CHECKLIST FOR CLINICAL DIAGNOSIS OF BRAIN DEATH      (ICSI 2010)

Name ________________________________________________________________
Address ______________________________________________________________

Date of birth ______________________________
Condition which led to irremediable brain damage: _______________________________________________
Onset of apnoeic coma; Date __________ Time __________

<table>
<thead>
<tr>
<th>PRECONDITIONS; is apnoeic coma due to any of the following?</th>
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<td>Assessment A</td>
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<td>Depressant drugs</td>
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<td>Neuromuscular blocking drugs</td>
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<td>Hypothermia</td>
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<td>Metabolic causes</td>
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<td>Endocrine disturbance</td>
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<table>
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<th>CLINICAL TESTS OF BRAIN STEM FUNCTION:</th>
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<td>Assessment A</td>
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<tr>
<td>Is there a motor response to painful stimulus in cranial nerve distribution?</td>
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<tr>
<td>Do the pupils react to light?</td>
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<td>Are corneal reflexes present?</td>
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<tr>
<td>Do the eyes move on caloric testing?</td>
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<td>Is there a gag reflex?</td>
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<td>Is there a cough reflex?</td>
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<td>Were there respiratory movements during apnoea testing?</td>
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<tr>
<td>PaCO₂ pre and post apnoea test; Pre Post</td>
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<tr>
<td>pH pre and post apnoea test; Pre Post</td>
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</table>

Date and time of tests: Assessment A _______ Assessment B _______

Assessor(s) A __________________________________________ Assessor(s) B ______________________________________
Name(s) __________________________________________ Grade ______________________________________________
Grade __________________________________________ Signature _______________________________________

Confirmation of brain death

Do the above tests confirm brain death? Yes ■ No ■

Date of death __________________________ Time of death __________________________
Name __________________________________ Signature __________________________ Grade ___________________________________
**Medical Management of the Adult Organ Donor Patient**

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**Introduction**

Advances in transplant surgical techniques and immunosuppressive therapies have led to increasingly more patients with end-stage organ failure being treated with a transplant. Donor organs are scarce and the success rate of transplantation depends on appropriate management of the organ donor. Thus it is important after diagnosis of brain death and consent for organ donation that organs are maintained at their best possible level of function and that organ procurement occurs quickly.

The guidelines outlined should be implemented only after the diagnosis of brain death in patients who are potential organ donors. Before the diagnosis of brain death patients should be managed as appropriate for their underlying condition. After the diagnosis of brain death, treatment becomes orientated towards organs that may be transplanted rather than orientated towards protection of the brain. It is useful to consider that the outcome in up to seven transplant recipients will be improved by appropriate management of the organ donor.

These guidelines are written for adult organ donors; appropriate adjustments must be made for paediatric organ donors. These guidelines are based on recommendations from Canadian and American consensus conferences (1-2), on Guidelines from the UK and from the Australian and New Zealand Intensive Care Societies (3-4) and on our experience of clinical practice in Ireland.
Multisystem management of the multi-organ donor patient

The extent of monitoring and of laboratory investigations should be related to how unstable the patient is and how much support is required.

**Basic Standard monitoring:**
- Fluid intake and output, hourly urine output
- Pulse oximetry, ECG, temperature
- Arterial blood pressure
- Central venous pressure

**Laboratory investigations:** 12 hrly (+ more often if clinically indicated)
- Full blood count
- Urea and electrolytes
- Liver enzymes, INR (or PT) and APPT
- Blood glucose, arterial blood gases at least 6 hrly
- Daily blood cultures, cultures of sputum and urine

**Haemodynamic monitoring and therapy**

**General targets:**
- Heart rate: 60-120 / min
- Blood pressure: Systolic blood pressure 100 - 160mmHg
  MAP > 65 - 70 mmHg
- Cardiac output; > 2.4 l/min/m²
- Urine output; 50 - 100 ml/hr +
- Central venous O₂ saturation; > 70%
- Fluid administration; Adequate volume loading to maintain organ perfusion but avoid fluid overload.
  May use CVP 6-10mmHg as a target provided organ perfusion is maintained.

**Hypotension:**
This occurs commonly after brain death. Consider the following causes:

**Absolute hypovolaemia:**
Incomplete resuscitation following trauma. Osmotic diuresis secondary to mannitol or hyperglycaemia. Diabetes insipidus with massive diuresis.

