INTERNATIONAL SEVEN JOURNAL
OF MULTIDISCIPLINARY
ISSN: 2764-9547

THERAPEUTIC MANAGEMENT OF ACUTE TRAUMATIC BRAIN INJURY: RESUSCITATION AND NEUROPROTECTION PROTOCOLS

MANEJO TERAPÊUTICO DO TRAUMA CRANIOENCEFÁLICO NA FASE AGUDA: PROTOCOLOS DE RESSUSCITAÇÃO E NEUROPROTEÇÃO

MANEJO TERAPÉUTICO DEL TRAUMATISMO CRANEOENCEFÁLICO EN LA FASE AGUDA: PROTOCOLOS DE REANIMACIÓN Y NEUROPROTECCIÓN

https://doi.org/10.56238/isevmjv5n1-021

Receipt of originals: 01/14/2026 **Acceptance for publication:** 02/14/2026

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ABSTRACT

Moderate to severe traumatic brain injury (TBI) represents a critical global challenge, requiring accurate neuroprognostication to guide triage and decisions regarding withdrawal of life-sustaining therapy. Contemporary management emphasizes multimodal monitoring, in which invasive Intracranial Pressure (ICP) measurement is increasingly supplemented by Brain Tissue Oxygen Pressure ($PbtO_2$), a crucial marker of tissue hypoxia independently associated with unfavorable outcomes. In parallel, advances in serum biomarkers—particularly glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)—allow assessment of injury severity and monitoring of clinical trajectory through minimally invasive methods. Established predictive models such as the IMPACT and CRASH scores demonstrate moderate reliability (with AUC values up to 0.85 for mortality in IMPACT), although the overall quality of evidence is often downgraded due to self-fulfilling prophecy bias and heterogeneity in functional outcome assessment. In the pediatric setting, injury-specific characteristics necessitate greater reliance on advanced Magnetic

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Resonance Imaging (MRI), in contrast to the predominant use of computed tomography (CT) in adults. The integration of these objective data is essential to guide acute interventions—including ICP management and the judicious use of hyperosmolar therapies—and to inform long-term rehabilitation planning. Predictors such as bilateral absence of pupillary reactivity are considered moderately reliable indicators of in-hospital mortality.

Keywords: Traumatic Brain Injury. Trauma. Mortality.

RESUMO

O trauma cranioencefálico (TCE) moderado a grave (msTBI) é um desafio crítico global, exigindo neuroprognosticação precisa para guiar triagem e decisões sobre retirada de suporte vital. A abordagem contemporânea enfatiza a monitorização multimodal, onde a medição invasiva da Pressão Intracraniana (PIC) é crescentemente suplementada pela Pressão de Oxigênio Tecidual Cerebral, um marcador crucial da hipóxia tecidual que se correlaciona independentemente com desfechos desfavoráveis. Paralelamente, o avanço dos biomarcadores séricos notadamente GFAP, NfL e UCH-L1 permite a avaliação da severidade da lesão e o monitoramento da trajetória clínica com métodos minimamente invasivos. Modelos preditivos estabelecidos, como IMPACT (com AUCs de até 0.85 para mortalidade) e CRASH, oferecem confiabilidade moderada, mas a qualidade da evidência para estes modelos é frequentemente rebaixada devido ao viés de self-fulfilling prophecy e à heterogeneidade na avaliação de desfechos funcionais). No cenário pediátrico, as particularidades da lesão exigem o uso de Ressonância Magnética (RM) avançada, diferentemente da dependência do TC em adultos. A integração desses dados objetivos é imperativa para fundamentar a intervenção aguda que inclui o manejo da PIC e o uso criterioso de terapias hiperosmolares e para o planejamento da reabilitação a longo prazo, sendo que preditores como a ausência de reatividade pupilar bilateral são considerados moderadamente confiáveis para mortalidade hospitalar.

Palavras-chave: Trauma Cranioencefálico. Trauma. Mortalidade.

