Overview of Neurotrauma and Sensory Loss

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ABSTRACT

Neurotrauma can cause devastating outcomes for patients both from primary as well as secondary injury. Sensory loss following neurotrauma is often overlooked and undermanaged. To gain awareness about this important topic, we highlight key findings of visual, hearing, taste, and smell disturbances that can occur after injury. The pathways are highlighted as well as significant pathophysiology. Both primary disruption as well as secondary disruptions from ongoing inflammation are addressed. The figures are designed to be user friendly guides for the clinician to help manage these patients. In the final section, we address key management strategies and approaches. The strategies deal with multidisciplinary care as well as multimodality treatments. This review serves as a primer for early recognition of deficits and initiation of appropriate treatments.

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Introduction

Sensory deficits, emotional changes, and memory loss are common complaints following traumatic brain injury (TBI). These deficits are thought to arise from microstructural damage to brain tissue, known as diffuse-axonal injury (DAI). Clinically, DAI is considered as a diagnosis in patients with a Glasgow coma scale (GCS) of less than 8 for over 6 hours, excluding cases of swelling or ischemic brain lesions. DAI poses the most important prognostic factor for mortality, persistent vegetative state, and disability following head trauma [1]. The mechanism of DAI is related to sudden changes in acceleration/deceleration, in which inertia forces develop between the brain tissues of various densities. Consequently, surfaces located at borders of these structures and small blood vessels are likely to be injured. An elongating stretches greater than 10% that occurs in less than 100ms seems to represent an axonal injury threshold leading to secondary consequences [2]. Injuries in white matter axons can lead to swelling of nerve fibers, axonal transport dysfunction, and activation of specific cell death pathways [3]. Inertial forces shear axons to a breaking point (primary axotomy), or partially damage them, leading to molecular pathways that result in axon degeneration (secondary axotomy) [4]. Primary axotomies are characterized by a change in shape of severed nerve fibers, with distal microscopic swellings known as axon retraction bulbs. These retraction bulbs may result from a deposition of amyloid precursor protein and abnormal axonal transport. Secondary axotomies are derived from many interconnected pathologies caused by failed regeneration attempts and axonal dysfunction. These dysfunctions lead to discontinued protein transport along the axon, degradation of cytoskeleton network, calcium influx leading to oxidative stress, calpain-mediated hydrolysis of structural proteins, and changes of glial cells [5-7]. Interestingly, there is no association between the presence of skull fractures and diffuse axonal injury, yet focal penetrating TBI is associated with cognitive decline [8, 9].

Vision

Neurotrauma can have both direct and indirect effects on the visual pathway system and can cause visual deficits that are not easily detectable by patients or medical personnel. For this reason, it is important to have a systemic evaluation of visual function following a traumatic brain injury [10]. A thorough assessment is necessary to identify the source of acute primary visual dysfunction and ocular issues that may contribute to other non-vision processing symptoms such as headache and vertigo [11]. Most commonly, following neurotrauma, patients undergo a clinical examination to assess visual integrity, visual efficiency, and visual information processing [12]. Patients may then undergo x-ray computed tomography (CT) or magnetic resonance imaging (MRI) to identify the etiology of visual deficits revealed in clinical examination. To understand alterations of the visual system not explained by clinical exam or standard imaging, special diagnostic tools such as visual evoked potentials (VEP) testing and optical coherence tomography (OCT) are also used [13].

The clinical examination for visual deficit consists of the evaluation of the three components of vision as proposed by Dr. Mitchell Schieman; visual integrity, visual efficiency, and visual information processing [14]. Visual integrity/acuity is the ability to see objects at different distances in different types of lighting. To screen for visual integrity dysfunction, tools such as the Snellen Chart and the Lea Symbol test are used. A deficit in visual integrity is a potential sign of optic neuropathy [15]. It is however possible to have normal visual integrity while having other visual deficits, so it is important to complete subsequent examinations [16].

