

# Clinical Relevance of Blood Glucose Concentration and Hyperglycemia Management in Neurocritical Care Patients

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## Abstract

### Keywords

- ▶ acute brain injury
- ▶ blood glucose concentration
- ▶ insulin infusion therapy
- ▶ neurocritical care

In patients admitted to a neurocritical care (NCC) unit, management of blood glucose concentration (BGC) is a challenging clinical task. Several studies have shown that episodes of hypo- and hyperglycemia and high BGC variability are associated with poor short- and long-term outcomes. Optimal BGC target-range and BGC management in NCC patients have dramatically evolved in the past decades and new insulin infusion and adequate nutrition protocols are now available. The aim of this narrative review is to report the state-of-the-art on clinical relevance on BGC and hyperglycemia management in NCC patients.

## Introduction

In patients with acute brain injury (ABI) admitted to neurocritical care (NCC), the management of blood glucose concentration (BGC) is a controversial topic and a challenging clinical task.<sup>1–4</sup> It is well established that hypoglycemia—defined as BGC < 80 mg/dL—is a risk factor for cerebral dysfunction.<sup>1</sup> Hypoglycemia exerts its effects on the central nervous system through three mechanisms: induction of a systemic stress response (increased sympathetic tone), increase in cerebral blood flow, and modification of cerebral energy metabolism by use of nonglucose substrates (pyruvate, glycogen, ketone bodies, glutamate, glutamine, and aspartate).<sup>2</sup> More recently, also hyperglycemia and high BGC variability have been shown to predict adverse outcomes in patients with ABI due to various causes: traumatic brain injury (TBI), acute ischemic stroke (AIS), intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), etc.<sup>1,3</sup> Hyperglycemia in ABI is exacerbated primarily through the activation of the hypothalamo–hypophyseal–adrenal axis, consecutively by elevated cortisol secretion and induction of gluconeogenesis.<sup>4</sup>

Optimal BGC target-range and BGC management in NCC patients have dramatically evolved in the past decades

and new information on insulin infusion therapy and the relevance of adequate nutrition protocol are now available.<sup>3,5</sup>

A literature search of PubMed online medical database and EMBASE online medical database was performed in December 2018 using the following keywords: blood glucose concentration, acute brain injury, and insulin infusion therapy. A total of 256,452 results were obtained, and after screening and assessing the titles, abstracts, and full-texts, 38 manuscripts were retrieved.

In this narrative review, we report the state-of-the-art on clinical relevance on BGC and hyperglycemia management in NCC patients.

### Clinical Relevance of BGC in NCC Patients

In this section, evidence related to the predictive value of BGC abnormalities at admission (BGC within the first 24 h) and during NCC stay, including hypo- and hyperglycemia and high glucose variability, will be presented (▶ **Tables 1** and **2**).

### Predictive Value of BGC Abnormalities at NCC Admission

In patients admitted to NCC with mixed ABI diagnosis, both hyper- and hypoglycemia at admission predict mortality and neurological functional outcome.<sup>6–17</sup>

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**Table 1** Predictive value of BGC abnormalities at NCC admission

