UPDATES IN NEUROCRITICAL CARE

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DISCLOSURES

• None
OBJECTIVES

1. Describe briefly the history of neurocritical care.
2. Define neurocritical care.
3. Describe the updates in different neurocritical care conditions applicable neurologists and non-neurologists.
   - Acute Ischemic Stroke (AIS)
   - Intracerebral Hemorrhage (ICH)
   - Encephalitis
   - Status Epilepticus
   - Brain death
ORIGIN OF NEUROSCIENCES ICU

- Neurosurgeons performing extensive surgeries
- Dandy opened the first neurosurgical ICU in Johns Hopkins Hospital in 1932.
- Combine neurology and neurosurgical ICU started at Saint Mary’s Hospital under Mayo clinic.
- Increasing presence of a specific neurointensivists in the ICUs.
- 2004, Neurocritical Care Society was formed with accreditation through AAN and UCNS.

Widjicks, 2013
WHAT IS NEUROCRITICAL CARE?

• “…intensive care management of patients with life-threatening neurological and neurosurgical illnesses such as massive stroke, bleeding in or around the brain (subarachnoid hemorrhage, intracerebral hemorrhage, subdural hemorrhage, intraventricular hemorrhage), brain tumors, brain trauma, status epilepticus, nerve and muscle diseases (myasthenia gravis, Guillain-Barre Syndrome), spinal cord disorders and the cardiopulmonary complications of brain injury. Neurocritical care provides the interface between the brain and other organ systems in the setting of critical illness. Patients are taken care of within a single specialized unit. Neurocritical care units specialize in managing the unique needs of such critically ill patients.”

- www.neurocriticalcare.org
ACUTE ISCHEMIC STROKE UPDATES
ACUTE ISCHEMIC STROKE: STROKE STATISTICS 2015

- By 2030, 3.4 M people aged >18 years will have had a stroke, a 20.5% increase in prevalence from 2012.
- ~795,000 people experience a new or recurrent stroke
- 610,000 are first attacks
- 87% ischemic
- On average, every 40 seconds, someone in the US has a stroke
- ~1 of every 20 deaths in the US is due to stroke

Mozaffarian D et al., 2015
ACUTE ISCHEMIC STROKE: UPDATES

• Until when can we give Intravenous Tpa (IVtPA)?
• What are the newer oral anti-coagulants options for prevention of stroke in non-valvular atrial fibrillation?
• What are the new options for intra-arterial intervention in stroke?
**ACUTE ISCHEMIC STROKE: TIME TO TREAT WITH IV TPA**

- **IV tPA** (tissue plasminogen activator) can be given up to **4.5 hours** (Hacke, 2008)
- **Contraindications** for extended time include previous stroke AND diabetes, >80 years old, NIHSS >25, anticoagulation.
- Target remains to be as early as possible, the earlier the treatment, more likely to have a favorable outcome.
- **IV rtPA** remains to be the only FDA approved pharmacological therapy for AIS.
ACUTE ISCHEMIC STROKE: NEWER ORAL ANTICOAGULANTS

Fawole, 2013
ACUTE ISCHEMIC STROKE: NEWER ORAL ANTICOAGULANTS

- **RELY**
  - Direct thrombin inhibitor
  - Similar rates of stroke or systemic embolism compared to warfarin
  - Lower rates of major hemorrhage at 110mg twice daily
  - 150mg twice daily had lower rates of stroke and systemic embolism but similar major hemorrhage rates
  - Idarucizumab phase III trial ongoing for reversal
ACUTE ISCHEMIC STROKE: NEWER ORAL ANTICOAGULANTS

- ROCKET-AF
- 20 mg
- Rivaroxaban noninferior to warfarin for prevention of stroke or systemic embolism (2.1%/year vs 2.4%/year)
- No difference in risk of major bleeding (14.9%/year vs 14.5%/year)
- ICH (0.5% vs 0.7%, p=0.02) and fatal bleeding (0.2% vs 0.5%, p=0.003) less in rivaroxaban
ACUTE ISCHEMIC STROKE: NEWER ORAL ANTICOAGULANTS

• ARISTOTLE
• 5 mg twice daily
• Apixaban was superior to warfarin in preventing stroke or systemic embolism (1.27% vs 1.60%; p = 0.01 for superiority), caused less bleeding (2.13% vs 3.09%/year, p < 0.001), and resulted in lower mortality (3.52% vs 3.94%; p < 0.001).
### Acute Ischemic Stroke: Newer Oral Anticoagulants

