FLAGLER HOSPITAL PROTOCOL - MANAGEMENT OF ACUTE SPONTANEOUS INTRACRANIAL HEMORRHAGE

As with any protocol, this protocol serves to provide evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize as necessary the present protocol to meet individual patient needs. This Protocol is not intended to replace the physician's judgment; it is intended to provide guidance to the physician for the group of patients described in this Protocol.

This protocol is limited to spontaneous intracranial hemorrhage (ICH) that is not caused by a structural or traumatic cause such as head trauma, vascular malformation, saccular aneurysm, or hemorrhage-prone neoplasm.

In patients with hemorrhagic stroke is very important to develop a strategy to prevent, detect and correct secondary insults. For correct management, it is important to establish a strategy based on clinical stabilization, evaluation, and establishment of prognosis, avoiding secondary insults and adoption of specific individualized therapies, including hemostatic therapy, intensive control of elevated blood pressure and surgery when indicated. **Creation of a structured protocol is recommended by worldwide guidelines** (1 - 3).

OBJECTIVE:
To optimize the general care and physiological neuroprotection of patients with *acute spontaneous intracranial hemorrhage* at Flagler Hospital

The general care and physiological neuroprotection will be characterized by maintaining the following variables:

- Blood pressure control
- Reversal of anticoagulation and associated coagulopathies
- Neurosurgical interventions to reduce mortality and improve outcomes
- Maintenance of normothermia - Temperature less than 37.5 ℃ and evaluation and treatment of fever source
- Maintenance of euvolemia
- Maintenance of normoxemia: SaO2 greater than 94%
- Maintenance of normocapnia: PaCO2 35 to 40 mmHg
- Maintenance of glycemia: glucose 110 to 180 mg/dL
- Maintenance of normonatremia: sodium 135 to 145 meq/L
- Venous thromboembolism prevention
- Aspiration precautions
- Feeding must be supplied early

SCREENING:

All adult patients admitted to the hospital with suspected or confirmed diagnosis of *acute spontaneous ICH* will be eligible to be included in the protocol.

In patients presenting with stroke-like symptoms, a noncontrast CT brain will be performed to confirm the diagnosis of ICH.

MONITORING AND INTERVENTIONS:

- Guidelines from the American Heart Association (AHA) and American Stroke Association (ASA) recommend that patients with suspected or confirmed ICH receive monitoring and management in ICU (1).
- Consult neurosurgery and neurology for all patients admitted with diagnosis of ICH.
- Upon admission, the severity of ICH will be assessed in all patients using the ICH score (see Appendix 1).

Neuroimaging for ICH diagnosis and acute course

- Once the presence of intracranial hematoma is identified in the noncontrast CT brain by the radiologist, the volume of the hematoma will be determined by the radiologist using the ABC/2 method and markers of hematoma expansion such as heterogeneous densities within the hematoma or irregularities at its margins will be reported if applicable.
- Identification of patients with underlying macrovascular lesions is important because lesions such as arteriovenous malformations and aneurysms are associated with potential rebleeding that should be prevented.
- *To identify patients with underlying macrovascular lesions such as arteriovenous malformations and aneurysms and to exclude macrovascular causes of spontaneous ICH* (cerebral amyloid angiopathy, deep perforating vasculopathy, cavernous malformation, or malignancy), CT angiography (CTA) will be performed in patients with any of the following criteria:
- Lobar spontaneous ICH and age <70 years.
- Deep/posterior fossa spontaneous ICH and age <45 years.
- Deep/ posterior fossa and age 45 to 70 years without history of hypertension.

The likelihood of identifying an underlying structural lesion appears to be somewhat lower in unselected patients with ICH than in those in one of the higher risk categories listed above.

In patients without the above criteria, performing CTA to exclude macrovascular causes will be at the discretion of neurosurgery or neurology.

