Worldwide management of donors after neurological death: a systematic review and narrative synthesis of guidelines

Prise en charge des donneurs après un décès neurologique dans le monde : revue systématique et synthèse narrative des lignes directrices

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Abstract

Objective *The objectives of this study were to systematically identify and describe guidelines for the care of neurologically deceased donors and to evaluate their methodological quality, with the aim of informing and supporting the new Canadian guidelines for the management of organ donors.*

Methodology *Following a systematic search, we included any document endorsed by an organ donation*

organization, a professional society, or a government, that aims to direct the medical management of adult, neurologically deceased, multi-organ donors. We extracted recommendations pertaining to six domains: the autonomic storm, hemodynamic instability, hormone supplementation, ventilation, blood product transfusions, and general intensive care unit (ICU) care. Methodological quality of the guidelines was assessed by the validated AGREE-II tool.

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Main findings This review includes 27 clinical practice guidelines representing 26 countries published between 1993 and 2019. Using the AGREE-II validated tool for the evaluation of guidelines' quality, documents generally scored well on their scope and clarity of presentation. Nevertheless, quality was limited in terms of the scientific rigor of guideline development. Recommendations varied substantially across the domains of managing the autonomic storm, subsequent management of hemodynamic instability, hormone therapy, mechanical ventilation, blood product transfusion, and general ICU care. We found consistent recommendations for low tidal volume ventilation subsequent to the publication of a landmark clinical trial.

Conclusion Highly inconsistent recommendations for deceased donor care summarized in this review likely reflect the relatively slow emergence of high-quality clinical research in this field, as well as a late uptake of recent validated guideline methodology. Even in this context of few randomized-controlled trials, our group supported the need for new Canadian guidelines for the management of organ donors that follow rigorous recognized methodology and grading of the evidence.

Trial registration PROSPERO (CRD42018084012); registered 25 February 2016.

Résumé

Objectif Les objectifs de cette étude étaient d'identifier et de décrire de façon systématique les lignes directrices concernant les soins à prodiguer aux donneurs suivant un décès neurologique et d'évaluer leur qualité méthodologique, avec pour but d'informer et d'appuyer les nouvelles lignes directrices canadiennes de prise en charge des donneurs d'organes.

Méthodologie À la suite d'une recherche systématique, nous avons inclus tout document endossé par un organisme

de dons d'organes, une société professionnelle ou un gouvernement et ayant pour but d'orienter la prise en charge médicale des donneurs adultes d'organes multiples à la suite d'un décès neurologique. Nous avons extrait les recommandations touchant six domaines : la tempête catécholaminergique, l'instabilité hémodynamique, la supplémentation hormonale, la ventilation, les transfusions de produits sanguins et les soins généraux à l'unité de soins intensifs (USI). La qualité méthodologique des lignes directrices a été évaluée avec l'outil validé AGREE-II.

Constations principales Cette revue porte sur 27 guides d'exercice cliniques représentant 26 pays et publiés entre 1993 et 2019. En se fondant sur l'outil validé AGREE-II pour l'évaluation de la qualité des lignes directrices, les documents ont en règle générale obtenu un bon score en ce qui touchait à leurs objectifs et à la clarté de leur présentation. Toutefois, la qualité était limitée en matière de rigueur scientifique employée pour la mise au point des lignes directrices. Les recommandations variaient considérablement concernant les questions pertinentes à la prise en charge de la tempête catécholaminergique, à la prise en charge subséquente de l'instabilité hémodynamique, à l'hormonothérapie, à la ventilation mécanique, à la transfusion de produits sanguins, et aux soins généraux à l'USI. À la suite de la publication d'une étude clinique importante, les recommandations concernant la ventilation à volume courant bas étaient constantes.

Conclusion Le manque de cohérence des lignes directrices touchant les soins aux donneurs décédés résumés dans cette revue est probablement le reflet de l'émergence relativement lente de recherches cliniques de qualité élevée dans ce domaine, ainsi que de l'adoption tardive des méthodologies récentes et validées pour l'élaboration de lignes directrices. Même dans le contexte actuel de rareté d'études randomisées contrôlées, notre groupe appuie la nécessité de nouvelles lignes directrices canadiennes concernant la prise en charge des donneurs d'organes qui respectent une méthodologie reconnue et rigoureuse ainsi qu'une classification des données probantes.

Enregistrement de l'étude PROSPERO (CRD42018084012); enregistrée le 25 février 2016.