<table>
<thead>
<tr>
<th>Metric</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Thrombin</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td>Peak level (h)</td>
<td>2–3</td>
<td>3</td>
<td>3</td>
<td>1–2</td>
<td>3–4</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>12–17</td>
<td>5–9</td>
<td>9–14</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>6</td>
<td>80</td>
<td>&gt;50</td>
<td>62</td>
<td>34</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>80</td>
<td>66</td>
<td>~25</td>
<td>~50</td>
<td>17</td>
</tr>
<tr>
<td>Hepatic clearance (%)</td>
<td>~20</td>
<td>~28</td>
<td>~75</td>
<td>~50</td>
<td>~80</td>
</tr>
</tbody>
</table>

Abbreviation: NOAC, non-vitamin K antagonist oral anticoagulant

McMahon, 2015
ACUTE ISCHEMIC STROKE: NEWER ORAL ANTICOAGULANTS

If bleeding is severe or life-threatening:
Consider multidisciplinary team care in an intensive care unit
Mechanical compression of accessible sites
Surgical interventions as appropriate
Hemodialysis (only dabigatran)
Nonspecific prohemostatic agents:
Activated prothrombin complex concentrate 50–100 U/kg
Intravenously (preferred)
Prothrombin complex concentrate 50 U/kg
Recombinant factor VIIa 120 U/kg
ACUTE ISCHEMIC STROKE: INTERVENTIONAL THERAPIES FOR STROKE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke
ACUTE ISCHEMIC STROKE: INTERVENTIONAL THERAPIES FOR STROKE

Table 2. Designs of Endovascular Randomized Controlled Trials Testing the Efficacy of Endovascular Therapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>Device</th>
<th>Thrombus</th>
<th>Endovascular Start</th>
<th>NIHSS</th>
<th>Advanced Imaging Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASICS</td>
<td>All available options</td>
<td>Basilar</td>
<td>≤6 h</td>
<td>NIHSS≤10</td>
<td>No</td>
</tr>
<tr>
<td>DAWN</td>
<td>TREVO</td>
<td>ICA/M1</td>
<td>Randomized at 6-24 h</td>
<td>NIHSS≤10</td>
<td>Core and penumbra*</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>Available choices since 2013</td>
<td>ICA/M1/ICA/M1 equivalent (2 M2s)</td>
<td>≤12 h</td>
<td>NIHSS&gt;5</td>
<td>Core, collaterals, or penumbra†</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>Solitaire</td>
<td>ICA/M1/M2</td>
<td>≤6 h</td>
<td>N/A</td>
<td>Core and penumbra‡</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>All CE marked devices</td>
<td>ICA/M1/M2/ICA/M1A2</td>
<td>≤6 h</td>
<td>NIHSS≤2</td>
<td>No</td>
</tr>
<tr>
<td>PISTE</td>
<td>All CE marked since 2013</td>
<td>ICA/M1/M2</td>
<td>≤12 h</td>
<td>NIHSS≤8</td>
<td>No</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>Penumbra, Solitaire, and TREVO</td>
<td>ICA/M1</td>
<td>≤7.5 h</td>
<td>NIHSS≤10</td>
<td>Core</td>
</tr>
<tr>
<td>RESILIENT</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤7.5 h</td>
<td>NIHSS≤6</td>
<td>Core#</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤8 h</td>
<td>NIHSS≤8</td>
<td>Core and penumbra‡</td>
</tr>
<tr>
<td>SWIFT-PRIME</td>
<td>Solitaire</td>
<td>ICA/M1</td>
<td>≤8 h</td>
<td>NIHSS≤10, NIHSS≤30</td>
<td>Core++: Penumbra**</td>
</tr>
<tr>
<td>THERAPY</td>
<td>Penumbra</td>
<td>ICA/M1</td>
<td>≤5 h</td>
<td>NIHSS≤10 and ≤25</td>
<td>No</td>
</tr>
<tr>
<td>THRACE</td>
<td>MERCI, Catch, Penumbra, Solitaire, Trevo, ICA/M1/basilar-distal</td>
<td>Revive, Penumbra 3d Separator and ACE, Mindframe Capture and Flow, pRESt+</td>
<td>≤5 h</td>
<td>NIHSS≤10 and ≤25</td>
<td>No</td>
</tr>
<tr>
<td>THRILL</td>
<td>Solitaire or TREVO</td>
<td>ICA/M1</td>
<td>≤8 h</td>
<td>NIHSS≥7 and ≤26</td>
<td>Core‡</td>
</tr>
</tbody>
</table>