- Identification of a spot sign on CTA may help to identify patients at risk for hematoma expansion and will be reported by radiology if applicable.
- Although CTA does not appear to commonly trigger acute renal injury this risk remains a relevant consideration in obtaining this study.

In patients with suspected cerebral venous thrombosis, CT venography will be performed if recommended by neurosurgery or neurology.

In patients with spontaneous ICH with a negative CTA/venography, the need for magnetic resonance MRI/MRA will be at the discretion of neurosurgery or neurology.

In patients with spontaneous ICH and CTA or MRA suggestive of a macrovascular cause, catheter intra-arterial DSA should be performed as soon as possible to confirm and manage underlying intracranial

vascular malformations. If recommended by neurosurgery, patient will be transferred to tertiary center.

If a patient with spontaneous ICH and higher risk categories listed above *has a negative noninvasive imaging (CTA ± venography and MRI/MRA),* neurosurgery will determine the need for catheter intra-arterial digital subtraction angiography (DSA) to exclude a macrovascular cause and transfer to tertiary center.

In patients with spontaneous IVH and no detectable parenchymal hemorrhage, catheter intra-arterial DSA is recommended to exclude macrovascular causes. If recommended by neurosurgery, patient will be transferred to tertiary center.

Repeat neuro-imaging studies
Follow-up noncontrast CT scans will be performed at ≈6 and 24 hours from time of initial CT and when any neurologic deterioration occurs to exclude hemorrhage expansion, hydrocephalus, or perihematomal edema, and document final ICH volume. The decision when to repeat the CT scan will be at the discretion of Neurosurgery.

Beyond the first 24 hours serial imaging will be guided by the clinical condition of the patient.

Medical and neurointensive treatment

The following steps must be applied in parallel rather than in sequence:

A. Assess vital signs and neurochecks every 15 min during the initial hour, then Q1H x4, Q2H x4, Q4H x72H and then per unit protocol, or more frequently when clinically indicated.

B. Keep head elevated 30 degrees and in midline position unless otherwise specified by practitioner. Head elevation and midline position are important because they affect the brain venous drainage and consequently the intracranial pressure (ICP).

C. STAT labs: CBC with platelets, PT/INR, PTT, CMP, troponin, toxicology screen, PCT, CRP and EKG will be requested upon admission if not already done to help identify the type of hemorrhage, active medical issues, and risk of unfavorable outcomes.

D. Monitor continuous O2 Saturation in all patients and end-tidal CO2 when feasible. Administer oxygen by nasal cannula to hypoxemic patients. Hypoxemia is defined as "O2 sat less than 94% on room air." If supplemental oxygen is required, communicate this to practitioner. Routine supplemental oxygen is not required acutely in non-hypoxemic patients.

E. Determine if intubation is required to assure adequate oxygenation and ventilation, prevent aspiration, and manage increased intracranial pressure. As a general rule all patients in coma should be intubated.

Following a lung and brain protective strategy including use of physiologic tidal volume (6 ml/Kg IBW), lowest FIO2 possible and level of PEEP to maintain a plateau pressure less than 30 and driving pressure less than 15. Therapeutic targets will be directed at:

1. Maintain SaO2 greater than 94%. Tissue hypoxia is known to be detrimental but also brain hyperoxia is associated with deleterious effect including promoting inflammation through activation of free radicals.

2. Maintain normal levels of CO2 (PaCO2: 35 to 40 mm Hg) since hypercapnia causes cerebral vasodilatation and increase in ICP, whereas hypocapnia causes vasoconstriction triggering cerebral ischemia.
3. Selection of PEEP will be of paramount importance because it can affect the brain venous drainage and consequently the ICP (higher PEEP can decrease cerebral venous drainage).

F. Keep euvolemia with balance solutions (plasmalyte or LR) or NS, on average at 30 ml/Kg/d plus unusual losses.

G. Blood pressure management.

All patients who require treatment with continuous intravenous antihypertensive medications should undergo placement of an intra-arterial catheter for BP monitoring and those who need vasopressor therapy should have a midline, PICC line or central venous catheter unless contraindicated following the established Flagler Infusion Service Protocol.