Authors	Year of publication	Type of study	Number of patients	ICU/NCC patients	Objective of the study	Outcome(s)	p-Value
Walia and Sutcliffe <sup>6</sup>	2002	Retro-spective study	338	NCC	Hyperglycemia in the first 24 h and outcome in severely head injured adults	Mortality increases linearly as blood glucose increase	< 0.0001
Liu-DeRyke et al <sup>7</sup>	2009	Retro-spective study	380	NCC	BGC at admission and mortality and poor outcomes in TBI	Higher BGC (> 160 mg/dL) at admission and during the first 24 h of admission had higher mortality and poor outcome irrespective of severity of injury	< 0.001
Melo et al <sup>8</sup>	2010	Retro-spective study	286	NCC	High BGC at admission and in the first 48 h and outcome measured with GOS in children with severe TBI at hospital discharge and 6 months later	High BGC at admission is associated with mortality and bad outcome	< 0.001
Bhattacharjee et al <sup>9</sup>	2014	Pro-spective study	200	NCC	Relationship between intraoperative blood glucose variability in nondiabetic patients and severity, type of brain trauma, and patients' demographic variables	Independent predictors of intraoperative hyperglycemia are severe head injury (GCS < 9) and acute subdural hemorrhage	=0.001 (severity) =0.005 (type of trauma)
Bosarge et al <sup>10</sup>	2015	Retro-spective study	626	NCC	Stress-induced hyperglycemia vs. diabetic hyperglycemia in severe TBI patients	Patients with stress-induced hyperglycemia have higher mortality rate than diabetic hyperglycemia patients	< 0.04
Rau et al <sup>11</sup>	2017	Retro-spective study	1798	NCC	Stress-induced hyperglycemia vs. diabetic hyperglycemia in severe TBI patients	Stress-induced hyperglycemia patients have 6.6-fold higher odds of mortality compared to diabetic hyperglycemia patients	< 0.001
Salehpour et al <sup>12</sup>	2016	Pro-spective study	80	NCC	Relationship between serum BGC at admission and outcome in TBI patients	No differences reported in terms of mortality rate, GCS, BGC at discharge	> 0.05
Lee et al <sup>13</sup>	2010	Pro-spective study	1387	NCC	Relationship between BGC at admission and mortality in ICH patients	High admission BGC was associated with early and long-term mortality	< 0,001
Wu et al <sup>14</sup>	2012	Retro-spective study	62	NCC	BGC at admission and outcome after discharge in patients with acute cerebellar hemorrhage	BGC > 140 mg/dL on arrival is an independent risk factor for poor outcome	=0.008
Appelboom et al <sup>15</sup>	2011	Pro-spective study	104	NCC	Relationship between BGC at admission and clinical and radiographic parameters in ICH patients	Admission hyperglycemia is associated with poor outcome and the presence of intraventricular extension	< 0.04
Sun et al <sup>16</sup>	2016	Pro-spective study	2951	NCC	Relationship between admission BGC and clinical outcomes in diabetic and nondiabetic patients with ICH	Elevated admission BGC confers a higher risk of poor outcome at 3 months in nondiabetics than diabetics with similar glucose level with ICH	< 0.002
Kim et al. <sup>17</sup>	2016	Retro-spective study	538	NCC	Relationship between BGC at admission and 3-month mortality in patients with spontaneous supratentorial ICH	Admission BGC >134 mg/dL is associated with higher 3-month mortality	= 0.001

Abbreviations: BGC, blood glucose concentration; GCS, Glasgow coma scale; GOS, Glasgow outcome score; ICH, intracranial hemorrhage; NCC, neurocritical care; TBI, traumatic brain injury.

**Table 2** Predictive value of BGC abnormalities during ICU/NCC stay

Authors	Year of publication	Type of study	Number of patients	ICU/NCC patients	Objective of the study	Outcome(s)	p-Value
Elkon et al <sup>18</sup>	2014	Retrospective study	271	NCC	Relationship between high BGC and poor outcome in pediatric TBI	Severe hyperglycemic patients had a poorer outcome compared with the mild hyperglycemia group	> 0.05
Bian et al <sup>19</sup>	2013	Prospective study	239	NCC	Relationship between fasting glucose level on admission, day 14 or their variation and 1-year mortality in patients with aSAH	Fasting glucose level on admission day 14 or their variation are independent risk factors for death at 1 year	< 0.01
Koga et al <sup>20</sup>	2015	Prospective study	176	NCC	Relationship between BGC at admission and during the initial 72 h after acute ICH and outcomes in terms of hematoma expansion and disability (measured with modified Rankin scale)	High blood glucose levels at admission and 72 h were independently associated with higher disability at 3-month follow-up, but not with hematoma expansion	< 0.01
Sugiura et al <sup>21</sup>	2016	Prospective study	204	NCC	Clarify the predictors of symptomatic intracranial hemorrhage after endovascular treatment in patients with acute AIS	Patients with mild hyperglycemia had extremely higher risk of symptomatic intracranial hemorrhage compared to patients with normal BGC	< 0.04
Egi et al <sup>22</sup>	2010	Retrospective study	4,946	ICU	Relationship between moderate hypoglycemia and increased risk of death in ICU patients	Higher mortality in patients with moderate hypoglycemia	< 0.001
Krinsley et al <sup>23</sup>	2011	Retrospective study	6,240	ICU	Relationship between hypoglycemia (BGC < 70 mg/dL) and ICU-LOS	Patients with hypoglycemia had longer ICU LOS	< 0.0001
Naidech et al <sup>24</sup>	2009	Prospective study	172	NCC	Hypoglycemia and neurologic outcomes in patients with SAH	Progressive reductions of BGC (< 80 mg/dL) are associated with increasing functional disability at 3 months after SAH	< 0.001
Graffagnino et al <sup>25</sup>	2010	Retrospective study	3,709	ICU	Relationship between IIT and short-term outcome	The likelihood of mortality increased proportionally as the severity of hypoglycemia worsened	< 0.04
Hermanides et al <sup>26</sup>	2010	Retrospective study	5,728	ICU	Glucose variability in ICU population and mortality	Patients with higher mean glucose variability per hour have higher incidence of death	< 0.001
Matsushima et al <sup>27</sup>	2012	Retrospective study	109	NCC	Impact of glucose variability on long-term functional outcome of patients with TBI	Glucose variability is associated with lower GOSE score	< 0.04
Okazaki et al <sup>28</sup>	2016	Retrospective study	122	NCC	Increased glucose variability and neurological outcome in patients with aSAH	Glucose variability is associated with worse neurological outcome	< 0.04