Khatri et al, 2015
ACUTE ISCHEMIC STROKE: INTERVENTIONAL THERAPIES FOR STROKE

Table 3. Baseline Demographics and Results of the Recent Randomized Randomized Controlled Trials of Endovascular Therapy

<table>
<thead>
<tr>
<th>Trials</th>
<th>Age (median, y)</th>
<th>Baseline NIHSS (median)</th>
<th>IV r-PA Treatment Rate</th>
<th>mTICI 2b/3</th>
<th>Time to mTICI</th>
<th>mRS Common OR* (95% CI)</th>
<th>mRS 0–2, % Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>65</td>
<td>18</td>
<td>89%</td>
<td>50%</td>
<td>332 min</td>
<td>1.7 (1.2–2.3)</td>
<td>33 vs 19 21 vs 22</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>71</td>
<td>17</td>
<td>76%</td>
<td>72%</td>
<td>241 min</td>
<td>2.6 (1.7–3.8)</td>
<td>54 vs 29 10 vs 19</td>
</tr>
<tr>
<td>EXTEND-IA†</td>
<td>71.5</td>
<td>15</td>
<td>100%</td>
<td>86%</td>
<td>248 min</td>
<td>2.0 (1.2–3.8)</td>
<td>71 vs 40 9 vs 20</td>
</tr>
</tbody>
</table>

Khatri et al, 2015
ACUTE ISCHEMIC STROKE: INTERVENTIONAL THERAPIES FOR STROKE

- MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME and REVASCAT
- Intra-arterial thrombectomy should be offered to patients who have documented proximal artery lesions with relatively normal CT scan, severe deficits and can have thrombectomy within 6 hours of last seen normal
- Benefits are clear in patients who received rtPA + thrombectomy
- Do not withhold tPA for patients who qualify
- Importance of an endovascular stroke center with a multidisciplinary team that can minimize time to recanalization and may avoid general anesthesia

Khatri et al, 2015
INTRACEREBRAL HEMORRHAGE UPDATES
SPONTANEOUS INTRACEREBRAL HEMORRHAGE: STATISTICS

- ICH incidence, 4.30/10000
- 10% of all strokes
- 30-day case fatality, 46.5% in 2008

Mozaffarian D et al., 2015
SPONTANEOUS INTRACEREBRAL HEMORRHAGE: UPDATES

• How aggressive should blood pressure be controlled in the setting of acute ICH?
• What are the current surgical options for ICH?

Mozaffarian D et al., 2015
SPONTANEOUS INTRACEREBRAL HEMORRHAGE: BLOOD PRESSURE CONTROL

• Tested acute safety of 3 levels of SBP reduction in supratentorial ICH treated within 6 hours of symptom onset
• Multicenter prospective study
• 110-140, 140-170 and 170-200
• Feasibility multicenter study
• Concluded that study is safe in 3 tiers
• ATACHII pending

Qureshi et al., 2010
SPONTANEOUS INTRACEREBRAL HEMORRHAGE: BLOOD PRESSURE CONTROL

- INTERACT2 Tested if rapid lowering of elevated BP would improve the outcome of patients with ICH
- Multicenter RCT
- $\textless 140$ versus $\textless 180$ mmHg
- No significant reduction in death or severe disability