**Effective hypovolaemia:**
‘Neurogenic shock’ with loss of central vasomotor control and subsequent decrease in systemic vascular resistance. Rewarming of a hypothermic patient with resultant vasodilatation.

**Myocardial dysfunction:**
Secondary to trauma and myocardial contusion. The massive catecholamine surge that occurs after a neurologic catastrophe may result in myocardial dysfunction. Subendocardial myocardial ischaemia and ventricular dysfunction are common even in previously healthy hearts. Electrolyte disturbances may also contribute to ECG abnormalities which include ST segment and T wave changes, arrhythmias and conduction abnormalities. Most changes are temporary and reversible.

**Hypertension:**
During the period of brain stem ‘coning’ acute arterial hypertension may occur related to increased intracranial pressure. This period of care is not addressed in this document as these patients have not yet been diagnosed brain dead.

Following brain death, patients may develop hypertension in response to noxious stimuli. Rarely this may need treatment if severe or prolonged. If treatment is deemed necessary short acting agents are preferable because hypotension commonly supervenes.

**Agents;** nitroglycerine, nitroprusside, esmolol (100-500 microgram/kg bolus followed by 100-300microgram/kg per minute). Labetolol is often used because of familiarity but has a long duration of action.
**General principles:**

1. Ensure the patient is adequately volume loaded but not overloaded. Choice of replacement fluid will usually be a combination of crystalloid and colloid depending on the cause of the fluid deficit. Avoid nephrotoxic fluids e.g. dextran (and possibly hydroxyethyl starch).

   Dynamic indicators (e.g. response to a fluid challenge or to passive leg raising, pulse pressure variability or stroke volume variability) are accepted as a better guide to fluid requirements in ICU patients than static measurements like CVP and PAOP. However a number of studies in organ donors have shown improved recipient outcomes when CVP and PAOP are maintained in the low-normal range (while also ensuring adequate organ perfusion). Most Guidelines quote target ranges of 6-10 mmHg (CVP) and 6-10 mmHg (PAOP). Echocardiography may be useful in guiding fluid therapy and may also provide useful information in determining the suitability of the heart for transplantation.

   There may be a dilemma in fluid management between generous fluid administration (which tends to benefit kidneys and liver) and fluid restriction (which tends to benefit lungs and heart). In patients with healthy cardiovascular systems experienced clinicians can usually maintain adequate perfusion of liver and kidneys without causing fluid overload and pulmonary oedema.

2. Most patients need vasopressors
   - Pure vasopressors: Vasopressin, phenylephrine
   - Vasopressors with beta-agonist activity: noradrenaline, adrenaline, dopamine
   - Beta agonists: dobutamine and isoprenaline

   Vasopressin (0.5 - 2.4 international units/hour) is the agent of first choice in potential heart donors. Beta agonists can cause depletion of cardiac ATP and down-regulation of beta receptors (5). Vasopressin can cause vasoconstriction at higher doses and regular observation of the peripheries for signs of vasoconstriction is necessary.

   Many patients will require another agent.
   - Noradrenaline is most commonly used, with doses adjusted to maintain mean blood pressure > 70 mmHg.
   - If dopamine is used maximum dose should be ≤ 10 microgram/kg/min.
   - Inotrope use may be guided by central venous oxygen saturation measurements aiming for > 70% (sample from central line) (6).
   - If doses of inotropes are escalating consider inserting a pulmonary artery catheter. Haemodynamic targets: PAWP: 6-12 mmHg, cardiac index > 2.4L/min/m²(1). If echocardiography is available it is a useful guide to fluid and vasoactive therapy.
   - In patients with haemodynamic instability or an ejection fraction < 40% by echocardiography consider combined hormonal therapy (see below).

**Respiratory management**

Pulmonary dysfunction is common in the organ donor due to pneumonia, aspiration of gastric contents, neurogenic pulmonary oedema, pulmonary trauma or ALI / ARDS (which may be secondary to brain injury). This has led to a greater shortage of lungs for transplantation than of other organs.

**General principles:**

Pulse oximetry, serial arterial blood gas monitoring, endotracheal tube suctioning, physiotherapy, regular CXRs.

**Nursing care and physiotherapy:**

Routine physiotherapy, suctioning and mouth toilet should be standard care. Strict asepsis should be continued during tracheal toilet.

