

Canadian Council for Donation and Transplantation

**Medical Management to  
Optimize Donor  
Organ Potential:  
A Canadian Forum**

**February 23–25, 2004  
Mont Tremblant, Quebec**

**Report  
And  
Recommendations**

*October 1, 2004  
Strachan•Tomlinson*

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## CD-ROM

The CD-ROM included with this report includes electronic copies of the following documents:

1. Steering Committee, Medical Management to Optimize Donor Organ Potential – A Canadian Forum. *Report on Medical Management to Optimize Donor Organ Potential – A Canadian Forum*. Edmonton: The Canadian Council for Donation and Transplantation, 2004.
2. Kutsogiannis DJ, Shemie SD, Doig C *et al.* *Donor Organ Management: Literature Review (full version)*. Edmonton: The Canadian Council for Donation and Transplantation, 2004.
3. Kutsogiannis DJ, Shemie SD, Doig C *et al.* *Donor Organ Management: Literature Review (short version)*. Edmonton: The Canadian Council for Donation and Transplantation, 2004.
4. Hornby K, Shemie SD. *Donor Organ Management: Survey of Guidelines and Eligibility Criteria*. Edmonton: The Canadian Council for Donation and Transplantation, 2004.
5. Meggison H, Kanji S, Shemie SD. *The Role of Thyroid Hormone in Donation, Transplantation and Cardiovascular Diseases*. Edmonton: The Canadian Council for Donation and Transplantation, 2004.
6. Badovinac K. *Canadian Review of Organ Utilization*. Edmonton: The Canadian Council for Donation and Transplantation, 2004.
7. Hornby K, Ross H, Keshavjee S, Rao V, Shemie SD. *A Canadian Investigation Regarding Factors Contributing to Non-Utilization of Hearts and Lungs after Consent for Donation: An In-depth Multi-Centre Review for 2002*. Edmonton: The Canadian Council for Donation and Transplantation, 2004.
8. Planning Committee, Severe Brain Injury to Neurological Determination of Death – A Canadian Forum. *Report on Severe Brain Injury to Neurological Determination of Death – A Canadian Forum*. Edmonton: The Canadian Council for Donation and Transplantation, 2003.

## Preface

The mandate of the Canadian Council for Donation and Transplantation (CCDT) is to strengthen Canada's donation and transplantation system through advice to the Federal, Provincial and Territorial (FPT) Conference of Deputy Ministers of Health. The CCDT Donation Committee took an initial step in this strategy by holding the Forum *Severe Brain Injury to Neurological Determination of Death* in April 2003. This Forum developed recommendations for a national agreement on the processes of care, commencing with severe brain injury and culminating with neurological determination of death, including standard diagnostic criteria and procedures across all age groups. The final report on this initiative was released in December 2003.

A second Forum, *Medical Management to Optimize Donor Organ Potential*, was convened to develop guidelines and recommendations that will enable Canadian health professionals to maximize donor organ potential. There is a widely recognized need to address and incorporate evolving management strategies and therapies that may improve donor organ function for the purposes of transplantation. This Forum addressed the interval of care that begins with neurological determination of death and consent to organ donation and culminates with surgical organ procurement. During this period, there is significant opportunity for enhancing multi-organ function and improving organ utilization.

This Forum was the first structured, cooperative assembly of health professionals in the critical care and transplantation fields and can be viewed as a landmark event in Canada. Bridging of these specialties is required to develop expert consensus recommendations on multi-organ protective therapies. End-of-life care in the intensive care unit (ICU) includes all efforts to actualize the desire and opportunity to donate organs. This evolving collaboration to establish best donor management practices in the ICU and operating room must be linked to ensuring optimal organ utilization. In turn, improving the utilization of organs must be linked to transplant graft and patient outcomes.

We appreciate the hard work and dedication of all individuals whose participation made this Forum a success. The results of the Forum will make a significant contribution to optimizing donor organ management and solidifying the collaborative relationship between critical care, donation and transplantation in the best interests of organ donors, donor families and transplant recipients.

Sam D. Shemie, MD  
Forum Chair, Medical Management to Optimize Donor Organ Potential

## Steering Committee

### **Dr. Sam D. Shemie, Forum Chair**

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Montreal Children's Hospital,  
McGill University Health Centre  
Canadian Critical Care Society  
Canadian Council for Donation and Transplantation

### **Dr. Andrew J. Baker**

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Trillium Gift of Life Network  
Canadian Critical Care Society  
Canadian Anesthesiologists' Society

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## Facilitation

### **Dorothy Strachan**

Strachan•Tomlinson and Associates

### **Sponsored by:**

The Canadian Council for Donation and Transplantation

### **In collaboration with:**

The Canadian Critical Care Society  
The Canadian Association of Transplantation  
The Canadian Society of Transplantation



## Participating Organizations

- Alberta Health and Wellness
- Alberta Intensive Care Society
- American Organ Procurement Organizations
- British Columbia Transplant Society
- Canadian Anesthesiologists' Society
- Canadian Association of Critical Care Nurses
- Canadian Association of Emergency Physicians
- Canadian Association of Transplantation
- Canadian Critical Care Society
- Canadian Institute of Health Information
- Canadian Neurocritical Care Group
- Canadian Neurological Society
- Canadian Neurosurgical Society
- Canadian Organ Replacement Registry
- Canadian Society of Transplantation
- Health Canada
- Human Organ Procurement and Exchange (HOPE) Program
- International Society for Heart and Lung Transplantation
- New England Organ Bank
- New Brunswick Health and Wellness
- New Brunswick Organ and Tissue Procurement Program
- Papworth Program, Cambridge, United Kingdom
- Quebec Society of Intensivists
- Quebec-Transplant
- Saskatchewan Transplant Program
- Trillium Gift of Life Network
- United Network for Organ Sharing

## Forum Overview

Organ protective therapies rely on expert clinical management that is essential to promote donor eligibility and optimize organ function for the purposes of transplantation. There were two key areas of emphasis for experts involved in this Forum:

- How to enable optimal donor organ physiology
- How to expand eligibility and identify and explore logistical challenges from neurological determination of death to organ procurement.

This initiative did not address related challenges such as the consent process, post-procurement organ perfusion and preservation or surgical retrieval team logistics.

Forum objectives were:

1. To review and benchmark existing (national and international) practices, guidelines and policies related to donor organ management, including organ protective therapies; sources included articles and reports from basic science and clinical literature, regional, national and international donor management guidelines and related conferences and workshops
2. To develop expert consensus recommendations for organ protective therapies for the ICU and intraoperative management of the organ donor
3. To develop expert consensus recommendations for the Canadian Council for Donation and Transplantation, Canadian Society of Transplantation, Canadian Critical Care Society, Canadian Association of Transplantation, and other relevant organizations and groups
4. To develop a mechanism that bridges the critical care and transplant communities to review and update expert consensus recommendations for evolving therapies
5. To disseminate the Forum findings based on current research related to knowledge transfer in Canada
6. To develop recommendations for future research in this evolving field.

The Forum was held in Mont Tremblant, Quebec, on February 23–25, 2004, and was sponsored by the Canadian Council for Donation and Transplantation, in collaboration with the Canadian Critical Care Society, the Canadian Association of Transplantation and the Canadian Society of Transplantation. The participants were health care professionals from 27 organizations committed to optimizing the medical management of donor organs, including specialists in adult and pediatric critical care, physician and surgeon specialists in adult and pediatric organ-specific transplantation, neurologists, neurosurgeons, anesthesiologists, emergency medicine physicians, nurses and nurse practitioners. A working group of health administrators, policy makers, and donation/transplant agencies also provided input on logistical barriers and supports and knowledge transfer in support of effective medical management. Discussions focused on collaborative, consensus-based decision making at a national, strategic level.

Speakers and participants recognized that optimal resuscitation of the cardiopulmonary system benefits global multi-organ function and that this was represented in the distribution of Forum questions. The following five areas and related challenge questions were addressed at the Forum.

### **Part I – Multi-system Management of Multi-organ Donors**

Questions for this area explored:

- Systemic Arterial Hypertension Related to Intracranial Pressure
- Cardiovascular Performance, Monitoring and Hemodynamic Supports
- Glycemia and Nutrition
- Diabetes Insipidus and Hyponatremia
- Combined Hormonal Therapy
- Transfusion Thresholds, and
- Invasive Bacterial Infections.

### **Part II – Organ-Specific Considerations: Hearts, Lungs and Intra-abdominal Organs**

Questions for this area explored:

- Heart: indications and logistics for coronary angiography including luminal obstruction thresholds, optimal courses of action in the presence of coronary artery disease and reduced ejection fraction, and troponin levels for standard monitoring
- Lungs: bronchoscopy, bronchopulmonary infections and antimicrobial therapy, donor lung injury, oxygenation impairment and alveolar recruitment, lower limits of the PaO<sub>2</sub>/FiO<sub>2</sub> ratio that preclude transplantation, and lung protective strategies
- Liver: indications for percutaneous liver biopsy, upper limits of liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) precluding transplantability, and liver imaging
- Kidney: indications for routine biopsy and renal ultrasound, creatinine clearance, prevention of contrast induced nephropathy.

### **Part III – Other Systemic Challenges**

- Optimal Time of Organ Procurement, and
- Decisions Regarding Transplantability.

### **Part IV – National Research Agenda**

Potential research questions were identified by participants during their discussions and then summarized as a starting point for a national research agenda to optimize donor organ management.

**Part V – Logistics and Knowledge Transfer**

A panel of key stakeholders identified, described and summarized potential challenges and provided considerations related to disseminating and implementing the recommendations that were developed at the Forum.

## Process

Substantive background documents were provided by the Steering Committee in advance of the Forum, including comprehensive literature reviews and related practice surveys. Each area was addressed during the Forum using the following process:

1. Presentations by experts were followed by open plenary discussions. Participants then worked in small groups guided by worksheets that provided:
  - a. a description of current, well-accepted care in the Canadian context<sup>1</sup>
  - b. a summary of existing scientific evidence
  - c. key considerations
  - d. a summary of national and international donor management guidelines
  - e. a list of references.
2. Small group discussions focused on specific questions related to the processes of care.
3. Meetings of the Forum Recommendations Group (FRG) and the Pediatric Recommendations Group (PRG) reviewed the results of small group and plenary discussions and developed unanimous recommendations for adults and children that were returned to plenary for discussion.
4. Participants' input related to research questions was gathered and summarized.
5. The Logistics and Knowledge Transfer (LKT) Group considered issues related to logistics and knowledge transfer that were identified during the Forum.

## Outcomes

Results of the Forum will be used to help achieve the following overarching CCDT outcomes:

- increased number of donors providing transplantable organs
- increased number of organs transplanted per donor
- improved graft function, graft survival and patient survival.

Discussions at the Forum were lively, focused and collegial. Members of the FRG and PRG panels came to unanimous agreement on draft recommendations that mark a significant, positive advance beyond current practice. Potential areas for research issues related to organ transplantation were also identified, as well as logistical and knowledge transfer issues.

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<sup>1</sup> Well-accepted care in the Canadian context was based on a review of donor management guidelines in effect in Canadian health care facilities (Hornby, Karen, Shemie, Sam D., *Donor Organ Management: Survey of Guidelines and Eligibility Criteria*. Edmonton: The Canadian Council for Donation and Transplantation, 2004). These guidelines, acknowledged to have variable application in practice, serve as the basis for well-accepted care in Canada.

## Overarching Themes

Several overarching themes were identified during discussions:

- There is a need for prospective research to augment the existing levels of evidence used by experts to develop consensus on standards of care.
- The brain dead organ donor is a distinct pathophysiological condition.
- Temporal changes in multi-organ function after neurological determination of death (NDD) demand flexibility in identifying the optimal time of procurement. Participants recognized that:
  - Resuscitation of the cardiopulmonary system benefits the function of all end organs.
  - It is important to take the time necessary in the ICU to optimize multi-organ function for the purposes of improving transplant outcomes.
  - Reversible organ dysfunction may be improved with aggressive resuscitation and frequent re-evaluation.
  - Once organ dysfunction is optimized, surgical procurement should be arranged emergently.
- A four-centre Canadian review of heart and lung utilization identified potential deficits in the consent to individual organs, the offering of organs, and the utilization of offered organs. The Forum recommends that there be no predefined demographic or organ dysfunction that precludes:
  - consent for individual organs
  - offering of organs for transplantation.
- Final decisions about transplantability rest with the individual transplant programs represented by the organ-specific transplant doctors.
- Any initiatives aimed at improving donor organ potential should be evaluated not only by increases in organ utilization, but also linked to the corresponding transplant outcomes.
- ICU-transplant collaboration in this field involves ensuring reciprocal accountability by procurement and transplant services for the non-utilization of organs.

## Expert Speakers

Forum expert speakers provided detailed presentations that were instrumental in the development of the recommendations in this report. They are listed below in the order in which they appeared on the agenda.

### Part I – Multi-system Management of Multi-organ Donors

<b>Dr. Sam D. Shemie</b>	Challenge Address
<b>Dr. Joe Pagliarello</b>	Fundamentals of ICU-Based Donor Management
<b>Mr. Kevin O’Connor</b>	U.S. Perspectives on Donor Management
<b>Dr. Bruce Rosengard</b>	International Perspectives on Donor Management: From Crystal City to Papworth
<b>Dr. Dimitri Novitzky</b>	The Scientific Rationale for Hormonal Therapy in the Organ Donor
<b>Dr. Myron Kauffman</b>	Hormonal Therapy and the Impact on Transplantability in the USA

### Part II – Organ-Specific Considerations: Hearts, Lungs and Intra-abdominal Organs

<b>Dr. Vivek Rao</b>	Expert Organ-Specific Panel Presentation – Heart
<b>Dr. Shaf Keshavjee</b>	Expert Organ-Specific Panel Presentation – Lungs
<b>Dr. Paul Greig</b>	Expert Organ-Specific Panel Presentation – Liver
<b>Dr. Sandra Cockfield</b>	Expert Organ-Specific Panel Presentation – Kidneys

### Part III – Other Systemic Challenges

<b>Ms. Kim Badovinac</b>	Organ Utilization from Canadian Cadaveric Donors: Canadian Organ Replacement Registry Data
<b>Dr. Heather Ross</b>	Canadian Multi-centre Review of Heart and Lung Utilization

## Expert Working Group Members

<b>Dr. Andrew Baker</b>	Chair, Clinical Advisory Committee, Trillium Gift of Life Network Medical Director, Trauma and Neurosurgery, ICU, St. Michael's Hospital, University of Toronto Canadian Anesthesiologists' Society Canadian Critical Care Society	Forum Recommendations Group
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<b>Ms. Tracy Brand</b>	Provincial Program Manager, Saskatchewan Transplant Program President, Canadian Association of Transplantation	Forum Recommendations Group
<b>Dr. Sandra Cockfield</b>	Medical Director, Kidney Transplant Program, University of Alberta Hospital Canadian Society of Transplantation	Forum Recommendations Group
<b>Dr. David Creery</b>	Director, Pediatric Intensive Care Unit Children's Hospital of Eastern Ontario University of Ottawa Canadian Critical Care Society	Pediatric Recommendations Group
<b>Dr. Anne Dipchand</b>	Clinical Head, Heart Transplant Program, Hospital for Sick Children, University of Toronto Canadian Society of Transplantation	Pediatric Recommendations Group
<b>Dr. Christopher Doig</b>	Multisystems Intensive Care Unit, Foothills Hospital, Department of Critical Care University of Calgary Chair, Donation Committee, Canadian Council for Donation and Transplantation Canadian Critical Care Society	Forum Recommendations Group
<b>Dr. Catherine Farrell</b>	Chair, Organ Donation Committee Division of Pediatric Intensive Care, Hôpital Sainte-Justine University of Montreal Canadian Critical Care Society	Pediatric Recommendations Group



<b>Dr. Paul Greig</b>	Director, GI Transplant, University Health Network University of Toronto Canadian Society of Transplantation	Forum Recommendations Group
<b>Dr. Cameron Guest</b>	Chief Medical Officer, Trillium Gift of Life Network Department of Critical Care Medicine, Sunnybrook and Women’s College Health Sciences Centre, University of Toronto Canadian Critical Care Society	Forum Recommendations Group
<b>Dr. Diane Hebert</b>	Clinical Director, Pediatric Multi-organ Transplant Program, Hospital for Sick Children University of Toronto Canadian Society of Transplantation	Pediatric Recommendations Group
<b>Ms. Karen Hornby</b>	Critical Care Nurse and Research Coordinator, Pediatric Intensive Care Unit, Montreal Children’s Hospital, McGill University Health Centre Canadian Association of Critical Care Nurses	Pediatric Recommendations Group
<b>Dr. Shaf Keshavjee</b>	Director, Toronto Lung Transplant Program, University Health Network University of Toronto Canadian Society of Transplantation	Forum Recommendations Group
<b>Dr. Michel Lallier</b>	Surgical Director, Transplantation, Hôpital Sainte-Justine University of Montreal Canadian Society of Transplantation	Pediatric Recommendations Group
<b>Dr. Peter Nickerson</b>	Director, Immunogenetics Laboratory University of Manitoba Health Sciences Centre Canadian Society of Transplantation	Forum Recommendations Group
<b>Dr. Joe Pagliarello</b>	Medical Director, Organ and Tissue Donation Program, The Ottawa Hospital University of Ottawa President-Elect, Canadian Critical Care Society	Forum Recommendations Group
<b>Dr. Vivek Rao</b>	Surgical Director, Cardiac Transplant Program, University Health Network University of Toronto Canadian Society of Transplantation	Forum Recommendations Group

