Biomarkers in Neurocritical Care

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Disclosures

- Dr Suarez receives funding from NINDS for research: subarachnoid hemorrhage and the Neurocritical Care Research Conference.

- I’m JUST a neurointensivist.

- I’m wrong sometimes
Objectives

- Delineate the basic principles of brain monitoring in neurocritical care patients
- Define biomarkers
- Discuss the most commonly-used and promising biomarkers in the neuroICU environment
- Describe possible future research in neuro biomarkers
Outline

- Basic Principles
- Definition of biomarkers
- Approaches in the neuroICU
- Specific biomarkers
- Future research
- Conclusions
Basic Principles
NeuroICU Environment

- Determining a correct diagnosis in patients with acute neurological problems often presents a considerable challenge.
- Clinicians traditionally rely on:
  - Good history taking
  - Neurological examination
- Latter may be unreliable in the neurocritically-ill patient.
What you need. When you need it.
Multimodality Monitoring

 Courtesy of Peter Kirkpatrick
Neurointensive Care

Multimodality Neuromonitoring + Goal Directed Therapy
Multimodality Monitoring
Courtesy of Peter Kirkpatrick
Too Much Data. 
Not Enough Information.

Lack of Integration. Clinicians are forced to do this in their heads.

Lack of Processing. Basic statistical analyses are elusive. More sophisticated analyses are unavailable at the bedside. Once again, done in their heads.

Inability to Search. It is difficult for data to be indexed, searched, and assembled to provide accurate information to treat patients, because the original context of the data is lost.

“Computational Technology for Effective Health Care: Immediate Steps and Strategic Directions,” NRC, 2009

Courtesy of J Michael Schmidt
The Need for Enhanced Situational Awareness

Translating Raw Data into Actionable Information

“Safety and efficiency of flight have been increased with improved pilot understanding of the airplane's situation relative to its environment.”

www.nasa.gov/centers/langley
The Need for Enhanced Situational Awareness

Translating Raw Data into Actionable Information

In aviation, a systems engineering approach mitigated cognitive errors and reduced crashes 65%.

Wald, New York Times, October 1, 2007
Biomarkers
What is a biomarker?

- **Biomarkers Definitions Working Group:**
  - A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
  - *(Clin Pharmacol Ther 2001;69:89-95)*

- **Desirable Features:**
  - Brain specific
  - Increase or decrease significantly during the relevant neurological insult
  - Available within a few hours
Biomarkers

- How do we determine the ideal biomarkers?

- NeuroICU environment is busy and constantly evolving

- How do we tell the weed from the shaft?
Pathophysiology of brain injury

Stochetti N et al, Crit Care 2012 with permission
Biomarkers

- Biomarkers may play an important role:
  - Diagnosis
  - Monitoring

- Biomarkers studied:
  - Neuron-specific enolase (NSE)
  - S100-B
  - Myelin basic protein (MBP)
  - Glial fibrillary acidic protein (GFAP)
  - Ubiquitin c-terminal hydrolase (UCHL-1)

- Are we close or just hoping?
  - “Hope is the worst of evils” (Nietzsche)
Chart 2.1 The biosynthesis of ATP.
Biomarkers and Biomediators Detectable after Traumatic Brain Injury in CSF

Mediators of secondary injury
- Excitatory Amino Acids: Glutamate, Aspartate, Glycine
- Inflammation: IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, sP-Sel, sICAM-1, QUIN, sCD163
- Cell Death: Nucleosomes, sFas, Cytochrome-c, Caspases, NSE, UCHL-1, S-100B, GFAP, Poly(ADP-ribose)
- Oxidative Stress: F2-Isoprostane, Antioxidant reserve, Ascorbate, GSH, LMW-thiols
- Protection and cell signaling: Adenosine, cAMP, Adrenomedullin, BCL-2, Procalcitonin, HGF, HSP70, VEGF
- Danger Signals: HSP60, HSP70, HMGB1
- CBF-Related: Endothelin-1, Nitrate/Nitrite, Nitrosothiols, HETE/ETE
- Poly(ADP-ribose)
Creatine Kinase

“Condition”, muscular dystrophy

“Event”, myocardial infarction
Biomarkers Applications in the NeuroICU

- **Diagnosis** = detecting brain injury (occult or predicted)
- **Prognosis** = determining extent of brain injury or prediction of outcome
- **Discovery** = identification of pathologic mechanisms and drug development
- **Monitoring** = neurological deterioration and/or response to treatment
Approaches
Traditionally single or a few molecular processes related to CNS injury

