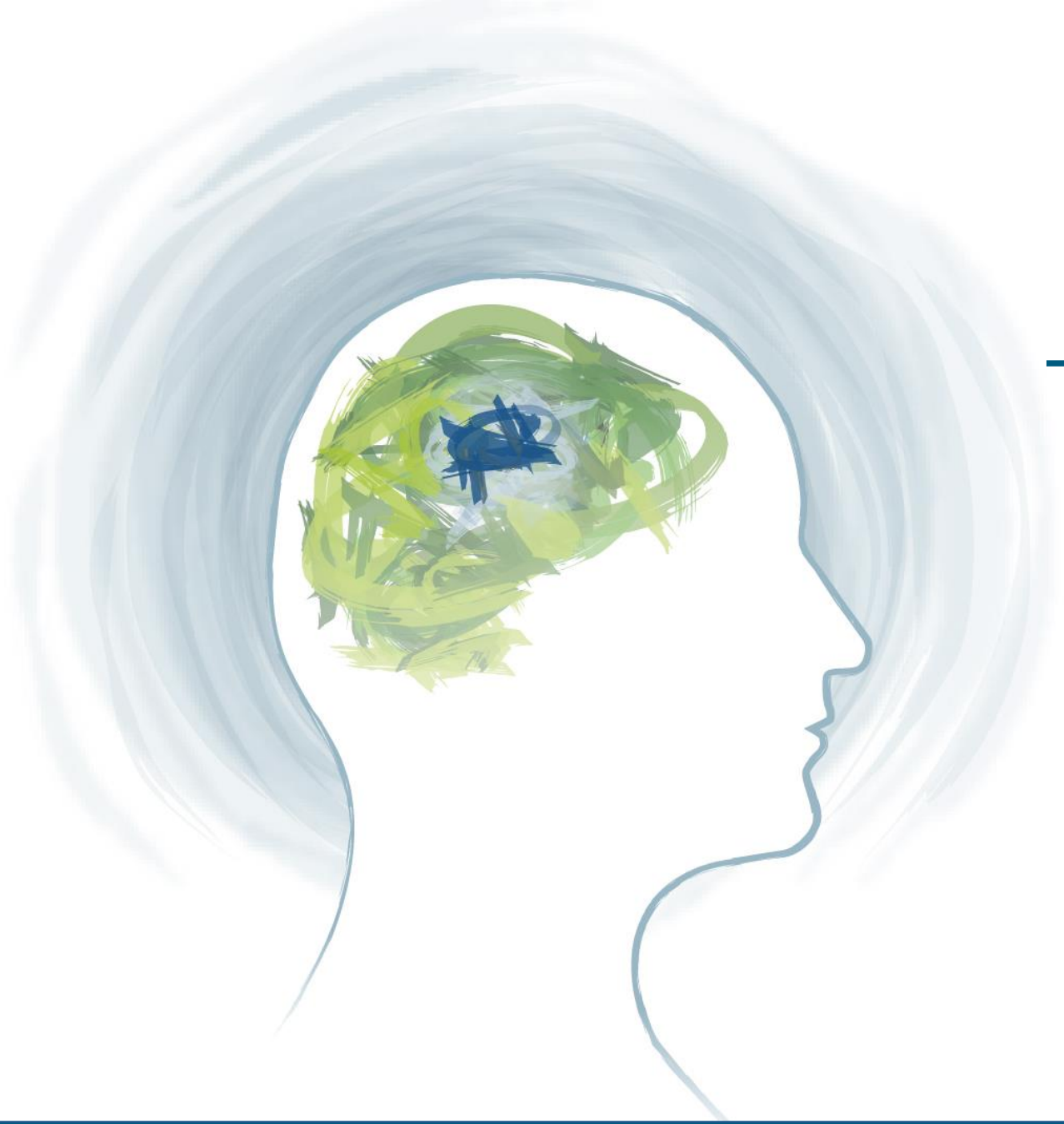

THE BIGGER PICTURE OF LARGE HEMISPHERIC INFARCTION

Disease and Management

TODAY'S PANELISTS

Panel Chair

Edward C. Jauch, MD, MS, FAHA

Expert Panelists

Tudor G. Jovin, MD

Stephan A. Mayer, MD, FCCM

Jeffrey L. Saver, MD, FAHA, FAAN, FANA

Sean I. Savitz, MD

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OBJECTIVES

Review complexities associated with the diagnosis, treatment, and management of LHI

Understand key considerations and decision points throughout the journey of a patient with LHI

Discuss forward-looking strategies to optimize patient outcomes

LHI, large hemispheric infarction.

