Trauma and Organ Donation: stabilisation of the brain dead patient

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Conflict of interest

- member of the UK Government Taskforce on Organ Donation
Outline

- physiological changes associated with brain death
- systemic physiological support after brain death
- evidence for outcome effects of donor management
- recommendations
Background

- gap between organ availability and those awaiting a transplant is a worldwide problem
  - limited donor pool
  - low number of potentially transplantable organs retrieved from each donor
- increase number and source of potential donors
Deceased donors per million population (pmp) in member Countries of the Council of Europe in 2014

DBD donors after brain death
DCD donors after circulatory death
Background

- gap between organ availability and those awaiting a transplant is a worldwide problem
  - limited donor pool
  - low number of potentially transplantable organs retrieved from each donor

- increase number and source of potential donors

- increase number of transplantable organs from each potential donor
  - optimizing donor maintenance and management strategies
  - implementing novel treatment and repair of donor organs using ex-vivo techniques
Intracranial events leading to brainstem death

- Rise in ICP
- Worsening cerebral ischaemia
- Brain swelling
- Downward shift of brain substance
- Brain swelling
- Cessation of intracranial circulation
Systemic physiological changes

**Pons**
- mixed vagal & sympathetic stimulation
- Cushing response

**Lower medulla**
- unopposed sympathetic stimulation

**Spinal sympathetic pathways**
- total sympathetic denervation
Complications of brainstem death

- hypotension 81% - 97%
- diabetes insipidus 46% - 78%
- DIC 29% - 55%
- cardiac arrhythmias 25% - 32%
- pulmonary oedema 13% - 18%
- metabolic acidosis 11% - 15%
Cardiovascular changes

Hypovolaemia
- inadequate resuscitation
- diuretics for raised ICP
- diabetes insipidus
- hyperglycaemia-induced diuresis
- venous pooling
Cardiovascular changes

**Sympathetic ‘storm’**
- massive rise in circulating catecholamines
- intense vasoconstriction
- hypertension & tachycardia
- no increase in myocardial oxygen delivery
  - subendocardial ischaemia
  - early impairment of cardiac function in organ donors
Cardiovascular changes

Myocardial structural damage

- local catecholamine effect
  - myocytolysis
  - contraction band necrosis
  - haemorrhage

- inflammatory response

- changes in myocardial gene expression
Cardiovascular changes

Loss of sympathetic activity

- secondary cardiovascular collapse
- occurs initially as a result of profound vasodilatation
- severe haemodynamic instability
- related to severity of brain injury
- cardiovascular system effectively uncoupled from autonomic control
Pulmonary changes

- high incidence of respiratory complications associated with severe brain injury
- catecholamine surge may cause direct pulmonary injury
  - ↑ pressure in pulmonary capillary bed → endothelial damage
  - ↑ pulmonary capillary permeability
- volume overload may precipitate pulmonary oedema
- aspiration pneumonia
Endocrine changes

- **↓ antidiuretic hormone levels**
  - diabetes insipidus in up to 80% brain stem dead patient
  - inappropriate diuresis, hypovolaemia, hypernatraemia, hyperosmolality
  - exacerbation of neurogenic pulmonary oedema
  - tissue hypoperfusion

- **↓ free tri-iodothyronine (T3)**
  - may contribute to deterioration in myocardial function
  - production of reverse T3 - sick euthyroid syndrome

- **↓ cortisol**
  - hypotension
  - catecholamine ‘resistance’

- **↓ insulin and development of insulin resistance**
  - hyperglycaemia
Other changes

- profound pro-inflammatory state
  - multiple effects
- disseminated intravascular coagulation
  - microthrombi formation
- dysregulated temperature homeostasis
  - hypothermia
- acute kidney injury
The case for donor management

- donation after brain death offers greater potential than donation after cardiac death
  - greater number of organs retrieved per donor
  - Improved post-transplant graft function

