long-term mortality rate[14,15] compared to the general population. These risks also occur in milder forms of TBI, especially after repetitive injuries. This accumulating knowledge makes it clear that TBI is not a single event, but can be a chronic and often progressive disease with long-term consequences (see Patient Testimony, which illustrates a continuing process of coping and adaptation – even following an ostensibly good recovery).

Clinical progress has not kept pace with the rising global burden of TBI and recognition of the prolonged effects of injury. The most recent major breakthrough in clinical management was the introduction of Computerized Tomography (CT) scanning into routine care – now more than 40 years ago. However, since then, outcome after TBI has seen no major improvement in HICs with developed trauma systems. This lack of progress is caused by many factors, both political and clinical. Public and political awareness of the magnitude of the problem caused by TBI—including the clinical impact on patients, families, and society, and public health burden and costs to society—is low. In addition, there has been insufficient clinical recognition of the complex heterogeneity of TBI, in terms of disease type, outcome, and prognosis. Treatment approaches provide insufficient recognition of specific needs of individual patients, and disconnects exist along the chain of trauma care, especially between acute- and post-acute care. Clinical research has, until recently, mainly focussed on more severe TBI, but the vast majority (70 to 90%) of patients suffer from mild TBI. Though the individual impact of mild TBI is less, the category as a whole makes the largest contribution to the global burden of disability, and structured follow-up and timely intervention in this group could deliver substantial gains in public health and societal costs.[16]

We believe that a strategic global collaboration is required at several levels. First, policy makers and funders need to support an integrated effort by the entire neurotrauma community to identify best practices for systems of care and management, including approaches to TBI prevention. Second, our research strategies need to better characterize TBI through the disease course, and incorporate emerging research paradigms and tools into clinical studies. While the need for increased research funding is undeniable, these organizational improvements are essential to maximize the benefit of developing global research collaborations, and achieve the best possible returns on research funding. Finally, we need an intensive knowledge transfer exercise to implement the outputs of these efforts into clinical practice. Such implementation requires that we inform and involve health policy makers, health care professionals, and the general public, regarding the magnitude of the problem, the extent of (and gaps in) our current knowledge, and emerging advances.

The overall aims of this Commission are to set out directions for improvements in clinical care and to establish research priorities. We aim to provide a foundation for implementation of policy measures that minimize the risk of TBI and maximize chances of recovery when it does happen. This manuscript represents the efforts of a consortium of leading health-care professionals with expertise in epidemiology, health economics, diagnosis, treatment, outcome assessment, biology, and ethics, all of whom are involved in the International Initiative for Traumatic Brain Injury Research (InTBIR) studies, with input provided by other collaborating specialists and, crucially, by patients.

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Figure 1: The multiple faces of TBI

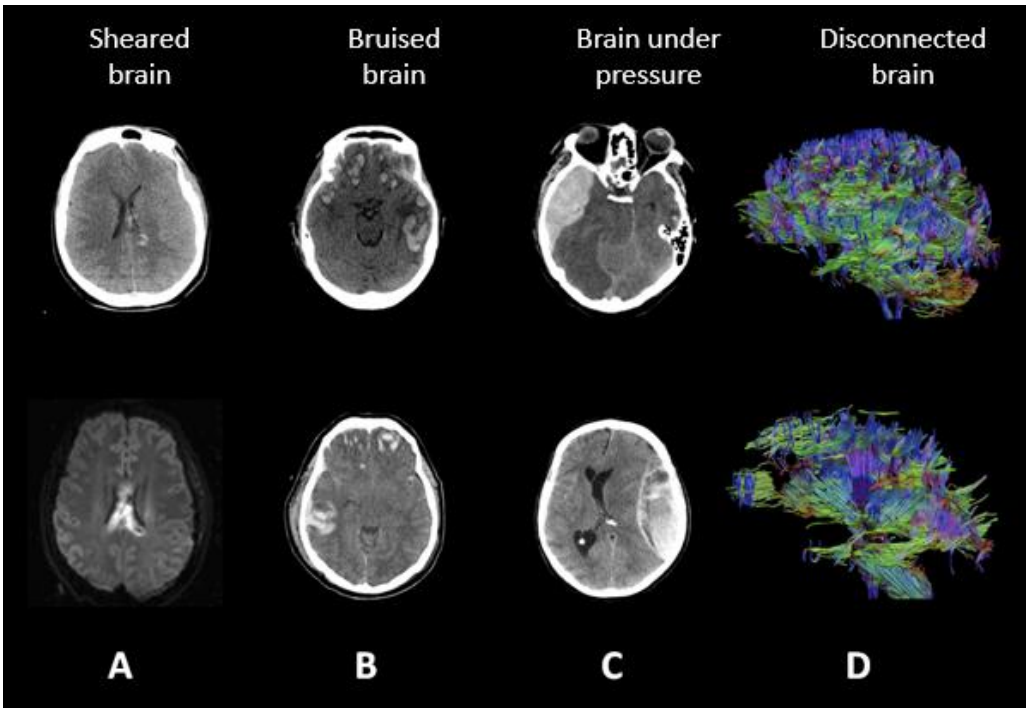


Fig 1A "Sheared brain": shows the typical picture of diffuse axonal injury on CT (top panel) and diffusion weighted MR imaging (lower panel).

Fig 1B "Bruised brain": shows contusional brain injury in two patients, typically located in the frontal and temporal regions.

Fig 1C "Brain under pressure" shows a typical epidural haematoma (bleeding between the skull and outer coverings of the brain) in two patients. This haematoma compresses the brain and is life-threatening due to

pressure on the brain stem (top panel). This constitutes a neurosurgical emergency (minutes count!), and patients may recover completely if operated on time.

Fig 1D "Disconnected brain" shows global imaging of white matter tracts in a patient with TBI, on day 12 (top panel) and at 6 month follow up (lower panel). Note the extensive progressive late white matter loss over time.

Living with traumatic brain injury - a patient testimony (abbreviated version)

By James Piercy, MSc – UK Acquired Brain Injury Forum (UKABIF) ambassador

I sustained a traumatic Brain Injury (TBI) in 2011. I have made a good recovery and learnt lots about what happened to me and the wider impacts of TBI. This is my story reflecting my experience and some of that learning.

The injury

Like many others I acquired my TBI in a car accident. I was unconscious at the scene and flown to my local trauma centre. A scan revealed a bleed in my frontal lobe and smaller haemorrhages through the brain. Prognostic indicators gave a poor chance of good outcome after six months but I have done better than expected. Better prognostic models for individual patients and families would be very valuable. I was monitored closely, emerging from post-traumatic amnesia after 25 days and transferring to a hospital closer to home. I was discharged after 7 weeks and began slow rehabilitation.

The aftermath

After 5 years I am doing well. I have made a very good recovery and am back to work part-time. I need to plan my time carefully and avoid situations which leave me very fatigued. This can leave me with speech problems and makes decision making and concentration difficult. Learning to live with these minor changes is the biggest challenge of TBI for many patients.

Despite improvements in acute care for patients, dealing with the chronic conditions which follow TBI remains a huge challenge for the individuals and those which support them. I consider myself lucky to have done so well putting my recovery down to prompt intervention, strong support from family and friends and my own determination to improve.

Read more: the full patient testimony is included in the supplementary material (ESM 1)

Part 1: Epidemiology of TBI

Key messages	Recommendations
1. Worldwide, TBI is the leading cause of injury-related death and handicap, and a huge burden to patients and families	1. Concerted efforts are required to address the vast global health problem posed by TBI. Policies aimed at reducing the burden and impact of TBI should focus on prevention, improving access to care and stimulating clinical research to improve treatment standards.
2. Current epidemiologic monitoring is incomplete, especially for mild cases of TBI.	2. Increased funding for rigorous epidemiological studies is needed to capture the changing patterns of epidemiology and identify high-risk groups and key targets for improved prevention and management of TBI.
3. In LMICs, the incidence of TBIs due to traffic incidents is increasing, whilst in HICs TBI increasingly affecting elderly patients, mostly due to falls. Methodological variations, however, confound comparisons of epidemiologic patterns of TBI between regions, countries and continents.	3. An international consensus is required on definitions and improved standardisation of epidemiological monitoring of TBI by health-care professionals and governmental agencies, to allow accurate measurement of incidence, prevalence, and mortality, and comparison of rates of access to community, hospital and institutional care.
4. Traumatic Brain Injury may represent an important modifiable risk factor for epilepsy, stroke and late-life neurodegenerative disease.	4. Studies are needed, both in children and adults, to determine links between all severities of TBI and an increased risk of epilepsy, stroke and neurodegenerative disorders.

Introduction

Globally, traumatic brain injury (TBI) is a major health and socioeconomic problem, associated with high costs. In LMICs, the rising burden of TBI from increases in road traffic incidents predominantly affects young individuals. Changing epidemiology of TBI in HICs is attributable to a high and increasing incidence of TBI in paediatric and elderly subpopulations. Increases in TBI are also occurring in the contexts of sports and conflict settings.

Reported incidence and mortality rates for TBI vary greatly between countries and regions. This, in part, reflects variations in acquisition and reporting of epidemiological data, making interpretation of official statistics difficult. There is considerable variability in defining TBI (panel 1·1), resulting in difficulties in diagnosis and case ascertainment. Relatively few epidemiologic studies on TBI report age-adjusted data, which are required for valid comparisons between different countries (which have differing population demographics).

Robust epidemiological data are essential to quantify the public health burden of TBI, to inform policies for prevention, to understand the health care needs imposed by the disease, and to allow appropriate allocation of health care resources. Substantial efforts are required to correct current deficiencies in epidemiologic monitoring.

This section provides an overview of the epidemiology of TBI, highlights the increasing burden of TBI in LMIC, and reviews the evidence for changing patterns of epidemiology in HIC. We propose ways to enhance epidemiological data collection, and to improve the utility of such data in informing health-care policy and prevention programmes.

Panel 1·1.: Definitions of TBI

WHO definition[17]

"An acute injury to the brain from mechanical energy to the head from external forces, excluding injuries relating to drugs, alcohol or substance abuse, medication or cause by other injuries or treatment."

- A broad definition of TBI, which is widely used, but some ambiguity exists as to what constitutes "an acute injury to the brain".

American Congress of Rehabilitation Medicine definition[18]

"A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: 1. any period of loss of consciousness; 2. any loss of memory for events immediately before or after the accident; 3. any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused); and 4. focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following: loss of consciousness of approximately 30 minutes or less; after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15; and posttraumatic amnesia (PTA) not greater than 24 hours."

- This definition is specific to mild TBI and excludes patients with more severe TBI, which conflicts with the concept that the severity of TBI lies along a continuum.

National Institute of Neurological Diseases and Stroke definition[1]

"TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force."

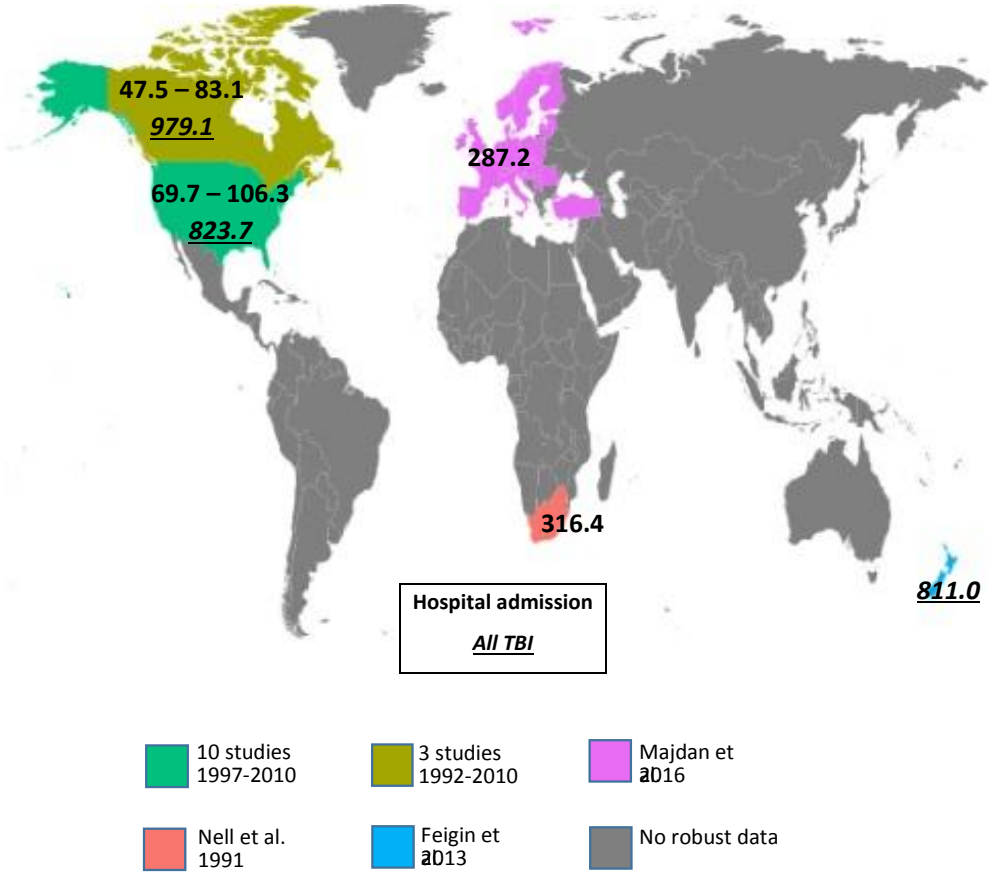
- This statement acknowledges potential confounders to TBI diagnosis, and suggests that symptomatology, imaging, details of the accident, and wider context should all be taken into account to inform diagnosis.[1]

[1]The term "concussion" is often used synonymously to characterise mild TBI.[19]

1·1 Incidence of TBI

Reported incidence rates of TBI across the world vary considerably, ranging from 47·5 to 979 per 100,000 population, with substantial gaps in robust data for many parts of the world - including those where TBI rates are likely to be high. *Figure 1·1* summarizes available data on age-adjusted incidence rates, the majority of which derive from upper and middle low-income countries.

Figure 1.1.: Worldwide incidence by age-standardised rates



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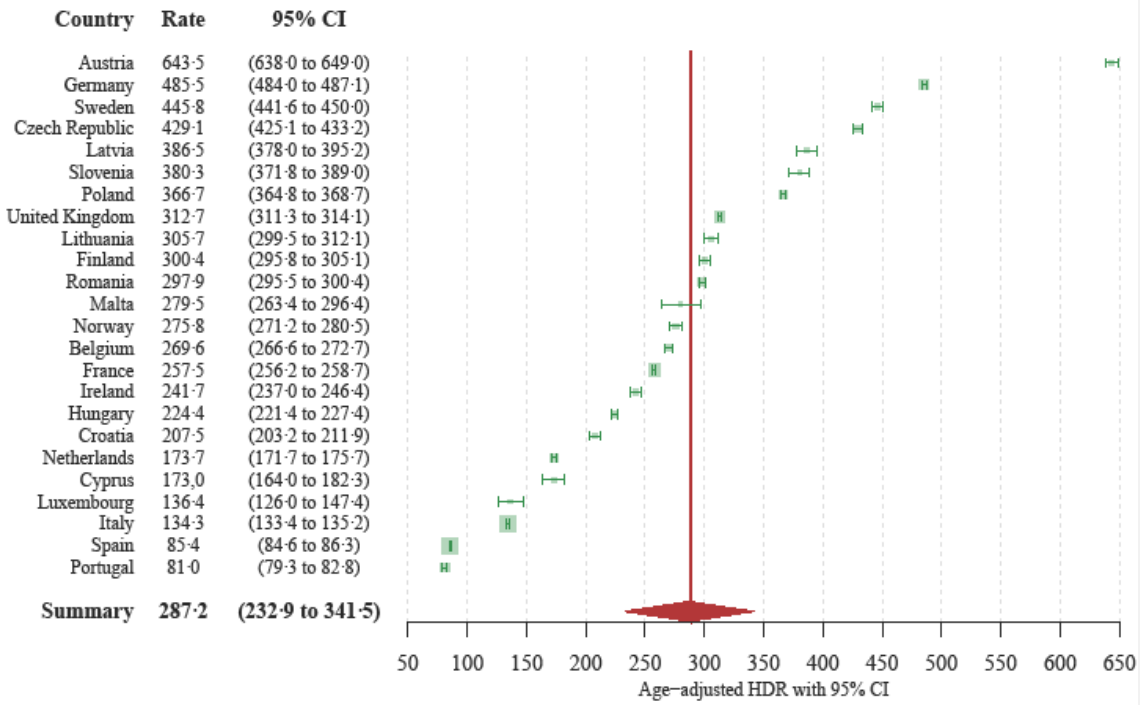
Canada: [30] [31] [32]

Europe: [33]

New Zealand: [3]

South Africa: [34]

Figure 1·2.: Age-adjusted rates of hospital discharge after TBI in Europe, differentiated by country with pooled estimates for 24 European countries



Reproduced with permission from Majdan et al 2016.[33]

Higher incidence rates for TBI are observed in population-based studies with broad definitions of TBI.[3,32] Projections from such population-based studies estimate 50-60 million new TBI cases occurring annually worldwide, over 90% of which are mild TBI.[3] For the European Union (28 Member States) we estimate at least 2·5 million new cases of TBI each year (*panel 1·2*), and in the US, the total number of patients with a new TBI has been reported to approach 3·5 million per year.[35] A recent study, using standardised Eurostat data from 24 countries, estimated 1·5 million hospital discharges and 57,000 TBI related deaths for the year 2012.[33] The pooled age-adjusted incidence rate of TBI (hospital discharges) was 287/100,000, with enormous differences between countries (*figure 1·2*). These differences are likely to be due to differences in methodology, rather than reflecting true variation.[33]

The US Centers for Disease Control (CDC) and Prevention surveillance studies of TBI have used standardized case definitions and methods of data collection for nearly three decades[36,37], and focus on emergency department (ED) visits, hospitalizations, and deaths. Recent data indicate that

each year 2·07 million Americans are treated and released from an ED, 300,000 are hospitalized and discharged alive, and 53,000 die as a consequence of TBI.[38] TBI is a contributing factor in a third (30·5%) of all injury-related deaths in the US (with an average reported number of 169,000 injury related deaths per year between 2002-2006).[39]

Panel 1.2.: Estimated annual TBI volume in the European Union and the USA*

	European Union	**USA**
Population (millions)	510	321
Total number of new cases annually *indexed per 100 million population*	2·5 million *0·49 million*	3·5 million *1·09 million*
Total number of hospital admissions annually *indexed per 100 million population*	1·5 million *0·30 million*	283,630 *0·09 million*
Total number of deaths from TBI annually *indexed per 100 million population*	57,000 *11,220*	53,000 *16,510*

*Estimates for the EU are based upon.[33,40,41,42] Estimates for the US are based on.[29,35,43]

The numbers for the EU and US are discordant. Relative to the population (EU: 510 million; US: 321 million) the number of deaths due to TBI appears lower in the EU than in the US. Much of this difference may arise from the high rate of death from firearm-related wounds in the US, which often involve head wounds in fatalities, and are estimated at 10·5/100,000[44] This rate is exceeded only by some Latin American nations, and far higher than average rates in the EU (1·1/100,000).[45]

Relative to population size, the reported number of hospital admissions for TBI is over three times higher in the EU compared to the US. In contrast, the reported number of new cases per year in the US, adjusted for population size, is double that of the EU. These differences are likely mainly due to differences in case ascertainment, although variation in hospital admission policies may also contribute. These discrepancies and differences in estimated costs of TBI *(see part 2·1)* within the EU, and between the EU and the US, motivate investigation, and reveal methodological diversity, which highlights a need to standardise the global conduct and reporting of incidence studies *(see part 1·7)*. Furthermore, studies in LMICs are urgently needed.

1·2 Prevalence of TBI

Accurate data on TBI prevalence are even more limited than for incidence, particularly for LMICs. A meta-analysis of 15 prevalence studies[46] revealed that of a total sample of 25,134 adults, 12% had experienced a more serious TBI with loss of consciousness, with males at more than double the risk

of females. Prevalence in young adults appears higher, with one birth-cohort study revealing that over 30% had experienced at least one TBI requiring medical attention before the age of 25 years.[47] Given the increasing incidence in elderly populations, it is reasonable to conclude that half the world's population have experienced a TBI. This inference is supported by a randomly-sampled population-based survey in Colorado, which revealed that 42% of respondents reported at least one TBI in their lifetime (36% mild and 6% moderate to severe injury).[48] TBI results in a substantial ongoing health impact: In the USA, an estimated total of 3·17 million people live with permanent sequelae of past TBI.[49] TBI is among the top three specific neurological diseases accounting for neurodisability globally, both at present, and in projections up to 2030.[4] Concerted efforts are required to reduce this high burden.

1·3 Mortality and years of life lost from TBI

Death rates after TBI are variably reported as mortality rates or as case-fatality rates in different studies. Mortality rates relate the number of deaths to the population size and are, for example, expressed as number of deaths per 100,000 population. Case-fatality rates relate to the number of deaths in a specific population with the disease, e.g. the death rate for patients admitted for TBI. Case fatality rates are therefore greatly influenced by case-mix, and will be higher for patients with severe TBI, compared to those with mild TBI. These parameters capture the number of deaths relative to different populations at risk. However, the public health consequences of TBI deaths are better captured by Years of Life Lost (YLL), which quantifies the numbers of years the person would have lived had he not have died due a TBI.

Reported mortality rates vary widely, with figures ranging from 0·33 (Spain)[50] to 39 (Brazil)[51] per 100,000 person-years. The US CDC reports population based mortality due to TBI at 17·1/100,000.[29] Using Eurostat data for the year 2012, Majdan and colleagues calculated an age-adjusted mortality rate of 11·7/100,000 (95% CI: 9·9-13·6) for 25 European countries,[33] but reported that study methodologies (diagnostic criteria, case-ascertainment) varied substantially, and did not always differentiate deaths directly due to brain injury from those due to other complications. Most studies focused on severe TBI, and little is known about how often a non-severe TBI contributes to mortality. Patterns of TBI mortality depend on age and injury mechanisms, and are changing over time. High-income countries show declining rates of traffic related TBI deaths and increasing death rates from fall-related TBI.[52] The highest mortality is in adults over 60 years of age *(see also part 1·5)*. Studies estimating YLLs attributable to TBI are relatively scarce: For the Netherlands[53] (2010-2012) a total of 118,207 YLL and for New Zealand (2010)[54] 14,386 YLL have been reported as caused by TBI. A recent analysis in 16 European countries revealed a total of almost 400,000 YLLs

because of TBI –translating to a pooled age-adjusted rate of 271·4 (95%CI = 214·7-328·2) YLLs per 100,000 person years and to an average of 25·4 (95% CI=23·0 – 27·9) YLLs with each TBI death. Nearly 74% of all YLLs due to TBI affect individuals in age groups with work potential (15-64 years) (personal communication, Majdan).