In patients in whom acute BP lowering is considered, treatment should be initiated as soon as possible reaching SBP target within 1 hour to reduce the risk of hematoma expansion and improve functional outcome.

1. Management of hypertension.

In general, the goal is to maintain the SBP within a range between 110 and 180 mmHg

a. In patients with mild to moderate severity presenting with SBP between 150 and 220 mmHg.
- Acute lowering of SBP to a target of 140 mm Hg with the goal of maintaining in the range of 130 to 150 mm Hg would be attempted.
- Acute lowering of SBP to <130 mm Hg is potentially harmful.

b. In patients with large and more severe ICH or those requiring surgical decompression, or those with SBP >220 mm Hg, who may be more susceptible to cerebral perfusion compromise attributable to high ICP, the safety and efficacy of early intensive blood pressure lowering is not established.
- Cautious BP lowering would be attempted. Acute lowering of SBP to a target of 160 mm Hg with the goal of maintaining in the range of 140 to 180 mm Hg would be reasonable to attempt.

c. In patients with large ICH (>30 mL) requiring ICP monitoring or severe IVH requiring EVD, BP reduction should be accompanied by maintenance of cerebral perfusion pressure of 60 to ≥70 mm Hg. Placement of ICP monitoring will be at the discretion of neurosurgery.
- Nicardipine: Start at 5 mg/hr and titrate by 2.5 mg/h every 15 minutes as needed to attain target blood pressure (as noted above). Maximum infusion rate of 15 mg/hr. Nursing to contact MD if goal is not attained at a dose of 15 mg/hr. Or,
- Labetalol: 20 mg IV every 10 minutes as needed to attain target blood pressure (as noted above), to a maximum total dose of 300 mg in 24 hours. Alternatively, can initiate a continuous IV infusion at 1 mg/min and titrate by 1 mg/min every minute as needed to attain goal blood pressure, to a maximum dose of 8 mg/min. Nursing to contact MD if goal is not attained at a dose of 8 mg/hr or if HR falls below 50.

- If the SBP level is still higher than the target, despite infusion of the maximum dose of Nicardipine or Labetalol for 30 minutes, add the second agent Labetalol or Nicardipine IV infusions.
- If BP not controlled despite combination of Nicardipine and Labetalol IV infusions for 30 minutes, consider IV sodium nitroprusside. Start IV infusion at 0.2 mcg/Kg/min and titrate by 0.2 mcg/kg/min every 3 minutes as needed to attain target blood pressure up to maximum dose of 10 mcg/Kg/min. Nursing to contact MD if target is not attained at a dose of 10 mcg/kg/min, or if a dose of greater than 2 mcg/kg/min is required for more than 1 hour.

2. **Management of hypotension** defined as SBP less than 110 mmHg or MAP less than 65 mmHg
    - **a.** Establish the etiology
    - **b.** Volume replenishment with isotonic crystalloids (normal saline, Lactated Ringers, or Plasmalyte) will be the first approach.
    - **c.** If hypotension persists after correction of volume deficit, continuous infusions of vasopressors (Norepinephrine or phenylephrine) should be started:
        - Norepinephrine IV infusion at 2 mcg/min and titrate by 2 mcg/min every 3 minutes as needed to maintain SBP ≥ 110 mmHg or MAP ≥ 65 mmHg. If SBP remains < 110 mmHg or MAP < 65 mmHg with an infusion rate up to 30 mcg/min, contact the practitioner. Or,
        - If HR greater than 130 or patient has atrial fibrillation with rapid ventricular response, start Phenylephrine IV infusion at 30 mcg/min and titrate by 20 mcg/min every 3 minutes as needed to maintain SBP ≥ 110 mmHg or MAP ≥ 65 mmHg. If SBP remains < 110 mmHg or MAP < 65 mmHg with an infusion rate up to 300 mcg/min, contact the practitioner.