## Medical Management to Optimize Donor Organ Potential: A Canadian Forum

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<b>Dr. Sam D. Shemie</b>	Division of Pediatric Critical Care, Montreal Children's Hospital, McGill University Health Centre Honourary Staff, Department of Critical Care Medicine, Hospital for Sick Children, University of Toronto Canadian Council for Donation and Transplantation Canadian Critical Care Society	Forum Recommendations Group  Pediatric Recommendations Group
<b>Dr. Lori West</b>	Section Head, Heart Transplant Program, Hospital for Sick Children, University of Toronto Canadian Society of Transplantation	Pediatric Recommendations Group
<b>Ms. Kimberly Young</b>	Senior Program Analyst, Canadian Council for Donation and Transplantation Secretariat, Health Canada Forum Project Manager, Medical Management to Optimize Donor Organ Potential	Forum Recommendations Group Pediatric Recommendations Group

## Logistics and Knowledge Transfer Group

<b>Ms. Debbie Gordon (Chair)</b>	Senior Operating Officer, Capital Health, Edmonton
<b>Ms. Kim Badovinac</b>	Consultant, Canadian Organ Replacement Registry, Ontario
<b>Mr. Bill Barrable</b>	Provincial Executive Director, British Columbia Transplant Society
<b>Ms. Tracy Brand</b>	Provincial Program Manager, Saskatchewan Transplant Program
<b>Ms. Mance Cl��roux</b>	President, Canadian Association of Transplantation Executive Director, Qu��bec Transplant
<b>Dr. Christopher Doig</b>	Multisystems Intensive Care Unit, Foothills Hospital, Calgary  Chair, Donation Committee, Canadian Council for Donation and Transplantation
<b>Mr. Thorsten Duebel</b>	Acting Director, Canadian Council for Donation and Transplantation Secretariat
<b>Ms. Nora Johnston</b>	Project Team Leader, Alberta Health and Wellness
<b>Mr. Darwin Kealey</b>	President and CEO, Trillium Gift of Life Network, Ontario
<b>Ms. Joyce MacMullen</b>	Manager of Critical Care, Queen Elizabeth II Health Sciences Centre, Nova Scotia
<b>Mr. Burton Mattice</b>	Chair/VP/COO, North Carolina Donor Services  Association of Organ Procurement Organizations, Procurement Council
<b>Ms. Ann Secord</b>	Senior Consultant, New Brunswick Department of Health and Wellness



**Part I –**

**Multi-system Management  
of the Multi-organ Donor**



## 1. Systemic Arterial Hypertension Related to Intracranial Pressure

### 1.1 Thresholds and Preferred Therapy

*We recommend that arterial hypertension after neurological determination of death (NDD) be treated according to the following:*

*a. Thresholds:*

- Systolic blood pressure (BP) > 160 mmHg  
and/or*
- Mean arterial pressure (MAP) > 90 mmHg.*

*b. Preferred therapy:*

- Nitroprusside (dosage: 0.5–5.0 µg/kg/min)  
and/or*
- Esmolol (dosage: 100–500 µg/kg bolus followed by 100–300 µg/kg/min).  
Infusions should be titrated to the desired clinical effect.*

### Existing Canadian Practice

Significant practice variation.

### Key Considerations

- There is a need to distinguish acute intracranial pressure (ICP)-related autonomic storm and hypertension that may occur during herniation but prior to NDD. This period of care was not under consideration by this Forum.
- Given evolving changes and risk of deterioration in cardiovascular dysfunction after NDD, short-acting agents are preferable.
- Alternate agents include:
  - Nitroglycerin, e.g., to reduce the potential risk of coronary steal compared to nitroprusside
  - Labetolol, which is more commonly available and utilized than esmolol in clinical practice; however, there are concerns about its prolonged biologic half-life ( $t^{1/2} = 4\text{--}6$  hours).
- Hypertension in the setting of vasopressor use or inotropic support is an indication for decreasing support rather than initiating antihypertensives.

### Evidence

Recommendation 1.1: page 73.

## 2. Cardiovascular Performance, Monitoring and Hemodynamic Support

### Overall Considerations

1. The deterioration of cardiovascular function associated with intracranial hypertension will vary with:
  - a. rapidity of rise of intracranial pressure (ICP)
  - b. time after herniation
  - c. etiology of brain injury (e.g., traumatic myocardial contusion, ischemia after cardiac arrest or shock, hypoxemia).
2. It is recognized that intensivists titrate cardiovascular therapy to clinical, biochemical and hemodynamic endpoints that ensure restoration of intravascular volume status without hypervolemia and appropriate support of the myocardium and vascular system to ensure optimal cardiac output for organ perfusion.
3. The initiation of cardiovascular support assumes that patients will have been volume resuscitated to normovolemia.
4. Evaluation of cardiocirculatory status is a global assessment of multiple variables. No single measurement or one value in isolation should drive therapy.
5. Escalation of support should be accompanied by escalation of hemodynamic monitoring.
6. It is accepted that while these targets serve as guidelines for therapy, rigid adherence to numbers should be balanced by the overall evaluation of cardiovascular status by experienced clinicians.
7. Cardiovascular support should be based on rational physiology. Pure vasopressors (vasopressin, phenylephrine) should be distinguished from vasopressors with  $\beta$ -agonist inotropic action (norepinephrine, epinephrine).  $\beta$ -agonist therapy should be used with caution in potential heart donors given concerns about myocardial adenosine triphosphate (ATP) depletion and down regulation of  $\beta$ -receptors. If the heart is being considered for donation, dopamine or its equivalent should not be escalated beyond 10  $\mu\text{g}/\text{kg}/\text{min}$ .

### Existing Canadian Practice

The following were identified as areas of well-accepted practice and endorsed *a priori*:

- Standard monitoring: arterial line, central venous line
- Hemodynamic targets include:
  - i. Mean arterial pressure (MAP)  $\geq 70$  mmHg
  - ii. Systolic blood pressure (BP)  $\geq 100$  mmHg
  - iii. Heart rate  $\geq 60 \leq 120$  bpm
  - iv. Central venous pressure 6–10 mmHg (normovolemia).



## 2.1 Central or Mixed Venous Oxygen Saturation Monitoring

*We recommend that mixed venous oxygen saturation monitoring be indicated in patients with ongoing hemodynamic instability. Hemodynamic therapy should be tailored to reach a target  $\geq 60\%$ .*

### Existing Practice

Data not available.

### Key Considerations

- Serial trends are more useful than single measurements.
- Mixed venous oximetry may be determined by intermittent sampling from the pulmonary artery or continuously via oximetric catheters.
- Tissue oxygen extraction has not been well studied in patients declared neurologically dead. Low values may reflect reduced oxygen delivery; however, high values in the face of arrested neurological function and/or arrested brain circulation may not be interpreted reliably.
- Central venous oximetry is not well studied in patients declared neurologically dead.

### Evidence

Recommendation 2.1: page 75.

## 2.2 Serial Lactate Monitoring

*We recommend that serial lactate measurements be performed in all patients. In the presence of elevated or rising lactate levels, investigations are recommended to determine etiology.*

### Existing Practice

Data not available.

### Key Considerations

- Decreasing lactate levels reflect improvements in oxygen delivery.

### Evidence

Recommendation 2.2: page 75.

## 2.3 Indications for Pulmonary Artery Catheterization

*We recommend that pulmonary artery catheterization be applied when:*

a. *2D echocardiographic assessment of ejection fraction is  $\leq 40\%$ .*

*or*

b. *Patients require (i) dopamine  $> 10 \mu\text{g}/\text{kg}/\text{min}$  (or equivalent), (ii) vasopressor support (where vasopressin is not included as part of hormone therapy), and/or (iii) an escalation of supports.*

*Pulmonary artery catheter (PAC) hemodynamic targets are pulmonary capillary wedge pressure (PCWP) 6–10 mmHg, cardiac index (CI)  $> 2.4 \text{ L}/\text{min}\cdot\text{m}^2$ , systemic vascular resistance (SVR) 800–1200 dynes/sec-cm<sup>5</sup>.*

### Existing Canadian Practice

Significant practice variation.

### Key Considerations

- “Vasopressor” refers to a vasoconstricting agent.
- While there is diminishing use of pulmonary artery catheterization in adult intensive care practice, the brain dead organ donor is a distinct pathophysiological state.
- Justifications for PAC are not limited to the precise titration of hemodynamic support but are also required for the evaluation of suitability for heart and lung transplantation.
- 2D echocardiography is primarily indicated to evaluate cardiac function and the suitability of the heart for the purposes of transplantation. The role of single or serial echocardiography in the assessment of cardiac function as a guide to hemodynamic therapy in the unstable organ donor is not well established.

### Evidence

Recommendation 2.3: page 75.

## 2.4 First-Line Agents for Hemodynamic Support: Vasopressin

*We recommend that vasopressin be used for hemodynamic support when vasopressor agents are indicated. The maximum dose should be 2.4 Units/hour (0.04 Units/minute).*

### Existing Canadian Practice

Significant practice variation.

### Key Considerations

- Standard cardiovascular support includes dopamine  $\leq 10 \mu\text{g}/\text{kg}/\text{min}$  (or equivalent).
- Vasopressin is a special agent because it can be used in a variety of applications, i.e., hemodynamic vasopressor support, diabetes insipidus therapy and hormonal therapy.
- Dosing units require standardization.
- Weaning of catecholamine support is the first approach to arterial hypertension while on vasopressin.

### Evidence

Recommendation 2.4: page 78.

## 2.5 Second-Line Agents for Hemodynamic Support: Norepinephrine, Epinephrine and Phenylephrine

*We recommend that norepinephrine, epinephrine and phenylephrine be used for hemodynamic support. Therapy should be titrated to clinical effect with no predetermined upper limit of dosing.*

### Existing Canadian Practice

Significant practice variation.

### Key Considerations

- Escalating doses of catecholamines should be guided by PAC data. Doses beyond  $0.2 \mu\text{g}/\text{kg}/\text{min}$  for any of these agents should be used with caution.

### Evidence

Recommendation 2.5: page 78.

### 3. Glycemia and Nutrition

#### 3.1 Glycemic Control

*We recommend glucose control with insulin infusions titrated to a blood glucose target of 4–8 mmol/L.*

##### Existing Canadian Practice

Significant practice variation.

##### Key Considerations

- The use of insulin should not be misinterpreted as a form of insulin dependence that might preclude islet cell transplantation. If clarification is required, hemoglobin (Hgb) A1C levels should be measured under these circumstances.

##### Evidence

Recommendation 3.1: page 82.

#### 3.2 Nutrition

*We recommend that nutrition be provided as follows:*

- Intravenous (iv) dextrose infusions should be given routinely.*
- Routine enteral feeding should be initiated or continued as tolerated and discontinued on call to the operating room.*
- Parenteral nutrition should not be initiated; however, in circumstances where it has been initiated, it should be continued.*

##### Existing Canadian Practice

Data not available.

##### Key Considerations

Not applicable.

##### Evidence

Recommendation 3.2: page 82.

## 4. Diabetes Insipidus and Hypernatremia

### Existing Canadian Practice

The following were identified as areas of well-accepted practice and endorsed *a priori*:

- Serum sodium (Na): target range is  $\geq 130 \leq 150$  mmol/L
- Urine output: target range is 0.5–3 ml/kg/hr (in adults and children)
- Diabetes insipidus can be defined as:
  - urine output  $> 4$  ml/kg/hr in adults and children
  - associated with rising serum Na  $\geq 145$  mmol/L
  - associated with rising serum osmolarity  $\geq 300$  mosM and decreasing urine osmolarity  $\leq 200$  mosM
- 1-desamino-D-arginine vasopressin (DDAVP) dosing for diabetes insipidus:
  - adult: 1–4  $\mu\text{g}$  intravenous (iv) then 1–2  $\mu\text{g}$  iv q6h for urine output  $> 4$  ml/kg/hr
  - children: 0.25 to 1  $\mu\text{g}$  iv q6h for urine output  $> 4$  ml/kg/hr.

### 4.1 Diabetes Insipidus

*We recommend the following with respect to diabetes insipidus:*

- a. *Diabetes insipidus in isolation can be treated with a continuous iv vasopressin infusion (arginine vasopressin [AVP]  $\leq 2.4$  Units/hour) or intermittent iv DDAVP.*
- b. *Under the following circumstances, vasopressin infusion should be the first choice:*
  - *hemodynamic support with vasopressin required*
  - *combination hormonal therapy implemented.*
- c. *If required, DDAVP can be utilized as a supplement to vasopressin.*
- d. *DDAVP does not have to be discontinued prior to the operating room.*

### Key Considerations

DDAVP is an analog of AVP with a relatively pure antidiuretic effect and negligible vasopressor activity.

### Evidence

Recommendation 4.1: page 84.

## 4.2 Hyponatremia

*We recommend that hyponatremia be treated in all donors if serum sodium levels are greater than 150 mmol/L.*

### Key Considerations

- In addition to sodium control, calcium, phosphate, potassium and magnesium levels should be normalized.

### Evidence

Recommendation 4.2: page 84.

## 5. Combined Hormonal Therapy

### 5.1 Thyroid Hormone, Vasopressin and Methylprednisolone

*We recommend that combined hormonal therapy be used in donors with 2D echocardiographic assessment of ejection fraction  $\leq 40\%$  or hemodynamic instability. Consideration should be given to its use in all donors.*

*Combined hormonal therapy is defined as:*

- Thyroid hormone – intravenous (iv) tetra-iodothyronine ( $T_4$ ) dosage 20  $\mu\text{g}$  iv bolus followed by 10  $\mu\text{g}/\text{hour}$  iv infusion*
- Vasopressin – 1 unit iv bolus; 2.4 Units/hour iv infusion*
- Methylprednisolone – 15 mg/kg iv q24h.*

#### Existing Canadian Practice

Significant practice variation.

#### Key Considerations

- Hemodynamic instability includes shock unresponsive to restoration of normovolemia and requiring vasoactive support (dopamine  $> 10 \mu\text{g}/\text{min}$ ) or any vasopressor.
- The weight of currently available evidence in a large retrospective U.S. cohort study (United Network for Organ Sharing [UNOS]) suggests a substantial benefit from triple hormone therapy with minimal risk. A multivariate logistic regression analysis of 18,726 brain dead donors showed significant increases in kidney, liver and heart utilization from donors receiving three-drug hormonal therapy. Significant improvements in one-year kidney graft survival and heart transplant patient survival were also demonstrated (Rosendale, Kauffman et al. manuscript in preparation, 2004). It is recognized that a prospective randomized trial has not been performed.
- As peripheral tissue conversion of  $T_4$  into tri-iodothyronine ( $T_3$ ) may be impaired in organ donors and in those on corticosteroids, iv  $T_3$  may be preferred but is not commercially available in Canada at this time. Intravenous  $T_4$  and enteral  $T_3$  are currently available.
- In those UNOS patients receiving hormone therapy,  $T_4$  was used in 93% and  $T_3$  in 6.9% of cases, with insufficient numbers to discriminate any benefit of  $T_3$  over  $T_4$ .
- When administered by continuous infusion, the bioavailability of iv  $T_4$  may be affected by stability in solution and potential adherence to plastic tubing resulting from its hydrophobic nature. The quantitative impact of this pharmacological concern is unclear. Alternatively, iv  $T_4$  may be given as follows: 100  $\mu\text{g}$  iv bolus followed by 50  $\mu\text{g}$  iv q12h.
- Should future data show a benefit of iv  $T_3$  over iv  $T_4$ , the recommendations subsequent to this Forum should be utilized to lobby the Canadian Health Protection Branch to make iv  $T_3$  therapy available in Canada for this indication.

- Absorption and pharmacokinetic data on enteral T<sub>3</sub> in organ donors is required before recommending its use.
- Vasopressin should be initiated at a fixed rate. If arterial hypertension ensues, catecholamines should be weaned prior to decreasing vasopressin infusion rate.

### **Evidence**

Recommendation 5.1: page 88.

## **5.2 Corticosteroids and Lung Protection**

*We recommend that methylprednisolone at 15 mg/kg iv q24h be administered to all donors, to be initiated following neurological determination of death.*

### **Existing Canadian Practice**

Methylprednisolone: 15 mg/kg iv ( $\leq$  1 gm) for potential lung donors.

### **Key Considerations**

- Corticosteroid therapy is currently indicated as the immune modulating therapy for potential lung donors, and protocols for administration of corticosteroids are non-uniform.

### **Evidence**

Recommendation 5.2: page 93.



## 6. Transfusion Thresholds

### 6.1 Acceptable Targets for Hemoglobin, Platelets and Coagulation Parameters

*We recommend the following with respect to hemoglobin, platelets and coagulation parameters:*

- a. A hemoglobin target of 90–100 g/L is most appropriate to optimize cardiopulmonary function in the face of hemodynamic instability. Hemoglobin  $\geq$  70 g/L is the lowest acceptable limit for the Intensive Care Unit (ICU) management of stable donors.*
- b. There are no defined targets for platelets, international normalized ratio (INR) or partial thromboplastin time (PTT) – platelet or plasma factor replacement are indicated for clinical bleeding only.*
- c. Blood drawing for donor serology and tissue typing should occur prior to transfusions to minimize the risk of false results related to hemodilution.*
- d. No special transfusion precautions are required in organ donors.*

#### Existing Canadian Practice

Significant practice variation.

#### Key Considerations

- Red blood cell transfusions can be associated with inflammatory activation related to the age of blood.
- Consider the crystalloid sparing effect of red cell transfusions in potential lung donors with alveolar-capillary leak.
- Invasive procedures associated with bleeding risk may require correction of thrombocytopenia and coagulation status.
- Intraoperative transfusion of red blood cells, platelets and plasma factors by anesthetists and the transplant team should be individually tailored.
- In Canada, blood is routinely leukocyte depleted, and the risk of transmission of cytomegalovirus (CMV) is negligible. It is not necessary to give CMV-negative blood to CMV-negative donors.