Abbreviations: aSAH, acute subarachnoid hemorrhage; BGC, blood glucose concentration; GOSE, extended Glasgow outcome score; ICH, intracranial hemorrhage; ICU, intensive care unit; IIT, intensive insulin therapy; LOS, length of stay; NCC, neurocritical care; TBI, traumatic brain injury.

In a retrospective study including 338 severe brain injured patients, severe hyperglycemia (BGC >180 mg/dL) was associated with increased morbidity (risk of brain edema, reduction in cerebral perfusion, inflammatory reaction) and

mortality.<sup>6</sup> In patients with TBI, severe and mild hyperglycemia predicts increased mortality and worse neurological outcome. In a retrospective observational study, data from 380 adult TBI patients were reviewed and demonstrated

that mild hyperglycemia (BGC > 160 mg/dL) was associated with a higher mortality.<sup>7</sup> Also in pediatric TBI patients, severe hyperglycemia (BGC > 200 mg/dL) at admission and in the first 48 hours after arrival to NCC was associated with increased mortality and worse neurological outcome (Glasgow outcome scale [GOS] at discharge and at 6 months) as reported in data from a retrospective study in 286 children with severe TBI (Glasgow coma scale [GCS] < 8).<sup>8</sup> In patients with TBI, hyperglycemia-induced “secondary brain damage” is caused by multiple mechanisms and involves the increased lactate/pyruvate ratio that results in cerebral metabolic acidosis and ultimately neuronal cell death.<sup>9</sup> In patients with TBI, increased mortality associated with hyperglycemia seems to correlate more with stress-induced hyperglycemia rather than with diabetic hyperglycemia. In a retrospective study, data analysis from 626 patients with severe TBI showed that admission hyperglycemia, with BGC > 200 mg/dL, was associated with increased mortality in patients with stress-induced hyperglycemia more than that in nondiabetic normoglycemic patients; while there was no difference in mortality between nondiabetic normoglycemic and diabetic hyperglycemia patients.<sup>10</sup> This result was confirmed by a retrospective study in 1,798 patients with moderate-to-severe TBI that showed a 6.6-fold higher mortality in severe stress-induced hyperglycemia (BGC > 200 mg/dL) than in severe diabetic hyperglycemia.<sup>11</sup> Evidence on hyperglycemia-associated worse outcome in TBI patients was partly challenged by a prospective study that included 80 patients with severe TBI (GCS < 8 at admission) and reported no differences in functional outcome at hospital discharge (measured by GOS) between patients presenting normal or high BGC.<sup>12</sup> The relatively limited number of recruited patients, the heterogeneity of clinical conditions at NCC admission, and the short follow-up might have prevented to detect differences between the groups. In patients with TBI, also severe hypoglycemia (BGC < 60 mg/dL) has been proven to predict higher mortality. In a retrospective observational study, data from 380 TBI patients were reviewed and demonstrated that severe hypoglycemia—when detected within the first 24 h after NCC admission—was associated with a higher mortality and worse clinical course in terms of longer mechanical ventilation and intensive care unit (ICU) and hospital stay.<sup>7</sup>