Visual efficiency is the ability to focus visual information through binocular vision, accommodation, and oculomotor motion [14].

Visual efficiency deficits are easily overlooked and are therefore examined through a battery of tests. The most common of these is visual field testing using automated perimetry [17]. Automated perimetry provides standardized, reproducible assessments of visual field impairment, and provides a clear understanding of a patient's field loss pattern [18]. This is extremely beneficial for narrowing down the location of a focal injury on the visual pathway (Figure 1). Other skills that are tested as a part of the visual efficiency examination include near-eye alignment, near convergence, saccades, and pursuits. These tests specifically evaluate a patient's oculomotor response and ability to focus on moving targets. Anomalies detected in these tests could result from deficiencies or damage to carinal nerves III, IV, or VI [19].

Visual information processing occurs primarily in the visual cortices of the occipital lobe [20]. The visual information pathway is detailed in figure 1. Visual information processing is the culmination of all the skills analyzed by visual integrity and visual efficiency testing. It is the brain's ability to interpret and analyze the information that is being received by the visual cortices. Dysfunctions in visual information processing include processing delays and processing errors, which are revealed through the examination of visual processing skills such as visual-motor processing, visual memory, spatial relationship processing, and visual discrimination [12, 21]. A thorough clinical examination with the analysis of visual integrity, visual efficiency, and visual information processing can narrow differential diagnoses, and potentially pinpoint the location of a visual neuropathic injury.

If a clinical examination is not sufficient for identifying the etiology of vision deficits, standard neuroimaging studies are performed to determine the location and extent of an injury. In general, MRI is the choice imaging modality for most intracranial neuro-ophthalmic applications given that it allows for a more detailed assessment of soft tissue unless there is a clear contraindication. CT is commonly used when it is important to visualize the skull, bony orbit, or blood entrapment following trauma. Regardless of the imaging modality used, the results of the clinical examination are essential for correct radiographic interpretation, and analysis of the comprehensive clinical picture [22, 23].

Sensitive measurement techniques like VEP and OCT are sometimes used when visual impairment exists but cannot be detected through the clinical exam. These subclinical disturbances of the visual pathway can be due to effects of neurotrauma such as traumatic axonal injury or loss of retinal ganglion cells [24-26]. VEP utilizes electroencephalogram (EEG) electrodes placed on the scalp above the visual cortices to record electrical potentials. Using signal averaging and visual stimuli such as checkerboard images, these electrical potentials are specifically enhanced to quantify the integrity of the neural visual pathways [27]. VEP is sensitive enough to detect electrical conduction disturbances but may still need to be used in conjunction with an imaging modality to determine the etiology of the injury. OCT utilizes high-resolution imaging to examine and quantify retinal layers [28]. Progressive retinal layer thinning has been linked to traumatic brain injury and the disappearance of retinal ganglion cells, resulting in accelerating vision loss. Given this association, OCT is extremely valuable in the clinical setting for chronic vision loss monitoring [29].
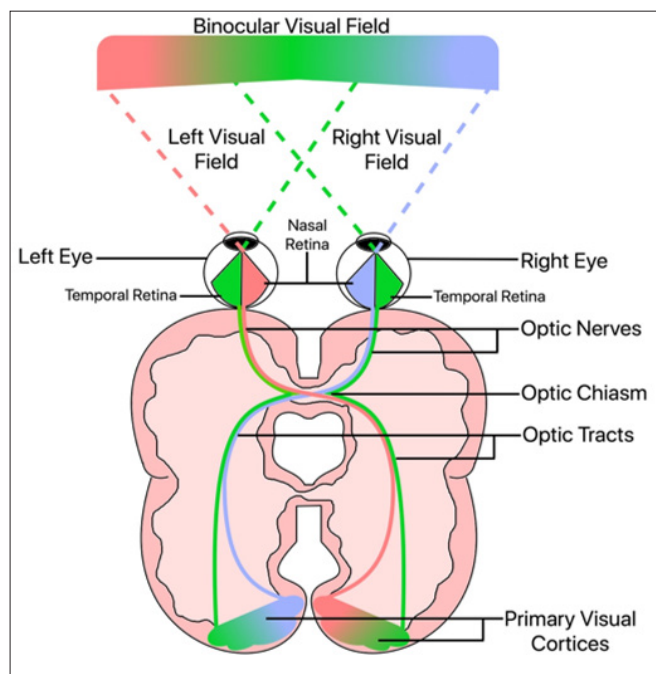