#### Evidence

Recommendation 6.1: page 95.

## 7. Invasive Bacterial Infections

### 7.1 Daily Blood Cultures

*We recommend the following with respect to blood cultures:*

- a. Initial baseline blood culture should be obtained for all donors and repeated after 24 hours and on an as-needed basis.*
- b. Positive blood cultures or confirmed infections are not contraindications to organ donation.*
- c. Antibiotic therapy should be initiated in cases of proven or presumed infection. Duration of therapy depends on the virulence of the organism and is determined in consultation with the transplant team and infectious disease services.*
- d. No minimum duration of therapy prior to organ procurement can be defined at this time.*

#### **Existing Canadian Practice**

Standard care includes urine cultures.

#### **Key Considerations**

Not applicable.

#### **Evidence**

Recommendation 7.1: page 96.

## 7.2 Broad Spectrum Antibiotics

*We recommend the following with respect to broad spectrum antibiotics:*

- a. Empiric broad spectrum antibiotics are not indicated during the Intensive Care Unit (ICU) care of the organ donor.*
- b. Decisions on the use of perioperative antibiotics should be at the discretion of the surgical team.*

### **Existing Canadian Practice**

Data not available.

### **Key Considerations**

Not applicable.

### **Evidence**

Recommendation 7.2: page 96.



**Part II –**

**Organ-Specific  
Considerations:  
Heart, Lungs and  
Intra-abdominal Organs**



## 8. Heart

### Existing Canadian Practice

The following were identified as areas of well-accepted practice and endorsed *a priori*:

- Potential cardiac donors undergo routine screening by electrocardiogram (EKG) and 2D echocardiography.

### 8.1 Initial Evaluation of Cardiac Function

*We recommend that if the initial evaluation of cardiac function demonstrates a 2D echocardiographic assessment of ejection fraction  $\leq 40\%$ , the optimal course be to insert a pulmonary artery catheter (PAC) and institute therapy tailored to the following PAC hemodynamic targets:*

- a. Pulmonary capillary wedge pressure 6–10 mmHg*
- b. Cardiac Index  $> 2.4$  L/min- $m^2$*
- c. Systemic vascular resistance 800–1200 dynes/sec- $cm^5$*
- d. Left ventricular stroke work index  $> 15$  g/kg-min.*

### Key Considerations

- Pulmonary artery catheterization data has been linked to favorable transplant outcomes.
- Initial echocardiography for heart donor evaluation should be performed only after hemodynamic resuscitation. Repeat echocardiography should be considered after  $\geq 6$  hours. There is a need to prospectively study the utility of serial echocardiography.
- Justifications for PAC are not limited to precision of hemodynamic support but are also required for the evaluation of suitability for heart and lung transplantation. Transplant decision making should reflect these recommendations. An abnormal echocardiogram followed by favorable hemodynamic data by pulmonary artery catheterization is acceptable assessment and does not mandate the need for a follow-up echocardiography.
- Pulmonary artery catheterization is recommended with the provision that appropriate technical and interpretive expertise is available.

### Evidence

Recommendation 8.1: page 97.

## 8.2 Troponin Levels

*We recommend that troponin (either I or T) levels measured q12h be standard monitoring for both clinical and prognostic information.*

### Key Considerations

- Troponin levels should not be used in isolation to reject hearts for transplantation.

### Evidence

Recommendation 8.2: page 97.

## 8.3 Coronary Angiography

*We recommend the following with respect to coronary angiography:*

- The following donor characteristics are indications for coronary angiography:*
  - *male > 55 years or female > 60 years*
  - *male > 40 years or female > 45 years in the presence of two risk factors (see Key Considerations)*
  - *presence of three or more risk factors at any age (see Key Considerations)*
  - *history of cocaine use.*
- If the hospital has angiography facilities and indications for angiography are present, an angiogram should always be performed to document coronary anatomy to assist in decision making.*
- There should be no absolute threshold for coronary luminal obstruction; decisions should be made in the context of the recipient status, heart function and the potential to intervene through coronary artery bypass grafting or percutaneous coronary interventions, e.g., stent.*
- The inability to perform an angiogram should not preclude transplantation. Where coronary angiography is not available, cardiac donor organ suitability should still be considered based on:*
  - *2D echocardiographic assessment of ejection fraction > 40% and/or*
  - *hemodynamic stability and/or*
  - *surgical inspection at time of procurement.*
- The option for patient transfer to a procurement hospital with angiogram capabilities should be considered on a case-by-case basis with full consent of the donor family.*



## Key Considerations

- Risk factors for coronary heart disease include:
  1. smoking
  2. hypertension
  3. diabetes
  4. hyperlipidemia
  5. body mass index > 32
  6. family history
  7. prior history of coronary artery disease
  8. ischemic EKG
  9. anterolateral regional wall motion abnormalities on echo
  10. 2D echocardiographic assessment of ejection fraction  $\leq$  40%.
- To minimize the risk of contrast nephropathy:
  - Normovolemia should be ensured.
  - N-acetylcysteine should be given prophylactically at doses of 600–1000 mg enterally bid with the first dose administered as soon as it is recognized that angiography is indicated. Alternatively, N-acetylcysteine may be administered intravenously at 150 mg/kg in 500 ml normal saline over 30 minutes immediately before contrast, followed by 50mg/kg in 500 ml of normal saline over 4 hours.
  - Angiograms should be performed with a low-risk radiocontrast agent (non-ionic, iso-osmolar), using minimum radiocontrast volume and without a ventriculogram.

## Evidence

Recommendation 8.3: page 97.

## 9. Lungs

Note: For recommendations related to corticosteroids and lung protection, see recommendation 5.2.

### Existing Canadian Practice

The following were identified as areas of well-accepted practice and endorsed *a priori*:

- Pulse oximetry, serial arterial blood gas monitoring, endotracheal tube suctioning, chest x-ray, bronchoscopy and bronchoalveolar lavage
- Mechanical ventilation with the following targets:
  - Fraction of inspired oxygen ( $\text{FiO}_2$ ) titrated to keep oxygen saturation  $\geq 95\%$ , partial pressure of arterial oxygen ( $\text{PaO}_2$ )  $\geq 80$  mmHg
  - pH 7.35–7.45,  $\text{PaCO}_2$  35–45 mmHg
  - Positive end expiratory pressure (PEEP) of 5 cm  $\text{H}_2\text{O}$ .

### 9.1 Oxygenation Impairment

*In cases where the  $\text{PaO}_2/\text{FiO}_2$  (P/F) ratio is  $< 300$ , we recommend the following:*

- Positional rotation therapy should be routine and defined as rotation to a lateral position q2h.*
- Routine suctioning and physiotherapy should be standard care.*
- PEEP of 5  $\text{cmH}_2\text{O}$  is recommended but periodic increases of PEEP up to 15  $\text{cmH}_2\text{O}$  are an acceptable form of alveolar recruitment.*
- Sustained inflations (peak inspiratory pressure [PIP] of 30  $\text{cmH}_2\text{O}$  x 30–60 sec) are an acceptable form of alveolar recruitment.*
- Diuresis to normovolemia should be initiated when indicated.*

### Key Considerations

- P/F ratio evaluation is performed on PEEP of 5  $\text{cmH}_2\text{O}$  and  $\text{FiO}_2 = 1.0$ .
- Recruitment maneuvers should be utilized periodically in all donors regardless of P/F ratio and should continue through the intraoperative period.
- Prone positioning is not recommended for adult or pediatric donors.

### Evidence

Recommendation 9.1: page 101.

## 9.2 Lower Limits of the Partial Pressure of Arterial Oxygen/Fraction of Inspired Oxygen Ratio

*We recommend the the following with respect to lower limits of the P/F ratio:*

- a. *There should be no predefined lower limit for the P/F ratio that precludes transplantation.*
- b. *Timing of evaluation, temporal changes, response to alveolar recruitment and recipient status should be considered.*
- c. *In cases of unilateral lung injury, pulmonary venous partial pressure of oxygen (PvO<sub>2</sub>) during intraoperative assessment is required to reliably evaluate contralateral lung function.*

### Key Considerations

Not applicable.

### Evidence

Recommendation 9.2: page 101.

## 9.3 Optimal Targets for Tidal Volume and PIP

*We recommend the following optimal targets for tidal volume PIP:*

- a. *Tidal volume should be 8 to 10 ml/kg.*
- b. *The upper limit of PIP should be  $\leq 30$  cm H<sub>2</sub>O.*

### Key Considerations

- Lung-protective strategies are currently used in patients with acute respiratory distress syndrome (ARDS) or at risk of ARDS, where pressure-limited ventilation is defined by a PIP < 35 cmH<sub>2</sub>O and tidal volume of 6–8 ml/kg). Benefits of these strategies apply to ARDS patients, and corresponding data are not available in organ donors.

### Evidence

Recommendation 9.3: page 101.

## 9.4 Bronchoscopy and Antimicrobial Therapy

*We recommend the following with respect to bronchoscopy and antimicrobial therapy:*

- a. Bronchoscopy can be performed by the local hospital expert and reported to the responsible transplant surgeon.*
- b. Antimicrobial therapy should be tailored to bronchial wash gram stain or culture results or suspected or confirmed bronchopneumonia.*
- c. Empiric broad spectrum antibiotics are not routinely indicated but may be used in donors at high risk for bronchopneumonia.*
- d. Intensive Care Unit (ICU) length of stay is not an independent indication for antimicrobial therapy.*

### Key Considerations

- Technology should be developed to enable:
  - remote review of bronchoscopy and chest x-ray images
  - three-way communication linkages between ICUs, organ procurement organizations (OPOs) and transplant surgeons.
- Nephrotoxic antimicrobials should be avoided when possible.

### Evidence

Recommendation 9.4: page 99.

## 10. Liver

### Existing Canadian Practice

The following was identified as an area of well-accepted practice and endorsed *a priori*:

- Potential liver donors should be assessed for the following:
  - History of jaundice, hepatitis, excessive alcohol ingestion
  - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (direct and indirect where available), INR (or prothrombin time [PT]), repeat q6h
  - Serum electrolytes, creatinine, urea
  - Hepatitis B surface antigen (HBsAG), hepatitis B antibody (HBcAb), hepatitis C virus antibody positive (HCV Ab).

### 10.1 Upper Limits of Hepatic AST and ALT

*We recommend that there be no upper limits of hepatic AST and ALT that preclude liver transplantability. All livers should be offered; decisions related to transplantability depend on organ status, trends in liver function over time and recipient status.*

#### Key Considerations

Not applicable.

#### Evidence

Recommendation 10.1: page 103.

### 10.2 Hepatic Ultrasound

*We recommend that there is no requirement for prospective liver donors to have an hepatic ultrasound.*

#### Key Considerations

Not applicable.

#### Evidence

Recommendation 10.2: page 103.

### 10.3 Indications for Liver Biopsy

*We recommend the following indications for ultrasound-guided percutaneous liver biopsy in the Intensive Care Unit (ICU) prior to procurement, in consultation with the liver transplant team, to enable decisions about transplantability:*

- Weight >100 kg or body mass index > 30 or hepatitis C virus antibody-positive donor*

*and*

- Distant procurement, i.e., when a procurement team is not immediately available.*

*Intraoperative biopsy by liver retrieval team is recommended in all other instances where liver biopsy is indicated.*

*If the biopsy cannot be done in the ICU and biopsy indications exist, the liver should be offered and transplantation should always be considered at the discretion of the liver transplant team.*

#### **Key Considerations**

Not applicable.

#### **Evidence**

Recommendation 10.3: page 103.

## 11. Kidney

### Existing Canadian Practice

The following were identified as areas of well-accepted practice and endorsed *a priori*:

- A normal creatinine clearance ( $> 80 \text{ ml/min/1.73 m}^2$ ) defines the optimal function threshold for transplantation. However, an abnormal serum creatinine or calculated creatinine clearance in a donor does not necessarily preclude use of the donor kidneys.
- Urinalysis is essential to rule out kidney abnormalities.
- Creatinine and serum urea (blood urea nitrogen) measurements should be taken q6h.

### 11.1 Creatinine Clearance

*We recommend that creatinine clearance be based on the Cockcroft-Gault equation. Urine collection to measure creatinine clearance is not indicated.*

#### Key Considerations

- There is no absolute contraindication to kidney donation based on a serum creatinine level or creatinine clearance alone.

#### Evidence

Recommendation 11.1: page 106.

### 11.2 Renal Ultrasound

*We recommend that renal ultrasounds be performed on a case-by-case basis, taking into account factors such as a history of renal disease.*

#### Key Considerations

- In general, there are no firm indications for renal ultrasound; this investigation tends to be low yield.

#### Evidence

Recommendation 11.2: page 106.

### 11.3 Indications for Kidney Biopsy

*We recommend that the following variables be considered in determining the need for intraoperative kidney biopsy at the time of procurement to enable decisions about transplantability:*

- *age > 65, or a younger age with a history of any of the following:*
  - *creatinine level > 133  $\mu\text{mol/L}$*
  - *hypertension*
  - *diabetes*
  - *abnormal urinalysis.*

#### **Key Considerations**

- Histological evaluation, assessing for glomerulosclerosis and/or vasculopathy, is required prior to excluding kidneys. The biopsy should be performed intraoperatively at the time of procurement, rather than in the ICU.

#### **Evidence**

Recommendation 11.3: page 106.



# **Part III – Other Systemic Challenges**



## 12. Optimal Time of Organ Procurement and Decisions Regarding Transplantability

### 12.1 Optimal Time of Organ Procurement

*It is important to take the necessary time in the Intensive Care Unit (ICU) to optimize multi-organ function for the purposes of improving transplant outcomes.*

*Reversible organ dysfunction can be improved with resuscitation and re-evaluation. 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.*

*Once optimized, donors should have surgical procurement procedures arranged emergently.*

#### Existing Canadian Practice

In general, after neurological death has been declared and consent to organ donation has been given, efforts are made to complete logistics and initiate procurement as quickly as possible.

#### Key Considerations

- This existing paradigm of care should be adjusted in view of the following situations that may be correctable or may benefit from resuscitation and re-evaluation:
  - myocardial/cardiovascular dysfunction
  - oxygenation impairment related to potentially reversible lung injury
  - invasive bacterial infections
  - hypernatremia
  - the need to evaluate temporal trends in aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
  - the need to evaluate temporal trends in creatinine
  - any other potentially treatable situation.
- Extending the interval of donor care in the ICU to optimize transplant outcomes should be factored into donation consent discussions and should be consistent with the wishes of the family or surrogate decision maker.

#### Evidence

Recommendation 12.1: page 110.

## 12.2 Decisions Regarding Transplantability

*We recommend that there be no predefined demographic factor or organ dysfunction thresholds that preclude consent for individual organs or the offering of organs for transplantation, and that:*

- a. Consent should be requested for all organs.*
- b. Within the context of existing legal and regulatory frameworks, all organs should be offered.*
- c. Ultimate decisions about transplantability rest with the individual transplant programs represented by the organ-specific transplant doctors.*

### Existing Canadian Practice

Significant practice variation.

### Key Considerations

- Accountability for non-utilization of organs is required from procurement and transplant services. The limited data currently provided to the Canadian Organ Replacement Register on reasons for the non-use of organs are inadequate.
- The utilization of organs should be linked with corresponding transplant graft and patient outcomes.
- Issues related to transmissible virus or malignancy should comply with existing Canadian standards and guidelines.

### Evidence

Recommendation 12.2: page 110.

## 13. Pediatric Age-Related Adjustments

### 13.1 Pediatric Age-Related Adjustments

*We recommend that the Forum recommendations (1–12) for Medical Management to Optimize Donor Organ Potential (MEMODOP) be applied to infants, children and adolescents with the following qualifications:*

#### Overarching

- *The pediatric organ donor is defined as:*
  - *newborn to 18 years*
  - and*
  - *care provided within a Pediatric Intensive Care Unit (PICU).*
- *Dosing recommendations apply to children  $\leq 60$  kg, beyond which adult dosing should apply.*

#### Section 1: Systemic Arterial Hypertension Related to Intracranial Pressure

- *Thresholds for treating arterial hypertension after neurological determination of death are:*

<i>Newborns–3 months</i>	<i>&gt; 90/60</i>
<i>&gt; 3 m–1 year</i>	<i>&gt; 110/70</i>
<i>&gt; 1 yr–12 yrs</i>	<i>&gt; 130/80</i>
<i>&gt; 12 yrs–18 yrs</i>	<i>&gt; 140/90.</i>

#### Section 2: Cardiovascular Performance, Monitoring and Hemodynamic Support

- *Experienced pediatric intensive care practitioners adjust therapies to general, rather than specific, age-related targets. For information purposes, a guide to age-related norms for heart rate and blood pressure is provided under “Key Considerations.”*

#### Section 2.1: Central or Mixed Venous Oxygen Saturation Monitoring

- *Central venous oximetry is currently used in many Canadian PICUs as a monitoring technique in patients with hemodynamic instability and is recommended for the pediatric donor. Therapy should be titrated to a central venous oximetry of  $\geq 60\%$ .*

## 13.1 Pediatric Age-Related Adjustments (cont'd)

### Section 2.3: Indications for Pulmonary Arterial Catheterization

- *The use of pulmonary arterial catheterization (PAC) is limited in PICU practice and is not routinely recommended in pediatric donors. PAC may be utilized at the discretion of the PICU practitioner who is experienced with its application and interpretation.*
- *Serial echocardiography is the recommended method to re-evaluate myocardial function for the purposes of transplantation. Its role as a potential tool to guide hemodynamic therapy should be individually tailored.*

### Section 2.4: Second-Line Agents for Hemodynamic Support – Vasopressin

- *The pediatric dose range for arginine vasopressin (AVP) is 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/hour.*

### Section 2.5: Second-Line Agents for Hemodynamic Support – Norepinephrine, Epinephrine and Phenylephrine

- *In the absence of PAC data, hemodynamic therapy should be titrated to clinical and biochemical evaluations.*

### Section 4.1: Diabetes Insipidus

- *The pediatric dose range for AVP in diabetes insipidus is 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/hour.*

### Section 5.1: Thyroid Hormone, Vasopressin and Methylprednisolone

- *The pediatric dose range for AVP in diabetes insipidus is 0.0003–0.0007 U/kg/min (0.3 – 0.7 mU/kg/min) to a maximum dose of 2.4 U/hour.*
- *Intravenous (iv) tetra-iodothyronine (T<sub>4</sub>): The precise dosing range for iv T<sub>4</sub> infusions is not known, and T<sub>4</sub>'s biological effect when given by infusion may be affected by stability in solution and potential adherence to plastic tubing resulting from its hydrophobic nature. Adult practitioners have used up to 300–500 µg iv bolus for potential donors, which is standard dosing for myxedema coma. Given the wide dosing range cited in the literature for iv T<sub>4</sub> and the low risk of toxicity for this current indication, the dosing range for adults (20 µg iv bolus followed by 10 µg/hour iv infusion) is also recommended in children.<sup>2</sup> Alternatively, iv T<sub>4</sub> may be given as follows: 50-100 ug iv bolus followed by 25-50 ug iv q12h.*

<sup>2</sup> Rodriguez I, Fluiters E, Perez-Mendez LF, Luna R, Paramo C, Garcia-Mayor RV. Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution. J Endocrinol 2004 Feb; 180(2):347-50.