- **Proteomics approach:**
  - Many simultaneously
  - gel electrophoresis
  - mass spectrometry
  - antibody arrays
  - high-throughput immunoblotting

- **Lipidomics approach:**
  - Lipid peroxidation in CNS injury
  - Lipids from serum, plasma, tissue or cell

- **Blood-based genetic markers:**
  - APOE genotype may be related to clinical outcome in brain injuries

- **MicroRNAs:**
  - short, noncoding RNA molecules
  - regulate gene expression through RNA interference

- **Other approaches:**
  - Multiplex bead technologies
Specific Biomarkers
First described in 1965 \textit{(J Biol Chem 1965;240:1647–53)}

Found in the cytosol of CNS glial cells (astrocytes) but also extracranially

S100-B is elevated in SAH compared to healthy subjects and is associated with vasospasm and poor outcome \textit{(Acta Neurochir 2007;149(3):231–7)}

Limitations:

- Acceptability range
- Short half-life: 2 hours
**NSE**

- **First described in 1960s** *(J Biol Chem 1965;240:1647–53)*
- A glycolytic enzyme found predominantly in the neuronal cytoplasm
- It has been studied in TBI, stroke, and HIE
- Patients with NSE > 28-97 µg/L post cardiac arrest had poor outcome
- Should not be used alone:
  - marker for neuroendocrine, bladder tumors, small cell lung cancer and neuroblastomas
GFAP

- First described in 1971 *(Brain Res 1971;28(2):351–4)*
  - An intermediate filament protein that is only found in the glial cells of the CNS
  - May have good specificity and moderate sensitivity for TBI, while also having good specificity for CT-confirmed brain injury (mass lesion vs diffuse injury) *(Crit Care 2011;15(3):R156)*
  - May not add predictive power to commonly used prognostic variables in a TBI population of varying severities *(Crit Care 2015;19(1):362; World Neurosurg [Internet] 2015)*
MMPs

- Large family of proteolytic enzymes:
  - Degrade basement membrane components
  - Constituents of BBB: collagen IV, laminin and fibronectin
- MMP-2 and MMP-9 has been implicated as a negative prognostic factor in stroke
- MMPs have not shown sufficient sensitivity and specificity for use in the clinical setting.
UCH-L1

- Involved in addition or removal of ubiquitin from proteins that are destined for metabolism

Limitations:
- Found in non-neuroendocrine carcinomas: breast, kidney, prostate, pancreas, lung and colon
- It does not add predictive power to commonly used prognostic variables in TBI
Limitations of biomarkers

- Typical pattern:
  - Initial period of optimism
  - Then: an individual biomarker may be of some use, but there are often multiple confounding factors

- Brain consists of multiple substructures that may share the same biomarkers that serve very different functions

- Rising costs of healthcare
<table>
<thead>
<tr>
<th>Diseases</th>
<th>Type of Tests</th>
<th>Potential Biomarkers</th>
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<tbody>
<tr>
<td>Intracranial hypertension</td>
<td>Head CT, MRI brain, ultrasound, ICP monitor</td>
<td>IL-6</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Head CT, MRI DWI ADC, angiography</td>
<td>S100-B</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>Head CT, MRI SWI FFE, angiography</td>
<td>Leptin in basal ganglia hemorrhage, fibrinogen in post-tPA</td>
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<tr>
<td>Traumatic brain injury</td>
<td>Head CT, MRI brain, MRS, DTI</td>
<td>S100-B, NSE, UCH-L1, NFLP, MBP, GFAP</td>
</tr>
<tr>
<td>SAH vasospasm</td>
<td>TCD, CT angiography, invasive cerebral angiography, EEG</td>
<td>Nitrate, Nitrite, ADMA, S100-B</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>EEG, MRI</td>
<td>UCH-L1, MiRNA</td>
</tr>
<tr>
<td>Cardiac injury</td>
<td>EKG, 2D/3D Echogram, MRI heart</td>
<td>Troponin, CKMB</td>
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Conclusions

- Despite multiple studies and the enthusiasm towards development, no single biomarker has proven to be applicable clinically.

- Biomarkers may be used as an adjunct, supplementing a good neurological examination and neuroimaging to help in the diagnosis and prognostication in near future.

- Challenge will be to address the validity of biomarkers in different scenarios of brain injuries.

- To advance this field, multinational and multi-institution collaborations will be needed.
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Thank you!

Baylor St Luke’s Medical Center