Neurocritical Care Management: Acute Ischemic Stroke

Joshua M. Levine, MD
Associate Professor
Chief, Division of Neurocritical Care
Co-Director, NeuroIntensive Care Unit
University of Pennsylvania
Presenter Disclosure Information

Joshua M. Levine, MD

Neurocritical Care Management of Acute Ischemic Stroke

FINANCIAL DISCLOSURE:

No relevant financial relationships exist
Background

• AIS patients are increasingly admitted to ICUs (15-20%)

• Care in a NeuroICU by trained neurointensivists may be associated with better outcome.

• The Joint Commission, 2011, comprehensive stroke center requires presence of “an intensive care unit for complex stroke patients that includes staff and licensed independent practitioners with expertise and experience to provide neurocritical care.”

Background

• Common indications for intensive care
  • Risk/presence of hemorrhagic transformation
  • Risk/presence of significant cerebral edema
  • Intubation due to brainstem stroke/compression
  • Hemodynamic instability (e.g. Afib w/RVR, MI)
  • Post-procedure, post-surgical care
Background

• Four authoritative sets of guidelines for management of AIS
• Relatively little robust data on ICU aspects of care
• Only 4 interventions are supported by class I evidence
  • Care on a stroke unit
  • IV r-tPA within 4.5 hours
  • Aspirin within 48 hours
  • Decompressive craniectomy for malignant hemispheric infarction
AIS: “routine” ICU issues

- Airway and ventilator
- Hemodynamic, cardiac, and fluid status
- Temperature and glucose
- Anemia and transfusion
- VTE prevention and treatment
- Seizures
- End-of-life care, organ donation
AIS-specific ICU issues

- Unstable (perfusional) exam, induced hypertension
- Hemorrhagic conversion
- Cerebral edema, brainstem compression, hydrocephalus
- Orolingual angioedema from r-tPA
- Post-surgical, post-IR
AIS:ICU issues

- The “routine” issues are boring but important and covered well in published guidelines.
- Far less data about many of the AIS-specific issues.
Agenda

- Review some of routine ICU management
- Management of massive stroke with brain swelling
- Is there a better way?
Airway, oxygenation, ventilation

1. Hypoxemia
2. Hypocapena
3. Intubation, tracheostomy
Hypoxemia, Hypercapnea

- Hypoxemia is common and adversely affects outcome
- Causes: Aspiration, infections, ALI/ARDS, PE, edema, OSA, altered central respiratory control
- Supplemental O\textsubscript{2} only if SpO\textsubscript{2} < 94%
- Upright position may improve hypoxemia - unclear effects on CBF
- Hypercapnea associated with poor outcome (despite increased CBF) - avoid
Intubation

- RSI preferred

- Prognosis in those requiring intubation is poor - up to 50% mortality within 30 days
Tracheostomy

• 15-35% require trach - usually w/severe dysphagia, bulbar palsies, prolonged mechanical ventilation

• Optimal timing of trach unknown - ongoing RCT, SETPOINT, assessing early trach vs. prolonged orotracheal intubation in patients w/ AIS, SAH, ICH
Hemodynamic optimization

1. Hypertension
2. Hypotension
3. Induced Hypertension
Blood Pressure

Monitoring and Outcome

• Regular BP monitoring should occur, typically by A-line

• Both very high and very low BP deleterious. There is a “U-shaped” relationship between blood pressure and outcome.

Stroke. 2002;33:1315-1320
Hypertension

- Approximately 85% AIS patients are hypertensive (SBP > 140 mmHg) at presentation

- Severe hypertension —> cardiac/pulmonary/renal complications, may exacerbate cerebral edema, ? hemorrhagic transformation

- Although hypertension associated with poor outcome, the impact of lowering BP is unclear.
Hypertension

• Current recommendations:

  • No thrombolytic therapy: permissive hypertension up to 220/120 mmHg unless contraindication (e.g. aortic dissection, MI). If BP is lowered, caution! (e.g. 15% in first 24 hours).