### 13.1 Pediatric Age-Related Adjustments (cont'd)

#### Section 8.1: Initial Evaluation of Cardiac Function

- *Serial echocardiography is recommended to evaluate myocardial function for the purposes of transplantation. The initial echocardiogram should be performed only after stabilization with adequate volume resuscitation.*
- *The echocardiogram should be repeated at q6–12h intervals under the following conditions:*
  - *initial 2D echocardiogram demonstrates an ejection fraction  $\leq 40\%$*
  - or*
  - *escalation of supports as defined by dopamine  $> 10\mu\text{g}/\text{kg}/\text{min}$  and/or the use of vasopressor agents.*

#### Section 11.1: Creatinine Clearance

- *For children  $> 1$  year of age, a normal creatinine clearance is  $> 80 \text{ ml}/\text{min}/1.73 \text{ m}^2$ , as estimated by the Schwartz formula.<sup>3</sup>*

#### Section 11.3: Indications for Renal Biopsy

- *Creatinine level greater than normal for age.*

### Key Considerations

Table 1. Age-related norms for heart rate and blood pressure (BP)

Age	Heart Rate beats/min	Systolic BP (mmHg)	Diastolic BP (mmHg)
0–3 mo	100–150	65–85	45–55
3–6 mo	90–120	70–90	50–65
6–12 mo	80–120	80–100	55–65
1–3 yr	70–110	90–105	55–70
3–6 yr	65–110	95–110	60–75
6–12 yr	60–95	100–120	60–75
$>12$ yr	55–85	110–135	65–85

Adapted from: Mathers LH, Frankel LR. Stabilization of the critically ill child. Nelson Textbook of Pediatrics, 17th edition, 2004.

<sup>3</sup> Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatric Clinics of North America* 1987; 34 (3): 571-590.







# **Part IV – Standing Orders for Organ Donor Management**



## 1. Standing Orders for Organ Donor Management: Adults

It is important to take the time necessary in the Intensive Care Unit (ICU) to optimize multi-organ function for the purposes of improving transplant outcomes. Resuscitation and re-evaluation can improve reversible organ dysfunction (myocardial/cardiovascular dysfunction, oxygenation impairment related to potentially reversible lung injury, invasive bacterial infections, hypernatremia or any other potentially treatable situation) and can allow the evaluation of temporal trends in aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatinine. 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. Once optimized, donors should have surgical procurement procedures arranged emergently.

**There are no predefined demographic factors or organ dysfunction thresholds that preclude the consent for donation and offering of organs for transplantation.**

### Standard Monitoring

1. Urine catheter to straight drainage, strict intake and output
2. Nasogastric tube to straight drainage
3. Vital signs q1h
4. Pulse oximetry, 3-lead electrocardiogram (EKG)
5. Central venous pressure monitoring
6. Arterial line pressure monitoring
7. ± Pulmonary arterial catheterization.

### Laboratory Investigations

1. Arterial blood gas (ABG), electrolytes, glucose q4h and as needed (PRN)
2. CBC q8h
3. Blood urea nitrogen (BUN), creatinine q6h
4. Urine analysis
5. AST, ALT, bilirubin (total and direct), internal normalized ratio (INR) (or prothrombin time [PT]), partial thromboplastin time (PTT) q6h.

### Hemodynamic Monitoring and Therapy

#### General targets:

1. Heart rate  $\geq 60 \leq 120$  bpm, systolic blood pressure (BP)  $> 100$  mmHg, mean arterial pressure (MAP)  $\geq 70$  mmHg
2. Fluid resuscitation to maintain normovolemia, central venous pressure (CVP) 6–10 mmHg

3. If arterial blood pressure (ABP)  $\geq$  160/90 then:
  - a. Wean inotropes and vasopressors, and, if necessary
  - b. Start
    - nitroprusside 0.5–5.0  $\mu\text{g}/\text{kg}/\text{min}$ , or
    - esmolol 100–500  $\mu\text{g}/\text{kg}$  bolus followed by 100–300  $\mu\text{g}/\text{kg}/\text{min}$
4. Serum lactate q2–4h
5. Mixed venous oximetry q2–4h; titrate therapy to mixed venous oxygen (MVO<sub>2</sub>)  $\geq$  60%.

### Agents for Hemodynamic Support

1. Dopamine  $\leq$  10  $\mu\text{g}/\text{kg}/\text{min}$
2. Vasopressin  $\leq$  2.4 units/hour (0.04 units/minute)
3. Norepinephrine, epinephrine, phenylephrine (caution with doses  $>$  0.2  $\mu\text{g}/\text{kg}/\text{min}$ ).

### Indications for Pulmonary Arterial Catheterization

1. 2D echo ejection fraction  $\leq$  40% and/or
2. Dopamine  $>$ 10  $\mu\text{g}/\text{kg}/\text{min}$  (or equivalent) and/or
3. Vasopressor support (not including vasopressin if part of hormone therapy) and/or
4. Escalation of supports.

### Glycemia and Nutrition

1. Routine intravenous (iv) dextrose infusions
2. Initiate or continue enteral feeding as tolerated
3. Continue parenteral nutrition if already initiated
4. Initiate and titrate insulin infusion to maintain serum glucose 4–8 mmol/L.

### Fluid and Electrolytes

Targets:

1. Urine output 0.5–3 ml/kg/hr
2. Serum sodium (Na)  $\geq$  130  $\leq$  150 mM
3. Normal ranges for potassium, calcium, magnesium, phosphate.

### Diabetes Insipidus

Defined as:

1. Urine output  $>$  4 ml/kg/hr, associated with
  - a. Rising serum Na  $\geq$  145 mmol/L and/or
  - b. Rising serum osmolarity  $\geq$  300 mosM and/or
  - c. Decreasing urine osmolarity  $\leq$  200 mosM.

### Diabetes insipidus therapy

1. Titrate therapy to urine output  $\leq 3$  ml/kg/h
  - a. iv vasopressin infusion  $\leq 2.4$  units/hour, and/or
  - b. Intermittent 1-desamino-D-arginine vasopressin (DDAVP) 1–4  $\mu\text{g}$  iv then 1–2  $\mu\text{g}$  iv q6h.

### Combined Hormonal Therapy

Defined as:

1. Tetra-iodothyronine ( $T_4$ ) 20  $\mu\text{g}$  iv bolus followed by 10  $\mu\text{g}/\text{hour}$  iv infusion (or 100  $\mu\text{g}$  iv bolus followed by 50  $\mu\text{g}$  iv bolus q12h)
2. Vasopressin 1 unit iv bolus followed by 2.4 Units/hour iv infusion
3. Methylprednisolone 15 mg/kg ( $\leq 1$  gm) iv q24h.

Indications:

1. 2D echocardiographic ejection fraction  $\leq 40\%$ , or
2. Hemodynamic instability (includes shock unresponsive to restoration of normovolemia and requiring vasoactive support [dopamine  $>10$   $\mu\text{g}/\text{min}$  or any vasopressor agent])
3. Consideration should be given to its use in all donors.

### Hematology

1. Hemoglobin (Hgb): optimal  $\geq 90$ –100 g/L for unstable donors, lowest acceptable  $\geq 70$  g/L
2. Platelets, INR, PTT: no predefined targets, transfuse in cases of clinically relevant bleeding
3. No special transfusion requirements.

### Microbiology (baseline, q24h and PRN)

1. Daily blood cultures
2. Daily urine cultures
3. Daily endotracheal tube (ETT) cultures
4. Antibiotics for presumed or proven infection.

### Heart Specific

1. 12-lead EKG
2. Troponin I or T, q12h
3. 2D echocardiography
  - a. Should only be performed after fluid and hemodynamic resuscitation
  - b. If 2D echo ejection fraction  $\leq 40\%$  then,
    - insert pulmonary arterial catheter (PAC) and titrate therapy to the following targets:

- pulmonary capillary wedge pressure (PCWP) 6–10 mmHg
  - cardiac index (CI)  $> 2.4$  L/min-m<sup>2</sup>
  - systemic vascular resistance (SVR) 800–1200 dynes/sec-cm<sup>5</sup>
  - left ventricular (LV) stroke work index  $> 15$  g/kg-min
- PAC data is relevant for hemodynamic therapy and evaluation for suitability of heart transplantation independent of echo findings
- c. Consider repeat echocardiography at q6–12h intervals.
4. Coronary angiography

Indications:

- a. History of cocaine use
- b. Male  $> 55$  yrs or female  $> 60$  yrs
- c. Male  $> 40$  yrs or female  $> 45$  yrs in the presence of  $\geq$  two risk factors
- d.  $\geq 3$  risk factors at any age.

Risk factors:

- smoking
- hypertension
- diabetes
- hyperlipidemia
- body mass index  $> 32$
- family history
- prior history of coronary artery disease
- ischemic EKG
- anterolateral regional wall motion abnormalities on echo
- 2D echocardiographic ejection fraction  $\leq 40\%$ .

Precautions:

1. Ensure normovolemia
2. Prophylactic N-acetylcysteine 600–1000 mg enterally bid (1st dose as soon as angiography indicated) or iv 150 mg/kg in 500 ml normal saline (NS) over 30 minutes immediately before contrast followed by 50 mg/kg in 500 ml NS over 4 hrs
3. Low-risk radiocontrast agent (non-ionic, iso-osmolar), using minimum radiocontrast volume, no ventriculogram.

### Lung Specific

1. Chest x-ray q24h and PRN
2. Bronchoscopy and bronchial wash gram stain and culture
3. Routine ETT suctioning, rotation to lateral position q2h

4. Mechanical ventilation targets:
  - a. Tidal volume ( $V_t$ ) 8–10 ml/kg, positive end expiratory pressure (PEEP) 5 cm H<sub>2</sub>O, peak inspiratory pressure (PIP)  $\leq$  30 cm H<sub>2</sub>O
  - b. pH 7.35–7.45, partial pressure of arterial carbon dioxide ( $P_aCO_2$ ) 35–45 mmHg, partial pressure of arterial oxygen ( $P_aO_2$ )  $\geq$  80 mmHg, oxygen ( $O_2$ ) sat  $\geq$  95%.
5. Recruitment maneuvers for oxygenation impairment may include:
  - a. Periodic increases in PEEP up to 15 cm H<sub>2</sub>O
  - b. Sustained inflations (PIP @ 30 cmH<sub>2</sub>O x 30–60 sec)
  - c. Diuresis to normovolemia.

## 2. Standing Orders for Organ Donor Management: Pediatrics

(Apply from newborn to 18 years; intended for care provided within a Pediatric Intensive Care Unit [PICU])

It is important to take the time necessary in the PICU to optimize multi-organ function for the purposes of improving transplant outcomes. Resuscitation and re-evaluation can improve reversible organ dysfunction (myocardial/cardiovascular dysfunction, oxygenation impairment related to potentially reversible lung injury, invasive bacterial infections, hypernatremia or any other potentially treatable situation) and can allow for the evaluation of temporal trends in aspartate aminotransferase (AST), alanine aminotransferase (ALT) or creatinine. 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. Once optimized, donors should have surgical procurement procedures arranged emergently.

**There are no predefined demographic factors or organ dysfunction thresholds that preclude the consent for donation and offering of organs for transplantation.**

Note: Dosing recommendations apply to children  $\leq 60$  kg, beyond which adult dosing should apply.

### Standard Monitoring

1. Urine catheter to straight drainage, strict intake and output
2. Nasogastric tube to straight drainage
3. Vital signs q1h
4. Pulse oximetry, 3-lead electrocardiogram (EKG)
5. Central venous pressure (CVP) monitoring
6. Arterial line pressure monitoring.

### Laboratory Investigations

1. Arterial blood gas (ABG), electrolytes, glucose q4h and PRN
2. CBC q8h
3. Blood urea nitrogen (BUN), creatinine q6h
4. Urine analysis
5. AST, ALT, bilirubin (total and direct), international normalized ratio (INR) (or prothrombin time [PT]), partial thromboplastin time (PTT) q6h.



## Hemodynamic Monitoring and Therapy

General targets: age-related norms for pulse and blood pressure (BP)

1. Fluid resuscitation to maintain normovolemia, CVP 6–10 mmHg
2. Age-related treatment thresholds for arterial hypertension:

Newborns–3 months	> 90/60
> 3m – 1 year	> 110/70
> 1 yr – 12 yrs	> 130/80
> 12 yrs –18 yrs	> 140/90

  - a. Wean inotropes and vasopressors, and, if necessary,
  - b. Start
    - nitroprusside 0.5–5.0 µg/kg/min, or
    - esmolol 100–500 µg/kg bolus followed by 100–300 µg/kg/min
3. Serum lactate q2–4h
4. Central venous oximetry q2–4h; titrate therapy to central MVO<sub>2</sub> ≥ 60%.

## Agents for Hemodynamic Support

1. Dopamine ≤ 10 µg/kg/min
2. Vasopressin 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/hour
3. Norepinephrine, epinephrine, phenylephrine (caution with doses > 0.2 µg/kg/min).

## Glycemia and Nutrition

1. Routine intravenous (iv) dextrose infusions
2. Initiate or continue enteral feeding as tolerated
3. Continue parenteral nutrition if already initiated
4. Initiate and titrate insulin infusion to maintain serum glucose 4–8 mmol/L.

## Fluid and Electrolytes

Targets:

1. Urine output 0.5–3 ml/kg/hr
2. Serum sodium (Na) ≥ 130 ≤ 150 mM
3. Normal ranges for potassium, calcium, magnesium, phosphate.

## Diabetes Insipidus

Defined as:

1. Urine output  $> 4$  ml/kg/hr, associated with:
  - a. Rising serum Na  $\geq 145$  mmol/L and/or
  - b. Rising serum osmolarity  $\geq 300$  mosM and/or
  - c. Decreasing urine osmolarity  $\leq 200$  mosM.

Diabetes insipidus therapy

1. Titrate therapy to urine output  $\leq 3$  ml/kg/h
  - a. iv vasopressin infusion 0.0003 – 0.0007 U/kg/min (0.3 – 0.7 mU/kg/min) to a maximum dose of 2.4 U/hour, and/or
  - b. Intermittent 1-desamino-D-arginine vasopressin (DDAVP) 0.25 to 1  $\mu$ g iv q6h.

## Combined Hormonal Therapy

Defined as:

1. Tetra-iodothyronine ( $T_4$ ) 20  $\mu$ g iv bolus followed by 10  $\mu$ g/hour iv infusion (or 50-100  $\mu$ g iv bolus followed by 25-50  $\mu$ g iv bolus q12h)
2. Vasopressin 0.0003–0.0007 U/kg/min (0.3–0.7 mU/kg/min) to a maximum dose of 2.4 U/hour.
3. Methylprednisolone 15 mg/kg ( $\leq 1$  gm) iv q24h.

Indications:

1. 2D echocardiographic ejection fraction  $\leq 40\%$ , or
2. Hemodynamic instability (includes shock unresponsive to restoration of normovolemia and requiring vasoactive support [dopamine  $>10$   $\mu$ g/min or any other vasopressor agent])
3. Consideration should be given to its use in all donors.

## Hematology

1. Hemoglobin (Hgb) optimal  $\geq 90$ –100 g/L for unstable donors, lowest acceptable  $\geq 70$  g/L
2. Platelets, INR, PTT no predefined targets, transfuse in cases of clinically relevant bleeding
3. No special transfusion requirements.

## Microbiology (baseline, Q24h and PRN)

1. Daily blood cultures
2. Daily urine cultures
3. Daily endotracheal tube (ETT) cultures
4. Antibiotics for presumed or proven infection.

### Heart Specific

1. 12-lead EKG
2. Troponin I or T, q12h
3. 2D echocardiography
  - a. Should only be performed after fluid and hemodynamic resuscitation
  - b. If 2D echo ejection fraction  $\leq 40\%$  then repeat echocardiography at q6–12h intervals.