- transplant outcomes improved by effective potential donor management

- donor management guidelines emphasize the importance of maintenance of physiological stability throughout the peri-donation period
Odds ratios (95% confidence intervals) for organ transplantation with or without intensivist-led donor management

Singbart et al, Am J Transplant 2011; 11: 1517-21
The evidence for donor management

<table>
<thead>
<tr>
<th>VENTILATORY SETTINGS</th>
<th>Low tidal volumes (TV 6-8 ml/kg) + PEEP ≥ 8 [RCT evidence]</th>
<th>Prudent fluid administration (PVC ≤ 8) [NO RCT evidence]</th>
<th>Cleaning bronchoscopy [NO RCT evidence]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPROVE HEMODYNAMICS</td>
<td>Maintain MAP &gt; 60, HR &lt; 100,</td>
<td>Vasopressin (0.01 – 0.04) widely used [NO RCT evidence]</td>
<td>Low dose corticosteroids [NO RCT evidence]</td>
</tr>
<tr>
<td></td>
<td>Use of others beta-adrenergic drugs (Dopamine &gt; 4 mcg/kg/min,</td>
<td>Noradrenaline, Dobutamine, Phenylephrine [NO RCT evidence]</td>
<td>T3 (4 mcg bolus + 3 mcg/h infusion) [NO RCT evidence]</td>
</tr>
<tr>
<td>KIDNEY FUNCTION OPTIMIZATION</td>
<td>Adequate perfusion pressure (PAM &gt; 60; urine output &gt; 1 ml/kg)</td>
<td>Mild Hypothermia (34-35° C) reduces the rate of delayed graft function in recipients [RCT evidence]</td>
<td>Avoid hypovolemia Treat DI: Desmopressin 1mcg [NO RCT evidence]</td>
</tr>
<tr>
<td></td>
<td>Low dose Dopamine (4 mcg/kg/min) is associated with better kidney graft function in recipient [RCT evidence]</td>
<td>Glycemia &lt; 180 mg/dl</td>
<td></td>
</tr>
</tbody>
</table>

Greer et al, Intensive Care Med 2015; 41: 537-40
Haemodynamic management

random assignment to protocolised (n=279) or usual (n=277) care

PPV, pulse pressure variation
CI, cardiac index
MAP, mean arterial pressure

Al-Khafaji, Intensive Care Med 2015; 41: 418-26
- random assignment to protocolised (n=279) or usual (n=277) care
- protocol implemented in 76% of randomised patients
- no difference in mean number of organs transplanted per donor (3.39 vs. 3.29)

**Difference in mean number of organs transplanted**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>nP</th>
<th>nU</th>
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<tbody>
<tr>
<td>ITT</td>
<td>249</td>
<td>259</td>
</tr>
<tr>
<td>mITT</td>
<td>189</td>
<td>259</td>
</tr>
<tr>
<td>Responders</td>
<td>54</td>
<td>259</td>
</tr>
</tbody>
</table>
• random assignment to protocolised (n=279) or usual (n=277) care
• protocol implemented in 76% of randomised patients
• no difference in mean number of organs transplanted per donor (3.39 vs. 3.29)
• no difference in recipient mortality
  – 12-month overall survival
  – 6-month hospital-free survival
• more effective and easier to implement strategies required

Kaplan-Meier curves for overall survival
PC, protocolised care; UC, usual care

Al-Khafaji, Intensive Care Med 2015; 41: 418-26
Vasopressors/inotropes

- insufficient evidence to recommend one vasopressor/inotrope over another
- dopamine conventionally been used as first line treatment
  - low dose (< 4 µg/kg/min) associated with improved renal graft function
- no evidence to support use of other beta-adrenergic drugs (including dopamine > 4 µg/kg/min)
- high dose norepinephrine (> 0.05 µg/kg/min) associated with increased cardiac graft dysfunction
- vasopressin may be appropriate first choice
  - particularly in presence of diabetes insipidus
Hormone replacement

- increases the number of organs suitable for transplantation

- methylprednisolone
- T3
- vasopressin/desmopressin
- insulin

Odds of an organ being recovered and transplanted: hormone resuscitation vs. standard care

Odds ratio > 1 = higher odds of transplant

Rosendale et al, Transplantation 2003; 75: 482-7
Number of donors and organs successfully procured 2002 to 2012

Black bar, number of donors; white bar, number of organs.

