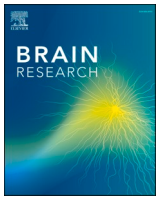
Brain Research 1845 (2024) 149271

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres



Review

Traumatic brain injury: Symptoms to systems in the 21st century

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ARTICLE INFO

Keywords:
Brain
Injury
Trauma
Inflammation
Immune
Coagulopathy
Specific-pathogen free

ABSTRACT

Severe traumatic brain injury (TBI) is a devastating injury with a mortality of ~ 25–30 %. Despite decades of high-quality research, no drug therapy has reduced mortality. Why is this so? We argue two contributing factors for the lack of effective drug therapies include the use of specific-pathogen free (SPF) animals for translational research and the flawed practice of single-nodal targeting for drug design. A revolution is required to better understand how the whole body responds to TBI, identify new markers of its progression, and discover new system-acting drugs to treat it. In this review, we present a brief history of TBI, discuss its system's pathophysiology and propose a new research strategy for the 21st century. TBI progression develops from injury signals radiating from the primary impact, which can cause local ischemia, hemorrhage, excitotoxicity, cellular depolarization, immune dysfunction, sympathetic hyperactivity, blood-brain barrier breach, coagulopathy and whole-body dysfunction. Metabolic reprograming of immune cells drives neuroinflammation and secondary injury processes. We propose if sympathetic hyperactivity and immune cell activation can be corrected early, cardiovascular function and endothelial-glycocalyx-mitochondrial coupling can be restored, and secondary injury minimized with improved patient outcomes. The therapeutic goal is to switch the injury phenotype to a healing phenotype by restoring homeostasis and maintaining sufficient tissue O_2 delivery. We have been developing a small-volume fluid therapy comprising adenosine, lidocaine and magnesium (ALM) to treat TBI and have shown that it blunts the CNS-stress response, supports cardiovascular function and reduces secondary injury. Future research will investigate its suitability for human translation.

1. Introduction

> TBI has consistently been the leading cause of post-injury mortality, without successful breakthroughs in treatment.
>
> Fitzgerald and colleagues (2022) (Fitzgerald et al., 2022) p217.

Traumatic brain injury (TBI) is a global healthcare priority that affects ~ 69 million people annually or ~8000 per hour (Dewan et al., 2018; Wiles, 2022; Izzy et al., 2023). It is a leading cause of death and disability in both adults and children (Araki et al., 2017; Maas et al., 2022) mostly caused from motor vehicle accidents (50 %), falls (21 %), assaults and violence (12 %), and sports and recreation (10 %) (Maas et al., 2022). Overall, adult males are nearly two times more likely to be hospitalized and three times more likely to die from a TBI than females (Peterson et al., 2022). However, after moderate-to-severe TBI, females appear to have a significantly higher in-hospital mortality risk than males for reasons not well understood (Mollayeva et al., 2018; Breeding et al., 2024). Where you live also matters with people residing in rural and remote areas having higher mortality rates compared to those living in urban areas (Peterson et al., 2022; de Souza et al., 2024; Gabbe et al., 2024; de Souza et al., 2024). TBI is of increasing concern in contact sports, particularly in the young, with long-term adverse outcomes (Izzy et al., 2023). In moderate-to-severe TBI cases, around 30 to 50 % will have concurrent chest, abdominal or extremity polytrauma, which further complicates treatment and recovery (Watanabe et al., 2018; Faden et al., 2021).

TBI is classified as mild, moderate, or severe based on the Glasgow Coma Scale (GCS), which includes eye opening, verbal response, and motor function (Maas et al., 2022; Saatman et al., 2008; Pugh et al., 2021). A GCS score of 13 to 15 indicates a mild injury, 9 to 12 a moderate injury and 3 to 8 a severe TBI (Maas et al., 2022). While this scoring system remains a practical measure of consciousness, there are limitations (de Souza et al., 2024; de Souza et al., 2024) which highlight the increasing need to incorporate imaging findings and biomarkers into its severity classification to improve personalized care (Vande Vyvere et al., 2024). Mild TBI or concussion is the most common injury (Dewan

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https://doi.org/10.1016/j.brainres.2024.149271
Received 1 October 2024; Accepted 7 October 2024
Available online 10 October 2024

et al., 2018) and is responsible for ~90 % of TBI incidents among military personnel in the Iraq and Afghanistan conflicts (Madhok et al., 2022; Dengler et al., 2022; de Souza et al., 2023). A mild TBI should not be viewed as an inconsequential injury as some studies suggest that up to 50 % of hospitalized patients may take 6 months to recover from their symptoms (Maas et al., 2022). In contrast, a moderate-to-severe TBI carries a high mortality of 25–30 %, with less than 50 % of survivors returning to a full independent and productive lifestyle (Fitzgerald et al., 2022; Maas et al., 2022). Survivors have longer hospital stays, increased risk of neurodegenerative disease, chronic psychological problems and reduced life expectancies (Maas et al., 2022; Wilson et al., 2017; Krishnamoorthy and Vavilala, 2022; Coburn et al., 2023). In 2022, the Lancet Commission proposed that moderate-to-severe TBI should be viewed as a chronic disease because of its long-term consequences (Maas et al., 2022).

Despite decades of high-quality research, no therapy for TBI has been shown to significantly improve mortality and morbidity. Why is this so? In this review, we present a brief history of TBI, discuss its pathophysiology from a system's perspective, and address the question on why there are so few breakthroughs and possible solutions for the 21st century. We propose that a new revolution is required to better understand how the body responds to TBI, identify new markers to detect its progression and discover new system-acting drugs to treat it.

2. The Past: A brief history of TBI

Trepanned skulls from the Neolithic and Mesolithic periods, some as much as 10,000 years old, have been found in Japan, the Iberian peninsula, Germany, Ukraine, the Czech Republic, Hungary, France, Syria, Chile, Mexico, Peru, and Bolivia.

Collado-Vázquez and Carillo (2014) (Collado-Vázquez and Carrillo, 2014) p433

Humans, since time immemorial, have experimented with treating a severe blow or penetrating injury to the head (Fig. 1). Local fighting, battles and warfare demanded improvement in knowledge, as well as surgical techniques and skills to treat their injuries. Evidence of some of the oldest practices date back to ~8000 BC, or earlier, and include healed trepanations, presumably from scraping, grooving, cutting or boring into the skull (Collado-Vázquez and Carrillo, 2014; Lillie, 1998; Kshettry et al., 2007) (Fig. 1). Trepanation (trephination, trepanning, or burr holing) involves removing a piece of the skull to release pressure on the brain after an impact. The practice was most likely performed to clean out bone fragments after injury or from ritualistic burr holing to release evil spirits (Collado-Vázquez and Carrillo, 2014; Kshettry et al., 2007). Different surgical methods are described in detail in ancient Egypt and Classical Greece (Collado-Vázquez and Carrillo, 2014; Kshettry et al., 2007; Kamp et al., 2012) (Fig. 1). Hippocrates, for example, believed that stagnant blood, like stagnant water, could decay and turn into pus and by trephining the skull allowed blood to flow before it spoiled (Kshettry et al., 2007). Galen continued the tradition

Fig. 1. A brief history of the major events that led to advances in treating head trauma from prehistoric time to present. Methods ranged from spells, superstitions and concoctions to more objective surgical procedures to release intracranial pressure. Early trepanation procedures date back thousands of years using stone tools. The timeline provides a perspective of the changing ideas, practices, and outcomes from which the current thinking and treatments have developed. One is immediately captivated by how far we have come in advancing knowledge, on one hand, and the apparent long road ahead to improve current treatments, on the other. For references see text. A.D., anno Domini; BBB, blood-brain barrier; B.C., before Christ; CNS, central nervous system; GCS, Glasgow Coma Scale; ICP, intracranial pressure; TBI, traumatic brain injury.

and taught that letting the blood ooze after a head injury reduced the effect of "bad humours" (Fig. 1).

During the Renaissance (c1400-1600 AD) there was a marked shift away from the older Classical Greek and medieval supernatural approaches to more empirical observations from medicine and science (Dobson, 2016). Fast forward to the late 19th and 20th centuries where major advances in biology, physiology, medicine and surgery led to the wider use of aseptic procedures, improved anesthesia methods and later antibiotics (Fig. 1). Before this time, according to Gurdjian's compilation of statistics of brain penetrating wounds during the U.S. Civil War (1861–1865), a fatality rate of ~70 % was not uncommon (Head, 1973). In the 20th century, with new surgical techniques and perioperative care, mortality rates began to decline by ~50 % compared to the late 1800 s (Stein et al., 2010). Two most influential surgeons were George Crile (1864–1943) and Harvey Cushing (1869–1939) who together established the modern era of neurosurgery (Fig. 1). The next major advance occurred during World War I where patient rehabilitation became a healthcare priority, and after World War II led to the rise of new specialized rehabilitation Medical Centers and improved patient outcomes.

In the 1950s, major advances in neurobiology and pathophysiology led to new diagnostic TBI methods and treatments (Casper, 2018). The 1970 s witnessed another rapid growth phase driven largely by the hundreds of thousands of TBI injuries sustained in the Vietnam war (Lindquist et al., 2017; Cernak et al., 2017; Agimi et al., 2019). There was also an unprecedented increase in the incidence of TBIs from speed-related road accidents and contact sports, making it a global public health problem. New technologies, such as computerized tomography (CT) scans and magnetic resonance imaging (MRI), were developed to guide new medical diagnoses, treatments and surgeries (Pinky et al., 2022) (Fig. 1). Advances in molecular biology set the next stages of development in treating TBI and the 'omics era' continues to develop today. Since the 2000s, the spotlight further expanded from the focus on single TBIs of different severities to repeated head knocks with lifelong implications (Pinky et al., 2022; McKee et al., 2023). This is of increasing concern in children, adolescents and adults playing contact sports or victims of family/domestic violence, and its association with latter-life chronic traumatic encephalopathy, Alzheimer's disease, and Parkinson's disease (McKee et al., 2023; Gr et al., 2017; Snyder et al., 2018) (Fig. 1). Despite decades of technological advances and research, no TBI therapy has been shown to significantly improve patient outcomes after a mild-to-severe TBI.

3. The Present: TBI pathophysiology from a system's perspective

Primary injury mechanisms result from the mechanical damage that occurs at the time of trauma to neurons, axons, glia and blood vessels as a result of shearing, tearing or stretching. Collectively, these effects induce secondary injury mechanisms.

Kumar and (2012) (Kumar and Loane, 2012) p1191.