Also, in patients with ICH, severe and mild hyperglycemia at NCC admission is associated with higher mortality and worse functional outcome. A prospective study that reported data from 1,387 patients with ICH demonstrated that mild hyperglycemia (BGC > 160 mg/dL) at NCC admission was an overall independent predictor of early mortality at 30 days of follow-up.<sup>13</sup> In the same study, the analysis of the clinical course in nondiabetic hyperglycemic patients showed a BGC-dependent increase in long-term mortality.<sup>13</sup> This evidence was confirmed in 62 patients with ICH in whom mild hyperglycemia (BGC > 140 mg/dL) at NCC arrival independently predicted increased mortality and worse neurological outcome.<sup>14</sup> Also in 104 patients with ICH, severe hyperglycemia (BGC > 180 mg/dL) at admission independently predicted higher mortality and worse functional outcome at 3 months, and correlated with severity of intraventricular hemorrhage.<sup>15</sup> In 2,951 patients

with ICH, mild hyperglycemia (BGC > 136 mg/dL) at NCC admission independently predicted 3 months mortality and worse neurological outcome evaluated by modified Rankin Scale functional status. In the same study, patients without a previous history of diabetes had a higher risk of mortality and poor outcome when compared with diabetic patients.<sup>16</sup> More recently, the relevance of BGC > 136 mg/dL at NCC admission in patients with ICH was further confirmed in a retrospective data analysis of 538 cases in whom the 3-month mortality increased in a dose-dependent manner (hazard ratio: 1.004; per 1 mg/dL increase).<sup>17</sup>

To conclude, the actual state-of-the-art evidence in literature supports that both hyperglycemia and hypoglycemia at NCC admission of adult and pediatric ABI patients (TBI, acute subarachnoid hemorrhage [aSAH], ICH, and AIS) correlate with higher morbidity (worse GOS, longer length of stay [LOS], etc.) and mortality.

**Predictive Value of BGC Abnormalities during ICU/NCC Stay**  
During NCC stay, patients with TBI, ICH, SAH, or AIS who present BGC abnormalities (hyperglycemia, hypoglycemia, and glucose variability) have worse clinical course.<sup>18–28</sup>

In 271 pediatric patients with moderate-to-severe TBI, severe hyperglycemia (BGC > 200 mg/dL) was associated with poorer neurologic outcome than in those presenting mild hyperglycemia (BGC: 110–160 mg/dL) and normal glycemia.<sup>18</sup> Similarly, in patients with aSAH, ICH, and AIS, hyperglycemia was found to be a strong predictor of worse clinical course. A prospective study including 239 patients with aSAH evaluated the relationship between BGC at admission and BGC abnormalities during the first 14 days of NCC stay and correlation with 1-year mortality.<sup>19</sup> In these patients, fasting glucose level at admission and extent of BGC abnormalities were independent risk factors for death at 1 year. In a prospective observational study that included 176 patients with ICH, the relationship between severe hyperglycemia (BGC > 200 mg/dL) at 24 hours and 72 hours and functional outcomes at 3 months (measured as death and disability) was studied and showed an inverse relationship between good functional status at follow-up and BGC values at 24 hours and 72 hours after admission and a positive relationship between BGC at 24 hours after admission and death.<sup>20</sup> In 204 patients with AIS undergoing endovascular treatment, mild hyperglycemia (BGC ≥ 160 mg/dL) independently predicted occurrence of symptomatic intracranial hemorrhage within 24 hours from symptoms onset when compared with normoglycemic patients.<sup>21</sup>

