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Guidelines for potential multiple organ donors (adult). Part II. Mechanical ventilation, endocrine metabolic management, hematological and infectious aspects

Diretrizes para manutenção de múltiplos órgãos no potencial doador adulto falecido. Parte II. Ventilação mecânica, controle endócrino metabólico e aspectos hematológicos e infecciosos

ABSTRACT

The role of intensive care specialists in the maintenance of deceased potential donors is not restricted to hemodynamics. Appropriate endocrine-metabolic management is fundamental to maintaining energy support and hydroelectrolytic control, which cooperate for hemodynamic stability. Hematological changes are also important, especially considering the issues caused by inappropriate transfusions. In addition, this article discusses the role of appropriate protective ventilation to prevent inflammatory responses and to provide more transplantable lungs. Finally, judicious assessment of infections and antibiotic therapy is discussed.

INTRODUCTION

During progression to brain death (BD), several physiological changes associated with loss of brainstem functions are observed. Initially, sympathetic storming is associated with massive releases of adrenaline, corticosteroid and glucagon.

Adrenergic hyperactivity, with eventual left ventricular overload, leads to hydrostatic lung edema and ischemia-reperfusion injuries and to intensive inflammatory processes, which can affect the pulmonary tissues.

From a metabolic point of view, energy expenditure and glycogenesis are increased. These increases are a consequence of the peripheral tissues' increased insulin resistance and reduced pancreas insulin release, resulting in hyperglycemia. The progression involves pituitary-hypothalamic dysfunction, leading to diabetes insipidus, with a lack of antidiuretic hormones, resulting in severe hydroelectrolytic disturbances.

Management of these endocrine-metabolic disorders is fundamental to assuring good heart contractility and hemodynamic stability. Studies have shown that combined hormone therapy (insulin, corticoid, thyroid hormone, vasopressin) improves hemodynamic stability, resulting in an increased number of available organs and improved quality transplants.

In association with brain tissue injury, tissue thromboplastin (largely available in the brain) is released and may lead to depletion of coagulation factors and platelets, causing bleeding.

In addition to insults from sympathetic storming, pituitary-hypothalamic axis disorders and brain tissue injury, treatment effects, such as hyperhydration,

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and mechanical ventilation injuries, such as barotrauma and volutrauma, can contribute to worsened respiratory function. It is essential to establish a ventilation strategy that adds no pulmonary injury. Therefore, protective low tidal volume ventilation is recommended.

Many potential donors are lost due to either suspected or confirmed infection by the time brain death is diagnosed. However, there is currently a strong trend toward using expanded donation criteria, i.e., using borderline donors. Therefore, positive cultures or a clinical diagnosis of infection is not an absolute contraindication for donation, and the maintenance of a deceased donor should not be discontinued based on these criteria.

OBJECTIVE

These guidelines are aimed at contributing to the institutional coordination of transplants and to guide and standardize the management of deceased donors, appropriate to Brazilian settings. They are also aimed at increasing the quality and quantity of transplantable organs.

METHODOLOGY

Based on an extensive literature review conducted by the Writing and Planning Committee, which is constituted by intensive care specialists and intensive care medicine residents, preliminary questions were formulated and forwarded to all authors as a starting point for receiving suggestions, replacements and definitions of other questions.

The finally prepared questions were revised by the Executive Committee and then sent back to the authors to develop the text.

These questions guided the literature search using the PICO methodology, in which P stands for the target population, I for intervention, C for control or comparative group and O for clinical outcome.

The retrieved articles were critically analyzed and categorized according to their grade of recommendation and the strength of their evidence:

A: More consistent experimental or observational studies;

B: Less consistent experimental or observational studies;

C: Case reports (non-controlled studies); and

D: Opinions lacking critical evaluation, based on consensus, physiological trials or animal models.

Given the paucity of evidence from trials involving deceased donors, part of these recommendations was based on analogies with other clinical conditions. Therefore, physiological, epidemiological and experimental considerations were used.

There were seven discussion subgroups: 1) Overview; 2) Hemodynamic support; 3) Endocrine-metabolic management; 4) Mechanical ventilation and pulmonary maintenance; 5) Liver maintenance; 6) Renal maintenance; and 7) Heart maintenance. Each subgroup had a coordinator who was responsible for stimulating and guiding the discussions via email messages. The texts from each subgroup were organized by the Writing and Planning Committee, presented for review by the Executive Committee and then returned for subgroup review. The full text was provided to all panel members and discussed in a meeting held during the XIVth South Brazilian Intensive Care Medicine Congress in May 2001 at Joinville, Santa Catarina, Brazil. The coordinators presented their recommendations, which were then discussed. Considering that a large portion of the recommendations had poor strength of evidence, the grades of the recommendations were added according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system. This system grades the quality of recommendations as 'strong' (should be done), 'weak' (perhaps should be done) or 'non-specific' (there are no advantages or disadvantages). A strong recommendation means that a given intervention benefits outweigh its risks and burdens; a weak recommendation of a given intervention means that its benefits are likely to outweigh its risks and burdens, but the group is not confident either because the evidence is not good enough or because more studies on the subject are warranted. A non-specific recommendation means that the group considers the benefits, risks and burdens to be balanced, so a case-by-case assessment is advisable. A strong recommendation should be understood as 'recommended' and a weak recommendation as 'suggested'.

Description of the evidence collection method

The primary searched source was MEDLINE, accessed via the PubMed service. The search was based on the PICO methodology. Using the MeSH interface (Medical Subject Heading), the following search terms were used: (organ donor OR donor management OR brain death AND recommendation OR consensus), (organ donor OR donor management OR lung transplantation AND mechanical ventilation OR strategies of ventilation), (organ donor OR donor management OR lung transplantation AND

fluid challenge OR fluid resuscitation OR positive balance), (organ donor OR donor management OR lung transplantation AND bronchoscopy OR bronchoalveolar lavage), (organ donor OR donor management OR lung transplantation AND pneumonia-ventilator associated), (organ donor OR donor management OR lung transplantation AND prevention and control), (brain-death organ donor AND corticosteroid), (hormonal therapy AND brain-death organ donation), (brain-death organ donor AND management), (thyroid hormone AND brain-death organ donor), (organ donor AND serum sodium), (brain death AND nutrition), (organ donors AND metabolic disturbances OR insulin therapy), (organ donors OR brain death AND coagulopathy OR coagulation OR blood transfusion OR transfusion of plasma or platelets), (contraindication AND infection AND organ donor AND transplant), and (organ donor AND brain death AND infection AND transplantation). Secondary sources were the Cochrane, Ovid and Trip databases.

MECHANICAL VENTILATION

How should a healthy lung be ventilated?

Patients diagnosed with brain death and with relatively normal lung function may worsen within a few hours. Only 15% to 20% of these lungs are transplantable (**C**).[1-3] Brain death causes pathophysiologic changes involving severe endocrine disorders and intensive inflammatory reactions that may affect pulmonary tissues. Although pulmonary injury is associated with the severity of the primary brain injury (**C**),[4] it may be iatrogenic from mechanical ventilation (**C**).[5] It is essential to establish a ventilation strategy that does not harm pulmonary tissue.

High tidal volume ventilation in brain death subjects is an independent factor for acute lung injury (ALI).

Mascia et al. (**B**)[6] conducted a multicenter, randomized, controlled trial involving 12 European intensive care units (ICUs) between September 2004 and May 2009, in which conventional ventilation and protective ventilation (low tidal volume) were compared in BD potential lung donor patients. Unfortunately, this study had to be discontinued after 118 patients were included (59 conventional strategy and 59 protective strategy) due to decreased financial resources. However, after a 6-hour observation time, only 32 (54%) of the conventional strategy patients complied with the lung donation eligibility criteria versus 56 (95%) of the patients in the protective strategy group (a 41% difference [95% confidence interval (95%CI) 26.5% to 54.8%]; p

< 0.001). Overall, 16 (27%) of the conventional strategy patients had their lungs transplanted versus 32 (54%) protective strategy patients (27% difference [95%CI 10.0% to 44.5%]; p = 0.004). No 6-month survival rate intergroup difference was detected.

In this study, the protective strategy consisted of a 6 to 8 mL/kg ideal body weight tidal volume, with 10 cmH_2O. A closed circuit system was used for tracheal aspiration to prevent losing pressurization and pulmonary recruitment (**C**).[7] An apnea test was performed with ventilation in the continued positive airway pressure (CPAP) mode (**D**),[8] maintaining CPAP at the same positive end-expiratory pressure (PEEP) that the patient was using for mechanical ventilation. Recruitment maneuvers were conducted following any ventilator disconnection (**D**).[9] The respiratory rate was adjusted to maintain 40 to 45 mmHg $PaCO_2$, and the inspired oxygen fraction (FiO_2) was adjusted to achieve $PaO_2 \geq 90$ mmHg.

Recommendation

- Maintain all potential donors with normal lungs under protective strategy ventilation (**B**).[6] Use the volume or controlled pressure mode with 6 to 8 mL/kg ideal body weight tidal volume, and adjust FiO_2 to achieve $PaO_2 \geq 90$ mm Hg, PEEP 8 to 10 and Pplateau < 30 cmH_2O. **Strong Recommendation.**

How to ventilate subjects with difficult oxygenation?

Approximately 30% to 45% of deceased potential donors have pulmonary injury, more frequently acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (**C**)[2](**D**).[10] However, other injuries, such as pulmonary contusions, blood transfusion injuries, pneumonia and atelectasis, can occur, in addition to previous pulmonary conditions (**D**).[11,12]

Many factors may impact respiratory outcomes, particularly hydrostatic pulmonary edema (secondary to sympathetic storming with eventual left ventricular overload) and the underlying disease inflammatory process (head trauma, meningeal bleeding, etc.) or the consequences of brain death itself, which may cause capillary permeability changes (non-cardiogenic pulmonary edema) and ischemia-reperfusion injuries. Additionally, treatment effects, such as hyperhydration or harmful mechanical ventilation effects (such as barotrauma and volutrauma), and oxygen toxicity may contribute to worsened pulmonary function (**C**).[2]

Ventilation management in these patients should be similar to ventilation in patients without BD (**D**).[11,13] Mechanical ventilation objectives in a potential deceased

organ donor with a lung injury ($PaO_2/FiO_2 < 300$) include normalizing arterial blood gas; preventing atelectasis/alveolar collapse; and maintenance of mechanical ventilation parameters, indicating no alveolar distension or worsened pulmonary injury. These principles are valid even when lung donation is not anticipated (sites in which this transplant modality is not performed) because inappropriate ventilation management (with alveolar hyperdistension and/or atelectrauma) can induce pulmonary inflammatory substance release, causing the worsening of other organ dysfunctions (**D**).[14]

Several methods have been tested for reverting hypoxemia or preventing mechanical ventilation-induced pulmonary injury. The airway pressure release ventilation (APRV) mode can be used when available. Due to providing two pressure levels, this method could prevent alveolar distension (**C**)[15](**B**).[16]

In hypoxemic patients, alveolar recruitment maneuvers as well as nitric oxide inhalation can be used, or a prone position can be chosen. The prone position has certain inconveniences, such as rendering management difficult (e.g., for echocardiography) and the risk of losing catheters and tubes. Additionally, the prone position has technical disadvantages for eventual lung donation (**D**).[17] Nitric oxide was shown to have no significant impact on ARDS patients' mortality and was shown to increase the risk of renal dysfunction (**B**).[18]

Alveolar recruitment maneuvers are very popular in ventilation management of organ donors (**D**),[19] although they have not been shown to be effective in randomized trials in this population. PEEP is an alveolar recruitment maneuver that, most of the time, prevents or even reverts alveolar collapse and atelectasis (potential causes of organ loss) (**A**).[20] One of its advantages is that it is not necessary to be concerned with worsened intracranial hypertension. However, high PEEP values may impact hemodynamics. Additionally, in asymmetric pulmonary injuries, high PEEP values could hyperinflate the contralateral (healthier) lung, rendering it unavailable for donation.

Therefore, intermittent alveolar recruitment maneuvers (such as suspiration or high sustained pressures for a few seconds or up to 2 minutes) constitute methods that could be used as therapeutic or even prophylactic measures. Aggressive 'pulmonary recruitment' maneuvers allow the use of up to one-third of a lung previously categorized as inappropriate (**B**)[6,16](**C**).[19,21]

High-frequency ventilation (HFV) allows alveolar recruitment and protective mechanical ventilation. This technique has been shown to be effective for severe ARDS patients' management and has been proposed for the maintenance of deceased potential donors (**D**).[22] Bovine surfactant instilled into the tracheal cannula may be an option for reverting hypoxemia and improving pulmonary compliance (**C**).[23] However, there is no evidence of this improvement.

Recommendations

- Ventilation for all potential donors with ALI/ARDS should be undertaken, as for other patients with this syndrome (**B**).[18] Use the volume or controlled pressure mode and a tidal volume 5 to 8 mL/kg ideal body weight, and adjust FiO_2 to achieve $PaO_2 > 60$ mmHg and/or an arterial blood gas $SatO_2 > 90$; titrate PEEP according to hypoxemia and hemodynamic impairment, and use a Pplateau < 30 cmH$_2$O (**A**).[6,17] **Strong Recommendation.**

- Recruitment maneuvers can be considered. **Strong Recommendation.** After an apnea test, perform at least one recruitment maneuver (**B**).[6,16] **Strong Recommendation.**

- In case of failure with PEEP, consider other alternatives. Other options can include a prone position; consider nitric oxide and alternative modalities, such as APRV and HFV (**C**).[22] **Weak Recommendation.** Surfactant instilled into the tracheal cannula should not be used (**C**).[23] **Strong Recommendation.**

ENDOCRINE-METABOLIC MANAGEMENT

Should nutritional support be maintained? How much energy should be supplied?

Severe diseases are typically associated with high metabolic stress, which may be caused by an exaggerated systemic inflammatory response. This hypercatabolic condition is found in severe head trauma patients progressing to brain death. In these subjects, the energy expenditure can be as high as 2.5 times the basal metabolic rate (**C**)[24](**D**).[25] Sympathetic storming upon brain death is a result of massive releases of adrenaline, corticosteroid and glucagon (**C**).[26,27] After sympathetic storming, the total energy expenditure decreases by between 15% to 30% compared to the Harris-Benedict equation-predicted value, likely due to a lack of spontaneous muscle activity, a lack of brain metabolism and hypothermia (**D**)[28](**C**).[29]

According to the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, nutritional support in severely ill patients should be used to provide exogenous fuel to preserve lean body mass, preserve immune function and avert metabolic complications (**D**).[30] However, in cases with severe hemodynamic instability, in which high vasopressor drug doses are required, feeding should be

withheld until reversion (**D**).[30] Similarly, the Canadian recommendations for the maintenance of deceased donors suggest maintaining nutritional support in this setting (**D**).[31]

Eleven cases of prolonged somatic support in pregnant women after brain death have been reported. The longest support time was 107 days. In all of these cases, some type of nutrition therapy was provided, and in some instances, total parenteral nutrition was used (**C**).[32] No prospective studies assessing the influence of the nutrition of deceased potential donors on the organ outcomes following donation are available.

Recommendation
- Provide enteral or parenteral nutritional support (**D**).[31] **Strong Recommendation.** Discontinue nutritional support if high vasoactive drug doses are required or if there are signs of tissue hypoperfusion (**D**).[30] **Strong Recommendation.** Provide only 70 to 85% of the basal energy expendure calculated by the Harris-Benedict e read as equation (**C**).[29] **Strong Recommendation.**

Should blood glucose be controlled in a potential organ donor? What are the blood glucose limits? How should blood glucose be maintained and monitored?

Sympathetic storming in deceased potential donors causes marked gluconeogenesis due to the increased insulin resistance of the peripheral tissues and reduced insulin release from the pancreas, almost always resulting in marked hyperglycemia (**C**).[27] After this process, the inflammatory response persists and may lead to stress-related hyperglycemia.

Despite the enthusiasm caused by the article by van den Berghe et al. (**A**),[33] which pointed to the reduced mortality of surgery patients subjected to strict blood glucose control, maintained between 80 mg/dL and 110 mg/dL, other trials have failed to reproduce their results (**A**).[34-38] In the largest study on strict blood glucose control available to date (**A**),[37] patients under strict blood glucose control had an increased mortality rate. Currently, the American Association of Clinical Endocrinologists and the American Diabetes Association (**D**)[39] recommend that critically ill patients be started on protocol-guided intravenous insulin infusions when blood glucose levels remain above 180 mg/dL, aiming to maintain blood glucose levels between 140 and 180 mg/dL.

Blasi-Ibañez et al. collected the demographic, clinical and laboratory parameters of 458 brain-dead organ donors, which included 4,512 blood glucose measurements. Multivariate analysis showed a strong correlation between serum glucose and serum creatinine immediately before the kidneys were removed – the higher the blood glucose level was, the higher the serum creatinine level (**C**).[40] The incidence of hyperglycemia was very high in this group: only 28% of the patients had < 200 mg/dL blood glucose when the organs were removed. Based on these findings, the authors started a prospective and randomized trial entitled the Intensive Insulin Therapy in Deceased Donors – to Improve Renal Allograft Function and Transplanted Allograft Outcomes.[41] Although no direct evidence is available on deceased donors' blood glucose control, the United Network for Organ Sharing (http://www.unos.org/) guidelines recommend blood glucose control with intravenous insulin infusion, aimed at serum glucose levels of 120 mg/dL to 180 mg/dL (**D**).[42]

Recommendation
- Perform capillary blood glucose monitoring at least every 6 hours in all potential donors and more frequently after continued insulin infusion is started (**D**). [31,39,41] **Strong Recommendation.** Start protocol-guided insulin infusion if the blood glucose level is > 180 mg/dL (**D**).[31,39,41] **Strong Recommendation**.

How should diabetes insipidus be treated? When should vasopressin or desmopressin be used? Can intranasal desmopressin be used?

Progressive pituitary-hypothalamic axis dysfunction is very common in brain death. Diabetes insipidus (DI) due to a lack of antidiuretic hormone is seen in approximately 80% of cases. Other clinical changes may be present. Hyperosmolar polyuria (> 4 mL/kg/hour) is the main pathophysiological mechanism, and if not appropriately corrected by an infusion of hypotonic solutions, it leads to secondary hypovolemia, serum hypernatremia (> 145 mEq/L) and hyperosmolarity (> 300 mOsm/L) (**D**).[43]

DDAVP (desmopressin) should be the drug of choice for treating DI due to its exclusive action on V2 receptors (antidiuretic) and its negligible hemodynamic effects. The DDAVP dose should be 1-2 mcg IV as a bolus infusion every 4 hours until achieving a urinary output < 4 mL/kg/hour. IV administration effects are more reliable than oral and nasal administrations (**D**).[31] Vasopressin may be used when its hemodynamic action can be useful for the sake of stability, but it should be used cautiously due to potential coronary, renal and splanchnic vasoconstriction (especially in doses greater than 0.04 U/min) (**C**).[31,44,45]

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Recommendation

- DDAVP should preferably be given as a 1-2 mcg IV bolus every 4 hours or at longer intervals to maintain urinary output < 4 mL/kg/hour (**D**).[31] **Strong Recommendation.** Consider using vasopressin (1 U bolus followed by continued 0.5 to 2.4 U/hour infusion) (**D**).[31] Consider associating DDAVP and vasopressin in refractory cases (**C**).[31,44,45] **Strong Recommendation.**

What serum Na⁺ and urinary output should be maintained in an (adult) deceased donor? How should hypernatremia in diabetes insipidus be dealt with (in addition to hormone replacement)?

There is evidence that deceased donor hypernatremia can be predictive of poorer allograft function outcomes (**C**),[46] although this correlation was not shown in some trials (**C**).[47,48] Whether organ donor hypernatremia is associated with allograft dysfunction, especially in liver transplantation, remains to be clarified (**B**).[46,49,50]

Urinary output changes are frequent during care for deceased donors, in particular polyuria associated with diabetes insipidus, which may lead to hemodynamic instability if not appropriately treated (**D**).[51] However, reduced urinary output may be a sign of poor organ perfusion and may harm the allograft function (**D**).[52] Diuresis should be normalized to improve the maintenance of volemia, perfusion and hydroelectrolytic balance.

Recommendation

- Maintain serum sodium between 130-150 mEq/L and urinary output between 0.5 and 4 mL/kg/hour (**D**).[43,46] **Strong Recommendation.** Correct hypernatremia administrating IV water as 5% blood glucose or 0.45% saline solution (**D**).[45] **Strong Recommendation.** Maintain crystalloid solution infusion if hemodynamic instability is associated with hypernatremia (**D**). **Strong Recommendation.**

How should monitoring of Mg⁺⁺, PO₄⁻, Ca⁺⁺ and K⁺ replacement be done if necessary?

Electrolytic abnormalities may be related to hemodynamic disorders (hypophosphatemia and hypocalcemia may reduce myocardial contractility and contribute for hypotension), and hypocalcemia and hypomagnesemia can cause arrhythmia (**D**).[31]

Recommendation

- Measure Mg⁺⁺, PO₄⁻, Ca⁺⁺ and K⁺; repeat every 6 hours if abnormal. **Strong Recommendation.** Correct

serum magnesium, phosphorus, calcium and potassium levels, as for other critically ill patients (**D**).[31] **Strong Recommendation.**

What is the ideal arterial blood pH? Can abnormalities cause consequences to the donor?

Acid-base disturbances may be potentially harmful in deceased potential donors and may impair organ function. Respiratory alkalosis is generally a consequence of hyperventilation and diuretic therapy in an attempt to reduce intracranial pressure. It can cause coronary vasoconstriction and increase oxygen hemoglobin affinity, making its microcirculatory release difficult. Metabolic acidosis is caused by tissue hypoperfusion and leads to a worsened heart contractility and a reduced endothelial catecholamine response, leading to increased vasodilation and hypotension. The target pH should be between 7.35 and 7.45 (**D**).[53,54] Acidemia or alkalinemia therapy is suggested to be focused primarily on changing mechanical ventilator parameters, using $PaCO_2$ to change blood pH while respecting its physiological levels. The use of sodium bicarbonate can be harmful, aggravating hypernatremia. Therefore, mild acidosis (pH > 7.2) can be tolerated (**D**).[53,54]

Recommendation

- Maintain a pH > 7.2 (**D**).[53,54] Acidosis may contribute to hemodynamic instability and hypoxemia. **Strong Recommendation.**

Are corticosteroids indicated for deceased potential (adult) donors? What dose? Which drug is best?

Several publications and medical society protocols have suggested hormone replacement strategies for the maintenance of brain-dead potential donors (**D**).[8,44,54,55] However, none of these recommendations are based on randomized, controlled, prospective trials. All literature recommendations for hormone replacement therapy rely on common references of retrospective and non-controlled trials, although there is a large number of assessed patients (more than 10,000 patients), and the use of combined hormone therapy resulted in more organs with better post-transplant quality for some of them (**C**).[56,57]

These studies are mostly clinical, observational and retrospective, and they are also based on experimental data of pathophysiological changes following brain death (**C**).[58-64]

Regarding corticoid administration, there is evidence that 15 mg/kg intravenous methylprednisolone every 24 hours contributes to better pulmonary transplant

effectiveness (**C**).[65] Due to its anti-inflammatory action on the liver allograft, corticoid administration to the deceased donor is associated with reduced post-transplant liver dysfunction (**C**).[63] Similarly, adrenal failure following BD can be additionally responsible for hemodynamic instability.

Recommendation

- Administer methylprednisolone at 15 mg/kg every 24 hours after brain death is diagnosed (**C**).[65] **Strong Recommendation.**

What are the indications for thyroid hormones in a deceased potential donor? How should they be dosed?

The clinical and physiological bases for thyroid hormone replacement are apparently more robust than those for corticosteroid replacement (**D**).[66]

There is evidence that thyroid hormone replacement in brain-dead potential donors results in increased hemodynamic stability and more hearts being available for transplant (**C**).[58-61,66,67]

Intravenous administration is preferred, as no pharmacokinetic trials on gastrointestinal absorption in this setting are available. For triiodothyronine (T_3), the recommended dose is 4 mcg as an intravenous bolus, followed by a 3 mcg/hour infusion. If thyroxine (T_4) is chosen, the recommended dose is a 20 mcg intravenous bolus, followed by a 10 mcg/hour infusion (**D**)[8,31,55] (**C**).[56,60]

Recommendation

- Always use thyroid hormones (T_3 – 4 mcg IV bolus followed by 3 mcg/hour by infusion pump or T_4 – 20 mcg IV bolus followed by 10 mcg/hour by infusion pump (**C**).[8,31,55] **Strong Recommendation.** Enteral levothyroxine (1 to 2 mcg/kg) should be given immediately following brain death diagnosis if intravenous forms are not available (**D**). **Non-specific recommendation.**

HEMATOLOGICAL ASPECTS

What hemoglobin (Hb) limits should be used for red blood cell transfusion in a deceased potential donor? Should the red blood cell transfusion strategy be liberal or restrictive?

The appropriate oxygen offering (DO_2) to maintain metabolic needs and tissue oxygenation in brain-dead subjects is currently unknown. Oxygen consumption (VO_2) is known to decrease after BD, similar to general anesthesia patients, in whom VO_2 may be reduced by roughly 25% (**B**).[68]

BD is also associated with lost peripheral vasomotor tonus and inappropriate blood flow redistribution. Consequently, regional DO_2/VO_2 is changed, potentially leading to injury of poorly perfused organs, even when systemic DO_2 is appropriate. Therefore, DO_2 is not able to effectively assess the perfusion of different organs and vascular beds (**B**).[68]

Theoretically, providing supranormal O_2 could prevent damage from irregular oxygen distribution. Although this theory is apparently reasonable for high lactate organ donors, there are no studies proving that increased DO_2 can reduce lactate levels and improve transplant outcomes (**B**).[68]

Liberal or restrictive transfusion concepts are based on Hb levels tolerated in severely ill patients: transfusing to correct Hb < 10 g/dL is liberal, while transfusing only to correct Hb < 7 g/dL levels is restrictive (**B**).[44]

A liberal strategy is apparently more appropriate in brain-dead subjects, considering that Hb > 10 g/dL levels could compensate for hemodynamic conditions and improve the tissue oxygen offering (**D**).[8,44,69-73] Additionally, there are recommendations that maintaining Hb levels between 9 and 10 g/dL is more appropriate for maintaining cardiopulmonary function in hemodynamically unstable subjects. The lowest acceptable Hb level during the management of stable deceased potential donor is 7 g/dL (**D**).[31,45]

Recommendation

- Do not transfuse red blood cells if Hb > 10 g/dL or for Hb between 7 and 10 g/dL in hemodynamically stable potential donors with appropriate tissue perfusion (**D**).[31,45] Transfuse red blood cells if Hb < 7 g/dL (**D**).[31,45] For Hb < 10 g/dL in potential donors, transfuse red blood cells only with hemodynamic instability either associated or not associated with achieving resuscitation goals (**D**).[8,44,69-73] **Strong Recommendation.**

When should platelets and/or coagulation factors be transfused?

Coagulopathy occurs in approximately 45% of severe head trauma patients. The time for bleeding manifestations depends on the injury extension, and they may occur within the first 5 days after trauma (**C**).[74]

Injured brain tissue releases tissue thromboplastin (the main coagulation cascade activator), which is largely present in the brain. Depending on the injury extension, tissue thromboplastin may lead to disseminated fibrin deposition, microvascular thrombosis, organ failure and coagulation factor and platelet depletion, resulting in bleeding (**D**).[75]

Additionally, coagulopathy may result from reduced platelets and coagulation factors due to blood loss. Coagulation disorders may be worsened by dilution, acidosis and hypothermia, which should be corrected first. There is no single laboratory test establishing or excluding disseminated intravascular coagulation (DIC). Laboratory changes, in their order of frequency, are thrombocytopenia, increased fibrin degradation products, prolonged prothrombin activity time (PAT) and activated partial thromboplastin time (aPTT). Low platelet counts are strongly correlated with thrombin generation, as thrombin-induced platelet aggregation is responsible for platelet consumption. A continued platelet count drop, even within the normal range limits (150,000 – 450,000/mm³), can indicate thrombin generation. Similarly, platelet count stabilization suggests that thrombin formation was discontinued (**D**).[76]

No randomized trials are available on organ donors developing coagulation disorders. Therefore, most recommendations are based on consensus recommendations and pathophysiology transpositions from other medical conditions.

No predefined targets are available for platelet counts, PAT, IRN or aPTT. Fresh plasma, platelets and cryoprecipitate transfusions should not be exclusively based on laboratory test results. Overall, platelet and fresh plasma transfusions should be given only for bleeding. However, some protocols recommend maintaining platelet counts > 50,000/mm³ (**D**).[31,77] Decisions on intraoperative red blood cells, fresh plasma and platelet transfusions should be individualized (**D**).[45,77]

In cases of DIC, blood components should be transfused for high bleeding risk before invasive procedures in cases of active bleeding associated with platelet counts less than 50,000/mm³ and/or with INR > 1.5. For persistent severe hypofibrinogenemia (fibrinogen < 100 mg/dL), even after fresh plasma infusion, cryoprecipitate should be transfused (**D**).[76]

There is a recommendation that laboratory monitoring should be repeated every 6 hours for blood and platelet counts and at least every 24 hours for PAT and aPTT (**D**).[31] Standardized blood draws every 6 hours for full blood chemistry panels can facilitate these potential donor maintenance operations.

Recommendations

- Transfuse platelets if there is significant active bleeding associated with thrombocytopenia (100,000/mm³) (**D**)[45,77] or if a platelet count < 50,000/mm³ is associated with increased bleeding risk or occurs before an invasive procedure (**D**).[31,77] **Weak Recommendation.**

- Transfuse fresh plasma if INR > 1.5 and it is associated with increased bleeding risk, occurs before an invasive procedure or is associated significant active bleeding (**D**).[76] **Strong Recommendation.**

- Transfuse cryoprecipitate if fibrinogen < 100 mg/dL (even after fresh plasma transfusion) and it is associated with increased bleeding risk, occurs before an invasive procedure or is associated significant active bleeding (**D**).[76] **Strong Recommendation.**

INFECTION ASPECTS

Is infection a contra-indication for transplant?

Many potential donors are excluded due to either suspected or proven infection when brain death is diagnosed. However, there is currently a strong trend toward expanded donation criteria or, as it is commonly stated, using borderline donors. This expansion includes those patients with either bacterial, fungal, viral or parasitic infections (**B**).[78-80]

Case reports indicate that even Gram-negative bacteremia donors can provide favorable outcomes in kidney, liver and heart transplantations (**C**).[81] Similarly, Caballero et al. reported using 4 donors with left heart bacterial endocarditis in a consecutive series of 355 donors. The organisms involved were *Staphylococcus aureus,* coagulase-negative *Staphylococcus, Staphylococcus hominis* and *Streptococcus viridans.* Kidney and liver transplants were made from these donors with culture-guided antibiotic therapy, with no recipient infection-related complications (**C**).[82] Similarly, a donor who died from *Naegleria fowleri* amoebic meningoencephalitis had kidneys, the pancreas, one lung and the liver transplanted, with no recipient infectious complications (**C**).[83] Also, Zibari et al. published their experience with 599 donors with positive blood cultures (7.5% of the cases) and urine cultures (4.5% of the cases). The donor-related infection rate was 8% of the 179 recipients, with no increased morbidity/mortality or worsened allograft outcomes (**B**).[84]

However, Rogers et al. highlighted the mortality risk for renal allograft recipients from one donor with positive IgG serology for *Toxoplasma gondii.* Both recipients had negative serology and died from multiple organ dysfunction, with histology evidence of systemic protozoan involvement (**C**).[85] Another report described *Aspergillus fumigates* infection in a series of recipients whose donor had died from a brain

hemorrhage, which was later confirmed to be from aspergillosis lesions (**C**).[86]

Regarding virus infections, potential donors with hepatitis B or C, previously considered as absolute contra-indications, can currently have their livers transplanted to recipients infected by the same viruses (**C**).[87]

Cytomegalovirus (CMV) infections in transplanted patients have high morbidity and mortality rates. However, patients receiving transplants due to the consequences of CMV therapy have routinely received organs from donors with CMV (**B**).[8,88]

Recommendation

- Positive culture results or a clinical infection diagnosis should not lead to an absolute contra-indication of organ donation, nor should the deceased donor's maintenance be discontinued (**D**)[31](**B**).[89,90] **Strong Recommendation.**

When is infection a contra-indication for transplant?

There are many unanswered organ transplantation questions. There are no objective and appropriate lung transplant criteria excluding deceased donors with infection. Fisher et al., using traditional criteria from medical, imagery, fibroscopy and oxygen findings criteria, failed to discriminate donors with positive bronchoalveolar lavage (BAL) culture from those with negative results. From the accepted donors, 75% had positive BAL cultures, and only 43% of the rejected donors had positive culture results (**B**).[89]

Despite the severity of several microorganism infections, the literature reports on donors with *Acinetobacter baumannii* bacteremia and septic shock whose organs were successfully transplanted with pre- and post-transplant antibiotic therapy support, with no additional recipient morbidities (**B**).[90]

When donor risk scores combined with receptor risk scores are analyzed for renal transplants, hepatitis C appears to be an independent rejection factor (**B**).[91]

The same risk scores, analyzed for liver transplant donors, show no infectious causes as risk factors for worsened medical outcomes (**B**).[92] Most of the recommendations for different solid organ transplants have contra-indications for systemic viral infections (HTLV I, HTLV II, rabies, adenovirus, enterovirus, measles, West Nile, parvovirus and herpes meningoencephalitis), parasitic infections (leishmaniasis, trypanosomiasis and malaria) and prion-related diseases. HIV infection is considered a contra-indication for transplant, but it was recently reported that 4 cases of HIV-infected donors and recipients showed good medical outcomes (**C**).[93]

Recommendation

- Organ transplantation should be contra-indicated for uncontrolled bacterial infection, as defined by the medical team assisting the deceased donor (**D**).[31] **Strong Recommendation.** Other non-bacterial infections should be analyzed on a case-by-case basis, along with the organ-obtaining center and transplant team. **Strong Recommendation.**

Should antibiotic therapy (either empirical or culture-guided) be maintained during deceased donor maintenance?