- PEEP of 5 cmH₂O is recommended as a routine
- Recruitment may be achieved by periodic increases in PEEP up to 15 cmH₂O or by sustained inflations (peak inspiratory pressure of 30 cmH₂O for 30 secs.)
- Diuresis to normovolemia should be initiated if fluid overload occurs
- 30° head-up position, cuff pressure ≤ 25 cmH₂O
PaCO₂: 4.8 - 5.8 kPa (36-44 mmHg), pH 7.35-7.45
FiO₂: lowest FiO₂ to maintain PaO₂ ≥ 10 kPa (80 mmHg).
PEEP: 5 cmH₂O, ↑ levels of PEEP if clinically indicated
Tidal volume (Vt): 8-10 ml/kg (see below)
Peak inspiratory pressures: ≤ 30 cmH₂O

Lung protective strategies in patients with ALI/ARDS, are defined by a peak inspiratory pressure < 30 cmH₂O, high levels of PEEP and Vt = 6-8 ml/kg. However some guidelines for management of lung donors suggest larger Vt of 10-12 ml/kg (2). A reasonable compromise seems to be the Canadian recommendation of 8-10 ml/kg (1). If the patient is not going to be a lung donor, possibly Vt should be reduced to 6-8 ml/kg so that worsening ALI/ARDS does not affect the function of other organs (6).

There is considerable interest currently in increasing the number of lungs which can be made suitable for transplantation by active measures to improve lung function (7). These measures include active physiotherapy, recruitment manoeuvres, bronchoscopy and bronchial toilet, measures to prevent aspiration, aggressive diuresis and delay in organ retrieval to allow time for improvement in lung function.

**Diabetes Insipidus and Hypernatraemia**

**Features of diabetes insipidus:**
1. Urine output > 4 ml/kg/hour
2. Increasing serum sodium > 145 mmol/L
3. Increasing serum osmolarity > 300 mOsm/L
4. ↓ urine osmolarity < 300 mOsm/L, ↓ urine specific gravity (< 1.005).

In theory this diagnosis should be made on the basis of osmolarity but the time delay in waiting for these results may lead to significant clinical deterioration (hypovolaemia and hypernatraemia). Thus the diagnosis is often made on the basis of 1. and 2. above.

Haemodynamic instability may occur secondary to hypovolaemia. Metabolic derangements include hypernatraemia, hypomagnesaemia, hypokalaemia, hypophosphataemia and hypocalcaemia.

**Management of diabetes insipidus:**

1. Replace the fluid deficit and ongoing fluid losses with hyponatraemic fluid. 0.45% saline is an appropriate first choice. It will replace volume deficits and bring down serum Na⁺ in a controlled fashion.
   
   If it is difficult to bring serum Na⁺ despite adequate fluid replacement with 0.45% saline it is reasonable to change to Solution 18 or 5% dextrose. However these may lead to hyperglycaemia or very rapid falls in serum Na⁺ particularly when combined with ADH replacement therapy.

2. If the urine output is > 200 ml/hour then i.v. vasopressin infusion or intermittent s.c. or i.v. DDAVP should be used.
   
   • If vasopressor support is required then IV vasopressin should be used; 0.5 - 2.4 international units/hour. This may not be adequate to control diuresis.
   
   • DDAVP is an analog of arginine vasopressin with enhanced anti-diuret effect, negligible vasopressor activity and a prolonged half-life compared to vasopressin. Dose of DDAVP in adults is 1-2 microgram s.c. or i.v., then 1-2 microgram s.c. or i.v. PRN to achieve urine output < 3 ml/kg/hr.

Aim to maintain serum Na⁺ in the normal range if possible. Aim for normal values of potassium, magnesium, phosphate and calcium. Hypernatraemia is independently associated with hepatic dysfunction and graft loss (8).

**Glycaemic control and nutrition**

Hyperglycaemia is common in organ donors due to large volumes of glucose-containing solutions, peripheral insulin resistance and inotrope infusions. The major consequences include osmotic diuresis, ketosis and potential pancreatic graft dysfunction in the recipient following transplantation.