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Audience Question: What is your primary specialty?

Please go to **Slido.com** to participate in the audience response questions

- Event code: **BiogenLHI**

ICU, intensive care unit.

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Audience Question: How many patients with LHI do you typically see per month?

Please go to **Slido.com** to participate in the audience response questions

- Event code: **BiogenLHI**

LHI, large hemispheric infarction.

THE CASE OF MS. S[a]

- Ms. S, 59 years old, is a mother of 2 children and grandmother of 3 children, with a history of atherosclerosis
- On Monday afternoon, she was at the park with her grandchildren when she noticed she was having trouble seeing clearly
- She also noticed some weakness on her right side but was unconcerned and continued on with her daily activities
- 4 hours later, Ms. S's son came over to pick up his kids and noticed that Ms. S had paralysis in her right arm and on the right side of her face and was having difficulty communicating
- Ms. S's son immediately dialed 9-1-1

[a]The case study described here and throughout the presentation is a single ideal patient case study that is based on multiple real-life patients from the presenters' clinical experience.

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FUNDAMENTALS OF LHI AND ASSOCIATED LIFE-THREATENING EDEMA

Speaker: Sean I. Savitz, MD

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LHI IS ONE OF THE MOST DEVASTATING FORMS OF ACUTE ISCHEMIC STROKE[1]

Constitutes ~14% of all strokes[2]

Has an annual incidence of 10-20 per 100,000 people[3] and a mortality rate of up to 80%[1]

Source is almost exclusively cardioembolic[4]

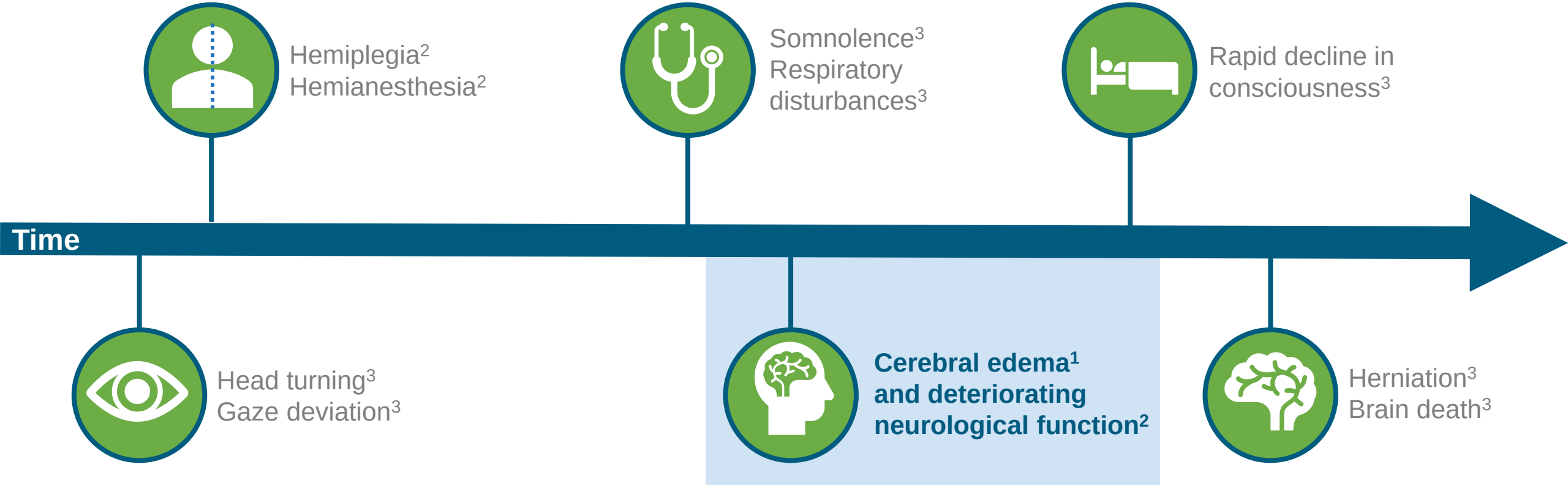
Is a malignant infarction caused by an occlusion that can affect the entire territory of the middle cerebral artery[5]

- At least partially involves the basal ganglia

LHI, large hemispheric infarction.