H. Reversal of anticoagulation and underlying coagulopathy

- All anticoagulant and antiplatelet drugs will be discontinued, and anticoagulant effect should be reversed immediately (1, 4) as guided by the Flagler Hospital Protocol for Reversal of Anticoagulation in Patients with Life Threatening Bleeding.
- Reversal of VKA-related ICH (to a goal INR <1.3) combined with BP control is associated with a significant reduction in hematoma expansion and lower in-hospital mortality.
- In patients with VKA-associated spontaneous ICH and INR ≥1.3, 4-F PCC (Kcentra) plus vitamin K will be used to achieve rapid correction of INR targeting value of <1.3 and limit hematoma expansion.
- In patients with DOAC- direct factor Xa inhibitor - associated spontaneous ICH, 4-F PCC (Kcentra) will be used to improve hemostasis. The balance of the expense against the benefit of using the specific reversal agent - andexanet alfa is not favorable.
- In patients with dabigatran-associated spontaneous ICH, idarucizumab is not available to improve hemostasis.
- In patients with unfractionated heparin or LMWH (enoxaparin) - associated spontaneous ICH, intravenous protamine will be used, not exceeding 50 mg/10 min because of the risk of hypotension and bronchoconstriction; repeated smaller doses will be preferable.
- For patients with spontaneous ICH being treated with antiplatelet agents and who require emergency neurosurgery, platelet transfusion will be given to reduce postoperative bleeding and mortality.

- For patients with spontaneous ICH being treated with antiplatelets agents and not scheduled for emergency surgery, platelet transfusions are potentially harmful and should not be administered unless patient has severe thrombocytopenia.
- For patients with spontaneous ICH being treated with antiplatelet agents, will use desmopressin to reduce the expansion of the hematoma.

I. Seizure prophylaxis and treatment

Current AHA/ASA guidelines recommend against the use of anti-epileptic drugs for seizure prophylaxis, as available evidence suggests that prophylaxis is associated with poorer outcomes. However, first RCT assessing the effects of seizures prophylaxis with levetiracetam in spontaneous ICH concluded that levetiracetam might be effective in preventing acute seizures (*Lancet Neurol 2022; 21: 781-91)*. Based on this study we recommend consideration for:

- Levetiracetam 500 mg every 12 h IV for at least 48 h, then transition to oral dosing at the same dosage after evaluation of swallowing function.
- Anti-epileptic therapy should always be used for treatment of known clinical or electrographic seizures. Current Guidelines recommend anti-epileptic treatment for up to one month, after which therapy should be discontinued in the absence of seizures.

J. Glycemic Control

Maintenance of normoglycemia: Both hyperglycemia and hypoglycemia should be avoided. Blood glucose will be maintained within a range of 110 to 180 mg/dL.

1. For glucose less than 70 mg/dl, institute the Flagler Hospital hypoglycemia protocol.
2. For glucose between 70 and 149 mg/dl continue monitoring per unit protocol
3. For glucose greater than 149 mg/dl, institute the standard Flagler Hospital sliding scale insulin dose regimen.
4. For glucose greater than 215 mg/dl for two consecutive tests institute continuous IV insulin infusion per Flagler hospital protocol.

K. Temperature Control

- Maintain temperature less than or equal to 37.5 degrees Celsius using PO/PR acetaminophen 650 mg every 6 hour as needed along with evaluation and treatment of fever source. If temperature remains elevated despite acetaminophen, consider external cooling.
- Clinical trial evidence does not support the benefit of therapeutic temperature modulation, either surface devices or catheter-based normothermia.

L. Serum Na levels

Maintain serum sodium to 135 to 145 mmol/L. Serum Na levels will be checked daily or more frequently if needed x 3 days and then on as needed basis.

M. Intracranial pressure monitoring and management

1. Elevate the head of the bed to 30 degrees with head midline, once hypovolemia is excluded and providing it is not stated as a contraindication.

