Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Optimal Oxygen Saturation Range for Adults Suffering from Traumatic Brain Injury: A Review of Patient Benefit, Harms, and Guidelines

DATE: 11 April 2014

CONTEXT AND POLICY ISSUES

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults in the developed world.[1] While the prevalence of TBI in Canada is unknown, studies have estimated that the annual incidence in Canada of severe TBI is 11.4 per 100,000, and of mild TBI is 600 per 100,000.[2] TBI occurs as a result of an initial physical insult (primary injury), with the pattern and extent of damage depending on the nature, intensity, and duration of impact.[1,3] Neurological injury progresses over hours or days, with secondary injury occurring as a result of inflammatory and neurotoxic processes.[1] Secondary injuries include cerebral edema, hematomas, intracranial hypertension, infection, and seizures.[3]

TBI can be classified by severity using the Glasgow Coma Scale (GCS), which is a sum of three subscales: eye, motor, and verbal.[1] TBI is classified as mild (GCS 13 to 15), moderate (GCS 9 to 13), and severe (GCS < 8).

Patients with severe head injury often will have other traumatic injuries, making the management of TBI a complex process. One of the primary goals of prehospital management is to prevent hypoxia (PaO_2 < 60 mm Hg; O_2 saturation < 90%), a major cause of secondary injury after TBI.[1] Hypoxia can be reversed by aggressive airway management to increase oxygen tension.[4] While the association between hypoxia and poor outcomes from TBI has been well documented, less is known about the impact of other oxygen levels on patient outcomes.[4]

The purpose of this review is to examine the clinical outcomes and safety of different oxygen saturation levels in adults with TBI. The guidelines associated with oxygen saturation for adults with TBI will also be examined.

RESEARCH QUESTIONS

1. What are the patient benefits and harms of high oxygen saturation compared with lower oxygen saturation for adults suffering from traumatic brain injury?

2. What are the guidelines associated with oxygen saturation for adults suffering from traumatic brain injury?

KEY FINDINGS

According to retrospective studies, hyperoxia appears to be associated with a lower likelihood of in-hospital survival compared to normoxia in patients with traumatic brain injury (TBI). One guideline recommends that an oxygen saturation of < 90% be avoided in patients with severe TBI.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Heath Devices Gold), Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 11, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults ≥ 18 years of age who have suffered a traumatic brain injury (TBI)
Intervention	High oxygen saturation (hyperoxia)
Comparator	Lower oxygen saturation (normoxia)
Outcomes	Patient benefits and harms, guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to 2009.

Critical Appraisal of Individual Studies

The quality of included non-randomized studies were evaluated using the Downs and Black instrument.[5] Guidelines were assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.[6] A numeric score was not calculated for each study. Instead, strengths and limitations of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 170 citations. Upon screening titles and abstracts, 165 citations were excluded and five potentially relevant articles were retrieved for full-text review. Three additional reports were retrieved through grey literature searching. Of the eight potentially relevant reports, five did not meet the inclusion criteria. Three publications were included in this review. The study selection process if outlined in a PRISMA flowchart (Appendix 1). Two non-randomized studies and one guideline met inclusion criteria.

Summary of Study Characteristics

Details on study characteristics can be found in Appendix 2.

Study design

Two retrospective observational studies were included in this review.[7,8] One retrospective study used a prospectively compiled database of patients from multiple critical care units across all disciplines.[7] The other retrospective study reviewed consecutive patients that were admitted to a trauma center.[8] One evidence-based guideline was also included in this review.[9]

Country of origin

Both retrospective studies were conducted in the United States.[7,8] The guideline was from the United States and produced by the Work Loss Data Institute.[9]

Patient population

One retrospective study included ventilated patients ≥ 17 years of age with TBI consecutively admitted to an adult intensive care unit (ICU).[7] The median age was 41 years (IQR 25 to 58 years) and the majority of patients were female (79%). The median baseline GCS of patients was 7 (IQR 3 to 12).