Figure 1: Pathway of Visual Projection

Hearing

Temporal bone fracture is a common result in head trauma and is present in about 20% of all patients with skull fractures [30, 31]. Hearing loss is a significant source of morbidity following temporal bone trauma and is present in 24% of patients [32]. Click or tap here to enter text. Fractures of the temporal bone are classified according to their orientation along the long axis of the pyramid-shaped petrous bone. Longitudinally fractures comprise 70-80% of temporal bone fractures and are parallel to this axis, and transverse fractures are perpendicular to it [33, 34]. The vestibulocochlear nerve and cochlea, two neural structures critical to hearing, are found in the temporal bone. Of patients suffering transverse temporal bone fractures, up to 50% have sensorineural hearing loss (SNHL) tied to cochlea or vestibulocochlear nerve damage [35]. In one study, temporal bone fractures which progressed into the otic capsule were associated with more than 25 times greater risk of sensorineural hearing loss [36]. Even in head trauma patients without any skull fractures, the incidence of hearing loss has been reported to be as much as 58%, underscoring the prevalence of this complication in neurotrauma patients [37].

Clinical decision making in temporal bone fractures is largely based on evidence from high resolution CT scans [38]. Radiologic findings in CT consistent with a temporal bone fracture in patients with head trauma is an indication for auditory testing [39]. Early auditory testing is thought to play an important role in the prognostic evaluation of the patient's baseline post-traumatic injury hearing and is repeated 3-6 weeks following the injury to assess for any changes [32]. Brainstem auditory evoked potential testing is a promising backup modality for patients who cannot comply with standard auditory testing [40]. Despite its prognostic value, auditory testing does not play a role in the decision making on timing of surgery for either conductive or sensorineural hearing loss [35].

An inflammatory pathway may play a key role in the cascade which follows head trauma leading to hearing loss. For one, dexamethasone has been shown to confer an otoprotective effect 30

days following traumatic electrode insertion by upregulating anti-apoptotic genes like BCL2 and downregulating the pro-apoptotic BAX [41-43]. Further, oxidative stress-mediated activation of the Jun-N-terminal kinase pathway has been shown to cause a signal cascade culminating in apoptosis in acoustic and electrode insertion trauma-related hearing loss [44, 45]. Though these inflammatory pathways have only been described in the context of electrode insertion and acoustic trauma, the association between inflammation and SNHL following neurotrauma is inferred from the elevated oxidative state and inflammation-induced vasospasm present in TBI [46, 47]. Moreover, an interesting inflammatory phenomenon known as sympathetic hearing loss leads to contralateral loss of hearing following temporal bone fracture. This is thought to be mediated by an autoimmune process whereby immune cells are sensitized to privileged cochlear antigens which are released following injury [48, 49]. Taken together, this evidence underscores the crucial role of inflammation in the events leading to hearing loss following traumatic injury (Figure 2).
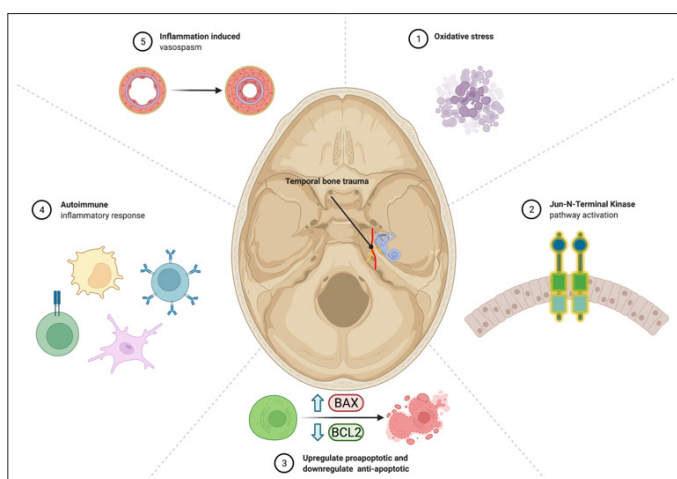