1. Treadwell and Thanvi. *Postgrad Med J*. 2010;86:235-242. **2.** Remedy Pharmaceuticals. White Paper: A Guide to Understanding Large Hemispheric Infarction. 2016. http://www.remedypharmaceuticals.com/uploads/7/1/7/3/71731607/lhi.whitepaper.3jun16.pdf. **3.** Heiss. *Cerebrovasc Dis*. 2016;41:1-7. **4.** Subramaniam and Hill. *Neurologist*. 2005;11:150-160. **5.** Torbey et al. *Neurocrit Care*. 2015;22:146-164.

LHI IS DEFINED BY VARIOUS CLINICAL FEATURES[1]



LHI, large hemispheric infarction.

1. Treadwell and Thanvi. *Postgrad Med J.* 2010;86:235-242. **2.** Kimberly and Sheth. *Neurol Clin Pract*. 2011;76(7 suppl 2):S50-S56. **3.** Steiner et al. *Neurology*. 2001;57:S61-S68.

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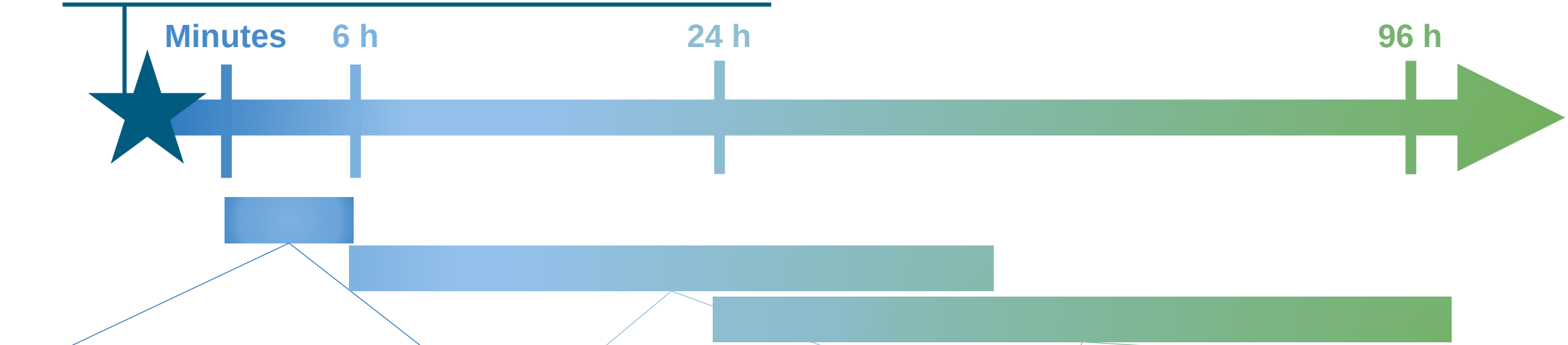
CEREBRAL EDEMA MAY PROGRESS OVER TIME AS THE PATIENT PROGRESSES TO LHI

Ischemic injury and large-vessel occlusion: Reduced cerebral blood flow[1]



Cytotoxic edema[1]
- Failure of Na^+/K^+ pumps
- Calcium influx
- Cell swelling

Vasogenic edema[1]
- BBB deterioration
- Leakage of serum proteins into brain

Progressive cerebral edema can result in
- Increasing intracranial pressure, worsening ischemia[1]
- Midline shift and brain herniation leading to progressive brainstem dysfunction[2]

BBB, blood-brain barrier; LHI, large hemispheric infarction.

1. Heiss. *Cerebrovasc Dis*. 2016;41:1-7. **2.** Treadwell and Thanvi. *Postgrad Med J*. 2010;86:235-242.

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STROKE SOCIETIES PROVIDE GUIDELINES FOR MANAGEMENT OF AIS, LHI, AND CEREBRAL EDEMA[1,2]

Available guidelines are based largely on expert experience[1,2]

Management of AIS[1] and cerebral edema[3]	AHA/ASA
Management of LHI[2]	NCS and German Society for Neuro-Intensive Care and Emergency Care

Guidelines emphasize the need for early diagnosis[1]

AHA, American Heart Association; AIS, acute ischemic stroke; ASA, American Stroke Association; LHI, large hemispheric infarction; NCS, Neurocritical Care Society.

1. Powers et al. *Stroke*. 2018;49:e46-e110. **2.** Torbey et al. *Neurocrit Care*. 2015;22:146-164. **3.** Wijdicks et al. *Stroke*. 2014;45:1222-1238.

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INITIAL ASSESSMENT AND DIAGNOSTIC WORKUP

Speaker: Jeffrey L. Saver, MD, FAHA, FAAN, FANA

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SEVERAL APPROACHES FACILITATE ASSESSMENT OF PROGRESSION TO LHI

The neurological exam and various neuroimaging methods provide a range of information[1,2]

Neurological Exam

Neuroimaging

LHI, large hemispheric infarction.