RESUMEN

El traumatismo craneoencefálico (TCE) moderado a grave representa un desafío crítico a nivel mundial, que requiere una neuroprognosticación precisa para orientar el triaje y las decisiones sobre la retirada del soporte vital. El abordaje contemporáneo enfatiza la monitorización multimodal, en la cual la medición invasiva de la Presión Intracraneal (PIC) se complementa cada vez más con la Presión de Oxígeno Tisular Cerebral ($PbtO_2$), un marcador crucial de hipoxia tisular asociado de manera independiente con desenlaces desfavorables.Paralelamente, los avances en biomarcadores séricos—en particular la proteína ácida fibrilar glial (GFAP), la cadena ligera de neurofilamento (NfL) y la ubiquitina carboxi-terminal hidrolasa L1 (UCH-L1)—permiten evaluar la gravedad de la lesión y monitorizar la trayectoria clínica mediante métodos mínimamente invasivos. Modelos predictivos establecidos, como IMPACT y CRASH, ofrecen una confiabilidad moderada (con valores de AUC de hasta 0,85 para mortalidad en el modelo IMPACT); sin embargo, la calidad de la evidencia suele verse reducida debido al sesgo de profecía autocumplida y a la heterogeneidad en la evaluación de desenlaces funcionales. En el contexto pediátrico, las particularidades de la lesión exigen mayor utilización de la Resonancia Magnética (RM) avanzada, a diferencia de la dependencia predominante de la tomografía computarizada (TC) en adultos. La integración de estos datos objetivos es fundamental para orientar la intervención aguda—incluyendo el manejo de la PIC y el

uso prudente de terapias hiperosmolares—y para la planificación de la rehabilitación a largo plazo. Predictores como la ausencia bilateral de reactividad pupilar se consideran indicadores moderadamente confiables de mortalidad intrahospitalaria.

Palabras clave: Traumatismo Craneoencefálico. Trauma. Mortalidad.

1 INTRODUCTION

Traumatic brain injury (TBI) remains a leading cause of global neurosurgical mortality and morbidity, disproportionately affecting children and young adults (Figaji, 2023; Pinggera et al., 2023). Brain injury stems from two distinct processes: primary injury, resulting from immediate mechanical impact, and secondary injury, which develops within hours or days of trauma due to complex pathophysiological cascades (Pinggera et al., 2023). The acute phase of clinical management is critical, as interventions aim to mitigate the progression of this secondary lesion by ensuring systemic and brain homeostasis (Slot et al., 2025).

Early stabilization focuses on maintaining adequate cerebral perfusion pressure (CPP) and tight control of intracranial pressure (ICP), avoiding episodes of hypoxia and hypotension that worsen the prognosis (Slot et al., 2025; Pinggera et al., 2023). In parallel, advances in multimodal neuromonitoring and the identification of serum biomarkers have allowed for a more personalized and accurate approach (Wilde et al., 2022). The understanding of post-traumatic inflammatory and neuroendocrine mechanisms has also revealed new targets for neuroprotection strategies and management of long-term sequelae (Mu et al., 2023; Gasco et al., 2021). In addition, recent neuroprognostication guidelines in critically ill adults with moderate to severe TBI reinforce the need to integrate clinical, neurological, laboratory, and imaging data over time, avoiding early decisions based on a single parameter, given the high prognostic uncertainty in the acute phase (Muehlschlegel et al., 2024). This paper reviews contemporary resuscitation protocols and the frontiers of neuroprotection in acute TBI.

The therapeutic management of TBI in the acute phase is a dynamic process, whose central objective is to limit the progression of secondary brain injury. Even after primary injury, which is often inevitable at the time of trauma, neurological evolution can be modulated by early and systematized interventions that ensure oxygenation, perfusion, and control of metabolic and inflammatory aggressions (Pinggera; Geiger; Thomé, 2023; Slot et al., 2025). In recent decades, the clinical approach has migrated from algorithms based only on clinical and tomographic findings to integrated strategies, combining intracranial monitoring, serial evaluation of neurological examination and, more recently, biomarkers and non-invasive tools with the potential to anticipate clinical deterioration (Wilde et al., 2022; Martínez-Palacios et al., 2024).

TBI is a pathology with multiple facets, as numerous changes occur even in short periods of time, for this reason the diagnosis, prognosis and recovery are uncertain and difficult to interpret. In this scenario, biomarkers have been shown to be efficient, facilitating the clinical management of this neurotrauma by presenting itself as an efficient way to assess the progression of the injury, leading to more specific care and better prognosis (Wilde et al., 2022).