Hypoglycemia, in general ICU and in NCC patients (with SAH, mixed ABI), predicts increased mortality, poor neurological outcome, and longer LOS. In two retrospective observational studies that enrolled 4,946 and 6,240 general ICU patients, an episode of mild hypoglycemia (BGC < 82 mg/dL) was independently associated with an increased risk of death and longer ICU-LOS than in patients who did not present hypoglycemia.<sup>22,23</sup> Also in patients with SAH, as reported by a prospective study that included 172 patients, there was a relationship between mild hypoglycemia (BGC < 80 mg/dL), the clinical course (intended as radiographic

cerebral infarction and vasospasm), and functional neurological outcomes (measured through modified Rankin Scale at 14 days, 28 days, and 3 months). Patients with at least one episode of mild hypoglycemia had more radiographic cerebral infarction and symptomatic vasospasm and worse functional neurological status at 3 months follow-up.<sup>24</sup> In 3,709 mixed neurological and neurosurgical patients admitted in NCC, there is a positive relationship between hypoglycemic episodes and mortality before as proven in a prospective study designed to evaluate the impact of intensive insulin therapy (IIT) protocol implementation. The severity of hypoglycemia was defined as moderate (BGC < 70 mg/dL), severe (BGC < 40 mg/dL), and extreme (BGC < 20 mg/dL). The implementation of IIT protocol was associated with an increased incidence of hypoglycemic episodes. Furthermore, mortality increased proportionally with the severity of hypoglycemia.<sup>25</sup>

High blood glucose variability in ICU/NCC patients correlates with mortality and with a worse neurological outcome in NCC patients affected with TBI and SAH. Data from a retrospective study including 5,728 ICU patients treated with a computerized insulin algorithm (target BGC 72–126 mg/dL) evaluated the relationship between glucose variability and ICU and in-hospital mortality. The glucose variability was calculated as mean absolute glucose change per hour and standard deviation. The highest mean absolute glucose change per hour was correlated with ICU mortality.<sup>26</sup> Also in patients with TBI, as reported by a retrospective study including 109 patients, glucose variability predicts worse long-term functional outcome (Extended Glasgow Outcome Scale [GOSE] at a median of 6 months after injury). The glucose variability was calculated by standard deviation and percentage of excursion from the target BGC range. In these patients, higher mean BGC, percentage of excursion > 60%, and single episode of BGC < 60 mg/dL correlated with a lower GOSE score.<sup>27</sup> The predictive value of glucose variability was also confirmed in patients with SAH as reported by a retrospective study that included 122 patients.<sup>28</sup> The glucose variability was an independent predictor of unfavorable neurological outcomes in patients who presented BGC values in the 80 to 139 mg/dL range. This predictive value was not confirmed in patients presenting BGC > 140 mg/dL.

To conclude, the actual state-of-the-art evidence in literature supports that BGC abnormalities (hyperglycemia, hypoglycemia, and high glucose variability) in both adults and pediatric ICU/NCC patients correlate with higher morbidity (worse GOS and modified Rankin Scale, higher hematoma expansion, higher LOS, etc.) and mortality.

### Hyperglycemia Management in NCC

In this section, evidence related to conventional or intensive glycemic control, optimal glycemic target range, and nutrition supply in general ICU and NCC patients will be presented (► Tables 3 and 4).

#### Conventional versus Intensive Glycemic Control and Optimal Glycemic Range

In general ICU patients, IIT aimed to tight glycemic control is associated with lower morbidity and mortality and a higher

rate of severe hypoglycemia.<sup>29,30</sup> In 2001, a seminal randomized controlled trial (RCT) by Greet van den Berghe and her group enrolling 1,548 ICU patients, originally demonstrated that patients assigned to IIT, titrated to BGC between 80 and 110 mg/dL, had lower mortality and morbidity (bloodstream infections, acute renal failure, red-cells transfusions, and polyneuropathy) than those assigned to conventional insulin therapy (CIT), in whom insulin was administered when BGC > 215 mg/dL to maintain BGC between 180 and 200 mg/dL.<sup>29</sup> This study was an irreversible step to reconsider the conventional approach to BGC management and insulin use in ICU patients, but had several controversial aspects and most important, only a fraction of enrolled patients suffered from ABI (63 patients). In 2009, a larger RCT—that enrolled 6,104 ICU patients—was conducted by NICE-SUGAR study investigators.<sup>30</sup> Primary end point was comparison of 90-day mortality in patients receiving IIT (BGC, 81–108 mg/dL) or CIT (< 180 mg/dL). In CIT group, insulin infusion was discontinued when BGC < 144 mg/dL. Authors found that patients receiving IIT had a higher mortality rate and more severe hypoglycemic episodes (BGC < 40 mg/dL) compared to patients treated with CIT. There was no difference in the median ICU-LOS or the median number of days of mechanical ventilation.