1. Powers et al. *Stroke*. 2018;49:e46-e110. **2.** Birenbaum et al. *West J Emerg Med*. 2011;12:67-76.

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EARLY ASSESSMENT OF NEUROLOGICAL FUNCTION GUIDES NEXT STEPS[1]

Standardized scales can be used to assess LHI progression and guide treatment initation[1,2]

NIHSS: Most widely used for initial stroke assessments[2]

Dominant severe hemispheric infarctions[3]

NIHSS score >20

Nondominant severe hemispheric infarctions[3]

NIHSS score >15

Visual disturbance, aphasia, and neglect are also important clinical markers[4]

LHI, large hemispheric infarction; NIHSS, National Institutes of Health Stroke Scale.

1. Powers et al. *Stroke*. 2018;49:e46-e110. **2.** Kasner. *Lancet Neurol*. 2006;5:603-612. **3.** Kimberly and Sheth. *Neurol Clin Pract*. 2011;76(7 suppl 2):S50-S56. **4.** Teleb et al. *J NeuroIntervent Surg*. 2017;9:122-126.

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THE CASE OF MS. S: USING IMAGING TO FACILITATE DIAGNOSIS

- Ms. S was taken to the ER following her aphasia and right-sided paralysis

Next Steps

- Upon initial evaluation of Ms. S, Dr. Smith noticed gaze deviation, global aphasia, and hemiparesis
- Dr. Smith's notes indicate
  - NIHSS score of 22
  - Global left hemisphere syndrome
  - Time last known well, 4 hours ago

Audience Question: The first imaging procedure you perform is NCCT. What imaging would you perform next?

CTA, computed tomography angiography; CTP, computed tomography perfusion; ER, emergency room; MRI, magnetic resonance imaging; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale.

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NEUROIMAGING PROVIDES VALUABLE INFORMATION FOR NEXT STEPS

Imaging is an important aspect of the evaluation of patients with stroke and possible progression to LHI

- Noncontrast computed tomography
- Computed tomography angiography
- Computed tomography perfusion
- Diffusion-weighted MRI
- Magnetic resonance angiography
- Perfusion-weighted MRI
- Cerebral angiography

DW-MRI, diffusion-weighted magnetic resonance imaging; MRI, magnetic resonance imaging.

Birenbaum et al. *West J Emerg Med*. 2011;12:67-76.

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PREDICTORS OF CEREBRAL EDEMA AND POOR OUTCOME FOLLOWING ISCHEMIC STROKE

Neurological exam and imaging can reveal features associated with increased risk of developing LHI

- High NIHSS score[1]
- Depressed level of consciousness[2]
- Unilateral or bilateral pupillary dilation[1]
- Early nausea and vomiting[2]

- Early ischemic change on CT affecting >50% of MCA territory[2]
- >145 mL lesion volume on DW-MRI[3]
- Infarct volume >220 mL on CT[3]
- ASPECT score ≤7[3]

ASPECT, Alberta Stroke Program Early CT; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; LHI, large hemispheric infarction; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

1. Kimberly and Sheth. *Neurol Clin Pract*. 2011;76(7 suppl 2):S50-S56. **2.** Treadwell and Thanvi. *Postgrad Med J*. 2010;86:235-242. **3.** Heiss. *Cerebrovasc Dis*. 2016;41:1-7.

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MANAGEMENT STRATEGIES

Speaker: Tudor G. Jovin, MD

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GUIDELINES EMPHASIZE PROMPT TREATMENT[1]

Guidelines recommend therapies for AIS, LHI, and associated edema[1-3]

Management of AIS[1] and cerebral edema[3]	AHA/ASA
Management of LHI[2]	NCS and German Society for Neuro-Intensive Care and Emergency Care

Prompt treatment is important to minimize long-term disability and impairment[4]

AHA, American Heart Association; AIS, acute ischemic stroke; ASA, American Stroke Association; LHI, large hemispheric infarction; NCS, Neurocritical Care Society.

1. Powers et al. *Stroke*. 2018;49:e46-e110. **2.** Torbey et al. *Neurocrit Care*. 2015;22:146-164. **3.** Wijdicks et al. *Stroke*. 2014;45:1222-1238. **4.** Roth. *Proc (Bayl Univ Med Cent).* 2011;24:257-259.

