We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Benefits of Early Tracheostomy in TBI Patients

*Sabrina Araujo de França, Wagner M. Tavares,
Wellingson S. Paiva and Manoel J. Teixeira*

Abstract

Severe traumatic brain injury (TBI) patients are constantly submitted to interventions to cope secondary injury and insults. Oxygen therapy is mostly initiated by endotracheal intubation at the scene of the accident. Due to the severity of the trauma, prolonged mechanical ventilation is expected and tracheostomy (TQT) is often indicated. TQT became one of the most common bedside surgical procedure performed in an Intensive Care Unit (ICU). However, discussion regarding the optimal time for TQT placement to improve outcomes of severe TBI patients remains under discussion. This chapter aims to review TBI's physiopathology and enlighten early tracheostomy's role in severe TBI management.

Keywords: benefits, early medical intervention, outcome, severe brain injury, tracheostomy, traumatic brain injury

1. Introduction

The major focus on traumatic brain injury (TBI) management is to avoid and restrain ongoing brain damage and to increase brain recovery chances by reducing brain edema and intracranial pressure (ICP). Optimizing oxygenation, perfusion, nutrition, glycaemia and temperature homeostasis are paramount [1]. In this chapter, we will discuss the role of oxygenation in TBI management with a special focus on early indication of tracheostomy (TQT) as a support to oxygen therapy.

2. Incidence and prevalence of TBI

TBI is a critical public health concern with large socioeconomic repercussions. The main causes of TBI include violence, falls and road traffic accidents [2]. In 2010, the global burden of disease (GBD) reported 89% of trauma-related deaths occurring in low- and middle-income countries (LMICs) [3]. In 2030, the worldwide estimated incidence of TBI places this type of trauma as a 4th leading cause of lost disability adjusted life years (DALYs) and 7th cause of death [4].

The Centers for Disease Control and Prevention (CDC) estimated 2.53 million emergency department (ED) visits, 288.000 hospitalizations and 56.800 deaths related to TBI, in 2014 [5]. The TBI's lifetime economic costs (direct and indirect medical costs) was estimated at \$76.5 billion (2010) and fatal TBIs can account for up to 90% of total medical costs. Since TBI is a growing health burden, it is an utmost importance the optimization of hospital resources and staff [2, 6].

TBI can be classified following its severity: Mild, Moderate and Severe [7]. This classification is based on the Glasgow Coma Scale (GCS), with Mild - GCS Score 13–15; Moderate - GCS Score 9–12; and Severe - GCS Score 8–3. Subsequent TBI management will rely on the first evaluation and the prevention of secondary injuries.

3. TBI physiopathology and oxygen importance

TBI presents two main classifications for intracranial lesions: focal or diffused [7–9]. Focal brain damage is the consequence of cortical lacerations, compression, or concussion forces, compromising blood supply and culminating in neuronal and glial necrosis. The structural injury is resulted from the brain collision to rigid structures, depressed skull fractures, vascular injuries or penetrating trauma [8–11].

Diffuse brain damage is caused by acceleration/deceleration forces, that shears and stretches brain tissue, causing functional disturbance, culminating in brain swelling or diffuse axonal injury [8–11]. The co-existence of both types of injuries are frequently present, as a result from the mechanical distortion of the head that leads to a combination of neural and vascular events [10–13].

Additionally, the TBI process can be breakdown in two successive, intertwined, pathophysiological moments, labeled as primary and secondary injury.

3.1 Primary injury

The primary injury arises from the mechanical damage occurring at the time of the impact, being exclusively responsive to preventive measures [8, 14]. On the macroscopic level, damage can be recognized by shearing of white-matter tracts, diffuse swelling, focal contusions, and intracerebral and extracerebral hematomas [15–17].

On the cellular level, mechanoporation of axolemma (caused by the traumatic axonal injury) results in sodium channelopathy [18] and unregulated influx of Ca^{2+} , which initiates calpain activation and mitochondrial swelling [19–22]. Calpain activation and cytochrome *c* accumulation increases axonal injury, detachment and apoptosis [23]. This cascade of events occurs 24 to 72 hours after the trauma and is denominated as secondary axotomy [11]. Injured axons are also susceptible to demyelination [17].

The microvasculature suffers from injury changes, such as swelling of perivascular astrocytic end-feet, increased adherence of intravascular leukocyte, perivascular hemorrhage, transvascular erythrocytes diapedesis, and increased activity of endothelial microvacuolation and micropseudopodia [24, 25].

3.2 Secondary injury

The second injury emerges from a complex series of molecular and cellular interrelated events, resulted from the biochemical cascades triggered by the trauma [9, 11]. An essential goal in the critical care is to establish recognition and treatment for secondary injury, and prevent secondary insults, which worsen patient's outcomes [26, 27].

Post-traumatic edema likely occurs by the dysfunction of sodium-potassium pump, due to pH-induced conformational change or cellular energy failure, resulting in water and sodium accumulation within the cell [11, 25]. Other factors that contributes to intracranial edema are excitotoxicity (induces intracellular sodium accumulation) [28], and membrane disruption [29] and depolarization (induced by influx of chloride, due to sodium influx) [30].

Excitotoxicity is the result of the excess of excitatory amino acids (EAA) that are released in the extracellular space, such as glutamate and aspartate, which raises intracellular sodium, calcium, chloride and water [10, 15]. This accumulation results in organelle and plasma membrane swelling [31], apoptosis, activation of destructive enzymes (such as calpain, nitric oxide synthase) [32], positive feedback loop by voltage-gated calcium channels [33], and necrosis [34].

Besides other secondary brain injuries, such as calcium dysregulation (which leads to cytoskeletal degradation), patients experience superimposed secondary insults (with intracranial or systemic repercussions) [10, 14, 15, 27]. Systemic repercussions are hypotension, hypoxia, hyperthermia, and hypoxemia. **Figure 1** recapitulate TBI's sequence of events. **Figure 2** recapitulate TBI's neurometabolic cascade.