In general ICU patients, optimal BGC target range evolved: relationship between mortality and hypo/hyperglycemic episodes was described by a “U”-shaped curve; the lower the target range of BGC, the higher was the risk to induce hypoglycemia.<sup>5,31,32,33</sup> An editorial reported lower incidence of hyper/hypoglycemia and glucose variability for BGC target range between 140 mg/dL and 180 mg/dL in general ICU patients, whereas more recent evidence suggested that BGC target range between 129 mg/dL and 145 mg/dL was more effective, as it reduced the risk of hypoglycemia and hospital mortality rate.<sup>5,31</sup> In trauma patients without TBI, BGC < 140 mg/dL reduced mortality. An RCT enrolling 2,038 general ICU patients divided them into three different BGC target range groups (group H < 200 mg/dL; group M < 150 mg/dL; group L < 120 mg/dL) and evaluated the incidence of hypoglycemia, morbidity and mortality.<sup>32</sup> Group L had a higher incidence of moderate and severe hypoglycemia (< 60 mg/dL; < 40 mg/dL). There were no differences among the groups in terms of morbidity and mortality. A retrospective study including general ICU patients reported that there was a “U”-shaped relationship between mortality and hypo/hyperglycemia during admission (BGC < 120 and > 170 mg/dL respectively).<sup>33</sup>

In NCC patients, IIT aimed to tight glycemic control was associated with a higher risk of inducing hypoglycemia.<sup>3,34</sup> The use of IIT has also been re-evaluated in NCC patients.<sup>3</sup> An RCT conducted in severe TBI patients (GCS ≤ 8) assigned to receive IIT to maintain BGC between 80 mg/dL and 120 mg/dL or CIT to maintain BGC < 220 mg/dL showed that hypoglycemia incidence (BGC < 80 mg/dL) was higher in the IIT group, ICU-LOS was shorter in the IIT group, whereas infection rate and mortality at 6 months were similar in the two groups.<sup>34</sup> Another RCT conducted 1 year later, enrolled 483 NCC patients (ICH, neurovascular disease, tumor, and trauma) undergoing neurosurgery and compared the IIT approach titrated to BGC between 80 mg/dL and 110 mg/dL to the CIT

**Table 3** Conventional versus intensive glycemic control and optimal glycemic range

Authors	Year of publication	Type of study	ICU/NCC patients	Objective of the study	Outcome(s)	p-Value
van den Berghe et al <sup>29</sup>	2001	RCT	ICU	IIT (BGC 80–110 mg/dL) vs. CIT (BGC 180–200 mg/dL) in terms of mortality and morbidity	IIT group had lower mortality and morbidity	≤ 0.02
NICE-SUGAR Study Investigators et al <sup>30</sup>	2009	RCT	ICU	IIT (BGC 81–108 mg/dL) vs. CIT (BGC ≤ 180 mg/dL) in terms of mortality within 90 days	IIT group had higher mortality rate	=0.02
Al-Tarifi et al <sup>31</sup>	2011	RCT	ICU	IIT (BGC 80–110mg/dL) vs. CIT (BGC 180–200 mg/dL) in terms of mortality rate and hypoglycemia incidence	BGC ≤ 146mg/dL reduces mortality and hypoglycemia incidence	≤ 0.02 (mortality) < 0.0001 (hypoglycemia)
Okawa et al <sup>32</sup>	2013	RCT	ICU	Three groups with different target BGC: group H < 200 mg/dL; group M < 150 mg/dL; group L < 120 mg/dL to evaluate incidence of hypoglycemia, morbidity, and mortality	Higher incidence of moderate and severe hypoglycemia in group L; no differences in morbidity and mortality rate	< 0.01
Siegelaar et al <sup>33</sup>	2010	Retrospective study	ICU	Effects of hypo/hyperglycemia in admission on mortality rate	“U”-shaped relationship between hypo/hyperglycemia (BGC < 120 mg/dL and >170 mg/dL) and mortality rate	=0.001 (hypoglycemia) < 0.001 (hyperglycemia)
Bilotta et al <sup>34</sup>	2008	RCT	NCC	IIT (BGC < 220 mg/dL) vs. CIT (BGC 80–120 mg/dL) in terms of hypoglycemia incidence, ICU-LOS, infection and mortality rate	IIT group had higher hypoglycemia incidence, shorter ICU-LOS, while infection and mortality incidence were similar among the groups	< 0.0001 (hypoglycemia) < 0.05 (ICU-LOS) > 0.05 (infection/mortality)
van Iersel et al <sup>35</sup>	2012	Retrospective study	NCC	To identify risk factor for hypoglycemia incidence	The reduction in nutrition calories supply and/or gastric residual without insulin dose reduction	< 0.04
Bilotta and Rosa <sup>5</sup>	2012	Editorial	ICU/NCC	Management of BGC in ICU/NCC patients	“Advanced” BGC target range: 129–145mg/dL	—
Bilotta et al <sup>36</sup>	2015	RCT	ICU	Comparison of pharmacodynamic of Humulin insulin (regular) and Humalog insulin (short acting) in patients receiving IIT	Humalog insulin had less profound carryover effect and shorter duration of carryover	< 0.001