In addition to the management of acute aggressions, the understanding of the chronicity of TBI has revealed that brain injury is not a static event, but an evolutionary process that can result in persistent multisystem dysfunctions. Among these, post-traumatic hypopituitarism stands out as a frequent and often underdiagnosed complication, and can manifest months or years after the initial injury, (Gasco et al. 2021)l. Growth hormone (GH) deficiency is the most common neuroendocrine abnormality, directly correlating with neurocognitive deficits, changes in body composition, and a significant reduction in the quality of life of survivors. In parallel, the persistence of neuroinflammatory processes, mediated by mechanisms such as the formation of extracellular neutrophil traps (TENs), has been associated with impairments in vascular remodeling and poorer long-term functional recovery. Therefore, the integration of endocrine and immunological surveillance with longitudinal follow-up becomes essential to optimize rehabilitation and mitigate the chronic sequelae of neurotrauma (Mu et al. 2023).

In the pediatric setting, additional challenges include limitations of robust evidence, heterogeneity of mechanisms, and the need to adapt adult protocols, while collaborative networks and comparative studies have broadened the knowledge base (Figaji, 2023). In adults, recent reviews in intensive care highlight the growing role of multimodal approaches, with a simultaneous emphasis on brain-targeted interventions and meticulous systemic care (Slot et al., 2025). Within this context, topics such as hemoglobin and transfusion targets, individualization based on clinical trajectories, incorporation of biomarkers, and exploration of immunomodulatory targets have become central to updating practices and guiding translational research (Wiegers et al., 2021; Åkerlund et al., 2024; Mu et al., 2024).

2 METHODOLOGY

The present study is characterized as a narrative literature review, developed with the objective of synthesizing and analyzing the most recent scientific evidence related to the therapeutic management of traumatic brain injury in the acute phase. Bibliographic research was performed in the PubMed database, using the descriptors "Traumatic Brain Injury", "Treatment" and "Diagnosis", combined using the Boolean operators AND and OR, according to the Medical Subject Headings (MeSH) terminology. Articles published in the last five years, available in full and written in English, that directly addressed resuscitation, monitoring, and neuroprotection protocols were selected. Studies with low methodological rigor, duplicate publications, and articles with no direct correlation with the central theme were excluded. The selection of works was conducted in stages of screening titles and abstracts, followed by the qualitative evaluation of the full texts to confirm scientific relevance. The information extracted was organized in a descriptive and integrated way.

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In addition to the above criteria, the following were included as a priority: (1) randomized controlled trials and multicenter studies on resuscitation strategies and systemic support relevant to TBI (including transfusion goals and volume management); (2) recent guidelines, consensuses, and reviews on intracranial monitoring and multimodal neuromonitoring, focusing on intracranial pressure, cerebral tissue oxygenation, and noninvasive methods (pupillometry, transcranial Doppler, and other correlates); (3) studies and reviews on blood biomarkers applicable to severity stratification, prognosis, and screening/monitoring decisions; (4) recent translational and clinical evidence on immunoinflammatory pathways and neuroprotection/immunomodulation strategies in TBI; and (5) publications focused on the recognition and management of endocrine complications in the acute course and in

follow-up, with an emphasis on post-trauma hypopituitarism and its impacts on rehabilitation.

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3 RESULTS AND DISCUSSION

3.1 RESUSCITATION AND SYSTEMIC STABILIZATION PROTOCOLS

The cornerstone of the management of severe TBI in the intensive care unit (ICU) is the prevention of secondary brain injury through tight systemic support. The current focus has progressed to multimodal approaches that prioritize maintaining cerebral tissue oxygenation ($PbtO_{2}$) and controlling ICP (Slot et al., 2025). Monitoring of PbtO_{2} is critical, as values below 20 mmHg (cerebral hypoxia) are independently associated with worse functional outcomes and higher mortality, even when ICP remains within normal limits (Slot et al., 2025). Invasive ICP monitoring remains the gold standard, allowing for rapid therapeutic adjustments to keep PCP within safe limits (Pinggera et al., 2023). For the management of intracranial hypertension, in addition to cerebrospinal fluid drainage, osmolar therapy with hypertonic saline or mannitol is recommended, and the choice is guided by the patient's volume status and serum osmolarity (Pinggera et al., 2023).

