PICU monitoring with
Scale of Problem

• Brain injury kills five times more children than cancer

• Nearly 25% PICU adm: risk of acute neurological injury

• High incidence of traumatic brain injury (TBI)
  
  – In US: 35,000 severe TBI and 7440 deaths/yr (CDC)

• Apprx 50% poor neurological outcomes at 6 mo

• Mean age ~ 9 yrs, productive life-years 1.3 million/yr

  PCCM 2011;12:601-2
  Neurotherapeutics 2012;9:3-16
Critical Illness induced acute neurological injury

Trauma

Infection/inflammation

Secondary Insult

Neuro-Oncology

Hypoxic-ischemic insult
# TABLE 1. Updated Recommendations: Monitoring

<table>
<thead>
<tr>
<th>Topics</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial pressure monitoring</td>
<td><strong>Level III</strong></td>
</tr>
<tr>
<td></td>
<td>To Improve Overall Outcomes</td>
</tr>
<tr>
<td></td>
<td>III.1. Use of ICP monitoring is suggested.</td>
</tr>
<tr>
<td>Advanced neuromonitoring</td>
<td><strong>Level III</strong></td>
</tr>
<tr>
<td></td>
<td>To Improve Overall Outcomes</td>
</tr>
<tr>
<td></td>
<td>III.1. If Pbro₂ monitoring is used, maintaining a level &gt; 10mm Hg is suggested.</td>
</tr>
<tr>
<td></td>
<td>Note 1: There was insufficient evidence to support a recommendation for the use of a monitor of Po₂ in brain interstitium (Pbro₂) to improve outcomes.</td>
</tr>
<tr>
<td></td>
<td>Note 2: Use of advanced neuromonitoring (brain oxygenation) should only be for patients with no contraindications to invasive neuromonitoring, such as coagulopathy, and for patients who do not have a diagnosis of brain death.</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td><strong>Level III</strong></td>
</tr>
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<td></td>
<td>To Improve Overall Outcomes</td>
</tr>
<tr>
<td></td>
<td>III.1. Excluding the possibility of elevated ICP on the basis of a normal initial (0–6hr after injury) CT examination of the brain is not suggested in comatose pediatric patients.</td>
</tr>
<tr>
<td></td>
<td>III.2. Routinely obtaining a repeat CT scan &gt; 24hr after the admission, and initial follow-up is not suggested for decisions about neurosurgical intervention, unless there is either evidence of neurologic deterioration or increasing ICP.</td>
</tr>
</tbody>
</table>
### TABLE 2. Updated Recommendations: Thresholds

<table>
<thead>
<tr>
<th>Topics</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold for treatment of intracranial hypertension</td>
<td><strong>Level III</strong>&lt;br&gt;<strong>To Improve Overall Outcomes</strong>&lt;br&gt;III.1. Treatment of intracranial pressure targeting a threshold of $&lt; 20 \text{ mm Hg}$ is suggested.</td>
</tr>
<tr>
<td>Thresholds for cerebral perfusion pressure</td>
<td><strong>Level III</strong>&lt;br&gt;<strong>To Improve Overall Outcomes</strong>&lt;br&gt;III.1. Treatment to maintain a CPP at a minimum of $40 \text{ mm Hg}$ is suggested.&lt;br&gt;III.2. A CPP target between 40 and $50 \text{ mm Hg}$ is suggested to ensure that the minimum value of $40 \text{ mm Hg}$ is not breached. There may be age-specific thresholds with infants at the lower end and adolescents at or above the upper end of this range.</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td><strong>Level III</strong>&lt;br&gt;<strong>To Improve Overall Outcomes</strong>&lt;br&gt;III.1. Excluding the possibility of elevated ICP on the basis of a normal initial (0–6hr after injury) CT examination of the brain is not suggested in comatose pediatric patients.&lt;br&gt;III.2. Routinely obtaining a repeat CT scan $&gt; 24 \text{ hr}$ after the admission, and initial follow-up is not suggested for decisions about neurosurgical intervention, unless there is either evidence of neurologic deterioration or increasing ICP.</td>
</tr>
</tbody>
</table>

*Note 2: Use of advanced neuromonitoring (brain oxygenation) should only be for patients with no contraindications to invasive neuromonitoring, such as coagulopathy, and for patients who do not have a diagnosis of brain death.*
Cerebral perfusion pressure: management protocol and clinical results

CPP above: 70? ....65?...