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The high acute mortality in severe TBI is well recognized: TBI is a contributing factor in 39% of injury –related deaths in the EU[33] and a third (30·5%) of all injury-related deaths in the US.[39] Long-term mortality in TBI is a substantial, but less well recognized problem: TBI survivors continue to experience mortality rates that exceed those both in age and sex matched population controls, and in comparable cohorts with non-TBI trauma, for many years.[55] In patients aged 15-54 years, the death rate 13 years post-TBI was more than 6 times higher than in community controls.[14] The Global Burden of Disease studies showed a pooled standardized mortality ratio of 2·18 (95% CI=1·88- 2·52) for TBI survivors.[56] This excess mortality is in part attributable to expected consequences and associations of TBI, such as epilepsy, but also due to an increased risk of illnesses not directly related to injury, such as pneumonia, septicaemia and respiratory and digestive disorders.[57] TBI has been shown to shorten life expectancy by 6 years.[58]

1·4 TBI as a risk factor for neurodegenerative disease and stroke

TBI may be a major risk factor for late neurodegenerative disorders such as dementia and Parkinson's disease (PD), reinforcing the view that TBI may evolve into a progressive lifelong illness. A meta-analysis reviewing 15 case-controlled studies showed a pooled odds ratio of 1·58 (95% CI 1·21 to 2·06) for development of later life dementia after a single TBI with loss of consciousness.[6] TBI sustained after 55 years of age is associated with a 44% increased risk of developing Parkinson's disease within the subsequent 5-7 years.[11] A more recent population-based clinical and neuropathology survey confirms this for the incidence and progression of Parkinsonism, and for Lewy body disease, but not for dementia or dementia related pathology more generally.[12]

TBI associated dementia may clinically and pathologically be distinct from AD, with more patients experiencing behavioural symptoms such as depression, agitation and irritability.[59] Preliminary estimates of population attributable risk, based on TBI prevalence and the relative risk of dementia in TBI survivors, indicate that as much as 5-15% of the population burden of dementia may be due to brain trauma.[60]

Repetitive mild TBI can result in a distinct pathology, chronic traumatic encephalopathy (CTE).[61] In his landmark clinical account of the punch-drunk syndrome in boxers, Martland provided the first clinical description of the progressive neuropsychiatric sequelae associated with repetitive mild

TBI,[62] and its neuropathological substrate was detailed by Corsellis et al.[63] (see also review on long-term consequences of TBI). Recent autopsy reports identify similar clinical phenotypes in non-boxer athletes from 'high exposure' (to concussion/mild TBI) sports such as American football, Ice hockey, soccer and rugby, and in ex-military personnel (*see Section 1·7*). In these descriptions, the distinguishing clinical features comprise a triad of behavioural, mood, and cognitive deficits,[64] variably associated with pyramidal and extra-pyramidal dysfunction and cerebellar impairment. [65] These phenotypes provide the clinical correlate to pathology of CTE.[66]

A related (but distinct) issue is the fact that some TBI survivors experience ongoing cognitive decline in the medium term (months to years), rather than showing clinical improvement or remaining static. Long-term disability may change with time, and age-related decline in cognitive reserve may unmask the consequences of an earlier TBI.[7] A 13-year longitudinal study in Glasgow[14] found such late deterioration in up to 50% of patients, which may be visualized by progressive changes on advanced neuroimaging.[67]

Other evidence suggests that TBI is an independent risk factor for stroke.[8] A retrospective case-control study from Taiwan showed that a past history of TBI doubled the risk of stroke (hazard ratio [HR], 1·98; 95% CI, 1·86-2·11) and increased post-stroke mortality (odds ratio, 1·57; 95% CI, 1·13-2·19).[9]

Post-traumatic epilepsy (PTE) is a well-recognized complication of TBI[13], occurring in up to 15 – 20% of cases of severe brain trauma, and 3–5% of those who suffer moderate TBI.[68,69] Even mild TBI increases the risk of epilepsy by a factor of 1.3 over the general population.[69] TBI accounts for approximately 4% of epilepsy in the general population and is the leading cause of epilepsy with onset in young adulthood.[68]

The association between TBI and an increased risk of late neurodegenerative disease[62,70] remains poorly understood, largely a consequence of the retrospective nature and limited scope in many past studies, and small cohort sizes in recent, more comprehensive reports. There is a pressing need for research into the incidence, clinical presentations and risk factors in TBI-associated neurodegenerative diseases and their overlap with existing, better-characterised disorders, such as AD and PD.

1·5 TBI and crime

TBI appears to be a risk factor for criminal behavior. A Finnish birth cohort study showed that a TBI during childhood or adolescence was associated with a fourfold increased risk of mental disorder with coexisting offending in adult males.[71] A Swedish total population, data linkage study, showed that 8·8% of those with TBI committed violent crime, compared with 3% of non-injured controls – with risk being greater among TBI cases when compared with siblings.[72] Prevalence of TBI is much greater – 3 to 8 times as high - in offender populations compared to non-offender groups.[73] In an UK prison study Williams et al. found that 16% had experienced moderate-to-severe TBI and 48% mild TBI[74]. About half of young offenders have had loss of consciousness, with repeated injury being very common[73]. TBI in offenders is associated with earlier offending, higher levels of re-offending[74], violence[75], and suicidality.[76] A neuroimaging study of prisoners in Germany revealed offenders displayed a significantly higher rate of morphological abnormality.[77] Violent offenders had significantly higher rates compared to nonviolent offenders and controls.

Intervention for the neurodisability of ADHD in offenders - possibly moderating impulse control - has reduced crime by 30%.[78] Screening for, and managing TBI, in offenders is possible.[76] Such initiatives may enable offenders to change behaviour and reduce crime in society.

TBI: a big problem in big countries	
China	**India**
China has a population of 1·3 billion. No reliable nationwide data are available on the epidemiology of TBI in China. Several large-scale population-based studies, conducted in the 1980s[79,80,81], report an incidence of head trauma of 55·4 to 64·1 per 100,000 population. This incidence is much lower than reported from other countries, and is likely caused by incomplete case ascertainment. The current burden of care for TBI is experienced as very high in many Chinese centres with many neurosurgical departments nearly exclusively treating TBI. Traffic incidents are the most common cause of TBI (54%), followed by falls (32-33%) and violence (9-11%)[82,83]. The high rate of traffic-related TBI is unsurprising, as car ownership has increased at a compound rate of ~12% per annum between 1980 and 2009,	India has a population of 1·2 billion. Accurate data on TBI epidemiology in India are lacking, and there is no national trauma registry. Estimates show that nearly 1 million persons are disabled due to TBI in India annually.[87] Between 60% and 70% of TBI results from road traffic incidents.[88,89] Data from the National Crime Record Bureau[90] report an increase of accident-related deaths over the period 2004-2013 of 63%, compared to a population growth of 14·6%. Poor recognition and inadequate early management of brain injuries, delays between injury and reaching definitive hospital (only 24% arrive within 1 hour, 30% within 2-3 hours and 24% take more than 24 hours), lack of adequate pre-hospital care services, and limited trauma care services, may account for poor outcomes in individuals who sustain a TBI in India. High level care can be provided in the few specialized neurotrauma centres, but access to such resources is scarce[91]. Many districts

resulting in a 35-fold increase in car ownership (from 0·018 to 0·628 per capita)[84]. In response to a high rate of traffic deaths and injuries associated with alcohol use, the Chinese ministry of public safety issued the national alcohol penalty law on May 1, 2011, which stated that all drunk drivers should be sent to jail. Since then, alcohol-related accidents have declined rapidly. Falls as cause of injury for TBI appear to be increasing, when compared to a rate of 12% reported by Hu in 2008.[85] Interpersonal violence is among the top three leading causes of TBI in China[86], but gunshot wounds as cause of TBI are rare (<1%) since firearms are strictly prohibited and illegal in China. According to Chinese law, a Chinese citizen or foreigner in China is sentenced to jail if he/she owns, sells/buys, or transports firearms.	lack even CT scanning equipment and crucial equipment, such as mechanical ventilators, and a great need exists for rehabilitation services.[90,91,92,93] 

1·6 Changing epidemiologic patterns

The epidemiology of TBI in HICs is changing. TBI due to traffic related incidents has decreased, and falls are the leading cause of TBI, particularly in elderly patients.[94,41] The average age of patients with TBI has nearly doubled since the 1980's (ESM 2). While these conclusions are often based on comparisons between studies, which are confounded by differences in enrolment criteria, a few longitudinal studies are available. The Nordic countries were amongst the first to describe an increase in TBI in elderly patients.[95,96] In Europe, a decrease in overall TBI incidence rates has been reported in Scotland[97], in Spain[98] and in Portugal,[99] mainly due to a decrease in traffic related injuries. Most of these studies reported an increase in incidence of TBI in elderly patients. The observed decrease in hospital admissions for TBI in Europe has not been reported for other high-income countries such as Canada[100] and the US.[35] A decrease in mortality due to TBI has been reported in many studies[52,101], mainly attributable to fewer traffic related deaths.

A systematic review of TBI over the last 150 years suggests that improvements in the clinical management of severe TBI (defined as GCS ≤ 8, or patients presenting in coma in the pre-GCS era) have reduced case-fatality rates by over 50%.[102] However, this decline appeared to have stagnated

over the past 25 years[102], an impression confirmed in a comparative overview of observational studies, which showed similar rates of unfavourable outcome over the past decades (ESM 3)[2] Further improvements in care are needed, both to reduce mortality and to improve the outcomes for survivors of TBI.

1·7 TBI in specific populations

Child and Adolescent TBI: the smaller the person, the bigger the problem?

Despite the growth and dissemination of injury prevention programs and education, TBI remains the leading cause of death in children and adolescents in the developed world.[29] In fact, the full scope of the public health crisis of TBI is only now emerging. US Data show over 640,000 ED visits for TBI in children < 14 years of age.[39,103] However, this staggering number is still a likely underestimate. Data from large health networks suggest that about 80% of mild TBI presents to primary care physicians and not to hospitals,[104] suggesting a real incidence that is 4–5 fold higher. The most recent CDC data[103] report that US Emergency Department visits for TBI increased for all age ranges (0 – 4 y, 5 – 14 y, 15 – 18 y), rising more than 50% in the youngest age group (2200 cases per 100,000 population), where the incidence of TBI is higher that any subgroup except adults over 75 y. TBI affects males more than females, with a 1.4-fold increase in incidence in children < 10 years and a 2·2-fold increase in children > 10 years of age[105]. Additional disparities in incidence and outcomes are associated with race and ethnicity. For instance, African-American children were at 40% increased risk of suffering a TBI compared to non-Hispanic white children.[106] African American, Hispanic and Native American children were more likely to experience TBI from violence, suffer from more severe TBI, and higher mortality rates compared to non-Hispanic white children in the US.[107,108] [109] Injury mechanisms also vary with age. Falls predominate in the younger age group, falls and being struck by (or having the head strike) an object are equally common in the intermediate age groups, while assaults, falls and motor vehicle incidents predominate in the oldest cohort. Within Europe, the rates of TBI and its complications in children and adolescents appear similar to the US, but are higher in other areas of the world, such as China, India and South America.[110] A unique aspect of TBI in children includes injuries inflicted by child abuse. In abusive head trauma (AHT), children are generally too young – or sometimes too injured – to be reliable historians and investigations are required to eliminate risks for other children in the environment and discover the circumstances surrounding the injury. A comprehensive analysis of fatal AHT cases over the past 15 years appeared to show declining trends for fatal AHT.[111] Nevertheless recent evidence suggests that AHT is the most common mechanism for severe TBI in children under 2 years of age.[112] At a societal level, the impact of childhood TBI is enormous, with burdens on (i) the

health care system, (ii) scarce resources for rehabilitation and (iii) the school system, and (iv) socioeconomic impact on family.

TBI in the elderly: an increasing problem in a vulnerable population

The definition of "elderly" in the context of TBI is variable: cut offs in published papers range from 55 to 75 years of age. However, regardless of the cutoff used, older patients are clearly at high risk of TBI and experience more severe consequences even from seemingly mild TBI.[3,39,113,29] Demographic projections suggest that future rates of TBI amongst older individuals in LMICs are likely to approach current levels in HICs, and hence represent a huge health economic and public health burden.

Patients over 65 years of age represent 10% of TBI cases, but account for 50% of TBI related 10-year mortality[114] and have high and increasing rates of hospitalization.[28] The rise in TBI incidence in older patients is not solely attributable to an ageing population. Many elderly patients remain mobile and "semi-independent", due to decreasing morbidity from cardiovascular disease and cancer. They are then at risk for falls, which is the major cause among TBI in the elderly.[37,41,94,115] Loneliness and depression may lead to alcohol abuse, and such abuse is increasingly being recognised in older individuals, can potentially increase the risk of falls and compromise chances of recovery due to decreased cognitive reserve.[116] Moreover, increased use of CT imaging may have improved case ascertainment for TBI in older people. Age is amongst the strongest outcome predictors in TBI, with mortality and unfavourable outcome increasing continuously with age (ESM 4) [117,118]. A recent meta-analysis of 24 studies in moderate and severe TBI, with a pooled sample size of 93,115 older adults (≥60 years), revealed an in-hospital case-fatality of 57% (95%CI = 43-71%) and 6 month case-fatality of 75% (CI=62-84%).[119] The perception of a universally poor outcome has sometimes led to nihilism and less aggressive therapy for older patients with TBI, who experience delayed CT imaging, a lower likelihood of transfer to specialist neurosurgical facilities, and care by more junior medical staff.[120] Treatment limiting decisions may be taken sooner in older patients. The poor outcome resulting from such suboptimal treatment may fuel "self-fulfilling prophecies" of poor prognosis, and reinforce current prejudices (see series paper on Targeted management in the ICU). Such nihilism is unjustified. Overall, when older patients are treated aggressively and promptly following ICU admission, favourable outcomes are seen in 39% of patients between the ages of 60 and 69 years.[121]

Concussion in sport

Sports-related concussion represents a frequent cause of TBI, and is stirring public debate and controversy, arguably not so much in view of its immediate effects, but because of its reported association with uncommon (but dramatic) complications such as second impact syndrome,[122,123] and its association with late cognitive decline [65] [124] and chronic traumatic encephalopathy. In the US, the CDC estimates that between 1·6 and 3·8 million concussions occur annually.[125] However, this may be a considerable underestimate, as many concussions do not reach medical attention. In North America, cycling is responsible for the majority of sport concussions, according to the American Association of Neurological Surgeons[126], while in New Zealand, rugby (both league and union combined), cycling, and equestrian sports were linked to highest rates of sports-related concussion.[127] A recent systematic review reported an overall concussion incidence of 0·23 per 100 athlete exposures, with the highest incidence in rugby, ice-hockey and American football.[128] Variations in participation in each sport and in definition of concussion in different countries results in inconsistent statistics. Concussion rates vary by age group, sport and gender, and are generally reported to be higher in competition than practice.[129] In terms of head injuries per hours of sport, equestrian sports appear to have the highest rate of concussions.[130] There is currently a lack of research on the epidemiology of sports-related injury, across all sports, in Europe.

Notwithstanding inconsistencies, the reported incidence of sport concussion is steadily rising. Between 2001 and 2009, the CDC reported a 62% increase in sport-related TBI treated in Emergency Departments[131] and annual increases between 7%-15% have been suggested for concussion rates in collegiate and high-school sports in North America[132,133] over the last two decades. These concerns are not confined to the USA. For example, the English -Rugby Football Union[134] report year-on-year increases in concussions in professional rugby since 2003.[135] These trends are generally attributed to increased awareness and reporting of concussion, partly promoted by media attention. Concerns have also been expressed about players becoming progressively heavier and stronger, and more emphasis being placed on the physical element of sport. Nevertheless, the underlying true rate of concussion remains unclear, as the majority of these injuries are not reported, either deliberately, or due to lack of awareness.[136]

TBI in military conflict situations

Current global conflicts, and the increasing burden of terrorism across the world, have resulted in a steady increase in the number of patients seen with military and military-type injuries.[137] The number of terrorism-related deaths has approximately increased 10-fold in the first decade of this century[138] and this trend is continuing.

Understanding the epidemiological and clinical issues in these contexts is important, since the lessons learned apply beyond the confines of conflict.[139] US data show that TBI is the signature injury of the Iraq and Afghanistan conflicts, accounting for approximately 20–25% of the Joint Theater Trauma Registry (JTTR) reviewed combat casualties.[140] Between Jan 2010 and Aug 2016, there were 352,619 incidences of TBI in Service Members.[141] Of these, 82% are classified as "mild", 9% as "moderate", and the remaining 9% as severe/penetrating, or not classifiable (including instances of death in action, and/or inadequate or incomplete documentation). As with civilian populations, mTBI constitutes the largest proportion of TBI, and while most of these individuals return to full duty with no lasting complications, approximately 10% result in symptoms that do not resolve.

Overall, Combat-related TBI (CRTBI) is a significant cause of morbidity and mortality, and unlike civilian TBI, often includes blast-related TBI and extracranial polytrauma such as amputation, internal haemorrhage, and burn. Blast is an injury mechanism was until recently largely confined to conflict settings. Injury mechanisms can be more complex than in non-blast TBI, and experience in the military setting is that the clinical course may also be different.[142] Several active research programs address this problem. The most substantial of these, from the US Department of Defense, includes efforts to understand the epidemiology, identification, management, and treatment of mTBI; including protocols for mandatory screening and detailed clinical recommendations.[143,144] As with civilian TBI (see Part 4), a key consideration is development of an integrated and effective chain of care throughout the casualty care continuum including (1) battlefield first responder care, (2) tactical field and tactical evacuation care, and (3) subsequent care across the global military care system.[145]

The US data from recent conflicts in Iraq and Afghanistan document the lowest killed-wounded ratio in the history of warfare, with many casualties surviving what would have been unsurvivable injuries. While a significant part of this may be due to advances in body armour, it is clear that developments in military medical care contributed substantially.[146] It is sobering, however, to recognize that, over the same period, there have been less impressive advances in the treatment of moderate to severe TBI, especially on the battlefield.[146] Potential challenges in this context include triaging intracranial bleeds, and the stabilization/treatment of concomitant polytrauma accompanying TBI from the point of injury through transport to higher echelon of care.[146] TBI-related disabilities pose formidable challenges for treatment and rehabilitation. Strategies to address these issues include ambitious plans to bring definitive care to forward locations so as to ensure timely access within the golden hour.[147] These advances are important, not just for military

TBI (and trauma in general), but also for civilian TBI, since the technologies and systems developed and refined by these initiatives can inform civilian TBI care.[147]

1·8 Recommendations for improving epidemiologic studies in TBI

TBI is a huge but poorly quantified public health problem. The vast reported differences in incidence and mortality rates between countries highlight a need for better standardisation of epidemiological data gathering on TBI, both for administrative purposes and for formal research. Recommendations for improving epidemiologic studies are summarized in ESM 5, and emphasize the need for standard definitions, standard methods, and standard data presentation.

Future studies also need more standardized data collection, especially for mild TBI, to facilitate pooling of data and epidemiological comparisons between countries and over time. We need population-based studies on the prevalence, incidence, and mortality of TBI across the lifespan, particularly in lower income countries, to provide more accurate estimates of the global impact of TBI. Capture-recapture methodology[148,149] could usefully supplement population-based studies, particularly when resources are limited. More advanced metrics including YLLs, YLDs or DALYs should be employed more often to better quantify the burden of TBI.

A simple and cost-efficient approach might be to include a question on TBI in routinely conducted health interviews. For example, the European Health Interview Survey has a section on self-reported injury in the past 12 months. Adding a question on TBI could yield insight on incidence and prevalence of TBI in the general population.

Improvements in epidemiological data completeness and quality are required for development and implementation of policy measures through detection of high-risk populations (such as the very young and very old), and identification of key targets for improved prevention and management of TBI.

Part 2: Health economics of traumatic brain injury

Key messages	Recommendations
1. Traumatic Brain Injury results in substantial health care and societal costs.	1. More effective TBI prevention is vital, and could deliver cost savings that help fund improved access to health care and research for TBI.
2. High-quality data on the health-economic effects of TBI are not available for many regions and countries, especially for lifetime costs.	2. Increased funding for rigorous and long-term health-economics studies on direct and indirect costs is needed to inform rational decisions about allocation of resources for management and research of TBI.
3. Methodological variations confound comparisons of health economic impact of TBI between regions, countries and continents.	3. International consensus on definitions and improved standardisation of methods in heath-economics research on TBI are required to measure and compare costs.

Introduction

TBI poses a substantial economic burden on affected individuals and families, and on society as a whole. Understanding costs associated with TBI is important, since it provides insight in the magnitude and scope of the problem, and generates knowledge necessary to anticipate and budget for health care services needed to prevent, detect and treat TBI. Accurate estimates of the costs of TBI allows assessment of potential savings from interventions aimed at reducing the incidence, or improving treatment for TBI. Monitoring costs can identify disparities and inequities in access to and delivery of health care. From an equity standpoint, evidence of differential access to services provides information on the extent to which various health systems are meeting the health needs of disadvantaged populations. Here, costs reflect resources used per individual, and provide a proxy measure of health care utilisation. Identification of possible problems in access to care, critical to the receipt of good treatment, allows researchers and decision makers to identify areas where public health could intervene. The total cost and pattern of health services usage post-TBI can hence be used for health services planning. This section reviews available health economic data on the costs related to TBI and discuss the implications for health care policy.

2·1 Direct and indirect costs

The economic consequences of TBI for the individual and for society are enormous. *Panel 2.1* summarizes definitions of types of costs used in research studies. TBI-related costs in Europe for 2010 have been estimated at €33 billion (*approximately USD 48·7 billion in 2016 value*), of which direct cost accounted for 41% and indirect cost 59%.[150,151] In the United States, reported aggregated direct and indirect cost estimates ranged from USD 60·4 billion (*approximately USD 84·6 billion in 2016 value*) in 2000[152] to USD 221 billion (*approximately USD 248·9 billion in 2016 value)* in 2009.[153]In the study reported by Finkelstein (2006)[152], 15% of the costs were accounted for by lifetime medical costs and 85% by lifetime productivity losses. For the data from 2009, 31% of the costs were due to loss in productivity and 62% estimated for intangible costs (lost quality of life). The difference in total costs reported in these two studies may relate to the inclusion of intangible costs, resulting in higher estimates.