Another retrospective study included patients with severe TBI, defined as a head Abbreviated Injury Score of ≥ 3, consecutively admitted to a single trauma center who survived past 12 hours.[8] The mean age of patients was 41 years and the majority of patients were male (77%). The mean baseline GCS of patients was 8.3.

The guideline focused on workers with occupational head trauma.[9]

Interventions and comparators

Both retrospective studies defined three oxygen exposure groups a priori using partial pressure of oxygen (PaO_2). The multicenter retrospective study defined hyperoxia as a $PaO_2 \geq 300$ mm Hg and hypoxia as a $PaO_2 < 60$ mm Hg.[7] The single-center retrospective study defined hyperoxia as a $PaO_2 > 200$ mm Hg and hypoxia as a $PaO_2 < 100$ mm Hg.[8] Normoxia was defined as a PaO_2 in between hyperoxia and hypoxia in both studies. In the single-center retrospective study, PaO_2 values were obtained from arterial blood gas measurements a mean of 4.3 times per patient during the first 24 hours of admission.[8]

Outcomes measured

The multicenter retrospective study used in-hospital case fatality as a primary outcome, and also examined hospital length of stay (LOS), and whether patients were discharged with independent status (living at home and requiring no assistance in completing the activities of daily living).[7] The single-center retrospective study examined mortality, ICU LOS, hospital LOS, and discharge GCS score as outcomes.[8]

The guideline provided recommendations for the initial management and treatment of pain and symptoms of workers with head trauma or headache.[9] Recommendations were not graded.

Summary of Critical Appraisal

Details on critical appraisal can be found in Appendix 3.

Both retrospective studies used a large sample size (N > 1000) and defined hyperoxia, normoxia and hypoxia a priori.[7,8] One retrospective study used a multicenter database, while the other study used a single-center database, which may limit generalizability of results. As these were retrospective observational studies, there were several limitations linked to the study design such as a lack of randomization and blinding, and possibility of confounding. The multi-center study reported sensitivity analyses while the single center study did not. The single center study did not report the proportion of patients with a severe GCS score, and hospital and ICU length of stay for individual oxygen exposure groups.

The guideline was based on a literature search, but it was unclear whether this was a true systematic review as articles outside of their pre-specified criteria were also included if there was a limited number of articles pertaining to a topic.[9] A list of included studies was not presented. The evidence was weighted according to a pre-defined scheme, but recommendations were not graded. Patient preferences and views were not taken into consideration and the costs and barriers to guideline implementation were not evaluated or reported.

Summary of Findings

Details on study findings can be found in Appendix 4.

<u>What are the patient benefits and harms of high oxygen saturation compared with lower oxygen saturation for adults suffering from traumatic brain injury?</u>

The multicenter retrospective study found that there was a statistically significantly greater proportion of ventilated patients with TBI admitted to an ICU in the hyperoxia ($PaO_2 \geq 300$ mm Hg) group that met the primary outcome of in-hospital fatality than the normoxia (> 60 mm Hg to < 300 mm Hg) group (crude OR 1.5, 95% CI 1.1 to 2.5; $P = 0.013$).[7] Using Kaplan-Meier survival curves, the proportion of survivors at 30 days after admission was found to be statistically significantly higher in the normoxia group compared to the hyperoxia group (log-rank $P < 0.0001$).There was no statistically significant difference in in-hospital fatality between the hyperoxia and hypoxia ($PaO_2 < 60$ mm Hg) groups ($P = 0.03$, did not meet the $\alpha = 0.017$ significance level). A multivariable sensitivity analysis was conducted to control for confounding variables such as age, co-morbidities, GCS score, and mean arterial pressure. Hyperoxia was found to be an independent predictor of death when adjusted for the probability of being exposed to hyperoxia. There was no statistically significant difference between hyperoxia and normoxia groups in hospital length of stay and in the proportion of surviving patients that were discharged with independent status.