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BIOCHEMICAL TESTS CAN IDENTIFY CLINICAL PARAMETERS THAT SHOULD BE MANAGED AFTER STROKE

Biochemical tests can identify parameters associated with unfavorable outcomes after acute ischemic stroke to aid in initial treatment selection

- Blood glucose
- Oxygen saturation
- Renal function
- Troponin levels
- Complete blood count
- Cardiac markers
- Prothrombin time
- International normalized ratio
- Activated partial thromboplastin time
- Sodium levels

LHI, large hemispheric infarction.

Jauch et al. *Stroke*. 2013;44:870-947.

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THE GOAL IN SEVERE STROKE IS TO PREVENT PROGRESSION FROM LVO TO LHI

Reperfusion strategies aim to maximize the probability of good functional clinical outcomes[1,2]

rt-PA: Beneficial in patients presenting within ≤4.5 hours of symptom onset[1]

Thrombectomy: Treatment window may be extended to 24 hours[3]

LHI, large hemispheric infarction; LVO, large vessel occlusion; rt-PA, recombinant tissue plasminogen activator.

1. Powers et al. *Stroke*. 2018;49:e46-e110. **2.** Jauch et al. *Stroke*. 2013;44:870-947.
3. Nogueira et al. *N Engl J Med*. 2018;378:11-21.

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THE CASE OF MS. S: MANAGING PATIENT AFTER ADMISSION TO ICU

- Dr. Smith noted that Ms. S displayed global left hemisphere syndrome and had an NIHSS score of 22

Next Steps

- 8 hours after hospital admission and 12 hours after initial onset of symptoms, Dr. Smith performed thrombectomy on Ms. S
- Dr. Smith noted TICI 2B and BP 192/108 and had Ms. S admitted to the ICU, where her BP was controlled
- Upon re-examination of Ms. S, Dr. Smith noted the following:
  - Stable NIHSS score of 20
  - CT shows large infarct but no bleeding or MLS
  - Ms. S is euvolemic, with Na^+ levels at 138
  - IVC is noncollapsing, CVP = 7 mm Hg
  - Temperature is 37.7° C
  - Blood glucose is 160 mg/dL

BP, blood pressure; CT, computed tomography; CVP, central venous pressure; ICU, intensive care unit; IV, intravenous; IVC, inferior vena cava; MLS, midline shift; NIHSS, National Institutes of Health Stroke Scale; TICI, thrombolysis in cerebral infarction.

Audience Question: Which of the following orders is your next priority?

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GENERAL MEASURES AIM TO REDUCE SYSTEMIC COMPLICATIONS[1]

Clinicians may use a variety of approaches to reduce systemic complications, including cerebral edema[1]

- Control of fever[1]
- Maintenance of normoglycemia[1]
- Head elevation[1]
- Maintenance of normovolemia[1]
- Blood pressure management[1]

Supportive clinical evidence is limited[2]

1. Subramaniam and Hill. *Neurologist*. 2005;11:150-160. **2.** Jauch et al. *Stroke*. 2013;44:870-947.

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EARLY MEDICAL MANAGEMENT SHOULD FOCUS ON PREVENTING EDEMA AND INCREASES IN ICP[1]

Methods of reducing ICP differ in their mechanism of action

Osmotherapy	Hyperventilation	Barbiturates	Anti-edema Therapy
Creates an osmotic gradient across the BBB[1] *Mannitol and hypertonic saline are commonly used*[2]	Induces hypocarbia[2]	Lowers cerebral metabolic activity[2]	Various mechanisms of action, including some (eg, SUR1 inhibition[3]) currently under investigation

Choice of methods is based on patient symptoms[4]

BBB, blood-brain barrier; ICP, intracranial pressure; SUR1, sulfonylurea receptor 1.

1. Subramaniam and Hill. *Neurologist*. 2005;11:150-160. **2.** Treadwell and Thanvi. *Postgrad Med J*. 2010;86:235-242. **3.** Sheth et al. *Lancet Neurol*. 2016;15:1160-1169. **4.** Simard et al. *Curr Treat Options Neurol.* 2011;13:217-229.

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THE CASE OF MS. S: CONSIDERING CRITERIA FOR HEMICRANIECTOMY

- Several general measures were taken to control Ms. S's BP and fluid levels, and her NIHSS score was stable going into her neurology consultation

Next Steps

- During the consultation, the neurosurgeon noted the following:
  - E3 M6 V4 but aphasic with R neglect and RHH
  - Flaccid R hemiplegia, normal LUE tone, and shows 2 fingers
- Ms. S's family hears Dr. Smith consulting with the neurosurgeon and wants to understand what "hemicraniectomy" means, including the potential risks and benefits

Audience Question: What would be an appropriate trigger for a hemicraniectomy?

