Diagnosis of Brain Death

&

Medical Management of the Organ Donor

Guidelines for Adult Patients

2010

Intensive Care Society of Ireland

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Diagnosis of Brain Death in adult patients - Guidelines

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These Guidelines are based on our interpretation of existing legislation and practice in Ireland, on previously published Guidelines in Ireland and internationally, and on published literature in this area.

Introduction

Brain death as a concept is ubiquitous in medical, nursing and lay literature. This is a recognition that some brain injured patients maintained on artificial ventilation develop complete and irreversible loss of brain stem function. Brain death is accepted as the equivalent of cardiac death (the usual statutory cause of death). Cardiac asystole usually follows within days or weeks despite continuation of mechanical ventilation and full supportive therapy (1).

The ability to certify death when there is irreversible cessation of brainstem function enables intensivists and specialists working in Intensive Care to withdraw futile treatment (e.g. mechanical ventilation), on humanitarian, ethical and (coincidentally) utilitarian grounds.

There is no statutory law on this area in the Republic of Ireland but the draft version of the proposed Human Tissue Bill (2009) proposes a definition of brain death as "the irreversible cessation of all functions of the entire brain, including the brain stem". The draft Bill further states that "A determination of death must be made in accordance with accepted medical standards" (2). Pending enactment of this Bill into law, compliance with the recommendations of the Irish Memorandum on Brain Death (3), (which is in accordance with the approach outlined in this document), has the legal status of 'custom and practice' in the Republic of Ireland.

History of the establishment of the criteria for brain death:

1959: Moularet P, Goudon M. Coma depasse et necrosis nerveuses centrales massives. Revue Neurologique 101:116-139. This was the reference publication proposing a name (Coma depasse) for the 'death of the nervous system', the clinical, electrophysiologic and angiographic features of which had been described in the French and Scandanavian literature between 1956-1959.

1968: The concept of brain death as death was proposed by an Ad Hoc Committee of Harvard Medical School

1976: UK Royal Medical Colleges defined brain death as complete irreversible loss of brainstem function and specified clinical criteria to certify brain death.

1981: USA Presidents Commission published Guidelines. Recommended confirmatory tests to reduce the required period of observation. Recommended a period of 24 hours observation for patients with anoxic brain damage.

1988: Irish Medical Journal published a Memorandum on Brain Death from an ad-hoc Irish Working Party essentially constituting guidelines for Ireland on the clinical criteria for diagnosis of brain death (3).

1995: Australian publication of Guidelines on clinical confirmation of brain death (4).

2006: Canadian Council for Donation and Transplantation published national Guidelines for determination of brain death (5).

Approach to the Clinical Diagnosis of Brain Death:

Assessment of brain death in a comatose patient should proceed with certain principles in mind; establishing the cause of coma, ascertaining irreversibility, excluding major confounders and accurately testing all possible brainstem reflexes.

A diagnosis of brainstem death based on clinical tests should not be made unless the pre-conditions in A) and B) have been met.

(A) Proof that the patient's condition is due to irreversible structural brain damage

The diagnosis of a disorder that can lead to brain death must be clearly established. Brainstem death is not the only cause of loss of brainstem reflexes. Brainstem encephalitis may also cause loss of brainstem reflexes but patients can recover after a period of supportive treatment (6). If there is any doubt about the primary diagnosis, do not diagnose brain death clinically.

In each patient therefore, the underlying neurological diagnosis which caused the severe neurological injury and the accompanying loss of brain stem reflexes must be apparent and must be well documented.

Supplementary proof of sufficient brain pathology from CT scan, angiography or MRI scan is usual. A CT scan with abnormalities consistent with brain death does not obviate the need to search for confounders. Conversely, a normal CT scan can be seen early on after a cardiac or respiratory arrest. In patients with acute hypoxic-ischaemic brain injury clinical evaluation should be delayed for at least 24 hours after the cardio-respiratory arrest.

(B) Exclusion of reversible causes of coma

a) Toxins, poisons, sedative drugs and many other agents may cause coma when patients are exposed to large quantities. The drug history should be reviewed and if necessary a toxicology screen obtained.

b) If sedative drugs have been used, adequate time must be allowed for residual effects to have worn off. If sedatives have been used for a prolonged period or in large doses (e.g. with head injury) it may be difficult to decide whether these are still contributing to the depth of coma. Particular difficulty arises with highly lipid soluble drugs like thiopentone. A recent review suggests waiting four times the elimination half-life of the sedatives used (7); however this does not take into account the duration of infusion (i.e. context-sensitive half-life), altered pharmacokinetics with high doses or the presence of active metabolites.

c) The use of antagonist agents may be useful. If muscle relaxants have been used, confirm that neuromuscular conduction is intact with a peripheral nerve stimulator. Administer the antidotes naloxone and flumazenil when opioids or benzodiazepines have been administered and look for a change in brainstem reflexes.

d) Measurement of plasma concentrations of drugs should reveal drug concentrations below the therapeutic range e.g. alcohol in levels below the legal limit for driving. The median concentration of thiopentone permitting motor response is 12 mg/l (8) but there is considerable individual variation with levels as low as 4mg/l required in some individuals for return of motor response (8-9).

   The exclusion of sedative agents as a contributing cause of coma may require considerable knowledge and experience. In complicated cases we suggest getting advice from a specialist in Intensive Care Medicine who undertakes brainstem tests on a regular basis. Ultimately the clinician must use their knowledge and judgement to decide whether or not to undertake brainstem testing.

   If sedation may be contributing to the absence of brainstem reflexes then brainstem death cannot be diagnosed on clinical testing alone. The use of additional confirmatory tests (i.e. cerebral angiography) may allow the diagnosis of brain death to be made (see Section D below).

e) Hypothermia as a cause of coma must be excluded. Core body temperature should be more than 35°C when clinical assessment of brain stem reflexes is carried out.

f) Metabolic or endocrine causes that may contribute to coma must be excluded. Hypothyroidism, panhypopituitarism, adrenal dysfunction, uraemia and hepatic failure can lead to a profound decrease in the level of consciousness. Disorders of sodium, phosphate, magnesium and glucose can affect the response to brain stem tests.

   The commonest metabolic abnormality in brain dead patients is hypernatraemia, often related to diabetes insipidus. Serum sodium should not be grossly abnormal; we use 150 mmol/dl as the upper acceptable limit for brain stem tests.

g) Severe hypotension precludes testing of brain stem reflexes. Blood pressure should be greater than 90mmHg systolic (MAP > 60mmHg) for brain stem tests. Infusion of fluid and vasoactive drugs may be needed to maintain blood pressure.

(C) Formal clinical testing for Brainstem reflexes

The first formal examination can be undertaken when the patient fulfils the pre-conditions in A) and B) above and has been observed to have fixed pupils and absent cranial nerve reflexes for at least four hours.

(1) No motor response within the cranial nerve distribution in response to adequate stimulation of the trigeminal area and of the limbs. Absence of response to a painful stimulus applied peripherally could be the result of a high cervical injury, thus testing within the distribution of cranial nerves must always be performed. Trigeminal stimulation can be applied by pressure on the supraorbital notch or at the level of the temporomandibular joint. Reflex: afferent nerve V and efferent nerve VII.

(2) No pupillary response to light. A history of pre-existing abnormalities of the pupil or previous surgery to the eye (e.g. iridectomy) may influence interpretation of this test. Examine each eye with lights in the room dimmed and use a strong light. The pupils should be more than 4mm in diameter. The normal response is brisk constriction of the pupil. Round, oval or irregularly shaped pupils are compatible with brain death. In most brain dead patients pupils are in the mid position (4-6mm). Reflex: afferent nerve II and efferent nerve III.

(3) Corneal reflex. Test the corneal reflex by touching the cornea with a wisp of cotton wool. If this fails to elicit a response a stronger stimulus is applied with for example, a sterile throat swab and firm direct pressure. Blinking of the eyelids is the normal response and both eyelids must be observed. Reflex: afferent nerve V and efferent nerve VII

(4) Oculocephalic reflex (Doll's head eye phenomenon). This test must not be performed in patients with an unstable cervical spine injury. The examiner holds the patient's eyes open and the head is turned suddenly from the middle position to 90 degrees on both sides. When the reflex is intact the eyes turn opposite to the side of head movement as if lagging behind. The reflex is absent when the eyes move with the head and do not move within the orbit. If Test (5) below can be performed this test may be omitted.

(5) Oculovestibular reflex (caloric testing). Before testing this reflex, both ears are inspected using an auroscope to confirm that the tympanic membrane is intact and the external auditory canal is not obstructed by wax or other material. A fractured base of skull resulting in blood, CSF or brain tissue in the external auditory canal is a contra-indication to performing the test on that ear. The patients head is placed in the midline and elevated 30° from the supine position. This ensures that the lateral semi-circular canal is vertical, maximising the response. A soft catheter is introduced into the external auditory canal for gentle, slow irrigation with at least 50ml of iced water while the eyes are held open by an assistant. The eyes should be observed for a minute after irrigation is completed. There should be a 5 minute interval before repeating the test on the opposite side.

In an unconscious patient, an intact oculovestibular reflex causes tonic (slow) deviation of the eyes towards the irrigated ear. During testing to confirm brain death, any movement of one or both eyes, whether conjugate or not, excludes a diagnosis of brain death. When the reflex is absent the eyes remain fixed. Reflex: afferent nerve VIII and efferent nerves III and VI.

(6) Pharyngeal (gag) reflex. A tongue depressor is used to stimulate each side of the oropharynx and the patient observed for any pharyngeal or palatal movement. Reflex: afferent nerve IX and efferent nerve X.

(7) Laryngeal (cough) reflex. A suction catheter is introduced into the endotracheal or tracheostomy tube to deliberately stimulate the carina. The patient is observed for any cough response or movement of the chest or diaphragm. Reflex: Afferent nerve IX and efferent nerve X.

(8) Apnoea test. This test, which is an essential part of the confirmation of brain death, should be performed when all other brain-stem reflexes are absent. It may not be possible to perform the test in patients with a high cervical cord injury, that may have abolished phrenic nerve function. In such patients, clinical determination of brain death will not be possible and additional tests e.g. by demonstrating absent intracranial blood flow may be needed to confirm brain death. (see item (D) below)

The three components of the test are:

(a) Disconnection from mechanical ventilation for a sufficient period for arterial CO_2 tension to reach a critical point (causing acidaemia).

(b) Prevention of hypoxaemia during this period.

(c) Absence of spontaneous respiratory efforts during this period.

Ventilate the patient with 100% oxygen before the test to ensure pre-oxygenation. Check the patient's arterial blood gases. If the $PaCO_2$ is not within normal limits adjust the ventilator and repeat blood gases until a $PaCO_2$ between 36-44mmHg (4.8-5.8 kPa) is achieved. Disconnect the ventilator. Disconnecting the patient from the ventilator removes the chance of artefactual detection of breathing by the ventilator due to the cardiac impulse. Deliver oxygen via a C-circuit with the valve fully open or via a narrow suction catheter inserted into the endotracheal tube.

Inspection of the reservoir bag will enable monitoring of respiration; visual inspection for chest and abdominal movement is also required. Visual inspection of the chest and abdomen typically show minimal movement

synchronous with heart beat. At five minute intervals, the arterial blood gases are checked until the $PaCO_2$ rises above 8.0 kPa (60 mmHg) or higher and associated acidaemia has developed (10). Occasionally the duration of the test takes greater than 10 minutes until the required changes in $PaCO_2$ develops.

The apnoea test may lead to instability in the condition of the patient and deaths have occurred during this procedure. Oxygen saturation levels should be maintained within the normal range. Ensure that a Valsalva effect or barotrauma do not occur. If hypotension occurs vasopressors may need to be increased.

If, despite hypercarbia and acidaemia, there is no attempt at spontaneous respiration, the test is positive.

If the patient has a history of chronic respiratory disease due allowance must be made for decreased sensitivity to a high $PaC0_2$. Achievement of acidaemia should be ensured.

More detailed descriptions of the clinical tests of brainstem function are available if required (7, 10-12)

Spinal reflexes. Body movements, secondary to spinal cord reflexes, have been observed after death. These may persist until all circulation has ceased. These movements represent only spinal cord activity as evidenced by the consistent clinical documentation of brain death in such patients with confirmation by an isoelectric electroencephalogram or the absence of intracranial blood flow. Movements noted include abduction or adduction of the arms, leg movements, head rotation (due to cervical muscle activity) and even a brief attempt of the body to sit up to 40 – 60 degrees (Lazarus sign). A recent prospective study of 38 patients with brain death, mostly young adults, found a 39% frequency of spinal generated movements (13).

(D) Situations where a diagnosis of Brain Death is not possible using clinical criteria alone:

The diagnosis of brain death by clinical examination leads to withdrawal of ventilatory support and cardiac death. Thus it is extremely important that the preconditions for testing are fulfilled and that an adequate number of clinical tests (to include apnoea testing) confirm absence of brainstem function.

Severe head and facial injuries can make it impossible to test all the brainstem reflexes. Facial and head injuries may affect the ability to test pupillary and corneal reflexes, through severe facial or periorbital swelling or direct eye injury. Likewise such injuries may preclude the oculovestibular reflex, because of cerebrospinal fluid otorrhoea or occlusion of the external auditory canal. There is no reported consensus on the minimum number of brainstem reflexes, that must be tested although apnoea testing is seen as essential. The ANZICS Guidelines contain a useful rule of thumb that you must be able to test ‘at least one eye and at least one ear’ (10).

Brainstem death is a clinical diagnosis. Clinicians must use their clinical judgement in conjunction with formal guidelines in assessing whether the pre-conditions are fulfilled and whether sufficient brainstem tests can be performed to diagnose brain death. You must be in a position to justify the diagnosis of brain death if asked to do so subsequently. If not, you cannot diagnose brain death on the basis of brainstem tests.

When there are limitations to the clinical tests which can be undertaken the diagnosis of brain death may still be possible if confirmatory tests are used. Confirmatory tests may also enable the diagnosis to be made in patients who do not fulfil the pre-conditions e.g. those who have received large doses of sedative agents.

If the pre-conditions for clinical determination of brain death are not met or if insufficient clinical tests can be performed, brain death cannot be diagnosed using clinical examination alone. It may then be appropriate to support the clinical signs suggestive of brain death by using a confirmatory test. Four vessel cerebral angiography that demonstrates absence of intracranial blood flow is the 'gold-standard' test to confirm a diagnosis of brain death (6-7, 10-12). This aid to diagnosis of brain death is only possible in specialist centres where cerebral angiography is available. There is a detailed description in the ANZICS guidelines (10).

Declaration of death

It is standard practice to repeat the tests described in (C) to confirm the absence of brainstem reflexes. When organ donation is being considered, this is regarded as essential. A 'reasonable' period of time should intervene between the two sets of tests (although no specific minimum time period has been recommended (3, 10, 12).

The apnoea test is the final test to be done. If it is positive for the second time, the patient should then be declared dead and the time and date noted. This is the time of death. Many critical care units use a check list to be completed by the doctors concerned. An example of such a list is appended.

Who should do the tests?

Two sets of tests should be undertaken by different doctors; one a consultant, the other a doctor fully registered for at least five years and engaged in acute patient care in hospital. If organ donation is being considered, the doctors certifying brain death should not be involved in any proposed transplant procedure.

Communication, Organ donation and other considerations

If the first set of formal tests show no sign of brain stem activity, it is advisable to inform the family of the findings and that confirmation of these findings on second testing (which is anticipated) will lead to a diagnosis of brain death.

As brain death provides the opportunity to donate organs for transplantation and given the need of patients on transplant waiting list for donated organs, it is important for clinicians, usually the Intensive Care team, to inform the family sensitively that this option is likely to arise.They may be asked to begin to consider what the patient would have wished in relation to organ donation if brain death is confirmed.

Contact with the transplant co-ordinator may be warranted as a request for organ donation would be pointless if the patient is not suitable as an organ donor. In many cases in whom brain death is diagnosed the circumstances of the brain injury make it mandatory to report the death to the Coroner (as per Coroner's Guidelines). In such cases the Coroner must be informed and permission requested for organ retrieval for transplantation. The Coroner normally grants permission for this but usually requires a post-mortem examination and may wish to place limitations on transplant procedures.

If organ donation is not to take place, then a time should be set to withdraw ventilation. Most families prefer to be in attendance while the subsequent cessation of the circulation occurs – usually over the course of 10-20 minutes. Privacy and religious or other ceremonies should be facilitated as much as possible during this time.

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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 ☐

PRECONDITIONS; *is apnoeic coma due to any of the following?*

	Assessment A Yes	Assessment A No	Assessment B Yes	Assessment B No
Depressant drugs	☐	☐	☐	☐
Neuromuscular blocking drugs	☐	☐	☐	☐
Hypothermia	☐	☐	☐	☐
Metabolic causes	☐	☐	☐	☐
Endocrine disturbance	☐	☐	☐	☐

CLINICAL TESTS OF BRAIN STEM FUNCTION:

	Assessment A Yes	Assessment A No	Assessment B Yes	Assessment B No
Is there a motor response to painful stimulus in cranial nerve distribution?	☐	☐	☐	☐
Do the pupils react to light?	☐	☐	☐	☐
Are corneal reflexes present?	☐	☐	☐	☐
Do the eyes move on caloric testing?	☐	☐	☐	☐
Is there a gag reflex?	☐	☐	☐	☐
Is there a cough reflex?	☐	☐	☐	☐
Were there respiratory movements during apnoea testing?	☐	☐	☐	☐
$PaCO_2$ pre and post apnoea test;	Pre ☐	Post ☐	Pre ☐	Post ☐
pH pre and post apnoea test;	Pre ☐	Post ☐	Pre ☐	Post ☐

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

	Assessor(s) A	Assessor(s) B
Name(s)		
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; appropropriate 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 /m^2
Urine output;	50 - 100 ml/hr +
Central venous O_2 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, arrythmias 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. dextrans (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/m^2(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 prinicples:

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 cmH_2O is recommended as a routine
- Recruitment may be achieved by periodic increases in PEEP up to 15 cmH_2O or by sustained inflations (peak inspiratory pressure of 30 cmH_2O for 30 secs.)
- Diuresis to normovolaemia should be initiated if fluid overload occurs
- 30° head-up position, cuff pressure ≤ 25cmH_2O

$PaCO_2$:	4.8 - 5.8kPa (36-44mmHg), pH 7.35-7.45
FiO_2:	lowest FiO_2 to maintain PaO_2 ≥ 10Kpa (80mmHg).
PEEP:	5 cmH_2O, ↑ levels of PEEP if clinically indicated
Tidal volume (Vt);	8-10 ml/kg (see below)
Peak inspiratory pressures:	≤ 30cmH_2O.

Lung protective strategies in patients with ALI/ARDS, are defined by a peak inspiratory pressure < 30 cmH_2O, 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 8-10ml/kg (1). If the patient is not going to be a lung donor, possibly Vt should be reduced to 6 -8ml/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 > 4ml/kg/hour
2. Increasing serum sodium > 145mmol/L
3. Increasing serum osmolarity > 300mOsm/l
4. ↓ urine osmolarity < 300mOsm/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 > 200ml/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-diuretic potency, 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 < 3ml/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 5-8mmol/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 arrythmias, 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.

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