Figure 2: Mechanisms Involved in Hearing Loss Following Neurotrauma

Taste and Smell

Taste and smell are perceived through olfactory receptors of the olfactory epithelium and gustatory receptors in the tongue and epiglottic region. Action potentials provoked by activation of olfactory receptors travel caudally through the various foramina of the cribriform plate and synapse into the nuclei of the olfactory bulb. Axon's projecting from the olfactory bulb (olfactory tract) directly deliver olfactory information to the piriform cortex (PC) of the temporal lobe, which sends third order signals to the orbitofrontal cortex (OFC). The olfactory tract also sends projections toward other forebrain structures such as the hypothalamus and amygdala [50].

Unlike olfactory information which travels through a single cranial nerve (CN I), gustatory information is perceived through taste cells differentially innervated depending on their location in the nasopharyngeal mucosa. Special sensory outputs originating from the anterior two-thirds of the tongue, posterior third of the tongue, and epiglottic region travel respectively through the chorda tympani (branch of CN VII), glossopharyngeal nerve (CN IX), and vagus nerve (CN X). Each afferent nerve fiber enters the skull through their respective foramina and synapse onto the nucleus solitarius where all three gustatory signals converge. Second-order fibers then synapse onto the ventral posteromedial nucleus (VPMpc) of the thalamus and the OFC. Third order fibers originating from the VPMpc terminate at the frontal operculum, anterior insular cortex (IC) and the Brodmann area 3B [51].

Integration of gustatory and olfactory information was therefore placed on the OFC, while studies from recent years identify neurons exchanging information between the IC and PC thereby presenting the OFC, IC, and PC as the central locations of gustatory and olfactory integration [52-54].

The described anatomy and neural pathways responsible for taste and smell elucidates mechanisms by which chemosensory dysfunction arises because of neurotrauma. Firstly, these dysfunctions may be divided into sensorineural or conductive dysfunctions. Injury disrupting the nerves carrying afferent information to their respective brain regions are sensorineural, while mechanisms inhibiting the access of chemosensory molecules to their respective receptors are conductive.

Fractures of the maxillofacial skeleton can lead to bony obstructions impairing odorant access to receptors. A 2017 study evaluating the effectiveness of reducing nasal bone fractures to treat secondary olfactory dysfunction shows that 46.4% of patients presenting with nasal bone fracture present with secondary olfactory dysfunction assessed by the Korean version of Sniffin' Sticks test (KVSS II). The study did not show significant restoration of olfactory function at 6 months, highlighting the importance of associated mechanisms impairing olfaction [55]. Other mechanisms for conductive olfactory dysfunction include nasal trauma and life support or surgical interventions that lead to edema and hematoma. These mechanisms provide a barrier to olfactory receptors like excess sinonasal secretions in rhinosinusitis [56].