CPP may be low; ICP<15 mmHg

Set thresholds: Is it wise?

Too low CPP: ischaemia

Too high CPP: hyperaemia
Cerebrovascular Dynamics in Children

- Age/gender related differences: ICP, CBF, CA
- LLA may not be lower in lower age groups
- Association of autoregulation with outcome
- Impaired CA in 29-63% paediatric TBI

Age-related changes in mean flow velocity of middle cerebral artery (VMCA) in both genders, cerebral blood flow (CBF), cerebral metabolic rate of glucose (CMRglu) (Adult values: VMCA ~ 50 cm/sec, CBF 50 ml/100g/min, CMRglu 19-33 μmol/100g/min)

Pediatr Neurol 2008;38:225-34
N=12 (8 survivors)

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 7)</th>
<th>Non-survivors (n = 5)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP (mm Hg)</td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>13.07</td>
<td>3.23</td>
<td>21.64</td>
</tr>
<tr>
<td>%time ICP &gt; 20 mm Hg</td>
<td>9.73</td>
<td>9.84</td>
<td>60.47</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>77.07</td>
<td>17.69</td>
<td>93.00</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>63.42</td>
<td>8.10</td>
<td>61.11</td>
</tr>
<tr>
<td>CPPopt (mm Hg)</td>
<td>63.68</td>
<td>8.94</td>
<td>66.45</td>
</tr>
<tr>
<td>PRx (a.u.)</td>
<td>0.02</td>
<td>0.19</td>
<td>0.39</td>
</tr>
<tr>
<td>RAP (a.u.)</td>
<td>0.64</td>
<td>0.27</td>
<td>0.46</td>
</tr>
<tr>
<td>%time CPPopt available</td>
<td>55.96</td>
<td>13.84</td>
<td>43.48</td>
</tr>
<tr>
<td>Duration (hours)</td>
<td>75.3</td>
<td>22.3</td>
<td>82.3</td>
</tr>
<tr>
<td>%time CPPopt available</td>
<td>55.96</td>
<td>13.84</td>
<td>43.48</td>
</tr>
<tr>
<td>%time CPP-CPPopt &lt; -10 mm Hg</td>
<td>4.70</td>
<td>5.68</td>
<td>15.17</td>
</tr>
<tr>
<td>%time CPP-CPPopt -10 to 10 mm Hg</td>
<td>90.68</td>
<td>12.64</td>
<td>70.61</td>
</tr>
<tr>
<td>%time CPP-CPPopt &gt; 10 mm Hg</td>
<td>5.09</td>
<td>10.03</td>
<td>11.62</td>
</tr>
</tbody>
</table>
Fig 2. Example of a 4 hour epoch of multimodality monitoring signals in pediatric TBI. In this screenshot, CPP is shown in the top panel and the pressure reactivity index in the second panel over a 4 hour period from 06:00 to 10:00. In the third panel is a risk chart whereby a negative PRx (good autoregulation) is denoted by a grey colour, and a disturbed PRx (>0.3) is denoted in black. In two instances, CPP drops below 60 mm Hg. During these drops in CPP, PRx is deranged (black on the risk chart). On the bottom panel, CPP is plotted against PRx and a polynomial curve is fitted. The minimum of this curve is around 65 mm Hg, which would therefore indicate the optimal CPP at time point 10:00.
Fig 3. Real-time calculation of CPPoptimal in-vivo. Fig 3A is an example of a pediatric TBI patient. ICP is displayed in the top panel, followed by CPP (both the absolute CPP (line) and the calculated CPPopt (circles)), a risk chart of PRx and finally a histogram indicating the time spent at various distances from the calculated optimal CPP. Although this patient's CPP was above 60 mm Hg for the whole of this recording, CPP was consistently below the calculated optimal CPP. This is depicted in the histogram which indicates that over this 2 day period, the patient spent almost 20% of time (expressed as a percentage of the total time CPPopt available) > 10 mm Hg below the instantaneous CPPopt. In the second day of this recording we see persistently disturbed PRx. This patient died three days after admission. Fig 3B shows an analogous example in another pediatric TBI patient. This patient demonstrated multiple plateau waves of ICP and a CPP between 60 and 70 mm Hg. Autoregulation as indicated by the PRx risk chart was mainly good. CPP was mainly close to the calculated optimal CPP as seen in both in the time series view (panel 2) and in the CPP-CPPopt time-histogram (bottom panel). This patient survived.
Sample Size calculation