  • Thrombolytic therapy: BP should be stable at < 185/110 mmHg prior to r-tPA administration, then kept < 180/105 mmHg for first 24 hours.
Hypotension

- Mild/relative hypotension is associated with larger infarct volumes
- Frank hypotension should be treated in a cause-specific way
- Optimal pressor choice/combination unknown. Decide based on individual patient characteristics, pathophysiology of hypotension.
Induced Hypertension

• Should blood pressure be raised with pressors (induced hypertension) in patients with relative hypotension?

• Not routinely.

• Data derive from case reports, case series, small retrospective studies, very small randomized trials. No definitive conclusions may be made regarding safety and efficacy.
Fluid Management

1. Goals
2. Fluid composition
Fluid Balance

- Goal is euvoolemia.  **How can you tell??**
Fluid Composition, Administration

- IV fluids should be dosed each day and not delivered at a fixed dose.
- AIS patients have a relative hyper-viscous state. However, hemodilution does not improve outcome.
- Isotonic crystalloid (0.9 NS) is currently IVF of choice. Albumin has no incremental benefit on outcome (ALIAS).*
- Dextrose-containing fluids should be avoided unless hypoglycemia.

Glucose Control

1. Hyperglycemia
2. Intensive Insulin Therapy (IIT)
Hyperglycemia

• Hyperglycemia is common - occurs in up to 50%

• Independently associated with poor outcomes

  • Larger stroke, more infections, more death, more disability, more post-thrombolytic ICH, ? less effective r-tPA

• May vary by stroke type - suggestion that moderate hyperglycemia may be associated with favorable outcome after lacunar stroke.*

*Brain. 2007;130:1626-1630
Glucose Control

• Optimal glucose range unknown, treatment targets vary across guidelines, RCTs have been inconclusive.

• *Cochrane meta-analysis* (2011, n=1,296): IIT (72-135 mg/dl) increased risk of symptomatic hypoglycemia but did not affect functional outcome, death, or final neurological deficits.

• *INSULININFARCT trial* (2012, Stroke): IIT (< 126 mg/dl) provided superior control c/w SQ insulin but assoc. w/ larger infarct size. Similar SAE and mortality rates, not powered to detect clinical changes.

• *SHINE trial* (ongoing): multicenter RCT, IIT (80-130 mg/dL) vs. < 180 mg/dl.
Current AHA/ASA recommendations:

- Maintain glucose between 140 and 180 mg/dl with insulin infusion if needed.
Temperature Control

1. Fever
2. Therapeutic hypothermia
Fever

- Fever affects up to 50% and is strongly, consistently, and independently associated with poor outcome.

- Relative risk of poor outcome is 2.2 for every 1°C elevation in admission temperature!*

  - Evaluate and treat infectious causes.
  
  - Treat fever itself. No evidence that this improves outcome.
  
  - Antipyretic medications are largely ineffective (PAIS, PAIS II).
  
  - Consider using non-pharmacological means - little literature.

*Lancet 1996;347:422
Therapeutic Hypothermia

- The role of therapeutic hypothermia in AIS is unclear
- Feasibility studies: COOL-AID, ICTuS-L
- Ongoing studies:
  - ICTuS2/3: phase II/III trial comparing hypothermia and thrombolysis to thrombolysis alone
  - EuroHYO-1: phase III trial of hypothermia in patients eligible and ineligible for thrombolysis
Hemoglobin Management

1. Anemia
2. Transfusion
Anemia

• Anemia occurs in up to 97% of severe AIS patients in ICU

• Anemia → decreased tissue O$_2$ delivery.

• However, increased hemoglobin → hyper viscosity, which may exacerbate ischemia. There is a “U-shaped” relationship between hemoglobin and outcome.

Anemia might have a different impact on mortality after stroke at higher vs. lower values. Anemia may induce hypoxia at the most vulnerable regions when hemoglobin is reduced below a critical level, while high hemoglobin may increase blood viscosity, affect cerebral blood flow and be associated with pulmonary disease. Moreover, chronic high values might enhance cerebral atherogenesis leading to a diseased and dysfunctional collateral bed.