The single-center retrospective study found that there was a statistically significantly greater proportion of patients that met the outcome of in-hospital mortality in the hyperoxia ($PaO_2 > 200$ mm Hg) group compared to the normoxia (PaO_2 100 mm Hg to 200 mm Hg) group (OR 1.50, 95% CI 1.15 to 1.97, $P = 0.003$).[8] A statistically significantly greater proportion of patients in the hyperoxia group had a discharge GCS score of 3 to 8 than in the normoxia group (OR 1.52, 95% CI 1.18 to 1.96, $P = 0.001$). A statistically significantly smaller proportion of patients in the hyperoxia group had a hospital length of stay greater than seven days than the normoxia group (OR 0.75, 95% CI 0.60 to 0.94, $P = 0.01$), but this may be due to the differences in mortality between the groups. There was no statistically significant difference between the hypoxia and normoxia groups in ICU length of stay.

What are the guidelines associated with oxygen saturation for adults suffering from traumatic brain injury?

One evidence-based guideline was identified from the Work Loss Data Institute (WLDI).[9] The WLDI recommends that “hypoxia (apnea, cyanosis, or an oxygen saturation < 90% in the field or a partial pressure of oxygen in arterial blood < 60 mm Hg) be monitored and scrupulously avoided, if possible, or corrected immediately in severe traumatic brain injury patients.” The WLDI also recommends that “mean arterial blood pressure should be maintained above 90 mm Hg through the infusion of fluids throughout the patient’s course to attempt to maintain cerebral perfusion pressure greater than 60 mm Hg.” There were no guidelines identified that gave recommendations regarding an upper oxygen saturation limit in patients with TBI.

Limitations

Only retrospective observational studies were identified regarding patient benefit and harms of high oxygen saturation levels compared to lower oxygen saturation levels in patients with TBI. Retrospective studies are subjected to many limitations, including a risk of confounding. One retrospective study reported sensitivity analyses to control for these risks. Both retrospective studies had differing definitions of hyperoxia, normoxia and hypoxia and different proportions of males and females, making it difficult to compare results across studies. In addition, deaths that occurred beyond the hospital stay were not documented, meaning that overall TBI-related mortality may not have been captured.

All of the included studies were conducted in the United States, limiting the generalizability of findings to the Canadian context where practices may differ. One study was conducted in multiple centers in a general ICU setting, which would suggest that patients may have been requiring ventilation for physiological reasons outside of a brain protective strategy.[7]

There were no guidelines identified that specified an upper oxygen saturation limit in patients with TBI. The included guidelines did not provide a grading system to denote the strength of their recommendations.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

According to two retrospective observational studies, hyperoxia appears to be associated with a lower likelihood of in-hospital survival compared to normoxia. As the definitions of hyperoxia and normoxia differed between the studies, it is difficult to define a specific oxygen saturation level above which the maximal risk of death would occur.

The Work Loss Data Institute recommended that hypoxia be avoided in patients with severe TBI (oxygen saturation < 90% or PaO_2 < 60 mm Hg) and that the PaO_2 be maintained above 90 mm Hg through the infusion of fluids. There were no guidelines identified that gave recommendations regarding an upper oxygen saturation limit in patients with TBI.

All of the included studies were conducted in the United States, limiting generalizability to the Canadian context.

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REFERENCES

1. Dinsmore J. Traumatic brain injury: an evidence-based review of management. Contin Educ Anaesth Crit Care Pain. 2013;13(6):189-95.

2. Canadian Institute for Health Information. The burden of neurological diseases, disorders and injuries in Canada [Internet]. Ottawa: CIHI; 2007. [cited 2014 Mar 28]. Available from: https://secure.cihi.ca/free_products/BND_e.pdf

3. Haddad SH, Arabi YM. Critical care management of severe traumatic brain injury in adults. Scand J Trauma Resusc Emerg Med. 2012;20:12.