Intracranial insults include cerebral ischemia, elevated ICP (or intracranial hypertension), and cerebral fluid-mediated swelling. The Monroe Kellie doctrine (**Figure 3**) demonstrates the constancy relationship in the sum of volumes of brain, intracranial blood and cerebrospinal fluid (CSF) [7, 36, 37]. Once the brain suffers from the intracranial insults and equal volumes of CSF and intracranial blood are compressed, ICP remains normal (compensated state). When the brain enters in a decompensate state (after exhaustion of compensate state), the balance is interrupted and the ICP raises exponentially [7, 16].

It is important to mention that secondary injury does not have the same meaning as a secondary insult [11, 14]. Secondary insult occurs at the organ system level, being considered as a second hit event, exacerbating the damage from the primary

Figure 1.
TBI's sequence of events.

Figure 2.

[35] TBI's neurometabolic cascade. (1) nonspecific depolarization; (2) neurotransmitter release - excitatory neurotransmitters (EAAs); (3) increase potassium efflux; (4) increased membrane pumping to restore homeostasis; (5) Hyperglycolysis to increase adenosine triphosphate (ATP) availability; (6) lactate accumulation; (7) calcium sequestration and mitochondria dysfunction resulting in oxidative metabolism; (8) decreased ATP production; (9) Calpain activation and apoptosis initiation. A - Axolemma and calcium influx. B - Neurofilament compaction. C - microtubule disassembly. D - axonal swelling and secondary axotomy. K⁺: potassium; Na⁺: sodium; Glut: glutamate; Mg²⁺: magnesium; Ca²⁺: calcium; NMDA: N-methyl-D-aspartate; AMPA: d-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid.

TBI. The same reasoning is applied to the primary insult, which alters the cerebral metabolism and blood flow, resulting in cellular dysfunction and predisposition to cognitive impairment, seizures, hypotension and hypoxia [8].

3.3 Oxygen and TBI

The brain requires an uninterrupted supply of glucose and oxygen to maintain cellular viability and metabolism, consuming up to 20% of individual's total oxygen, with an average of cerebral metabolic rate of oxygen (CMRO₂) between 3 and 3.8 ml/100 g/min [38–41]. Brain metabolism represents the largest source of energy consumption in the human body, since neuronal activity is supported through the production of adenosine triphosphate (ATP), which consumes nearly 60% of oxygen [42, 43]. When cerebral oxygenation is maintained, minimization of secondary insult can be achieved [44].

Brain's energy consumption fluctuates following neuronal activity on localized regions, and in order to provide adequate energy supply, neurovascular and neurometabolic coupling mechanisms are involved [42]. However, within hypoxia or low oxygen conditions, prolyl hydroxylase domain-containing enzymes (PHDs) are

Figure 3.
The Monro Kellie doctrine.

inhibited, reducing inproline hydroxylation, and altering availability of hypoxia-inducible factor-1 α (HIF-1 α), which assist the metabolism adaptation and function during hypoxic conditions [42, 45–47]. Then, nuclear accumulation of HIF-1 α enhance transcriptional activity within HIF- β , promoting gene expression that contains a hypoxia response element (HRE) [42, 46, 48]. Remarkably, HIF-2 α is also induced in hypoxic brain, being expressed in astrocytes and endothelial cells [49]. This dysfunction is associated with poor neurological outcomes [50].

In order to cope hypoxia stress, this adaptive response converts cellular metabolism to anaerobic metabolism and induces erythropoiesis, glycolysis, angiogenesis (by vascular endothelial growth factor), among other events [46, 48, 51]. Nevertheless, anaerobic glycolysis is unable to apport sufficient energy to sustain brain demands, depleting ATP stores, which results in failure of ATP dependent membrane ionic pumps [52]. Likewise, under chronic hypoxic conditions, there is an increase in oxidative stress, cell death, inflammation and the interruption of cerebral blood flow (CBF), directly affecting brain structure and function, leading to neuronal damage and death [51, 53, 54]. A normal average of CBF in adults is 44–45 ml/100 g/min. However, the CBF threshold for irreversible tissue damage (in TBI) occurs with the decrease to 15 ml/100 g/min [27, 41, 55] and cellular function is disrupted under 10 ml/100 g/min [56]. Neurons in the hippocampus, striatum and cortical regions die after 5, 10, and 15–20 min of ischemia [57, 58], respectively.

Considering that the brain is susceptible to ischemic injury, cerebral perfusion and oxygenation are vital to be maintained. In TBI setting, cerebral ischemia occurs due to different mechanisms: damage to blood vessels, hypotension, mechanical compression, and reduced perfusion (impaired autoregulation, which leads to greater propensity to hypoperfusion) [16, 59]. Hypoxemia can represent a relative risk of mortality of 75%, when associated with hypotension [7].

According to the Brain Trauma Foundation [60], patients with severe TBI present pulmonary aspiration risks or compromised airway function, and initial treatment goals include early airway protection, adequate supplemental oxygen, and circulation support, ensuring that adequate oxygen and blood flow are delivered to the brain [61].

4. Prehospital care and oxygenation

TBI management begins at the prehospital care, assuring that the patient has no signs of upper airway obstruction, maintaining Oxygen saturation (spO_2) $> 90\%$ and considering intubation in patients that presents Glasgow Coma Scale (GCS) < 9 , altered swallowing reflex or contributing to hypoventilation [60, 62–64]. However, it is of substantial value that the prehospital team is technically qualified (within technical skills, medical devices/medication, and protocols) to perform airway management and control possible detrimental effects of therapeutic interventions (such as worsening of cervical spine injury during endotracheal intubation [65]).

Studies examining the impact of prehospital intubation have conspicuously conflicting results. A Finnish [66] comparison between physician-staffed prehospital team and paramedics team (PM) demonstrated that the physician team performed 98% of advanced airway management against 16% in paramedics patient's group. Hypoxia was higher in the PM group at the emergency department arrival. Furthermore, one-year mortality rate was higher in the PM group. Singularly, anesthetics were available for physician teams only, while PM were limited to the sedatives. Patients that were submitted to emergence intubation during prehospital care presented an increased risk of morbidity and mortality (poor neurologic outcome [67, 68] and decreased survival rate [68–71]).

The French Society of Anesthesia and Intensive Care Medicine strongly recommends a prehospital medicalized team to assess patients, claiming higher survival rates [72]. Divergently, an Australian study [73] indicated that rapid sequence intubation performed by paramedics increased the 6 months rate of favorable neurologic outcome. The Trauma Research and Education Foundation of San Diego [74] also demonstrated improved survival in patients intubated in the field. Meanwhile, any benefit or harm of pre-hospital intubation could be stated [63].