2. Analgesia and sedation, particularly in unstable, intubated patients. Sedation and analgesia should be titrated to control pain and minimize ICP elevation, while still permitting clinical evaluation of the patient's neurologic status targeting RASS 0 to -1 and BPS less than or

equal to 3 per Flagler ABCDEF protocol. Consider neuromuscular blockade to reduce ICP only in patients who are not responsive to analgesia and sedation titrated to a RASS of -5.

3. Monitor and treatment of elevated ICP should be considered for comatose patients with GCS less than 8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus. ICP monitoring is encouraged in those patients that merit aggressive medical care and are suspected to have increased ICP. Placement of intraventricular catheter (ventriculostomy) will be at the discretion of Neurosurgery.

Therapies for reducing elevated ICP:
There is no clear evidence of superiority of either mannitol or hypertonic saline at reducing intracranial pressure. Either can be used to achieve plasma hyperosmolality (300 to 320 mOsm/L) and serum sodium to 145 to 155 mmol/L until the limit of serum osmolality of 320 mOsm/L or sodium 155 mmol/L respectively.

- **Hypertonic saline solution:**
  - 3% NaCl (513 mmol/L) 150 mL IV bolus over 10 to 15 min, or
  - 7.5% NaCl (1283 mmol/L) 75 ml over 20 min, or
  - 23.4% NaCl (4008 mmol/L) 30 mL over 2 to 10 min.
    - 7.5% NaCl and 23.4% NaCl will be given preferably through a PICC line or central venous access, but emergent use through a peripheral line can be authorized by the intensivist.
  - If Na levels persist below 145 mEq/L despite boluses administration of hypertonic saline solution, a titratable continuous infusion of 3% NaCl at initial rate of 30 – 50 ml/h targeting serum Na levels of 145-155 mmol/L and serum osmolality 300 – 320 mOsm/L can be used.
- **Mannitol 20%**
  - Initial 1 g/kg IV infusion over 30 min, followed by repeat dosing of 0.25 to 0.5 g/kg IV infusion over 30 min every six hours as needed. Check osmolarity and serum Na in 6 hours before additional doses. Hold for serum osmolality equal or greater than 320 mOsm/L or serum Na equal or greater than 155 mmol/L.
- Repeat hypertonic solution or mannitol dosing can be given as needed
- Check osmolarity and serum Na in 6 hours before additional doses.
  - Hold for serum osmolality equal or greater than 320 mOsm/L or serum Na equal or greater than 155 mmol/L.
- ICP measurement
  - Allows directed treatment of ICP and blood pressure
  - Goal of keeping ICP less than 20 mmHg and maintaining a cerebral perfusion pressure (CPP= MAP – ICP) of 60 to 70 mmHg.
  - Drainage of cerebrospinal fluid (CSF) is an effective means of lowering ICP
    - Drainage of CSF will be set to be drained intermittently at no more than 20 mL per hour to maintain the ICP less than 20 mmHg in those patients with intraventricular catheter (ventriculostomy) in place.
- After the above therapies have been maximized consider hyperventilation to a PaCO2 of 25 to 35 mmHg over 1 hour.

- Hyperventilation causes dramatic and rapid lowering of ICP, however, the effect only lasts for minutes to a few hours.

N. Surgery

The benefits of minimally invasive approaches for evacuation of supratentorial ICH and intraventricular hemorrhages to improve functional outcomes is uncertain. Compared with medical management alone, have demonstrated reductions in mortality but the evidence for improvement of functional outcome with these procedures is neutral.

- For patients with supratentorial ICH of >20- to 30-mL volume with GCS scores in the moderate range (5–12), minimally invasive hematoma evacuation with endoscopic or stereotactic aspiration with or without thrombolytic will be at the discretion of neurosurgery.