Costs attributable to TBI in Australia in 2008 were estimated to be AUD 1**.**28 billion (*approximately* USD *1·04 billion in 2016 value*), of which absenteeism from work or productivity loss due to TBI form 55%. [154]

In TBI, lifetime costs are high due to loss of productivity in a substantial number of younger victims, which are not always considered in all studies. For example, in Europe the reported health service related and indirect costs for stroke have been estimated to be twice as high as TBI,[150,151] but these comparisons, limit reported cost estimates for TBI to the direct and indirect costs for the first year. Such calculations grossly underestimate the actual societal costs for TBI.

Average lifetime cost for TBI in the US was estimated to be USD 396,000 per person (*approximately USD 544,000 in 2016 value*).[155] In Australia, per-person long term healthcare costs for the first six years post-injury ranged from AUD 160,388 for moderate TBI (*approximately USD 130,000 in 2016 value*) to AUD 337,077 for severe TBI (*approximately USD 272,000 in 2016 value*).[154] Most US studies use charges instead of unit prices for cost calculations,[53] which may be an underestimate, as many patients with mild TBI do not seek immediate medical attention or are misdiagnosed. Accurate total cost information for TBI is lacking internationally, and despite current studies on the outcomes and cost of TBI, information on direct costs (including third party payments) and indirect costs is limited. The recently completed Brain Injury Outcomes New Zealand in the Community (BIONIC) study was the first to assess the incidence of TBI for all severities across all age groups, in both rural and urban populations.[3] The BIONIC collaborators found that the cost of treating TBI varies greatly, with first year and lifetime costs of mild TBI (calculated at USD 3,395 and USD 4,636, respectively) being significantly lower than those of moderate/severe TBI (USD 21,379 and USD

36,648, respectively).[16] Other estimates, based on patients admitted to a rehabilitation facility, are higher (~$350,000 in severe TBI, for example), underlining the substantially higher costs of survival. Costs in individual patients can be ten-fold higher, and vary with both injury severity and demographic features.[156] Despite the lower cost of individual cases, the high incidence of mild TBI results in a the total cost treatment nearly 3 times that of moderate/severe TBI.[16] Extrapolation from data[16] suggest that the global economic burden for TBI may range between USD 355 billion (EUR 268 billion) and USD 436 billion (EUR 329 billion) in 2016, which equates to 0.5% of the annual global output, estimated at of USD 73.7 trillion[5].

While all studies attest to the high societal costs of TBI, both in terms of medical costs and lost productivity, the variation in estimates is striking. Some differences are likely to be real. However, rigorous comparison of these figures is impossible, since the source data are of relatively poor quality, calculations involve several assumptions and variable methods, inflation-related changes in exchange rates are usually ignored, and the precise cost items included in estimates (and the duration of post-injury period referred to) vary substantially, or are simply not specified (see ESM 6).

Other indirect consequences, which rarely (if ever) have been taken into account in calculating TBI-related costs, include caregiver time and expense, caregivers' working ability and health, increased psychiatric morbidity and injury risk among the TBI survivors, increased likelihood of alienation, and societal costs, as well as costs related to long-term complications of TBI, including those of dementia care (see Part 1.4).[157] Together, these limitations suggest that the currently estimated health service use and cost of services should be interpreted with caution. As with other epidemiological data, there is a pressing need to ensure uniformity of reporting of health economic data.

Panel 2.1.: Definitions of various types of costs used in economic studies

Direct costs: all resources consumed (quantified in costs) within the health care sector; may also include out of pocket expenses and resources outside the health care sector.

Indirect Costs: all resources forgone as a result of a health condition. Costs are included in this category vary by study but most include productivity loss, which arises when people who would otherwise be employed, are not able to work or work fewer hours because of their TBI. Indirect costs may also include intangible costs due to TBI, such as reduced quality of life.

Life time cost: costs incurred over a life time to provide services to people with TBI that would not be required in the absence of the injury such as on-going medical care and community services.

2.2 Implications for health care policy

The economic burden of TBI worldwide is enormous, additionally motivating improved prevention and treatment strategies from a health economic perspective. However, accessing accurate data that allow costs to be used as a proxy measure of healthcare utilisation is challenging. Current estimates of the range of total costs are incomplete, for both mild and severe TBI. For severe patients, we need better insight into the long-term costs of specialized hospital and rehabilitation care. Furthermore, more insight is needed into impaired work performance, and consequently production losses. There is a critical requirement to couple improved epidemiological and economic data collection to rigorous analysis of health care and lifetime costs of TBI, so that we can identify patient groups with high costs and deficiencies in access to care, and make rational decisions about allocation of health care resources.

Substantial cost saving may be achieved by preventing TBI. For individuals, this may be more relevant at the more severe end of the spectrum, but the large number of patients with mild TBI suggests a greater potential at a societal level by strategies to reduce incidence of mild injuries through effective prevention. Realisation of such cost savings will require investment in prevention. In addition to governmental funding, an additional source could follow the example set by Italy, where a portion of the fees for traffic law violations must be spent on prevention.

Productivity costs dominate the economic burden of TBI. Future research should incorporate the productivity costs in their cost assessment, as this is important input for policy decisions and enables priority setting based on the total direct and indirect expenses due to injuries. These data are also critical to calculate the cost-effectiveness of programs / treatments to improve return to work in working age survivors of TBI.

Part 3: Prevention of TBI

Key messages	Recommendations
1. TBI is, to a large extent, preventable, and societies can achieve considerable gains by decreasing its occurrence.	1. Policies aimed at reducing the burden of TBI should focus on awareness campaigns and prevention of TBI in general, and specifically target high-risk groups.
2. In LMIC, the incidence of TBIs due to traffic incidents is increasing.	2. The recommendations of the World Health Organisation on road safety need to be implemented in all countries.[158]
3. In high-income countries, epidemiologic patterns are changing, with an increase in elderly patients, mostly due to falls.	3. Prevention programs and healthcare delivery need to be tailored to changing epidemiological patterns of TBI, and specifically address fall prevention in the elderly.
4. Any risk of an early second injury after even a mild TBI should be avoided.	4. Professional sporting organisations should set an example for children and amateurs by removing any player with a suspected concussion from play immediately.

Introduction

TBI is, to a large extent, preventable, and TBI prevention saves lives, reduces prevalence of disabilities, and saves costs inside and outside the health care system. While some TBI prevention strategies (such as those aimed at road traffic safety) have been remarkably successful, these successes are not universal. Increased motorization in LMICs, coupled with an inadequate infrastructure and insufficient adoption of safety measures, have resulted in substantial increases in the burden of TBI. Successes achieved in prevention of TBI from road traffic incidents in HICs need to be translated to LMICs. Furthermore, increases in TBI in other demographic contexts need attention: for example, specific measures are required to contain and reduce the increase in TBI caused by falls in the elderly, and to prevent brain damage in children and amateur and professional athletes.

Prevention measures targeting injury occurrence can be primary or secondary, and should be informed by knowledge of epidemiology, TBI cause, and identification of risk groups. Primary prevention is directed at prevention of injury occurrence, while secondary prevention aims to reduce the occurrence of TBI or limit its severity, if an injury happens.

Both approaches may be effective in isolation, but tend to be synergistic when used together. Prevention initiatives can be widely population based (legislation, improvements in infrastructure, vehicle safety design, trauma care, and workplace safety), focus on (high-risk) subgroups (alcohol-impaired driving, seatbelt use, speeding, distracted driving, helmet use, elderly living alone, unattended children, etc.), or specifically targeted at individuals – addressing their behaviour and risk taking patterns.[159] Irrespective of the target population, information campaigns should employ a range of measures to raise awareness of key issues in prevention and care of TBI. In this section, we discuss directions and approaches to reduce the occurrence and impact of TBI.

3.1 Prevention of TBI from Road Traffic Incidents

Globally, TBI remains predominately a disease of the young with the major vectors in LMIC being road traffic incidents, where vulnerable road users (pedestrians/cyclists) are particularly at risk.[160] Even though LMICs have only half of the world's vehicles, they account for 90% the world's road fatalities, a substantial proportion of which is preventable.

Reduction of traffic-related injuries is the focus of a major United Nations Decade of Action for Road Safety (2011-2020), which aims to halve the 1.3 million traffic related deaths each year by 2020 through improvements in road safety management, safer roads, safer vehicles, better informed road users, and an improved post-crash response.[161] These improvements are relevant to TBI, since it is a major cause of all injury related deaths (see part 1).[33, 35, 162] A recent WHO report on road safety[158] provides specific recommendations for improving road safety, based on interventions with proven efficacy. Reductions in speed limits have played a crucial role in decreasing crash incidence and injury severity – the lower the speed, the less severe the injury.[163,164,165] A systematic review of studies from HICs confirmed that enforcement of traffic rules decreases road user deaths.[166,167] Non-legislative approaches are equally relevant, and include developing safer roadway infrastructure (separating pedestrians and cyclists from motorized vehicles), introducing traffic calming, and implementation of vehicle and safety equipment standards.[168] Population-wide strategies that have been shown to be effective in preventing road crashes, injuries, and fatalities, include the installation of red-light cameras[169] and street lighting.[170] Secondary prevention includes protective head gear and car safety measures. Mandatory helmet use has decreased the number and severity of head injuries in both motorcycle[171] and bicycle users.[172,173,174] In Taiwan, introduction of the motorcycle helmet law in 1997 reduced motorcycle-related head injuries by 33%, and injuries that did occur were less severe and associated with shorter hospital stay.[175] Mandatory seat belt use on all seats and the use of child restraints can reduce the risk of motor vehicle occupant injuries by 33–55%.[176]

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In HICs, recent attention has focused on the risks incurred by distracted drivers.[177] The likelihood of a safety critical event during traffic has been reported to be six times higher for drivers dialling a cell phone and 23 times higher for those texting. Whilst campaigns aiming at influencing drivers' behaviour remain relevant, technological solutions should also be considered. In particular, there have been suggestions to develop smart solutions to recognise and block non-hands-free cell phone use whilst driving[177].

3.2 Prevention of TBI in Children and Adolescents

Most prevention strategies outlined for RTI (see 3.1) and for concussive sports injuries (see 3.4)– particularly those related to concussion detection/prevention from sports injuries and helmet laws for bicycles/motorcycles - apply to both children and adults. However, two aspects of injury prevention are unique to children: the use of car seats and the concepts of multiagency safeguarding for children at risk of abuse, with infants being the most vulnerable. [112]

In the US and other areas of the world, local laws require that children be restrained in car seats while the motor vehicle is in motion. For example, the US state of Pennsylvania requires that all children under 8 years of age in cars be in a child restraint system, with children under the age of 2 years rear-facing. Furthermore, the law mandates seat belts for children aged 8-18 years. These state laws[178] are broadly replicated in national best practice recommendations from the US Preventive Services Task Force.

The concept of "safe havens" has been advanced in the US for children at risk for abuse.[179] In the past, the legal system has argued that child abandonment – for whatever the reason – was a serious crime and parents were justifiably fearful of legal ramifications of leaving their children. However, as child abuse awareness has increased and family risk factors have been elucidated, there are now local efforts to develop "safe havens" where parents who fear they may harm their child can leave their child without legal ramifications. These "safe havens" are often paediatric hospitals, where the hospital is required to provide emergency medical care for the child and assume protective custody of the child until the appropriate state authorities can find more definitive placement.

3.3 Prevention of TBI in the Elderly

Prevention strategies need to take account of changing epidemiologic patterns, which show increases in falls-related TBI in older individuals (see part 1).[41, 94, 180,181,182,183] There is a clear need,

therefore, to address causal risk factors and to explore preventive strategies that address the association between frailty and vulnerability to TBI through falls. The older frail population are more likely to fall, more likely to suffer a TBI when a fall occurs, and more likely to suffer long-term adverse effects even from a seemingly mild TBI. The assessment of frailty now involves validated tools, and can be implemented as part of policy.[184] Such assessment is clearly important as a primary TBI prevention strategy. Detection of frailty can trigger evaluation and modification of the physical environment (including the provision of safety rails for stairs and steps), and/or prompt critical evaluation of the risk/benefit ratio of medication that increases the likelihood of an adverse impact of falls (sedative drugs and medications associated with postural hypotension, anticoagulants, and antiplatelet agents). Frailty assessments (and subsequent interventions) were originally the domain of geriatricians rather than primary care physicians, and initial trials focused on reducing falls and fall related-injury in acute hospital settings.[185] However, emerging data suggest that the most useful role of these interventions may be in primary care.[186] An example is the Stopping Elderly Accidents, Deaths, and Injuries (STEADI) initiative of the CDC.[187] Fall risk assessment, followed by implementation of an individualized management plan, may reduce falls by 24%,[188,189] highlighting the critical importance of fall prevention in the elderly as a potentially high-impact TBI-preventive approach.

3.4 Prevention of concussions and other forms of TBI in sports

The long-term consequences of a single concussive injury represent an area of ongoing research. However, an increasing evidence indicates that multiple concussive and subconcussive impacts can lead to cumulative effects including prolonged recovery, more severe symptomatology, increased vulnerability to brain injury, and heightened risk of any injury.[190,191] In children and adolescents there are additional concerns about cumulative cognitive and behavioral sequelae of multiple concussions on brain development and education, as well as the risk of Second Impact Syndrome, a rare but potentially catastrophic form of acute brain injury attributed to two or more TBIs occurring in short succession, often in the setting of subdural bleeding.[122,123,192]

These emerging concerns underscore the importance of immediately removing anyone from play whenever there is any suspicion of a possible TBI. These needs are highlighted in training programs for coaches and parents, but unfortunately not always applied in professional sports. The FIFA (Fédération Internationale de Football Association) World Cup in 2014 highlighted several incidents of players clearly concussed who were allowed to continue play, and led th FIFA Medical Committee to change rules.[193] We posit that that professional sports organizations should be obliged to remove any patient with a suspicion of TBI from play immediately, thus setting an

example for amateur athletes, and in particular, young players. Such decisions should not be taken by interested parties (e.g. coaches), but rather by a neutral party, for example an independent medic, or – if not available - the referee. Various international efforts have been initiated to develop, refine, and implement rational guidance for players, parents, and coaches regarding the time that needs to be spent away from training and contact sport following a concussion. However, further refinement in diagnosis is needed, as is guidance on action required when concussion is reliably diagnosed.[194,195]

Part 4: Systems of care

Key messages	Recommendations
1. Access to health care is often inconsistent between centres, regions, and countries, especially with regard to acute and post-acute care.	1. Health care policies are needed to improve access to acute- and post-acute care to reduce the impact on patients, families, and society.
2. Substantial variation exists in systems and quality of care for TBI between centres, regions, and countries.	2. Where best practice is reasonably well defined, this should be used as a treatment standard to improve the quality of care. Where not defined, increased funding to identify best practice is needed; such changes could improve patient outcomes and cost-effectiveness.
3. For optimal care, patients should be moved along a chain of increased expertise, with excellent communication between caregivers.	3. Improving systems of care for TBI and ensuring continuity of care, through urgent and acute care, rehabilitation, and community reintegration should be high on the policy agenda.
4. Centres with higher caseload and specialised facilities have better outcomes for patients with severe TBI compared to smaller centres.	4. Implement incentives to stimulate transfer of adult and paediatric patients with severe TBI to specialist centres.
5. The epidemiology of TBI and problems of TBI care in LMICs is different from that seen in HICs	5. Solutions for improving TBI care and outcome in LMICs should be tailored to local needs and resource availability, rather than replicating strategies in HICs

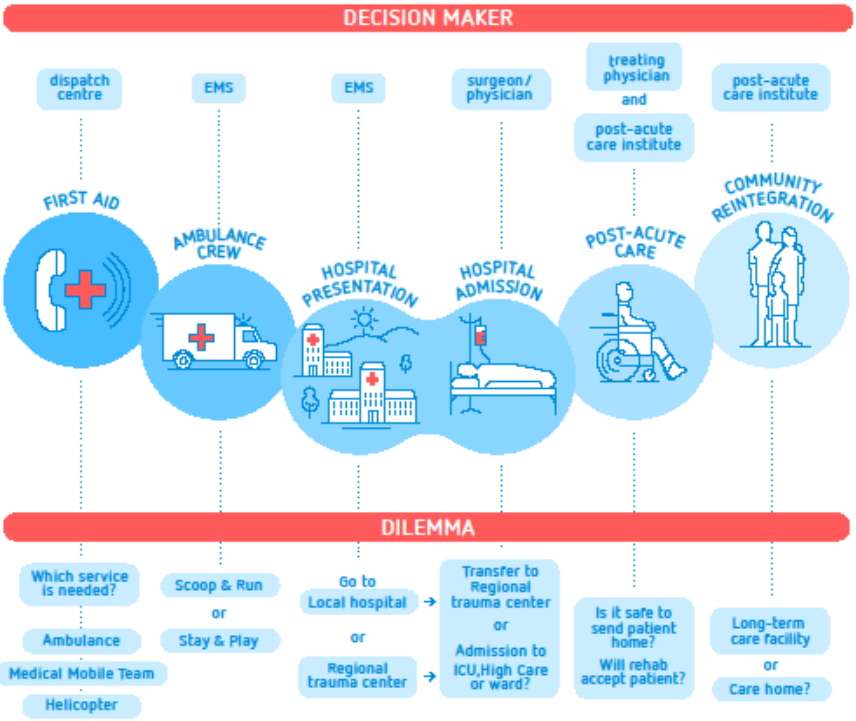
Introduction

In an ideal world, all patients would have access to optimal care, meeting standards of best practice, with continuity of care guaranteed from prehospital to post-acute care. In the real world, systems of care for patients with TBI show substantial variation across and within countries[196,197,198,199], with disconnects between links in the trauma chain, particularly between acute and post-acute care. Understanding such variation is critical: Improving care pathways may hold great potential for improving overall outcome after TBI. Practice variations influence TBI outcome and health care costs, and broad implementation of best practices and guidelines could improve cost-effectiveness.

The spectrum of clinical care for TBI extends from immediate on-site emergency care (lasting minutes to hours) to long-term post-acute care (extending for years or even a lifetime). This care pathway includes several decision points regarding competing options for care (*figure 2.1*), where appropriate choices can deliver high quality, cost effective care. Conversely, poor choices incur the risk of disrupting continuity, and reducing quality of care. Variations in systems of care are largely driven by differences in resource availability, local practice, financial frameworks[200] and beliefs.

In this section, we discuss the current structure and practice of healthcare for patients with TBI, focusing on variations in systems of care, both in the pre-hospital, acute, and post-acute phases, and addresses specific challenges in LMICs to understand the barriers and opportunities for implementation of improved systems of care and best practice.

Figure 4.1.: No chain is stronger than its weakest link*



***** Multiple decision points present along the chain of trauma care. Any delays, inappropriate intervention or miscommunication across the links of the trauma chain, incur an increased risk to the patient for complications, poorer recovery or death. EMS: Emergency Medical Service.

4.1 Pre-hospital care

Pre-hospital care marks the start of the chain of trauma care and is composed of various components; first responders, dispatch systems, basic response, mobile medical team (MMT), helicopter emergency medical services (HEMS) and hospital choice.[201] Together, they form the essential bridge to definitive care. The concept of the initial post-injury "golden hour" is particularly pertinent to TBI. Suboptimal care in the prehospital phase may result in a progressive cascade of events with detrimental effects throughout the subsequent disease course.

Lack of adequate prehospital care is a particular problem in LMICs (see boxes on India (part 1) and Latin America (part 4.5)). A recent clinical trial conducted in Bolivia and Ecuador showed that one third of patients with severe TBI were brought to hospital in vehicles other than ambulances and reported long transit times[202]. In HICs, large variations exist in structure and process of prehospital care.[203–207] Specific questions here include whether there is benefit obtained from spending more time stabilising patients at the scene of the accident before transfer, whether transfer teams should include physicians, and when the use of helicopters becomes clinically beneficial and cost-

effective. A survey conducted in 71 neurotrauma centres in Europe revealed striking differences in dispatch system (23% dynamic vs 73% selective) , in basic response (58% advanced life support vs 41% basic life support) and with regard to policy on scene (35% scoop and run vs 51% stay and play) van den Brande, personal communication). Uncertainty exists what best practice may be and if this should depend on local settings, for example rural or urban, and distances.

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4.2 Hospital setting

Controversy exists if patients with more severe TBI should be transported to the nearest hospital or directly taken to a trauma centre. This is, in part due to our inability to reliably diagnose TBI at the scene of injury. A prehospital diagnosis of TBI may be confounded by the insensitivity of the GCS, particularly in older patients[208] and by many extracranial causes of a drop in GCS.[209] Decision rules for CT, and the results of CT scans, provide useful decision support in the emergency department, but are of limited applicability in the prehospital phase.

Retrospective analyses[210,211,212] of administrative and registry databases suggest mortality, functional outcome, and cost-effectiveness benefits from secondary transfer to specialist trauma or neurosurgical centres, and possibly from transfer to high volume centres. In addition, many studies suggest that patients with severe TBI who are cared for in centres that practice intensive protocol-driven therapy (typically including intracranial pressure (ICP) monitoring) experience lower mortality and better outcomes.[213,214,215,216,217,218] Whilst the benefits of concentration of care are generally accepted for patients requiring neurosurgical intervention, identification of such patients at the scene of the accident is seldom possible - only 7% of patients triaged as TBI require neurosurgery.[209] Consequently, policies regarding primary transfer to trauma centres vary widely.

Transfer to specialist centres may also benefit patients who do not require operative neurosurgical intervention at presentation. Supporting evidence comes from registries[210], and from a large prospective CER study of TBI patients requiring intensive care, which corrected for key known covariates.[219] This study showed substantial improvements in risk-adjusted odds ratio [95% CI] for mortality (0.52 [0.34, 0.80]).[219] An equally important consideration is to identify patients who do not benefit from acute transfer to a specialist centre, since avoidance of such transfers could have substantial health-economic and social benefits. In addition, there are clear risks of transfer, such as worsening oxygenation or low blood pressure, which may be detrimental even at levels above the commonly quoted systolic threshold of 90 mmHg.[220] These risks need to be balanced against the advantages of care in a specialist centre, which include specialist expertise and other

supportive services, the benefits that accrue from increased caseload, and more rapid access to neurosurgical intervention if the need for surgery emerges. Furthermore, in the most severely injured patients, experience and multidisciplinary approaches are essential to deal professionally with questions concerning diagnosis of brain death and possible organ donation. Despite some uncertainty, authoritative national and regional guidelines recommend the transfer of this patient group to specialist centres.[221] Despite incomplete implementation, this practice seems to show outcome benefits over time in some settings.[218] However, in other settings, practice remains variable, with inconsistent referral patterns and fractionated care.