A severe blow, jolt or penetrating injury to the head is associated with differential neuronal, axonal, cerebrovascular and metabolic damage with impaired autoregulation (Ng and Lee, 2019). The primary traumatic injury can be a discrete "focal" lesion, such as laceration or contusion, with local hemorrhage, or it can be a more diffuse axonal injury affecting larger areas of the brain, including white matter junctional tracts (Pinky et al., 2022; Snyder et al., 2018; Signoretti et al., 2010; Demirtas-Tatlidede et al., 2012). The injury can involve white matter degradation, neuronal loss, modification of neurotransmitter systems, protein misfolding and persistent neuroinflammation (Fig. 2). Spreading depolarization waves are evident in about 56 % of patients with severe TBI (Seidel et al., 2016; Balanca et al., 2017). Secondary injury progresses like ripples in a pond radiating from the primary injury, first locally then systemically, with dysfunctional changes in central nervous system (CNS) sympathetic outflows, immune function, inflammation, endothelial-glycocalyx function, coagulopathy and multiple organ dysfunction syndrome (MODS) (McKee and Lukens, 2016; Lazaridis et al., 2019; Dobson et al., 2021; Krishnamoorthy et al., 2021) (Fig. 2). Hypotension, pneumonia, infection and sepsis are further complications and associated with high mortality (Corral et al., 2012). As with all major traumatic injuries (blunt, penetrating, hemorrhagic and burn), the pathophysiology of TBI occurs in the setting of stress-related catecholamines in proportion to injury severity, which can last for many days before gradually declining (Rizoli et al., 2017; Dobson et al., 2022; Dobson et al., 2024; Dobson et al., 2024). Although our focus is on moderate-to severe TBI in adults, it is important to acknowledge that children may have different responses attributable to age-related structural changes (Araki et al., 2017). These age differences are under-researched and a critical topic for future research.

4. Early immune activation and inflammation

The neuro-critical care of traumatic brain injury patients carries a considerable value in initial management, especially in the golden hour.

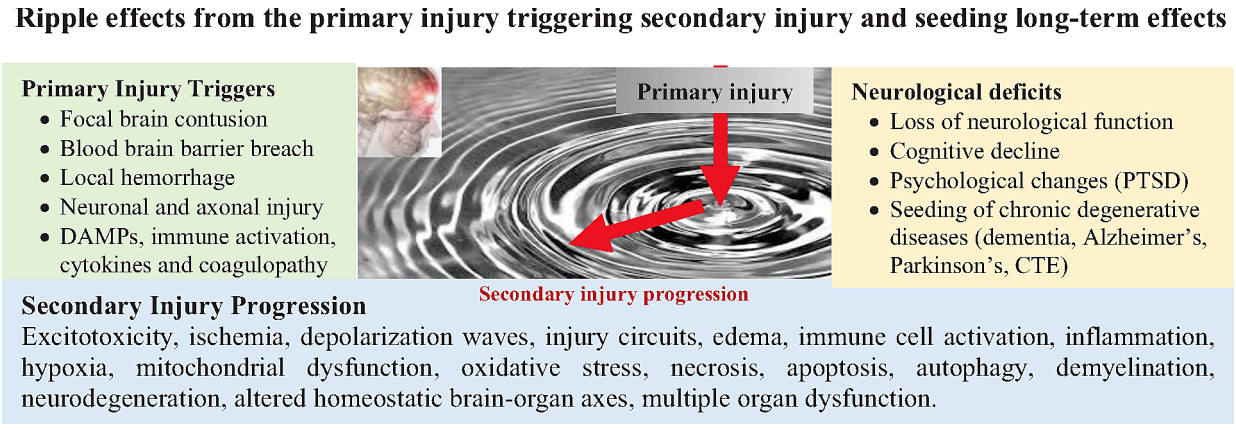

Fig. 2. A severe blow, jolt or penetrating injury to the head radiates an injury wave throughout major regions of the brain like ripples in a pond, first locally then systemically via immune, inflammatory and neurohormonal mechanisms. The primary injury often involves the shearing, tearing or stretching of neurons, axons, glia and blood vessels. Secondary injury is defined as a progressive process that begins with the primary injury and leads to CNS dysfunction, immune dysfunction, excessive inflammation, coagulopathy, oxidative stress and mitochondrial energy deficit. The progression involves partial uncoupling of the brain and multiple organ circuits (or axes), which in severe cases can lead to widespread tissue hypoperfusion, infection, immunosuppression and multiple organ dysfunction. CTE, chronic traumatic encephalopathy; DAMPs, damage-associated molecular patterns; PTSD, post-traumatic stress disorder.

Maurya and colleagues (2022) (Maurya et al., 2022) p45.

After a severe head injury, time to definitive care is critically important because secondary injury can lead to further cellular damage. Within minutes, a barrage of damage-associated molecular patterns (DAMPs) are released from damaged or dying neuronal cells (Dobson et al., 2021), which in turn activate resident immune cells to produce a non-resolving cytokine storm. The cytokine storm comprises proinflammatory cytokines, chemokines, immune modulators, neuropeptides, neural afferents, complement, oxidants, proteases, and toxic extracellular traps (Fajgenbaum, 2020) (Fig. 3). Damage to the blood-brain barrier (BBB) further accelerates the cytokine storm, particularly if polytrauma and hemorrhage are present (Fig. 4). DAMPs include brain-derived extravascular vesicles, microparticles, fibrinogen, annexins, platelet components, fibronectin, S100 proteins, syndecan-1, F-actin, adenosine-5-triphosphate (ATP), histones, deoxyribonucleic acid (DNA), mitochondrial factors, high mobility group box protein-1 (HMGB1), heparan sulfate, tenascin C, defensins, amyloid-β, and many others (Kumar et al., 2017; Roh and Sohn, 2018).

DAMPs are detected by the host's innate defence system, which include pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), expressed on immune cells (Kawai and Akira, 2005; Akira et al., 2006; Vijay, 2018; Takeuchi and Akira, 2020) (Fig. 3). Both injury signals and receptors are highly conserved motifs that have been selected to increase host survival following a barrier breach like a TBI (Dobson et al., 2021; Janeway and Medzhitov, 2002; Matzinger, 2012). These receptors are expressed on resident microglial cells, NG2-glia, astrocytes, dendritic cells, neurons and endothelial cells, and on infiltrating immune cells and platelets recruited from the periphery (Fig. 3). Blood borne neutrophils are the first to cross the BBB followed by bone marrow-derived monocytes and macrophages (Dobson et al., 2021; Shrivastava and Shukla, 2019; Kanashiro et al., 2020). Other immune cells are recruited, such as dendritic cells, natural killer (NK) cells, B-cells, T-cells and innate lymphoid cells (ILC) (McKee and Lukens, 2016; Bouras et al., 2022) (Fig. 3). As secondary injury progresses, BBB permeability, immune dysfunction and inflammation increases leading to a pathophysiological 'runaway' cascade and poor outcomes (Chen et al., 2017) (Fig. 4).

Notwithstanding the complexity of the early inflammatory response (Xiao et al., 2011); the transition to a proinflammatory state could be a prime target for potentially resolving drug therapies. After injury, new evidence suggests that the rapid activation, differentiation and survival of immune cells appears to involve a PRR-activated change in the mitochondrial-glycolytic switch in immune cells (Dobson et al., 2021; Kumar, 2019; Wang and McLean, 2022; Namgaladze and Brune, 2023).

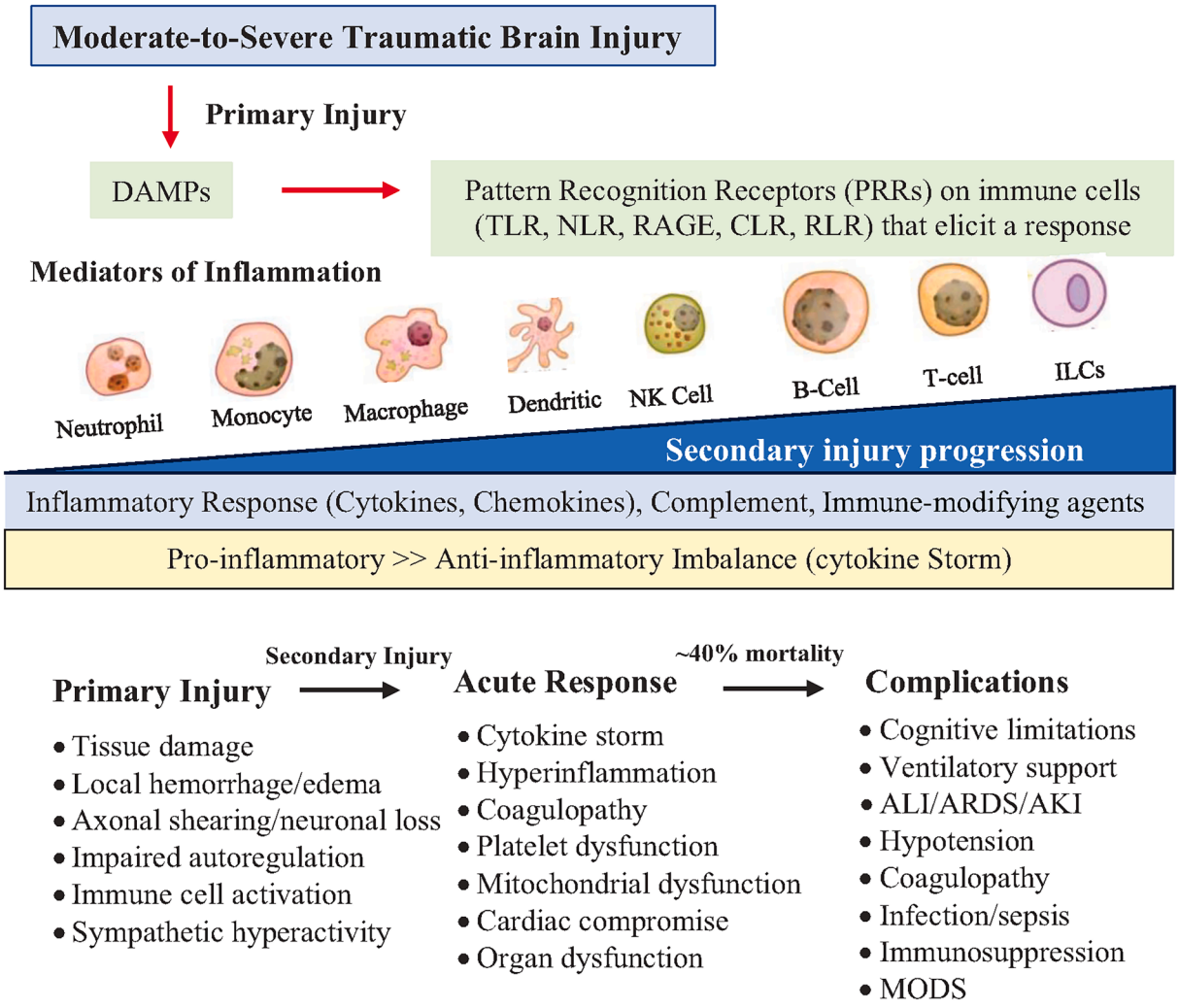

Fig. 3. After a moderate-to-severe TBI, the extent of secondary injury depends upon the release of damage-associated molecular patterns (DAMPs) from damaged and/or dying cells. These injury signals are recognized by a diverse group of innate immune cells resident in the brain and peripheral blood that, if left unchecked, leads to a cytokine storm that drives CNS-driven secondary injury and whole-body dysfunction and poor outcomes. ALI, acute lung injury; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ILC, innate lymphoid cell; MODS, multiple organ dysfunction syndrome; NK, natural killer; NLR, Nod-like receptor; PRR, pattern recognition receptor; RAGE, receptor for advanced glycation end products; RLR, retinoic acid-inducible gene-I like receptor; TLR, Toll-like receptor.

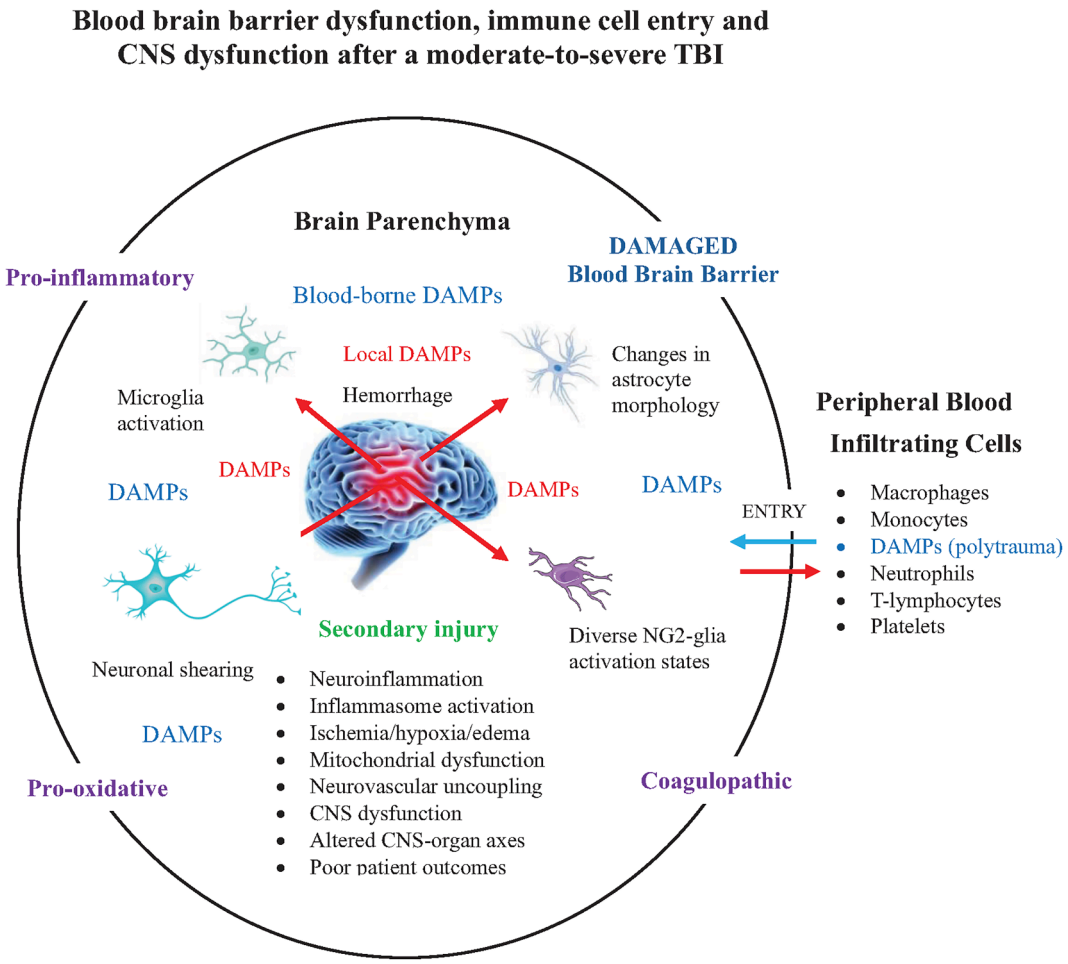

Fig. 4. A schematic showing the changing intra-cranial milieu after a moderate-to-severe TBI amplified by disruption of the blood-brain barrier (BBB). The BBB is a boundary between the brain parenchyma and the bloodstream. A leaky BBB allows entry of blood-borne immune cells, DAMPs and other immune-modifying factors, which amplifies the activation states of pericytes, microglia and astrocytes. These changes lead to further immune dysfunction, inflammation, coagulopathy, oxidative stress and mitochondrial dysfunction in the brain and whole body. CNS, central nervous system; DAMP, damage-associated molecular pattern.

If immune cell metabolism can be modified, inflammation may be reduced by increasing anti-inflammatory processes (Kanashiro et al., 2020; Bouras et al., 2022; Xiao et al., 2011; Manson et al., 2016; Dobson et al., 2022). The key point is that *restoring the balance of pro-inflammatory and anti-inflammatory cytokines is critical for an effective immune system response without propagating collateral damage.* Another potential target to restore inflammatory balance is blunting the multi-protein inflammasome complex in immune cells, which is pivotal in amplifying early pro-inflammatory processes (Fig. 4).

5. CNS stress response, sympathetic activation and collateral damage

> Experimental stressors that directly engage the HPA axis represent important areas for future research to better define the role of stress-immune pathways in mediating outcome following TBI.
>
> Tapp and colleagues (2019) (Tapp et al., 2019)p1.

TBI-induced amplification of local and systemic inflammation has a profound influence on CNS control of whole-body homeostatic functions (Fig. 4 and Fig. 5). The CNS responds to inflammation by eliciting a systemic stress response. Proinflammatory cytokine interleukin (IL)-6, for example, has been shown to activate the hypothalamic–pituitary–adrenal (HPA) axis and nucleus tractus solitarius (NTS) that leads to the release of sympathetic catecholamines (Dobson et al., 2021; Dobson et al., 2022; Tapp et al., 2019; Silverman et al., 2005; Barman, 2020). The early shift to sympathetic dominance perpetuates a proinflammatory state (Letson et al., 2022; Coppalini et al., 2024) that Rizoli and colleagues have correlated with adverse outcomes (Rizoli et al., 2017; Robba et al., 2020; McDonald et al., 2020; Yan et al., 2024; Krishnamoorthy et al., 2021). Activation of the HPA axis can also lead to excessive increases in glucocorticoids (GC) (Tapp et al., 2019). Since microglia, and many other immune cells, are rich in GC receptors, their stress-induced priming further exacerbates neuroinflammation (Tapp et al., 2019). In addition, GCs increase circulating levels of IL-6, which may further amplify the HPA axis and systemic inflammation (Tapp et al., 2019). Notably, the sympathetic discharge of catecholamines after a severe head injury can also profoundly alter multiple organ function and energy metabolism throughout the body (Fig. 5) (discussed later).

An area that has received little attention in TBI research is the effect of sex and age on a patient's HPA and NTS responsiveness following injury. In healthy human subjects, females appear to have greater HPA axis responses to a physiological stressor than males (Babb et al., 2013), although it is not known if these differences exist when the stressor is TBI. Female mice do appear to have greater HPA axis responses to a mild TBI than males, however, further work is required (Russell et al., 2018). Younger TBI patients also appear to have different catecholamine responsiveness than older patients (Krishnamoorthy and Vavilala, 2022). As more high-quality research emerges, the HPA and NTS responses may offer a new target for therapeutic intervention to reduce the whole-body effects of a moderate-to-severe TBI.