In addition, non-invasive technologies, such as quantitative pupillometry, have gained relevance because they offer objective data on brainstem function and the risk of herniation, aiding in screening and immediate prognosis (Slot et al., 2025). In pediatric patients, although computed tomography (CT) is the standard, the use of rapid magnetic resonance imaging (MRI) sequences without sedation has grown in the front line for a more detailed evaluation of pathology without the risks of radiation (Figaji, 2023).

The strategies to avoid/prevent secondary brain injuries are several, hemodynamic stabilization and prevention of hypotension is essential, evidence shows that the ideal is to maintain a Systolic Blood Pressure (SBP) ≥ 100mmHg in adults aged 50 to 69 years and ≥ 110 mmHg in adults aged 15 to 49 or over 70 years, systolic hypotension (< 90mmHg) is an independent risk factor for worse outcome and should be corrected

(Pinggera et al., 2023). As for fluid management, normovolemia should be maintained, avoiding fluid overload and hemoglobin targets values > 9 g/dL, while values ≤ 7.5g/dL in TBI patients showed higher mortality and worse functional outcome (Slot et al., 2025).

For the control of Intracranial Pressure (ICP), staggered protocols can be used, such as the SIBICC algorithm ("Seattle International Severe Traumatic Brain Injury Consensus Conference"), which guide pharmacological and surgical interventions to reduce the measurement (Pinggera et al., 2023; Slot et al., 2025). The use of tranexamic acid in the acute phase showed a reduction in mortality in cases of mild and moderate TBI, with no significant increase in adverse events, as long as it was used within 3 hours of the moment of trauma (Pinggera et al., 2023). Thermal control is also important in order to maintain body temperature between 36 and 37.5ºC to avoid aggravation of secondary injuries (Slot et al., 2025). In addition, it is recommended to maintain normocapnia (PaCO2 between 35 and 45 mmHg), since severe hypocapnia (< 32 mmHg) and hypercapnia (> 45 mmHg) are associated with higher mortality (Slot et al., 2025).

In the acute phase of TBI, resuscitation should be oriented towards reducing systemic factors associated with worsening neurological outcome, recognizing that hypoxia, hypotension, and metabolic disorders fuel secondary injury. In the ICU, recent reviews reinforce that optimal management requires continuous precision of both intracranial and systemic parameters, with an emphasis on hemodynamic goals that sustain adequate cerebral perfusion and avoid extremes of osmolarity, ventilation, and temperature (Slot et al., 2025; Pinggera; Geiger; Thomé, 2023).

Water balance emerges as a relevant prognostic variable. Observational data suggest that seeking a mean fluid balance close to neutral (normovolemia), associated with hemodynamic monitoring when necessary, may contribute to better outcomes in critically ill patients with TBI (Wiegers et al., 2021; Slot et al., 2025). In practice, this supports a view of resuscitation that is less focused on "volume by routine" and more guided by physiological profiles, avoiding fluid overload and worsening of cerebral edema, without sacrificing systemic perfusion.

A current point of debate refers to red blood cell transfusion. Recent studies in acute brain injury have evaluated more liberal transfusion strategies, with signs of possible reduction in unfavorable neurological outcomes compared to restrictive strategies, although with variations in magnitude and statistical significance between trials (Taccone et al., 2024; Turgeon et al., 2024). At the same time, multicenter analyses point

to an association between low hemoglobin levels and worse outcomes, encouraging the reassessment of traditionally restrictive transfusion thresholds in the specific context of TBI (Guglielmi et al., 2024; Slot et al., 2025). Thus, transfusion is now discussed not only as a "laboratory correction", but as a potentially neuroprotective intervention in selected scenarios, especially when integrated with the assessment of cerebral perfusion/oxygenation.

In the pediatric setting, although there are physiological particularities and evidence gaps, the same logic of preventing systemic aggressions is reinforced, added to the need for collaborative networks and protocols adapted to the context and available resources (Figaji, 2023).

3.2 NEUROPROTECTION IN TRAUMATIC BRAIN TRAUMA: CONCEPT, THERAPEUTIC WINDOW AND INDIVIDUALIZATION OF TREATMENT

Neuroprotection in TBI has evolved from an approach focused on isolated interventions to an integrated and dynamic concept, based on the prevention of secondary brain injury and the preservation of viable brain tissue. Currently, it is understood that TBI does not represent a static entity, but rather a heterogeneous biological process, in which multiple pathophysiological cascades—including inflammation, vascular dysfunction, excitotoxicity, and metabolic changes—develop over time after the initial insult (Pinggera et al., 2023; Wilde et al., 2022).