Overall, the evidence for centralisation of care is stronger in paediatric TBI, particularly for more severely injured children[222,223]. At the milder end of the TBI spectrum, more advantage may accrue from dissemination of knowledge regarding best care of TBI to community professionals, who manage the vast majority of children with minor or mild TBI. In adults, so-called mild TBI should not be underestimated: postconcussion symptoms have been reported in up to 64% of patients with mild TBI[224,225] (see review on postconcussive symptoms). Written discharge instructions and standard follow-up, either in the out-hospital setting or by general practitioners, are advocated, but inconsistently implemented. A survey among 71 European neurotrauma centers found that the majority of centers (n = 54, 79%) did not provide written discharge information for patients with mild TBI who were discharged home from the ER, and only 10% of centres indicated to routinely schedule follow-up visits for these patients.[226]

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4.3 Post-acute care

The post-acute phase shows great disparities in systems of care and individual patient management between countries, within countries, between institutions, and even between patients. A common disconnect between acute and rehabilitation services further compounds these problems. Inadequate access to rehabilitation can slow or complicate recovery, increasing the burden of care and compromising functional outcomes. Patients who experience discontinuities in care do less well than those in whom the chain of rehabilitation is continuous.[227]

A substantial proportion of persons with severe TBI regain functional independence between 1 and 5 years post-injury[228,229], but this is dependent on specialized neuro-rehabilitation.[230] In practice, many patients (up to 55%) are discharged home or referred to a non-specialized facility after acute care – often without any attempt for rehabilitation therapy.[231,232] This raises questions about equity of access to health care, which should be high on the policy agenda.

4.4 Cost effectiveness of system level management strategies in TBI

While the clinical benefit of care of severe TBI in neuroscience centres has reasonably wide acceptance, formal assessment of the cost-effectiveness of such strategies is extremely limited. The RAIN study suggested that transfer to neuroscience centres was cost effective, even when neurosurgical intervention was not indicated.[219] However, broader analysis of the economic benefit of interventions and care pathways is patchy. The UK NICE Guidelines, for example, provide assessments of the CT head and CT spine rules[221], but most system-level interventions in TBI remain unassessed in this context. A recent systematic review found that evidence was only available for a minority of interventions (*see panel 4.1*), much of which was of poor quality.[233]

The evaluation of cost effectiveness of rehabilitation interventions in TBI is limited. An NIH Consensus Statement[234] outlined the current state of literature in this area more than fifteen years ago. It noted a scarcity of quality publications on this topic, and made recommendations to address evidence gaps. There has been limited progress since. Some organisational approaches, such as the appointment of a case manager to facilitate rehabilitation access, have face validity and are highly valued in anecdotal accounts from patients and families, but have been subjected to hardly any formal evaluation.[235] On the other hand, a recent decision tree analysis of rehabilitation of TBI compared the cost effectiveness of a broken chain of care with a more integrated approach, and concluded that adopting the latter strategy yielded a clinically relevant decrease in disability, whilst saving over $4000 per patient.[227]

Good data on cost-effectiveness of systems of care for TBI are critical for planning resource allocation and for identifying interventions that are most cost-effective. Such data need to be viewed in relation to local case-mix, resource availability, and cultural contexts. Thus, patients with mild and severe TBI will have different rehabilitation needs, and survivors who have extended family based support may have different rehabilitation needs compared to those who do not. Different treatment recommendations may apply to such subgroups, and cost-effectiveness models should be developed separately for each subgroup. Sensitivity analyses are essential when cost effectiveness evaluations are undertaken in potentially heterogeneous populations.

Panel 4.1.: Topics on which cost-effectiveness analysis is available regarding interventions in TBI

- Selective secondary transfer of patients to neurosurgical centres for patients who present with GCS less than 9 at the injury scene: £20,000 per QUALY gained [209]
- Low medical threshold for computed tomography (CT) scanning of asymptomatic infants with possible inflicted TBI: saves costs and gains QUALYs.[236]
- Liberal use of CT scanning in adults with mild TBI based on a high sensitivity decision rule: gains QUALYs and saves costs.[237]
- Selective CT scanning of adults with mild TBI using the biomarker S100B can save up to EUR 71 per patient if guidelines are strictly followed.[238]
- Management of severe TBI according to guidelines: implemention across the USA would yield societal savings over $ 3 billion.[155]
- Management of TBI in dedicated neurocritical care units: cost-effective at a cost of £14,000 per QUALY gained.[239]
- Early transfer of patients with TBI to neuroscience centres in the absence of neurosurgical need: cost effective at a cost of £11,000 per QUALY gained.[239]

4.5 Specific challenges in low- and middle-income countries

About 90 % of trauma-related deaths occur in the developing world. Disability-Adjusted Life Years (DALYs) losses due to injury progressively rise with decreasing income levels,[240] the relative proportion of TBI in injury cases is greater,[241] and the odds of dying due to TBI are more than doubled in low income settings.[242] These poorer outcomes are largely caused by insufficient pre-hospital services, lack of post-acute care, and inconsistent access to care (see Box on Latin America in this part). In particular, the lack of post-acute care could offset any potential benefit obtained in the acute phase. Notwithstanding the substantial burden of disease, disability, and death in LMICs, the participation of these centres in international TBI research and subsequent knowledge transfer is skewed. The development of centres of excellence in TBI treatment has meant that many of these countries are strong contributors to influential international randomised controlled trials, such as the CRASH[243] and CRASH-2[244] trials; and occasionally provide the sole context for other key studies (such as the BEST-TRIP trial[202] of ICP monitoring in TBI). However, this involvement in knowledge generation does not translate into knowledge transfer or appropriate influence in clinical guideline development. This disparity reflects a particular narrative of the 10/90 gap[245] within the context of a single disease.

There is a pressing need to involve LMICs in the guideline development process, beginning with centres of excellence and taking advantage of local developments that might provide opportunities

for change. For example, the recent Transportation Research and Injury Prevention Programme report[246] provided a comprehensive assessment of road safety in India, and triggered policy initiatives[247] which promise to improve emergency trauma care along key national highways. These operational guidelines for trauma networks published by the Indian Ministry of Health and Welfare[248] aim to reduce case fatality rates from road traffic accidents to 10% by developing a pan-India trauma care network, where a designated Level III receiving trauma centre, with facilities and personnel for resuscitation and onward transfer is available every 100 km. Emergency neurosurgical interventions would be undertaken in Level II trauma centres available every ~250 km or so on key national highways, and could be conducted in some of these Level II Centres by general surgeons with some neurosurgical training, increasing access to emergency neurosurgery within existingresource limitations.

Challenges to the care for TBI in low-/middle-income countries: a report on Latin America.

Open links in the trauma chain

Whilst ICU care in Latin America often meets high standards of care despite resources and funding limitations, such facilities are not universally available, and pre-hospital and post-acute care are underdeveloped. One-third of patients with TBI arrive at hospital in vehicles other than ambulances, and ambulances generally only provide transportation, without major resuscitation interventions. Post-ICU care is also disproportionately under-developed. For example, nurse to patient ratios are very low, much routine care is left to families, and rehabilitation modalities are largely unavailable. In a recent clinical trial, none of the 324 study participants received rehabilitation care. [202] Although the risk-adjusted in-ICU death rate is similar to HICs at 14 days, post-ICU-discharge mortality is three times higher. In effect, the high-level ICU care has effectively outrun its support, compromising its longterm influence on outcome. Programmatically addressing these deficiencies is required to improve the outcome of TBI in LMICs. Prospective trials of specific interventions (e.g. physiotherapy, inpatient rehabilitation) are impossible in HIC contexts where their availability is standard, but are feasible and ethical in LMIC contexts. When appropriate decisions are taken at each step in the care pathway and the links in the trauma chain remain connected, high-quality care with positive outcomes can be achieved (see patient testimony in the appendix). Access and continuity of care should however be structural assured, and not dependent on chance or socioeconomic privilege.

Quote patient testimony

It happened in Mexico when I was 12 years old and fell of down an orchestra pit, fracturing my skull.

Laura G. suffered an epidural hematoma, a potentially life-threatening condition.

In my case, all pieces fell into place to make mine a success story. I wish the care and support I received were accessible to all patients.

Read more: see patient testimony ESM 7

4.6 Current challenges and future goals

The cumulative evidence strongly suggests that patients with more severe TBI benefit from transfer to specialist clinical neuroscience facilities, irrespective of whether or not they need definitive neurosurgical intervention. Implementation of such a policy is not simple and requires adequate infrastructure, and clear policy articulation and implementation. Critically, such initiatives need to be supported by publications of quality guidelines that reach and influence key clinical stakeholders. The creation of Major Trauma Networks in the UK, for example, along with the clear national guidelines for TBI triage, increased compliance with current best practice[249], and improved outcomes[250]. However, the available infrastructure (e.g. number of beds in trauma centres) may make full compliance with guidelines difficult. Success of any ensuing strategies will depend on effective knowledge transfer (part 9), and on resource allocation that makes such change in practice possible. Achieving improvement is an incremental process, and the gains that are targeted (and achieved) will need to take account of local health care systems and resources.

The role of rigorous assessment of needs and the articulation of effective policies are particularly relevant to LMICs. Some LMICs are moving towards models of care delivery, which though ambitious by recent standards, adopt pragmatic approaches to specialist care. The challenge in these settings is to allocate new resources in ways that serve local needs best, rather than using frameworks developed for western health economies (see part 4.5)

Evolution of TBI care in China:

The care for TBI in China is primarily coordinated by neurosurgeons. The progress of Chinese neurosurgery, first founded with Russian cooperation in the 1950's was completely halted during the "Cultural revolution" from 1966 to 1975. Since then, the implementation of modern imaging and monitoring equipment has advanced TBI care. This process has been enhanced by periods of training spent in Europe and North America by Chinese neurosurgical trainees. Shortages of neurosurgeons remain in the western regions of China and in smaller cities, where many patients suffer a TBI. Improved systems for pre-hospital management and transfer to nearby level I or II neurotrauma centres have gradually been implemented. The 120 Emergency call system has been set up in most areas across the country, to facilitate rapid response and quick transportation. Nevertheless, long transport times from the scene of accident to hospital are not uncommon, because of large distances or serious traffic jams in most cities in China. Only few patients with severe TBI are transported by helicopter or medical airplanes.

Teaching programs and other implementation strategies have increased awareness for the importance of guideline-based management of TBI. Chinese TBI guidelines have been issued for management, drug treatment, ICP monitoring, and decompressive craniectomy.[251,252,253,254] Catheters for ICP monitoring, however, still need to be paid for by the patient's family, contributing to a relatively low rate (24·5%) of ICP monitoring for severe TBI in China.[82] International collaborations are increasingly being established, facilitating integration of Chinese research into the international community.

The rapid economic growth in China has been accompanied by substantial advances over the past decade in the care for TBI in China, but challenges remain . These include incomplete cost coverage, long transfer times to specialist centres, shortages of trained neurosurgeons, and limited access to specialist care, especially outside large cities. Specific gains have been achieved through legislation on alcohol and driving, improved prehospital management, increased access to CT scanners, wider availability of neurosurgical services out of hours and at weekends, increased access to neurointensive care, effective guideline implementation, and increased international collaboration. Comparative analyses that emerge from such collaboration provide cause for optimism: mortality and unfavourable outcome of severe TBI (GCS 3-8) in high level centres is 22% and 50% respectively,[82] which compares favourably to other reported mortality rates.[102]

Nevertheless, the implementation of evidence-based management across China still has a long way to go. Despite efforts towards standardization, use of unproven treatments is common: too many

neurosurgeons in China still treat TBI patients according to their personal experience.

Neuroprotective agents without proven therapeutic effects are often used.

Part 5: Current Clinical Management

Key messages	Recommendations
1. Evidence underpinning guidelines for medical and surgical interventions and rehabilitation for TBI is weak.	1. Increased funding is needed to develop robust evidence to inform medical, surgical and rehabilitation management to improve outcomes for patients with TBI.
2. Current clinical protocols, based on population targets, do not account for differences between patients, and within patients at different stages of injury evolution	2. Research funding should encourage clinical studies to account for between-patient differences, and the fact that disease mechanisms may vary at different stages after injury.
3. Existing guidelines are not implemented consistently between centres and regions.	**3.** Information campaigns to improve awareness among clinicians about guidelines and recommendations for best practice are needed.
4. Existing guidelines for clinical management promote a "one-size-fits-all" approach and do not take into account clinical and mechanistic variability between patients.	4. New evidence-based guidelines should emphasise implementation of best practice in the context of an understanding of individual pathophysiology and clinical needs and permit flexibility to achieve an individualised approach to management. Consensus-based guidelines may be necessary where evidence is not clinically definitive

Introduction

Cornerstones of initial care at hospital reception are rapid detection and treatment of intracranial bleeding, prevention of second insults such as hypoxia and/or hypotension and, for more severe patients, maintenance of cerebral blood flow, perfusion pressure and oxygenation. The current evidence underpinning guidelines for medical, surgical and rehabilitation interventions in TBI is weak, and substantial knowledge gaps exist. As a consequence, substantial practice variation exists.

Debate often exists about which subgroups of patients might benefit most from specific therapies. This is especially pertinent to decisions on surgical management, where alternative medical options, expected outcome, and patient and family preferences should be taken into account.

In the intensive care setting, clinical management has evolved over the past two decades towards standardized approaches based on guidelines derived from evidence obtained in selected patient groups or on targets derived for population averages, which may not be applicable to all patients. This "one-size-fits-all" approach ignores the complex clinical and mechanistic heterogeneity of TBI.

Guidelines based on high-quality evidence for rehabilitation are generally unavailable. Even when there is recognised best practice, implementation is inconsistent between centres, and takes little account of the diversity of disability after TBI, which warrant individualised application of robust recommendations.

In this section, we consider the challenges in medical, surgical and rehabilitation management in TBI, and emphasise the need for both more robust evidence and for better targeting of treatment based on improved understanding of individual pathophysiology and clinical needs.

5.1 Intensive care management of severe TBI

Current guidelines for the non-surgical management of TBI are based on optimising cardio-respiratory physiology, controlling intracranial pressure (ICP), and maintaining cerebral perfusion pressure (CPP: the difference between mean arterial pressure and ICP) in a target range.[255] A range of therapies are used to attain these targets, including sedation, hyperosmotic infusions (to reduce brain oedema), limited hyperventilation (to reduce intracranial volume through hypocapnic cerebral vasoconstriction without causing ischemia), draining cerebrospinal fluid, and varying degrees of temperature control (ranging from meticulous control of normothermia to induced hypothermia). Removing bone at the time of emergency surgery for mass lesions to accommodate expected swelling is another common approach (see part 5.2). Aggressive cooling (to core temperatures of 32-34^{o}C), deep sedation (to achieve deep metabolic suppression as evidenced by a near-isoelectric EEG), and decompressive craniectomy (removal of a portion of the skull to make more room for brain swelling; see 5.3), are often classified as "third tier therapies" and reserved for patients who show refractory ICP elevation.[256] Such stratification, with prioritisation of more conservative medical approaches, is rational, since none of our therapies are risk free, and can be associated with a worse outcome.[257,258] However, at least in some of these trials, the use of these interventions in the investigated setting may not have replicated common clinical settings or timing.[259,260]

Treatment approaches aim to maintain single target values (or ranges) for ICP and CPP, derived from analyses in populations of patients with TBI.[255] However, these ranges are seldom directed at

the needs of individual patients. Evidence in support of this single goal-directed approach is inconsistent: one meta-analysis suggests benefit from treatment in a centre with ICP-driven management[261], but two meta-analyses suggest no overall benefit from aggressive, ICP guided management.[262,263] The single available RCT in this area, conducted in Latin America, suggests that clinical care based on imaging and serial clinical examination is not inferior to one that is based on ICP guided management – at least in that setting.[202] The generalizability of these results, obtained in LMICs, to practice in HIC, is debated since substantial differences in the chain of trauma care exist between the two settings (*see box*).

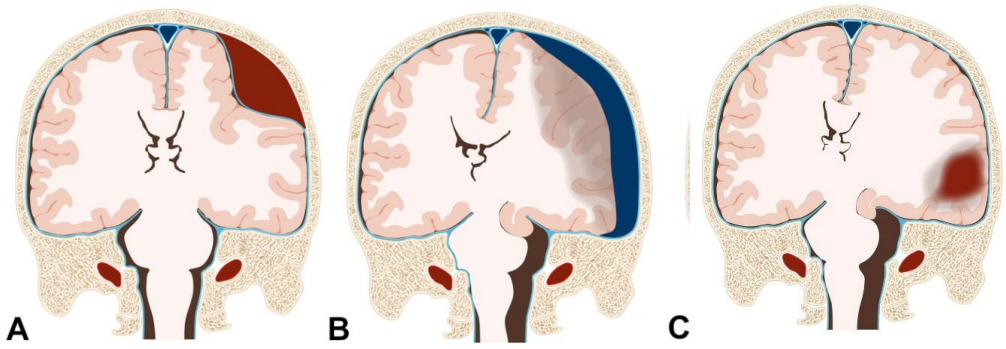
It is important to recognize that clinical TBI is pathophysiologically heterogeneous, and the dominant pathological processes can vary between patients, within individual patients over time, and even between different parts of the brain at any given time. Using a one-size-fits-all management strategy, as is currently standard, is unlikely to be optimal. A number of neuromonitoring modalities (ICP measurement being the best known) aim to detect incipient secondary injury. However all these techniques – taken in isolation – are at best indirect, and at worst crude measures of a complex disease in very complex organ. It is unsurprising that it is hard to prove efficacy of treatments based on such "unidimensional" targets. There continues to be lack of certainty about what thresholds of ICP justify therapies with intrinsic toxicities, and definition of the critical "dose" of intracranial hypertension remains an important goal[264], only just beginning to be rationally quantified.[265] While population based targets of ICP and CPP management represent a good initial basis for care, more rational decisions regarding therapy choice and intensity must account for individual and temporal variations in pathophysiology (see Series Paper on ICU management of TBI) for more on this topic. Further, systemic responses and coagulation status (see Series Paper on Coagulopathy) need to be considered. The initial management of a multi-trauma patient with TBI is complex and requires appropriate expertise, coordination and organisation. Timely intervention delivered by a well-coordinated multi-disciplinary team of experts will minimize the risk of missed opportunities for optimizing outcome.

5.2 Surgical management

Different types of traumatic intracranial hematoma exist (figure 5.1), all of which can compress the brain and represent a threat to life. Timely surgery can then be life-saving, but depends on getting the patient to a centre with surgical facilities on time (see 4.1). Initial surgical treatment in TBI can be either causally directed (e.g., to remove space-occupying intracranial hematomas)[266], or symptomatic (e.g., to decrease pressure on the brain in order to prevent or minimize damage to

important brain structures and prevent life-threatening herniation events). Symptomatic approaches include insertion of an external ventricular drain for drainage of cerebrospinal fluid (CSF)[267], and removal of a large part of the skull to alleviate raised ICP. The latter procedure, called decompressive craniectomy (DC), may be performed in the same setting as the evacuation of a hematoma or later to treat diffuse brain swelling that is refractory to conservative medical management (see below).

Figure 5.1.: Different types of post-traumatic intracranial hematomas*



* A: epidural; B: subdural hematoma; C: 53 intracerebrali hematoma or contusion
Drawings created by Maartje Kunen (medvisuals@maartjekunen.nl)

Despite the existence of international guidelines on surgical indications, substantial practice variation exists. The main reasons for this variation are weakness of evidence, and debate among professionals about which patients might benefit from some procedures (i.e., surgical treatment for traumatic intracranial lesions and/or raised ICP) and optimum timing of surgery.[268,269,270] Surgery might save life and preserve neurological function in some patients,[271] but others may survive with an unfavourable functional outcome, ranging from severe neurological and cognitive deficits to a persistent vegetative state. [272,273,274] Conversely, surgery may not always be necessary and a substantial proportion of patients managed conservatively have favourable outcomes.[275,276,277,278,279] Consequently, the decision to operate requires comparison against medical therapies that may be effective in achieving the same physiological goals. Too liberal surgical indications may lead to an increased number of survivors with severe disabilities, but inappropriate conservative management may result in unnecessary death and disability. The decision to operate is not only based on medical, but also on ethical considerations. The patient's and relatives' view of a meaningful quality of life might be different from our medical perception of favourable outcome. These differences may be due to several factors, not least cultural and

religious in origin. When time permits and opportunities to discuss the expected outcome with relatives exist, past views expressed by patients on an acceptable quality of life should be taken into account.

Accumulating evidence provides useful support for such decision-making. An illustrative example is the use of DC for intracranial hypertension. While the procedure can be life-saving by lowering ICP, it is associated with surgical complications, and structural distortions associated with removal of a portion of the skull may be responsible for additional brain injury in some patients.[280] Initially used over a century ago, the intervention came back into use over the last two decades, but given the need to balance risks and benefits, a clear definition of its role was difficult.[281–283] Two important RCTs have provided useful guidance in this context. The DECRA trial[257] showed that very early use of DC for modest rises in ICP in patients with diffuse injuries was associated with worse outcomes. More recently, the RESCUEicp trial[284] showed that, when used for refractory severe intracranial hypertension, DC can save lives, but resulted in a 9% increase in severely dependent survival at 6 months. However, by 12 months there were 13% more survivors who were at least independent at home. The intervention is not uniformly beneficial, and individual wishes should be taken into consideration. Other studies address similar surgical dilemmas. A recent study suggested that in patients with a traumatic acute subdural hematoma, early evacuation was associated with better outcome compared to a more conservative approach.[285] Similar trends were noted in the STITCH trial, which reported better outcome with early surgical management in patients with traumatic intracerebral haematoma.[286] Unfortunately, the results of STITCH were not statistically significant due to inadequate sample size caused by premature discontinuation of the trial by the funding agency.[286] While surgical trials are difficult, funders should recognise that these and ongoing studies (e.g. http://www.rescueasdh.org) are critical in creating a rational evidence base for surgical practice. Clinical decision-making could be greatly improved by identification of patient subgroups most likely to benefit from the intervention, and, importantly, those who would likely not.

5.3 Rehabilitation after TBI

The multidimensional sequelae of TBI include long-term physical, cognitive, behavioural and emotional impairments, difficulties with activities of daily life, community integration, work, social life, family functioning, and partner relationship (see Series Paper on long-term consequences of TBI for more on this topic). Rehabilitation of patients with TBI is a complex process, and varies with time after injury, the nature of TBI, pre-morbid functional status, and levels of social support.[230]

Recognition of the need for rehabilitation of individuals with TBI depends on both the delivery of therapy, and having good metrics to characterise the intensity and effects of such therapy. Payor sources often justify bypassing specialized rehabilitation programs by pointing to the absence of randomized controlled trials,[287] Acquisition of such data would however require withholding treatment from the most severely injured patients who are most in need of care. Such a standard is uncommon in other specialty areas. Given these difficulties in conducting RCTs, other evidence generation models, such as CER (see part 9), can be used to interrogate natural variations in care, and use these to derive inferences about the best interventions and care models.