Callahan et al, J Am Coll Surg 2014; 219: 752-6
Incidence of hormone replacement therapy and high-yield (4 organs) procurement 2002 to 2012

Black bar, hormone replacement therapy; white bar, high-yield procurement

Callahan et al, J Am Coll Surg 2014; 219: 752-6
Low dose hydrocortisone – CORTICOME study

- random assignment to steroid replacement (n=102) or usual care (n=157)
- hydrocortisone 50 mg bolus followed by 10 mg/h
- exclusions – previous steroid administration, adrenal insufficient before brain death

Pinsard et al, Crit Care 2014; 18: R158
Low dose hydrocortisone – CORTICOME study

- no difference in number of organs retrieved or delayed graft function

### Organs recovered/organs recoverable

<table>
<thead>
<tr>
<th>Organs</th>
<th>All patients (n = 208)</th>
<th>Control group (n = 128)</th>
<th>Steroid group (n = 80)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>394/403 (97.7)</td>
<td>243/248 (98)</td>
<td>151/155 (97.4)</td>
<td>0.65</td>
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<tr>
<td>Liver</td>
<td>162/172 (94.2)</td>
<td>99/105 (94.3)</td>
<td>63/67 (94)</td>
<td>0.61</td>
</tr>
<tr>
<td>Heart</td>
<td>66/80 (82.5)</td>
<td>47/56 (83.9)</td>
<td>19/24 (79.1)</td>
<td>0.74</td>
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<tr>
<td>Lung</td>
<td>71/93 (73.9)</td>
<td>44/62 (70.9)</td>
<td>27/34 (79.4)</td>
<td>0.36</td>
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<tr>
<td>Pancreas</td>
<td>21/47 (44.6)</td>
<td>16/39 (41)</td>
<td>5/8 (62.5)</td>
<td>0.43</td>
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<tr>
<td>Total</td>
<td>714/798 (89.5)</td>
<td>449/510 (88)</td>
<td>265/288 (92)</td>
<td>0.07</td>
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</tbody>
</table>

Organ/donors, n (SD) 3.43 (1.37) 3.51 (1.39) 3.31 (1.36) 0.23

Pinsard et al, Crit Care 2014; 18: R158
Low dose hydrocortisone – CORTICOME study

- no difference in number of organs retrieved or delayed graft function
- vasopressor administration significantly lower in steroid group

Pinsard et al, Crit Care 2014; 18: R158
Corticosteroids in the management of brain-dead potential organ donors: a systematic review

Green: corticosteroids associated with a positive result  
Blue: corticosteroids associated with neutral result  
White: outcome not assessed

Low quality and conflicting evidence supporting the routine use of corticosteroids in the management of organ donors

<table>
<thead>
<tr>
<th>Donor outcomes</th>
<th>Haemodynamics</th>
<th>Oxygenation</th>
<th>Lung procurement</th>
<th>Heart procurement</th>
<th>Any organ procurement</th>
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<tr>
<td>Randomized controlled trials</td>
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<tr>
<td>Chatterjee 1977&lt;sup&gt;24&lt;/sup&gt;</td>
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<td>Dienst 1977&lt;sup&gt;25&lt;/sup&gt;</td>
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<td>Jeffery 1978&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>Soulliol 1979&lt;sup&gt;27&lt;/sup&gt;</td>
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<td>Corry 1980&lt;sup&gt;28&lt;/sup&gt;</td>
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<td>Mariot 1991&lt;sup&gt;29&lt;/sup&gt;</td>
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<tr>
<td>Kotsch 2008&lt;sup&gt;30&lt;/sup&gt;</td>
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<tr>
<td>Venkateswaran 2008&lt;sup&gt;31&lt;/sup&gt;</td>
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<tr>
<td>Venkateswaran 2009&lt;sup&gt;32&lt;/sup&gt;</td>
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<tr>
<td>Kainz 2010&lt;sup&gt;33&lt;/sup&gt;</td>
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<tr>
<td>Amatschek 2012&lt;sup&gt;34&lt;/sup&gt;</td>
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</tbody>
</table>