In this context, neuroprotection should be understood as a continuous strategy, initiated early in the acute phase, aimed at optimizing cerebral oxygenation, maintaining adequate cerebral perfusion pressure, and mitigating avoidable secondary insults, such as hypotension, hypoxia, hypercapnia, and hyperthermia. Recent evidence reinforces that the identification of the so-called "therapeutic window" is crucial, since interventions performed in the first hours after trauma have a greater potential impact on neurological outcomes (Pinggera et al., 2023).

The advancement of multimodal neuromonitoring and serum biomarkers has allowed a more individualized approach to neuroprotection. Biomarkers such as glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal L1 hydroxylase (UCH-L1), and light chain neurofilament (NfL) make it possible to stratify the severity of the injury, detect subclinical neuronal damage, and monitor the therapeutic response in a minimally invasive way (Wilde et al., 2022). The integration of these markers with clinical data,

neuroimaging, and physiological parameters contributes to reducing patient heterogeneity and improving therapeutic decision-making.

Thus, neuroprotection in TBI should be seen as a multimodal and personalized process, in which the combination of continuous monitoring, early interventions, and serial assessment of neurological parameters constitutes the basis for the reduction of unfavorable outcomes. This integrated approach represents an advance in relation to traditional models and reinforces the need for strategies adapted to the individual pathophysiological profile of each patient.

Neuroprotection, in acute TBI, should be understood as a set of time-dependent interventions aimed at minimizing cascades of ischemia, edema, metabolic dysfunction, and inflammation, with decisions guided by risk-benefit and individual physiology. From this perspective, intracranial monitoring maintains a central role, especially in severe TBI, as it allows interventions aimed at controlling intracranial hypertension and preserving perfusion pressure (Slot et al., 2025). Contemporary consensuses discuss the perceived utility of intracranial pressure monitoring, with pragmatic recommendations that reflect the heterogeneous reality between centers and the need for operational standardization (Chesnut et al., 2023).

The individualization of treatment also advances with the incorporation of cerebral tissue oxygenation monitoring ($PbtO_2$) as a complement to intracranial pressure. Recent trials have evaluated approaches that seek to optimize brain oxygenation, suggesting that $PbtO_2$-guided interventions may offer benefits in subgroups, by expanding the ability to detect and treat "silent" cerebral hypoxia that is not expressed only by intracranial pressure elevation (Payen et al., 2023; Slot et al., 2025). At the same time, recent reviews highlight challenges and innovations in the field of intracranial pressure monitoring, reinforcing that the current trend is not to replace invasive monitoring with a single alternative method, but to combine signals for better decision-making (Zoerle et al., 2024).

In parallel, non-invasive and bedside tools are gaining ground as extensions of serial neurological assessment. Quantitative pupillometry, for example, has been described as more accurate than traditional clinical assessment and can provide early warning of deterioration and increased intracranial pressure, especially in patients sedated or on opioids (Martínez-Palacios et al., 2024; Slot et al., 2025). Although it does not replace invasive methods, its serial use can reinforce the "continuous

neuroprotection" approach, in which decisions are reevaluated based on trends and not just on specific measures.

Finally, neuroprotection also involves the staggered management of intracranial hypertension. Recent multicenter studies describe treatment practices, temporality, and association with outcomes, reinforcing the need for gradual and consistent protocols to avoid late, inconsistent, or overly aggressive interventions (Robba et al., 2023).

3.3 BIOMARKERS AND PRECISION DIAGNOSTICS

The use of blood biomarkers, such as glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal L1 hydroxylase (UCH-L1), has transformed the ability to diagnose the severity of axonal and cellular damage in a minimally invasive way (Slot et al., 2025; Wilde et al., 2022). For the management of intracranial hypertension, in addition to cerebrospinal fluid drainage, osmolar therapy with hypertonic saline or mannitol is recommended, and the choice is guided by the patient's volume status and serum osmolarity (Pinggera et al., 2023). These markers allow not only the detection of lesions not visible on conventional imaging tests, but also aid in the prediction of functional outcomes throughout the first year after trauma (Muehlschlegel et al., 2024). The integration of clinical prediction models based on large cohorts, such as TRACK-TBI, provides a robust basis for family counseling and decision-making about treatment intensity (Muehlschlegel et al., 2024; Wilde et al., 2022). Models such as IMPACT and CRASH, while useful, should be interpreted with caution, as their accuracy may be limited by variables such as advanced age and pupillary reactivity prior to resuscitation (Muehlschlegel et al., 2024). Contemporary guidelines emphasize that neuroprognostication should be performed in a multimodal and serial manner, combining neurological examination, pupillary reactivity, structural and functional neuroimaging, electrophysiology, and serum biomarkers, reducing the risk of biases such as *self-fulfilling prophecy*, often associated with early therapeutic limitation decisions (Muehlschlegel et al., 2024).