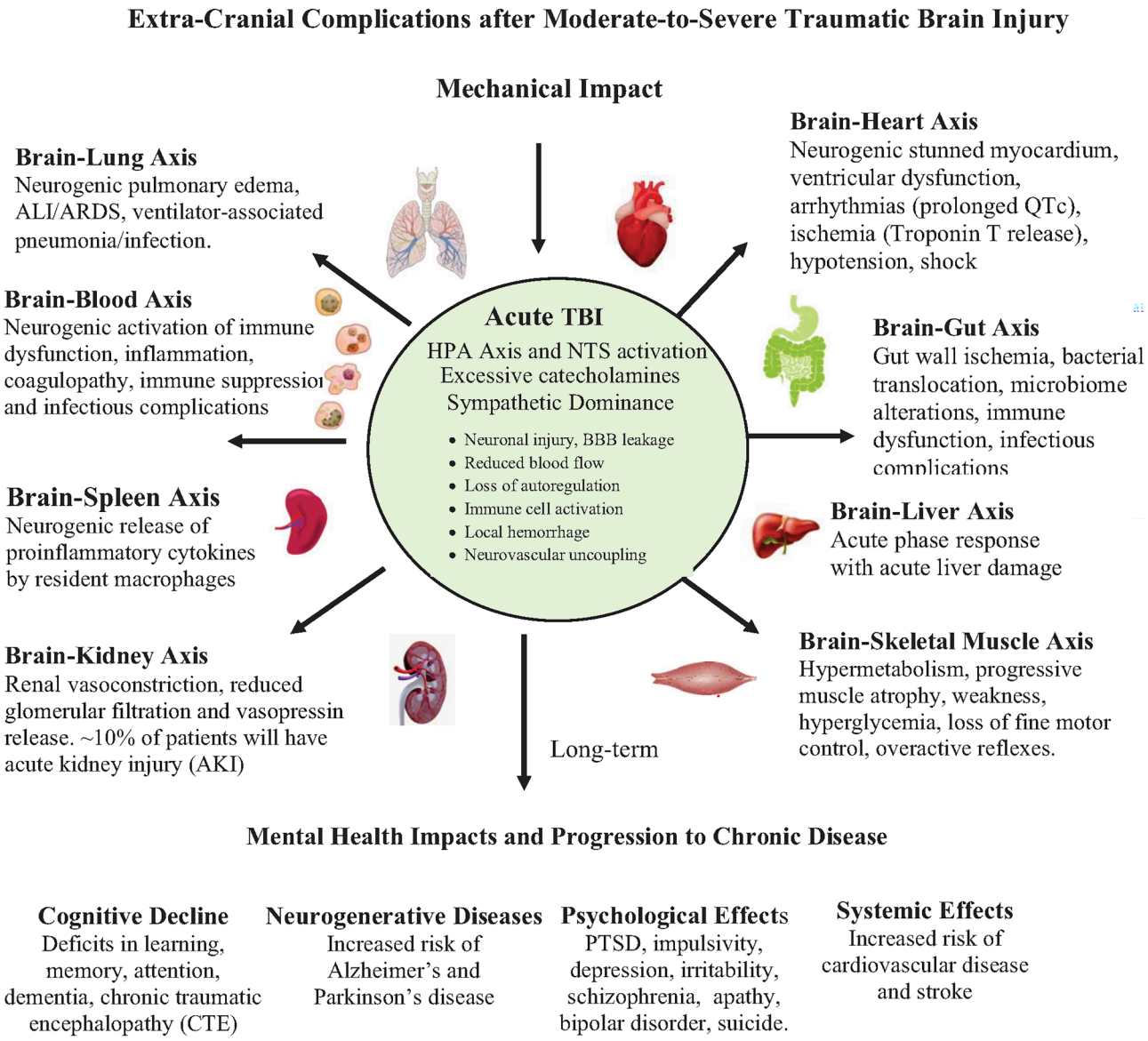

Fig. 5. Schematic of the systems effect of moderate-to-severe TBI on the organs of the body. Common to nearly all severe pathologies is a massive catecholamine discharge and immune-mediated inflammatory response that drives systemic complications. If the sympathetic discharge and inflammatory response can be blunted and blood-brain barrier (BBB) leakiness reduced, the uncoupling of the brain-organ circuits (or axes) may be minimized and lead to reduced morbidity and mortality. New drug therapies are required to reduce the perpetuation of these central nervous system (CNS)-driven injury cycles. AKI, acute kidney injury; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CTE, chronic traumatic encephalopathy; HPA, hypothalamic pituitary axis; NTS, nucleus tractis solitarius; PTSD, post-traumatic stress disorder; TBI, traumatic brain injury.

6. TBI-induced endotheliopathy

The breakdown of the glycocalyx exposes endothelial cells to circulating cytokines, immune cells, and other factors that trigger several responses, potentially leading endotheliopathy.

Gonzalez Rodriguez and colleagues (2018) (Gonzalez Rodriguez et al., 2018)p7.

Another important area of TBI research is to understand how endothelial activation and glycocalyx shedding exacerbates secondary injury progression (Xu et al., 2020). The endothelial-glycocalyx forms a nexus between the blood and the tissues and covers a surface area of over 55,000 m^2 (Dobson et al., 2022), and when it becomes activated is termed endotheliopathy (Neubauer and Zieger, 2022; Zou et al., 2021; Lu et al., 2022). *TBI-induced endotheliopathy is a process, not an endpoint, and is associated with activation and entry of immune cells, inflammation, coagulopathy and differential vascular reactivity* (Neubauer and Zieger, 2022; Zou et al., 2021; Lu et al., 2022). Glycocalyx shedding is facilitated by stress-activated membrane-bound sheddases that respond to many factors, such as tumor necrosis factor (TNF)-α, IL1-β, reactive oxygen species (superoxide and hydroxyl radicals), and/or aggressive fluid resuscitation (see Fluid Management) (Dobson et al., 2022; Zou et al., 2021; Anand et al., 2023). A proposed link between TBI severity and endotheliopathy is the release of endothelial biomarkers, such as syndecan-1, hyaluronan (HA), thrombomodulin and cell adhesion molecules, into the circulation (Gonzalez Rodriguez et al., 2018; Di Battista et al., 2016). Of clinical significance, glycocalyx shedding appears to repair itself relatively quickly (Zeng and Tarbell, 2014). Luft states that "these cells usually are able to replace their missing coats in a matter of minutes" (Luft, 1976). However, very little is known about the loss and recovery of the glycocalyx after moderate-to-severe TBI (Zou et al., 2021).

In severe TBI cases, early cerebral endotheliopathy may be

associated with localized posttraumatic intravascular microthrombosis that leads to ischemia, hypoxia and neuronal death (Albert-Weissenberger et al., 2019). Platelet activation and excessive production of von Willebrand factor (VWF) multimers adhere to endothelial cells as elongated strings and form platelet-vWF "microthrombi" (Xu et al., 2020; Ince et al., 2016; Chang, 2019). If the pathology becomes more diffuse and systemic, the progression may lead to a rare lethal condition known as disseminated intravascular coagulopathy (DIC) (see Coagulopathy). Reducing the early activation of the endothelial glycocalyx or facilitating its rapid recovery after shedding may be potential targets for new therapeutics.

7. Cardiac dysfunction: Acute and chronic effects

Acute brain injury triggers a systemic inflammatory response and a surge of catecholamines, leading to the release of neurotransmitters and cytokines. These substances have detrimental effects on the brain and peripheral organs, creating a vicious cycle that exacerbates brain damage and cellular dysfunction.

Coppalini and colleagues (2024) (Coppalini et al., 2024)p1.

Acute neurogenic myocardial injury: The effect of a moderate-to-severe TBI on cardiovascular instability is poorly understood (Chen et al., 2017; Coppalini et al., 2024; McDonald et al., 2020; Venkata and Kasal, 2018). As early as 1947, Byer and colleagues reported a head injury caused myocardial damage and arrhythmias (Byer et al., 1947). Today, cardiovascular complications affect 25–35 % of severe TBI patients (Krishnamoorthy et al., 2021; Coppalini et al., 2024; Cuisinier et al., 2016; Mathias et al., 2000). It has been proposed that the CNS-sympathetic discharge, increased catecholamines and changing neurogenic brain–heart axis can lead to ventricular dysfunction, regional wall motion alteration, troponin elevation, myocardial stunning and Takotsubo cardiomyopathy (Coppalini et al., 2024; Gregory and Smith, 2012). The severity of cardiac dysfunction and arrhythmias correlates with the severity of neurologic injury (McDonald et al., 2020; Salim et al., 2008; Cai et al., 2016). Rat studies support a neurogenic basis of cardiac dysfunction after a moderate TBI (Letson and Dobson, 2018). In mice, cardiac dysfunction has also been shown to involve inflammatory cell infiltration from the spleen since its removal reduced the injury (Zhao et al., 2019). *Interestingly, the pathophysiology of TBI appears to share many features of a stunned myocardium found after hemorrhagic shock, burns or sepsis, suggesting a similar and perhaps unifying underlying etiology* (Dobson et al., 2022; Dobson et al., 2024; Dobson et al., 2024). Further basic research is required to elucidate these mechanisms and differences.

Chronic effects: cardiovascular disease and stroke: In addition to long-term adverse neurological outcomes after a severe TBI, it appears that the injury can predispose a patient to various chronic diseases. A recent cohort study of military Veterans from Iraq and Afghanistan showed that they were significantly more likely to develop later-life coronary artery disease, stroke, and peripheral artery disease after a TBI compared to those Veterans who did not sustain an injury (Stewart et al., 2022). A similar relationship was found in the general population after even a mild TBI with increased risks of coronary artery disease, hyperlipidemia, hypertension and obesity over 10 years (Izzy et al., 2023), as well as later-life ischemic stroke (Radmanesh et al., 2024). These findings indicate that a mild-to-severe TBI occurs in two phases; 1) an acute phase, and 2) a chronic phase, which provides support for Lancet Commission's proposal that TBI should be viewed as a chronic disease (Maas et al., 2022). The two-phase trajectory offers the possibility of developing new drugs to treat the acute phase that may have flow-on effects to reduce later-life complications.

8. Coagulopathy, hemorrhage and variable fibrinolysis

Analysis of the benefits of viscoelastic test-guided management of TBI and coagulopathy of TBI is in its infancy, yet it is important to acknowledge that significant gaps in knowledge persist.

Bradbury and colleagues (2021) (Bradbury et al., 2021).

Coagulopathy is a systems defect that describes an abnormality in coagulation profile with variable fibrinolysis (Dobson et al., 2020). Normal hemostasis is a fine balance between prothrombotic, anticoagulant and fibrinolytic pathways, which in turn depends on a healthy CNS, cardiovascular system, endothelial-glycocalyx, circulating platelets and robust immune system (Dobson et al., 2020; Dobson et al., 2015). Coagulopathy occurs in around 30–50 % of moderate-to-severe TBI patients, and is associated with higher mortality and morbidity (Epstein et al., 2014; Juratli et al., 2014; Nakae et al., 2022) and nearly 50 % of these cases have hemorrhagic progression (Juratli et al., 2014; Nakae et al., 2022; Maegele et al., 2017; Zhao et al., 2023;11:tkad033.). In TBI patients that are bleeding systemically with demonstrated fibrinolysis, the antifibrinolytic tranexamic acid (TXA) has been shown to reduce mortality if administered within 3 to 6 h of injury (Collaborators, 2019). *However, if hyperfibrinolysis cannot be demonstrated, there is increasing concern that TXA may cause harm* (Sigmon et al., 2023; Letson and Dobson, 2017; Myers et al., 2019). On the other hand, if TBI patients have intracranial hemorrhage, TXA appears to have little or no effect on TBI pathology (Jakowenko et al., 2022), although some studies report a benefit (Xiong et al., 2023). Given the ongoing controversies surrounding TXA use in TBI patients, it is imperative that hemorrhagic status, coagulopathy, and the state of fibrinolysis, be accurately assessed to guide optimal care (Shammassian et al., 2022).

A review of TBI-induced coagulopathy reveals a spectrum of coagulopathy with variable fibrinolysis, D-dimer production and platelet dysfunction (Nakae et al., 2022; Samuels et al., 2019; Meizoso et al., 2022; Kockelmann and Maegele, 2023; Chen et al., 2023). Possible reasons for this wide variability may be linked to: 1) type and severity of head trauma, 2) methods of measurement and timing, 3) extent of intracranial hemorrhage, 4) presence of polytrauma, and 5) differences in patient age, sex and health status (Bradbury et al., 2021). *In general, the severe TBI phenotype appears to be a hypocoagulopathy of varying degrees (worse with cerebral bleeding) with minimal fibrinolysis* (Fig. 6) (Letson and Dobson, 2018; Shammassian et al., 2022; Samuels et al., 2019; Van Beek et al., 2007; Schöchl et al., 2011; Kunio et al., 2012). Minimal fibrinolysis is a curious finding in TBI patients and very different from a trauma patient's response to hemorrhagic shock despite similar mortality rates (Dobson et al., 2020; Dobson et al., 2015; Cardenas et al., 2019). This difference may be due the timing and extent of endothelial activation and tissue hypoperfusion which, in the case of hemorrhagic shock, appears to be more aggressive and widespread leading to hyperfibrinolysis (Dobson et al., 2020).