It is also important to recognize that the anatomical placement of the olfactory pathway makes olfaction especially vulnerable to sensorineural injury secondary to neurotrauma. Head trauma leading to skull base fractures and intracranial hemorrhage or hematoma are significantly associated with post-traumatic anosmia [57]. Fractures of the cribriform plate through which olfactory nerves travel to synapse onto the olfactory bulb are thought to cause nerve damage through shearing [58]. With the addition of hematoma and intracranial hemorrhage, these fractures can lead to fibrotic deposition around the damaged nerve and impede sheared nerve regeneration causing irreversible or delayed restoration of olfaction [59]. Although no direct studies have been done to test this hypothesis, it is a plausible explanation for impaired olfactory recovery in patients with posttraumatic olfactory loss compared to patients with anosmia after upper respiratory tract infection [60]. Penetrating or contusive injuries to brain cortices responsible for olfaction, such as the OFC and PC, may also impair olfaction, although at higher order processing levels (discrimination, recognition) than detection [56]. In fact, a study of anosmia in the SHEFBIT cohort containing 774 consecutive traumatic brain injury (TBI) injury admissions over two years reports a 19.7% incidence of anosmia post-TBI with a positive relationship to TBI severity (mild = 9.55%, moderate = 20.01%, and severe = 43.5%) [61]. It is interesting to note that even mild TBI (mTBI) resulting from incidents such as falls is still associated with olfactory dysfunction. Its prevalence and under-diagnosis in mTBI patients are highlighted in a 2016 systematic and illustrated review [62]. Changes to the olfactory centers are not limited to immediate change after injury. In analyses of MRI studies for gray matter (GM) density after TBI, patients who developed anosmia post-TBI had a decreased GM density in the primary and secondary olfactory areas such as the gyrus rectus, medial OFC, anterior cingulate cortex, insula, and cerebellum. Interestingly, the authors also reported that time since TBI was positively correlated with GM density in the frontal and temporal gyrus in patients with anosmia, while time since TBI was negatively

correlated with GM density in secondary olfactory areas for patients with hyposmia [63]. These reports allude to different compensatory and recovery mechanisms between anosmic and hyposmic patients. Gradual increases in frontal and temporal gyrus in anosmic patients suggests compensatory activity, while temporal decreases in GM density of secondary olfactory areas suggests progressive neuromolecular mechanisms that may explain a delay or inability to recover olfaction after injury. Elucidation of these mechanisms may address the low rate (10%) of 14-month recovery in posttraumatic olfactory loss [60].

Unlike olfactory dysfunction, taste impairment after head trauma is not as well represented in the literature. Ballester's 2019 study is among the few demonstrating a 38.3% prevalence of taste and/or smell dysfunction in a population of veterans with TBI, but the study did not make a distinction among patients with impairments of taste, smell, or both [64]. The general prevalence of overlapping taste and smell dysfunction is rare compared to taste or smell dysfunction alone (2.2% vs 13.5% smell vs 17.3% taste) according to a cross-sectional analysis of the National Health and Nutrition Examination Survey (NHANES 2013-2013). It is important, however, to recognize its potential occurrence after head trauma [65]. Possible mechanisms for concurrent olfactory and gustatory dysfunction are through TBIs affecting cortical regions specifically responsible for the integration of smell and taste (OFC, IC, and PC) or concurrent damage to lower-order nuclei independently processing these senses (Figure 3).
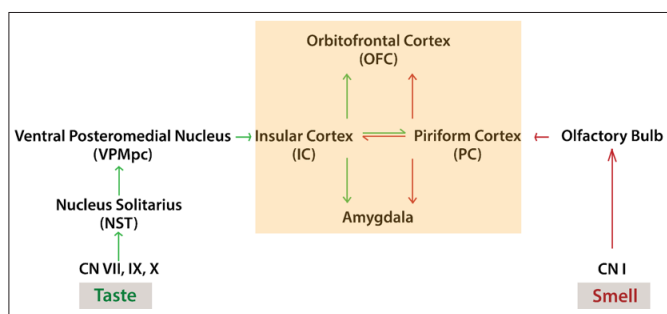

Figure 3: Damage to brain regions responsible for processing olfactory and gustatory information (highlighted in yellow box) may result in concurrent taste and smell dysfunction. This figure also traces the most basic path of gustatory and olfactory information originating from their respective receptors discussed in the beginning of this section. Green arrows trace gustatory information. Red arrows trace olfactory information. Note that a more complex exchange in information among these regions exist, but we only highlight those discussed in this review.