Potential limitations of this study should be considered. First, it is an observational study and therefore causality cannot be inferred from the observed associations. The effects of unmeasured confounding variables such as nutritional status, frailty, cognitive function or complex interactions between covariates on the observed association cannot be ruled out. Second, we were unable to examine whether the relationship was due to increased blood loss, impaired red blood cell production, and/or increased red blood cell destruction (in the case of low hemoglobin levels) or increased red cell production (in the case of high hemoglobin levels). Third, the use of blood transfusions was not considered.

Figure 2

Loess curve (with 95% confidence intervals) of hemoglobin concentrations versus the estimated probability all-cause death after 1-year.

Tanne et al. BMC Neurology 2010, 10:22

http://www.biomedcentral.com/1471-2377/10/22
Transfusion

- Transfusion (PRBC) —> increased viscosity; immune suppression, lack of efficacy (storage lesion)

- In general critical care, restrictive transfusion practice (hgb > 7) is preferred. Optimal hemoglobin range, transfusion trigger in AIS are unclear.

- Recommendation: avoid anemia, avoid “aggressive” transfusion practice.
Massive Brain Swelling

1. “Malignant” infarction
   A. Medical management
   B. Surgical management
"Malignant" Infarction

- Brain infarction with life-threatening space-occupying edema - usually due to occlusion of the ICA or proximal MCA
- Occurs in up to 10% of stroke patients
- Life-threatening edema usually occurs between 3-5 days after stroke onset - but may occur within 24 hours.
“Malignant” Infarction

• High risk of brain (uncal, subfalcine) herniation.

• Nearly 80% mortality rate

• No medical therapy has proven effective
“Malignant” Infarction

Clinical Features

- Declining level of consciousness
- Headache
- Nausea/vomiting
- Brainstem signs
- Paralysis ipsilateral to hemispheric infarction
- Cushing’s triad (hypertension, bradycardia, irreg respiration)
“Malignant” Infarction

Clinical Predictors

- Onset of nausea/vomiting within 24 hrs of symptom onset
- SBP $\geq$ 180 mmHg after 12 hrs from symptom onset
- History of hypertension
- History of heart failure
- Elevated white blood cell count
- Younger age
- No history of stroke
- Female sex
- Heart weight
- Abnormal ipsilateral circle of willis
- Carotid occlusion

“Malignant” Infarction

Radiological Predictors

• CT
  • Early hypodensity of > 50% MCA territory
  • Involvement of MCA + other territories
  • Midline shift of septum pellucidum of > 5 mm

• MRI
  • Infarct volume: DWI/ADC volume > 82 - 145 cm³
“Malignant” Infarction

Practical Predictors

- NIHSS > 15 for right-sided infarction
- NIHSS > 20 for left-sided infarction
- Major (> 50%) early CT changes
Medical Management

• Typically ineffective. May be harmful.

• Options:
  • Hyperventilation - transient, emergency, bridging measure
  • Osmotic therapy - mannitol, hypertonic saline
  • Hypothermia?
  • Barbiturates?
  • ICP monitoring - probably not
• Do NOT use steroids
Surgical Therapy

Craniectomy: Rationale

- Potential benefits/goals: To reduce ongoing injury through:
  - Immediate reduction in ICP
  - Improvement in blood flow
  - Herniation of brain out (through craniotomy defect) instead of in or down (through the tentorium, across the falx) - i.e. decompression of vital structures, esp. brainstem.
Decompressive Hemicraniectomy

Surgical Technique

- LARGE incision, LARGE bone flap
- Durotomy
- Resection of infarcted tissue?
- Bone flap stored in freezer or in abdominal pouch
- Cranioplasty in 1 - 3 months
Decompressive Hemicraniectomy

Surgical Technique

“Go big or go home!”
Decompressive Hemicraniectomy

Surgical Technique

“Go big or go home!”
Decompressive Hemicraniectomy

Important Questions

• Does DHC improve outcomes after stroke? Which outcomes?