Different rehabilitation interventions are appropriate at different phases after injury (*panel 5.1*). In the sub-acute phase, attention tends to focus on retraining activities of daily life and adjusting environmental factors that allow discharge home. In the longer term, rehabilitation goals focus on community reintegration, such as social participation, return to work, and other meaningful activities that restore quality of life. However, debate exists on the optimal timing for rehabilitation: some centres advocate early in-hospital initiation,[227] but most rehabilitation centres will only accept patients when they are "trainable", i.e. after return of consciousness and once they are out of post-traumatic amnesia. Therefore, in practice, these goals are often addressed – if at all – by different health care providers, and the services that address them tend to develop in isolation. Rigorous studies are needed on best practice in the acute setting and optimum timing of specific rehabilitation approaches.

Panel 5.1.: Categories of rehabilitation interventions

Intervention class	**Description**
Restitutional	Strategies that focus on strengthening or re-establishing previously learned patterns of behavior through repetition and rehearsal.
Compensatory	Strategies that exploit intact strengths to substitute for impaired functions.
Adaptive	Strategies that seek to accommodate residual impairment or disability through re-appraisal of self-percept (e.g. cognitive re-structuring).

The diversity and complexity of TBI consequences are best addressed with a comprehensive, holistic rehabilitation delivered by a specialized multidisciplinary team, in close liaison with the patient and family or caregivers (the Patient Centred Care approach). This is consistent with the framework for understanding disability, established by the International Classification of Functioning, Disability and Health (ICF) and endorsed by the WHO.[288] One of the important features

of the ICF is that it goes beyond traditional bio-medical views of examining disability in patients, by providing a bio-psychosocial, integrative, and comprehensive approach, which addresses disability by taking into account factors such as health condition, body functions and structures, activities and participation, and various contextual factors (personal factors and environmental factors) pertinent to the patient. This is critical, because the level of functioning for a patient is determined not only by what is happening at the level of the body, but also how the environment can affect overall disability level. This approach facilitates identification of rehabilitation needs and areas of interventions (*panel 5.2*).

Panel 5.2.: Domains of TBI rehabilitations and outcome targets

Physical	Speech, movement, sensation, perception
Behavioural	Initiation, persistence, flexibility, impulse control
Cognitive	Concentration, memory, executive function, communication
Emotional	Management of anger, irritability, anxiety, frustration
Personal	Socialization, academics, employment

5.4 Future perspectives for intervention studies and guideline development

Many past clinical trials of medical and surgical interventions have often involved strict protocols and recruitment criteria (typically restricted by age, GCS, and comorbidity). Despite this, these trials have largely failed to show benefit, in part because they do not recognise patient heterogeneity and hence do not match treatments to patients[260,289,290] (and consequently do not deliver Precision Medicine)[291]. Conversely, the selected patient groups and small sample sizes. In these studies limit generalizability to the wider population of TBI patients. More commonly, clinical care in individual patients tends to be broadly based on international or local clinical guidelines, an approach that has both advantages and limitations.

Generation of evidence-based guidelines for best practice will require that we supplement conventional evidence generation tools (such as RCTs) with novel approaches, such as CER. The best use of available evidence requires the rapid integration of new studies into the evidence base and their translation into guidelines that reflect the latest evidence – these aspirations are being addressed through development of Living Systematic Reviews (LSRs) and Living Guidelines. The implementation of such guidelines will necessitate effective knowledge transfer. These issues are addressed in Part 9.

Management needs to account for the clinical and mechanistic heterogeneity of TBI, and provide better matching of patients to therapies. Clinical studies should be designed to identify populations

of sufficient size in whom the given target mechanism might be dominant, conforming with current aims to practice Precision Medicine. Patient stratification for clinical and research interventions will depend on improved characterisation of initial severity and mechanism (see Part 6), and the assessment of benefit of these therapies will depend on better characterisation of outcome (Part 7). Linking initial presentation to expected outcome through the development of robust and widely applicable prognostic schemes can provide substantial benefits for research design, comparative audit, clinical decision support, and resource allocation (see Part 8).

Besides these general considerations, specific contexts of care can provide additional opportunities for improved management. Technical advances in invasive and non-invasive monitoring of blood flow, brain metabolism and electrical activity combined with neuroinformatic approaches to detect hidden features, provide a novel approach to such targeted therapy development and implementation in the ICU setting (Part 6; see also Series Paper on management of severe TBI for more on this topic).

Studies of surgical interventions for TBI should focus on identifying subgroups of patients most likely to benefit from surgery, rather than investigating its use across all possible subjects, and future guidelines should allow for a flexible approach that also takes into consideration non-medical aspects such as quality of outcome and patient and family choice.

There is a clear need for studies to inform guidelines on rehabilitation approaches and optimal timing of rehabilitation in TBI. Such guidelines would need to take into account the growing evidence that the diversity of disability after TBI is best addressed through holistic rehabilitation delivered by a multidisciplinary team.

Thus, a change in focus in the clinical management of TBI towards understanding the clinical needs and pathophysiology in individual patients is required while ensuring that implementation of an individualised approach occurs within the setting of robust evidence-based guideline recommendations.

Part 6: Towards better initial characterization of TBI for Precision Medicine

Key messages	Recommendations
1. There is a need to improve the diagnosis and classification of patients with TBI, and to better target current and new therapies to the needs of individual patients.	1. Funding bodies should implement targeted funding calls for research that improves the precision of diagnosis, classification and characterisation of TBI using multi-domain approaches.
2. Few tissue archives containing specimens suited to studies in TBI exist, and their continuity to the future is insufficiently guaranteed.	2. Funding agencies need to secure existing research archives and to develop new archives of suitably characterized human tissue to support collaborative research in TBI.
3. Emerging technologies in genetics, brain injury biomarkers, advanced neuroimaging, and pathophysiological monitoring promise more precise characterization of clinical and mechanistic types of TBI as well as outcome and prognosis, but progress is limited due to small study sizes.	3. Increased funding is needed for studies using emerging technologies to allow improved targeting of treatment strategies to individual patients on the basis of clinical and pathophysiological characteristics.
4. Progress in biomarker and neuroimaging studies is hampered by lack of standardisation.	4. Regulatory agencies should mandate standardization (or at least harmonization) of biomarker technology and advanced neuroimaging, to facilitate data sharing in large studies and accelerate improved management and outcomes of patients with TBI.
5. Emerging technology in digital analysis of large datasets has the power to help clinicians make better clinical decisions, especially in critically ill patients with TBI, where the volume of physiologic monitoring data is challenging.	5. Target funding of “big data” solutions to develop decision support systems especially for critically ill patients with TBI.

Introduction

Conventionally, the initial severity of TBI is classified as mild, moderate, or severe, based on assessment of the level of consciousness, measured by the Glasgow Coma Scale (GCS). This unidimensional classification has limitations, as it neglects the mechanistic heterogeneity of TBI. More patho-anatomically oriented insights have come from neuropathology studies, which have highlighted the importance of ischaemic and inflammatory responses after TBI and have led to the recognition of diffuse axonal injury and chronic traumatic encephalopathy as specific entities in the acute and chronic phase of TBI, respectively.

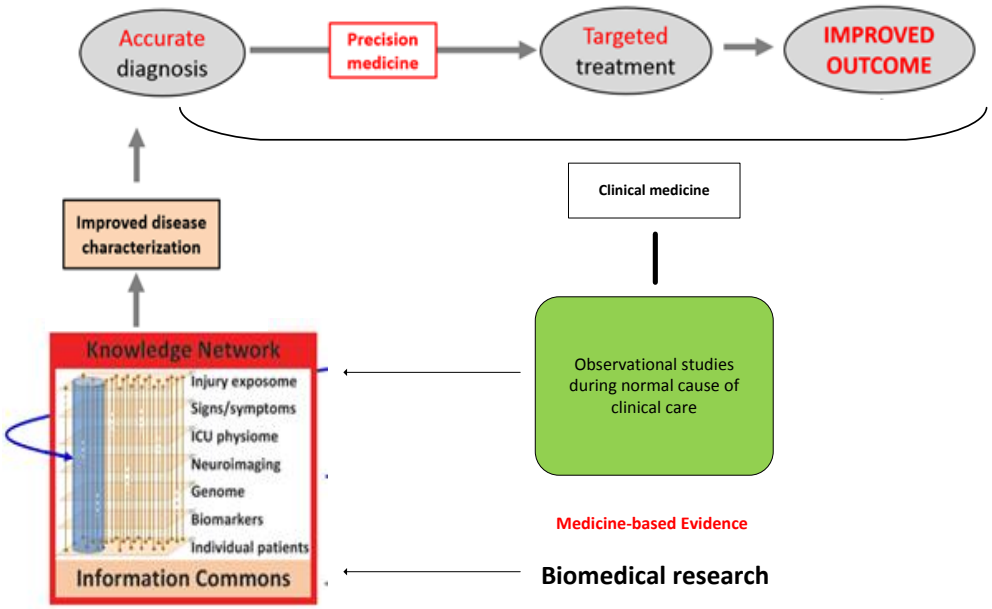
Improved characterisation and better understanding of pathophysiology in individual patients is necessary to permit appropriate targeting of therapy and evaluation of outcome. This approach reflects the concept of Precision Medicine, defined as "an

".[292] Precision medicine, as advocated by the US National Academy of Science[291], aims to tailor therapy to the needs of individual patients, thus moving away from the conventional "one size fits all" concept.[293]

Opportunities for improvement in this area come from advances in the fields of genomics, blood biomarkers, advanced MR imaging, and new approaches to pathophysiological monitoring, coupled with informatics to integrate data from multiple sources (Fig 6.1). These technologies are at varying stages of maturity in terms of integration into clinical care: some, such as genomic stratification for therapy and outcome prognostication, are at a very early level of development, while others, such as the blood biomarker S-100B, are already integrated in some guidelines, though not widely accepted.

This Part considers current approaches to TBI characterisation, discusses the continuing relevance of neuropathologic studies, and explores how incorporation of emerging technologies could improve disease characterisation and monitoring. We consider the challenges and opportunities for integration of multiple sources of data to facilitate translation of these aims.

Figure 6.1: The application of precision medicine approaches to TBI*

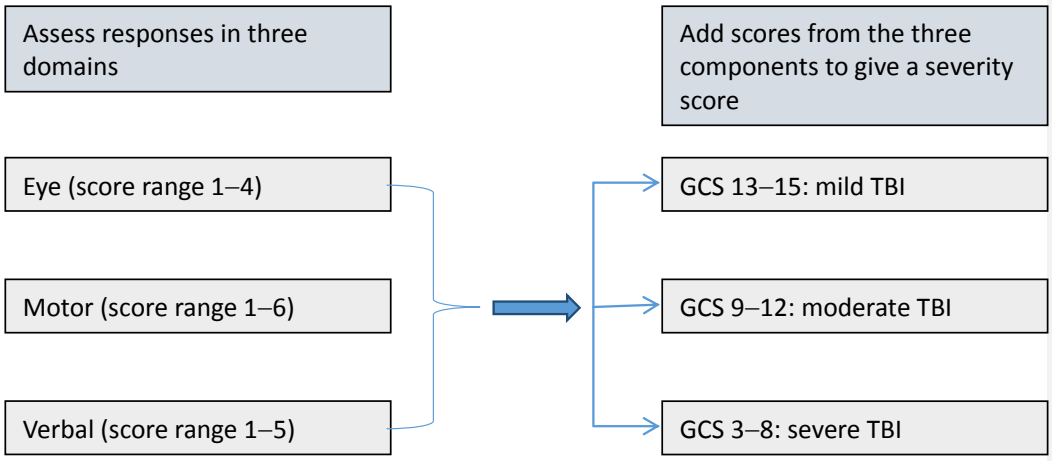


*Improved characterization and understanding of the disease process will lead to a more accurate diagnosis, more targeted treatment, and thus to improved outcome

6.1 Current approaches to classification and characterisation

There are wide variations in TBI type and severity. In addition, the integrated picture of TBI is made of a range of different pathologies (e.g. diffuse axonal injury, contusion, brain swelling, or – brain(stem) compression by extracerebral hematoma) which contribute in varying degrees to the different clinical pictures in individual patients. There has been little attempt to systematically use the range of pathoanatomic lesions as a basis for more rational planning of management. It is common to separate penetrating from closed TBI, a rational discrimination, since the management principles may be substantially different. However, grading the severity of TBI presents a more difficult problem: the severity of TBI can range from a hit to the head with symptoms of disorientation or some alteration of consciousness that quickly resolves, to high energy insults leading to loss of consciousness and coma - a range of presentations which can make the classification of TBI even more challenging. There are currently no refined criteria to classify TBI severity. The Glasgow Coma Scale Score[294] represents the most common approach to classifying TBI severity[295] (*panel 6.1*), but is relatively crude and does not reflect different pathoanatomic subsets.The increasing use of pre-hospital sedation and tracheal intubation often confounds assessment of the GCS and has reduced its utility as a metric of injury severity.[296]

Panel 6.1.: Classification of clinical severity of TBI by the GCS*



Existing ICD codes do not adequately capture the severity of TBI. Alternate TBI coding taxonomies, including the Abbreviated Injury Scale (AIS; which categorises severity of cranial and extracranial injury),[297] and the Marshall classification system (based on head CT findings),[298] are antomically oriented and summarize the type, location and severity of injuries. The AIS is globally utilised by trauma registries where the totality of each patients anatomical (intra- and extracranial) injuries can be summated in the Injury Severity Score (ISS).[299] The AIS, however, is generally scored retrospectively and severity ratings influenced by process characteristics (eg. admission to hospital/ICU; surgery). The Marshall CT Classification is unidimensional, being restricted to CT findings, and is essentially based on only two discriminating features: 1) need for surgery and 2) radiological signs of raised ICP.

There is an increasing recognition that appropriate classification of the initial type and severity of TBI should not be restricted to one dimension (e.g. GCS or CT classification), but should include multiple domains, including clinical features, neuro-imaging studies and major prognostic variables.

6.2 Brain banks and lessons from the dead

Efforts to improve clinical characterisation of TBI can learn lessons from neuropathology, which provided a foundation for our current understanding of key pathological processes in TBI, including traumatic axonal injury, ischaemia, neuroinflammation, and processes such as amyloid deposition, which link TBI to neurodegeneration. These insights afforded by detailed neuropathological examination of human brain tissue[300], remarkably few research archives containing biospecimens suited to studies in TBI. Indeed, only one comprehensive archive of human brain tissue exists, dedicated to studies across the spectrum of TBI, the Glasgow TBI Archive.[301] This unique archive contains material from patients over a range of injury severities, survival times and ages, with the

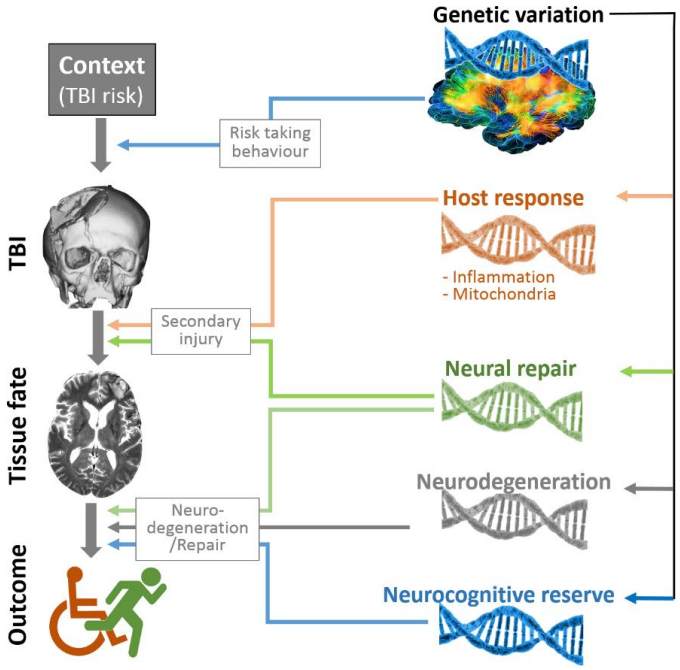
value in such a resource traced through the literature with over 150 peer-reviewed publications supported by material from the archive, including many of the landmark studies in DAI and neurodegenerative pathology following TBI[302,303,304]. More recent, high-profile reports in CTE have facilitated limited accrual of material directed towards studies in retired athletes, such as the Boston University Center for the Study of CTE.[305] Nonetheless, this growing, focused archive and the existing Glasgow TBI Archive cannot reasonably sustain the international field of TBI research.

There remains a pressing need to archive material linked to robust and prospectively accrued clinical information. The richness of knowledge provided by these resources could be substantially amplified by correlations with post mortem imaging, which will allow correlation between the gold standard of neuropathology, and the potential for 'virtual autopsy'[306], based in advanced and tailored MRI techniques.[307,308] Finally, these precious archive resources must be networked and widely accessible to suitable international collaborative research."

6.3 Genetic analysis

Only 35% of the variance in outcome is explained by available prognostic models (see part 8). It is likely that at least part of the unexplained variance and differences in disease course may be explained by genetic variability between patients, both in the acute and the post-acute phase after injury. In oncology, precision medicine approaches are mainly based on knowledge of molecular genetics of the tumor. However, in TBI, the key focus is on the genomics of the host response, which can modulate injury as well as repair. Compared to oncology, genomics characterization of TBI is practically at a seminal level.

Figure 6.2.: Potential areas of impact of genetic variation on clinical outcome from TBI



The most extensively studied gene in the field of TBI is Apolipoprotein E (APOE), which codes for a 34kDa protein with a central role in CNS lipid transport, including movement of cholesterol into cells to aid repair in damaged neurones. Three alleles have been characterised (ε2, 3, and 4), of which ε4 has been reported to have detrimental effects in experimental systems[309] and increase the risk of late onset Alzheimer's disease.[60] Genetic polymorphisms in APOE have been variably shown to modulate TBI outcome.[310] One large study[311] found an altered trajectory of recovery in ε4 carriers, but ultimately the same outcome over a 2 year period. It is possible that interactions exist with age and severity. Teasdale et al[312] found that paediatric ε4 carriers had poorer outcome, in effect neutralising the protective influence of youth. While the risk of late neurodegenerative disease scales with severity of TBI, possession of an ε4 allele may modulate this risk.[60] Mayeux et al[313] found that in the general population ε4 increases the risk of dementia two fold, but in TBI ten-fold. In the longer term, there is evidence that in patients who have sustained a single mild TBI, only ε4 carriers have a subsequently increased risk of dementia compared to the general population.[314] Despite extensive research, the exact relationship of APOE genotype to TBI outcome remains uncertain. Initial findings that the ε4 allele had a deleterious influence[315] could not be replicated in a larger cohort[312], and a recent systematic review[310] concluded that the effect size might only be significant in severe TBI.

Other genetic targets of interest include the mitochondrial DNA haplotype, mediators of inflammatory responses and genetic factors involved in regenerative and neurotrophic responses such as Brain Derived Neurotrophic Factors (BDNF).

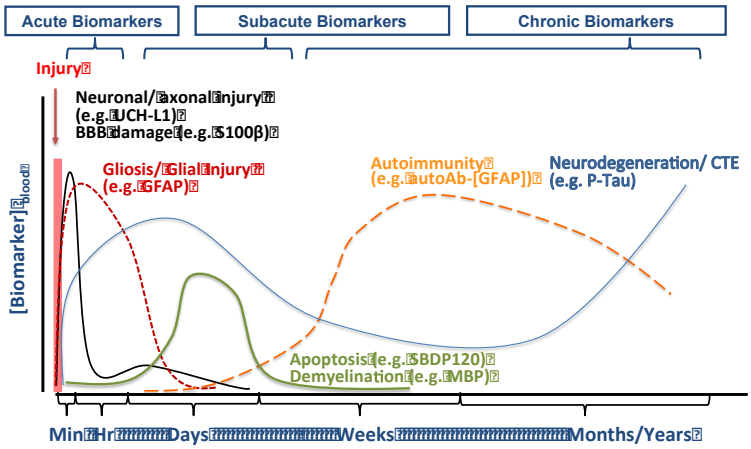
The potential application of this emerging genomic information to TBI care and research is evolving. Potential roles include better characterization, identification of patients at increased risk for progressive damage, more accurate prognostication and therapy stratification, and identification of molecular targets for future drug development (figure 6.2). Current evidence is limited by insufficiently powered studies.To explore the role of genetic characterization for precision medicine in TBI, we need large, prospective studies simultaneously analysing the effect of multiple genes in well-defined populations. APOE is an obvious prognostic candidate, but genes with a greater predictive value for early catastrophic clinical outcomes, such as death or haemorrhagic events, may be of greater clinical use.

6.4 Blood biomarkers

There is an unmet medical need for rapid blood-based biomarker tests, as an adjunct to imaging studies, for optimizing diagnosis, tracking disease progression, and refining prognostication in TBI. Substantial scientific advances in the last decade have resulted in identification of a large number of blood-based protein biomarkers that are relevant to different phases of TBI (*figure 6.3;* ESM 8).[316,317,318] Ongoing research efforts[319–321] are yielding new classes of biomarkers, including metabolomic markers, microRNAs, and exosomes. All of these hold potential, but are not yet in advanced clinical development.

Acute phase biomarkers (eg GFAP, UCH-L1) have substantial potential in the prehospital and emergency room where large numbers of patients with head trauma present, but of whom fewer than 5% will have abnormal CT brain findings.[322,323] This phase of TBI management is probably closest to broader implementation of the use of protein biomarkers in clinical practice, and one of these (S100B) is already part of an algorithm to triage patients for CT imaging after head trauma.[317,324] In the subacute phase, biomarkers can be used to track disease progression (eg Neurofilament proteins and auto-antibodies).[325,326,327] In the chronic stages, markers of neurodegeneration (eg Tau and phosphor-Tau) are being explored for *in vivo* detection of long-term sequelae including degenerative disorders linked to TBI, such as chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD).[328,329,330]

Figure 6.3: Schematic of the continuum of pathophysiology-linked biomarkers in TBI.