• Based on our paediatric TBI experience

• Mean (± SD) PRx of 0.03 ± 0.13 for favourable outcome and mean (± SD) PRx of 0.10 ± 0.17 (SD) for unfavourable outcome

• One sided analysis, favourable: unfavourable ratio of 0.77 (80% power and alpha error of 5% & allowance for losses (protocol violations, withdrawal of consent, or loss of FU))

• Total: 135 patients.
Multicentre UK study: 10 sites

- 135 patients over 3 years with one year follow-up

Objectives:

- Primary: Optimal PRx with 12 mo outcome (GOSE peds)
- Secondary: Optimal CPP
- Research Database
STARSHIP

• 16 years or younger admitted to PICU

• TBI confirmed on CT or MRI

• Clinical requirement for monitoring ICP & ABP

• No exclusion criteria

• Consent for Follow-up before hospital discharge
## STARSHIP: Sites

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Lead Consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambridge University Hospitals (Sponsor)</td>
<td>Dr Shruti Agrawal (CI)</td>
</tr>
<tr>
<td>Birmingham Children’s Hospital</td>
<td>Dr Hari Krishnan</td>
</tr>
<tr>
<td>Great Ormond Street Hospitals</td>
<td>Dr Harish Bangalore</td>
</tr>
<tr>
<td>Leeds Children’s Hospital</td>
<td>Dr Santosh Sundarajan</td>
</tr>
<tr>
<td>Manchester Children’s Hospital</td>
<td>Dr Gayathri Subramaniam</td>
</tr>
<tr>
<td>Nottingham Children’s Hospital</td>
<td>Dr Dusan Raffaj</td>
</tr>
<tr>
<td>Oxford University Hospitals</td>
<td>Dr Avishay Sarfatti</td>
</tr>
<tr>
<td>Royal London Hospital</td>
<td>Dr Simona Lampariello</td>
</tr>
<tr>
<td>Sheffield Children’s Hospital</td>
<td>Dr Anton Mayer</td>
</tr>
<tr>
<td>Southampton Children’s Hospital</td>
<td>Dr Oliver Ross</td>
</tr>
</tbody>
</table>
Progress (8th September 2019)

• Software licensing fee for ICM+ waived for study
• Hardware supplies by Academic Neurosciences, Cambridge
• Study live from 1st July 2018, 10/10 sites set-up and recruiting
• 53 patients recruited, 2 refused consent, 2 technical problems
• Collaboration with KidsBrainIT.
Plateau waves in children

- 42 TBI patients 16 years old and younger

- Plateau waves:
  - $\uparrow$ICP > 40 for at least 5 minutes
  - Mean ICP < 25, 30 min prior to plateau wave
  - $\downarrow$CPP > 15 from before to during plateau
  - $\downarrow$ICP < 25, in 30 min following the plateau wave.
Plateau waves as frequent as in adult TBI.

Associated with ↑ ETCO$_2$ or ↑/↓ MAP.

Short-lived plateau did not affect prognosis.
A multiplex network approach for the analysis of intracranial pressure and heart rate data in traumatic brain injured patients

Giovanna Maria Dimitri, Shruti Agrawal, Adam Young, Joseph Donnelly, Xiuyun Liu, Peter Smielewski, Peter Hutchinson, Marek Czosnyka, Pietro Lió and Christina Haubrich
Simultaneous Transients of Intracranial Pressure and Heart Rate in Traumatic Brain Injury: Methods of Analysis.