BP, blood pressure; E, eye opening; LUE, left upper extremity; M, motor response; NIHSS, National Institutes of Health Stroke Scale; R, right side; RHH, right homonymous hemianopia; V, verbal response.

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DECOMPRESSIVE SURGERY MAY RELIEVE HIGH ICP ASSOCIATED WITH CEREBRAL EDEMA

The decision to perform a hemicraniectomy requires assessment of multiple factors

Potential benefit[1]
- Increasing the likelihood of survival
- Increases likelihood of favorable functional outcome

Timing of possible procedure
- Within 24-48 h of stroke onset but prior to herniation symptoms[2]

Potential risks include[2]
- Disability and functional dependency
- Pain, infection, bleeding, and fluid collection

Individual patient characteristics, including[2]
- Patient age
- Dominant vs nondominant hemisphere involvement

ICP, intracranial pressure.

1. Vahedi et al. *Lancet Neurol*. 2007;6:215-222. **2.** Torbey et al. *Neurocrit Care*. 2015;22:146-164.

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MONITORING TOOLS

Speaker: Stephan A. Mayer, MD, FCCM

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THE CLINICAL EXAM IS RECOMMENDED TO MONITOR DISEASE PROGRESSION IN PATIENTS WITH LHI[1]

Scales allow objective measurement of changing clinical status[1]

National Institutes of Health Stroke Scale	Glasgow Coma Scale	Oculomotor Exam
Provides a quantitative measure of key components of a standard neurological exam[2]	Measures best eye, motor, and verbal response to assess levels of consciousness[3]	Identifies impaired visual function[4]

Important note: Oversedation can cause these types of clinical changes to be missed

LHI, large hemispheric infarction.

1. Powers et al [Erratum appears in *Stroke*. 2018;49:e128]. *Stroke*. 2018;49:e46-e110. **2.** Kasner. *Lancet Neurol*. 2006;5:603-612. **3.** Weir et al. *Q J Med*. 2003;96:67-74. **4.** Rowe. *Brain Behav*. 2017;7:e00771.

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THE CASE OF MS. S: NEUROMONITORING CONSULTATION

- Given Ms. S's current stable condition, the neurosurgeon holds off on performing decompressive surgery

Next Steps

- The neurosurgeon and Dr. Smith discuss neuromonitoring options for Ms. S

Audience Question: Neurosurgery asks whether you want an ICP monitor. In addition to the clinical exam, what is your next neuromonitoring plan?

cEEG, continuous electroencephalography; ICP, intracranial pressure; TCD, transcranial Doppler.

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MULTIPLE APPROACHES FOR MONITORING DISEASE PROGRESSION

In addition to clinical measures, physicians may use other strategies to monitor

TCD Ultrasonography	ICP Monitors	EEG	Pupilometer	Oxygen Monitoring
Assesses midline shift[1] and offers a minimally invasive alternative to neuroimaging[2]	Measures ICP via ventricular catheters or intraparenchymal/ extradural/subdural/ subarachnoid probes[3]	Helps predict clinical course and estimate prognosis[1]	Evaluates pupil size and reactivity to light[4]	Measures partial oxygen pressure of brain tissue[5]

Guidelines for these techniques are generally based on observational evidence[1]

CT, computed tomography; EEG, electroencephalogram; ICP, intracranial pressure; LHI, large hemispheric infarction; MRI, magnetic resonance imaging; TCD, transcranial Doppler.

1. Torbey et al. *Neurocrit Care*. 2015;22:146-164. **2.** Kilburg et al. *Neurosurg Focus*. 2017;42:E10. **3.** Simard et al. *Curr Treat Options Neurol.* 2011;13:217-229. **4.** Couret et al. *Critical Care*. 2016;20:99-107. **5.** Steiner et al. *Stroke.* 2001;32:2500-2506.

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THE CASE OF MS. S: PREPARING FOR HEMICRANIECTOMY

- Unfortunately, after her original neurosurgery consultation, Ms. S's condition begins to deteriorate

Next Steps

- Ms. S becomes more lethargic and is barely able to follow commands, and Dr. Smith notes the following:
  - LUE is flexing to midline
  - Left pupil is mid-position but is less reactive than right pupil
- The neurosurgeon is called, and Ms. S is taken to the OR for a hemicraniectomy
- During the post-op examination
  - Post-op CT shows a good surgical result, with restoration of midline structures
  - Ms. S has a stable GCS score of E3 M5 V3 and tolerates CPAP for 8 h

Audience Question: What is the most important next step to minimize postoperative complications and length of stay?