Individual plots depict current (and still evolving) understanding of temporal signatures of pathophysiology in peripheral blood, and examples of relevant biomarkers. For a more complete biomarker list, see ESM 8. UCH-L1 (ubiquitin C-terminal hydrolase-L1), S100β, GFAP (glial fibrillary acidic protein), SBDP120 (αII-spectrin breakdown product 120 kDa), MBP (myelin basic protein), autoAb-[GFAP] (autoantibodies to GFAP), P-Tau (phosphorylated Tau).[326]

Despite the multitude of candidate molecules proposed, translation and widespread adoption into clinical diagnostics remain elusive. Progress has been hampered by small numbers of patients studied in most studies, pre-analytical and analytical variability, lack of reference standards, and incomplete understanding of underlying biomarker biology. Transport of biomarkers from damaged tissue to the blood is much more complex in the brain than in the heart, due to additional clearance pathways, such as the cerebrospinal fluid and glymphatic system. It is therefore less straightforward to relate biomarker levels to outcome in TBI than, for example, troponin to the extent of heart damage. In the brain, small lesions in vital areas can lead to deep coma, although the number of cells lost acutely may be relatively small. Conversely, more extensive damage in relatively silent areas may cause high levels of brain biomarkers in the absence of major clinical symptoms.[331] We anticipate a shift from a single-marker approach towards compilation of biomarkers panels that can overcome diagnostic confounders (e.g. extra-cerebral sources, haemolysis etc.) and prevent the over-, or mis-interpretation of information based on a single-marker analysis. A panel of multiple biomarkers that reflect multiple pathogenic mechanisms holds promise for personalized TBI care.

High quality, large scale validation studies are needed to ensure robust evidence of analytical validity and clinical utility, to lay the foundations for integration of TBI biomarkers into clinical practice.[332] Critically, regulatory authorities need to oversee standardisation and comparability of

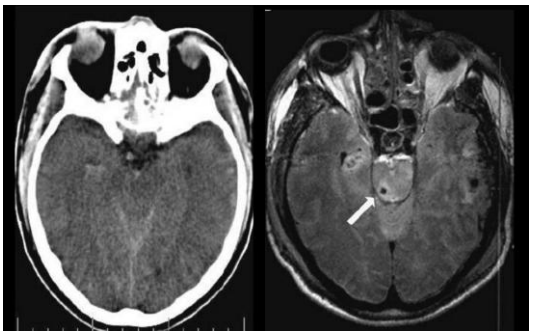
assay results across different platforms, and ensure a clear labelling of approval for research use versus use as diagnostic standard in clinical practice.[333]

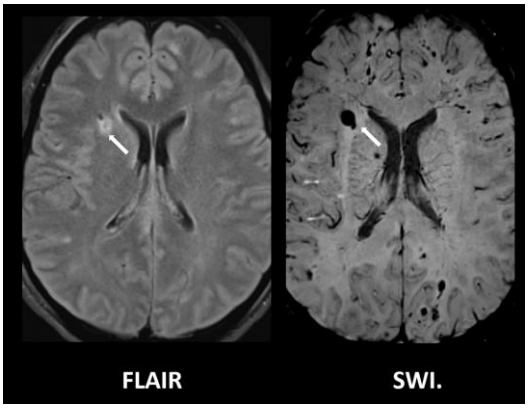
6.5 MR imaging

Computed tomography (CT) is the primary imaging modality for TBI, driving key decisions regarding the need for surgical intervention for space occupying lesions. Scanning times are fast and image processing instantaneous. However, CT is relatively insensitive, and in patients suspected of having a mild TBI, less than 5% will show CT abnormalities.[249,322,323] Conventional MRI provides greater sensitivity for parenchymal lesions, especially in the posterior fossa, brainstem and superficial cortical areas (figure 6.4). Advanced MRI can characterise pathophysiology from ictus to outcome.-[334], Diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) are exquisitely sensitive for mapping traumatic axonal injury and the microhaemorrhages that accompany it (*figure 3.5*), and functional MRI maps functional disconnections that underlie deficits. Although MRI protocols are speeding up[335], scanning takes longer (30-45 min), limiting emergency use.

Figure 6.4. Detection of structural damage by MR compared to CT*

A





B

MR imaging is more sensitive to detect structural damage than CT
*CT scan on admission (left panel) and MRI within 48 hours of admission (FLAIR sequence) showing a dorsolateral brainstem haemorrhage and surrounding oedema which was undetected by CT.

Advanced MR Imaging* optimizes detection of traumatic axonal injury
***** Images acquired using fluid attenuation inversion recovery (FLAIR; left) and susceptibility weighted imaging (SWI; right) microhaemorrhages associated with diffuse traumatic axonal injury are only visible on the SWI sequence.

While the potential diagnostic and prognostic importance of these approaches is undeniable, generalizability to everyday clinical use remains an enormous challenge. Any use of MR must address the need for readily available and non-expensive MR-compatible clinical monitoring equipment to allow use in the sickest patients. More open (often low field) MR systems may ease some logistic difficulties in this context. However, this would be contrary to prevailing trends: neuroimaging is increasingly moving to 3 Tesla as the standard field strength, and 7 Tesla systems are on the cusp of approval for clinical imaging.

Regardless of the field strength at which imaging is undertaken, regulatory authorities and vendors alike must address cross-centre (and inter-device) comparability of images, particularly with regard to quantitative assessments. Complete standardisation may not be possible. CT images can be calibrated in Hounsfield units, but such a calibration unit does not exist in MR. Experience of international collaborations in TBI research, however, does suggest that harmonisation of protocols can and should be achieved.[336,337] Such harmonisation is essential for large, multicentre clinical studies. Translation of research protocols to routine clinical imaging will be a challenging task that requires extensive interaction between vendors, MR experts and regulatory authorities.

6.6 Physiological monitoring

Current technology now offers opportunities to dissect pathophysiological mechanisms, defining individualised therapy targets, and personalising ICU management of TBI. Such technology includes the use of advanced signal processing of ICP waveforms to derive measures of autoregulation, and the addition of more novel sensors to monitor oxygenation, metabolism and cortical electrical activity and spreading depolarizations, respectively. [338, 339–341,342]

The combination of these different sources of information provides a more complete understanding of brain physiology and could potentially be used to individualise therapy. However, these approaches have the inherent disadvantage of requiring the insertion of multiple intracranial sensors, each with its own operative risk (Figure 6.5). These risks can be mitigated by the development of multiparametric sensors, which incorporate all the monitoring modalities in a single device.[343] An alternative approach, which completely removes these risks, is to develop and validate non-invasive monitors.[343] Unfortunately, the medical field is lagging behind technological developments, and such developments will require substantial input from industry, academia and funders. Regardless of whether the data emerge from invasive or noninvasive sensors, and irrespective of whether these consist of multiple sensors or a single multiparametric sensor, a major challenge is the integration of this information in an understandable format to ensure that it is clinically useful.

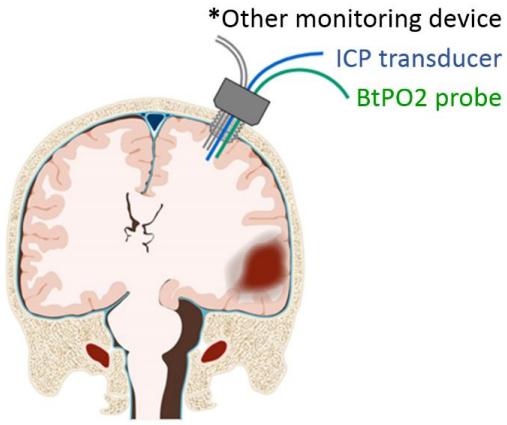


Figure 6.5. Probing the Brain

Multiparameter intracranial access device with three lumens. Commonly, an ICP transducer and a brain tissue pO_2 (BtpO2) probe (often incorporating a brain temperature sensor) are inserted through two of the lumens. The third probe can be used for a microdialysis catheter, cerebral blood flow sensor, depth electrode

6.7 Data integration: challenges and opportunities

Incorporating data from current and emerging technologies for more accurate characterization and classification of TBI is a substantial endeavor, which will require integration of information from

multiple sources, including clinical, radiological, biochemical, genetic and monitoring data. Merging diverse information streams requires substantial information technology input. In the intensive care setting, multimodal monitoring is emerging as a clinical tool, with guidelines for use of brain tissue pO_2 monitoring[338] and microdialysis.[340] However, the accompanying developments in neuroinformatics that will ensure optimal synthesis and interpretation of these data are very much in their infancy.[344] The idea of identifying clinically important and treatable parameters, not immediately obvious from raw bedside data (hidden features), by computational and informatics techniques is compelling and potentially rewarding. Extracting hidden information from this multidimensional space is challenging. In recent years, machine learning has provided new and sophisticated statistical and computational techniques for dealing with high dimensional data, which have diverse application in science and engineering. Such approaches may also prove fruitful in the analysis of time-dependent neuromonitoring data, both for real-time prediction of events and for characterising physiological states which respond to specific therapies. In the future, multimodality monitoring with computer-supported analysis of data, in combination with neuroimaging, genetic and circulating biomarkers, might also allow the classification of patients into with more homogeneous populations for targeted trials of novel neuroprotective interventions. These approaches depend on access to large data sources and substantial input from the field of neuroinformatics and computational sciences, both of which require interdisciplinary and inter-centre collaboration (part 9).

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Part 7: Towards better characterisation of outcome in TBI

Key messages	Recommendations
1. Trauma affects the brain in complex ways which impact multiple outcome domains.	1. Implement targeted fundig calls to facilitate the development and validation of multidimensional outcome constructs that quantify the overall burden of disability from TBI.
2. A substantial number of patients with a even mild TBI experience long-term pain, sleep disorders and mental health illnesses including posttraumatic stress disorder and major depression.	2. Understanding the long term effects of TBI and implementing best practice should be prioritized by politicians and health care professionals
3. Patients with TBI may demonstrate late deterioration or recovery of function even after one year following injury.	3. Fund long-term longitudinal studies to better capture occurrence of late deterioration after TBI and the recovery process after TBI.

Introduction

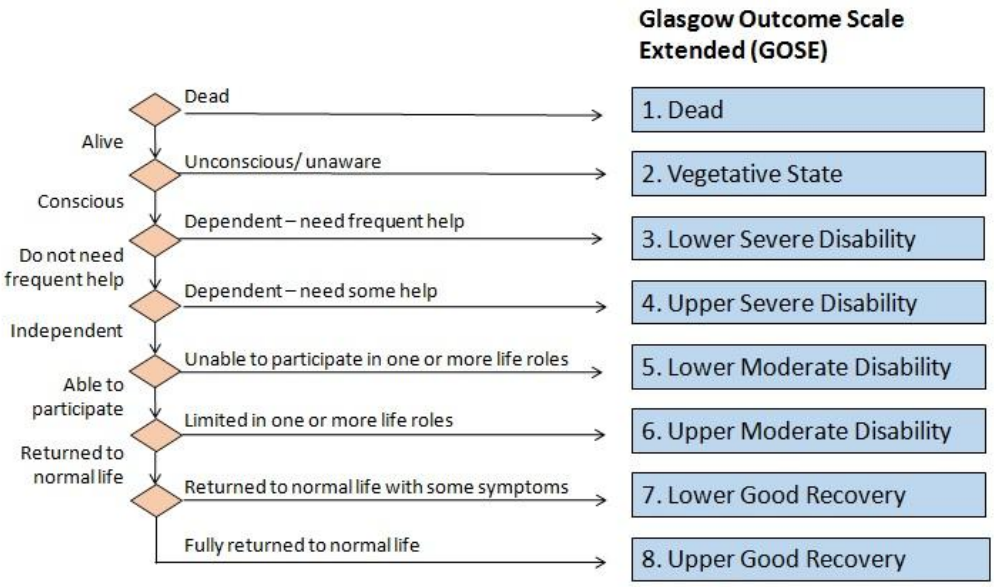
Whilst better characterisation of initial injury severity is a prerequisite for developing precision medicine approaches in TBI, more refined assessment of outcome is equally essential to measure effectiveness of early treatments and to guide further treatment in the post-acute phase. Accurate characterisation of outcomes can also be used to understand the impact of clinical care, compare inter-institutional differences in outcome, evaluate the efficacy of therapeutic interventions and project long-term care needs for patients and families. Functional outcome is equally, or perhaps more relevant in TBI than mortality because of the high rate of disability in survivors, and is generally assessed with the Glasgow Outcome Scale (GOS)[345] or its extended version (GOSE)[346]. Despite its clinical appeal, the GOS/GOSE categorises patients very broadly and therefore insufficiently accounts for the multidimensional nature of outcome following TBI.

In this section, we discuss the limitations of current approaches to outcome assessment and classification, and emphasize the need for multidimensional approaches.

7.1 Current approaches to outcome assessment

Currently, characterisation of outcome in clinical practice and research in hospitalized patients with acute TBI is mainly based on the Glasgow Outcome Scale (GOS)[345] or its extended version (GOSE)[346,347] This is a valuable, but relatively simplistic scale for global outcome. The GOS was introduced by Jennett and Bond in 1975[345] as a five category scale to capture functional outcome: alterations in major roles such as work and independent living as assessed by the investigator are used to summarize the effects of diverse changes caused by injury. Although attractively simple, the limited sensitivity of the GOS led to development of the GOS-extended (GOSE), in which the categories of severe disability, moderate disability and good recovery are subdivided into a lower and an upper subcategory (*figure 7.1*). A structured assessment was proposed in order to facilitate standardized administration.[346] Despite more refined outcome characterisation, the 8-category GOSE scale still lacks sensitivity to changes *within* specific domains of function (e.g., cognition, emotional well-being, life satisfaction). Further, increasing the number of outcome categories from the original 5-level scale to 8 levels can increase misclassification.[348] Insensitivity of outcome metrics decreases chances to detect treatment effects in clinical trials, and is enhanced by the common practice in TBI to dichotomize the GOSE into two categories: unfavourable (dead, vegetative, severe disability) versus favourable (moderate disability, good recovery). This approach is statistically inefficient and should be discouraged.[349,350] Currently recommended approaches for analysing the GOS employ a proportional odds analysis (evaluating a shift across the categories of outcome), or sliding dichotomy (where the GOS is still dichotomized, but the point of dichotomy varies according to individual baseline prognostic risk).[351] However, even this more refined application of the GOSE would be unsatisfactory for mild TBI, where patients who achieve the best possible outcome (GOSE 8) may still have clinically important cognitive or psychological problems (e.g., posttraumatic stress disorder and other depressive or anxiety disorders,[352,353] which may not register on the GOSE. Ceiling effects of the GOS may partly explain why methods for predicting outcome in patients with milder forms of TBI are largely lacking.

Figure 7.1.: Glasgow Outcome Scale Extended*



***** Glasgow Outcome Scale Extended: Schematic diagram of the decisions involved in assigning an outcome. The 8-point GOSE scale is formed by subdividing three of the categories on the 5-point GOS into upper and lower bands.

Formal categorization on the GOS(E) is less common in the clinical care of individual patients, where management is usually targeted at individual problems, rather than based on a summary measure of outcome. An additional challenge in clinical management is to ensure sufficient discrimination to allow detection of recovery or deterioration, and assessment of treatment benefits. These considerations suggest the need for more detailed assessments, which account for smaller transitions in the outcome scale. Critically, these need to take account of separate aspects of outcome, including cognitive deficits, psychological health, and quality of life (including the impact of common symptoms such as sleep disturbance and pain.)[354,355,356]

Summary or integrated measures of outcome may still allow a useful basis to allocate patients to broad care pathways, and such applications are worth developing.

These aspirations are challenging. There are a multitude of instruments for assessing outcome, disagreement on their relevance, and lack of consensus on a key set of assessments. Recent overviews identified nearly 1000 (mostly non-overlapping) outcome assessment instruments in TBI (*ESM 9*).[357,358,359,360,] While diversity in assessment is an asset in clinical practice, it is a major

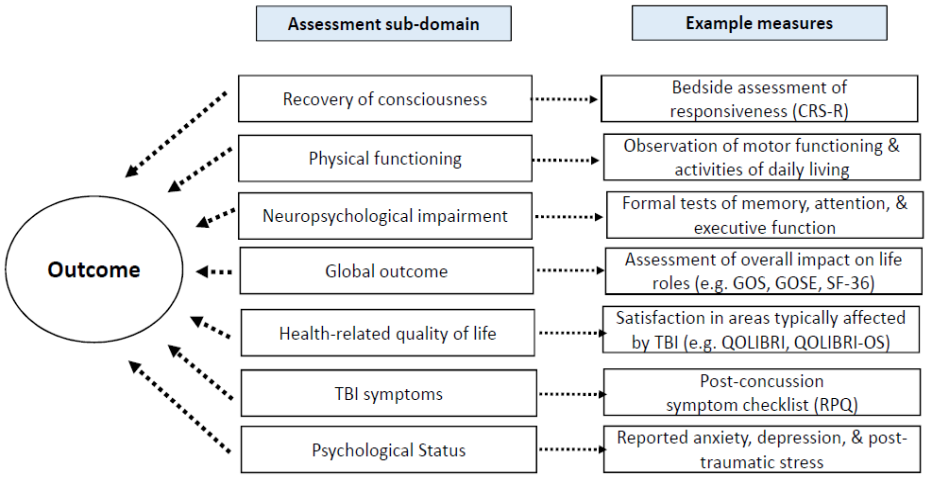
obstacle to research progress in TBI, because it inhibits pooling of data and undertaking meta-analyses. While there may be a need for different assessments for different purposes, it would be a major step forward if a limited subset of assessments could be agreed as covering key dimensions of outcome that go beyond the GOSE, and can be used across studies and over time.

7.2 Multidimensional assessment of outcome

TBI is a major cause of long term changes in functional, physical, emotional, cognitive, and social domains (see series paper on postconcussional symptoms and TBI as a chronic health condition). Heterogeneity in the consequences of TBI, and the wide variety of short- and long-term recovery patterns, place high demands on outcome assessment. For many years, clinical practice has embraced the use of multiple specialized outcome assessments, particularly in the management of TBI after the acute stage. However, their use in research has been limited, since the very complexity that allows them to provide a fuller description of deficits makes it difficult to derive single endpoints that can be used to power clinical trials.

It is increasingly evident that a single outcome parameter is insufficient to demonstrate the efficacy of an intervention or to be an endpoint in clinical studies and that multidimensional outcomes that cover a broad range of outcome domains (*figure 7.2*).[361] are essential to describe the consequences of TBI. While it is commonly percieved that regulatory authorities require the GOS or GOSE as an efficacy parameter, experience suggests that regulators are open to considering other early or late outcome measures,[362] as long as there is evidence to support their use and clinical validity. In the USA, the FDA has recently implemented a formal qualification process for clinical outcome assessments that should help to facilitate adoption of a range of instruments in TBI trials. Collaboration between FDA and clinical investigators has been established in the context of the TBI Endpoints Development project.[363]

Figure 7.2: Multi-dimensional outcome assessment*



***** Sub-domains of outcome assessment included in both adult and paediatric Common Data Elements for TBI (specific instruments mentioned in the text are in brackets). "Outcome" is defined by selecting multiple sub-domains of assessment, and choosing measures that reflect each domain. CRS-R = Coma Recovery Scale – Revised; GOS = Glasgow Outcome Scale; GOSE = GOS-Extended; SF-36 = Short-Form 36; QOLIBRI = Quality of Lifte after Brain Injury Scale; QOLIBRI-OS = QOLIBRI Overall Scale; RPQ = Rivermead Post-concusision Symptom Questionnaire. (Adapted from Kean & Malec, 2014)[364]

Assessment methods have different strengths and weaknesses, and few can be applied across the complete TBI severity spectrum. Health related Quality of Life (HRQoL) assessment can effectively combine different domains, but HRQoL would still only rarely be considered adequate on its own as an endpoint in TBI, and severely injured individuals may be too cognitively impaired to complete these assessments. The reliability of exclusively self-reported measures is hampered by limited self-awareness of deficit, necessitating access to caregivers' views, which may be different, and possibly more accurate.[365] Neuropsychological tests cover a range of domains, and provide a sensitive index of impairment, but are challenging to complete for TBI survivors: in a trial of hypothermia only just over half of patients with severe TBI completed cognitive assessment at 6 months.[366]

Various approaches to the development of multidimensional approaches to outcome assessment can be considered:

- Identification of a core set of outcome instruments.

- Application of a 'sliding' dichotomy approach that accommodates assessments appropriate at different levels of severity of impairment, similar to the concept of the sliding dichotomy for outcome analysis of the GOS, in which the point of dichotomy of the GOS is differentiated by initial baseline risk.[351]

- Development of global tests or composite endpoints.

Composite endpoints have been pioneered in a few clinical trials[361,367,368], including the recent BEST TRIP trial of intracranial pressure management.[202] Using more than one outcome measure creates a difficulty for traditional methodological and statistical approaches. Typically, a single measure is used to calculate the effect size and power of a study. Choosing a measure that is likely to change over time may lead to underpowered results for other outcomes. However, by using the measure that is least likely to change, the trial may become impractical.[361] Other issues for the use of global tests or composite measures include the weighting of individual components and interpretation of the overall result. There is a need for further work to establish multidimensional outcomes as endpoints for clinical studies in TBI. Importantly, buy-in from regulators is essential. There have been major initiatives to develop multi-dimensional assessment tools that can be used across different diseases. The CANTAB[369] and the NIH Toolbox[370] are sets of computerized measures designed to assess cognition, emotion, and motor and sensory functions across the age range. The Patient Reported Outcomes Measurement Information System (PROMIS) project[371] has developed a set of instruments that can be used across a wide range of chronic conditions. These tools potentially meet the need for a standard set of assessments that are useful both in research and the clinical setting. Practical problems may, however, hamper implementation of any comprehensive scheme in an international setting (*panel 7.1*).

Panel 7.1: Barriers to widespread adoption of recommended assessments in an international setting

Item	**Barrier**
Language	Lack of availability of good quality versions in languages other than English
Cost	Initial costs of some instruments and stipulation of payment per use
Copyright	Copyright issues and consequent difficulties

	reproducing materials
Access	Restriction of some assessments to particular professional groups
Scoring	Imposition of proprietary scoring systems

The limited availability of many instruments in languages other than English provides a major barrier to their use in international settings, and high priority should be given to funding cross-cultural validation of assessments.[372] In the context of CENTER-TBI (*see part 9*), translations of common outcome assessments have been linguistically validated and made available without restrictions to the neurotrauma community. Such validation is not simple: cross-cultural comparability of assessment methods is important when analysing data across countries. Charges and restrictions on proprietary measures represent a substantial hurdle. We strongly believe that outcome assessments advocated by the Common Data Elements for TBI should be freely available to the clinical and research communities without charge, and that public funding should support ready access to high quality instruments. Developing multidimensional outcome tools and novel ways to integrate the various domains of outcome will require collaborative efforts in large-scale studies with novel approaches to data sharing (see Part 9).