In addition, neurophysiological diagnostic biomarkers have been studied, demonstrating that a careful evaluation of vision and oculomotor function, with the aid of devices such as eye tracking, can enable a more accurate analysis of cases of mild traumatic brain injury (TBI) and concussion. This process occurs through the analysis of symptomatological anamnesis in both pediatric and adult populations, making this

approach an important means of rapid, non-invasive, and direct diagnosis. However, there is still no consensus on which visuomotor metrics are most sensitive to changes associated with brain injuries, which reinforces the need for further studies in this area (Wilde et al., 2022). Concomitantly, with regard to neuroimaging prognostic biomarkers, computed tomography (CT) is still the most widely used method for prognosis after traumatic brain injury, since other approaches remain limited and are not yet sufficient to obtain more accurate prognosis. However, CT is mainly considered for patients with moderate to severe TBI. In this context, two main classification systems are used: the Marshall classification, which evaluates the presence of cerebral edema, possible intracranial hemorrhages, and midline deviations, and the Rotterdam score, which encompasses different types of lesions, including the presence of subarachnoid hemorrhage. Therefore, further studies focused on cases of mild TBI are still needed, as this could contribute to the prevention of a more severe clinical course (Wilde et al., 2022).

The development of biomarkers in TBI aims to reduce diagnostic uncertainties, improve prognosis, and guide therapeutic and screening decisions. A recent central contribution has been the proposition of a framework to advance the validation and implementation of biomarkers along the clinical continuum (from screening to prognosis and therapeutic response), emphasizing standardization, reproducibility, and integration with clinical and imaging phenotyping (Wilde et al., 2022).

In addition to the diagnostic aid set of blood biomarkers (GFAP, UCH-L1) and imaging methods (CT and MRI), neurophysiological biomarkers complement diagnostic tests, are considered to have high temporal resolution, and provide complementary information to MRI. These neurophysiological biomarkers are EEG and QEEG and have subtle differences between them, while clinical EEG is essential to detect epileptic seizures and dysfunctions related to the breakdown of the blood-brain barrier, QEEG stands out when detecting small changes in mild TBI (mTBI), such as balance instability. In addition, studies indicate that during the post-acute period of a trauma, the parameters of coherence, phase and amplitude have 95% sensitivity and 97% specificity to discriminate the severity of the injury. Therefore, the combination of EEG with Transcranial Magnetic Stimulation (TMS) shows promise for mapping the reorganization of neural connectivity after trauma (Wilde et al., 2022).

In ICU practice, reviews highlight the potential of markers such as GFAP, UCH-L1, and light chain neurofilament (NfL) to estimate severity and predict outcomes, with the

prospect that serial measures can improve prognostic accuracy and support monitoring of disease progression (Slot et al., 2025). Multicenter analyses associate early biomarkers with functional outcomes at six months, reinforcing clinical plausibility for future use in decision models (Wilson et al., 2024). Accordingly, recent systematic reviews seek to consolidate the predictive utility of biomarkers in moderate to severe TBI, delineating heterogeneity limits and gaps for broad adoption (Bagg et al., 2024).

A key challenge of "precision diagnosis" is to integrate biomarkers into clinical trajectories and pathophysiological profiles. Observational studies describe disease trajectories in severe TBI in the ICU, suggesting that evolutionary patterns and biological signatures can inform risk and guide decisions over time, not just at admission (Åkerlund et al., 2024). In this scenario, the promise is not to replace clinical judgment, but to raise the resolution with which subgroups are distinguished, responding to the need for more targeted therapies.