CPAP, continuous positive airway pressure; CT, computed tomography; E, eye opening; GCS, Glasgow Coma Scale; IV, intravenous; IVC, inferior vena cava; LUE, left upper extremity; M, motor response; OR, operating room; V, verbal response.

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LOOKING TO THE FUTURE

Speaker: Edward C. Jauch, MD, MS, FAHA

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THE CASE OF MS. S: HOSPITAL DISCHARGE AND FOLLOW-UP

- Despite her deteriorating condition, the hemicraniectomy was successful

Next Steps

- Ms. S is discharged from the hospital 12 days after her surgery and is sent to long-term acute care after tracheotomy and PEG
- 3 months after her initial symptoms, Ms. S is doing well
  - At her follow-up, Dr. Smith notes an mRS score of 3
- Ms. S is able to walk with the aid of a cane and is once again able to visit the park with her grandchildren

mRS, modified Rankin Scale; OR, operating room; PEG, percutaneous endoscopic gastrostomy.

In this fictional case study, the patient was able to return home but was not able to resume all of her normal activities

However, there are numerous strategies that should be considered to optimize patient treatment

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STRATEGIES FOR THE FUTURE

Establish Stroke Protocols for Ground and Air Transport Crews[1] and Implement MSUs[2]

Provide Education and Protocols to Smaller Remote Hospitals and Establish Telestroke[1]

Develop Recommendations for Palliative Care[1]

MSU, mobile stroke unit.

1. Jauch et al. *Stroke*. 2013;44:870-947. **2.** Bowry et al. *Stroke*. 2015;46:3370-3374.

CLINICAL TRIALS SEEK TO EVALUATE OPTIONS TO IMPROVE TREATMENT OF STROKE AND/OR LHI

	THROMBECTOMY		DHC		PHARMACOLOGICAL TREATMENTS	
	Trials	**Objectives**	**Trials**	**Objectives**	**Trials**	**Objectives**
COMPLETED	**MR CLEAN**[1] (Phase 3) **DEFUSE 3**[2] (Phase 3) **DAWN**[3,4] (Phase 2/3)	Functional outcomes within different therapeutic windows[1-3]	**DECIMAL**[6,7] (Phase 3) **DESTINY**[6,8] (Phase 3) **HAMLET**[6,9] (Phase 3)	Effect of hemicraniectomy on functional outcomes[6]	**GAMES-RP**[10] (Phase 2)	Effects of SUR1 inhibitor on prevention/ treatment of severe cerebral edema following LHI[10]
PLANNED	**TENSION**[5] (Phase 3)	Comparative safety/efficacy vs best medical care alone[5]			**CHARM**[11] (Phase 3)	Effects of SUR1 inhibitor on functional outcomes in patients with LHI[11]

DHC, decompressive hemicraniectomy; LHI, large hemispheric infarction.

1. Berkhemer et al. *N Engl J Med*. 2015;372:11-20. **2.** Albers et al. *Int J Stroke*. 2017;12:896-905. **3**. Nogueira et al. *N Engl J Med*. 2018;378:11-21**. 4.** https://www.clinicaltrials.gov/ct2/show/NCT02142283.
5. https://clinicaltrials.gov/ct2/show/NCT03094715. **6**. Vahedi et al. *Lancet Neurol*. 2007;6:215-222. **7.** https://clinicaltrials.gov/ct2/show/NCT00190203**. 8.** http://www.isrctn.com/ISRCTN01258591.
9. http://www.isrctn.com/ISRCTN94237756. **10.** Sheth et al. *Lancet Neurol*. 2016;15:1160-1169. **11**. https://clinicaltrials.gov/ct2/show/NCT02864953.

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SUMMARY

Disease Fundamentals	Initial Assessment	Management	Monitoring
A large vessel occlusion may progress into a malignant infarction that affects the entire territory of the middle cerebral artery[1]	The clinical exam and neuroimaging assess patient progression to LHI[2,3]	Early medical management focuses on preventing edema and increases in ICP[4]	The clinical exam is useful in monitoring disease progression[5]

Expanding access to stroke education and protocols and seeking improved therapy options are additional strategies for patient success[6]

ICP, intracranial pressure; LHI, large hemispheric infarction.