Organs transplanted from donors with bacteremia rarely transmit the bacterial infection, and the outcomes for patients receiving organs from infected donors are not significantly worse in comparison with uninfected donors (**C**).[94]

The consequences of donor-originated bacterial infections depend on the bacterial virulence (*P. aeruginosa*), the trend of causing metastatic infection (*Staphylococcus aureus*), antimicrobial drug resistance, and the time for infection acknowledgement and therapy (**C**).[95]

Decisions regarding the use of organs from active or suspected infection donors should include considerations on the urgency of the transplant for the recipient, the available organ alternatives and the recipient's informed consent (**C**).[96]

Any active bacterial or fungal infection in a donor should be treated and, if possible, resolved before the transplant (**C**).[96] However, no data are available recommending the optimal therapy duration or the interval between infection resolution and transplantation (**D**).[96]

Recommendation

- Maintain or start antibiotic therapy in deceased potential donors as clinically indicated (**C**),[96] and inform the transplant coordination team about the possible infection (**D**).[96] **Strong Recommendation.**

Should blood, urine and tracheal secretion cultures be used? How frequently? When?

Screening procedures for all transplants should include blood and urine cultures every 24 hours, in addition to a review of recent microbiological data and previously treated infections (**C**).[96] Although there is no evidence on culture frequency, cultures are recommended to be repeated every 24 hours or upon suspected infection (**D**).[96] *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteremia may result in early post-transplant sepsis

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or with a mycotic aneurism at the recipient's vascular anastomosis (**D**).[97,98]

The International Society for Heart and Lung Transplantation Acceptance's (ISHLT) criteria are strict and, overall, based rather on clinical impressions from lung transplantations than on evidence (**D**).[99]

These criteria are to be assessed during organ selection, based on the donor history, arterial blood gas, chest radiography, bronchoscopy and physical examination of the lungs. The exclusion criteria for transplant are aspiration, sepsis, purulent secretion on bronchoscopy and Gram-stained organisms in pulmonary secretions (**C**).[12]

Attempts to assert flexible lung transplant contra-indications (as related to bronchoscopic criteria) have resulted in increased mortality in several case series (**C**).[21,100]

Recommendation

- Two blood cultures should be drawn from all organ donors upon starting an organ transplant protocol (**C**).[96] **Weak Recommendation.** Cultures should be obtained if a clinical infection is suspected (**D**).[31] There is no evidence recommending a frequency for obtaining cultures. **Strong Recommendation.**

RESUMO

A atuação do intensivista durante a manutenção do potencial doador falecido na busca da redução de perdas de doadores e do aumento da efetivação de transplantes não se restringe aos aspectos hemodinâmicos. O adequado controle endócrino-metabólico é essencial para a manutenção do aporte energético aos tecidos e do controle hidro-eletrolítico, favorecendo inclusive a estabilidade hemodinâmica. A abordagem das alterações hematológicas é igualmente importante considerando as implicações da prática transfusional inapropriada. Ressalta-se ainda o papel da ventilação protetora na modulação inflamatória e conseqüente aumento do aproveitamento de pulmões para transplante. Por fim, assinala-se a relevância da avaliação criteriosa das evidências de atividade infecciosa e da antibioticoterapia na busca do maior utilização de órgãos de potenciais doadores falecidos.

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Guidelines for potential multiple organ donors

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6. Renal maintenance
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Participants: Anderson Ricardo Roman Gonçalves, Marilda Mazzali, Valter Duro Garcia.

7. Heart maintenance
Coordinator: Cristiano Franke
Participants: Alfredo Fiorelli, Ben-Hur Ferraz Neto, Fernando Suparreghi Dias, Frederico Bruzzi, Marcelo Maia.

ERRATUM

In the special article **Guidelines for potential multiple organ donors adult. Part II. Mechanical ventilation, endocrine metabolic management, hematological and infectious aspects**. Rev Bras Ter Intensiva. 2011;23(3):269-82, in the first recommendation under the title Endocrine-metabolic management (p. 273), instead of "Provide 15% to 30% of the energy, as calculated with the Harris-Benedict equation (C). Strong Recommendation", it should be read as "Provide only 70 to 85% of the basal energy expendure calculated by the Harris-Benedict e read as equation (C). **Strong recommendation**".