In resource-constrained environments, or when invasive monitoring is not available, non-invasive methods have also been studied to support stratification and monitoring. Reviews and meta-analyses on transcranial Doppler for noninvasive intracranial pressure estimation suggest complementary utility in specific contexts, although without equivalence to replace invasive monitoring (Dokponou et al., 2023; Slot et al., 2025).

3.4 NEUROPROTECTION AND IMMUNOMODULATION STRATEGIES

New frontiers in neuroprotection focus on the control of the exacerbated inflammatory response. Recent research has identified that the formation of extracellular neutrophil traps (NETs) is correlated with worse outcomes in TBI, as it impairs vascular remodeling and aggravates neuroinflammation (Mu et al., 2023). Neutrophil-targeted drug delivery platforms to inhibit the formation of NETs have shown potential to improve neurological impairments and increase survival rates in experimental models (Mu et al., 2023). In addition, recent evidence demonstrates that persistent neuroinflammation corroborates blood-brain barrier dysfunction, cerebral edema, and progression of neuronal damage, strengthening the relevance of early interventions targeting the inflammatory cascade. In addition to inhibition of NETs formation, contemporary neuroprotection approaches in traumatic brain injury (TBI) emphasize the integrated

management of the inflammatory response, cerebral oxygenation, and prevention of secondary injury. (Mu et al., 2023).

Multimodal neuromonitoring has emerged as an important resource to direct individualized neuroprotection strategies, including intracranial pressure (ICP) monitoring, cerebral tissue oxygenation ($PbtO_2$) and brain microdialysis. Figaji (2017) points out that the optimization of cerebral perfusion linked to the strict control of ICP considerably minimizes scenarios of cerebral hypoxia, while neurological outcomes produce related improvement.

In light of this context, Muehlschlegel (2021) emphasizes that current neurocritical intensive care protocols favor the maintenance of adequate cerebral perfusion pressure, normocapnia, normoxemia, and glycemic control, including the prevention of hyperthermia, fundamental indicators to attenuate the recrudescenced inflammatory response and limit secondary damage.

Post-TBI systemic inflammation has a direct impact on neurological recovery, thus associated with higher mortality and worse functional prognosis. In addition, immunomodulatory tactics, such as early infection management, rigorous hemodynamic management, and possible future use of targeted anti-inflammatory therapies, configure a new therapeutic frontier. Slot et al. (2022). In general, Wilde et al. (2019) add that the persevering structural and functional changes observed in neuroimaging are vehemently linked to the initial inflammatory response, to the point of consolidating the value of neuroprotective interventions still in the acute phase as decisive for long-term recovery and brain plasticity.

The immunoinflammatory dimension of TBI has gained prominence as a critical component of secondary injury and as a therapeutic frontier. After trauma, activation of neutrophils, microglia, and pro-inflammatory pathways may contribute to blood-brain barrier dysfunction, edema, and neurotoxicity. Within this field, there is growing interest in NETs as mediators of vascular injury and persistent inflammation. Recent translational studies have investigated neutrophil-targeted therapeutic platforms aimed at reducing NETs and improving theranostics in TBI and related conditions, pointing to plausibility for future more specific immunomodulatory strategies (Mu et al., 2024).

Despite the enthusiasm, the clinical translation of immunomodulatory therapies requires caution. The heterogeneity of TBI and the risk of iatrogenic immunosuppression make it critical to identify targets, therapeutic window, and subgroups with the highest

likelihood of benefit. In this sense, the current trend of classifying patients by phenotypes and trajectories may be especially useful for selecting anti-inflammatory interventions in appropriate settings, reducing the risk of indiscriminate approaches (Åkerlund et al., 2024; Wilde et al., 2022). Thus, "neuroprotection" no longer means only intracranial pressure control, but also incorporates the modulation of biological cascades when clinical evidence matures. Where the accommodation of advanced neuromonitoring, neurocritical resuscitation and immunomodulatory strategies translates a precedent paradigm in the management of severe TBI, it thus leads the hemodynamic axis to a systemic and personalized interpellation of traumatic brain injury.