Abbreviations: BGC, blood glucose concentration; CIT, conventional insulin therapy; ICU, intensive care unit; IIT, intensive insulin therapy; LOS, length of stay; NCC, neurocritical care; RCT, randomized controlled trial.

approach to maintain BGC < 215 mg/dL.<sup>3</sup> The IIT group had shorter ICU-LOS and infection rate and higher hypoglycemia incidence (BGC < 50 mg/dL), whereas the 6-month GCS score and mortality were similar. Of note, risk factors for mild hypoglycemia (BGC < 80 mg/dL) in NCC patients who received IIT were reviewed in a retrospective case-control study that included 786 patients with nervous system disorders.<sup>35</sup> The results from this study demonstrate that to reduce the nutrition calories supply without a simultaneous insulin dose reduction as an hyperglycemic event in the previous 24 hours or the presence of gastric residual in the previous 6 hours without insulin dose reduction is associated with an increase in the incidence of hypoglycemia.

In NCC patients, insulin infusion should be started when BGC ≥ 180 mg/dL and should be stopped when BGC ≤ 140 mg/dL.<sup>1</sup> Some studies recommend IIT to manage BGC in NCC patients.<sup>1,5,36</sup> In these cases, a different approach should be applied to prevent iatrogenic-induced hypoglycemia. Here are some tips: subcutaneous and intravenous injecting insulin bolus and infusing high glucose concentration solution should be avoided; continuous parenteral/enteral nutrition (PN and EN) and (near) continuous glucose monitoring should be used to maintain BGC in the optimal target range and to reduce BGC variability; shorter acting insulin formulation should be used as it leads to better outcomes compared with regular insulin formulation because of the quicker on

**Table 4** Nutrition (enteral vs. parenteral)

Authors	Year of publication	Type of study	ICU/NCC patients	Objective of the study	Outcome(s)	p-Value
Desai et al <sup>37</sup>	2014	Review	ICU	Comparison of EN and PN	Use of EN whenever possible	—
Bilotta and Rosa <sup>1</sup>	2010	Review	ICU/NCC	Management of BGC using IIT	Continuous EN/PN when IIT is instituted	—
Tripathy <sup>38</sup>	2018	Review	ICU	Complications associated with EN or PN	EN and PN are associated with different complications	—
Gramlich et al <sup>39</sup>	2004	Review	ICU	Comparison of EN and PN	EN caused less infectious complications and PN was associated with higher incidence of hyperglycemia. There was no difference in mortality rate or ICU-LOS	0.004 (infectious complications) < 0.04 (hyperglycemia incidence) 0.7 (mortality rate) 0.6 (ICU-LOS)
Härtl et al <sup>40</sup>	2008	Prospective study	NCC	Effect of timing and quantity of nutrition on death within the first 2 weeks of injury	Patients who were not fed within 5 and 7 d after TBI had a two- and fourfold increase of mortality respectively and every 10-kcal/kg decrease in caloric intake was associated with a 30–40% increase in mortality	< 0.04
Carney et al <sup>41</sup>	2017	Guidelines	NCC	Management of severe TBI patients	Reduced mortality if an appropriate nutrition approach is started at least by the 5th day and at most by the 7th day post-injury.	—

Abbreviations: EN, enteral nutrition; ICU, intensive care unit; IIT, intensive insulin therapy; LOS, length of stay; NCC, neurocritical care; PN, parenteral nutrition; TBI, traumatic brain injury.

and offset time; and more dilute insulin preparations (50 UI in 500 mL instead of 50 UI in 50 mL) should be used.