Part 8: Prognosis in TBI: linking initial severity to outcome

Key messages	Recommendations
1. Prognostic models can help clinicians provide information to patients and families to facilitate and improve treatment decisions.	1. There is an urgent need for further development, validation and implementation of these prognostic models in TBI, especially for mild TBI.
2. TBI impacts multiple outcome domains and prognostic models are needed to predict this range of outcomes, including quality of life.	2. Funding agencies should support the development of new prognostic models that focus on predicting outcome beyond mortality and the Glasgow Outcome Scale.
3. No validated quality indicators for TBI exist. A validated set of quality indicators is essential for benchmarking quality of care	3. Funding bodies should stimulate the development of quality indicators for TBI which should represent a mix between structure, process and outcome indicators

Introduction

Outcome in TBI is not only dependent on the quality of care provided, but also on patient and injury characteristics such as premorbid state (e.g. related to age or co-morbidities), mechanism of trauma; injury severity, presence and severity of extracranial injuries, host response and social environment. Linking initial severity to outcome is the science of prognosis and prognostic modelling. Prognostic models combine different characteristics of an individual in a mathematical formula, and have diverse applications (panel 8.1) in clinical practice and research in TBI. These include provision of personalized information on expectations to patients and their relatives, adjustment for differences in case mix between studies in clinical research, and for calculating standardized outcome rates for benchmarking quality of care. Robust prognostic models have been developed for moderate and severe TBI. However, they are not used in mainstream practice, and their precision could be improved, primarily by better characterization of injury severity and host factors at presentation (Section 6), and by including outcomes beyond the GOS/GOSE. Prognostic schemes for mild TBI are much less advanced and will require more refined description of outcome (section 7).

In this section, we explore the links between initial severity and outcome with use of prognostic models and their applications in clinical practice and research, and discuss the developments and refinements needed to improve models and to enhance their use.

Panel 8.1: ***What has Prognostic Modelling to offer?***

- Realistic information to patients and relatives
- Insight into possible causes of poor outcomes
- Identification of potentially modifiable causes
- Informing triage decisions
- Risk adjustment for comparing patient series
- More efficient design and analysis of clinical trials
- Benchmarking quality of care

8.1 Applications for prognostic modelling

Outcome predictions are highly relevant to providing realistic information to relatives (see patient testimony). Models provide the probability of an outcome and have an inherent degree of uncertainty. This should always be taken into consideration when applying the model to an individual patient.

Prognostic models can also be used to inform our understanding of cause and effect, and provide insight into potentially modifiable causes of poor outcomes. However, since an association may not be causal, clinical benefit of correction of the modifier would need to be proven by thorough evaluation of an intervention, preferably in a randomized controlled trial. Use of prognostic models could enable more efficient design and analysis of clinical trials, and enable risk adjustment when comparing patient series.

An emerging application of prognostic models is to improve benchmarking quality of care. Benchmarking is a specific approach to implement the best available evidence into practice and to optimize quality of care. It allows continuous comparisons between hospitals and can identify areas for improvement. Ideally, a set of quality indicators includes outcome indicators (e.g. mortality rate), process indicators (e.g guideline adherence) and structure indicators (presence of facilities to provide good care). Specific challenges in the development of quality indicators for TBI include mortality being a poor outcome metric for benchmarking in TBI, and that outcome is not only dependent on treatment but heavily influenced by injury severity and patient characteristics. Survival with extreme severe disability is considered by many as an undesirable outcome, and survival in a vegetative state may even be an outcome worse than death. When patient

populations differ across hospitals, outcomes cannot be simply compared. Prognostic models provide estimates of the expected institutional outcome. Contrasting observed to expected outcomes allows comparisons across hospitals with different case-mix. There are currently no broad quality indicators available for TBI, and the development of an internationally accepted set of quality indicators should be considered a high priority to advance quality of care for TBI patients and to ensure implementation of evidence based care.

8.2 Prognostic models in moderate and severe TBI

Many prognostic models have been developed since the 1970s, with varying methodological quality.[373,374] One driver for development of some of these models was to refine efficacy analysis in clinical trials. These models specifically focused on baseline risk assessment using characteristics available on admission, and on mortality and the Glasgow Outcome Scale (GOS) at 6 months after injury as outcomes of interest. For severe and moderate TBI, two sets of prognostic models, using information available upon admission, have been developed on large datasets, using state of the art methods. These are the IMPACT models (developed on eight large datasets)[375] and the CRASH models (developed on the database of a large clinical trial).[376,] We should recognize, however, that the development populations for both models were weighted towards more severe TBI, and that patients with moderate TBI were underrepresented.[377] An additional focus on moderate TBI is required. Both the IMPACT and CRASH models shared some key predictors of outcome: age, GCS (the full score in CRASH, the motor component in IMPACT), and pupillary reactivity, second insults (hypoxia and hypotension), CT characteristics and laboratory parameters. Most predictive information is contained in the core predictors: age, GCS motor score and pupillary reactivity. Taken together, these predictors can explain approximately 35% of the variance in outcome (ESM 10). Both the CRASH and IMPACT models have been extensively validated in populations external to the development setting. External validation is an absolutely crucial step in prognostic modelling, as it tests generalizability of a model beyond the development setting.[378] The development of new models in small studies with flawed methods and without external validation, is likely to lead to false positive identification of features of prognostic importance, and result in limited generalizability.

8.3 Prognostic models for outcome prediction in mild TBI

The sequelae of mild TBI may include physical symptoms, behavioural disturbances, and cognitive dysfunction, any of which may interfere with return to work or resumption of social activities (*see* Series Paper on mild TBI for more on this topic). Prognostic analyses can identify patients at increased risk, who may then be followed more closely and receive early interventions to alleviate the psychological burden of injury. Mortality is not an appropriate endpoint for prognostic analysis in these patients, and the usefulness of the GOS is doubtful. Although a substantial number of patients with so-called mild TBI may have disabling complaints, most will be in the upper segment of the GOS categories.[379] More sensitive outcome measures (see part 7) as endpoints for prognostic analyses are required, though these have so far been insufficiently or inconsistently investigated.

There are no good prognostic models with proven generalizability available for mild TBI[380–382], and there is an urgent need for development and robust validation of models in this group of patients.

8.4 Advancing the science of prognosis in TBI

The availability of robust and well-validated prognostic models for severe/moderate TBI is a major step forward. They allow us to deal appropriately with the inherent heterogeneity of TBI populations. However, taken together, these models only explain 35% of the variance in outcome, implying that there are other key patient and injury characteristics that contribute to outcome. Identifying these could improve prognostication and, if modifiable, could provide therapeutic targets. Genetic variance, advanced neuroimaging, and other precision medicine features described in Part 6 might explain part of the residual variance. Inclusion of these features could provide some refinement of prognostic models, but it is likely that part of the variance is explained by treatment differences and centre effects.

Comment [a8]: @ Editor: Agree good to add – have modified sentence slightly – OK?

Panel 8.2: Directions for advancing prognosis in TBI.

- Refinement of models for moderate and severe TBI (adapt to changing epidemiology and outcome).
- Exploration of "new" markers, tests, and imaging (e.g. MRI, genotype: adding information).
- Dynamic predictions beyond baseline assessment (e.g: serial clinical or imaging assessment: adding the time dimension).
- Development and validation of models for mild TBI, using sensitive endpoints.
- Development and validation of models to predict quality of life and other outcomes

Various directions for prognostic research in TBI can be identified (*panel 8.2*). Prognostic models may be improved by including new predictors, by better characterizing existing predictors, by adding new information as it becomes available as the disease evolves (dynamic predictions), and by predicting other relevant outcomes. New predictors that hold promise include biomarkers and advanced MR Imaging (see section 6). Various studies have explored the prognostic value of such newer predictors, often reporting promising results. Most have, however, been limited to relatively low numbers and have compared performance based on information obtained later (e.g. advanced MR imaging at 1 -3 weeks) to predictions based on admission characteristics (such as the IMPACT and CRASH models).[383,384] A more rigorous approach would be to compare the new predictive tool (e.g. MRI) to the clinical information available at the same time as the newer predictor. Dynamic predictions are complex and require specific statistical techniques since those dying in the first days are excluded from further consideration.[385] Recently developed machine learning techniques may be useful when data structures become more complex and may lead to deeper insights.

We need to focus on the incremental value of new or more extended markers, (i.e. prognostic value beyond readily available characteristics). Such evaluation should be phased, starting with technical validation of marker measurement, followed by evaluation in small series, and eventually by rigorous validation in independent cohorts. Several statistical measures have recently been proposed to quantify the impact of a marker on classification.[386] Decision analysis[387] and cost-effectiveness analyses should eventually be performed to assess the clinical usefulness of any new marker.[388]

A related challenge is to make predictions optimally targeted to the specific setting of application. The CRASH model was developed with variants for developed and less developed countries. Further site-specific customization may be attempted using advanced statistical approaches such as random effect models. Such model updating aims to improve the calibration of predictions for individual patients in specific settings,[389] recognizing that trauma organization and treatment policies may differ between sites or change over time. [378]

International collaborative studies that collect high-quality data on large numbers of patients across the full injury severity spectrum, including mild TBI, are required to advance the science of prognosis in TBI (see part 9). Outcome measures beyond the currently established GOS/GOSE assessments are required. Prognostic models are needed that extend over a longer time horizon and include multidimensional outcomes, such as the various cognitive, psychosocial, HRQoL and other patient reported outcome measures *(see section 7)*. The absence of good prognostic models for mild TBI highlights an important gap in our knowledge that requires attention.

Part 9: New directions for acquiring and implementing evidence

Key messages	Recommendations
1. Substantial between-centre variability in treatment and outcome in TBI offers unique opportunities for comparative effectiveness research (CER) to provide stronger evidence.	1. Fund CER to identify best practices and to improve the level of evidence for systems of care, and diagnostic and therapeutic interventions.
2. Coordinated research efforts on a global basis are required to address TBI.	2. A commitment of governmental and non-governmental funding bodies, as well as industrial partners is desired to facilitate global collaborations and legacy research.
3. Standardization of clinical data collection, based on the TBI common data elements, provides a common language for world-wide research.	3. For global standardization of clinical data collection, the common data elements need to be made internationally applicable.
4. CER studies and research on disease characterisation, outcome, and prognosis will require many patients, large-scale datasets and data-sharing.	4. Fund systems for efficient collection and sharing of data across borders, including funding of costs for rigorous data curation, annotation, and long-term database maintenance to maximize return on research investment from (public) funding.
5. Collaborations, formalized in data use agreement, offer the best guarantee for driving research and care forward and require re-assessments of existing frameworks for assigning academic credits.	5. Funders and academic assessment systems need to critically assess and revise the current system of academic credits to provide incentives for data collection and sharing.
6. Overly restrictive interpretation of privacy legislation can inhibit greatly needed research and productive datasharing in TBI, and may even make it impossible.	6. Regulation should avoid unnecessarily restrictive interpretation of privacy clauses and complex bureaucratic procedures, which inhibit important research in TBI and other conditions that result in loss of capacity to consent
7. Traumatic brain injury is often	7. Ensure that regulatory frameworks for

characterized by incapacity of patients to provide informed consent themselves.	research take account of acute loss of capacity in conditions such as TBI, and include appropriate provisions to allow vital research to continue
8. There are substantial delays in integrating research results into clinical practice.	8. Funders and publishers should support rapid transfer of new research results into the evidence base, facilitated by new digital tools for their subsequent collation and integration into living systematic reviews and clinical guidelines.
9. Barriers to transfer of knowledge from research to the clinic can result in poorer patient outcomes. Transfer of knowledge involves more than dissemination. Strategies to implement a transfer of knowledge to practice are essential.	**9.** Resources and information campaigns are needed to overcome barriers to knowledge transfer and ensure implementation of guidelines and best practice to optimise benefits of future research advances in clinical practice and improve outcomes and make cost savings in health care.
10. In TBI, as in many areas of medicine, substantial gaps exist between best current evidence and practice.	10. Funders should encourage efforts to optimise synthesis of research findings through living systematic reviews and use theory-informed strategies to change clinicians behaviour.

Introduction

Heterogeneity of the at-risk TBI population, variations in injury patterns, and wide variation in systems of care pose particular challenges for clinical evidence generation and implementation in TBI. Evidence underpinning guidelines for trauma care pathways and clinical interventions is often weak and recommendations inconsistently implemented. Conventional approaches to reduce heterogeneity in randomized controlled trials of medical or surgical interventions have mostly used strict enrolment criteria and tight protocols, typically focussing on age, GCS, and pre-injury morbidity but neglecting mechanistic differences. This approach has reduced their generalizability, whilst increasing duration and consequently costs of studies. Moreover, the vast majority of multicentre studies have failed to convincingly demonstrate efficacy in the populations studied[289,390] A recent systematic overview of RCT's in acute moderate/severe TBI identified a total of 191 completed RCT's, of which 26 were considered as robust (high quality, sufficient numbers). Of these, only 6 showed a statistically significant effect, 3 positive and 3 negative. The authors concluded that considerable investment of resources had resulted in very little translatable evidence.[390]

We must rethink approaches to the generation, analysis and implementation of evidence.[291] One alternative approach might be to consider exploiting the heterogeneity of TBI in terms of disease type, management, and outcome in comparative effectiveness research (CER), rather than attempting to reduce the heterogeneity as commonly performed in RCT's. Such research would allow us to assess therapies in real world conditions. CER requires large studies, international collaboration, and advanced statistical expertise. It also demands a change in research culture to recognize CER outputs as high quality evidence, and to embrace broad data sharing. Data sharing and large-scale collaborative studies are also needed to generate high-quality research on characterization of TBI, outcome assessment, and prognosis; such research would help to advance precision medicine approaches to target treatment strategies to individual patients on the basis of clinical and pathophysiological characteristics. Such paradigm changes are endorsed by the InTBIR initiative, a collaboration of funding agencies. Global collaborations modeled on InTBIR need to be promoted.

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This section evaluates the application of CER approaches, and explores the advantages and challenges for collaborative efforts and data sharing in TBI research. We also discuss living systematic reviews as an approach to optimize existing evidence and review the potential for knowledge transfer to facilitate implementation of evidence into practice.

9.1 A new paradigm for evidence generation: comparative effectiveness research

Comparative Effectiveness research (CER) is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, monitor and treat a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.[391] Central to CER is the applicability of results to daily clinical practice. Study designs for CER can vary, including both experimental and non-experimental designs. Experimental designs include pragmatic RCTs. In contrast to traditional RCTs, pragmatic RCTs employ broad inclusion criteria to increase generalizability, whilst maintaining the benefits of randomization.[392] Non-experimental designs are generally based on observational studies, which use existing variability in care and outcome to compare interventions. Non-experimental designs are methodologically challenging and a high risk exists of so-called "confounding by indication". This implies a particular risk of finding an association between the intervention of interest and different outcome, because the choice of intervention is not at random, but likely influenced by physician preferences, patient characteristics and other uncontrolled factors. Expert methodological input is required to deal with the potential problems of confounding by indication. Large-scale studies based on collaborative efforts and capture of sufficient detail are essential ingredients for a robust design and analysis plan.

The application of Comparative Effectiveness Research to TBI

CER has particular potential in TBI for several reasons. *First*, there are large between centre and between country differences, in both outcome and management. *Second*, robust risk adjustment models are available for TBI, allowing adjustment for patient characteristics that affect outcome. *Third*, advanced statistical models, including random effect models, are available to analyze differences between centres. Existing variability may relate to 'structural parameters' (e.g. level 1 *vs.* level 2 trauma centres; high *vs.* low patient volume centres) or 'process parameters' (e.g. choice of surgical procedures, ICP monitoring and management protocols).

The IMPACT studies, analyzed data of 9578 patients with moderate or severe TBI from 265 centres, and found a 3·3 fold difference in the odds of unfavourable outcome at 6 months between very good and very poor centres ($2{\cdot}5^{th}$ vs. $97{\cdot}5^{th}$ percentile), after adjustment for chance effects and differences in case-mix.[393] Similarly, an analysis of 9987 patients across the TBI severity spectrum from 237 centres in 48 countries from the CRASH MRC trial, showed 6·6-fold between-centre

differences in 14 day mortality (ESM11).[394] Both studies, however, had insufficient detailed data to relate these outcome differences to differences in structure or process of care.

Many interventions that are part of current clinical practice (such as the order in which aggressive therapies are used, or the decision to surgically treat contusions) are not readily addressed using RCTs. CER approaches could provide a more cost effective means of evaluating these interventions (and, potentially, novel therapies) in real world settings. Early evidence in support of non-experimental designs as a promising approach for severe TBI comes from studies relate outcome to structure and process parameters[210,211,219] (see part 4) or compare surgical interventions using CER[268] (see part 5).

In guideline development, however, evidence from non-randomised clinical studies is regarded as inferior to that generated by RCTs. The recent update of the guidelines on management of severe TBI[255] illustrates the current methodological rigour with which literature evidence is being evaluated, resulting in level 1 recommendation for just a single topic. We suggest that evidence from high quality non-randomised and observational studies could be as valuable as RCTs, since their increased generalizability provides specific practical benefits.

9.2 Collaborative approaches to accelerate TBI research

There has been a rich tradition of academic collaboration for advancement of TBI management. The National Traumatic Coma Data Bank in the USA[395] provided important data on acute physiology and outcome, which underpins much of current clinical practice. This tradition continues in the USA, perhaps best exemplified by the TBI Model Systems Project which provide important data based on everyday practice in collaborating US centres. Other important outputs have resulted from international consortia (The European Brain Injury Consortium: EBIC)[396,397], from clinical trials consortia (such as the Australia and New Zealand Intensive Care Society Clinical Trials Group; ANZICS CTG)[257,398,399] or audit programs (the UK Intensive Care National Audit and Research Centre; ICNARC).[219] More recent initiatives address TBI Endpoints Development[363] and chronic effects of neurotrauma.[400] However, the last few years have seen a more strategic approach to encouraging such collaboration, which represents a synergy not of researchers, but of national and international funding agencies.

Comment [OT10]: Margin Link: http://www.msktc.org/tbi/model-system-centers

International initiative on TBI research

A need for a re-appraisal of research design and implementation of broad based, sustainable multidisciplinary and international approaches was recognized in 2010 by major funding agencies. This led to establishment of InTBIR (the International Initiative on TBI Research), which represents a concerted effort to tackle the vast global health problem posed by TBI. InTBIR was initially arose as a collaboration between the European Commission (EC), the US National Institute of Neurological Disorders and Stroke (NIH-NINDS), and the Canadian institute of Health Research (CIHR)[401] and was more recently joined by One Mind (a non-governmental organisation) and the US Department of Defense (DoD). *Table 9.1* summarizes the studies supported within the InTBIR collaboration, which cover the entire spectrum of TBI. Each has a different focus, but a common goal: to better understand the disease TBI, and to improve its prevention, treatment and outcome.

Comment [OT11]: Margin link: http://intbir.nih.gov

Comment [OT12]: Margin link: http://onemind.org/

Table 9..1.: InTBIR studies**

	Project title	Project acronym	Funding agency	Target enrolment	Current enrolment	Focus of study	Funding	Study duration
Europe	Collaborative European NeuroTrauma Effectiveness Research in TBI[402] www.center-tbi.eu	CENTER-TBI	European Commission	5400 adult and paediatric TBI patients, all severities	4000 patients	Biomarkers, CER, classification, prognosis	€ 29,998,310	2013-2020
	Collaborative REsearch on ACute Traumatic brain Injury in intensiVe care medicine in Europe www.creactive.marionegri.it	CREACTIVE	European Commission	7000 paediatic and adult patients in intensive care	4.200 patients	Biomarkers, imaging analysis, CER, prognosis	€ 5,443,350	2013-2018
USA	Transforming Research and Clinical Knowledge in Traumatic Brain Injury https://tracktbi.ucsf.edu/	TRACK-TBI	NIH/NINDS	2700 adult TBI patients, all severities, 300 controls	1850	Biomarkers, CER, classification, prognosis	$ 18,800,000	2013-2018
	Multiple medical therapies for paediatric TBI: Comparative Effectiveness Approach www.adapttrial.org	ADAPT	NIH/NINDS	1000 paediatric patients in intensive care	Completed: 1000	CER	$ 16,147,544	2013-2018
	Managing severe TBI without ICP monitoring - guidelines development and testing		NIH/NINDS	780 adult TBI patients in intensive care	256/256 for phase I 137/256 for phase II	CER	$ 2,586,216	2012-2017

Canada	Predicting and Preventing Post-concussive Problems in Pediatrics (5P) study: a prospective multicentre clinical prediction rule derivation and validation study in children with concussion[403]	5P	CIHR	Mild paediatric and adolescent TBI: derivation cohort 2000 patients; validation 800 patients		Prognosis	$ 1,273,705	2013-2018
	Improving the diagnosis and treatment of mTBI in children and youth: the power of common data	PedCDE	CIHR	Paediatric and adolescent mild TBI: two rounds of 500 patients		Tool development (CDEs); CER, Prognosis	$ 1,400,000	2013-2018
	A 5-year longitudinal cohort study of mTBI in youth ice hockey players www.siprc.ca	Safe to play	CIHR	Prospective study on 1000 paediatric and adolescent ice hockey players to evaluate risk factors and the occurence of sports-related concussion		Prevention, diagnosis, prognosis, management	$ 1,500,000	2013-2018
	Post-Concussive Syndrome in youth: GABAergic effects of melatonin www.playgametrial.ca	PLAYGAME	CIHR	RCT 166 children and adolescents with post-concussion syndrome		Clinical trial	$855,000	2013-2018

	'NeuroCare' as Innovation in Intervention: A Neurophysiological Approach to Determine Readiness for Return to Activity	NeuroCare	CIHR	1400 paediatric and adolescent athletes; 140 paediatric and adolescent mild TBI patients and 140 control		Tool development	$ 1,065,728	2013-2018
	Early determination of neurological prognosis in ICU patients with severe Traumatic Brain Injury www.tbi-prognosis.ca	TBI-prognosis	CIHR	315 critically ill adults with severe TBI		Biomarkers, prognosis	$ 1,053,131	2012-2017

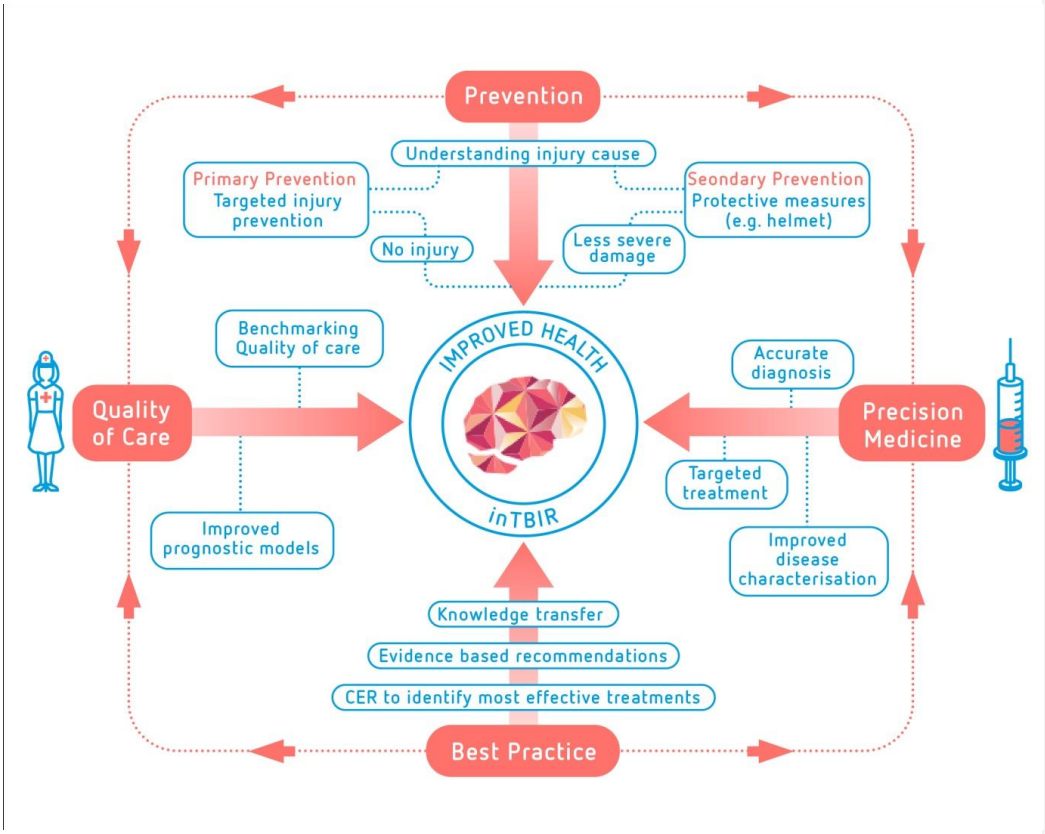
*** Details of current InTBIR supported studies;** Co-funding partners of the Canadian Institutes of Health Research (CIHR) for the Team Grants are: Fonds de recherche du Québec Santé (FRQS); Hotchkiss Brain Institute; Ontario Brain Institute; Ontario Neurotrauma Foundation. Co-funding of CENTER-TBI is provided by ONE MIND and the Hannelore Kohl Stiftung (Germany).