### Lung Specific

1. Chest x-ray q24h and PRN
2. Bronchoscopy and bronchial wash gram stain and culture
3. Routine ETT suctioning, rotation to lateral position q2h
4. Mechanical ventilation targets:
  - a. Tidal volume (Vt) 8–10 ml/kg, positive end expiratory pressure (PEEP) 5 cm H<sub>2</sub>O, peak inspiratory pressure (PIP)  $\leq 30$  cm H<sub>2</sub>O
  - b. pH 7.35–7.45, partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) 35–45 mmHg, partial pressure of arterial oxygen (PaO<sub>2</sub>)  $\geq 80$  mmHg, oxygen (O<sub>2</sub>) sat  $\geq 95\%$
5. Recruitment maneuvers for oxygenation impairment may include:
  - a. Periodic increases in PEEP up to 15 cm H<sub>2</sub>O
  - b. Sustained inflations (PIP @ 30 cm H<sub>2</sub>O x 30–60 sec)
  - c. Diuresis to normovolemia.





# **Part V – National Research Agenda**



## National Research Agenda

Forum participants concluded that there are significant limitations to existing clinical research that can support Forum recommendations. Participants encouraged the development of local and multi-centre research initiatives, as well as those at national and international levels. The following potential research topics were collected during small group discussions.

### 1. Questions Amenable to Survey Methodology

- A cross-sectional survey examining current practice in the cardiopulmonary support of donors, including hemodynamic targets and supports, ventilation and lung recruitment strategies.

### 2. Questions Amenable to Observational Studies

The following questions include survey methodology, prospective and retrospective studies and database reviews:

- Contribution of serial echocardiography or dobutamine stress echocardiography to the evaluation of patients with reduced myocardial function compared to PAC alone
- Effect of radiographic contrast exposure (during cerebral angiography or coronary angiography) on renal graft function
- Investigation of the factors contributing to variability of organ utilization rates between centres and correlates to post-transplant function
- Optimal vasopressor and inotrope combinations and the influence of delayed procurement on organ utilization.

### 3. Questions Amenable to Non-randomized Intervention Studies

- Effect of serial lung recruitment maneuvers in organ donors on the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and lung procurement rates
- Pharmacological studies of orally and intravenously administered T<sub>4</sub> and T<sub>3</sub> in humans, including kinetics, biological effects, optimal dosing, peripheral conversion times and effect of corticosteroids.

### 4. Topics Amenable to Simple Randomized Controlled Clinical Trials

- Does combined hormonal therapy improve hemodynamics, organ function or organ utilization?
- Do PAC and goal-directed therapy improve hemodynamics, organ function or organ utilization?
- Evaluating the use of prophylactic N-acetyl cysteine to prevent contrast nephropathy and delayed graft function of deceased donor kidneys.





**Part VI –**

**Logistics and  
Knowledge Transfer**



## Logistics and Knowledge Transfer

Optimizing donor management and organ utilization for transplantation requires widespread communication of MEMODOP recommendations combined with the broad engagement of individuals and organizations across the health system. To address these interdependent requirements, a Logistics and Knowledge Transfer (LKT) Group met throughout the Forum to address the question,

*How can we ensure that the agreements developed at this Forum are transferred into the field efficiently and effectively so that improvements in medical management occur as soon as possible?*

Members of the LKT Group developed recommendations to address both logistical and knowledge transfer challenges in relation to clinical practice and systemic change.

### Logistical Challenges

For the purposes of this Forum, logistical challenges included the identification and description of supports (e.g., clinical excellence and constructive policies) and blocks (e.g., logistical, systemic and fiscal restraints) and recommendations for addressing them (e.g., consideration of resource implications for extended stays in the ICU, reduced organ recovery options due to lack of access to operating room time and definition of what constitutes an organ procurement hospital).

Members of the LKT Group identified the following recommendations (alphabetical order) in response to their discussions:

- Develop a cost/benefit analysis of donation, including implications for the health care system and quality-of-life issues.
- Identify logistical challenges (barriers and supports) in maximizing donation.
- Monitor and report on the resolution of logistical challenges on an individual case basis with respect to impacts on optimal organ utilization.

### Knowledge Transfer Challenges

The Canadian Institutes of Health Research (CIHR) describe knowledge transfer (KT) as the process that transfers research results from knowledge producers to knowledge users for the benefit of Canadians. It comprises three interlinked components:

- knowledge exchange
- knowledge synthesis
- ethically sound application of knowledge.

The goal of KT is to improve health processes, services and products as well as the health care system itself.

Members of the LKT Group identified the following recommendations (alphabetical order) to maximize KT and enhance organ utilization:

- Develop policies to guide the donation process that clearly identify roles and responsibilities for health care professionals, e.g., incorporation of MEMODOP recommendations in standard operating procedures at OPOs and hospitals.
- Encourage national and international exchange of information to advance knowledge and care within and beyond Canada.
- Ensure that allocation issues do not complicate utilization, resulting in unused organs.
- Include the identification of potential organ and tissue donors as part of quality end-of-life care to maximize organ utilization.
- Provide health care professionals with ongoing education and skill development in support of quality care for donors and their families. To enable knowledge transfer, develop quick reference tools for protocols and guidelines.
- Support the implementation of MEMODOP recommendations in organizations and institutions affiliated with the Forum.
- Support initiatives to enhance reporting and accountability. Encourage standardization of data and terminology both nationally and internationally. Develop quality measurements that reflect directly on the donation process, including identification of donors, requests for consent, consents and utilization of organs.

# Appendix #1: Summaries of Evidence

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## 1. Systemic Arterial Hypertension Related to Intracranial Pressure

In the face of markedly elevated intracranial pressure (ICP), mean arterial pressure (MAP) rises in an effort to maintain cerebral perfusion pressure. As ICP rises further, cerebral herniation into the brainstem ensues, and brainstem ischemia is initiated in an orderly, rostral-caudal fashion. Initial apnea, bradycardia, hypotension and drop in cardiac output are mediated by vagal (parasympathetic) activation resulting from midbrain ischemia (Van Bakel 1997). Brainstem ischemia then progresses toward the pons, where sympathetic stimulation is superimposed on the initial vagal response, resulting in bradycardia and hypertension (Cushing's reflex). During this period, the EKG may be characterized by sinus bradycardia, junctional escape beats and even complete heart block (Novitzky 1997). Further extension into the medulla oblongata occurs, at which point the vagal cardiomotor nucleus becomes ischemic, preventing tonic vagal stimuli (Tuttle-Newhall et al. 2003). This results in unopposed sympathetic stimulation which may last for minutes to hours and manifests as hypertension with elevated cardiac output with the potential for tachyarrhythmias (Novitzky 1997). This period of unopposed sympathetic stimulation is often termed "autonomic storm," during which time severe vasoconstriction may compromise end organ perfusion.

The autonomic storm is also believed responsible for potentially reversible myocardial injury and cardiovascular dysfunction associated with intracranial hypertension best studied in subarachnoid hemorrhage (Mayer et al. 1994) and termed "neurogenically stunned myocardium" (Kono et al. 1994). Endogenous catecholamine-related increases in peripheral resistance (Novitzky et al. 1984) may result in a sudden increase in myocardial work and oxygen consumption leading to myocardial ischemia or infarction and subsequent elevation of cardiac troponin I and T (Macmillan et al. 2002). Patients dying of acute intracranial events show scattered foci of transmural myocardial injury that are not seen in patients dying of noncerebral causes (Kolin et al. 1984). Myocardial necrosis after subarachnoid hemorrhage is a neurally mediated process that is dependent on the severity of neurological injury (Tung et al. 2004). The magnitude of the rise of epinephrine after brain death and the extent of myocardial damage also depend on the rate of rise in ICP in a canine model (Shivalkar et al. 1993; Takada et al. 1998). Dogs given a sudden rise in ICP demonstrated a higher epinephrine surge and poorly functioning donor hearts.

Animal studies suggest that sympathetic blockade in ICP-related catecholamine cardiotoxicity may effectively prevent the electrophysiologic, biochemical and pathologic changes characteristic of neurogenic injury in the heart, lung, gut and other organs. Labetalol, a mixed alpha- and beta-adrenergic antagonist administered before brain death in animals, blunts the hemodynamic storm triggered by increased cardiac sympathetic activation and preserves myocardial contractile function (Siaghy et al. 1998). However, because of the rapid appearance of neurogenic lesions, these agents may be effective only when given prophylactically before sympathetic storm occurs (Cruickshank et al. 1987). Intravenous atenolol significantly lowered the incidence of myocardial band creatine kinase elevation and electrocardiographic abnormality in a group of head-injured patients (Cruickshank et al. 1987). The alpha-2-agonist clonidine diminishes central adrenergic outflow and has a protective role against myocardial injury induced by hypertension (Frohlich et al. 1984).

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## 2. Cardiovascular Performance, Monitoring and Hemodynamic Support

### a. Cardiovascular Performance and Monitoring

#### Biochemical Perfusion Markers

Traditional hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure and urinary output may fail to detect persistent global tissue ischemia/hypoxia. A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload and contractility to achieve a balance between systemic oxygen delivery and oxygen demand (Beal et al. 1994). Resuscitation endpoints include normalized values for mixed venous oxygen saturation, serum lactate, base deficit and pH (Elliot, 1998; 3rd European Conference of ICM, 1996). Mixed venous oxygen saturation has been shown to be a surrogate for cardiac index as a target for hemodynamic therapy (Gattinoni et al. 1995). In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation (Reinhart et al. 1989). This is common practice in pediatric care. Venous oximetry can be measured by intermittent blood sampling or by the use of continuous oximetric catheters. A randomized controlled trial (RCT) of early goal-directed therapy titrated to CVP, central venous O<sub>2</sub> saturation and blood pressure provides evidence of significant mortality and morbidity benefits in adults with septic shock (Rivers et al. 2001).

Elevated initial and 24-hour lactate levels are significantly correlated with mortality and are superior to base deficit levels in critically ill surgical patients (Husain et al. 2003). Lactate clearance time may be used to predict morbidity and mortality (Husain et al. 2003). Lactate is the best marker of perfusion, which best discriminates survivors from non-survivors of childhood sepsis (Duke et al., ICM, 1997) and is predictive of adverse events after pediatric cardiac surgery (Duke et al., JTCVS, 1997).

#### Echocardiography

Echocardiographic parameters have also been demonstrated to be beneficial in predicting successful cardiac transplant outcomes (Dujardin et al. 1996; Yokoyama et al. 1992). In a study of 66 consecutive patients with brain death, echocardiographic systolic myocardial dysfunction was present in 42% and associated with ventricular arrhythmias (Dujardin et al. 1991). Diffuse wall motion abnormalities are a risk factor for 30-day heart transplant mortality (Young et al. 1994). Single echocardiographic evaluations may have limitations in detecting the reversible myocardial dysfunction often seen after brain injury (Kono et al. 1994). Dobutamine stress echocardiographic studies can detect dobutamine-responsive wall motion abnormalities that may distinguish the potentially reversible myocardial dysfunction in a “neurogenically stunned myocardium” (Kono et al. 1999). Evaluation of the utility of serial echocardiograms, with or without dobutamine stress tests, to evaluate improvement in myocardial dysfunction in the brain dead donor and to better predict cardiac allograft survival has not been reported.

## Pulmonary Arterial Catheterization and Thermodilution Cardiac Output Monitoring

Right-sided pressures may underestimate left-sided pressures after brain death and may increase risk for elevated left-sided filling pressures and pulmonary edema (Pennefather et al. 1993). A similar disparity between right and left ventricular heart function has also been observed in experimental canine models of brain death (Bittner et al. 1996). Expert consensus supports Pulmonary arterial catheterization (PAC) and cardiac output monitoring, particularly if the donors are hemodynamically unstable (Rosengard et al. 2002; Wheeldon et al. 1995). Pulmonary arterial catheterization and goal-directed hemodynamic therapy of initially unacceptable donors, in conjunction with hormonal therapy (glucocorticoids, insulin, vasopressin, and tri-iodothyronine ( $T_3$ )), may improve the rate of organ procurement without compromising transplant outcomes (Wheeldon et al. 1995). The Transplantation Committee of the American College of Cardiology has recommended titrating volume infusions and dopamine to thermodilution indices (Hunt et al. 1996).

The variety of changes in volume status, cardiac inotropy, and peripheral vascular resistance that occur after brain death are similar to those in any critically ill patient with shock of diverse etiologies. The clinical value of data obtained from PAC remains unproven (Cooper et al. 1996). Evolving ICU practice for hemodynamic management has reduced the use of the PAC, given concerns about increased mortality risks and a lack of therapeutic benefit in large prospective cohort studies (Connors et al. 1996) and systematic reviews (Heyland et al. 1996; Ivanov et al. 1997). Clinical management involving the early use of a PAC in patients with shock, ARDS or both does not significantly affect mortality and morbidity (Richard et al. 2003). A large Canadian RCT showed no benefit in PAC-directed therapy over standard care in elderly, high-risk surgical ICU patients (Sandham et al. 2003).

Proponents argue that physiological measurements provided by the use of a PAC permit refinements of treatment that improve patient outcomes. Although unproven, this argument has driven the use of a PAC in the preoperative, perioperative, and postoperative treatment of high-risk surgical patients. The use of PAC in pediatric ICU care is extremely limited.

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## **b. Hemodynamic Targets and Supports**

Following the autonomic storm, a reduction in sympathetic flow results in a normotensive or hypotensive phase. This stage is characterized by impaired cardiac inotropy and chronotropy, impaired vascular tone and a reduced cardiac output (Pratschke et al. 1999). Clinical deterioration (progressive hypotension, oligo-anuria  $\pm$  cardiac arrest) during the interval from brain death to procurement is common without aggressive intervention (Lagiewska et al. 1996).

### **Preload**

Significant volume depletion is anticipated in brain-injured patients after neurological determination of death (NDD) due to fluid restriction and diuretics, hyperosmolar therapy, 3rd space losses, hemorrhage or diabetes insipidus. In addition, a low systemic vascular resistance (SVR) state may result in relative hypovolemia. In a Canadian study of 77 pediatric organ donors, 41 (53.2%) suffered from sustained hypotension and 35% deteriorated to cardiac arrest. This was more common in patients treated with inotropic agents in the presence of a low central venous pressure and in those without anti-diuretic hormone replacement, emphasizing the importance adequate restoration of intravascular volume (Finfer et al. 1996).

The optimal volume status of the brain dead patient is controversial and transplant-organ specific. Disparity exists between lung and kidney interests (dry lungs versus wet kidneys). In a study of crystalloid fluid management in 26 brain dead donors, a significant increase in the alveolar-arterial oxygen gradient was seen in those who achieved a central venous pressure (CVP) of 8–10 compared to those whose CVP was maintained at 4–6 mmHg (Pennefather et al. 1993). Some authors advocate maintaining a CVP of 10–12 mmHg to volume replete those patients in whom only abdominal organs are to be procured, a CVP < 8 mmHg for potential lung donors and a CVP of 8–10 mmHg if both thoracic and abdominal organs are to be harvested (Tuttle-Newhall et al. 2003).

### **Systemic Afterload/Vascular Resistance and Vasoconstrictor Agents**

The sympathectomy associated with brain death results in a low SVR that often requires the use of vasopressor agents. The concern over the use of alpha-agonists such as norepinephrine has arisen because of the fear of inducing central and peripheral vasoconstriction and subsequent ischemia in vascular beds supplying potentially transplantable organs. However, in studies of other causes of shock states with low SVR (septic patients), norepinephrine, as compared to dopamine, was demonstrated to increase mean perfusion pressures without adverse effects to renal and splanchnic blood flow (Marik et al. 1994; Martin et al. 1993).

### **Vasopressin and Catecholamine Sparing in Brain Death**

Brain death and hypotension are often associated with vasopressin deficiency (Chen et al. 1999). Low-dose arginine vasopressin (AVP) infusions have been shown to improve hemodynamic stability and spare catecholamine use (Kinoshita et al. 1990; Chen et al. 1999). Prolonged hemodynamic stability can be maintained after brain death with low-dose AVP (1–2 units/hour), permitting a significant decrease in epinephrine and extended preservation of renal function (Yoshioka et al. 1986). In a rigorous randomized study of volume-resuscitated brain dead organ donors supported with dopamine, 300  $\mu$ U/kg/min infusion of AVP significantly increased MAP

and SVR and spared dopamine use compared to further fluid loading (Pennefather et al. 1995). Pediatric donors given AVP ( $41 \pm 69$  mU/kg/hr) respond by increasing MAP and weaning alpha-agonists (norepinephrine, epinephrine, phenylephrine) without significant differences in the quality of kidneys, livers and hearts recovered (Katz et al. 2000).

Similar catecholamine-sparing effects of AVP have been demonstrated in septic shock patients with low SVR (Landry et al. 1997; Malay et al. 1999; Holmes et al. 2001). Although it is suggested that doses of AVP exceeding 0.04 U/min (approx. 40 mU/kg/hr) may be associated with excessive vasoconstriction in sepsis (Holmes et al. 2001), brain dead donors requiring catecholamine vasopressors can respond to AVP infusion of 0.04 to 0.1 U/min (40 to 100 mU/kg/hr) by increasing mean arterial pressure (MAP) and sparing other vasopressors (Chen et al. 1999). No histologic evidence of cardiac damage is demonstrable at this dose (Kinoshita et al. 1990).

Although optimal dosing of AVP and its effects on organ procurement and graft survival are unclear, available literature suggests that the use of AVP at doses up to 0.04 U/min (2.4 U/hr, 40 mU/kg/hr) can be recommended to support the MAP and spare catecholamines in adult and pediatric brain dead organ donors. The variety of dosing units expressed in the literature are a source of confusion.