Dimitri GM¹, Agrawal S², Young A³, Donnelly J⁴, Liu X⁴, Smielewski P⁴, Hutchinson P³, Czosnyka M⁴, Lio P¹, Haubrich C⁵,⁶.

Advanced Neuromonitoring in PTBI

- 10 patients > 3 years old with severe TBI
- Triple bolt: ICP, PBtO$_2$ and microdialysis catheter
- Glucose, lactate, pyruvate, glutamate and glycerol
Figure 4. Time line of intracranial pressure (ICP) and microdialysis trace. This is a 7-year-old girl sustained severe traumatic brain injury (TBI) with moderate diffuse axonal injury (Marshall grade 3) on initial computed tomography (CT) scan. The timeline points represent 2-h sampling averages. A clear lag of one sampling point can be observed between the measured ICP and the lactate/pyruvate ratio.

Multimodality neuromonitoring in severe pediatric traumatic brain injury

Adam M.H. Young¹, Mathew R. Guiffoyle¹, Joseph Donnelly¹, Peter Smielewski¹, Shruti Agarwala², Marek Czosnyka¹ and Peter J. Hutchinson¹

Volume 83 | Number 1 | January 2018 | Pediatric RESEARCH
FIGURE 1 | (A) Observed mean arterial glucose (SD) in pediatric traumatic brain injury (TBI) patients during the first 5 days since ictus, stratified by fatal outcome. (B) Observed mean arterial lactate (SD) in pediatric TBI patients during the first 5 days since ictus, stratified by fatal outcome.

FIGURE 2 | Correlation between mean arterial glucose and PRx in pediatric traumatic brain injury patients during the first 5 days since ictus. There was a significant positive relationship between blood glucose and PRx (Pearson correlation = 0.351; p < 0.001). Each data point represents the mean of the available arterial glucose concentration and PRx measurements during the first 5 days since ictus.
Transcranial Doppler

- Non-invasive
- Used in paed TBI for autoregulation and blood flow measurement
- Figaji et al: 52 patients severe TBI
  - Autoregulatory index (ARI) after increasing ABP by 20%
  - Found correlation with ICP, PbtO$_2$
- Vavilala et al: 36 patients with severe TBI
  - ARI and MCA flow velocity measured
  - Good correlation of loss of autoregulation & outcome

*J Neurosurg Pediatrics 2009;4:420-8*
*J Neurotrauma 2009. 10.1089/neu.2008.0770*
Transcranial Doppler as a non-invasive method to estimate cerebral perfusion pressure in children with severe traumatic brain injury

Francisco Abecasis¹, Danilo Cardim², Marek Czosnyka³,⁴, Chiara Robba⁵, Shruti Agrawal⁶

Diagram a: R=0.99
Diagram b: R=0.99

Child’s Nervous System
https://doi.org/10.1007/s00381-019-04273-2
NIRS measurements

- FV [cm/s]
- MAP [mmHg]
- HR [c/min]
- TOI [%]
- THI [au]
- SpO₂ [%]
- RR [c/min]
Determination of Optimal MABP in Preterm Infants

Optimal MABP vs Mortality

Mean = 2.1
CI (1.64, 2.56)

Mean = 4.2
CI (3.44, 4.96)

abs(abp-abpopt)

Survived

Not Survived

p=0.013

Aspirations
Aspirations

• Expand STARSHIP database
Aspirations

- Expand STARSHIP database
- Introduce TCD, NIRS, PbTO$_2$
Aspirations

• Expand STARSHIP database
• Introduce TCD, NIRS, PbTO$_2$
• Non-invasive surrogates, autonomic function
Aspirations

• Expand STARSHIP database
• Introduce TCD, NIRS, PbTO₂
• Non-invasive surrogates, autonomic function
• Apply CA in non-TBI critically ill children
Aspirations

- Expand STARSHIP database
- Introduce TCD, NIRS, PbT0
- Non-invasive surrogates, autonomic function
- Apply CA in non-TBI critically ill children
Acknowledgments:

Brain Physics Department
Academic Neurosciences
Department of Paediatrics
All Starship Site teams, Patients