Marehbian et al. [75] inferred that these inconsistencies may be attributed to multiple factors: GCS applied as a single scale to identify intubation candidates (can be misinterpreted by illegal substances or sedative effects), variability of protocols, and inadequate intubation or ventilation approaches, that can lead to hypo or hyperventilation.

Hyperventilation is commonly revealed as a higher incidence among pre-hospital intubated patients. Hemodynamically, hyperventilation rises the intrathoracic pressure, leading to a decrease in cardiac output [76–78]. Regarding the cerebral perfusion, hypocapnia decrease the cerebral blood volume (CBV), which directly decrease the cerebral blood flow (CBF), and lower ICP [79–82]. Studies had shown regional and local ischemia with tissue lactic acidosis immediately after hyperventilation, suggesting harmful effects in cerebral tissue due to cerebral vasoconstriction [7, 81, 82]. Currently, hyperventilation should be reserved to

refractory cases immediately before surgical intervention. It should not be used in ICU management of refractory ICP because of its detrimental hypoperfusion properties [7, 83–85].

The use of supplemental oxygen is required to correct hypoxemia and attempt to avoid secondary injury. Therefore, initial management for severe traumatic brain injury involves intubation and ventilation for airway management [7, 72]. However, the decision to perform invasive procedures on the trauma stage should be evaluated in a case to case basis since the experience of the team involved together with the conditions of the patient/surroundings (patient inside a car wreckage or in a war site) of the trauma can have a great influence in the decision making.

5. Tracheostomy and oxygenation

To prevent or reverse hypoxemia and provide oxygen to the tissues during acute respiratory failure, airway access is often provided by translaryngeal endotracheal tube. When mechanical ventilation is expected to be prolonged, TQT tube is frequently chosen as part of the airway management care plan [86–88].

Earlier TQT records were found in the Edwin Smith Papyrus (1600 BC), whereas an emergency airway was performed after a trauma [89]. The first surgical description of successful case of TQT was performed by Antonio Musa Brasavola (1546) [90] and a full book dedicated to this procedure, previously known as bronchotomy, was published in 1620 [91] by Nicolas Habicot, who pictured it as demonstrated in Figure 4.

Figure 4.
[92] Patient's tracheostomy by Nicolas Habicot. A: the patient; B: the larynx; C: bronchotomy insertion; D: bronchotomy's instrument; E: the cannula; F: cannula's strap; G: a band to apply over the cannula to control the air leakage; H: the needle to suture the wound when needed.

During the Second World War, TQT grown relevance in chest trauma patients [93] and since then, it is expanding its role in airway management, as well improvement of the surgical techniques, instruments and cannulas.

Prolonged/impractical intubation, ventilation support for weaning, pulmonary hygiene management and airway protection are main indications for TQT placement [86–88, 94]. Patients can benefit from tracheostomy that is performed by open surgical (OST) or percutaneous dilatory (PDT) techniques.

Patient's individual aspects assist the medical team to decide whether to use PDT or OST. PDT is recommended for patients who can hyperextend the neck, tolerate hypercarbia and hypoxemia, and present at least 1-cm distance between the inferior cricoid cartilage and the suprasternal notch (in case of needed re-intubated after accidental extubation) [86–88]. PDT relative contraindications are emergency airway access, anatomical incompatibility, coagulopathies, higher levels for support oxygenation (e.g. positive end-expiratory pressure ≥ 10 mm Hg or fraction of inspired oxygen ≥ 0.7), and infection at insertion site surroundings [86–88].

Studies were carried out to establish advantages and preferences between techniques. A Cochrane review did not find statistical difference for mortality and serious life-threatening adverse events between techniques [95]. However, PDT presented significantly reduced rate for wound infections/stomatitis and unfavorable scarring. Other systematic reviews and meta-analysis confirmed the same result trend: no difference in mortality and life-threatening complications [96–100]. Significant positive outcomes for PDT was cited as less infection rate [97–100] and less procedure time [96, 100–102]. Besides these results, OST could also impact hospital expenditures, since the procedure can require an operatory room and staff [88, 103, 104].

6. The benefits of tracheostomy on TBI

A multidisciplinary team collaborates in patient's care for adequate communication, ventilation and oxygenation [104]. The presence of a TQT may promote greater airway security, assisting in patient's mobilization and engagement to physical therapies [88]. Likewise, TQT allows sedation reduction or cessation, reduction of laryngeal lesions, assist in weaning protocol and improve oral nutrition and communication [105–107]. Mentioned risks are tracheal stenosis, tracheomalacia and hemorrhage [108]. However, TQT benefits overcome procedures risks [94, 109, 110].

Over the past decade, extensive research has been done concerning TQT timing for optimal results in patient's care, and an oscillation of a cut out day to consider TQT as an early procedure (ET) is perceived. Literature reveals authors acceptance of TQT as an early procedure, as those ones performed between 2 and 12 days after admission [111–116].

A systematic review and meta-analysis [115] revealed that ET, in severe TBI patients, is associated with shorter length of mechanical ventilation and intensive care unit (ICU) and hospital stay. Likewise, decreased risk of ventilator associated pneumonia was found. Complementary literature comparing early and late tracheostomy (LT) populations demonstrated lower ICU stay [113, 117–120], lower hospital stay [117, 120], lower rates for pneumonia [113, 117, 119, 120] and lower costs [113, 117].

Healthcare cost management has increasing its role as part of patient's care plan. Given an aging population and rising medical comorbidities, expertise in resource allocation is crucial. Herriot and colleagues [121] demonstrated the average weighted cost of ET (≤ 4 days) patients in ICU is \$4316 less when compared with

LT (≥ 11 days). A continuous demand/importance of resources was produced and exposed by the latest worldwide health care crisis caused by Corona Virus 19 (Covid-19). Mattioli et al. [122] briefly exposed that ET (≥ 7 days < 14 days) could promote expedited ICU beds availability. Nonetheless, studies are needed to assure TQT role for COVID-19 management [123].