- Aim for a blood glucose level 5-8 mmol/L with an insulin infusion.
- Routine enteral nutrition should be initiated or continued as tolerated.
- TPN should not be initiated; however when it has been initiated it should be continued.
Maintaining normothermia
Hypothermia is common in organ donors due to loss of thermoregulatory control, exposure to cold ambient temperatures or massive infusions of cold i.v. fluids or blood products. The consequences of hypothermia include arrhythmias, myocardial depression, hypotension, hypoxia, hyperglycaemia and coagulopathy.

- Aim for a core temperature > 36°C. Active measures are often needed including warming blankets, fluid warmers and heated humidifiers in ventilator circuits.

Antimicrobial therapy
The principles of antimicrobial therapy are similar to those in patients who are not organ donors. Antimicrobial therapy should be based on the results of gram staining or culture or may be empirical based on treating suspected likely pathogens causing infection. Nephrotoxic antimicrobials should be avoided when possible. Prophylactic antimicrobials are not routinely indicated.

If there are clinical signs of sepsis the transplant teams may want to wait 24hrs for the result of blood cultures to ensure the patient does not have systemic sepsis. Undertaking daily blood cultures in all patients who are potential organ donors will reduce this delay. Advice should be sought from a microbiologist to determine the significance of any positive cultures.

Transfusion thresholds
General principles:
Haemoglobin: A target haemoglobin level of 9-10g/dl is most appropriate to optimize cardiopulmonary function in the face of haemodynamic instability. A level of 7 g/dl is the lowest acceptable limit for management of stable donors in the ICU. Drawing of blood for donor serology and tissue typing should occur before transfusions to minimize the risk of false negatives related to haemodilution.

Other blood indices: There are no defined targets for platelet concentration, INR, PT or APPT. Platelet, fresh frozen plasma or cryoprecipitate replacement is indicated for clinical bleeding only. CMV negative blood products should be used.

Antifibrinolytics such as epsilon aminocaproic acid may cause microvascular thrombi in donor organs and should be avoided.

Combined hormonal therapy
In humans, endocrine dysfunction seems limited to isolated diabetes insipidus as the anterior pituitary gland receives blood supply from extradural inferior hypophyseal arteries. A large retrospective cohort study suggests that triple hormone therapy led to significant increases in kidney, liver and heart utilisation from donors and in 1 year survival of kidneys and hearts (9-10). A prospective randomized trial has not been performed.

There is a strong case to be made for using hormonal therapy in all organ donors (2). Combined hormonal therapy is particularly indicated in patients with haemodynamic instability in whom volume loading and vasoactive medications have not produced a stable state.

Drugs and Doses for Combined Hormonal Therapy:
- T3 (tri-iodothyronine); 4 microgram bolus followed by infusion at 3 micrograms/hour
  T3 is the most readily available agent in Ireland and is preferable as the active agent.
- Vasopressin, 1 international unit bolus followed by 2.4 units/hr infusion
- Methylprednisolone, 1 Gram i.v. every 24 hours
- Insulin as indicated by blood sugars, minimum 1 unit/hr
Timing and conduct of organ retrieval

There is increasing recognition of the benefit of taking the necessary time in ICU to optimise organ function to improve transplant outcomes. Therapy can improve reversible organ dysfunction including myocardial dysfunction, impaired gas exchange in the lung, bacterial infections and acute impairment in renal or hepatic function. This treatment period can range from 12-24 hours and should be accompanied by frequent re-evaluation to demonstrate improvement in organ function toward defined targets. Final decisions about transplantability rest with the relevant transplant teams. The benefits of delay in organ retrieval to improve the condition of organs must be balanced against the risk of increasing distress in the patients family.

Retrieval of donated organs in the operating theatre can take 2-4 hours to complete. A volatile agent (± an opiate) and muscle relaxant are normally administered to ensure cardiovascular stability and optimal operating conditions (although ‘anaesthesia’ to prevent awareness is not required in a brain dead patient). Management to optimise the condition of the organs should continue until the organs are removed. At the end of the procedure the ventilator is switched off and the endotracheal tube removed.

Psychological issues for staff and relatives.

Staff need to have a clear understanding of the moral, ethical, legal and clinical principles in caring for a patient who is now legally dead. Education and training of medical and nursing staff is important.

These cases can be demanding psychologically both in the clinical management of the patient and in dealing with their relatives (11). Junior medical and nursing staff particularly need education and support for appropriate management of the patient and also for skilled and appropriate communication with relatives.

REFERENCES: