DIAGNOSIS AND TREATMENT OF ACUTE ISCHEMIC STROKE



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OBJECTIVES

Upon completion of this activity, learners will be able to:

- 1. Explain the diagnosis and treatment of acute ischemic stroke
- 2. Review treatment time windows for acute ischemic stroke
- 3. Discuss post-thrombolytic management



WHAT IS A STROKE?

Ischemic Stroke

• Due to thrombosis or embolism resulting in the occlusion of a cerebral, retinal or spinal artery, resulting in permanent tissue injury

Hemorrhagic Stroke

- · Due to leakage of blood into brain tissue or the subarachnoid space
- Can be due to primary rupture of small branch arteries (hypertension), or from rupture of aneurysms or other vascular malformations

TIA (Transient Ischemic Attack)

• Transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia *without acute infarction*

It is *not* an accident, thus neurologists prefer *not* to use the term "cerebrovascular accident"



TRANSIENT ISCHEMIC ATTACK (TIA)

Transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia *without acute infarction*¹

Definition tissue-based versus time-based¹ 2009

- TIA is associated with high incidence of subsequent stroke
 - 2-17% followed by stroke²
- 25% mortality in one year²
- $1/_3 2/_3$ clinically diagnosed TIA patients have been found to have infarction on DWI-MRI³



DWI-MRI: Distinguishes between TIA and AIS Predicts TIAs at highest risk for AIS

EPIDEMIOLOGY: STROKE IN THE U.S.

- Prevalence: 3.3% in U.S.
 - Increases with advancing age in both males and females
 - Over **9.4** million <u>></u>20 years of age have had a stroke
- Incidence: ~795,000 new or recurrent strokes each year
 Projections show by 2030, an additional 3.4 million will have stroke
- **Disability:** Stroke is a leading cause of disability in the U.S.
 - Reduces mobility in more than half of survivors <u>></u> 65 years old
- Mortality: Stroke is the 5th leading cause of death in the U.S.
 - Every **3 minutes 14 seconds** someone dies of stroke (was 3 min and 17 sec)
 - 162,890 Americans each year
- Cost: \$56.2 billion annually (2019/20 direct & indirect)

TIME IS BRAIN

The average stroke patient loses approximately **1.9 million** neurons every one minute



TIME FRAME	NEURONS LOST	AGES THE BRAIN BY
Every second	32,000	8.7 hours
Every minute	1.9 million	3.1 weeks
Every hour	120 million	3.6 years
10 hours	1.2 billion	36 years

"Save a minute, save a day"



CASE

- A 71 year old woman is found down at her home by her daughter. She was last seen normal by another family member about one hour prior.
- Patient was mumbling incoherently and was noted to have a right facial droop and rightsided weakness
- Daughter called 911 and patient was taken to the closest ER



INITIAL ED ASSESSMENT OF SUSPECTED STROKE

ABCs

- Vital signs
- O₂
- Monitor
- IV
- Glucose
- STAT non-contrast head CT
- CTA head and neck

History

Establish time of Last Known Well

- Discovery of acute onset of focal neurologic symptoms
 - If < 24 hours then consider acute therapies
- Vascular risk factors

Physical Exam

- General exam with emphasis on cardiac and vascular systems
- Neurologic exam: Pattern of deficits suggests the probable location, size, and vascular distribution of the stroke
 - NIHSS assessment
 - Determine level of debilitating effect of deficits, especially if mild
- History





Best Practice = Door to CT

- Can anonymize registration of patient
- RN can quickly assess ABCs and assess glucose
- Assessment can begin while CT being interpreted
- Obtain actual weight ASAP

If NIHSS <u>></u> 6 consider pre-notification of EMS for inter-facility transport to TSC or CSC





ED STROKE ALERT: TURNAROUND TIME GOALS



COMMON REASONS FOR DELAY

Lack of trained staff and protocols	Stroke Alert process not activated	Slow radiology read/report times
Lack of information from family/caregiver	Not having all information compiled for consultation	Delay in treatment decisions



It is important to analyze delays in treatment in order to consider potential opportunities for improvement

WHY CT FIRST THING?

Ischemia:

- Appears normal while acute
- Can look dark, but may take 8-72 hours to show up

• Edema:

 $_{\circ}$ $\,$ Will look dark and may have mass effect

• Hemorrhage:

- Is bright when acute
- Becomes the same color as brain tissue when subacute
- Darkens over time



Rule-out hemorrhage and/or other non-stroke cause of symptoms ... not to diagnose ischemic stroke

EARLY HEAD CT FINDINGS IN ISCHEMIC STROKE

- Head CT often without acute abnormalities
 - i.e., a normal head CT does not exclude acute ischemic stroke

• May see:

- $_{\odot}$ Loss of gray-white junction/cortical ribbon
- Blurring of the basal ganglia or internal capsule
- Effacement of sulci
- Hyperdense vessel (thrombus)
- Massive core infarct (>1/3 hemisphere) may show up in the hyper-acute phase











CASE (CONT.)

- On arrival to ER
 - o BP 162/89
 - HR 108
 - O2 saturation 97% on room air
 - \circ FSBG 122
- Paramedics report that she takes aspirin daily but no other anticoagulants. They also noted atrial fibrillation on monitor during transport.



CASE (CONT.)

- By time of arrival to ER, her last know well was about 1 hour and 45 minutes prior
- Initial NIH Stroke Scale Score was 15 due to aphasia, unable to move the right upper extremity, right lower extremity with limb drift, and left gaze preference
- Head CT shows no intracranial hemorrhage and no obvious ischemic changes
- Is she a candidate for IV thrombolytics?



INTRAVENOUS THROMBOLYSIS

- Alteplase
- Tenecteplase
- Alteplase remains the only FDA approved therapy but use of tenecteplase becoming widespread
- Treatment time window 0-4.5 hours
- Numerous inclusion and exclusion criteria



ALTEPLASE

- Activase®
 - A Recombinant Tissue Plasminogen Activator (rt-PA)
- FDA approved within 3 hours of last known well for selected patients ([e19] COR I; LOE A)
- Evidence-based practice includes 3 4.5 hour window for selected patients ([e20] COR I; LOE B-R)
- Cleared primarily by the liver with an initial pharmacological half-life of fewer than 5 minutes and a terminal half-life of 72 minutes



Only ~5% of stroke patients receive alteplase

Mostly due to time delays

GOAL: DOOR TO NEEDLE

"Establishing and monitoring target time goals for ED door-totreatment IV fibrinolysis time can be beneficial to monitor and enhance system performance" ([e9] COR I; LOE B-NR)

Door-to-needle goals:

 ≤ 60 minutes 85%
 ≤ 45 minutes 75%
 ≤ 30 minutes 50%
 American Heart Association. Target: Stroke







NINDS TRIAL (1995)

BENEFITS

- Neurologically normal at 3 months
 - 55% relative increase
 - 12% absolute increase
- Very robust effect: NNT = 8

RISKS

- Symptomatic ICH was 6.4% in the original trial
- **UPDATE:** Actual clinical practice: 3.3%⁷

Risk of ICH increases with protocol violations:

Alteplase protocol violations, poor blood pressure and sugar control, using prohibited agents, wrong dose



Marler, et at., 2000 Gladstone & Black, 2001

EFFECTS OF ALTEPLASE: OVER TIME





ALTEPLASE: OUTCOMES

Alteplase for Cerebral Ischemia within 3 Hours of Onset - Changes in Outcome Due to Treatment

Changes in final outcome as a result of treatment:

Normal or nearly normal
 Better
 No major change
 Worse

Severely disabled or dead

Early course:

No early worsening with brain bleeding

Early worsening with brain bleeding



STROKE CARE NETWORK



Use with patient education

TENECTEPLASE

TNKase®

A tissue plasminogen activator

- A genetically modified variant of alteplase
- o Greater fibrin specificity

- Quicker administration
- Longer half-life
- "It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy." (Powers, 2019 [e28] COR IIb; LOE BR)
- "Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion." (Powers, 2019 [e28] COR lib; LOE BR)
- "The current body of clinical trial evidence and American Heart Association/American Stroke Association Guidelines support the potential of tenecteplase as an option for stroke thrombolysis within 4.5 hours from time last known well." (Warach, 2020)

Act TRIAL

Intravenous Alteplase Compared to Tenecteplase in Acute Ischemic Stroke (AcT) (Phase 3)

Table 2: AcT Trial - Efficacy and Safety Outcomes ² Intention-to-Treat Analysis			
Primary Outcome	Tenecteplase n=806	Alteplase n=771	Unadjusted difference in proportion (95% CI)
mRS 0-1 at 90-120 days (n=1,567), %	36.9	34.8	2.1 (-2.6, 6.9)
Secondary Outcomes	Tenecteplase n=806	Alteplase n=771	Risk Ratio – adjusted* (95%CI)
mRS 0-1 at 90-120 days (n=1,567), %	36.9	34.8	1.1 (1, 1.2)
mRS 0-2 at 90-120 days (n=1,567), %	56.4	55.6	1 (1, 1.1)
mRS at 90-120 days, median (n=1,567), (IQR)	2 (1-4)	2 (1-4)	0.9 (0.8, 1.1) [†]
Return to baseline function, %	29.6	27.9	1.1 (0.9, 1.2)
EVT utilization (n=1,577), %	32	32.2	1 (0.8,1.2)
Safety Outcomes	Tenecteplase n=800	Alteplase n=763	Risk Difference (95% CI)
Death in 90 days (n=1,554), %	15.3	15.4	-0.1 (-3.7, 3.5)
Symptomatic ICH [‡] within 24 hours, %	3.4	3.2	0.2 (-1.5, 2)
Parenchymal hematoma, type 2§	2.6	2.4	0.3 (-1.3, 1.8)

Notes: *Adjusted for age, sex, baseline stroke severity, stroke onset-to-needle time and registry as fixed effects variables with "site" as a random effects variable. [†]Adjusted common odds ratio. [‡]Symptomatic ICH was defined as any intracerebral hemorrhage temporally related to and directly responsible for worsening of the patient's neurological condition. [§]Hematoma occupying ≥30% of infarct with obvious mass effect. Abbreviations: EVT=endovascular treatment; ICH=intracranial hemorrhage; IQR=interquartile range; mRS=modified Rankin Scale.



IV TENECTEPLASE: DOSE

Tenecteplase dose for stroke is 0.25mg/kg (actual body weight)

- MAXIMUM DOSE of 25 mg
- Total concentration per vial is 5mg/mL
- IV push over five seconds
- Not compatible with any dextrose containing solutions
- Flush IV with normal saline before and after tenecteplase administration
- You will never administer a full vial to treat stroke
- The stroke dosage is **not** listed on the box



As a high-risk medication, your organization may benefit from a process for **Dual Signature** with administration

IV THROMBOLYTIC: ELIGIBILITY CRITERIA

- Clinical diagnosis of ischemic stroke causing measurable neurological deficit
 - Mild with disabling deficits through severe
 - Rapidly improving
- Computed tomography (CT) rules out hemorrhage or non-stroke cause of deficit
- 18 years old or older
- Time to treatment < 3 hours of confirmed time Last Known Well, or 4.5 hours with additional warning



IV THROMBOLYTIC: CONTRAINDICATIONS

- Unclear onset
- Sustained/uncontrolled BP > 185/110 mmHg
- Current intracranial hemorrhage
- Suspicion of subarachnoid hemorrhage
- Intra-axial intracranial neoplasm
- History of intracranial/intraspinal surgery within 3 months
- Severe head trauma within 3 months
- Gastrointestinal: malignancy or active internal bleeding within 21 days
- Bleeding diathesis
 - Platelets < 100,000/mm³

- Prothrombin time > 15 seconds
- Warfarin use with INR > 1.7
- International Normalized Ratio (INR) > 1.7
- Activated partial thromboplastin time > 40 seconds
- **Treatment dose** of low molecular weight heparin within 24 hours (not prophylactic dose)
- Direct thrombin inhibitors or direct factor Xa inhibitors (*unless not taken within 48 hours or absence of therapeutic effect on appropriate screening tests*)
- Infective endocarditis
- Aortic Arch dissection

IV THROMBOLYTIC: WARNINGS

- Recent intracranial hemorrhage
- Ischemic stroke within 3 months
- Extensive regions of clear hypo-attenuation on initial CT
- Un-ruptured/unsecured AVM
- >10 mm un-ruptured/unsecured aneurysm
- Major surgery within 14 days
- Major trauma within 14 days
- Arterial puncture of non-compressible vessel within 7 days
- Recent gastrointestinal or genitourinary hemorrhage
- Malignancy with life expectancy less than 6 months
- History bleeding diathesis
- Hemorrhagic ophthalmic condition
- Acute pericarditis
- Left sided heart thrombus
- History of myocardial infarction involving left anterior myocardium within 3 months
- Pregnancy/postpartum < 14 days
- Recent/active vaginal bleeding causing clinically significant anemia
- Sustained blood glucose levels <50 and > 400 mg/dL
- > ten cerebral microbleeds by previous imaging



IV THROMBOLYTIC: ELIGIBILITY CONSIDERATIONS

- Single deficit : lasting impact¹
- Early improvement is a risk factor for subsequent deterioration³
- AHA/ASA recommends taking disabling deficits and potential for disability into account when assessing stroke severity³
- Many with low National Institute of Health Stroke Scale (NIHSS) or with initial improvement can still have significant disability²
- The NIHSS should not be used alone to rule-out stroke⁴



1. Proctor, 2016 2. Khatri et al., 2012 3. Powers et al., 2019 4. Martin-Schild et al., 2011

IV THROMBOLYTIC: 3 - 4.5 HOUR WINDOW

3-hour window contraindications and warnings

continue to apply ...

Stroke symptoms (NIHSS greater than 25) is uncertain



Powers et al., 2019

IV THROMBOLYTIC: BP MANAGEMENT

- **Before** giving IV thrombolytic, the recommendation is to safely lower blood pressure (<185/110 mm Hg) with antihypertensive agents.
 - Assessing the stability of the blood pressure before starting IV thrombolytic
- After increase BP measurements if SBP>180 or DBP >105, administer antihypertensive medications to maintain BP at or below these levels for a least the first 24 hours.

Other agents (eg, Hydralazine, Enalaprilat) may also be considered

Labetalol

• 10–20 mg IV over 1–2 min, may repeat 1 time

Nicardipine

• 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h

Clevidipine

 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h





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- Blood glucose is the only lab value that must be checked on every patient prior to the initiation of IV thrombolytic.
- Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it may be reasonable not to delay the start of IV thrombolytic due to labs pending with no reason(s) to suspect an abnormal result.
 - If patient known to be on warfarin, need PT/INR measurement with INR
 <1.7 to be eligible for thrombolytics
- Other potential labs (not needed for treatment decision do NOT delay):
 - CBC with diff.
 Troponin
 - BMP or CMP Type & Screen





DIRECT ORAL ANTICOAGULANTS (DOACs)

- apixaban (Eliquis)
- betrixaban (Bevyxxa)
- dabigatran (Pradaxa)
- Consensus Statement

- edoxaban (Savaysa)
- rivaroxaban (Xarelto)

- Last dose within 48 hours = Contraindication to IV thrombolytic
- Or presence of therapeutic effect on appropriate screening tests = contraindication to IV thrombolytic
- If reason to suspect abnormal platelet counts or coagulation studies
 - aPTT for heparin; PT/INR for warfarin; Anti-factor Xa for LMWH;
 - Direct thrombin assay for dabigatran and direct factor Xa assays for rivaroxaban, edoxaban, & apixaban



DURING AND 24 HOURS AFTER IV THROMBOLYTIC

The following should be **avoided**:

- BP Elevations > SBP 180 and DBP 105
- Antithrombotics
- Invasive procedures, invasive lines, catheters or tubes *(unless deemed medically necessary)* ([e27] Table 9)



DURING AND 24 HOURS AFTER IV THROMBOLYTIC

The following **<u>may</u>** be avoided:

Mobilization

- Safety may be maximized when on bedrest precautions initially however early mobilization is also beneficial
- **High-dose** mobilization within 24 hours may result in a poor outcome at 3 months ([e43] COR III; LOE B-R)
- Work with the physician and therapist to determine patient-specific safety measures

Keep NPO until IV Thrombolytic is complete & no side effects are observed, and until dysphagia screen or evaluation passed



COMPLICATIONS

• Hemorrhage:

- Monitoring during and after IV thrombolytic for bleeding
 - Intracranial bleeding
 - Internal bleeding
 - Superficial bleeding
- Management of hemorrhage:
 - Reversal agents
 - Hospital protocols

Orolingual Angioedema:

- Angioedema is a rare (1-2%), but potentially serious complication
 - Especially experienced by those on ACE inhibitors
- Can be asymmetric and can occur contralateral to the ischemia



THROMBOLYTIC GIVEN ... NOW WHAT?



CASE (CONT.)

CTA head/neck were also obtained on arrival to
 ED





LVO DESIGNATION

- Stroke process due to occlusion of large vessel
- Analogy

 STEMI = ST Elevation Myocardial Infarction
 LVO = Large Vessel Occlusion
 30 50% of ischemic strokes

Endovascular Therapies (EVT)

*** Mechanical Endovascular Retrieval (MER) ***



WHAT CONSTITUTES LARGE VESSEL?!



ENDOVASCULAR THERAPIES (EVT)

Patients (if eligible) should receive IV thrombolytic even if endovascular therapies are being considered.

Mechanical thrombectomy is reasonable in selected patients up to 24 hours of last known well ([e30] COR IIa; LOE B-R)



Clot Retrieval Devices







- SWIFT PRIME
- ESCAPE
- ANGEL ASPECT
- SELECT2
- DAWN (NNT=2)
- DEFUSE 3 (NNT=3)

HOSPITAL CARE AFTER STROKE

Secondary Prevention

- Initiation of appropriate antithrombotic
- Maintenance of good glycemic control (140-180mg/dl) in hospital
- Cardiac monitoring for at least 24-48 hours
- Initiation of statin therapy for goal LDL <70mg/dL

Safety Measures

- DVT prophylaxis
- NPO including medications until dysphagia screen passed
- Assess for fall, aspiration, and seizure risk
 - Appropriate precautions in place



GENERAL CONSIDERATIONS

BP control	Avoid fever	Judicious use of IV fluids
 Permissive hypertension in first 24 -48 hours Up to 220/120 if no thrombolytic agent Up to 180/105 if receiving IV thrombolytic 	 Increases metabolic demand 	 Avoid hypo-osmolar fluids such as D₅W and ½ NS as these may worsen cerebral edema



ISCHEMIC STROKE: BP GREATER THAN 220/120 mm Hg

IF <u>></u>220/120 **and** no thrombolytic or EVT **and** no comorbid condition requiring tighter control

- Antihypertensive treatment in the first 48-72 hours is uncertain
- Might be reasonable to lower BP in a well-controlled manner
 - Lower by 15% during the first 24 hours following the stroke ([e38] COR IIb; LOE C-EO)
 - Dropping too quickly or too much can cause a loss of cerebral perfusion pressure



ISCHEMIC STROKE: BP LESS THAN 220/120 mm Hg

IF <220/120 and no thrombolytic or EVT and no comorbid condition requiring tighter control

- Antihypertensive treatment in the first 48-72 hours is not effective to prevent death or dependency ([e38] COR III; LOE A)
 - Elevated blood pressure can improve cerebral perfusion pressure

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Constant relationship between MAP & CPP
MAP - ICP=CPP
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To Calculate MAP: [(DBP x 2) + SBP] ÷ 3

Goal is CPP > 60





WHAT ABOUT LESS OBVIOUS STROKE SYMPTOMS?



ATYPICAL SIGNS & SYMPTOMS: POTENTIAL FOR MISDIAGNOSIS

Posterior Circulation Stroke:

- 20-25% of strokes
- In a 2016 study of missed ischemic stroke diagnoses in the ED, posterior circulation strokes were 3x more likely to be missed than strokes in the anterior circulation²
- o 5 D's of Posterior Circulation Stroke
 - o Dizziness
 - o Diplopia
 - o **Dysarthria**
 - o **Dysphagia**
 - o **Dystaxia**
 - Also consider: headache and nausea and vomiting²

Brain Stem Stroke:

 Included in the category of posterior circulation, but unique because they can demonstrate "crossed signs"

> Arch et al., 2016 Powers et al., 2019

VERTIGO: BRAIN STEM STROKE?

Head Impulse, Nystagmus, and Test of Skew

HiNTs exam:

- "HiNTs to INFARCT"
- With hours or days of vertigo
- Differentiates Acute Vestibular Syndrome (AVS) versus brainstem stroke
- 3 part exam:
 - $_{\circ}$ Head impulse
 - Nystagmus
 - $_{\circ}$ Test of Skew

More sensitive (100%) than early MRI in AVS 96% specific for stroke



HINTS: HOW TO PERFORM

Head Impulse Test	 -Have patient fix their eyes on your nose -Move their head in horizontal plane left and right -Look for catch up saccade When head is turned towards normal side, vestibular ocular reflex remains intact and eyes continue to fixate on visual target When head is turned towards affected side, vestibular ocular reflex fails and eyes make a corrective saccade to re-fixate on visual target
Nystagmus	-Observe for nystagmus in primary, right, and left gaze
Test of Skew	 -Have patient look at your nose with their eyes and cover one eye -Rapidly uncover the eye and watch to see if the eye moves to re-align -Repeat for both eyes



HINTS: INTERPRETATION

Reassuring Findings (not stroke) ALL of below:

Head impulse Test	Abnormal – due to dysfunction of the peripheral nerve
Nystagmus	None or horizontal, unilateral only
Test of Skew	Normal

Worrisome Findings ANY of below:

Head impulse Test	Normal, with continuous, ongoing vertigo and spontaneous nystagmus
Nystagmus	Bidirectional or any vertical component
Test of Skew	abnormal – dysconjugate gaze is a sign of a central lesion



STROKE MIMICS

- Metabolic disorders
 - **o** Hypo and Hyperglycemia
- Migraine
- Seizures: Todd's Paralysis
- Bell's Palsy
- Syncope
- Transient global amnesia
- Peripheral nerve disorders
- Intracranial masses
- Hypertensive Crisis
- Psychogenic presentations

Can you think of another common mimic?

• Urinary Tract Infection (UTI)





Arch et al., 2016 Powers et al., 2019

WHAT SHOULD WE TEACH OUR PATIENTS AND STAFF?

- B- Balance: sudden trouble with balance or walking
- E- Eyes: sudden loss of vision or double vision
- F- Face: does one side of face appear droopy?
- A- Arm: unable to lift arm or drifts downward
- S- Speech: slurring, garbled, unable to understand
- T- TIME! Call 911



CONCLUSIONS

- Stroke remains the 5th leading cause of death in the U.S.
- Patients with stroke and TIA are at increased risk for future stroke as well as MI and death
- IV thrombolytic is safe and effective for ischemic stroke treatment in selected patient up to 4.5 hours
- Endovascular therapy is recommended up to 24 hours of last known well
 - EVT beyond 24 hours may be considered in select cases





WEB-BASED PHYSICIAN EDUCATION

The Stroke Care Network is pleased to offer fully accredited web-based physician education.

- We know how demanding a physician schedule is and how difficult it can be to attend live training sessions.
- These web-based learning modules were created to provide an alternative to in-person training.
- Each module is fully accredited and can be done online at a time convenient for you.





QUESTIONS?





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