Despite the relative lack of current literature, older reports suggest that taste impairment may be more prevalent than expected after head trauma. Schecter and Henkin in 1974 noted a 59% incidence of hypogeusia in 29 patients after head trauma based on subjective survey. For an objective measure, they evaluated each patient's detection and recognition thresholds for NaCl, sucrose, HCl, and urea, and reported that all patients had an elevated detection and recognition threshold for at least one taste domain [66]. The study's sampling certainly needs to be expanded for sampling size, diversity and replication in other centers using modern assays and equipment; however, it is noteworthy that a large percentage of patients did not report hypogeusia despite elevated detection and recognition thresholds for at least one taste. This highlights the ease by which gustatory dysfunctions may be under-diagnosed leading to its underrepresentation in literature.

Gustatory dysfunction is likely more prevalent than observed in patients after neurotrauma. Notably, a major cause of taste impairment in patients with TBI are medications given to manage the condition, thus making a 59% incidence more reasonable. Antidepressants, antipsychotics, antispasmodics/anticholinergics, and narcotic analgesics are known to perturb gustation, while peripheral nerve injuries to CN VII, CN IX, and CN X are also possible, but rare [59].

Smell and taste disorders after neurotrauma can easily be overlooked in the acute treatment setting to focus on emergent conditions. Patients may not mention symptoms until days or weeks after the incident which may be due to later onset. As in the previous discussion, some patients may also be unable to identify lower intensity impairments to smell and taste despite quantitative and objective measures. Thus, it is important to discuss diagnostic considerations in patients after neurotrauma with suspicion for either or both dysfunctions. Afterall, chemosensory dysfunction is a potentially debilitating condition for their vocation or may impair detection of smells or taste that alert the patient to incidents such as gas leaks and spoiled food.

For trauma patients presenting with suspicion of head injury, primary evaluation often includes imaging studies, which may be referenced, despite lower resolution, for initial etiological investigation of olfactory dysfunction. To visualize sinonasal structures, high-resolution, thin-cut CT of the maxillofacial region is recommended, while MRI is recommended for investigation into cortical injury [56]. The cost-effectiveness of using MRI for these investigations, however, was brought to question by Hoekman et al's findings in a case series and chart review of patients with idiopathic olfactory loss showing that brain MRI demonstrated a comparable diagnostic yield to the general population (abnormalities in 4.6% of patients) [67]. Whether these results apply, in the setting of olfactory dysfunction secondary to neurotrauma, is yet to be investigated. Alternatively, use of fMRI for patients with traumatic anosmia has been shown to identify impaired activation in primary and secondary olfactory cortices of 16 patients after closed-head trauma compared to health controls [68]. This study provides great preliminary data, and future studies should be conducted to test the utility of fMRI as an objective diagnostic tool for traumatic anosmia. The use of imaging to identify gustatory dysfunction alone is not well discussed in current literature. Although recent reports studying taste and smell loss after COVID infection have used a task-based fMRI study to identify absent activation in the OFC, which contains secondary and tertiary olfactory and gustatory information [69]. The use of fMRI to diagnose gustatory impairment after neurotrauma also needs to be further studied.

Orthonasal smell tests, such as the University of Pennsylvania Smell Identification Test (UPSIT), are recommended as initial diagnostic tools for olfactory dysfunction by a recent systematic review [70]. The UPSIT utilizes scratch and sniff booklets containing odorants and a four-option multiple choice question format asking the patient to identify the odorant. Scores significantly less than chance performance raises suspicion for maligning in the setting of trauma for personal gain in legal proceedings. Evaluation for gustatory dysfunction includes taste tests, but special care for overlaps in perception of smell and taste must be considered [71]. Sodium chloride, sucrose, citric acid, and coffee are used to assess chemo sensation. In magnitude testing, these solutions are diluted to different concentrations, and detection threshold is identified by normalizing the results to magnitude test of a normally functioning

sense such as hearing. In spatial testing, cotton-tipped swabs are dipped into the diluted solutions and applied to different areas of the patient's tongue. The patient is subsequently asked about the quality and intensity of the taste.