4. Davis DP, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma. 2009 Dec;26(12):2217-23.

5. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2014 Apr 9];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

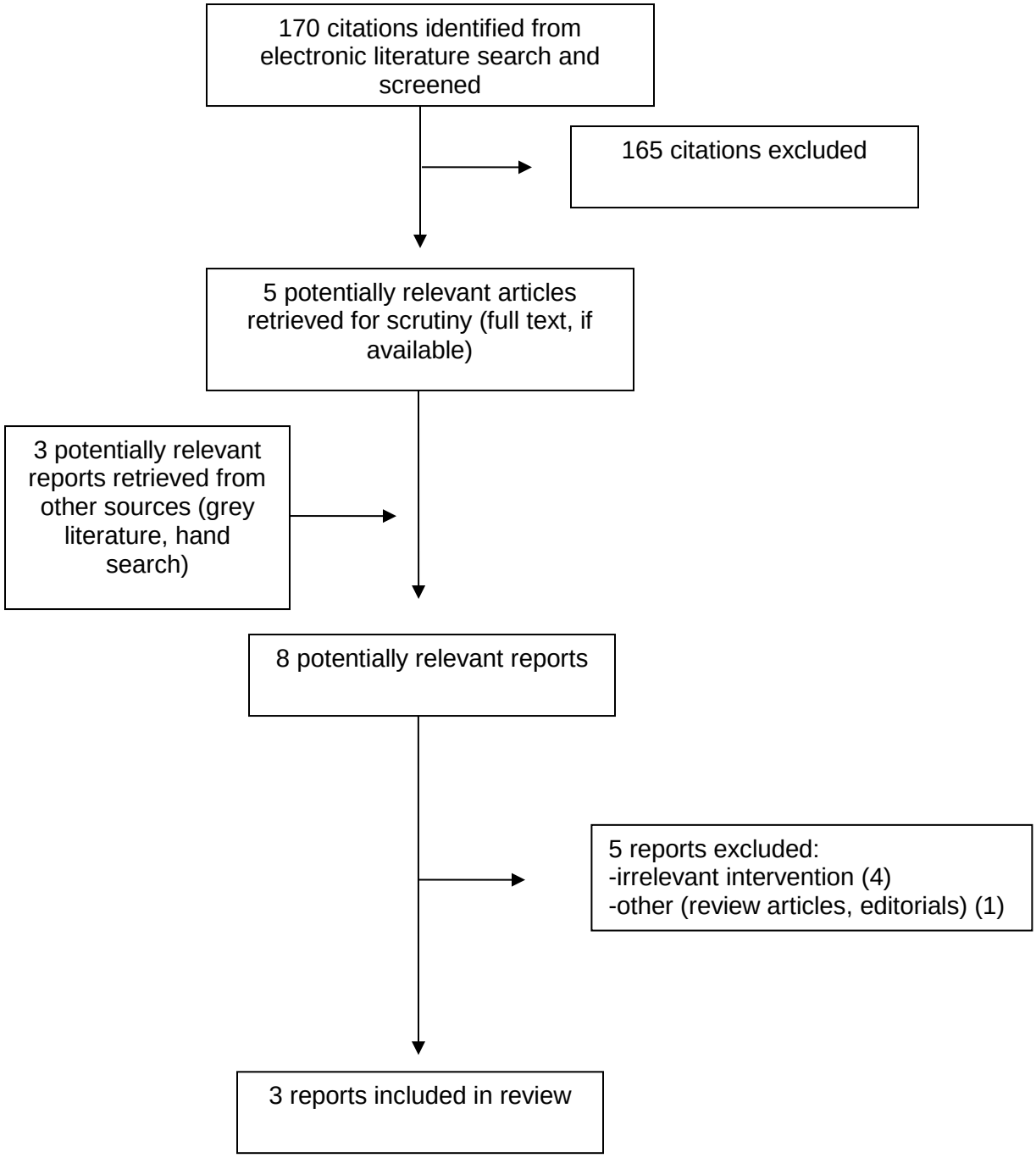
6. The AGREE Next Steps Consortium. Appraisal of guidelines for research and evaluation II [Internet]. London (UK): The AGREE Research Trust; 2009 May. [cited 2014 Apr 11]. Available from: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf

7. Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study. J Neurol Neurosurg Psychiatry. 2013 Jun 21.

8. Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Association between early hyperoxia and worse outcomes after traumatic brain injury. Arch Surg [Internet]. 2012 Nov 1 [cited 2014 Mar 17];147(11):1042-6. Available from: http://archsurg.jamanetwork.com/article.aspx?articleid=1216545

9. National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); [1997] -. Head (trauma, headaches, etc., not including stress & mental disorders); 2011 [cited 2014 Mar 25]. Available from: http://www.guideline.gov/content.aspx?id=33180

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Study Characteristics

Characteristics of included non-randomized studies

First Author, Publication Year, Country	Study Design and Length	Patient Characteristics	Intervention and Comparator(s)	Clinical Outcomes Measured
Rincon[7] 2013 USA	Retrospective study using a prospectively compiled and maintained registry (adult ICUs from 131 US hospitals) 2003-2008	1212 ventilated patients with TBI ≥ 17 years consecutively admitted to an ICU; median age 41 years (IQR 25-58 years); 79% female; median GCS 7 (IQR 3-12)	Hyperoxia (PaO_2 ≥ 300 mm Hg) n = 256 (21%); mean PaO_2 423 ± 83 mm Hg Normoxia (60 mm Hg ≤ PaO_2 < 300 mm Hg) n = 403 (33%); mean PaO_2 212 ± 49 mm Hg Hypoxia (PaO_2 < 60 mm Hg) n = 553 (46%); mean PaO_2 126 ± 86 mm Hg	In-hospital case fatality, discharged with independent status, hospital LOS
Brenner[8] 2012 USA	Retrospective study of a single trauma center June 2002-June 2007	1547 consecutive patients with severe TBI (head Abbreviated Injury Score ≥ 3) who survived past 12 hours after hospital admission; mean age 41.3 ± 20.6 years; 77% male; mean GCS 8.3 ± 4.7; mean ISS 31.9 ± 12.5	Hyperoxia (PaO_2 > 200 mm Hg) n = 666 (43%) Normoxia (PaO_2 100-200 mm Hg) n = 778 (50%) Hypoxia (PaO_2 < 100 mm Hg) n = 103 (7%) PaO_2 values obtained from arterial blood gas measurements a mean (SD) of 4.3 (3) times per patient during the first 24 hours of admission – values were averaged	In-hospital mortality, ICU LOS, hospital LOS, discharge GCS score

GCS = Glasgow Coma Scale; **ICU** = intensive care unit; **ISS** = Injury Severity Score; **IQR** = interquartile range; **LOS** = length of stay; **PaO_2** = partial pressure of oxygen; **TBI** = traumatic brain injury

Characteristics of included evidence-based guidelines

First Author, Publication Year, Country	Objective	Target Population	Outcome
Work Loss Data Institute[9] 2011 USA	To offer evidence-based step-by-step decision protocols for the assessment and treatment of workers' compensation conditions	Workers with occupational head trauma or headache	Effectiveness of treatments for relief of pain and symptoms

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Non-randomized studies		
Rincon[7] 2013	• Large, multicenter sample size (N=1212) • Interventions and outcomes were clearly defined a priori • Multivariate sensitivity analyses were performed to assess internal validity	• No randomization or blinding • Retrospective study • Deaths occurring outside of the hospital setting were not documented • Database consisted of patients from hospitals in the US only, so results may not be generalizable to other settings
Brenner[8] 2012	• Large sample size (N=1547) • Interventions and outcomes were clearly defined a priori	• No randomization or blinding • Retrospective study • Database used patients in the US only, so results may not be generalizable to other settings • Sensitivity analyses were not reported • Data was not reported for hospital and ICU length of stay, and for proportion of patients with severe GCS score by group
Guideline		
Work Loss Data Institute[9] 2011	• Objective and patient population clear described • Selection criteria clearly described • Evidence was weighted according to a rating scheme • Guidelines were peer reviewed	• Recommendations were not graded • Patient preferences and views not taken into consideration • Costs and barriers of guideline implementation not evaluated • Included studies were not presented