Anderson et al., 2010
<table>
<thead>
<tr>
<th>Trial design issues</th>
<th>INTERACT II design</th>
<th>ATACH II design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent transient or moderate elevation in SBP in subjects with ICH</td>
<td>Inclusion of patients with initial SBP of 150 mm Hg or greater</td>
<td>Inclusion of patients with initial SBP of 180 mm Hg or greater, exclusion of patients with spontaneous reduction in SBP prior to randomization</td>
</tr>
<tr>
<td>Short time window for preventing hematoma expansion</td>
<td>Inclusion and treatment of patients with symptom onset of 6 h or less Investigator judgment</td>
<td>Inclusion and treatment of patients with symptom onset of 4.5 h or less</td>
</tr>
<tr>
<td>Very high likelihood of death within 24 h in patients with high severity Surgery evacuation of ICH may confound the effect of trial intervention</td>
<td>Investigator judgment</td>
<td>Exclusion of patients with parenchymal hematoma volume &lt;50 cc, large amount of IVH, or pontine ICHs</td>
</tr>
<tr>
<td>High rate of hematoma expansion associated with anticoagulant related ICHs</td>
<td>Included with INR correction based on investigator discretion</td>
<td>Exclusion of cerebellar hemorrhages and those in whom surgery is indicated at time of randomization</td>
</tr>
<tr>
<td>Imbalance between treatment groups for known factors that influence prognosis or treatment responsiveness</td>
<td>Large sample size: sensitivity analyses after adjusting for potential confounders</td>
<td>Included but require INR correction to value &lt;1.5 prior to randomization using protrobin complex concentrate</td>
</tr>
<tr>
<td>Heterogeneity of IV antihypertensive treatment can reduce effectiveness of SBP lowering and effect ICP</td>
<td>Several BP-lowering protocols using urapidil, labetalol, hydralazine, metoprolol, and nicardipine</td>
<td>Post-randomization adjusted analyses (adjusted for GCS score, IVH, and hematoma volume)</td>
</tr>
<tr>
<td>Effect of intensive SBP reduction post-24 h independent of hematoma expansion</td>
<td>A SBP level of &lt;140 mmHg maintained for the next 7 days in intensive SBP reduction group</td>
<td>Single agent—IV nicardipine, in all patients</td>
</tr>
<tr>
<td>Time to achieve therapeutic goals important for benefit</td>
<td>33% reaching therapeutic goals within 1 h in those allocated to intensive SBP reduction</td>
<td>The SBP goals after first 24 h same in both treatment groups</td>
</tr>
<tr>
<td>Heterogeneity in intensity of medical care in subjects between sites can affect the rates of death and disability</td>
<td>Not addressed</td>
<td>ATACH I suggested that 90% of subjects can reach therapeutic goals within 2 h. Interim monitoring in ATACH II demonstrates similar observation</td>
</tr>
<tr>
<td>Definition of primary outcome easy to interpret with direct clinical relevance</td>
<td>A dichotomous outcome mRS score of 0–2 versus 3–6 Investigator judgment</td>
<td>Review of patient care profile at each site by IOC</td>
</tr>
<tr>
<td>Ascertainment of safety or adverse events with determination of causal effect of trial intervention</td>
<td>Absolute risk reduction anticipated ≥7%, actual 3.6%</td>
<td>Review by IOC regarding relationship to treatment intervention and intensity of medical care</td>
</tr>
<tr>
<td>Large magnitude of benefits of trial intervention required to change clinical practices</td>
<td></td>
<td>Absolute risk reduction anticipated ≥10%</td>
</tr>
</tbody>
</table>

Qureshi et al., 2014
SPONTANEOUS INTRACEREBRAL HEMORRHAGE: BLOOD PRESSURE CONTROL

For ICH patients presenting with SBP 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class IIa; Level of evidence B).

BP should be controlled in all ICH patients (Class I; Level of Evidence A) and measures should begin immediately after ICH onset (Class I; Level of evidence A) to prevent recurrent ICH.

Hemphill et al., 2015
SPONTANEOUS INTRACEREBRAL HEMORRHAGE: SURGICAL OPTIONS

• Tested if early surgery compared with initial conservative treatment could improve outcome in these patients.
• International, parallel-group trial, unmasked, intention to treat
• Early surgery does not increase the rate of death or disability at 6 months
• May have a small but clinically relevant survival advantage for patients with spontaneous superficial ICH without IVH

Mendelow et al., 2013
SPO NTA NEO US INTRAC EREBRAL HEM O RRHAGE: SURG IC A L O PTIONS

Minimally Invasive Surgery Plus Recombinant Tissue-type Plasminogen Activator for Intracerebral Hemorrhage Evacuation Decreases Perihematomal Edema

- Tested if hematoma evacuation will reduce perihematomal volume and that treatment with rt-PA will not exacerbate it.
- MISTIE phase II for safety and efficacy
- Hematoma evacuation is associated with significant reduction in perihematomal edema and it is not exacerbated by rt-PA
- MISTIE phase III is underway involving 90 centers in the US, Europe, Israel, China and Australia

Mould et al., 2013
SPONTANEOUS INTRACEREBRAL HEMORRHAGE: SURGICAL OPTIONS

- Tested if patients with ICH <30cc and relatively large IVH causing acute obstructive HCP would have improved clinical outcomes when given injections of low-dose rtPA to accelerate lysis and evacuation of IVH compared with placebo.

- CLEAR IVH III randomized, multicenter, double-blind, placebo-controlled study.

- Finished, results pending.