The objective tests are great tools to assess olfactory and gustatory function. These tools compliment a thoroughly gathered history and physical. Assessment of the patient's history may help the physician differentiate amongst underlying causes of smell and taste impairment such as medications, cortical injury, peripheral nerve injury, respiratory tract infection, and other causes that may be irrelevant to recent traumatic injuries.

Comprehensive Management

The diagnosis of neurotrauma proves to be complex, as the clinical presentations are very heterogenous, involving several structural and physiologic insults (primary and secondary). As such, this includes clinical and radiographic data (cranial and spinal CT), which may span more invasive procedures (such as intraparenchymal catheters for continuous ICP monitoring). A large part of neurotrauma care and management focuses on preventing secondary insults whenever possible, to improve long-term outcomes. Beginning with initial management, efforts should focus on the "ABCs," namely securing the airway, breathing, and circulation. Management efforts are largely stratified according to the Glasgow Coma Scale (GCS), where a score lower than 8 classified as severe injury [72]. Hypoxia and hypotension were associated an increase in mortality and morbidity. However, hyperventilation should be avoided, unless the patient is actively herniating. Other management techniques broadly include monitoring ICP (hyperosmolar therapy), fluid resuscitation, surgical decompression, steroids (especially to treat cerebral edema), seizure prophylaxis, and infection prophylaxis. For patient with acute spinal cord injury about T4, hemodynamic augmentation is practiced to maintain a mean arterial pressure greater than 85 mmHg. However, further studies are needed to determine the threshold and outcomes of vasopressors. Pharmacologically induced comas have been associated with reducing ICP in patient with refractory intracranial hypertension [73]. Lastly, while hypothermia and β-blockers have been proposed as being neuroprotective, the data is lacking to support widespread use [74]. This is by no means an exhaustive list of neurotrauma management, but highlights the key, broad categories of therapy.

It is vital for treatment to begin the second first responders monitor the patient till further interventions to improve long-term outcomes [72]. Furthermore, studies have shown the importance of a multidisciplinary, neurocritical care team in caring for neurotrauma patients [75, 76]. A 2004 study showed that the introduction of a specialized neurocritical care team, including a full-time neuro-intensivist coordinating care, was significantly associated with reduced in-hospital mortality and length of stay [76]. Neurocritical care units should include a collaborative effort between neurologists, neurosurgeons, neuro-intensivists, radiologists, pharmacists, nurse practitioners or physician assist, critical care nurses, rehabilitation specialists, social workers, and more. This is made more evident by the broad categories of management detailed above. When looking at the effectiveness of additional specialties such as physiotherapy, while physiotherapy was shown to be safe with few adverse events, further studies with larger sample sizes and longer follow-ups are needed for evidence of widespread use [77]. Lastly, addressing post-neurotrauma cognitive deficits is challenging in part due to the lack of consensus of how neuropsychological interventions

should integrate in the care of patients. However, recent papers have detailed how neuropsychology can play a beneficial role in providing comprehensive care to patients, ranging from early preventative interventions to strategy training in the chronic or long-term phase. This can include a holistic clinical interview, a battery of tests capturing all cognitive domains, and/or self-report measures evaluating patients' mood and symptoms. Strategies range from cognitive rehabilitation to psychotherapy, with adequate support shown for cognitive-behavioral support in the setting of post-concussive syndrome [78]. While more robust studies are needed to study the exact thresholds of these specialties in a typical neurocritical care team, it is evident that a multidisciplinary is necessary for appropriate management of neurotrauma.

Conflicts of Interest: authors have none to disclose.

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