| Non-randomized studies | | | | | |
| Zincke 1978<sup>34</sup> | | | | | |
| Novitzky 1987<sup>17</sup> | | | | | |
| Taniguchi 1992<sup>41</sup> | | | | | |
| Follette 1998<sup>16</sup> | | | | | |
| Follette 1999<sup>35</sup> | | | | | |
| McElhinney 2001<sup>36</sup> | | | | | |
| Rosendale 2003<sup>15</sup> | | | | | |
| Rosendale 2003<sup>14</sup> | | | | | |
| Van Bakel 2004<sup>42</sup> | | | | | |
| Salim 2005<sup>39</sup> | | | | | |
| Salim 2008<sup>38</sup> | | | | | |
| Selck 2008<sup>48</sup> | | | | | |
| Nath 2010<sup>37</sup> | | | | | |
| Dhar 2015<sup>43</sup> | | | | | |
• retrospective review of 63,593 brain-dead organ donors (2000-2009)
T3/T4 therapy associated with
- mean of 3.31 organs from donors who received T3/T4 vs. 2.87 from donors who did not (increase of 15.3%) (p < 0.0001)
- increased procurement of all organs except livers

beneficial effect of T3/T4 independent of other factors

<table>
<thead>
<tr>
<th>Organs</th>
<th>Group A (T3/T4) (donors, n=23,022)</th>
<th>Group B (no T3/T4) (donors, n=17,102)</th>
<th>Statistical significance A vs. B (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. organs transplanted</td>
<td>Percentage of donors from which organs were transplanted</td>
<td>No. organs transplanted</td>
</tr>
<tr>
<td>Hearts</td>
<td>8,055</td>
<td>34.99</td>
<td>4,406</td>
</tr>
<tr>
<td>Both lungs</td>
<td>8,070</td>
<td>17.53</td>
<td>4,278</td>
</tr>
<tr>
<td>Single lung</td>
<td>798</td>
<td>3.47</td>
<td>442</td>
</tr>
<tr>
<td>Both kidneys</td>
<td>33,722</td>
<td>73.24</td>
<td>22,018</td>
</tr>
<tr>
<td>Single kidney</td>
<td>1,566</td>
<td>6.80</td>
<td>1,234</td>
</tr>
<tr>
<td>Livers&lt;sup&gt;h&lt;/sup&gt;</td>
<td>18,461</td>
<td>80.26</td>
<td>13,642</td>
</tr>
<tr>
<td>Pancreas&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4,914</td>
<td>21.35</td>
<td>2,681</td>
</tr>
<tr>
<td>Intestine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>597</td>
<td>2.59</td>
<td>400</td>
</tr>
<tr>
<td>Total</td>
<td>76,183&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.59</td>
<td>49,101&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Mean no. organs per donor: 3.31±1.78<sup>e</sup> vs. 2.87±1.74<sup>d</sup> (p < 0.0001<sup>e</sup>)

Novitzky et al, Transplantation 2014; 98: 1119-27
A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors

- 37 original publications
  - 16 separate case series or retrospective audits
  - 7 randomized controlled trials, including 4 placebo-controlled

- all case series and retrospective audits reported beneficial effect of thyroid hormone administration

- all randomized controlled trials reported no benefit of thyroid hormone administration (alone or in combination with other hormones)

- meta-analysis of the 4 placebo controlled RCTs (209 donors)

• T3/T4 had no significant effect on donor cardiac index
  – pooled mean difference 0.15 L/min/m² (95% CI –0.18 to 0.48)
• T3/T4 had no significant effect on dose of inotropic agent at time of organ retrieval

Dopamine in Goarin et al and Perez-Blanco et al.
Dobutamine in Mariot et al.