Ziai et al., 2013
ENCEPHALITIS
UPDATES
ENC EPHALITIS

• What are the new challenges in encephalitis: autoimmune encephalitis?
ENCEPHALITIS: EPIDEMIOLOGY

• 7/100000 hospitalization rate of encephalitis
• Leading cause is viral encephalitis, 14% of all hospitalizations

Venkatesan, 2015
**ENCEPHALITIS: ANTIBODY-ASSOCIATED DISORDERS OF THE CNS**

<table>
<thead>
<tr>
<th>Paraneoplastic antibodies to intracellular neuronal proteins</th>
<th>Antibodies to intracellular synaptic proteins</th>
<th>Antibodies to synaptic or neuronal cell-surface antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu, Ri, Yo</td>
<td>Anti-GAD and anti ampiphysin</td>
<td>Autoimmune encephalitis syndrome NMDA, AMPA, GABA etc.</td>
</tr>
<tr>
<td>- Mediated by cytotoxic T-cell mechanisms</td>
<td>Unclear mechanism</td>
<td>- Antibodies to synaptic OR neuronal cell-surface antigens</td>
</tr>
<tr>
<td>- Antibodies markers of paraneoplasia</td>
<td></td>
<td>- Younger age group - with or without cancer association</td>
</tr>
<tr>
<td>With cancer association</td>
<td>Older age group</td>
<td></td>
</tr>
</tbody>
</table>

Rosenfeld, 2014
ENCEPHALITIS: GENERAL DIAGNOSTIC APPROACH

- Increase recognition:
  - Young
  - Rapid progressive encephalopathy of unclear etiology
  - "viral" etiology with negative viral studies
  - Psychiatric diagnosis
  - Abnormal movement

- CSF analysis: non specific, antibody testing
- Serum: antibody testing with basic bacterial and viral studies
- MRI with and without contrast
- PET scan
- CT chest, abdomen and Pelvis
- EEG
- Transvaginal ultrasound

Rosenfeld, 2014
ENCEPHALITIS:
GENERAL TREATMENT APPROACH

• NO GUIDELINES

• FIRST LINE:
  • Corticosteroids: 1 g/day x 5 days followed by taper
  • Plasma exchange vs IV Ig
  • Tumor treatment

• SECOND LINE:
  • Rituximab or cyclophosphamide

Rosenfeld, 2014
ENCEPHALITIS: OUTCOME

POOR OUTCOME FACTORS IN ENCEPHALITIS

- Age > 65y
- Immunocompromised
- Coma GCS < 8
- Mechanical ventilation
- Acute thrombocytopenia
- CSF polymorphonuclear cells

Singh, 2015
STATUS EPILEPTICUS UPDATES
STATUS EPILEPTICUS

• Updates in treatment of status epilepticus?
• What is non-convulsive status epilepticus?
STATUS EPILEPTICUS

• STATUS EPILEPTICUS- convulsions for 5 or more minutes or recurrent episodes of convulsions in a 5 minute interval without return to preconvulsive neurologic baseline.

• REFRACTORY SE- ongoing seizures failing to respond to first- and second-line anticonvulsant drugs

• SUPER REFRACTORY SE- no response to 3rd line therapy

• NON CONVULSIVE SE (NCSE)- no overt signs of convulsions but have seizure activity documented on EEG, can persist after CSE 20-48%

• 9-27% mortality rate

Al-Mufti, 2014
STATUS EPILEPTICUS

FIGURE 1: Cascade of selected mechanisms involved in the transition of a single seizure to status epilepticus

Betjemann and Lowenstein, , 2015
NON CONVULSIVE STATUS EPILEPTICUS

• 1/3 of patients in the NCCU may have NCSE
• In MICU, NCSE is 10% especially sepsis.
• With or without subtle convulsive movements: twitching of arms, legs, trunk or facial muscles, tonic eye deviation and nystagmoid eye jerking.
• Comatose patients should be highly considered for a continuous EEG.
• Mortality doubles with 24 hour delay in treatment

Al-Mufti, 2014
STATUS EPILEPTICUS: TREATMENTS

Betjemann and Lowenstein, 2015
### Alternative Therapies RSE

**Pharmacologic**
- Ketamine
- Corticosteroids
- Inhaled anesthetics
- Immunomodulation (intravenous immunoglobulin or plasmapheresis)

**Nonpharmacological**
- Vagus nerve stimulation
- Ketogenic diet
- Hypothermia
- Electroconvulsive therapy
- Transcranial magnetic stimulation
- Surgical management

**Case reports and small case series**
- Lidocaine
- Verapamil
- Paraldehyde
- Acetazolamide
- Deep brain stimulation

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Al-Mufti, 2014
REFERENCES


THANK YOU!