The InTBIR studies will include over 40,000 patients of all TBI severities, many of whom will provide novel information on genomics, biomarkers and advanced imaging. The outputs are expected to provide a rational basis for optimising health care delivery for populations, and clinical management for individual patients (*figure 9.1*). In addition, these studies will establish well-curated biorepositories and provide for legacy research with future new methodologies or longer follow up. All projects comply with standards based on the Common Data Elements.[404] European and Canadian studies will address the internationalisation of these CDEs, allowing a US-based process to be applied globally, and promote global data standards for TBI research. This harmonised data collection will permit meta-analysis of individual patient data in large numbers - essential for CER and improving TBI characterisation – and deliver outputs that would be impossible with any individual study.

Comment [a13]: @ Editor: Suggest to additionally include weblink as margin link http://www.commondataelements.ninds.nih.gov/tbi.aspx#tab=Data_Standards

The collaboration of international funding agencies is unique. The overall funding approximates a total of $90 million, representing an enormous uplift from past levels of funding for TBI research, but still disproportionally low when compared to other neurological diseases. An estimate based on figures from the International Alzheimer's Disease Research Portfolio[405] suggest global funding for Alzheimer's disease at $3.4 billion between 2008 and 2014.[406] A recent paper estimated that $432 million was spent on research in frontotemporal dementia,[407] a condition with a global incidence under 300,000.[408] Given the large number of patients of patients with TBI globally and the huge cost burden, the funding supporting neurotrauma research merits further increase.

Figure 9.1.: How InTBIR aims to improve healthcare for TBI*



***** The InTBIR studies will collect detailed clinical and outcome data in observational studies and pragmatic trials and established biorepositories, creating a highly granular "information commons". They aim to improve our understanding of the disease, both in terms of cause and mechanism, informing prevention strategies (Prevention) and in terms of disease characterization (Precision Medicine). CER analysis aims to identify more effective and targeted therapies (Best Practice). The increased data inputs will improve prognostic accuracy, allowing better benchmarking of care (Quality of Care).

Towards global collaborations

The concept of large-scale observational studies combined with comparative effectiveness research, as implemented in the InTBIR initiative, has attracted global interest, and has resulted in a number of collaborative linked projects.

In China, a large-scale observational study was initiated in August 2015 in which approximately 44 sites initially agreed to participate and this was recently expanded to 63 sites. By February 1st 2017 over 10.000 patients had been recruited to this study. In India, an observational study named CINTER-TBI (Comparative Indian Neurotrauma Effectiveness Research) was initiated in June 2016 and recruitment recently expanded to six centres. The data collection in both studies is harmonized

with CENTER-TBI in order to ensure meta-analysis across studies. The inclusion of these two populous countries, with a dramatically increasing burden of TBI provides a platform for high quality research in these countries. Both studies are autonomous and conducted nationally, mainly from scientific interest with minimal or very low local funding. For the first time ever, data collections across the world in the field of TBI are harmonized and globally coordinated. Given recent trends for movement of pharma-initiated clinical trials from Europe and the USA to the Far East, the international collaborations described above may deliver key insights regarding clinical trial design and generalizability. These global collaborations represent a new research, to which funding agencies must adapt. Major challenges include a lack of funding mechanisms for global research and restrictions of cross border data transfer due to existing privacy legislation. Despite the collaborative ethos of IntBIR, the studies conducted under its aegis are funded independently by respective funding agencies, and no funding mechanisms are currently planned for meta-analysis across IntBIR studies. Neither is funding available to support meta-analyses across InTBIR studies or with linked projects on a global basis such as the initiatives in China and India. The greatest synergies will emerge from integrated analyses of the combined data in all relevant studies. The initiative established by InTBIR needs to be globally expanded, and consolidated by facilitating meta-analysis across studies, thus ensuring future research continuity.

9.3 Data sharing

CER and Precision Medicine research in TBI require large sample sizes and data sharing. Funding bodies and research regulators promote such data sharing [409,410,411] [412,413,414,415,416,]

While the principle of data sharing receives almost universal support, implementation is less easy. Any solution must comply with privacy and ethical regulation, ensure high quality data standards, promote sensible data use, maintain incentives for researchers who collect data, and appropriately account for the true costs of data sharing. Balancing these competing demands provides challenges.[417]

Consent issues

In TBI, particular challenges arise from loss of capacity to consent, and from the need to initiate data collection as early as possible. In the USA, the Health Insurance Portability and Accountability Act (HIPAA) regulations[418] recognize proxy consent in principle, and permit the use of "waiver of consent", particularly if underpinned by community consultation. The regulatory situation in EU jurisdictions is in a state of flux: The General Data Protection Regulation (GDPR; regulation

2016/279) will apply from May 2018,[419] and though it makes provisions for research, it remains ambiguous with reference to incapacitated patients in emergency situations. There is a strong case for explicitly defining the acceptable use of data for legitimate clinical research in this context, and doing so in a way that meets the needs of TBI and other acutediseases, characterized by lack of capacity to consent.

Intellectual capital and costs of data sharing

The emergence of open data sharing has clear tensions with the current system of academic credits: The loss of intellectual capital that resides in data may represent a major obstacle to data sharing. These tensions are a particular issue for TBI, where the demands of acute data collection in critically ill, often multiply injured patients, can be substantial. Most of these patients will not have capacity to provide consent, and obtaining proxy consent from distraught family members requires sensitive and experienced research staff, who need to be available round the clock. Such coverage of recruitment opportunity is resource hungry, and rarely fully recompensated in publicly funded studies. Additional costs accrue from the process of data sharing itself. A recent commentary[420] identified four major categories of cost for data sharing, including infrastructure and administration, data standardization, human resources, and opportunity costs. It is essential that funders recognise these additional data-related costs, estimated to represent up to 15% of study costs.

Approaches to data sharing

The desire to obtain a justifiable return on intellectual capital and local resource subsidies has led many researchers to make data available primarily in the context of a collaboration, with an anticipated reward of at least one joint publication, which benefits both parties. This recapitulates arrangements in the open source community, where source code licenses (such as the GNU licenses)[421] require returning any improvements or new developments in the software product to the owner, thus ensuring a collaborative approach to product development. Many of the major InTBIR studies have elected to formalise such collaborative ventures through Data Use Agreements, which provide a clear understanding of data us between the collaborating parties.[422,423]

The NIH have mandated that all data from US publicly-funded TBI studies must be deposited in the Federal Interagency Traumatic Brain Injury Research (FITBIR)[424] repository, but transfer of data from European InTBIR studies to this repository may contravene the new European Union data privacy legislation. However, data collected in a standard manner does not necessarily have to be

stored together in order to be integrated for federated analysis. The pros and cons of central repositories, versus individual repositories for specific studies, were explored in a recent Wellcome Trust Report[417] and an abstracted summary is listed in ESM 12.

Irrespective of how data are stored, allowing open access while still ensuring personal privacy remains a work in progress. Additional privacy concerns arise from concerns that new data mining tools could identify individuals in supposedly "anonymised" datasets.[425] One possibility answer could be provided by "gatekeeper software", which allows access while balancing the seemingly irreconcilable demands of openness versus privacy, through "differential privacy" algorithms.[426,427] However, technology can only provide solutions in the context of rational regulation, and these digital solutions will need to be underpinned by new paradigms of consent[428] and social contracts between researchers and patients.[429] Emerging trends provide cause for optimism in this context.[430,431]

9.4 Optimizing existing evidence: Living Systematic Reviews

Healthcare decisions should be informed by knowledge about what works and what does not. Such knowledge is best understood by integrated results from multiple studies through systematic reviews that comprehensively search for all previous research and critically appraise it using transparent and reproducible methods.[432] However, conventional systematic review processes are labour-intensive and time consuming, often undertaken by small teams working in isolation and seldom updated as new research is published. In an analysis of 792 study reports incorporated into 73 systematic reviews across 28 neurotrauma topics, the median time from primary study publication to its inclusion in a published systematic review ranged from 2·5 to 6·5 years.[433,434] As a consequence, systematic reviews are often outdated by the time they are published.[435]

An innovative knowledge management approach known as Living Systematic Reviews (LSRs)[434,436] is currently being pioneered within the InTBIR collaboration. LSRs are high quality and up-to-date online summaries of health research, updated as new research becomes available.[434] LSRs transform the systematic review process from sporadic large projects undertaken every few years to, instead, an ongoing activity characterized by ongoing surveillance and more frequent smaller packages of work as new research findings emerge. Whereas the main questions driving conventional reviews are about what the totality of evidence tells us about the effectiveness of an intervention or the accuracy of a diagnostic test, the real-time nature of living reviews shifts the emphasis to answering '*how does this new evidence change what we already know?*'

By pairing clinical TBI experts with experts in systematic review methods, the teams leading the InTBIR studies are laying the foundations for an ongoing dynamic TBI knowledge community. To date, two Living Systematic Reviews have been published[94,207], and further topics developed in relevant research areas include diagnostics, prognosis, and interventions. Completed reviews are published in an open access format. Searches are being automatically run every three months, and we are piloting machine learning technology to reduce the work load.[437,438,439] Publishing a living manuscript is a particular challenge in academic publishing, but we have established an agreement with the editor and publisher of the Journal of Neurotrauma to include updates in the online version of the manuscript. In addition, continuous updates will be provided on the CENTER-TBI web site.[436] We will additionally seek to publish journal updates as new manuscripts- subject to peer review- when new evidence leads to a change in conclusions.

Interest in Living Systematic Reviews is growing exponentially, with multinational research collaborations forming to maintain and curate the evidence base in a range of clinical areas[440,441]. Notably, the global systematic review producer, Cochrane, is also piloting Living Systematic Reviews. In the field of TBI, and these pioneering efforts of CENTER-TBI are now being integrated within the IntBIR initiative. However, current funding is limited to the duration of current IntBIR studies. We need mechanisms to ensure future continuity, in terms of both knowledge management and funding.

One of the most tantalizing aspects of a living evidence synthesis model, is the potential to produce living clinical practice guidelines or recommendations, and this is currently being considered by the Brain Trauma Foundation, the main producer of guidelines in TBI.[442] Whilst we strongly support the concept of an evolution towards living guidelines, an alternative approach could be to consider living systematic reviews as the evidence-base upon which more practical treatment recommendations can be tailored to national and local settings. A major criticism of the current guidelines is that the emphasis on methodological rigour has decreased their practical value. Presenting the evidence-base and practice recommendations separately might be a way to combine methodological rigour with practical applicability. There is a growing recognition of the value of practice recommendations based on expert consensus to facilitate care delivery where rigorous guidance is lacking or unclear,[443] Whilst efforts continue to strengthen the evidence base, ensuring the practical relevance of guidelines is essential in order to stimulate their implementation into practice.

9.5 Implementing evidence into Practice and Policy: Knowledge translation

Translating evidence into practice has become a distinct science, which complements that of discovering, developing and synthesizing research results. The new emerging field of Knowledge Translation (KT) is defined as *"the science of developing strategies to integrate evidence-based knowledge into health policy and practice, based upon understanding of behavioural drivers of practice within specific settings".* [432] The science of KT has developed in response to the recognition of gaps between research evidence and clinical practice. The Evidence Based Practice (EBP) movement of the early 1990s[444] re-shaped approaches to clinical practice by consideration of best evidence, clinical expertise and patient preferences in making treatment decisions.[445]. A series of landmark studies published in the early 2000s revealed that only 55 – 67% of patients actually received recommended care, and 20 – 25% received care that was unnecessary or potentially harmful.[446,447,448,449] TBI is not immune to the evidence-practice gap. A recent systematic review[207] concluded that while guideline adherence was associated with improved outcome, general adherence to guidelines was highly variable, and in many instances, poor. For example, the mean figure for adherence to the Brain Trauma Foundation Guidelines for ICP management was 31% (range 18%-83%). [207]

There is much to be gained from harnessing KT to address the evidence-practice gap in TBI. Economic modelling has shown that more widespread adoption of Brain Trauma Foundation (BTF) guidelines across the United States would save over 3500 lives and, by raising the proportion of 'favorable' outcomes from 35% to 66%, would yield an estimated annual US $4 billion cost saving. [155]

Use of a KT approach involves three core tasks: defining the target behaviour, measuring current behaviour and understanding current behaviour. Defining the target behaviour establishes the desired healthcare standard by which the success of a KT intervention can be measured. For example, the BTF guidelines on nutrition following TBI recommend "feeding patients to attain basal caloric replacement at least by the fifth day and, at most, by the seventh day post-injury" to decrease mortality.[255] Next, knowledge of current practice is required to determine the scope and nature of the evidence-practice gap.[447,450,451] Härtl et al. (2008)[452] examined adherence to the guideline on nutrition and found that 1) Patients not fed within 5 and 7 days after TBI had a 2- and 4-fold increased likelihood of death, respectively; and 2) Every 10-kcal/kg decrease in caloric intake was associated with a 30–40% increase in mortality rates.[452] These data underscore the importance of ensuring that practice reflects evidence.

Finally, understanding behaviour is necessary for successful implementation of new practices. Quantifying the evidence-practice gap defines the problem, but does not give information on *why practice is the way it is*. The importance of gaining this understanding of behaviour *before* attempting a quality improvement (KT) strategy cannot be overestimated. Without this understanding, precious resources can be wasted. For example, a common assumption is that people are not following guidelines because they do not kno them. This frequently drives educationally-focused strategies such as lecture presentations and passive guideline dissemination. However, there are numerous barriers to best practice other than lack of knowledge. These include peer group influence, attitudes and beliefs of health professionals, organisational barriers such as lack of equipment, and structural barriers such as financial disincentives.[432] By only addressing the assumed barrier of lack of knowledge, an educational quality improvement strategy therefore risks being ineffective and a waste of resources.

Advances in both the science and the uptake of KT are required to close the evidence-practice gap. A key challenge for KT scientists is the 'terminology challenge' – the use of various terms to describe KT, including 'dissemination and implementation research,' 'quality improvement', 'implementation science' and 'research translation.' KT scientists are working to address this challenge through development of conceptually simpler and shorter frameworks that can standardise KT interventions, in a similar way to what the CONSORT statement has achieved in the clinical trials arena.[453] Uptake of KT science needs to be increased in clinical and other communities who are less familiar with applying behavioural theory to close evidence-practice gaps. It is hoped that clinician engagement in universal and simple frameworks can contribute to this.

Healthcare quality improvement is complex and there is never likely to be a one-size-fits-all approach. What is beyond dispute, however, are the words of the former Director General of the World Health Organization, Lee Jong-Wook: "*Health work teaches us with great rigour that action without knowledge is wasted effort, and knowledge without action is a wasted resource".*[454]

A thought experiment to engage the reader in the importance of knowledge transfer in TBI

We invite the reader to engage in frank introspection and challenge decision-makers and clinicians to develop an implementation "plan of attack" that guides efforts to embed evidence into practice. Every hospital that seeks to implement TBI guidelines will need to run its own thought experiment because the barriers may vary by location. Planning holds the promise of avoiding traditional

pitfalls if sufficient resources can be brought to bear on the question of not just "what" to implement, but "how."

Read more on this thought experiment in ESM 13.

Conclusions

Traumatic Brain Injury (TBI) is predicted to remain the largest global contributor to neurological disability for the next two decades, with a disease burden that far exceeds conditions such as cerebrovascular disease, and dementia. Critically, this disability often affects young individuals at their productive peak, and results in huge burdens to individuals, families, and society. Extrapolation from available estimates suggest a global annual cost of TBI as high as $400 billion (a figure that represents over 0.5% of global GDP). The precise magnitude of the problem remains, however, largely uncharted. Estimates of 50-60 million new TBIs a year represent an approximation due to wide variations that exist in reported data exist between countries, and differences in methodology. An urgent need exists for implementation of methods and descriptors that are common across countries. Patterns of TBI are changing across the world, with increases in road traffic injuries in LMIC, and a growing problem with falls amongst elderly individuals in HIC. Other key drivers that contribute to the burden of TBI include sports-related concussion, and international conflict. Whatever the cause, TBI results in an enduring burden of late morbidity and increased mortality, and may represent a risk factor for dementia in later life; the attributable risk from TBI to overall dementia incidence may be as high as 15%. This knowledge of epidemiology is important to target TBI prevention appropriately in different populations.

When TBI does occur, we need better ways to organise systems of care that provide cost-effective approaches to minimise preventable mortality and morbidity, ensuring that patients receive appropriate healthcare as soon as possible. Substantial variations in outcome exist between centres, and tackling these differences has potential to far outweigh any benefit that might be realistically expected from a new treatment. There is growing evidence of a relationship between patient volumes and centre outcomes and, as such, systems should centralise care for the sickest patients. Substantial gains may accrue from adequate pre-hospital care, appropriate referral and continuity along the chain of care with early access to effective rehabilitation. The solutions that relate to care systems for TBI must take account of local economic and social factors and in particular, work is needed to develop cost effective systems of care in LMICs.

Clinical management should be based on robust guidelines, but evidence in support of guideline recommendations is often weak and not applicable to all patients as most studies are population based and do not take into account the heterogeneity of the “disease” of TBI, severity and individual patient differences. As a result, current management strategies are based on guidelines

that favour a “one-size-fits-all” approach and the care of patients with TBI is therefore poorly individualised. Despite the investment of many billions of dollars by pharmaceutical companies, we have no effective drugs for acute treatment; a failing that is likely due to insufficient targeting of therapies to patients in whom the relevant mechanism is active. We need better methods of characterising patients with TBI to allow identification of patient subgroups with a common dominant disease mechanism, who are more likely to respond to the treatment - a concept now being popularized as “Precision Medicine”. We also need to better characterise outcome from TBI: mortality is an inappropriate metric for a disease that results in so much disability in survivors, and current outcome assessment tools are unidimensional. We need improved multidimensional outcome assessment schemes that take better account of the substantial physical, cognitive, behavioural, and mental health sequelae of TBI. Improved disease and outcome characterisation will also provide a robust foundation for better prognostication of outcome. This may improve comparative audit of care between centres and countries, facilitate research, and help plan management in individual patients. There are huge opportunities for improved characterisation of initial severity, outcome, and prognosis, and for more accurate tracking of disease processes, through building on the current scientific advances in modern neuroimaging, genomics, disease biomarker development, and pathophysiological monitoring. Developments in these technologies could facilitate the goals of precision medicine in TBI.

Comparative effectiveness research may provide a tool to exploit disease heterogeneity, in terms of clinical and pathophysiological type and outcome, and to use variations in clinical management and systems of care to identify best practices.

The data that we gather from such research in real-world situations could enrich the limited evidence base on clinical care of TBI. The critical gaps in our knowledge of how best to treat TBI necessitate common methods and descriptors for collaborative research efforts. The development of the Common Data Elements for TBI research is an important step, but these tools need to be internationalised, particularly for use in LMICs. Clinical research in TBI is also hampered by vendor-specific differences in platforms used for neuroimaging and laboratory investigation. It is critical that national and international regulators mandate common standards for imaging and laboratory results, so that outputs from different studies can be usefully integrated. Industry has been a valuable partner in improving TBI care in the past, and we need to continue to facilitate such support through regulatory design and collaborative funding arrangements.

Large cohorts of patients are needed to deliver meaningful advances in Precision Medicine, for robust Comparative Effectiveness Research, and to improve prognostic schemes. Such studies can only be realised through global collaboration. Current international initiatives for TBI research and a growing ethos of data sharing represent an unprecedented opportunity to achieve these aims. However, such collaborative approaches to research are dependent on ensuring that regulatory barriers do not prevent data sharing – a growing concern in the context of ever more rigorous privacy legislation, particularly in the context of TBI where capacity to consent is often lost at the onset of the condition. We need to recognise the right of individuals to personal privacy, but develop regulatory frameworks and technical solutions that do not require choice between personal privacy and research collaboration. Research funders also need to recognise the substantial costs of data sharing. The knowledge that is gained from clinical research must be rapidly translated to improvements in care. There is typically a gap of 5-8 years before the results of a study are integrated into systematic reviews and a further delay before such integrated information is translated into guidelines. Novel digital tools for literature searching and integration may allow us to speed up this process by develop living systematic reviews and living guidelines, which are continuously updated as new information is available.

The problems and potential solutions described in this Commissioned Issue have been inspired by patients and brought together by a wide international group of active clinical researchers who seek to improve TBI outcomes. Policymakers and funders need to ensure that the outputs of this process far exceed the sum of its parts.

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