### Dosing Ranges for Arginine Vasopressin (AVP)

	Diabetes Insipidus	Cardiovascular Support in Vasodilatory Shock
Adults	0.013–0.017 U/min (0.8–1.0 U/hour) (13–17 mU/kg/hour) (0.22–0.28 mU/kg/min)	$\leq 0.04$ U/min ( $\leq 2.4$ U/hour) ( $\leq 40$ mU/kg/hour) ( $\leq 0.67$ mU/kg/min)  $< 0.067$ U/min (hormonal cocktail recommendation)
Pediatrics	0.008–0.25 mU/kg/min (0.5–15 mU/kg/hour)	0.1–2.0 mU/kg/min (6.0–120 mU/kg/hour)

## Clinical trials of low-dose vasopressin in vasodilatory shock states

Adapted from Holmes CL, Landry DW, Granton JT. Science Review: Vasopressin and the cardiovascular system part 2—Clinical physiology. Crit Care. 2004;8(1):15-23. Epub 2003 Jun 26.

Reference	Year	Trial	n	Patients	Findings
Landry	1997	Case series	5	Septic shock	A, B, C
Landry	1997	Matched cohort	19	Septic shock	A, B, D in septic group
			12	Cardiogenic shock	
Malay	1999	RCT	10	Septic shock – trauma	A, B
Patel	2000	RCT	24	Septic shock	A, B, C, D
Dunser	2001	Retrospective	60	Septic and postcardiotomy shock	A, B, CI
Tuseneyoshi	2001	Prospective, case-controlled	16	Septic shock	A, B, C
Argenziano	1998	Retrospective case series	40	Postbypass vasodilatory shock	A, B, D
Argenziano	1997	RCT Placebo: NS	10	Vasodilatory shock post-LVAD implant	A, B in treatment arm; D in all
Argenziano	1999	Case series	20	Vasodilatory shock post-cardiac transplant	A, B
Rosenzweig	1999	Case series	11	Pediatric – vasodilatory shock postbypass	A, B, D
Morales	2000	Retrospective case series	50	Vasodilatory shock post-LVAD implantation	A, B
Dunser	2002	Retrospective	41	Postcardiotomy shock	A, B
Chen	1999	Case series	10	Organ donors with vasodilatory shock A, D	
Gold	2000	Case series	7	Milrinone – hypotension	A, B, C

Findings are classified as follows:

A = increase in BP

B = decrease or discontinuance of catecholamines

C = increase in urine output

D = low plasma vasopressin levels in subjects

Acronyms:

CI = cardiac index

LVAD = left ventricular assist device

NS = normal saline

RCT = randomized controlled trial

## Contractility

The preferred choice of contractility agents in ICU practice varies according to individual centre. Traditionally, dopamine has been used as the initial inotrope of choice in the brain dead patient. However, no RCTs exist comparing the hemodynamic effects of dopamine to other inotropes or vasopressors and their influence on graft survival. Despite frequent recommendations on “renal dose” dopamine in transplant practice, there is now substantial scientific evidence that low-dose dopamine is ineffective for the prevention and treatment of acute renal failure and does not improve hepatosplanchnic circulation in adults and children (Bellomo et al. 2000; Debaveye et al. 2004; Prins et al. 2001).

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### 3. Glycemia and Nutrition

#### Recommendation 3.1: Glycemic Control

Hyperglycemia is common in brain dead donors. It may be secondary to insulin resistance, as pancreatic function appears to be preserved (Masson et al. 1993), and aggravated by corticosteroid therapy and/or dextrose-based fluid replacements used in diabetes insipidus. Glucose concentrations greater than 11 mmol/L were observed in 60% of donors in a Warsaw study irrespective of hemodynamic stability (Lagiewska et al. 1996). The hypothesis that tight glycemic control in the brain dead donor improves graft survival has not been tested. Insulin is variably and inconsistently considered as part of hormonal resuscitation cocktails. However, strict glucose control (4.4–6.1 mM) has been well demonstrated to improve survival, primarily by reducing septic deaths in populations of critically ill patients (Van den Berghe et al. 2001).

#### Recommendation 3.2: Nutrition

Hyperglycemia has been shown to be an independent risk factor for poor outcome after severe brain injury in children and adults (Cochran et al. 2003; Bruno et al. 2002; Rovlias et al. 2000). Dextrose infusions and nutrition are generally withheld in the acute ICU management after brain injury (Kelly 1994), a practice supported by animal models (Cherian et al. 1998). Malnutrition or depletion of cellular glycogen stores may be common during the phase of care leading to NDD (Singer et al. 2001).

The influence of donor nutrition on graft survival has been studied in several small animal studies but not formally in humans. In a rabbit and porcine model, improved liver transplant survival was shown from donors receiving enteral nutrition versus fasting donors (Boudjema et al. 1990). Similarly, a significant improvement in hepatic sinusoidal lining cell viability has been demonstrated in rats receiving liver grafts from donors receiving enteral feeding and intraperitoneal glucose prior to liver procurement. Glycogen protects the hepatic graft upon rewarming in rats (Wakiyama et al. 1997). Donor pigs provided with parenteral nutrition in the form of 20% glucose had reduced preservation-reperfusion injury to their livers related to Kupffer cell activation as compared to donor pigs who were provided with an enteral laboratory diet.

The importance of nutritional support in the human multi-organ donor, however, is not clear. Studies of donor-specific predictors of graft function following liver transplantation have identified a length of stay in the ICU of greater than 3 days as a risk factor. A contributing factor to this association may be the effect of starvation on the liver with depletion of glycogen stores. In a controlled prospective randomized study of 32 patients it was shown that an intraportal infusion of insulin (1 IU/kg/hr) and glucose (to maintain systemic glucose at 14 mmol/l) could reglycogenate the liver, increase glycogen utilization during cold and rewarming periods and improve certain outcome measures (including peak postoperative aspartate aminotransferase [AST]) (Cywes et al. 1992). However, the only human series of liver transplants that included donor nutritional status failed to identify an independent effect of donor nutrition on postoperative liver graft function (Gonzalez et al. 1994).



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## 4. Diabetes Insipidus and Hypernatremia

Dysfunction of the posterior pituitary in brain dead donors is common; anterior pituitary function is often preserved (Howlett et al. 1989). Histologic observations of the pituitary gland demonstrate various degrees of edema, hemorrhage and tissue necrosis depending on the mechanism and site of traumatic or ischemic brain injury (Gramm et al. 1992). This is likely to be a result of compromised blood supply to the cell bodies arising in the deep supraventricular and paraventricular nuclei of the hypothalamus, whose neurons supply the posterior pituitary and regulate arginine vasopressin (AVP) secretion. Anterior pituitary function is often preserved, implying that some blood supply via the hypophyseal arteries, which arise extradurally, is reaching the median eminence of the hypothalamus (Howlett et al. 1989).

### Diabetes insipidus

Undetectable levels of antidiuretic hormone (ADH) have been noted in 75% of brain dead donors, and diabetes insipidus is present in up to 87% of brain dead donors (Tuttle-Newhall et al. 2003; Finfer et al. 1996; Howlett et al. 1989; Gramm et al. 1992; Sazontseva et al. 1991). Diabetes insipidus may commonly appear prior to the diagnosis of BD (Gramm et al. 1992) and is associated with hemodynamic instability and the compromise of transplantable organ function (Lagiewska et al. 1996; Finfer et al. 1996).

### Vasopressin

Vasopressin (known as arginine vasopressin or ADH) is the natural hormone released from the posterior pituitary and produces its physiological effects through three different receptors: V<sub>1</sub>, V<sub>2</sub>, and V<sub>3</sub> (Robinson 2003), as follows:

- V<sub>1</sub> receptors: – vascular smooth muscle – vasopressor effect
- V<sub>2</sub> receptors: – renal collecting duct epithelia – antidiuretic effect  
– vascular endothelial cells increase factor VIII production
- V<sub>3</sub> receptors are located on the anterior pituitary to stimulate adenocorticotrophic hormone (ACTH) release in response to AVP and corticotrophin releasing hormone acting together.

Vasopressin has a half-life of approximately 15 minutes and is available intravenously (recommended), subcutaneously or intranasally.

### Dosing Ranges for Arginine Vasopressin (AVP)

	Diabetes Insipidus	Cardiovascular Support in Vasodilatory Shock
Adults	0.013 – 0.017 U/min (0.8 – 1.0 U/hour) (13–17 mU/kg/hour) (0.22–0.28 mU/kg/min)	≤ 0.04 U/min (≤ 2.4 U/hour) (≤ 40 mU/kg/hour) (≤ 0.67 mU/kg/min) < 0.067 U/min (hormonal cocktail recommendation)
Pediatrics	0.008–0.25 mU/kg/min (0.5–15 mU/kg/hour)	0.1–2.0 mU/kg/min (6.0–120 mU/kg/hour)

DDAVP (known as analog 1-desamino-8-D-arginine vasopressin, or desmopressin) has a relatively pure antidiuretic effect; it is an analog of AVP with only 0.01 % of the vasopressor activity (Richardson et al. 1985). DDAVP is highly selective for the vasopressin V<sub>2</sub> receptor subtype found in the renal collecting duct with no significant vasopressor activity. The removal of the terminal amine increases the half-life of the parent hormone. DDAVP has multiple potential routes of administration (iv, IM, SC, intranasal, ETT) and corresponding variability of dose recommendations.

### **DDAVP and Diabetes Insipidus**

DDAVP is commonly used for the treatment of brain death–related diabetes insipidus without adverse effect on early or late graft function after renal transplantation (Ourahma et al. 1998). Its duration of action ranges from 6–20 hours and may be given at doses of 2–6 µg iv every 6–8 hours (Van Bakel, 1997). If DDAVP is administered, care should be taken not to administer it close to the time of organ procurement, given its long duration of action. Doses of 0.5–2.0 µg of DDAVP administered subcutaneously or intravenously every 6–8 hours are recommended for most patients with hypothalamic diabetes insipidus (Robinson et al. 2003). A randomized trial of 97 brain dead donors showed that DDAVP therapy had no adverse effect on early or late graft function after renal transplantation (Ourahma et al. 1998).

### **AVP and Diabetes Insipidus**

Many authors have advocated the use of AVP for the treatment of diabetes insipidus in organ donors (Hunt et al. 1996; Van Bakel, 1997; Rosengard et al. 2002; Rosendale et al. 2002; Zaroff et al. 2002). In case series of pediatric and adult traumatic brain injury, doses of vasopressin between 0.25 and 2.7 mU/kg/hr have been used to successfully treat hypothalamic diabetes insipidus (Lugo et al. 1997; Lee et al. 1995; Lee et al. 1995; Chanson et al. 1987; Ralston et al. 1990).

Doses between 0.5 and 15 U/hr of AVP have been advocated with concerns about high doses causing coronary, renal and splanchnic vasoconstriction, potentially jeopardizing cardiac, renal, pancreatic and hepatic function (Van Bakel, 1997). An early study of AVP use in brain dead donors suggested its use resulted in poor function of transplanted kidneys (Schneider et al. 1983). The safety and efficacy of a combination of DDAVP (for its antidiuretic effect) with AVP as a vasopressor on cardiovascular and laboratory endpoints has been described (Pennefather et al. 1995).

Although clinical trials of the optimal dosage of vasopressin in brain dead donors are lacking, based on a rigorous review of the limited use of vasopressin in sepsis and published series of traumatic brain injured and brain dead patients, a safe approach would be to limit the dose of vasopressin to 0.04 U/min (40 mU/kg/hr) (Holmes et al. 2001). This upper limit is within the recommendations of the Transplantation Committee of the American College of Cardiology, which advocates the use of vasopressin infusion at 0.8–1.0 U/hr (13–17 mU/kg/hr) to treat diabetes insipidus (Hunt et al. 1996).

## Serum Sodium

Hypernatremia is frequently encountered, resulting from the preceding hyperosmolar therapy for initial brain injury or poorly controlled diabetes insipidus. Donor hypernatremia > 155 mmol/L at procurement has been shown to be independently associated with hepatic dysfunction or graft loss after transplantation (Gonzalez et al. 1994; Totsuka et al. 1999, Figueras et al. 1996, Avolio et al. 1991). A prospective study has demonstrated the benefit of correcting donor sodium (Na) ≤ 155 mmol/L with equivalent graft success compared to donors who were never hypernatremic (Totsuka et al. 1999). The mechanism of hepatic injury related to hypernatremia is unclear but may be related to the accumulation of idiogenic osmoles resulting in intracellular swelling after transplantation into the normonatremic recipient.

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## 5. Combined Hormonal Therapy

### Recommendation 5.1: Thyroid Hormone, Vasopressin and Methylprednisolone

#### Thyroid Hormone

The thyroid gland produces all circulating tetra-iodothyronine ( $T_4$ ) and 20% of circulating tri-iodothyronine ( $T_3$ ) (Sypniewski 1993).  $T_3$  is the active form of the hormone, largely generated by peripheral conversion (deiodination) of  $T_4$  to  $T_3$ , a process that is inhibited during critical illness and after brain death. Low serum  $T_3$  is common in hospitalized patients (Chopra 1997) and predicts mortality in advanced congestive heart failure (Hamilton et al. 1993). The low  $T_3$ -low  $T_4$  syndrome (a form of sick euthyroid state) is observed more frequently in critically ill patients and correlates with a poorer prognosis (Slag et al. 1981) but is generally left untreated due to lack of clear treatment efficacy in early studies (Chopra 1997).

Thyroid hormone increases cardiac output by improving contractility, chronotropy and decreasing systemic vascular resistance (Kacsoh 2000, Klein et al. 2001). The use of thyroid hormone therapy in brain dead donors appears to be largely based on experimental animal models and human case series (Howlett et al. 1989). Investigators describe variable levels of thyroid hormones after brain death and varying effects of thyroid hormone administration.

Thyroid-stimulating hormone (TSH),  $T_4$  and  $T_3$  levels were below normal in a majority of 22 brain dead donors (Sazontseva et al. 1991). Other studies have shown that these patients are suffering from “sick euthyroid syndrome” rather than TSH deficiency and do not require thyroid supplementation (Howlett et al. 1989). In the baboon model,  $T_3$  levels become depleted after brain death and the resulting transition to anaerobic metabolism is reversed with  $T_3$  replacement (Novitzky et al. 1988). In a comparative study in brain dead patients,  $T_3$ , cortisol and insulin promoted aerobic metabolism, reduced the need for inotropic support and improved the rate of cardiac graft procurement (Novitzky et al. 1990; Novitzky et al. 1987). Other investigators were unable to demonstrate any improvement in echocardiographic function or organ retrieval rates with a similar hormone regimen (Roels et al. 2000). Serum free  $T_3$  concentrations in organ donors may not correlate with hemodynamic stability (Gramm et al. 1992).  $T_4$  infusion does not reduce vasopressor requirements in pediatric donors (Katz et al. 2000), but this may be related to impaired peripheral conversion to  $T_3$ .

The strongest evidence supporting the use of thyroid hormone in organ donors comes from the UNOS database with a 46% reduced odds of death within 30 days and a 48% reduced odds of early cardiac graft dysfunction with the use of triple hormonal therapy (Rosendale et al. 2003). Benefit was also found in those donors receiving corticosteroids alone or in combination with  $T_3$ /L-thyroxine.

$T_3$  may attenuate ischemia-reperfusion injury in the heart through effects on high-energy phosphate metabolism and membrane stability (Becker et al. 2002; Port et al. 2002; Tullius et al. 2001). Results of studies using  $T_3$  in patients undergoing coronary artery bypass grafting (CABG) have been conflicting, varying from beneficial (Novitzky et al. 1989, Mullis-Jansson et al. 1999) to no clinically significant effect (Teiger et al. 1993; Bennett-Guerrero et al. 1996).

Randomized clinical trials (RCTs) of thyroid hormone therapy in heart transplantation, donation, CABG, heart failure and pediatric cardiac surgery are summarized in tables 1–3.

In Canada, the enteral forms of T<sub>3</sub> and T<sub>4</sub> and parenteral T<sub>4</sub> are all readily available and inexpensive (table 4). Parenteral T<sub>3</sub> is not commercially available in Canada outside special access. The hospital pharmacist may also prepare parenteral T<sub>3</sub> by dissolving L-T<sub>3</sub> in 0.1N NaOH (Weiss et al. 1998), but in-house sterility and stability testing is prudent.