Mostly of the presented mortality rates between LT and ET analysis do not demonstrate statistical significance [113, 114, 117, 119, 120, 124–128], which could be a response of ET placement in critical state patients [86]. Hence, no definitive conclusion could be drawn by the absence of mortality significance, as well, patients functional state at discharge could not be assured.

The variation of tracheostomy protocols can contribute to misleading results. A retrospective study [129] across 19 countries and 54 TBI centers in Europe demonstrated that the incidence of ET (≤ 7 days after admission) ranged from 0 to 17.6% and LT from 7.9 to 32%. A delayed procedure was more likely to happen than an earlier one. LT patients presented higher reintubation, VAP and respiratory failure rates than ET.

7. Conclusion

Overall, ET could contribute to lower exposure to secondary insults and nosocomial adverse events, rising patient's early rehabilitation and discharge rates, and improve hospital/staff resources management. Establishment of guidelines for further homogenous approaches to better assist severe TBI patients and improve second injury control is concerned.

Acknowledgements

The authors acknowledge the support of the nonprofit organization Instituto Paulista de Saude para Alta Complexidade.

Conflict of interest

The authors declare no conflict of interest.

IntechOpen

Author details

Sabrina Araujo de França^{1*}, Wagner M. Tavares^{2,3}, Wellingson S. Paiva³
and Manoel J. Teixeira³

1 Department of Research of IPSPAC – Paulista de Saúde para Alta Complexidade (Paulista Institute of Health to High Complexity Instituto), 199 Padre Anchieta Avenue - Room 2, Jardim, Santo Andre, SP, 09090-710, Brazil

2 Department of Research of IPSPAC – Instituto Paulista de Saúde para Alta Complexidade (Paulista Institute of Health to High Complexity Instituto), 199 Padre Anchieta Avenue - Room 2, Jardim, Santo Andre, SP, 09090-710, Brazil

3 Institute of Neurology, University of São Paulo, 255 Dr. Enéas de Carvalho Aguiar avenue, Cerqueira César, São Paulo, SP, 05403-900, Brazil

*Address all correspondence to: pesquisacientifica@ipspac.org.br

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Vol. 7, *The Lancet Neurology*. Elsevier; 2008. p. 728-41.
- [2] Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: A global perspective. Vol. 22, *NeuroRehabilitation*. IOS Press; 2007. p. 341-53.
- [3] Rubiano AM, Carney N, Chesnut R, Puyana JC. Global neurotrauma research challenges and opportunities. *Nature*. 2015 Nov 18;527(7578):S193-7.
- [4] Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. Samet J, editor. *PLoS Med*. 2006 Nov 28;3(11):e442.
- [5] Centers for Disease Control and Prevention. Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths. 2019.
- [6] Chowdhury T, Kowalski S, Arabi Y, Dash HH. Specific intensive care management of patients with traumatic brain injury: Present and future. *Saudi J Anaesth*. 2014 Apr;8(2):268-75.
- [7] Advanced trauma life support (ATLS®). Student Course Manual. 10th ed. Chicago, United States: American College of Surgeons; 2018. 1363-1366 p.
- [8] Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth*. 2007 Jul;1(99):4-9.
- [9] Huffman JC, Brennan MM, Smith FA, Stern TA. Patients with Neurologic Conditions I. Seizure Disorders (Including Nonepileptic Seizures), Cerebrovascular Disease, and Traumatic Brain Injury. In: Stern TA, Fricchione GL, Cassem NH, Jellinek M, Rosenbaum JF, editors. *Massachusetts General Hospital Handbook of General Hospital Psychiatry*. 6th Editio. Elsevier; 2010. p. 237-53.
- [10] Ng SY, Lee AYW. Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. Vol. 13, *Frontiers in Cellular Neuroscience*. Frontiers Media S.A.; 2019. p. 528.
- [11] Zacko CJ, Hawryluk GW. Neurochemical Pathomechanisms in Traumatic Brain Injury. In: Winn RN, editor. *Youmans & Winn Neurological Surgery*. 7th Editio. Philadelphia: Elsevier; 2017. p. 2786-801.
- [12] Skandsen T, Kvistad KA, Solheim O, Strand IH, Folvik M, Anne V. Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: A cohort study of early magnetic resonance imaging findings and 1-year outcome: Clinical article. *J Neurosurg*. 2010 Sep;113(3):556-63.
- [13] Gennarelli TA, Graham DI. Neuropathology of the Head Injuries. *Semin Clin Neuropsychiatry*. 1998 Jul;3(3):160-75.
- [14] Aisiku IP, Silvestri DM, Robertson CS. Critical Care Management of Traumatic Brain Injury. In: Winn RN, editor. *Youmans & Winn Neurological Surgery*. 7th Editio. Philadelphia: Elsevier; 2017. p. 2876-97.
- [15] Kaur P, Sharma S. Recent Advances in Pathophysiology of Traumatic Brain Injury. *Curr Neuropharmacol*. 2017 Jul 12;16(8):1224-38.
- [16] O'leary RA, Nichol AD. Pathophysiology of severe traumatic brain injury. *J Neurosurg Sci*. 2018 Oct;62(5):542-8.
- [17] Stocchetti N, Carbonara M, Citerio G, Ercole A, Skrifvars MB,