APPENDIX 4: Summary of Findings

Summary of non-randomized studies

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Rincon[7] 2013	The Bonferroni method was used for multiple pairwise comparisons. For the three exposure groups, α = 0.017 (0.05/3) was accepted. **In-hospital case fatality, n (%)** Hyperoxia (N = 256): 80 (32), p = 0.013 (vs normoxia) Normoxia (N = 403): 90 (23) Hypoxia (N = 553): 224 (40), p < 0.0001 (vs normoxia), p = 0.003 (vs hyperoxia) Crude OR of hyperoxia vs normoxia: 1.5 (95% CI 1.1 to 2.5), p = 0.01 Kaplan-Meier survival estimates and log-rank tests were used for time to in-hospital case fatality. The proportion of survivors at 30 days was statistically significantly higher in the normoxia group compared to the hyperoxia group (log-rank p < 0.0001) **Median hospital length of stay, days (IQR)** Hyperoxia: 6 (2, 16) Normoxia: 10 (4, 17) Hypoxia: 7 (2, 17) No statistically significant difference between hyperoxia and normoxia groups. **Survivors with independent status, n (%)** Hyperoxia: 51 (20), p = 0.6 (vs normoxia) Normoxia: 89 (22) Hypoxia: 71 (13), p = 0.0003 (vs normoxia) **Sensitivity analysis** Predictors of hyperoxia exposure: GCS < 8; mean arterial pressure < 60 mm Hg; hypothermia; abnormal arterial blood gas. The adjusted OR for in-hospital case fatality for hyperoxia vs. normoxia was similar (1.4, 95% CI 1.01 to 2.3).	"In this large multi-centre cohort study of ventilated TBI patients admitted to an ICU, we have demonstrated that exposure to hyperoxia was prevalent and associated with lower likelihood of survival after hospital admission. Similarly, contrary to our a priori assumption, we demonstrated after controlling for confounding variables and for hospital-specific characteristics in a robust multivariable analysis that exposure to hyperoxia was an independent predictor of in-hospital case fatality." (p. 5)
Brenner[8] 2012	**Mortality, n (%)** Hyperoxia (N = 666): 207 (31) Normoxia (N = 778): 191 (25) Hypoxia (N = 103): 39 (38) **Hyperoxia versus Normoxia, OR (95% CI)** Mortality: 1.50 (1.15, 1.97), p = 0.003 Discharge GCS score 3-8: 1.52 (1.18, 1.96), p = 0.001 Hospital LOS > 7 days: 0.75 (0.60, 0.94), p = 0.01 ICU LOS > 7 days: 0.92 (0.74, 1.15), p = 0.46	**"**Hyperoxia within the first 24 hours of hospitalization worsens short-term functional outcomes and increase mortality after TBI." (p. 1045)

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	Hyperoxia versus Hypoxia, OR (95% CI) Mortality: 0.59 (0.35, 1.00), p = 0.05 Discharge GCS score 3-8: 0.81 (0.48, 1.37), p = 0.44 Hospital LOS > 7 days: 1.90 (1.22, 2.96), p = 0.005 ICU LOS > 7 days: 2.26 (1.38, 3.70), p = 0.001	

GCS = Glasgow Coma Scale; **ICU** = intensive care unit; **IQR** = interquartile range; **LOS** = length of stay; **OR** = odds ratio

Summary of guidelines

Guideline Society, Country, Author, Year	Recommendations
Work Loss Data Institute[9] 2011 USA	"Hypotension (systolic blood pressure < 90 mm Hg) or hypoxia (apnea, cyanosis, or an oxygen saturation < 90% in the field or a partial pressure of oxygen in arterial blood < 60 mm Hg) must be monitored and scrupulously avoided, if possible, or corrected immediately in severe traumatic brain injury patients." "Mean arterial blood pressure should be maintained above 90 mm Hg through the infusion of fluids throughout the patient's course to attempt to maintain cerebral perfusion pressure greater than 60 mm Hg."