It is essential to recognize that TBI often triggers hormonal dysfunctions. Post-traumatic hypopituitarism, once considered rare, is now recognized as a common sequela, with growth hormone deficiency (GHD) being the most frequent abnormality (Gasco et al., 2021). The acute phase of TBI may present with the phenomenon of 'sick euthyroid disease' or secondary adrenal insufficiency, which aggravates hemodynamic instability and makes it difficult to wean off vasopressor amines (Gasco et al., 2021). Secondary injury, mediated by biochemical and molecular cascades, can affect the hypothalamic-pituitary axis as early as the acute phase, negatively impacting the patient's neurocognitive and behavioral recovery (Gasco et al., 2021).

In view of this scenario, it is extremely important to analyze the metabolic impacts in patients with hypopituitarism after traumatic brain injury, because the metabolic profile is unfavorable, being a great challenge due to glycemic disorders, weight gain, reduction in bone mineral density, and changes in body composition, which contributes to a significant increase in morbidity and mortality in individuals with PTHT (Gasco et al., 2021). In this sense, it is necessary to carry out a joint assessment of the patient's life expectancy to ensure that those who may benefit from the use of hormone replacement therapy have access to this treatment, since the diagnostic process is expensive and difficult to access. In addition, the epidemiological profile should be evaluated, analyzing the frequency of PTHP according to previous GCS scores, especially in patients with moderate or severe traumatic brain injury (TBI), as this may contribute to better clinical outcomes. Among other factors to be evaluated in this process, age, the occurrence of seizures, and the presence of skull base fractures stand out. In cases of acute disease, endocrine assessment is essential. On the other hand, patients with TBI considered mild who required surgical intervention, hospitalization or other clinical measures should

initially be submitted to screening, and screening is indicated only in the presence of symptoms that raise clinical suspicion. In these cases, together with patients who presented possible alterations on the CT scan, follow-up and evaluation between three months and one year after the traumatic brain injury are recommended. If symptoms persist, more in-depth hormone screening should be performed. (Gasco et al., 2021).

Delayed hormone screening is especially indicated for patients who, after stabilization of neurological lesions, present chronic fatigue, depression, or persistent cognitive deficits, symptoms that may be masking undiagnosed hypopituitarism (Gasco et al., 2021).

Endocrine complications after TBI have a potentially underestimated impact on functional recovery and quality of life, requiring recognition both in the hospital period and in the follow-up. Post-trauma hypopituitarism, and in particular growth hormone (HG) deficiency, have been described as frequent events, with diagnostic challenges (nonspecific symptoms, interference from acute stress, need for dynamic testing) and relevant therapeutic implications (Gasco et al., 2021).

In the acute course, hydroelectrolyte changes (such as sodium disturbances) may reflect dysfunctions of the hypothalamic-pituitary axis and contribute to neurological instability. In the long term, failure to recognize hypopituitarism can limit rehabilitation, affect cognition, body composition, and functional performance. Thus, current models of care advocate structured clinical surveillance and timely referral for endocrine evaluation when suspected, especially in patients with moderate to severe TBI and less-than-expected recovery (Gasco et al., 2021).

4 CONCLUSION

The therapeutic management of Traumatic Brain Injury (TBI) in the acute phase remains a complex challenge, requiring early and systematized interventions to mitigate secondary brain injury. The evolution of care unequivocally points to a **multimodal and individualized** paradigm, which continuously integrates rigorous systemic assessment with advanced neuromonitoring.

The pillars of neuroprotection consist of maintaining cerebral oxygenation (increasing emphasis on $PbtO_{2}$) and controlling Intracranial Pressure (ICP) and Cerebral Perfusion Pressure (CPP). This approach is complemented by non-invasive tools, such as quantitative pupillometry, and the use of blood biomarkers (GFAP, UCH-

L1, NfL), which are consolidated as pillars of **precision medicine** for stratification of severity, prognosis, and therapeutic guidance. Prognostic accuracy requires serial, multimodal evaluations, advising against decisions to limit life support based on a single parameter in the hyperacute phase, given the initial uncertainty.

The frontiers of research and management include increasing attention to **endocrine complications** (such as post-traumatic hypopituitarism) and **immunoinflammatory pathways**. Strategies that aim to modulate the inflammatory response, such as inhibition of neutrophil extracellular traps (NETs), represent promising targets for the development of targeted neuroprotective therapies in the future.

In short, TBI care is migrating from uniform protocols to management that is more **responsive to the patient's individual physiology** , integrating neurocritical resuscitation, advanced monitoring, and the recognition of persistent biological cascades, with the ultimate goal of optimizing functional recovery and long-term quality of life.

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