1. Torbey et al. *Neurocrit Care*. 2015;22:146-164. **2.** Kasner. *Lancet Neurol*. 2006;5:603-612. **3.** Birenbaum et al. *West J Emerg Med*. 2011;12:67-76. **4.** Subramaniam and Hill. *Neurologist*. 2005;11:150-160. **5.** Powers et al [Erratum appears in *Stroke*. 2018;49:e128]. *Stroke*. 2018;49:e46-e110. **6.** Jauch et al. *Stroke*. 2013;44:870-947.

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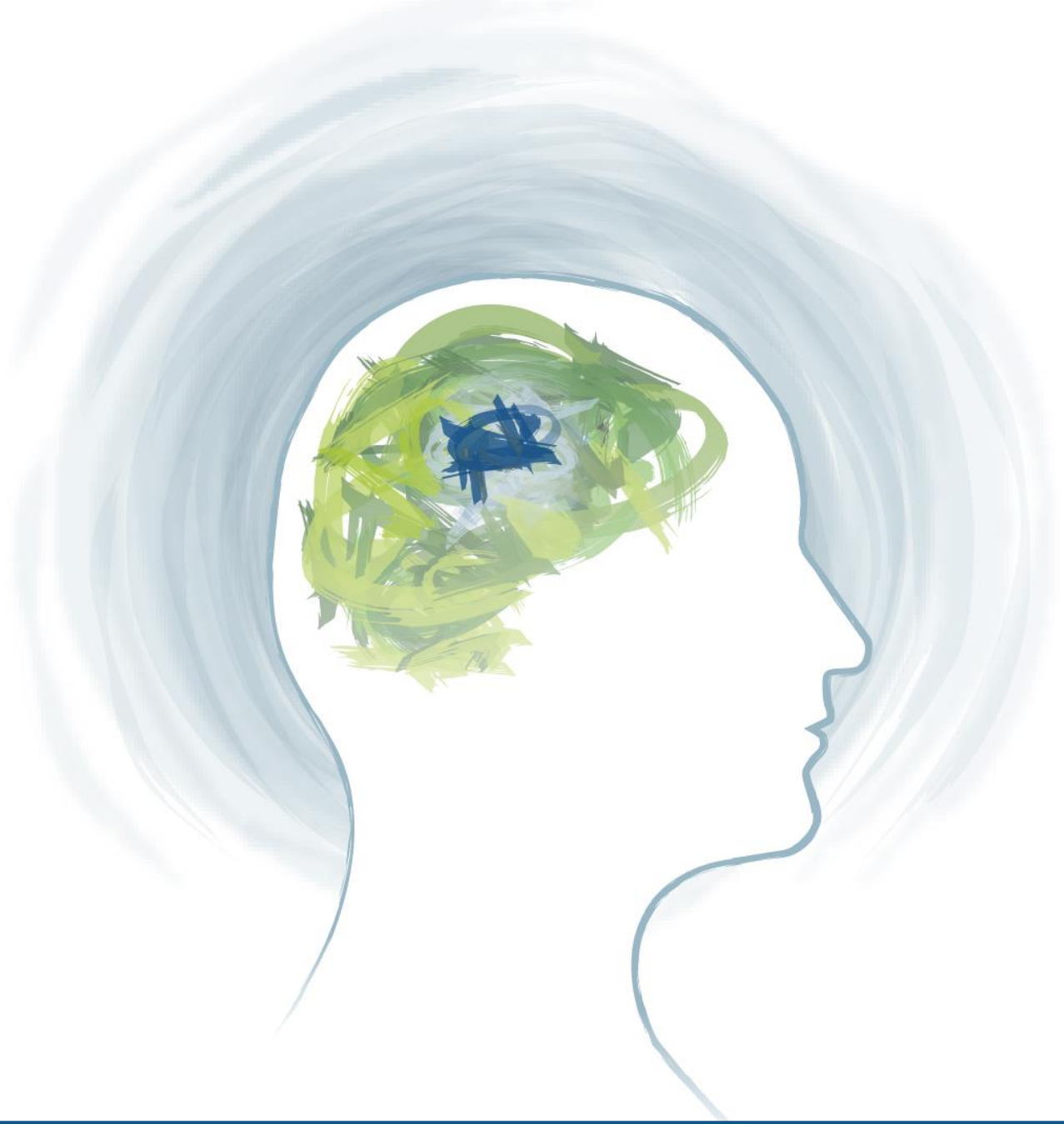
Audience Question: Please rank your agreement with the following statement: *"This symposium has improved my understanding of LHI."*

Please go to **Slido.com** to participate in the audience response questions

- Event code: **BiogenLHI**

LHI, large hemispheric infarction.



FINAL THOUGHTS

Please remember to fill out your evaluation forms. Thank you.