One of the early studies on TBI coagulopathy was the IMPACT (International Mission on Prognosis and Analysis of Clinical Trials) study which reported a prolonged prothrombin time (PT) on admission in 26 % of patients and a 64 % increase in mortality risk (Van Beek et al., 2007). In 2009, Talving and colleagues conducted a prospective study and found coagulopathy was present in 32 % of severe TBI patients with blunt injury and 54 % with penetrating injury (Talving et al., 2009). Coagulopathy was associated with longer ICU stays and ~10-fold higher risk of mortality (Talving et al., 2009). A year later, using plasmatic methods, Wafaisade and colleagues conducted a large retrospective analysis of isolated TBI patients and showed again that coagulopathy occurred in ~25 % of patients on hospital admission, and was an independent predictor of poor outcomes (Wafaisade et al., 2010). In 2012, Schreiber's group showed that 9 % of 69 TBI patients with intracranial hemorrhage were hypocoagulable based on thromboelastogram (TEG) upon hospital admission, and this was associated with more severe TBI injury (Kunio et al., 2012). They also found decreased fibrinogen levels

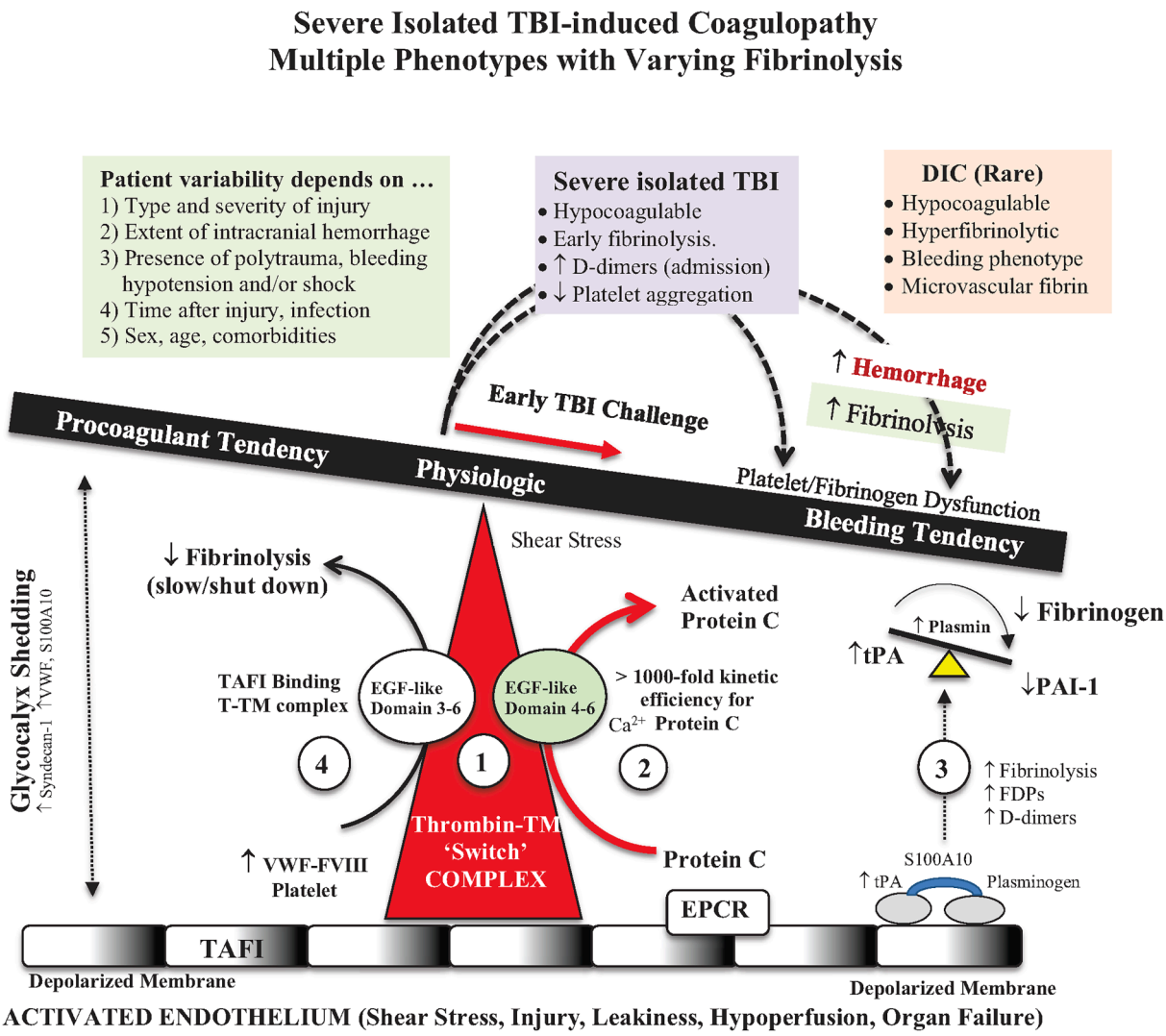

Fig. 6. Coagulopathy is a systemic pathology of the blood's ability to clot with varying degrees of fibrinolysis. The schematic illustrates the possible mechanisms of the different bleeding phenotypes after a severe TBI with variable fibrinolysis. If intra- or extra-cranial hemorrhage is present, hypocoagulopathy and fibrinolytic tendency are worse with lower fibrinogen, elevated D-dimers, and higher mortality. Coagulation and fibrinolysis are regulated at the thrombomodulin (TM)-thrombin 'switch' located on the endothelium. ①The direction of coagulation (hyper or hypo) depends on the different activators and inhibitors located at different epidermal growth factor (EFF)-like domains on the thrombin-TM complex (Dobson et al., 2020). After severe TBI, a hypocoagulable phenotype results from activation of Protein C on the EGF-like Domain 4–6 ②, and variable fibrinolysis from decreases in Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) at the EGF-like domain 3–6 ④, which results in increased plasmin levels, decreased fibrinogen and loss of platelet aggregation to form a weaker clot. ③ In rare cases, a lethal bleeding phenotype can occur after a severe TBI where hyperfibrinolysis is associated with microvascular fibrin deposits and termed disseminated intravascular coagulopathy (DIC) ③. Drugs that modulate the thrombin-TM "switch" are urgently required. EPCR, endothelial protein C receptor; FDP, fibrin degradation product; FVIII, Factor VIII; PAI-1, plasminogen activator inhibitor-1; S100A10, S100 calcium binding protein A10; TBI, traumatic brain injury; TPA, tissue plasminogen activator; VWF, Von Willebrand factor.

and increased partial thromboplastin time (PTT) were associated with increase mortality (Kunio et al., 2012). One of the first ROTEM studies carried out by Schochl's group on 88 severe TBI patients also reported hypocoagulopathy, which was associated with higher mortality (assumed from bleeding) *with only a few patients showing hyperfibrinolysis* (Schöchl et al., 2011). A recent systematic review of TEG and ROTEM indicates that the TBI-associated hypocoagulability is associated with increased risk of neurosurgical procedure, longer hospital and ICU stays and high risk of mortality (Shammassian et al., 2022).

Another recent high-quality TEG study by Samuels and colleagues showed a tendency for hypocoagulopathy with some fibrinolysis on hospital admission in 30-year-old males with isolated blunt TBI (Samuels et al., 2019). Fibrinolysis was based on clot lysis at 30 min after maximum clot strength (LY30 = 1.2 %) compared to normal human values (Samuels et al., 2019). Interestingly, the study found that clot strength and alpha angle were normal, despite 35 % mortality. In a second group with severe blunt TBI plus polytrauma, the tendency for bleeding was slightly higher (10 %) and mortality significantly higher (56 %) despite little or no change in fibrinogen (Samuels et al., 2019). Clearly, the phenotype in both patient groups was not hyperfibrinolytic. Nor does the study support a hypercoagulopathy from the massive release of TBI-related brain-derived tissue factor, extracellular vesicles or vWF (Meizoso et al., 2022; Kockelmann and Maegele, 2023). Most animal models support a hypocoagulopathy with minimal fibrinolysis (Fig. 6). In a rat model of moderate TBI, Letson and Dobson showed a significant hypocoagulopathy (increased PT and aPTT) after 1 h and 4 h compared to baseline, and this was confirmed by ROTEM (Letson and Dobson, 2018). Again, there was no evidence of hyperfibrinolysis despite a 50 % lower fibrinogen (Letson and Dobson, 2018). TBI animals also had a significant loss of platelet aggregation without change in

platelet numbers. The effect of injury severity on early coagulopathy, platelet dysfunction and fibrinolysis require further investigation (Davis et al., 2013).

Lastly, the DIC phenotype after a severe head injury deserves some mention. DIC is an extreme and rare phenotype associated with diffuse anatomopathologic fibrin deposition in small and mid-size vessels (Fig. 4) (Dobson et al., 2015; Hayakawa, 2017; Thachil, 2019). A common mistake in the literature is to equate hypocoagulopathy and fibrinolysis (a bleeding phenotype) with DIC (Toh et al., 2007; Levi and Scully, 2018; Unar et al., 2023; Buaboonnam et al., 2023). Clinically, it is diagnosed largely based on a scoring system involving PT, platelet count, fibrinogen, and D-dimer levels. We propose the concept of DIC should be confined to a specific phenotype with confirmed microvascular fibrin deposits. *By continuing to diagnose DIC based on a scoring system masquerades the real phenotype responsible for high mortality*. DIC is also rare in other major trauma states. In burns, Barret and Gomez retrospectively analyzed 3331 burned patients and found that no deaths were attributed to DIC at autopsy (Barret and Gomez, 2005). In septicemia and hypotension, McManus and colleagues reported five of 275 patients (1.8 %) had "supranormal in vitro clotting" that may have been DIC syndrome based on biopsy small vessel fibrin thrombi (McManus et al., 1973). No comparable studies have been undertaken in TBI patients. The key point is that without intravascular fibrin deposition, clinical diagnosis of coagulopathy may not be DIC, which may impact on optimal patient care and hinder the development of new drugs to correct its progression.

9. Multiple organ dysfunction: The uncoupling of CNS-organ circuitry

> In recent years, there has been a greater recognition of extracranial organ dysfunction following TBI. …. Unfortunately, most of this prior work has focused on the consequences of single organ dysfunction rather than multiple organ dysfunction, despite likely sharing common underlying mechanisms.
>
> Krishnamoorthy and colleagues (Krishnamoorthy et al., 2021).