- Smielewski P, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol*. 2017 Jun;16(6):452-64.
- [18] Wolf JA, Stys PK, Lusardi T, Meaney D, Smith DH. Traumatic axonal injury induces calcium influx modulated by tetrodotoxin-sensitive sodium channels. *J Neurosci*. 2001 Mar 15;21(6):1923-30.
- [19] Pettus EH, Christman CW, Giebel ML, Povlishock JT. Traumatically Induced Altered Membrane Permeability: Its Relationship to Traumatically Induced Reactive Axonal Change. *J Neurotrauma*. 1994 Jun 29;11(5):507-22.
- [20] Büki A, Siman R, Trojanowski JQ, Povlishock JT. The Role of Calpain-Mediated Spectrin Proteolysis in Traumatically Induced Axonal Injury. *J Neuropathol Exp Neurol*. 1999 Apr;58(4):365-75.
- [21] Shields DC, Schaeffer KE, Hogan EL, Banik NL. Calpain activity and expression increased in activated glial and inflammatory cells in penumbra of spinal cord injury lesion. *J Neurosci Res*. 2000 Jul 15;61(2):146-50.
- [22] Okonkwo DO, Povlishock JT. An intrathecal bolus of cyclosporin A before injury preserves mitochondrial integrity and attenuates axonal disruption in traumatic brain injury. *J Cereb Blood Flow Metab*. 1999 Apr;19(4):443-51.
- [23] Büki A, Okonkwo DO, Wang KKW, Povlishock JT. Cytochrome c release and caspase activation in traumatic axonal injury. *J Neurosci*. 2000 Apr 15;20(8):2825-34.
- [24] Maxwell WL, Bullock R, Landholt H, Fujisawa H. Massive astrocytic swelling in response to extracellular glutamate--a possible mechanism for post-traumatic brain swelling? *Acta Neurochir Suppl (Wien)*. 1994;60:465-7.
- [25] Bullock R, Maxwell WL, Graham DI, Teasdale GM, Adams JH. Glial swelling following human cerebral contusion: An ultrastructural study. *J Neurol Neurosurg Psychiatry*. 1991 May;54(5):427-34.
- [26] Le Roux P, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM, et al. Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive C. *Neurocrit Care*. 2014 Oct;21(2):1-26.
- [27] Shahlaie K, Zwienenberg-Lee M, Muizelaar JP. Clinical Pathophysiology of Traumatic Brain Injury. In: Winn RN, editor. *Youmans & Winn Neurological Surgery*. 7th Editio. Philadelphia: Elsevier; 2017. p. 2843-59.
- [28] Gaetz M. The neurophysiology of brain injury. *Clin Neurophysiol*. 2004 Jan;115(1):4-18.
- [29] Schroder ML, Muizelaar JP, Bullock MR, Salvant JB, Povlishock JT. Focal ischemia due to traumatic contusions documented by stable xenon-CT and ultrastructural studies. *J Neurosurg*. 1995 Jun;82(6):966-71.
- [30] Marmarou A. A review of progress in understanding the pathophysiology and treatment of brain edema. Vol. 22, *Neurosurgical Focus*. American Association of Neurological Surgeons; 2007. p. 1-10.
- [31] Choi DW. Calcium: still center-stage in hypoxic-ischemic neuronal death. *Trends Neurosci*. 1995 Feb;18(2):58-60.
- [32] Zipfel GJ, Babcock DJ, Lee JM, Choi DW. Neuronal apoptosis after CNS injury: The roles of glutamate and calcium. *J Neurotrauma*. 2000 Jan;17(10):857-69.

- [33] Gennarelli TA. Mechanisms of brain injury. *J Emerg Med.* 1993;11 Suppl 1:5-11.
- [34] Wyllie AH, Kerr JFR, Currie AR. Cell Death: The Significance of Apoptosis. *Int Rev Cytol.* 1980 Jan;68(C):251-306.
- [35] Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. *J Athl Train.* 2001 Sep;36(3):228-35.
- [36] Mokri B. The Monro-Kellie hypothesis: Applications in CSF volume depletion. *Neurology.* 2001 Jun 26;56(12):1746-8.
- [37] Kasper E, Chen C, Kasper B. Neurosurgical and Neurological Emergencies for Surgeons | Basicmedical Key [Internet]. 2016 [cited 2020 Aug 29]. Available from: <https://basicmedicalkey.com/neurosurgical-and-neurological-emergencies-for-surgeons/#F1-34>
- [38] Chesnut R, Videtta W, Vespa P, Le Roux P, Menon DK, Citerio G, et al. Intracranial Pressure Monitoring: Fundamental Considerations and Rationale for Monitoring. *Neurocrit Care.* 2014 Oct;21(2):64-84.
- [39] Ngwenya LB, Burke JF, Manley GT. Brain tissue oxygen monitoring and the intersection of brain and lung: A comprehensive review. Vol. 61, *Respiratory Care.* American Association for Respiratory Care; 2016. p. 1232-44.
- [40] Greve MW, Zink BJ. Pathophysiology of traumatic brain injury. *Mt Sinai J Med.* 2009 Apr;76(2):97-104.
- [41] Barrett KE, Barman SM, Boitano S, Brooks HL. Circulation through special regions. In: Barrett KE, Barman SM, Boitano S, Brooks HL, editors. *Ganong's review of medical physiology.* 24th ed. McGraw-Hill Companies; 2012. p. 601-17.
- [42] Watts ME, Pocock R, Claudianos C. Brain energy and oxygen metabolism: Emerging role in normal function and disease. *Front Mol Neurosci.* 2018 Jun 22;11:216.
- [43] Butterworth IV JF, Mackey DC, Wasnick JD. Neurophysiology & anesthesia. In: Butterworth IV JF, Mackey DC, Wasnick JD, editors. *Morgan & Mikhail's clinical anesthesiology.* 6th Editio. New York: McGraw-Hill Education; 2018. p. 979-1009.
- [44] Rose JC, Neill TA, Hemphill JC. Continuous monitoring of the microcirculation in neurocritical care: An update on brain tissue oxygenation. Vol. 12, *Current Opinion in Critical Care.* 2006. p. 97-102.
- [45] Pescador N, Cuevas Y, Naranjo S, Alcaide M, Villar D, Landázuri MO, et al. Identification of a functional hypoxia-responsive element that regulates the expression of the egl nine homologue 3 (egln3/phd3) gene. *Biochem J.* 2005 Aug 15;390(1):189-97.
- [46] Majmundar AJ, Wong WJ, Simon MC. Hypoxia-Inducible Factors and the Response to Hypoxic Stress. Vol. 40, *Molecular Cell.* Elsevier; 2010. p. 294-309.
- [47] Bogdanovski DA, DiFazio LT, Bogdanovski AK, Csóka B, Jordan GB, Paul ER, et al. Hypoxia-inducible-factor-1 in trauma and critical care. *J Crit Care.* 2017;42:207-12.
- [48] Wenger RH, Gassmann M. Oxygen(es) and the hypoxia-inducible factor-1. *Biol Chem.* 1997 Jul;378(7):609-16.
- [49] Chavez JC, Baranova O, Lin J, Pichiule P. The transcriptional activator hypoxia inducible factor 2 (HIF-2/EPAS-1) regulates the oxygen-dependent expression of erythropoietin in cortical astrocytes. *J Neurosci.* 2006 Sep 13;26(37):9471-81.

- [50] Patet C, Suys T, Carteron L, Oddo M. Cerebral Lactate Metabolism After Traumatic Brain Injury. *Curr Neurol Neurosci Rep*. 2016 Apr;16(4):31.
- [51] Kietzmann T, Knabe W, Schmidt-Kastner R. Hypoxia and hypoxia-inducible factor modulated gene expression in brain: Involvement in neuroprotection and cell death. *Eur Arch Psychiatry Clin Neurosci*. 2001;251(4):170-8.
- [52] Dash HH, Chavali S. Management of traumatic brain injury patients. Vol. 71, *Korean Journal of Anesthesiology*. Korean Society of Anesthesiologists; 2018. p. 12-21.
- [53] Baranova O, Miranda LF, Pichiule P, Dragatsis I, Johnson RS, Chavez JC. Neuron-specific inactivation of the hypoxia inducible factor 1 α increases brain injury in a mouse model of transient focal cerebral ischemia. *J Neurosci*. 2007 Jun 6;27(23):6320-32.
- [54] Mulvey JM, Dorsch NWC, Mudaliar Y, Lang EW. Multimodality monitoring in severe traumatic brain injury: The role of brain tissue oxygenation monitoring. Vol. 1, *Neurocritical Care*. Springer; 2004. p. 391-402.
- [55] Cunningham AS, Salvador R, Coles JP, Chatfield DA, Bradley PG, Johnston AJ, et al. Physiological thresholds for irreversible tissue damage in contusional regions following traumatic brain injury. *Brain*. 2005 Aug;128(Pt 8):1931-42.
- [56] Lipp LL. Brain perfusion and oxygenation. *Crit Care Nurs Clin North Am*. 2014 Sep;26(3):389-98.
- [57] Pulsinelli WA, Brierley JB, Plum F. Temporal profile of neuronal damage in a model of transient forebrain ischemia. *Ann Neurol*. 1982 May;11(5):491-8.
- [58] Schmidt-Kastner R, Freund TF. Selective vulnerability of the hippocampus in brain ischemia. *Neuroscience*. 1991 Jan;40(3):599-636.
- [59] Rodríguez-Baeza A, Reina-de la Torre F, Poca A, Martí M, Garnacho A. Morphological features in human cortical brain microvessels after head injury: a three-dimensional and immunocytochemical study. *Anat Rec Part A, Discov Mol Cell Evol Biol*. 2003 Jul;273(1):583-93.
- [60] Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery*. 2017 Jan;80(1):6-15.
- [61] Abdelmalik PA, Draghic N, Ling GSF. Management of moderate and severe traumatic brain injury. *Transfusion*. 2019 Apr;59(S2):1529-38.
- [62] Pélieu I, Kull C, Walder B. Prehospital and Emergency Care in Adult Patients with Acute Traumatic Brain Injury. *Med Sci*. 2019 Jan 21;7(1):12.
- [63] Von Elm E, Schoettker P, Henzi I, Osterwalder J, Walder B. Pre-hospital tracheal intubation in patients with traumatic brain injury: Systematic review of current evidence. *Br J Anaesth*. 2009 Sep;103(3):371-86.
- [64] Badjatia N, Carney N, Crocco TJ, Fallat ME, Hennes HMA, Jagoda AS, et al. Guidelines for prehospital management of traumatic brain injury 2nd edition. *Prehospital Emerg Care*. 2008;12(SUPPL. 1).
- [65] Chowdhury T, Kowalski S, Arabi Y, Dash H. Pre-hospital and initial management of head injury patients: An update. *Saudi J Anaesth*. 2014 Jan;8(1):114.
- [66] Pakkanen T, Virkkunen I, Kämäräinen A, Huhtala H, Silfvast T, Virta J, et al. Pre-hospital severe

traumatic brain injury - comparison of outcome in paramedic versus physician staffed emergency medical services. *Scand J Trauma Resusc Emerg Med.* 2016 Apr;24(1):62.

[67] Wang HE, Peitzman AB, Cassidy LD, Adelson PD, Yealy DM. Out-of-hospital endotracheal intubation and outcome after traumatic brain injury. *Ann Emerg Med.* 2004 Nov;44(5):439-50.

[68] Davis DP, Peay J, Sise MJ, Vilke GM, Kennedy F, Eastman AB, et al. The Impact of Prehospital Endotracheal Intubation on Outcome in Moderate to Severe Traumatic Brain Injury. *J Trauma Inj Infect Crit Care.* 2005 May;58(5):933-9.

[69] Eckstein M, Chan L, Schneir A, Palmer R. Effect of Prehospital Advanced Life Support on Outcomes of Major Trauma Patients. *J Trauma Inj Infect Crit Care.* 2000 Apr;48(4):643-8.

[70] Murray JA, Demetriades D, Berne T V., Stratton SJ, Cryer HG, Bongard F, et al. Prehospital Intubation in Patients with Severe Head Injury : *Journal of Trauma and Acute Care Surgery.* *J Trauma Inj Infect Crit Care.* 2000 Dec;49(6):1065-70.

[71] Bochicchio G V., Ilahi O, Joshi M, Bochicchio K, Scalea TM. Endotracheal Intubation in the Field Does Not Improve Outcome in Trauma Patients Who Present without an Acutely Lethal Traumatic Brain Injury. *J Trauma Inj Infect Crit Care.* 2003 Feb;54(2):307-11.

[72] Geeraerts T, Velly L, Abdenmour L, Asehnoun K, Audibert G, Bouzat P, et al. Management of severe traumatic brain injury (first 24 hours). *Anaesth Crit Care Pain Med.* 2018 Apr;37(2):171-86.

[73] Bernard SA, Nguyen V, Cameron P, Masci K, Fitzgerald M, Cooper DJ, et al. Prehospital Rapid Sequence

Intubation Improves Functional Outcome for Patients With Severe Traumatic Brain Injury. *Ann Surg.* 2010 Dec;252(6):959-65.

[74] Winchell RJ, Hoyt DB. Endotracheal intubation in the field improves survival in patients with severe head injury. *Arch Surg.* 1997 Jun;132(6):592-7.

[75] Marehbian J, Muehlschlegel S, Edlow BL, Hinson HE, Hwang DY. Medical Management of the Severe Traumatic Brain Injury Patient. *Neurocrit Care.* 2017 Dec;27(3):430-46.

[76] Aufderheide TP, Sigurdsson G, Pirrallo RG, Yannopoulos D, McKnite S, Von Briesen C, et al. Hyperventilation-Induced Hypotension during Cardiopulmonary Resuscitation. *Circulation.* 2004 Apr 27;109(16):1960-5.

[77] Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. *Crit Care Med.* 2004;32(9 Suppl).

[78] Davis DP, Idris AH, Sise MJ, Kennedy F, Eastman AB, Velky T, et al. Early ventilation and outcome in patients with moderate to severe traumatic brain injury*. *Crit Care Med.* 2006 Apr;34(4):1202-8.

[79] Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, et al. Effect of hyperventilation on cerebral blood flow in traumat... : *Critical Care Medicine.* *Crit Care Med.* 2002 Sep;30(9):1950-9.

[80] Marion DW, Puccio A, Wisniewski SR, Kochanek P, Dixon CE, Bullian L, et al. Effect of hyperventilation on extracellular concentrations o... : *Critical Care Medicine.* *Crit Care Med.* 2002 Dec;30(12):2619-25.

[81] Manley GT, Hemphill JC, Morabito D, Derugin N, Erickson V,

- Pitts LH, et al. Cerebral Oxygenation during Hemorrhagic Shock: Perils of Hyp... : Journal of Trauma and Acute Care Surgery. J Trauma Inj Infect Crit Care. 2000 Jun;48(6):1025-33.
- [82] Diringner MN, Videen TO, Yundt K, Zazulia AR, Aiyagi V, Dacey RG, et al. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. J Neurosurg. 2002 Jan;96(1):103-8.
- [83] Marhong J, Fan E. Carbon dioxide in the critically ill: Too much or too little of a good thing? Respir Care. 2014 Oct;59(10):1597-605.
- [84] Brambrink A, Orfanakis A. "Therapeutic hypercapnia" after ischemic brain injury: Is there a potential for neuroprotection? Anesthesiology. 2010 Feb;112(2):274-6.
- [85] Asehnoune K, Roquilly A, Cinotti R. Respiratory Management in Patients with Severe Brain Injury. Vol. 22, Critical Care. BioMed Central Ltd.; 2018. p. 76.
- [86] Cheung NH, Napolitano LM. Tracheostomy: epidemiology, indications, timing, technique, and outcomes. Respir Care. 2014 Jun 1;59(6):895-915; discussion 916-9.
- [87] Durbin CG. Tracheostomy: why, when, and how? Respir Care. 2010 Aug;55(8):1056-68.
- [88] Freeman BD. Tracheostomy Update: When and How. Crit Care Clin. 2017 Apr;33(2):311-22.
- [89] Cooper JD. Surgery of the airway: Historic notes. J Thorac Dis. 2016 Mar;8(2):S113-20.
- [90] Brasavola AM. Hippocrates. Sectio XXXV. In: In libros de ratione victus in morbis acutis, Hippocratis et Galeni commentaria et annotationes. 1st ed. Venetiis - G. Scotto; 1546. p. 106-30.
- [91] Habicot N. Question chirurgicale, par laquelle est démontré que le chirurgien doit assurément pratiquer l'opération de la bronchotomie, vulgairement dicte laryngotomie ou perforation de la fluste ou tuyau du polmon. Paris: J. Corrozet; 1620. 108 p.
- [92] Monteiro S, de Farias T, M de CM, Locio R. The history of tracheostomy. In: de Farias T, editor. Tracheostomy A Surgical Guide. 1st ed. Rio de Janeiro: Springer; 2018. p. 1-9.
- [93] Borman J, Davidson JT. A history of tracheostomy:: Si spiritum ducit vivit (cicero). Br J Anaesth. 1963 Jun;35(6):388-90.
- [94] De Leyn P, Bedert L, Delcroix M, Depuydt P, Lauwers G, Sokolov Y, et al. Tracheotomy: clinical review and guidelines. Vol. 32, European Journal of Cardio-thoracic Surgery. 2007. p. 412-21.
- [95] Brass P, Hellmich M, Ladra A, Ladra J, Wrzosek A. Percutaneous techniques versus surgical techniques for tracheostomy. Cochrane Database Syst Rev. 2016 Jul;2016(7).
- [96] Freeman BD, Isabella K, Lin N, Buchman TG. A meta-analysis of prospective trials comparing percutaneous and surgical tracheostomy in critically ill patients. Chest. 2000 Nov;118(5):1412-8.
- [97] Delaney A, Bagshaw SM, Nalos M. Percutaneous dilatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis. Crit Care. 2006;10(2):R55.
- [98] Higgins KM, Punthakee X. Meta-analysis comparison of open versus percutaneous tracheostomy. Laryngoscope. 2007 Mar;117(3):447-54.
- [99] Klotz R, Probst P, Deininger M, Klaiber U, Grummich K, Diener MK,

- et al. Percutaneous versus surgical strategy for tracheostomy: a systematic review and meta-analysis of perioperative and postoperative complications. *Langenbeck's Arch Surg*. 2018 Mar;403(2):137-49.
- [100] Johnson-Obaseki S, Veljkovic A, Javidnia H. Complication rates of open surgical versus percutaneous tracheostomy in critically ill patients. *Laryngoscope*. 2016 Nov;126(11):2459-67.
- [101] Oliver ER, Gist A, Gillespie MB. Percutaneous versus surgical tracheotomy: an updated meta-analysis. *Laryngoscope*. 2007 Sep;117(9):1570-5.
- [102] Iftikhar IH, Teng S, Schimmel M, Duran C, Sardi A, Islam S. A Network Comparative Meta-analysis of Percutaneous Dilatational Tracheostomies Using Anatomic Landmarks, Bronchoscopic, and Ultrasound Guidance Versus Open Surgical Tracheostomy. *Lung*. 2019 Jun;197(3):267-75.
- [103] Al-Shathri Z, Susanto I. Percutaneous Tracheostomy. *Semin Respir Crit Care Med*. 2018 Dec 14;39(6):720-30.
- [104] Parker V, Giles M, Shylan G, Austin N, Smith K, Morison J, et al. Tracheostomy management in acute care facilities--a matter of teamwork. *J Clin Nurs*. 2010 May;19(9-10):1275-83.
- [105] McWhorter AJ. Tracheotomy: timing and techniques. *Curr Opin Otolaryngol Head Neck Surg*. 2003 Dec;11(6):473-9.
- [106] Tong CCL, Kleinberger AJ, Paolino J, Altman KW. Tracheotomy timing and outcomes in the critically ill. *Otolaryngol neck Surg Off J Am Acad Otolaryngol Neck Surg*. 2012 Jul;147(1):44-51.
- [107] Heffner JE, Hess D. Tracheostomy management in the chronically ventilated patient. *Clin Chest Med*. 2001 Mar;22(1):55-69.
- [108] Mallick A, Bodenham AR. Tracheostomy in critically ill patients. *Eur J Anaesthesiol*. 2010 Jun;1.
- [109] Cipriano A, Mao M, Hon H, Vazquez D, Stawicki S, Sharpe R, et al. An overview of complications associated with open and percutaneous tracheostomy procedures. *Int J Crit Illn Inj Sci*. 2015;5(3):179.
- [110] Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients*. *Crit Care Med*. 2004 Aug;32(8):1689-94.
- [111] Pasini RL, Fernandes YB, Araújo S, Soares SM de TP. [The influence of early tracheostomy in the weaning of patients with severe traumatic brain injury]. *Rev Bras Ter intensiva*. 2007 Jun;19(2):176-81.
- [112] Elkbuli A, Narvel RI, Spano PJ 2nd, Polcz V, Casin A, Hai S, et al. Early versus Late Tracheostomy: Is There an Outcome Difference? *Am Surg*. 2019 Apr;85(4):370-5.
- [113] Hyde GA, Savage SA, Zarzaur BL, Hart-Hyde JE, Schaefer CB, Croce MA, et al. Early tracheostomy in trauma patients saves time and money. *Injury*. 2015 Jan;46(1):110-4.
- [114] Dochi H, Nojima M, Matsumura M, Cammack I, Furuta Y. Effect of early tracheostomy in mechanically ventilated patients. *Laryngoscope Investig Otolaryngol*. 2019 Jun 22;4(3):292-9.
- [115] Sabrina A de F, Tavares WM, Salinet ASM, Paiva WS, Teixeira MJ. Early Tracheostomy in Severe Traumatic

Brain Injury Patients. Crit Care Med [Internet]. 2020 Feb;1. Available from: <http://journals.lww.com/10.1097/CCM.00000000000004239>

[116] Andriolo BN, Andriolo RB, Saconato H, Atallah ÁN, Valente O. Early versus late tracheostomy for critically ill patients. Cochrane Database Syst Rev. 2015

[117] Lu W, Wu T, Cui P, Zhang J, Sheng X, Ding Z. Timing of Tracheotomy in Patients With Severe Traumatic Brain Injury. J Craniofac Surg. 2019 Oct;30(7):2168-70.

[118] Huang Y-H, Lee T-C, Liao C-C, Deng Y-H, Kwan A-L. Tracheostomy in craniectomised survivors after traumatic brain injury: A cross-sectional analytical study. Injury. 2013 Sep;44(9):1226-31.

[119] Gandía-Martínez F, Martínez-Gil I, Andaluz-Ojeda D, Bobillo de Lamo F, Parra-Morais L, Díez-Gutiérrez F. [Analysis of early tracheostomy and its impact on development of pneumonia, use of resources and mortality in neurocritically ill patients]. Neurocirugia (Astur). 2010 Jun;21(3):211-21.

[120] Khan M, Prabhakaran K, Jehan F, Anderson P, Con J, Lombardo G, et al. Early tracheostomy in patients with cervical spine injury reduces morbidity and improves resource utilization. Am J Surg. 2020 Feb

[121] Herritt B, Chaudhuri D, Thavorn K, Kubelik D, Kyeremanteng K. Early vs. late tracheostomy in intensive care settings: Impact on ICU and hospital costs. J Crit Care. 2018 Apr 1;44:285-8.

[122] Mattioli F, Fermi M, Ghirelli M, Molteni G, Sgarbi N, Bertellini E, et al. Tracheostomy in the COVID-19 pandemic. Eur Arch oto-rhino-laryngology Off J Eur Fed

Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology - Head Neck Surg. 2020 Jul;277(7):2133-5.

[123] Ferri E, Boscolo Nata F, Pedruzzi B, Campolieti G, Scotto di Clemente F, Baratto F, et al. Indications and timing for tracheostomy in patients with SARS CoV2-related. Vol. 277, European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2020. p. 2403-4.

[124] Siempos II, Ntaidou TK, Filippidis FT, Choi AMK. Effect of early versus late or no tracheostomy on mortality and pneumonia of critically ill patients receiving mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med. 2015 Feb;3(2):150-8.

[125] Romero J, Vari A, Gambarrutta C, Oliviero A. Tracheostomy timing in traumatic spinal cord injury. Eur Spine J [Internet]. 2009 Oct 5 [cited 2018 Oct 6];18(10):1452-7. Available from: <http://link.springer.com/10.1007/s00586-009-1097-3>

[126] Brook AD, Sherman G, Malen J, Kollef MH. Early versus late tracheostomy in patients who require prolonged mechanical ventilation. Am J Crit Care [Internet]. 2000 Sep [cited 2018 Oct 7];9(5):352-9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10976359>

[127] Jeon Y-T, Hwang J-W, Lim Y-J, Lee S-Y, Woo K-I, Park H-P. Effect of Tracheostomy Timing on Clinical Outcome in Neurosurgical Patients. J Neurosurg Anesthesiol [Internet]. 2014 Jan [cited 2018 Oct 7];26(1):22-6. Available from: <https://insights.ovid.com/crossref?an=00008506-201401000-00005>

[128] Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ* [Internet]. 2005 May 28 [cited 2018 Oct 7];330(7502):1243. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15901643>

[129] Robba C, Galimberti S, Graziano F, Wieggers EJA, Lingsma HF, Iaquaniello C, et al. Tracheostomy practice and timing in traumatic brain-injured patients: a CENTER-TBI study. *Intensive Care Med.* 2020 May;46(5):983-94.