• What factors guide patient selection?
  • Age?
  • Side of stroke?

• What is the optimal timing of DHC after symptom onset?
Decompressive Hemicraniectomy

Prospective Randomized Trials

- DECIMAL
- DESTINY
- HAMLET
- DESTINY II
Decompressive Hemicraniectomy

Pooled Analysis of 3 RCT

• Pre-planed (prospective) pooled analysis of the 3 European trials

• Individual data for patients aged 18-60 yo who had DHC w/in 48 hrs for large MCA infarction (either hemisphere)

• 1° outcome: 1-year dichotomized mRS (0-4 vs. 5 or death)

• 2° outcomes: a) 1-year case fatality; b) mRS 0-3 vs. 4-death

• 93 patients included in pooled analysis

• More patients in the surgical group had:
  • mRS ≤ 4 (75% vs. 24%, ARR 51%)
  • mRS ≤ 3 (43% vs. 21%, ARR 23%)

Decompressive Hemicraniectomy

Pooled Analysis of 3 RCT

Figure 1: Distributions of the scores on the mRS and death after 12 months for patients treated with or without decompressive surgery

Decompressive Hemicraniectomy

Pooled Analysis of 3 RCT

Numbers needed to treat:

• Need to treat 2 to prevent one death

• Need to treat 2 to prevent mRS 5 or death

• Need to treat 4 to prevent mRS 4 to death

Hemicraniectomy in Older Patients
with Extensive Middle-Cerebral-Artery Stroke

Eric Jüttler, M.D., Ph.D., Andreas Unterberg, M.D., Ph.D., Johannes Woitzik, M.D., Ph.D., Julian Bösel, M.D., Hemasse Amiri, M.D., Oliver W. Sakowitz, M.D., Ph.D., Matthias Gondan, Ph.D., Petra Schiller, Ph.D., Ronald Limprecht, Steffen Luntz, M.D., Hauke Schneider, M.D., Ph.D., Thomas Pinzer, M.D., Ph.D., Carsten Hobohm, M.D., Jürgen Meixensberger, M.D., Ph.D., and Werner Hacke, M.D., Ph.D., for the DESTINY II Investigators*

* A complete list of investigators in the Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery II (DESTINY II) study is provided in the Supplementary Appendix, available at NEJM.org.

NEJM. 2014;370(12):1091-1100
Decompressive Hemicraniectomy

DESTINY II: Older Adults

- RCT of early DHC vs. medical management in ICU for large MCA stroke in patients > 60 yo

- 1° endpoint: survival “w/o severe disability,” defined as mRS 0-4, at 6-months

- 2° endpoints: 12-month survival, NIHSS score, mRS score, Barthel index, quality of life (SF-36, EQ-5D), depression (HDRS), adverse events.

NEJM. 2014;370(12):1091-1100
Decompressive Hemicraniectomy

DESTINY II: Older Adults

- 112 patients randomized (surgery = 49, medical = 63)
- Treatment initiated within 48 hrs of symptom onset
- DSMB stopped recruitment after 82 patients (surgery = 40, medical = 42) had been assessed for 1° outcome

NEJM. 2014;370(12):1091-1100
No patients had mRS 0-2
Infecteds were more frequent in the hemicraniectomy group. In addition, 23 complications related to initial hemicraniectomy and bone-flap reimplantation were reported: 5 hemorrhages, 10 cases of pain requiring pharmacologic treatment, 1 hygroma, 1 incident related to anesthesia, and 6 non-specified events, 5 of which were classified as serious adverse events. The most frequent serious adverse events in the control group were nervous system disorders (mainly herniation and brain edema). Causes of death are listed in Table 3. An increased rate of early death due to herniation in the control group was the only major difference between the two treatment groups.

Discussion

The DESTINY II trial was stopped for reasons of efficacy after the reductions in deaths and severe disability at 6 months had become significant. This treatment effect remained stable after inclusion of all randomly assigned patients and after 12 months of follow-up.