Multiple organ dysfunction has been reported to occur early in up to 68 % of severe TBI patients (Faden et al., 2021; Yan et al., 2024; Krishnamoorthy et al., 2021). The secondary damage appears to be driven by neurogenic brain-organ uncoupling, cardiorespiratory dysfunction and prolonged tissue hypoperfusion. As already mentioned, early outcomes are worse if the TBI is accompanied by hemorrhage or polytrauma (Watanabe et al., 2018; Robba et al., 2020; McDonald et al., 2020). The organs affected include the lungs, heart, vasculature, gut, kidneys, liver, spleen, adipose tissue and muscle (Fig. 5) (Robba et al., 2020; Krishnamoorthy et al., 2021). Recently, a large retrospective study of Transforming Research and Clinical Knowledge (TRACK)-TBI investigators showed that TBI-associated MODS can persist for over a year, and these poor outcomes appeared to implicate the brain itself in addition to the initial polytrauma (McDonald et al., 2020; Krishnamoorthy et al., 2021; De Vlieger and Meyfroidt, 2023). It is possible these persistent CNS changes may be associated with the appearance of later life chronic diseases across all ages (Izzy et al., 2023), however further studies are required.

One of the most common complications of a severe head injury is respiratory dysfunction which leads to longer ICU stays, worse neurological outcomes and higher mortality (Robba et al., 2020; Krishnamoorthy et al., 2021; Astarabadi et al., 2020) (Fig. 5). CNS-sympathetic outflows and altered brain-stem reflexes are believed to be largely responsible for lung complications, inflammation and edema (Koutsoukou et al., 2016). Moreover, it has been reported that up to 50 % of ventilated TBI patients will develop acute lung injury (ALI) and 55 % will acquire an infection (Koutsoukou et al., 2016). In addition, up to 20 % of patients will develop acute kidney injury (AKI) (De Vlieger and Meyfroidt, 2023). ALI and AKI are further complicated by aggressive fluid resuscitation, vasopressor usage and osmotherapy agents (see Fluid Management) (Astarabadi et al., 2020; De Rosa et al., 2024). TBI also elicits a rapid hepatic response, which is believed to be an amplifier of secondary injury through the release of acute phase proteins and inflammatory mediators (Villapol, 2016). Similarly, splenic macrophages are stimulated by CNS-catecholamine discharge to secrete massive amounts of proinflammatory cytokines, such as TNF-α and IL- 1β into the peripheral circulation (Tracey, 2020), which can enter the damaged BBB and enhance the immune response (Chen et al., 2017) (Fig. 5).

After moderate-to-severe TBI, the catecholamine surge can also profoundly affect gastrointestinal function by decreasing mesenteric blood flow (McDonald et al., 2020; Deitch, 2012; Villalba et al., 2017) (Fig. 5). This is clinically significant because if the gut becomes ischemic, it can become leaky and gut bacteria, lipopolysaccharides, cytokines, neuropeptides, and protein messengers, can enter the circulation and exacerbate the immune and inflammatory load, worsen coagulopathy and contribute to multiple organ dysfunction (Deitch, 2012; Villalba et al., 2017; Hayakawa et al., 2011; Solari et al., 2021). In addition to intestinal barrier disruption, a severe TBI is associated with loss of lower GI motility and gastric mucosal damage (McDonald et al., 2020; Taraskina et al., 2022) (Fig. 5). Patients can further enter an acute catabolic state and require nutrition to maintain skeletal muscle mass, vital organ function, and cerebral metabolism (Yan et al., 2024; Foley et al., 2008; Kurtz and Rocha, 2020; Gribnau et al., 2024). This condition involves widespread mitochondrial dysfunction, which may uncouple to increase heat production, and in part be responsible for fever, which occurs in 40–70 % of severe TBI cases (Yan et al., 2024). Fever is further perpetuated by the endogenous release of pyrogens from damaged neurons, disrupting the hypothalamic set point (Yan et al., 2024). Whatever the underlying causes for multiple organ dysfunction and fever after a severe TBI, the injury collective is an independent predictor of very poor outcomes.

10. Fluid management: Helpful or harmful?

> Due to a lack of data, the optimal use of fluids is based on clinical scenarios and expert opinions. The choice of fluids to be given in the prehospital setting is a topic of debate at this time.
>
> Dawson et al (2022) (Dawson et al., 2022)p144.

In severely injured TBI patients, intravenous (IV) fluid therapy is essential to reduce brain edema, stabilize cerebral perfusion pressure (CPP), maintain blood flow autoregulation, improve parenchymal tissue oxygenation, treat dehydration and reduce secondary injury progression (Maas et al., 2022; Yan et al., 2024; Wiegers et al., 2021; Carney et al., 2017; van der Jagt, 2016; Gantner et al., 2014) (Fig. 7). If TBI is associated with cerebral or systemic hemorrhage, the combination can be life-threatening (Maegele et al., 2017; East et al., 2018; Montgomery et al., 2022; Sontakke et al., 2023). Over the past few decades, it has become increasingly apparent that too much or too little fluid can cause significant morbidity and mortality (Fig. 7) (Wiegers et al., 2021). Today, most fluid and transfusion management programs are consensus-based practices (Montgomery et al., 2022; Sontakke et al., 2023). Commonly used fluids to reduce cerebral edema and intracranial pressure (ICP) include mannitol (0.25–1 gm/kg) and hypertonic saline (3 % or 7.5 %) (East et al., 2018; Gharizadeh et al., 2022), and those recommended to stabilize hemodynamics (if hypotensive) and hydration status include normal saline (0.9 %), lactated Ringers or balanced crystalloid solutions (Dobson et al., 2024; Dobson et al., 2024; Dawson et al., 2022; Gantner et al., 2014; Myburgh, 2018). If anemia develops; red blood cell (RBC) infusions or other blood products are recommended (East et al., 2018; Montgomery et al., 2022). A challenging problem with IV fluid use is that up to 50 % of critical care adult patients are non-responders meaning that they fail to increase preload and stroke volume to improve tissue O_2 supply (Marik and Lemson, 2014; Hasanin, 2015). No trial to our knowledge has been carried out comparing non-

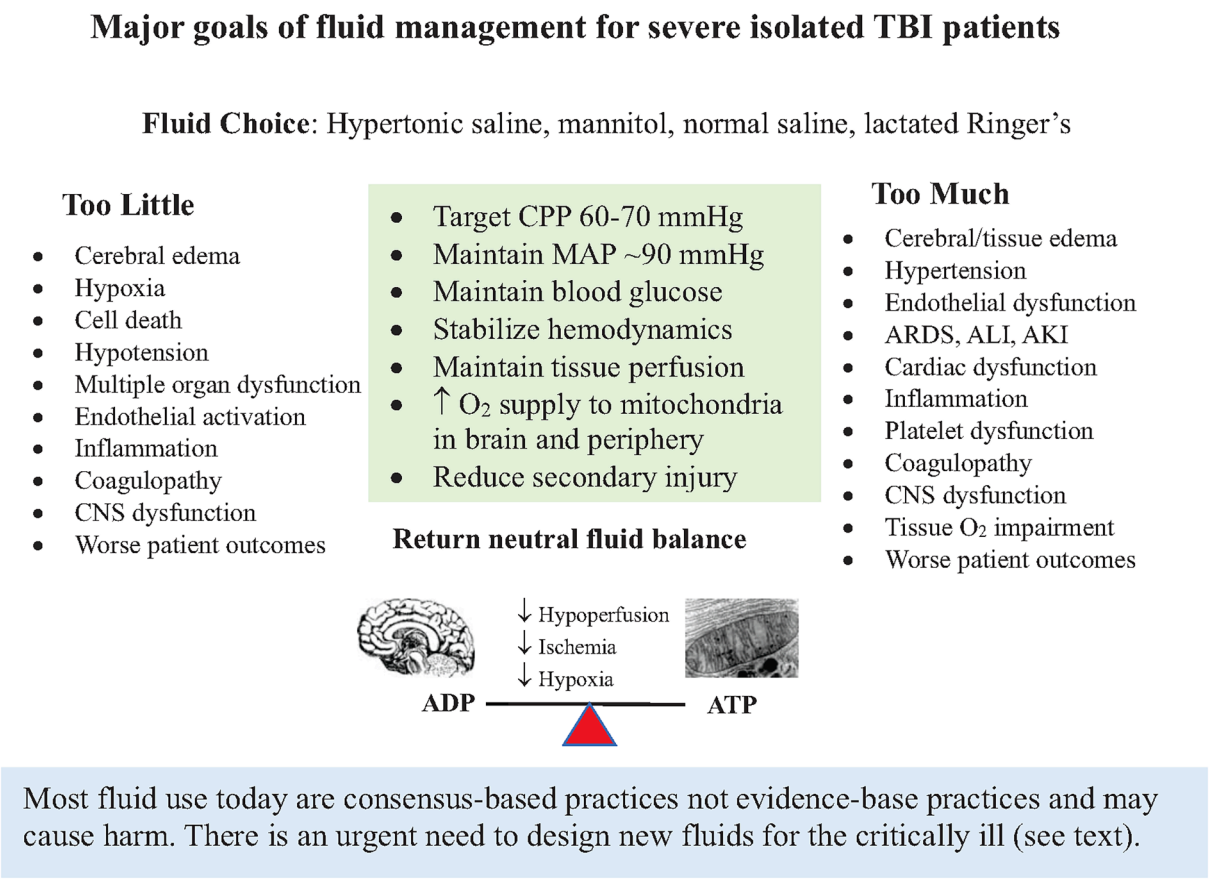

Fig. 7. Selecting the optimal intravenous (IV) fluid composition, volume and timing to treat severe TBI patients remains challenging. Decisions should be based on clinical assessment of the patient's individual needs and cardiac responsiveness to fluids. The primary goal of fluid management is to reduce brain swelling and optimize cerebral perfusion pressure (CPP) at a mean arterial pressure (MAP) of ~90 mmHg. Delivering a fluid too little, too much or too early, can do more harm than good. High-quality clinical trials are urgently required to inform guidance on the selection and administration of IV fluid therapy (Sontakke et al., 2023). ADP, adenosine diphosphate; AKI, acute kidney injury; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ATP, adenosine triphosphate; CNS, central nervous system.

responders and responders after moderate-to-severe TBI.