For patients with cerebellar hemorrhage, indications for immediate surgical evacuation with or without an external ventricular drain to reduce mortality will be at the discretion of neurosurgery. It will include:

- Larger volume (>15 mL).
- Neurological deterioration.
- Brainstem compression.
- Hydrocephalus.

In patients with spontaneous ICH or IVH and hydrocephalus that is contributing to decreased level of consciousness, ventricular drainage at the discretion of neurosurgery should be performed to reduce mortality.

O. Nutrition

- All patients will be placed on a strict nothing-by-mouth order until an assessment of the ability to swallow is completed.
- The swallow screening test 3-oz water challenge will be administered in all patients by nursing prior to the initiation of eating, drinking, or receiving oral medications unless there is an exclusion criterion (see appendix 2). If the patient does not meet criteria for the swallow screening, or does not pass the screening, an order will be submitted in Allscript for further assessment and dysphagia management by a speech therapist.
- Enteral feeding must be supplied early according to Flagler Hospital Protocol unless there is a concern for increased intracranial pressure with the placement of a nasogastric tube.

P. Venous thromboembolism prevention and treatment

- Patients should have intermittent pneumatic compression for prevention of venous thromboembolism beginning the day of hospital admission.
- After at least 48 hours and assurance of cessation of bleeding, chemical VTE prophylaxis with low-dose UFH or LMWH can be considered if agreed upon with Neurosurgery and Neurology as recommended in AHA/ASA 2022 guidelines (1).
- For patients with acute spontaneous ICH and DVT or PE, delaying treatment with UFH or LMWH for 1 to 2 weeks after the onset of ICH will be considered and temporary use of a retrievable filter will be indicated as a bridge until anticoagulation can be initiated.

Q. Mobilization

Mobilization will begin as soon as the patient's condition is considered stable following Flagler protocol. All patients will have PT-OT evaluation.

REFERENCES:

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2. Godoy DA et al. Steps to consider in the approach and management of critically ill patients with spontaneous intracerebral hemorrhage. *World J Crit Care Med*. 2015; 4(3): 213-229.
3. Andrews CH et al. Emergency Neurological Life Support: Intracerebral Hemorrhage. *Neurocrit Care*. 2012; 17: S37-S46
4. Frontera, JA et al. Guidelines for Reversal of Antithrombotic in Intracranial Hemorrhage. A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care* 2016; 24: 6–46.

Appendix 1

Intracerebral Hemorrhage (ICH) Score

The intracerebral hemorrhage (ICH) score is a prognostic model for predicting mortality among patients with spontaneous ICH. In an original study of 152 patients with ICH, the authors allocated points for Glasgow coma scale (GCS) score, ICH volume, presence of intraventricular hemorrhage (IVH), age, and infratentorial origin to predict 30-day mortality, which steadily increases with increasing scores.

Components for ICH score

GCS

- 3-4: 2 points
- 5-12: 1 point
- 13-15: 0 points

ICH volume

- ≥30 cm^3: 1 point
- < 30 cm^3: 0 points

IVH

- Yes: 1 point
- No: 0 points

Infratentorial origin of ICH

- Yes: 1 point
- No: 0 points

Age

Age 80 years or older: 1 point

Younger than 80 years: 0 points

Mortality rate based on ICH Score

ICH scores with corresponding mortality risk are as follows:

- 0 points: 0%
- 1 point: 13%
- 2 points: 26%
- 3 points: 72%
- 4 points: 97%
- 5 points: 100%
- 6 points: 100% (estimated)

Appendix 2

Exclusion Criteria for the swallow screening test 3-oz water challenge

Any YES answer to the following risk factors will defer administration of the swallow screening test 3-oz water challenge:

- Patient is unable to remain alert for testing
- Patient was eating a modified diet due to pre-existing dysphagia prior to intubation
- Patient has existing enteral tube feeding via stomach or nose
- Patient has a head-of–bed restriction less than 30 degrees
- Tracheostomy tube is present
- Patient is Nil per os by physician order
- Patient cannot follow simple commands