**Table 1. Summary of trials of DITPA (T<sub>3</sub> analog) use in congestive heart failure and iv T<sub>3</sub> in heart transplant recipients**

Author	n	Procedure	Intervention	Outcome	Treatment vs. Control	p Value
Morkin	19	Congestive Heart Failure	1.875mg/kg DITPA X 2 weeks	Atrial fibrillation CI SVR	No difference Improved Decreased	NA 0.04 0.02
			3.75mg/kg DITPA X 2 weeks	Inotropic support Death Length of stay	No difference No difference Not assessed	NA NA NA
Jeevanandam	74	Heart Transplant Donors (poor pre-operative function)	0.4 µg/kg bolus each hour for a maximum dose: 1.2 µg/kg	Atrial fibrillation CI SVR Inotropic support Death Length of stay	Not reported Not reported Not reported Improved on T3 5 hearts declined not applicable	N/A N/A N/A N/A N/A N/A
		Heart Transplant Donors (good pre-operative function)	No T <sub>3</sub> given	Atrial fibrillation CI SVR Inotropic support Death Length of stay	Not reported Not reported Not reported No change No hearts declined Not applicable	N/A N/A N/A N/A N/A N/A
Jeevanandam	74	Heart Transplant Recipients (6 months following transplant)	No T <sub>3</sub> given	Atrial fibrillation CI SVR Inotropic support Death Length of stay EF (%)	Not assessed No difference Not assessed Not applicable No difference Not applicable No difference	N/A N/R N/A N/A N/R N/A N/R
Jeevanandam	19	Heart Transplant Recipients	0.4 µg/kg before donor heart reperfusion  0.8 µg/kg/hr X 6 hours	Atrial fibrillation CI SVR Inotropic support Death Length of stay	Not assessed Not assessed Not assessed Less required Not assessed Not assessed	N/A N/A N/A < 0.05 N/A N/A

Intervention is iv T<sub>3</sub> unless otherwise indicated; NS = not statistically significant; NR = not reported; N/A = not assessed

**Table 2. Summary of trials of iv T<sub>3</sub> use in coronary artery bypass**

Author	n	Procedure	Intervention	Outcome	Treatment vs Control	p Value
Mullis-Jansson	170	Elective CABG	0.4 µg/kg bolus and 0.1 µg/kg infusion (6 hours)	Atrial Fibrillation CI SVR Inotropic support Death Length of stay	No difference Improved No difference No difference No difference Not assessed	1.00 0.0001 0.21 0.43 0.23 N/A
Klemperer	142	Elective CABG EF < 40%	0.8 µg/kg bolus and 0.113 µg/kg infusion (6 hours)	Atrial fibrillation CI SVR Inotropic support Death Length of stay	No difference Improved Decreased Not assessed No difference No difference	NR 0.007 0.003 N/A NR NR
Gudden	60	Elective CABG EF < 40%	0.8 µg/kg bolus and 0.113 µg/kg infusion (6 hours)	Atrial fibrillation CI SVR Inotropic support Death Length of stay	No difference No difference Decreased Not assessed No difference No difference	NR NR NR < 0.001 N/A NR NR
Bennet-Guerrero	211	Elective CABG	0.8 µg/kg and 0.12 µg/kg/hr for 6 hours	Atrial fibrillation CI SVR Inotropic support Death Length of stay	No difference No difference No difference No difference No difference No difference	NR NS NS NS NR NR
Novitzky	24	Elective CABG (EF < 30%)	<u>At CPB:</u> 0.1 µg/kg bolus <u>At cross clamp removal:</u> +5 mins: 0.075 µg/kg bolus + 4 hours 0.05 µg/kg bolus + 8 hours 0.05 µg/kg bolus	Atrial fibrillation CI SVR Inotropic support Death Length of stay	Not assessed No difference No difference Less required No difference Not assessed	N/A NS NS < 0.01 NS N/A
	24	Elective CABG (EF > 40%)	<u>At CPB</u> 0.2 µg/kg bolus <u>At cross clamp removal:</u> +4 hours 0.15 µg/kg bolus +8 hours 0.1 µg/kg bolus +12 hours 0.05 µg/kg bolus +20 hours 0.05 µg/kg bolus	Atrial fibrillation CI SVR Inotropic support Death Length of stay	Not assessed Improved No difference No difference None Not assessed	N/A < 0.009 NS NS NS N/A

Intervention is iv T<sub>3</sub> unless otherwise indicated; NS = not statistically significant; NR = not reported; N/A = not assessed



**Table 3. Summary of trials of iv T<sub>3</sub> use in pediatric cardiac surgery**

Author	n	Age	Procedure	Intervention	Outcome	Treatment vs Control	p Value
Portman	14	< 1 day	VSD repair or Tetralogy	0.4 µg/kg iv bolus pre CPB and 0.4 µg/kg iv bolus post CPB	Atrial fibrillation	1 reported case	NS
					CI	Not assessed	N/A
					SVR	Not assessed	N/A
					Inotropic support	No difference	NS
					Death	Not assessed	N/A
Length of stay	Not assessed	N/A					
Bettendorf	40	2 days to 10 yrs	Varied all requiring CPB	2 µg/kg iv bolus POD and 1 µg/kg iv bolus daily POD1–POD12	Atrial fibrillation	Not assessed	N/A
					CI	Improved	0.004
					SVR	Not assessed	N/A
					Inotropic support	less	NS
					Death	none	N/A
Length of stay	shorter	NS					

Intervention is iv T<sub>3</sub> unless otherwise indicated; NS = not statistically significant; NR = not reported; N/A = not assessed

**Table 4. Thyroid hormone preparations**

Drug	Brand Name (Manufacturer)	Route	How Supplied	Cost/day (\$CAD)
<b>Tetra-iodothyronine (levothyroxine, T<sub>4</sub>)</b>	Synthroid (Abbott)	PO	25, 50, 75, 88, 100, 112, 125, 150, 175, 200, 300 mcg tabs	0.06 <sup>a</sup>
		iv	500 mcg/10mL vial	30.76 <sup>b, f</sup>
	Eltroxin (GlaxoSmithKline)	PO	50, 100, 150, 200, 300 mcg tabs	0.03 <sup>a</sup>
<b>Tri-iodothyronine (liothyronine, T<sub>3</sub>)</b>	Cytomel (Theramed)	PO	5 and 25 mcg tabs	0.23 <sup>c</sup>
	Triostat (King) <sup>d</sup>	iv	10 mcg/ml vial	1966.44 (based on q8h–q6h dosing of a 10 µg dose) to 2621.91 <sup>e</sup>
	Hospital based conversion of enteral T <sub>3</sub> into iv T <sub>3</sub>	iv	25 µg/ml	~1.00

<sup>a</sup>Based on average maintenance dose of 150 mcg/day

<sup>b</sup>Based on average maintenance dose of 100 mcg/day

<sup>c</sup>Based on average dose of 50 mcg/day

<sup>d</sup>Triostat is not commercially available in Canada and thus is only available from the United States through the Special Access Program of Health Canada (1-613-941-2108)

<sup>e</sup>Based on average dose of 10 mcg iv q6h and a conversion rate of 0.7392 \$USD/\$CAD

<sup>f</sup>As of publication, iv thyroxine is now manufactured by American Pharmaceutical Partners

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## Recommendation 5.2: Corticosteroids and Lung Protection

### Corticosteroid Replacement

Compared to the rise of serum cortisol in response to traumatic brain injury, 50% of brain dead donors appear relatively ACTH deficient as defined by a serum cortisol less than 400 nmol/L (Howlett et al. 1989). Consequently, there may be some justification for corticosteroid replacement in brain dead donors without evidence for benefit in terms of graft survival. In critically ill patients suffering from septic shock, serum cortisol levels in response to ACTH have been demonstrated to predict survival, and supplementing hydrocortisone and fludrocortisone has been demonstrated to improve survival in those patients deemed to be relatively adrenal insufficient (Annane et al. 2000; Annane et al. 2002). The use of corticosteroid replacement is recommended in fluid-resuscitated, catecholamine-resistant septic shock in children (Carcillo et al. 2002).

### Immunomodulating Doses and the Lung

Brain death is associated with the induction of the inflammatory response (Avlonitis et al. 2003), and several publications have advocated the use of high-dose methylprednisolone in an effort to diminish inflammation thought to be present in donor lungs (Zaroff et al. 2002; Rosendale et al. 2003). The evidence for this is largely based on a single retrospective analysis of 118 consecutive lung donors administered a non-uniform protocol of methylprednisolone (mean 14.5 mg/kg) compared with 38 donors not receiving methylprednisolone and demonstrating a significant improvement in donor oxygenation and lung procurement rate (Follette et al. 1998). A recent analysis of the California Donor Network database demonstrated an independent effect of methylprednisolone on the successful procurement of lungs from the donor (McElhinney et al. 2001). Corticosteroids have also been successfully utilized in treating non-infected patients with acute respiratory distress syndrome (ARDS) during the later phase of the disease (Meduri et al. 1998). Evidence that neurogenic pulmonary edema may be alleviated with glucocorticoids also suggests that an inflammatory component exists in this process (Minnear et al. 1982; Edmonds et al. 1986).

The UNOS database showed that heart graft survival benefit was also found in those donors receiving corticosteroids alone (Rosendale et al. 2003).

The optimal dose and time effect (if any) of corticosteroids in brain dead donors are unresolved.

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## Medical Management to Optimize Donor Organ Potential: A Canadian Forum

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## 6. Transfusion Thresholds

There are no rigorous studies that assess the role of red blood cell transfusions for short-term organ preservation during organ donor maintenance. Consensus conferences recommend maintaining a hemoglobin level  $\geq 100$  g/L or a hematocrit greater than 30% (Van Bakel et al. 1997; Zaroff et al. 2002). In contrast, current adult critical care practice advocates red blood cell transfusions at a hemoglobin  $< 70$  g/L based on a large RCT showing equivalent survival at this restricted transfusion level versus a transfusion threshold of 100 g/L (Hebert et al. 1999). However, a subgroup analysis of 257 patients with severe ischemic heart disease randomized to the restricted transfusion group had lower (but not statistically different) absolute survival rates compared to patients in the liberal group (Hebert et al. 2001).

Large platelet transfusion requirements during liver transplant surgery are independently associated with more severe hepatic dysfunction after transplantation, but this is likely more indicative of a more technically complicated procedure and sicker recipient (Gonzalez et al. 1994).

There was no literature identified to guide platelet or plasma factor replacement in the donor.

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## 7. Invasive Bacterial Infections

Isolated cases of transmission of solid organ infection from donor to recipient may have significant consequences including graft infection, sepsis and poor initial graft function in a liver recipient (Gottesdiener et al. 1989; Ciancio et al. 1996; Doig et al. 1975; Weber et al. 1979; Nery et al. 1997). However, while approximately 5% of all donors will be bacteremic at the time of procurement, the routine use of prophylactic broad spectrum antibiotics (vancomycin and ceftazidime/cefotaxime) in the recipient has prevented transmission of bacterial infection in all organ recipients from a total of 124 bacteremic donors (Lumbreras et al. 2001; Freeman et al. 1999). No differences in acute mortality or graft survival were found. Other authors have described the successful transplantation of organs from donors declared brain dead from meningitis caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Escherichia coli* without transmission to the recipient (Lopez-Navidad et al. 1997).

Little or no literature exists on the use of prophylactic antibiotic therapy in the organ donor.

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## 8. Heart

Donor risk factors: In a large cohort study, donor risk factors associated with increased 30-day heart transplant mortality were older age, smaller size, greater inotropic support, diabetes mellitus, longer ischemic time and diffuse wall motion abnormalities by echocardiography (Young et al. 1994). Advances in expanding the cardiac donor pool include donor age and coronary artery disease, myocardial function, left ventricular hypertrophy, donor–recipient size mismatch and cold ischemia time (Zaroff et al. 2002). Older age is a risk factor for coronary artery disease development in the recipient (McGiffin et al. 1995) and has been associated with variable survival ranging from normal (Potapov et al. 1999) to reduced (Tenderich et al. 1998). Transplants from older donors (age > 63 years) may have increased cardiac morbidity (infarction, arrhythmias, coronary vasculopathy) without differences in ejection fraction after 1 year or survival (Potapov et al. 1999). Higher transplant mortality risk is reported from male donors (Tenderich et al. 1998). The use of hearts with mild left ventricular hypertrophy ( $\leq 13$  mm by echocardiography) have been recommended, particularly if cold ischemia time is short (Zaroff et al. 2002). High-risk donors (e.g., age > 40 years, systemic infection, ischemic time > 5h, dopamine > 10  $\mu\text{g}/\text{kg}/\text{min}$  or epinephrine > 5  $\mu\text{g}/\text{kg}/\text{min}$ ) have 76% 12-month survival rates (Sweeney et al. 1990).

Coronary angiography is often performed on cardiac allograft donors, particularly if they are of older age (over 40 years), require high inotropic support or have other risk factors for coronary artery disease such as diabetes mellitus (McGiffin et al. 1995; Young et al. 1994). The cardiac working group at the 2001 Crystal City Consensus Conference recommended that coronary angiography should be performed in male donors > 45 years, female donors > 50 years or history of cocaine abuse or  $\geq 3$  risk factors for coronary artery disease (hypertension, diabetes, smoking) (Zaroff et al. 2002).

Donor cardiac troponins: The value of donor cardiac troponin I and T has also been studied in relationship to early cardiac graft failure (Grant et al. 1994; Potapov et al. 2001). Changes in catecholamine levels resulting in an increase in peripheral resistance may result in a sudden increase in myocardial work and oxygen consumption leading to myocardial ischemia/infarction and subsequent elevation of cardiac troponin I and T. This had been well documented in massive subarachnoid hemorrhage (Macmillan et al. 2002). In a case series, brain dead cardiac donors with cardiac troponin I values > 3.1 ng/mL were found to have diffuse subendocardial myocytolysis and coagulative necrosis, and 5/8 of these hearts were diagnosed as having graft failure after transplantation (Grant et al. 1994). Myocardial band creatine kinase (CK MB) values were not associated with cardiac troponin I levels. In a larger study of 126 consecutive brain dead donors, the odds ratio for the development of acute graft failure after heart transplantation was 42.7 for donors with cardiac troponin I > 1.6  $\mu\text{g}/\text{L}$  and 56.9 for donors with cardiac troponin T > 0.1  $\mu\text{g}/\text{L}$  (Potapov et al. 2001). Higher donor troponin T levels are associated with more frequent requirement of epinephrine in corresponding heart transplant recipients within 24 hours of transplantation (Anderson et al. 1994). Higher cardiac allograft rejection rates have also been associated with high donor troponin levels (Vijay et al. 1998).

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## 9. Lungs

### a. Bronchoscopy, Bronchopulmonary Infections and Antimicrobial Therapy

The consensus of expert opinion supports the use of bronchoscopy for the purposes of examining the tracheobronchial tree for abnormalities and collecting microbiological specimens (Rosengard et al. 2002; Rosendale et al. 2002; Davis et al. 1995). Pathological studies of lungs unsuitable for donation have indicated that bronchopneumonia, diffuse alveolar damage, and diffuse lung consolidation are the three most common reasons for being deemed unsuitable (Aziz et al. 2002).

Between 76% and 97% of bronchoalveolar lavages (BALs) will grow at least one organism (Dowling et al. 1992; Low et al. 1995). The most commonly identified organisms included *Staphylococcus aureus* and *Enterobacter*, and in 43% of transplants, similar organisms were isolated from recipient bronchoscopy. Pulmonary infection in the graft recipient results in significantly lower survival compared with recipients who do not develop early graft infection (Zenati et al. 1990). Recipients with donor BAL cultures positive for either gram positive or gram negative bacteria had longer mean mechanical ventilation times and inferior 6-month to 4-year survival than those with negative bacterial BAL cultures (Avlonitis et al. 2003).

The etiology of donor death is not associated with lung transplant mortality (Christie 2003) but may influence the type of organisms found on BAL and subsequent graft infection risk. Trauma donors (versus intracerebral hemorrhage) may be at higher risk for aspiration and for intubation under less sterile field conditions and were generally ventilated longer (> 48 hours). Although no differences were found in P/F ratios or incidence of culture-positive BALs, gram negative enteric bacilli are found more commonly in trauma donors and associated with 30-day recipient mortality from gram negative pneumonia with the same organisms (Waller et al. 1995).

At present, no guidelines exist for the empiric use of antibiotics in donors in the absence of evidence for bronchopneumonia. Some authors have recommended that empiric therapy be initiated and modified based on the results of bronchoscopy (Low et al. 1995). If pulmonary infection is suspected, the use of antibiotics to cover both *Staphylococcus aureus* and enteric gram-negative bacilli should be considered, although there is insufficient evidence in the literature to firmly support this recommendation. In a canine model of brain death and lung transplant, the use of aerosolized and iv antibiotics combined, but not either alone, prevented pneumonia in lung recipients (Dowling et al. 1992).

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## **b. Donor Lung Injury, Oxygenation and Ventilator Strategies**

### Ideal lung donor (Orens et al. 2003)

- Age < 55
- ABO compatibility
- Clear chest radiograph
- PaO<sub>2</sub> > 300 on FiO<sub>2</sub> = 1.0, positive end expiratory pressure (PEEP) 5 cm H<sub>2</sub>O
- Tobacco history < 20 pack-years
- Absence of chest trauma
- No evidence of aspiration or sepsis
- No prior cardiopulmonary surgery
- Sputum gram stain: absence of organisms
- Absence of purulent secretions at bronchoscopy.

Etiologies of donor-related lung injury and dysfunction may include neurogenic pulmonary edema, aspiration, pulmonary contusion, bronchopulmonary infection, alveolar-capillary inflammation and diffuse alveolar damage. Pathological studies of lungs unsuitable for donation have indicated that bronchopneumonia, diffuse alveolar damage and diffuse lung consolidation are the three most common reasons for being deemed unsuitable (Aziz et al. 2002).

Acute pulmonary allograft failure is usually associated with inadequate lung preservation, ischemia-reperfusion injury and cellular rejection (Jahania et al. 2000). One-year survival for patients with primary lung allograft failure is 40% as compared with a 69% one-year survival for patients without graft failure (Jahania et al. 2000; Ware et al. 2002). The syndrome of primary pulmonary graft failure has pathological features of acute lung injury (ALI) and occurs in 12% to 50% of transplanted patients (Christie et al. 1998; Christie et al. 2003; Thabut et al. 2002).

Traditional oxygenation criteria used as a threshold in the acceptance of donor lungs include a donor PaO<sub>2</sub> > 300 mmHg on FiO<sub>2</sub> of 100% and PEEP of 5 cm H<sub>2</sub>O (Sundaresan et al. 1995; Davis et al. 1995). In a study of crystalloid fluid management in 26 brain dead donors, a significant increase in the alveolar-arterial oxygen gradient was seen in those who achieved a central venous pressure (CVP) of 8–10 versus those whose CVP was maintained at 4–6 mmHg (Pennefather et al. 1993).

Improving the current criteria for donor selection: Physiological, microbiological and histological evaluation of rejected lungs from the California transplant registry show 41% of rejected lungs were judged suitable for transplantation based on pulmonary edema, intact alveolar fluid clearance and histology (Ware et al. 2002). In a case series of 15 brain dead patients, lung grafts that did not meet the usual criteria for transplantation were found to have higher dynamic and static elastance measurements than donor lungs that met standard transplantation criteria (Labrousse et al. 1996). Investigators have challenged donor PaO<sub>2</sub> criteria by arguing that many physiological donor factors influence peripheral arterial PaO<sub>2</sub> independent of isolated individual lung function (Aziz et al. 2002). Despite poor global oxygenation, parenchymal abnormalities isolated to one lung may not preclude procurement of the contralateral lung (Puskas et al. 1992). The outcomes of 49 marginal donors (i.e., failing to meet one or more of the ideal criteria) showed no significant difference in duration of post-transplant mechanical ventilation or P/F ratio compared to ideal donors (Sundaresan et al. 1995).

Alveolar recruitment and ventilation strategy: Prolonged ventilation in the supine position results in loss of alveolar expansion and microatelectasis. In an experimental rat model, donor lungs develop microatelectasis despite PEEP and a relatively short ventilatory period before organ procurement (Tasker et al. 1995). Prevention of alveolar collapse enhances post mortem preservation of pulmonary grafts in a rabbit model (Van Raemdonck et al. 1998). Recruitment maneuvers in the form of high sustained PEEP for short durations may be a useful adjunct to the lung-protective ventilatory strategies used to prevent alveolar stress and collapse in ARDS/ALI (Moran et al. 2003). Lung donors failing traditional oxygenation criteria ( $P/F < 300$ ) respond to aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume and increasing PEEP with improvements in  $P/F$  ratio  $> 300$ . Lungs were subsequently transplanted without differences in ICU length of stay or 30-day mortality compared to recipients of ideal donors (Gabbay et al. 1999).

High PEEP and pressure-limited ventilator strategies to minimize tidal volumes and plateau pressures offer clear survival advantage in ARDS (ARDS Net 2000; Eichacker et al. 2002). While there is histological similarity between the diffuse alveolar damage seen in rejected donor lungs and ARDS, there are no studies comparing ventilator strategies in organ donors.

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## 10. Liver

### An “ideal” liver donor

- Age 1–45 years
- Normal liver biochemistry
- Normal blood gases and blood pressure (BP)
- No cardiopulmonary arrest and no vasopressors, or dopamine  $\leq 5 \mu\text{g/kg/min}$
- Normal serum sodium (Na) and creatinine
- Length of ICU stay  $< 3$  days
- Body Mass Index  $< 28$
- Predicted cold ischemia time (CIT)  $< 12$  hours
- No evidence of sepsis
- 1-desamino-D-arginine vasopressin (DDAVP), not vasopressin, for diabetes insipidus
- Identical blood grouping
- Hepatitis B and C virus (HBV and HCV) negative.

Primary liver dysfunction occurring in the first week is attributable to preoperative or intraoperative variables. Primary dysfunction (PDF) is subdivided into primary nonfunction (PNF = death or retransplantation within 7 days) and initial poor function (IPF = AST  $> 2000$  IU/L and PT  $> 16$  on postoperative days 2 to 7). In animal models, brain death has a detrimental role on hepatic dysfunction related to immune activation and independent of hemodynamic instability (van der Hoeven et al. 2000) and magnified by longer ischemic times (van der Hoeven et al. 2001). The sinusoidal lining cells (SLC) of the liver are particularly vulnerable to the effects of preservation-reperfusion injury, the extent of which depends on the duration of cold ischemia rather than reperfusion. Cold preservation causes the SLC to become edematous and detach into the sinusoidal lumen (Clavien et al. 1992).

Donor risk factors: Reduced size livers, older donor age ( $> 49$  years), moderate to severe fatty changes in the donor liver biopsy and prolonged preservation times ( $> 18$  hrs) are associated with a higher risk of PDF (Ploeg et al. 1993). Poor graft function has also been associated with a prolonged stay in the ICU ( $> 3$  days) and elevated bilirubin (Greig et al. 1990). In the European cohort, cold ischemic time  $> 16$  hours was an independent risk factor for long-term graft failure (Porte et al. 1998). Longer total ischemia time and large platelet transfusion during surgery are independently associated with more severe hepatic dysfunction after transplantation (Gonzalez et al. 1994). Large platelet requirements during surgery may be indicative of a more technically complicated procedure, sicker recipient or poorer quality graft with subsequently greater sequestration of platelets within the donor liver. In a large Spanish study, extended cold ischemia time  $> 12$  hrs was independently associated with biliary complications and donor hypernatremia was independently associated with death or retransplantation at 30 days (Figueras et al. 1996).

Donor liver age: Early UNOS data from 1987 to 1990 reported a survival difference of  $< 10\%$  from donors aged 45–55 years compared to those 15–45 years (Alexander et al. 1991). A Canadian study showed that grafts from older adult donors or younger pediatric donors had poorer transplant function (Greig et al. 1990). However, several studies have demonstrated equivalent liver transplant outcomes from donors  $> 50$  years as long as no additional risk factors exist (excessive steatosis or extended cold ischemic time) (Oh et al. 2000; Wall et al. 1990; Karatzas et al. 1997; Briceno et al. 1997). Shorter graft survival is reported from donors  $> 70$

years of age (Busquets et al. 2001; Cuende et al. 2002). Of note, recipients of older livers were themselves significantly older and suffered from a higher incidence of hepatocellular carcinoma and hepatitis C viral infection (Cuende et al. 2002). The combined effects of older donor age and prolonged cold ischemia time interact to produce worse outcomes (Busuttil et al. 2003).

Older donor age in adult transplantation and very young age in pediatric transplantation, moderate to severe steatosis on liver biopsy, prolonged cold ischemia time (> 12–18 hours) and donor hypernatremia (Na > 155 mmol/L) appear to be the most robust predictors of PNF and IPF related to the donor.

While some authors recommend routine donor liver biopsies in all liver donors in an effort to decrease the rate of IPF and PNF (Strasberg et al. 1994; Busuttil et al. 2003), the use of a biopsy in the decision making of liver suitability has generally been restricted to evaluating the amount of steatosis or in the presence of active hepatitis C in the appropriate risk groups.

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## 11. Kidney

### Donor Risk Factors Predicting Kidney Allograft Dysfunction

Donor hemodynamic instability is correlated with post-transplant acute tubular necrosis in adults (Lagiewska et al. 1996; Troppmann et al. 1995; Walaszewski et al. 1991; Szostek et al. 1997) and children (Finfer et al. 1996). Reduced graft survival or acute tubular necrosis may occur in organs retrieved from donors receiving high-dose dopamine ( $> 10 \mu\text{g}/\text{kg}/\text{min}$ ); these effects may be limited to donors who are hypotensive (mean arterial pressure [MAP]  $< 80 \text{ mmHg}$ ) at the time of organ retrieval (Walaszewski et al. 1991). Hemodynamic resuscitation may improve outcome as donor use of dopamine and/or noradrenaline is independently associated with a lower risk of acute rejection (Schnuelle et al. 1999) and a lower rate of delayed graft function (Schnuelle et al. 2004). A single study has linked longer duration of brain death (time from declaration of brain death to onset of cold ischemia) to improved initial graft function and graft survival, suggesting that the time taken to optimize donor cardiovascular status may reduce ischemic injury (Kunzendorf et al. 2002).

Delayed renal allograft function has been associated with the development of rejection in epidemiological studies (Troppmann et al. 1995). Brain death-related inflammatory activation may be related to early immune-mediated tissue injury (Tullius et al. 2001). Delayed graft function also predicts the development of adverse events such as decreased graft survival, decreased recipient survival and increased allograft nephropathy (Melk et al. 2002).

### Cold Ischemia Time

In an analysis of the Collaborative Transplant Study database of kidney transplants, cold ischemic preservation time  $> 12$  hours resulted in progressively worsening recipient graft survival, particularly once the cold ischemia time (CIT) was  $\geq 48$  hours (Opelz 1998). Other analyses have suggested that CIT is predictive of poorer graft survival (Port et al. 2002) or function (Troppmann et al. 1995) if it was  $> 24$  hours. Preservation incorporating pulsatile perfusion may reduce the incidence of delayed graft function (reviewed by Wight et al. 2003); currently its use is largely restricted to higher risk settings of older donor age or non-heart-beating donation.

### Donor Age

Age  $\geq 40$  or  $\leq 10$  years is independently associated with risk for graft failure (Port et al. 2002; Wigmore et al. 1999). Older kidneys have a higher incidence of renovascular or parenchymal injury (Wigmore et al. 1999). In a living donor study, donor age  $> 60$  years was the single most important risk factor for long-term graft failure (Toma et al. 2001).

Donor renal insufficiency has been identified as a risk factor for both delayed graft function and poorer long-term graft survival (Port et al. 2002). Controversy exists as to the most predictive serum creatinine, although most analyses have used terminal serum creatinine or calculated



creatinine clearance. A calculated creatinine clearance using the Cockcroft-Gault formula (using ideal body weight) correlated well with inulin clearance in a small cohort of critically ill patients and was superior to either 30-minute or 24-hour measured creatinine clearance (Zarowitz et al. 1993); newer formulas to estimate glomerular filtration rate have not been evaluated in this patient population.

Donor characteristics that were independently associated with graft failure risk were creatinine > 133  $\mu\text{mol/L}$ , history of hypertension independent of duration and cerebrovascular accident (CVA) as the cause of donor death (Port et al. 2002). Although traumatic (versus cerebrovascular) etiology of brain death is associated with improved renal graft survival, this association may be confounded by the lack of adjustment for the presence of atherosclerotic disease in older donors with CVAs (Ojo et al. 2001). Traumatic brain injury is associated with an increased risk of acute rejection (Schnuelle et al. 1999). Diabetes mellitus is not independently associated with graft failure (Port et al. 2002). Kidneys from type 2 diabetic donors have increased risk of renal dysfunction but have improved 5-year patient and graft survival and no difference in graft rejection rates (Becker et al. 2002).

### Expanded Kidney Donor Criteria

The potential kidney donor pool may be expanded by considering donors > 60 years of age, CVAs as an etiology of death, history of hypertension or diabetes mellitus, degree of glomerulosclerosis > 15 %, anatomic abnormalities (e.g., > 1 renal artery), serum creatinine > 133  $\mu\text{mol/L}$  (> 1.5 mg/dL) or creatinine clearance < 60–90 ml/min (Port et al. 2002; Carter et al. 2000; Sola et al. 2002; Becker et al. 2002 ; Ojo et al. 2001; Tullius et al. 2001). Combination risk factors (older age with hypertension, creatinine > 133  $\mu\text{mol/L}$  or CVA) decrease graft survival rates by approximately 4–6% at 1 year and 8–11% at 3 years (Port et al. 2002). Transplantation of marginal kidneys (defined as donors > 55 years, a > 10 year history of hypertension, diabetes mellitus > 10 years' duration, non-heart-beating donors and cold preservation time > 36 hours) results in 5-year graft and patient survival rates of 53% and 74% compared with 67% and 80% for recipients of ideal donor kidneys. The average increase in life expectancy advantage for recipients of marginal donor kidneys compared to those waiting for a kidney transplant was five years (Ojo et al. 2001). Dual kidney transplantation into a single recipient is a good alternative from older donors in the presence of glomerulosclerosis (Andres et al. 2000; Lu et al. 2000; Dietl et al. 2000 ).

### Contrast Nephropathy

If coronary angiography is performed, the use of N-acetylcysteine with hydration both before and after the angiographic procedure has been demonstrated to reduce the risk of developing contrast nephropathy in patients with chronic renal insufficiency in several studies (Tepel et al. 2000; Efrati et al. 2003; Shyu et al. 2002; Briguori et al. 2002; Diaz-Sandoval et al. 2002; Kay et al. 2003). N-acetylcysteine is thought to exert its beneficial effect against oxidative stress. Collectively, these and other studies have been analysed in a recent meta-analysis where the administration of N-acetylcysteine and hydration was found to reduce the relative risk of contrast nephropathy by 56% (Birck et al. 2003). Although the population of patients in these studies were not organ donors, the use of acetylcysteine may have a beneficial effect in preserving the renal function of marginal kidney donors such as those with age > 60, with a terminal creatinine

clearance < 90 ml/L or with a history of diabetes or hypertension. The majority of studies have used a dose of N-acetylcysteine of 600 mg orally every 12 hours for two doses before and 2 doses after angiography; however, other authors have used a dose of 1 gram of acetylcysteine twice daily 24 hours before and after coronary angiography with 0.45% normal saline hydration (Tepel et al. 2000; Efrati et al. 2003). There is limited experience with other dosing protocols that may be more feasible in the management of a deceased donor given relatively short timelines. Durham et al. administered N-acetylcysteine 1200 mg orally 1 hour before angiography and 3 hours after angiography, however failed to see an impact of N-acetylcysteine (Durham et al. 2002). In contrast, Baker et al. used iv dosing with 150 mg/kg in 500 ml of normal saline given over 30 minutes immediately prior to contrast administration followed by 50 mg/kg in 500 ml of normal saline infused over 4 hours; in this study there was a statistically significant reduction in the incidence of contrast nephropathy from 21% to 5% (Baker et al. 2003).

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## 12. Optimal Time of Organ Procurement and Decisions Regarding Transplantability

For renal allografts, a longer duration of donor brain death does not worsen short-term or long-term renal graft function, and a longer duration of the admission to neurological determination of death (NDD) to procurement intervals may improve graft survival. A trend to poorer kidney graft survival has been observed when organs from donors after CVA (compared to trauma) were procured between 24 and 59 hours after admission and may be the result of higher inflammatory activity during this time (Muruve et al. 2001). In a large cohort study of 1106 renal transplant recipients, a strong inverse association was found between the NDD to procurement interval and the incidence of primary renal graft dysfunction (Kunzendorf et al. 2002). Temporal trends in creatinine may be helpful.

Although liver allograft dysfunction has been associated with prolonged ICU stay (Greig et al. 1990; Brokelman et al. 1999), this was supported by univariate analysis but did not hold true by multivariate analysis (Brokelman et al. 1999). In a cohort of 323 orthotopic liver transplants (OLT), longer donor hospitalization was not found to be associated with primary liver graft dysfunction by a multivariate analysis (Ploeg et al. 1993). A period of time may be needed to determine the trend of an elevated AST or ALT. The generally accepted upper limit of 250–350 may be exceeded if the levels are falling rapidly (e.g., following a hypotensive episode with resuscitation).

The available literature on the timing of organ procurement for lung transplantation is limited and conflicting. Although the California Transplant Donor Network from 1995 to 1997 demonstrated an association between longer time to donor network referral and a reduced chance of lung procurement, an Australian centre has advocated delaying organ procurement until marginal donor lungs have been optimized with aggressive bronchial toilet using bronchoscopy, physiotherapy, increasing tidal volume and increasing positive end expiratory pressure (PEEP) (Gabbay et al. 1999; McElhinney et al. 2001).

Myocardial injury related to primary brain injury or intracranial hypertension is a neurally mediated process and may be potentially reversible with time and treatment (Tung et al. 2004).

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## Appendix #2: Key Terms and Acronyms

Ab	antibody
ABG	arterial blood gas
ABO	blood grouping
ABP	arterial blood pressure
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
ALI	acute lung injury
ALT	alanine aminotransferase (liver enzyme)
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase (liver enzyme)
AVP	arginine vasopressin
BAL	bronchoalveolar lavage
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass grafting
CCDT	Canadian Council for Donation and Transplantation
CI	cardiac index
CIT	cold ischemia time
CIHR	Canadian Institutes of Health Research
cmH <sub>2</sub> O	centimeters of water pressure
CMV	cytomegalovirus
CVA	cerebrovascular accident
CVP	central venous pressure
DDAVP	1-desamino-8-D-arginine vasopressin; desmopressin
EF	ejection fraction
EKG	electrocardiogram
ETT	endotracheal tube
FiO <sub>2</sub>	fraction of inspired oxygen
FRG	Forum Recommendations Group
HBcAb	hepatitis B virus antibody
HBsAG	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
ICP	intracranial pressure
ICU	intensive care unit
IM	intramuscular
INO	inhaled nitric oxide

INR	international normalized ratio
IPF	initial poor function (liver)
IV	intravenous
KT	knowledge transfer
LKT	logistics and knowledge transfer
LV	left ventricular
LVAD	left ventricular assist device
MAP	mean arterial pressure
MEMODOP	Medical Management to Optimize Donor Organ Potential
mmHg	millimeters of mercury
MVO <sub>2</sub>	mixed venous oxygen
NDD	neurological determination of death
NS	normal saline
OLT	orthotopic liver transplant
OPO	organ procurement organization
P/F	PaO <sub>2</sub> /FiO <sub>2</sub> ratio
PaO <sub>2</sub>	partial pressure of arterial oxygen
PAC	pulmonary artery catheter
PCWP	pulmonary capillary wedge pressure
PDF	primary dysfunction (liver)
PEEP	positive end expiratory pressure
pH	measure of the relative acidity or alkalinity of a solution
PICU	pediatric intensive care unit
PIP	peak inspiratory pressure
PNF	primary nonfunction (liver)
PO <sub>2</sub>	partial pressure of oxygen
PRG	Pediatric Recommendations Group
PRN	as needed
PT	prothrombin time
PTT	partial thromboplastin time
RCT	randomized controlled trial
SC	subcutaneous
SLC	sinusoidal lining cells (liver)
SVC	superior vena cava
SVR	systemic vascular resistance
T <sub>3</sub>	thyroid hormone (tri-iodothyronine)
T <sub>4</sub>	thyroid hormone (tetra-iodothyronine)
TSH	thyroid-stimulating hormone
UNOS	United Network for Organ Sharing

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## Medical Management to Optimize Donor Organ Potential: A Canadian Forum

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## Medical Management to Optimize Donor Organ Potential: A Canadian Forum

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