Notwithstanding the lack of high-quality clinical trials comparing the type, timing and composition of the different IV fluids (Fig. 7), there is an urgent need to design new fluids and therapies that protect the brain and whole body of TBI patients. Aggressive fluid volumes may cause widespread tissue edema, hyperchloremic metabolic acidosis, endothelial dysfunction, dilutional coagulopathy, renal dysfunction, and exacerbate inflammation and prolong ICU stays with high mortality (Dawson et al., 2022; Wiegers et al., 2021; Cheung-Flynn et al., 2019; Hayes, 2019; Chatrath et al., 2015) (Fig. 7). Normal saline is often considered safe and its continued use is supported by the Saline versus Albumin Fluid Evaluation (SAFE) trial conducted 20 years ago (Sontakke et al., 2023; Finfer et al., 2004). However, contrary to its name, normal saline is not normal, nor harmless (Myburgh, 2018; Awad et al., 2008; Liu and Lu, 2023). To address the issue, balanced isotonic solutions with physiological chloride concentrations and additional anions (lactate, acetate and gluconate) were introduced to compensate for the absence of bicarbonate and improved acid-base balance (Gantner et al., 2014; Rasouli, 2019). These balanced solutions are often preferred to normal saline with apparently improved outcomes reported in the critically ill (Semler et al., 2018). However, the Balanced Solutions in Intensive Care Study (BaSICS) trial (2017–20) compared balanced solutions to normal saline and found that the 90-day mortality rate in severe TBI patients (subgroup analysis) was significantly higher in those patients who received balanced solutions than those receiving normal saline (31 % vs 21 %; P = 0.02) (Shankar et al., 2022; Zampieri et al., 2021). This study highlights the need for improved understanding of the differences in safety and efficacy of current fluid therapies in TBI patients.

Lastly, the potential harmful effects of normal saline was aptly summed up over 100 years ago by US medical practitioner George Evans when he wrote in 1911: "*One cannot fail to be impressed with the danger of such procedure, if one observes the utter recklessness with which salt solution is frequently prescribed, particularly in the postoperative period, without previous knowledge of the condition of blood pressure, the ability of the heart to handle large amounts of fluid successfully, or the functional capacity of the kidneys to excrete the large amount of chloride thus formed on them*" (Awad et al., 2008; Evans, 1911). On the basis of current evidence, it appears that new systems-based, goal-directed therapies and evidence-based guidelines are urgently required to improve patient outcomes after moderate-to-severe TBI.

11. Why have there been so few drug breakthroughs?

> After physiology has taken Humpty Dumpty apart, it is difficult perhaps (even unfashionable) to put him back together again. Consequently, traditional analytical approaches like those in physiology can be positively misleading when applied to problems involving the performance of intact organism.
>
> George Bartholomew (1919–2006) (Bartholomew, 1986) p327

Despite decades of high-quality research, with >28,000 publications and >250 trials over the past five years, there are still no effective breakthrough drugs to treat a severe head injury (Kochanek et al., 2020).

There are multiple possible factors for lack of translational success:

- Failure of methodological rigor in preclinical research to ensure experimental reproducibility and high-quality data for human translation.
- Lack of preclinical consideration of sex, age and comorbidities (if possible).
- Poorly designed human trials.
- Failure of animal models to replicate the human condition.
- Inappropriate use of specific-pathogen free (SPF) animals.
- Flawed practice of single-nodal targeting in preclinical research.

Many studies, workshops, guidelines, commentaries, systematic reviews and editorials have discussed the ongoing problems of animal to

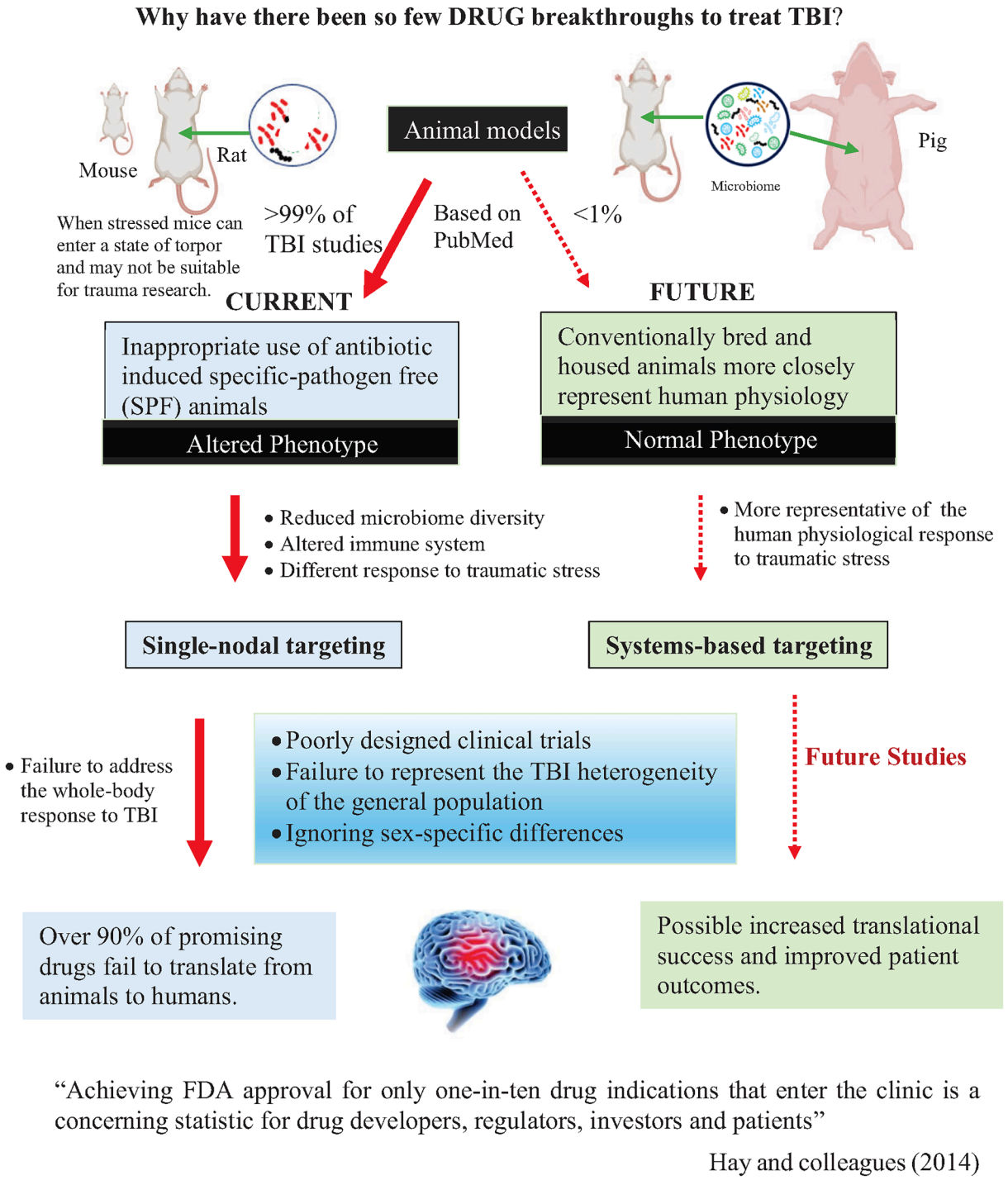

Fig. 8. A schematic of possible reasons for the lack of new effective drugs to treat moderate-to-severe TBI. Multiple factors include: 1) failure of animal models to replicate the human condition, 2) poorly designed human trials and ignoring age and sex-specific differences, 3) inappropriate use of specific-pathogen free (SPF) animals, and 4) the flawed practice of single-nodal targeting in preclinical research. Nearly all preclinical animal models use antibiotic-modified SPF animals, which do not represent the human condition, and single-nodal targeting occurs at the expense of the whole system (see text). A revolution is required to better understand how the whole body responds to TBI, identify new systemic markers of its progression, and discover new system-acting drugs to treat it. SPF, specific-pathogen free; TBI, traumatic brain injury.

human translational success (Kochanek et al., 2020; Choudhry et al., 2007; Lowenstein and Castro, 2009; Lee, 2018; Seyhan, 2019; Mauvais-Jarvis et al., 2020; Hart, 2021; Ivan et al., 2023; Carmody et al., 2022; Fogel, 2018; Lapchak et al., 2013; Ten, 2022). Lack of research rigor and reproducibility, both within and across animal studies, poor animal choice, strain to strain differences, and poorly designed experiments can all contribute to erroneous conclusions regarding a drug's safety and treatment effects (Kochanek et al., 2020; Choudhry et al., 2007; Lowenstein and Castro, 2009; Lee, 2018; Seyhan, 2019; Mauvais-Jarvis et al., 2020; Hart, 2021; Ivan et al., 2023; Carmody et al., 2022; Fogel, 2018; Lapchak et al., 2013; Ten, 2022; Ramirez et al., 2017; Schubert et al., 2010; Dobson, 2014). Even if a drug does show promise, less than 5 % of them translate to humans (Ineichen et al., 2024), and of those that receive FDA approvals, ~30 % have post-market adverse effects (Downing et al., 2017). These are troubling outcomes. Clinical trials themselves fail for many reasons including poor trial design, lack of drug efficacy, safety issues, failure to maintain good manufacturing protocols, lack of adherence to regulatory guidance, insufficient funds, low public engagement in patient selection, and problems with recruitment, enrollment, and retention (Fogel, 2018). Other reasons why potentially efficacious drugs fail to demonstrate efficacy in humans include two other issues rarely discussed: 1) the use of SPF animals for translational research, and 2) the flawed practice of single-nodal targeting (Dobson et al., 2024) (Fig. 8).

Specific-pathogen free animals: A quick search of PubMed shows that nearly all TBI animal studies use SPF animals (Fig. 8). SPF animals are animals that are bred and maintained free from certain gut pathogens (Dobson et al., 2019). Commercial and institutional animal husbandry facilities provide certification that a colony is free from a selection of common pathogens exposed to in the wild, and the pathogens excluded may vary from facility to facility (Dobson et al., 2019). SPF animals were introduced in the 1960s to minimize disease and infection as confounding variables in biomedical research (Dobson et al., 2019). A problem not recognized at that time was that treating animals with antibiotics to remove a 'list of gut pathogens' alters their gut microbiome and immune system (Dobson et al., 2024). The practice ignores that animals and humans have evolved two genomes; their own and the microbiome, which function in sync via bidirectional circuits to determine the health of the individual (Dobson et al., 2021). *In contrast, conventionally bred and housed animals are physiologically more intact and more representative of the human condition*. Different SPF, germ-free and transgenic strains may be ideally suited for mechanistic studies, however, they may have limited translation potential if their microbiome and immune system is far removed from the wild type.