• this systematic review does not support a role for routine administration of thyroid hormone in the brain-dead potential organ donor

• current recommendations regarding the use of thyroid hormone in marginal donors are based on low-level evidence

General management principle of the heart beating organ donor

<table>
<thead>
<tr>
<th>System</th>
<th>Monitoring and management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Invasive cardiovascular monitoring&lt;br&gt;Maintain euvoemia&lt;br&gt;Target mean blood pressure ≥70 mmHg&lt;br&gt;Insufficient data to recommend one vasopressor/inotrope over another&lt;br&gt;Vasopressin (0.5–1.0 millunits/kg/h) is a first-line choice in many centers and may reduce catecholamine requirements&lt;br&gt;High-dose norepinephrine (&gt;0.5 μg/kg/min) should be avoided if possible&lt;br&gt;Consider triiodothyronine for resistant hypotension</td>
</tr>
<tr>
<td>Respiratory</td>
<td>‘Protective’ lung ventilation: tidal volume 6–8 ml/kg, PEEP 6–8 cmH₂O&lt;br&gt;PaO₂ ≥ 10.7 kPa, PaCO₂ 4.7–6.0 kPa, pH 7.35–7.45&lt;br&gt;Recruitment maneuvers as required&lt;br&gt;Ventilation ‘care bundle’ including elevation of head of the bed</td>
</tr>
<tr>
<td>Fluids and electrolytes</td>
<td>Maintain euvoemia&lt;br&gt;Avoid hypernatremia&lt;br&gt;Urine output 0.5–2.5 ml/kg/h&lt;br&gt;Consider DI if urine output &gt;4 ml/kg/h and treat with vasopressin infusion or desmopressin&lt;br&gt;Insulin infusion to maintain blood glucose between 4 and 8 mmol/l</td>
</tr>
<tr>
<td>Hormone replacement</td>
<td>Vasopressin as above&lt;br&gt;Methylprednisolone 15 mg/kg bolus after brain death confirmed and daily thereafter&lt;br&gt;Both triiodothyronine (T3) and levothyroxine (T4) have been used for thyroid hormone replacement: T3 iv 4.0 μg bolus followed by 3 μg/h infusion or T4 20 μg iv bolus followed by 10 μg/h infusion</td>
</tr>
<tr>
<td>Blood and coagulation</td>
<td>Correct coagulopathy&lt;br&gt;Consider packed red cells if hemoglobin &lt;70 g/l&lt;br&gt;Maintain thromboprophylaxis</td>
</tr>
<tr>
<td>Temperature</td>
<td>Minimize heat loss&lt;br&gt;Maintain core temperature at 35 °C&lt;br&gt;Humidified inspired gases&lt;br&gt;Warmed iv fluids&lt;br&gt;Treat intercurrent infections</td>
</tr>
</tbody>
</table>

Citerio et al, Intensive Care Med 2016; Jan, Epub ahead of print
Management of the Potential Organ Donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement

Robert M. Kotloff, MD; Sandralee Blosser, MD; Gerard J. Fulda, MD; Darren Malinoski, MD; Vivek N. Ahya, MD; Luis Angel, MD; Matthew C. Byrnes, MD; Michael A. DeVita, MD; Thomas E. Grissom, MD; Scott D. Halpern, MD; Thomas A. Nakagawa, MD; Peter G. Stock, MD; Debra L. Sudan, MD; Kenneth E. Wood, DO; Sergio J. Anillo, MD; Thomas P. Bleck, MD; Elling E. Eidbo, MBA; Richard A. Fowler, MBA; Alexandra K. Glazier, JD, MPH; Cynthia Gries, MD; Richard Hasz, MFS, CPTC; Dan Herr, MD; Akhtar Khan, MD; David Landsberg, MD; Daniel J. Lebovitz, MD; Deborah Jo Levine, MD; Mudit Mathur, MD; Priyumvada Naik, MD; Claus U. Niemann, MD; David R. Nunley, MD; Kevin J. O’Connor, MS; Shawn J. Pelletier, MD; Omar Rahman, MD; Dinesh Ranjan, MD; Ali Salim, MD; Robert G. Sawyer, MD; Teresa Shafer, RN, MSN; David Sonneti, MD; Peter Spiro, MD; Maryam Valapour, MD; Deepak Vikraman-Sushama, MD; Timothy P. M. Whelan, MD; for the Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Donor Management Task Force
Cardiovascular targets

- maintenance of physiological stability throughout the peri-donation period
  - monitoring modalities, which physiological variables to treat, and which potential donors are most likely to respond remain undefined

- judicious fluid replacement and inotropic/vasopressor support
  - MAP > 60 - 70 mmHg
  - urine output > 1 ml/kg/h
  - left ventricular ejection fraction > 45%
  - vasopressin may be appropriate first choice
  - avoid high-dose norepinephrine (0.05 µg/kg/min)
  - avoid hypervolaemia

- consider hormone replacement therapy in unresponsive patients

Kotloff et al, Crit Care Med 2015; 43: 1291-1325
Hormone replacement

- arginine vasopressin deficiency
  - desmopressin for diabetes insipidus
  - vasopressin for hypotension despite adequate filling

- high dose corticosteroids
  - reduces effects of inflammatory cascade on donor organ function
  - resistant hypotension
  - catecholamine sparing

- T3/T4
  - routine use not supported by RCTs
  - consider in haemodynamically unstable donors
  - cardiac donors with LVEF < 45%

- insulin
  - hyperglycaemia managed according to local protocols

Kotloff et al, Crit Care Med 2015; 43: 1291-1325
Pulmonary targets

- damage to lungs may occur before or after brain death
  - trauma
  - infection
  - barotrauma
  - pulmonary oedema

- ventilation strategies
  - TV 6-8 ml/kg
  - PEEP ≥ 8 cm H₂O
  - judicious fluid therapy
  - bronchoscopy

Kotloff et al, Crit Care Med 2015; 43: 1291-1325
Temperature targets

- warm to ≥ 35°C
- recent RCT showed that cooling to 34-35°C might be beneficial after renal transplantation

Kotloff et al, Crit Care Med 2015; 43: 1291-1325
• donor hypothermia (34 to 35°C) vs. normothermia (36.5 to 37.5°C)

• hypothermia reduced incidence of delayed graft function (28% vs. 39%) (OR 0.62, \( p=0.02 \))

Niemann et al, New Engl J Med 2015; 373: 405-14
The future

- extended donor criteria
- heparin to minimize ischaemic injury from microthrombi formation
- strategies to attenuate inflammatory response
- extracorporeal membrane oxygenation
- ex-vivo perfusion viability of organs prior to transplantation

Kotloff et al, Crit Care Med 2015; 43: 1291-1325
Summary

• profound systemic physiological disturbances after brain death
  – adversely affect number of organs procured and post-transplant function

• protocolised-donor management strategies and continued application of
good critical care
  – increase numbers of organs retrieved and post-transplant function
  – low-quality evidence for benefit from individual components of donor
    management

• current guidelines emphasize the importance of
  – maintaining physiological stability throughout the peri-donation period
  – treating hypotension
  – treating diabetes insipidus
  – avoiding hypothermia
THANK YOU