To conclude, the actual state-of-the-art evidence in literature supports the use of IIT in order to maintain BGC < 146 mg/dL. We recommend maintaining BGC between 90 and 140 mg/dL using the right approach, in order to reduce incidence of iatrogenic-induced hypoglycemia.

### Nutrition (Enteral versus Parenteral)

In general ICU patients, guidelines recommend the use of EN whenever possible, while EN and PN are both associated with complications.<sup>1,37–39</sup> Despite there are no conclusive data that demonstrate a PN superiority as compared with EN, available guidelines in general ICU patients recommend the preferential use of EN, whenever possible.<sup>37</sup> In NCC patients, the priority is to warrant an adequate nutrition supply in a timely manner; therefore, EN/PN should be started when needed, with a particular approach of continuous EN/PN if IIT is instituted.<sup>1</sup> A narrative review reported that EN was associated with fewer infections, greater feasibility, and lower costs.<sup>38</sup> Both EN and PN are associated with different complications that the caregiver must be vigilant for: (enteral) insertion problems, accidental removal, ulceration, tissue necrosis along the pathway of the tube, nausea, bloating, diarrhea, aspiration, gastric infection, etc.; (parenteral) insertion of central venous access, pneumothorax, vascular/neural injury, arrhythmias, venous thrombosis, sepsis at site of central venous catheter, etc.<sup>38</sup> Furthermore, a systematic review of RCTs reported that

PN was associated with higher incidence of hyperglycemia, while mortality, days on a ventilator, and ICU-LOS were similar among patients receiving EN or PN.<sup>39</sup> A prospective study enrolling 797 patients with severe TBI showed that patients who were not fed within 5 and 7 days after TBI had a two- and fourfold increase in mortality, respectively, and every 10-kcal/kg decrease in caloric intake was associated with a 30 to 40% increase in mortality.<sup>40</sup> To conclude, TBI guidelines delivered by Brain Trauma Foundation suggest an appropriate nutrition approach at least by the 5th day and at most by the 7th day post-injury in severe TBI patients to decrease mortality with a level IIA evidence indication.<sup>41</sup>

### Conclusion

In this narrative review, we report evidence related to the predictive value of BGC abnormalities (hyperglycemia, hypoglycemia, and high BGC variability) and optimal management of insulin infusion and nutrition supply in patients admitted to general ICU and to NCC with ABI. Several and consistent studies demonstrate that BGC values at admission and during ICU/NCC stay have a strong predictive value on the clinical course and short- and long-term outcomes.<sup>8–20</sup> In NCC, evidence on optimal BGC target range and on the use of IIT has evolved over the course of past two decades and current information supports to maintain BGC values < 146 mg/dL with IIT. At the same time, the importance of adequate and timely delivered nutrition, either through PN

or EN supply, is now confirmed, and to establish early and appropriate nutrition in patients with ABI caused by TBI has now been included among the suggested approaches in the guideline delivered by Brain Trauma Foundation with a level IIA evidence indication.<sup>41</sup>

## Future Perspective

NCC patients present some unique features, and within patients with ABI there are some differences between some of the subgroups (TBI, AIS, SAH, and ICH). In patients with ABI admitted to NCC, a careful BGC management is a priority. Available clinical evidence now supports the use of IIT in NCC patients. In this subset, the target BGC should be kept between 90 and 140 mg/dL to reduce the incidence of iatrogenic-induced hypoglycemia. This recommendation is a result of a critical study of the manuscripts retrieved and our experience in our own department. Of great importance is to run IIT only when an effective nutrition supplementation is established and to stop insulin infusion when BGC is lowering and reaches values < 140mg/dL to prevent iatrogenic-induced hypoglycemic episodes. Future studies should clarify the optimal timing and nutrition supply necessary to manipulate BGC in NCC patients. The development of “closed-loop systems” that regulate the calories supply and insulin infusion titrated by a “real-time” continuous BGC monitor might contribute to further optimize clinical management.

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### Conflict of Interest

None declared.

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