For example, Beura and colleagues showed that SPF adult mice had "immature" immune systems and were more prone to infection compared to wild mice (Beura et al., 2016). The problem was solved by co-housing SPF animals with pet store 'dirty' mice, which produced an immune system closer to adult humans (Beura et al., 2016). Similarly, Rosshart and colleagues showed SPF-type mice reconstituted with natural microbiota exhibited reduced inflammation and increased survival following influenza virus infection, and colorectal tumorigenesis (Rosshart et al., 2017; Rosshart et al., 2019). These two independent groups warn that SPF animals are not suitable for translational studies. More recently, Letson and colleagues showed SPF rats have a different response to traumatic stress. SPF animals displayed abnormal hemodynamics, increased bleeding, arrhythmias, and changing hematological status in response to anesthesia and minor surgery compared to conventionally bred and housed animals (Letson et al., 2019; Dobson et al., 2020). Letson et al., reverted back to utilizing conventionally bred and housed animals to complete their translational trauma studies (Letson et al., 2019; Dobson et al., 2020). *Ironically, since its introduction in the early 1960s, SPF status itself may have become a confounding variable to human translation* (Kochanek et al., 2020; Dobson et al., 2020). The potential inappropriate use of SPF animals in preclinical research needs further scrutiny by funding bodies worldwide *if translation to humans is the endgame*. At a very minimum, we have proposed that SPF status should be included in the *Data Availability Statement* at the end of each scientific publication for transparency (Dobson et al., 2019).

Flawed practice of single-nodal targeting in preclinical research: Another possibility for the lack of translation is the problem of single-nodal targeting in preclinical research. Single-nodal targeting is a research philosophy or treatment strategy that focuses on a single step, pathway or symptom to reduce secondary injury progression. It forms the basis of the current treat-as-you-go approach in medicine, which identifies and treats one defect at a time, and so on down the line, that often leads to what US surgeon William C. Shoemaker considered: "an uncoordinated and sometimes contradictory therapeutic outcome" (Shoemaker and Beez, 2010). Targeting an individual step to treat TBI or other trauma states, such as a pro-inflammatory cytokine (e.g. IL-1) (Lindblad et al., 2023) or canonical signalling pathway (e.g. Nuclear factor kappa B (NF-κB) pathway) (Guo et al., 2024), have so far had limited success. We predict that many new emerging TBI drugs, such as anti-excitotoxic agents, TNF-α inhibitors, calcium channel blockers, statins, recombinant erythropoietin, endogenous neuroprotectors, anti-inflammatory agents, and mesenchymal stromal cells (Yan et al., 2024; Pordel et al., 2024) will also likely fail to translate because they ignore the complexity of the system. We argue that a systems approach to drug development is much more likely to increase animal to human translation success (see below).

For decades, scientists and medical practitioners have been trained to reduce a complex living system into its simpler parts, which makes a question more amenable to study (Dobson, 2016). Using this approach, an enormous amount of mechanistic knowledge and insight have been generated. What has not kept pace, however, is how this genetic or molecular data relates to the whole body (Dobson et al., 2024; Dobson et al., 2024; Dobson et al., 2022; Dobson et al., 2020; Dobson et al., 2024). As stated in Bartholomew's quote, we have failed to put Humpty Dumpty back together (Bartholomew, 1986). Probing the underlying mechanisms of pathological processes or how drugs affect cells or tissue culture are only small steps toward understanding how they behave inside a living organism (Dobson et al., 2019). This disconnect appears to a product of last century's molecular revolution, which focused on mechanisms at the expense of the intact system (Dobson et al., 2024). In the 1960s, Nobel Laureate Sir Francis Crick encouraged the practice when he wrote "The ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry" (Crick, 1966). Around 2000, Bloom referred to this 'one-way' approach as only one piece of solving the puzzle (Bloom, 2001; Van Regenmortel, 2004; Strange, 2005), which pertains to current TBI research. Scientific reductionism is important in breaking a system into its constituent parts, and studying them, however, *it does not do away with the system*.

Anticipating the problems of animal to human translation 20 years ago, the US Food and Drug Administration (FDA) proposed a Critical Path Initiative by recommending that: "strengthening and rebuilding the disciplines of physiology, pharmacology and clinical pharmacology, will be necessary to provide the capacity to develop and evaluate new biomarkers and bridge across animal and human studies" (FDA, 2004; Mahajan and Gupta, 2010). This Critical Path appears to have been forgotten as it relates to treating TBI and other major trauma. *Importantly, we are not arguing that current reductionist practices should be halted, as they continue to bear fruit in designing new drugs and therapies to treat cancers, heredity diseases, infectious diseases and disabling diseases of the CNS*. However, this approach has not worked for trauma. We propose that the major national and international and funding bodies should revisit the FDA's Critical Path Initiative and divert equal funds to better understand the whole system and develop new system-acting drugs to treat TBI, and other trauma states.

12. The future: Symptoms to systems in the 21st century

> New neuroprotective therapies for severe TBI have not translated from pre-clinical to clinical success.
>
> Kochanek and colleagues (2020) (Kochanek et al., 2020) p2353.

Shifting TBI research from a symptoms-based to a systems-based approach may lead to new drugs that improve patient outcomes (Dobson et al., 2024). The transition would include a renewed focus on conducting high quality preclinical studies comparing SPF (with defined pathogen exclusions) and non-SPF animals as they pertain to a multi-system, whole-body response to TBI, not simply a compilation of individual components of that system, as has been done in the past. What would a systems-acting drug look like? Ideally, a systems-acting drug would initially target the early immune-driven CNS stress response, promote CNS-cardiovascular coupling, protect the endothelial-glycocalyx, reduce immune dysfunction, prevent hyperinflammation, correct coagulopathy, maintain or reduce metabolic demand and deliver sufficient O_2 to maintain mitochondrial ATP production (Dobson et al., 2022; Dobson et al., 2024). To our knowledge, no such drug exists for TBI (Kochanek et al., 2020) or any other trauma.

We have been developing a systems-acting drug comprising adenosine, lidocaine and magnesium (ALM) to treat hemorrhagic shock (Dobson et al., 2024; Dobson and Letson, 2020; Dobson et al., 2023), burn trauma (Dobson et al., 2024; Davenport et al., 2023); orthopedic trauma (Morris et al., 2021; Morris et al., 2023), surgical trauma (Davenport et al., 2017); and sepsis (Dobson et al., 2024; Griffin et al., 2016) using both rat and pig models. Interestingly, ALM therapy appears to shift early sympathetic hyperactivity to parasympathetic dominance (Letson et al., 2022), reduces internal blood loss and restores cardiac output (Letson and Dobson, 2017), protects against endothelial glycocalyx shedding with 97 % rapid restoration (Torres Filho et al., 2017) and protects against MODS (Letson et al., 2019). *After hemorrhagic shock, ALM is neuroprotective at low MAPs of 47 mmHg, which may have significance in treating TBI* (Dobson et al., 2024; Letson et al., 2020). ALM therapy has also been shown independently to be highly protective after ischemic stroke (Wang et al., 2022).

Early TBI experiments using a rat model of moderate lateral fluid-percussion injury showed that a small IV bolus of 3 % NaCl ALM followed by a 4 h 0.9 % NaCl ALM drip improved survival (100 % vs 75 % saline controls) (Letson and Dobson, 2018) (Supplementary File: Fig. 9). ALM also decreased brain edema, reduced focal hemorrhage, significantly increased brain blood flow 2.5-fold at a lower MAP of 50–60 mmHg, corrected coagulopathy, maintained platelet function and reduced blood lactate compared to saline controls (Letson and Dobson, 2018) (Supplementary File: Fig. 9). In addition, plasma levels of the danger signal HMGB1 fell by 30 %, and brain injury marker neuron specific enolase (NSE) fell by 73 % in ALM-treated rats. HMGB1 is an emerging marker of neuronal injury with high levels reflecting greater severity and heightened inflammatory response (Parker et al., 2017; Yang et al., 2021). The ALM survival phenotype was further associated with 70–80 % reduction in proinflammatory mediators IL-1β, TNF-α, and Regulation upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES) (de Souza et al., 2024) (Supplementary File: Fig. 9). A lower IL-1β may be significant because it is a signature cytokine that amplifies neuroinflammation (McKee and Lukens, 2016). Lastly, ALM prevented TBI-induced neurogenic cardiac dysfunction and failure compared in saline controls (Letson and Dobson, 2018). A limitation of this early study was that the animals were anesthetized and ventilated for the entire experimental period (~5 h), whereas future studies will use conscious animals monitored over many days with cognitive and motor function testing. These studies will include a comparison of traditional IV with intranasal delivery to bypass the BBB. While early proof-of-concept results appear promising, there is a long road ahead given the complexity of translation and regulatory pathway from animals to humans (see above) (Seyhan, 2019).

13. Conclusions

Severe TBI induces a CNS-driven stress response that affects almost every organ in the body. The injury phenotype is amplified by a rapid and relentless barrage of DAMPs signals from the primary injury which leads to local secondary brain and systemic immune dysfunction, inflammation, endotheliopathy, coagulopathy and multiple organ dysfunction. New systems-acting drugs are required to switch the TBI phenotype to a 'restorative' survival phenotype by blunting the CNS-sympathetic discharge, improving cardiovascular coupling, reducing endothelial activation, restoring inflammation, correcting coagulopathy and resupplying adequate oxygen to tissue mitochondria. Drug development in the 21st century requires pharmaceutical companies and funding bodies to collectively invest in a more systems-based approach to TBI research. We are developing a small-volume, systems-acting ALM fluid therapy for severe TBI that may be useful in the prehospital and hospital environments.

Funding statement

This work was supported by USAMRMC proposal TP220214 under Award No. W81XWH-22-TBIPHRP-IIRA. The opinions, interpretations, conclusions are those of the authors and are not necessarily endorsed by the US Department of Defense.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GPD is the sole inventor of the ALM concept for cardiac surgery, trauma and sepsis. JLM and HLL have no conflicts to declare.

Acknowledgements

The authors would like to thank the US Department of Defense and James Cook University's College of Medicine and Dentistry for their continued support.

Author contributions

Concept (GPD), data collection (GPD, JLM, HLL), data analyses and interpretation (GPD, JLM, HLL), manuscript preparation (GPD, JLM, HLL) and editing (GPD, JLM, HLL).

Declaration of generative AI in scientific writing

No AI methods were used in scientific writing.

Data sharing statement

The authors agree to make any data and materials supporting the results or analyses presented in their paper available upon reasonable request. The data presented in the review can be found in the papers cited or by contacting the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2024.149271.

Data availability

Data will be made available on request.

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