The question of an age limit for hemicraniectomy in patients with malignant middle-cerebral-artery infarction is controversial among neurologists and neurosurgeons. The uncertainty about whether surgery is beneficial in older patients with stroke, for whom the overall prognosis is poorer than that for younger patients with stroke,
Decompressive Hemicraniectomy

DESTINY II: Older Adults

No. at risk
Hemicraniectomy    49  41  40  37  36  35  33  30  30  29  29  27  5  3
Control            63  24  22  20  18  18  17  15  15  15  15  7  5

NEJM. 2014;370(12):1091-1100
Decompressive Hemicraniectomy

• For large supratentorial stroke:
  • For age ≤ 60, 75% will survive, nearly half will be severely disabled, nearly half will have depression
  • For age > 60, less benefit
  • Decisions regarding DHC should be made on an individual basis
Cerebellar Infarction

- Often fatal due to small compartment (posterior fossa)
- Edema
  - Compression of 4th ventricle, non-communicating hydro
  - Direct compression of brainstem
  - Upward or downward cerebellar herniation
Suboccipital Craniectomy

• Less controversial than DHC
• Less evidence - a few case series
• Generally agreed that SOC is lifesaving
• Little data to guide timing, patient selection
Suboccipital Craniectomy
Penn Guideline

Cerebellar ischemic stroke

Mass effect?

No

Observe

Yes

- Hydrocephalus with 4th ventricle obliteration
- Neurologic deterioration referable to brainstem compression in opinion of treating physician
- Neurologic deterioration suspected due to brainstem compression that improves with osmotic therapy

Yes to ANY of above

Urgent decompressive surgery

No to ALL of above

Increasing edema on serial scans over 3-5 days post stroke onset?

Yes

Consider prophylactic decompressive surgery

No

Observe

Notes:
- Above applies only to patients who are suitable candidates for surgery
- Involvement of vermis is associated with increased risk of neurologic deterioration and should lower threshold for surgery
- For uncomplicated cases, single anti-platelet therapy or IV heparin may be started 3 days post-op if there is a strong clinical indication
Future Directions

1. New therapies
2. New approaches
New Therapies

- IV glyburide
- Selectively blocks recently characterized ion channel* that promotes cerebral edema

* sulfonylurea receptor 1-transient receptor potential melastatin 4
New Approaches

- Abandon the current paradigm
- What is the current paradigm?
The current paradigm: population-based medicine

- We study populations, derive correlations between physiological parameters and outcome, then force/fit those parameters to all patients.
What has the current paradigm done for us lately?

• Optimal treatment thresholds are undetermined, resulting in vague guidelines with poor evidence base.
What has the current paradigm done for us lately?

- Optimal treatment thresholds are undetermined, resulting in vague guidelines with poor evidence base.

- ALL neuroprotective therapy trials in AIS have failed.

  - Citicoline
  - GV150526
  - Lubeluzole
  - Selfotel
  - Apiganel
  - Trafermin/bFGF
  - Enlimomab
  - FK-506
  - MK801
Problems with the current paradigm

• One size does not fit all

• Major heterogeneity:
  • Baseline patient physiology
  • Pathophysiology
Why does the current paradigm fail?

“Acute Ischemic Stroke”

Should we expect a single drug to work for all of these diseases?

Does each of these strokes require the same glucose/lactate?
A New Paradigm:
Individualized Goal-Directed Cerebral Resuscitation

- Hypothesis: treatment approaches (algorithms) that are based on biologically relevant individual patient physiology are superior to those derived from the broad application of population derived “norms.”

- Corollary: monitoring physiology and modifying the approach based on observation is essential.
Conclusions

• Therapy for acute ischemic stroke is guided by published guidelines.

• While an increasing number of patients with AIS are admitted to intensive care units, there is a relative paucity of data to guide ICU management.

• Both medical and surgical therapies for severe AIS require more study. Perhaps the approach should better account for heterogeneity in patient and physiology, disease pathophysiology.
Questions for the Audience
Questions?

Joshua.Levine@uphs.upenn.edu