Keywords organ donation · brain death · organ donor · clinical practice guidelines · systematic review

Organ transplantation saves lives and improves quality of life for thousands of chronically ill patients every year.^{1,2} In the United States in 2018, 113,000 patients were

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Fig. 1 Guideline selection flow diagram

registered on a transplant waiting list, and 20 people died every day while waiting for a transplant.² In 2012, the World Health Organization called for research to improve the hospital care of deceased organ donors.³ While research in this field is limited, current findings support the concept that improved organ donor care can increase the quantity and quality of organs for transplantation.^{4,5} Therefore, evidence-based recommendations are an important tool to guide best practices for the care of deceased donors in intensive care units (ICUs).⁶ Nevertheless, rigorous high-grade evidence in the organ donor care field is lacking and guidelines derived from expert consensus opinions may

represent the highest evidence to guide clinicians' practices.

In the past years, research in organ donor care has been slowly emerging, with the publication of randomized trials.^{4,5} If guidelines are not preceded by a systematic review of the evidence or lack mandatory update mechanisms or processes to dictate recommendations, they can rapidly become outdated, futile, and may lead to inappropriate clinical decisions. Hence, the quality of clinical decisions may suffer from misguided decisions, and ultimately the donor and recipient outcomes may be negatively affected by suboptimal clinical management.

Country, (first author /subcategory) Year (reference number)	Domain 1: Scope and purpose	Domain 2: Stakeholder involvement	Domain 3: Rigour of development	Domain 4: Clarity of presentation	Domain 5: Applicability	Domain 6: Editorial independence
Ireland (Conrick-Martin) 2019(30)						
India (Pandit) 2017(29)						
Australia 2016(22)						
Austria 2016(34)						
Germany 2016(35)						
Norway 2016(41)						
Denmark 2015(36)						
Europe (Eurotransplant) 2015(24)						
USA (Kotloff) 2015(27)						
Iran (Firoozifar) 2014(25)						
Switzerland (Haberthur) 2014(43)						
Oceania (ANZICS) 2013(20)						
Hungary 2013(37)						
Brazil (Westphal) 2011(15,16,17)						

Fig. 2 Risk of bias assessment using the AGREE-II instrument

For example, failure to include the recent recommendation to administer mild hypothermia^{7,8} to organ donors in specific guidelines, either because the publication was not detected or because of a subjective decision to ignore the recommendation, could jeopardize kidney function in recipients around the world.⁴

This review was conducted concomitantly with and in preparation for the 2020 Canadian guideline on organ donor management.⁹ The objective was to inform and support future Canadian guidelines by identifying and systematically reviewing existing guidelines for organ donor care, with the aim of listing and describing the recommendations and evaluating their methodological quality. We hypothesized that actual guidelines would suffer from low methodological rigor and that our systematic review could emphasize the need for evidence-based Canadian guidelines.

Methods

The protocol of the present systematic review was registered on PROSPERO and its last edition occurred on 1 June 2018 (CRD42018084012).

Literature search

In collaboration with a senior information specialist, we searched ten bibliographic databases from their inception: MEDLINE (Appendix 1), EMBASE, CistMef, Open Grey, LILACS, SciELO, NICE, Cochrane Database of Systematic Reviews, Global Health, and Base de Données de Santé Publique. We adapted the search strategy to French and Spanish languages for specific databases. To capture grey literature, we used Google (June 2020 for English, French, Spanish, Portuguese, Italian, Chinese, and German and February 2016 for Japanese and Arabic), we searched the TRIP database (28 May 2020) and we requested unpublished guidelines from each donation organization represented in the International

Table 1 Description of the included guidelines

Country, (first author/subcategory) Year (reference number)	Organizations	Language	Source
Ireland (Conrick-Martin) 2019 ³⁵	Intensive Care Society of Ireland	English	Peer review publication
India (Pandit) 2017 ³⁴	Indian Society of Critical Care Medicine	English	Peer review publication
Australia 2016 ²⁷	New South Wales Australia Ministry of Health	English	Website
Austria 2016 ³⁷	Gesundheit Oesterreich	German	Website
Germany 2016 ³⁸	Consul for Organ Donation; German Foundation for Organ Transplantation	German	Website
Norway 2016 ⁴⁴	Norks Ressursgruppe for Organdonasjon	Norwegian	Website
Denmark 2015 ³⁹	Neuro Anesthesia Committee of the Danish Society of Anesthesia and Intensive Care Medicine; Danish Neurological Society; Danish Transplantation Society	Danish	Website
Europe (Eurotransplant) 2015 ²⁹	Eurotransplant Foundation	English	Website
USA (Kotloff) 2015 ³²	Society of Critical Care Medicine; American College of Chest Physicians; Association of Organ Procurement Organizations; Donor Management Task Force	English	Peer review publication
Iran (Firoozifar) 2014 ³⁰		English	Peer review publication
Switzerland (Haberthur) 2014 ⁴⁶	Fondation Suisse pour le Don d'Organes; Société Suisse de Médecine Intensive; Swisstransplant	French	Website
Oceania (ANZICS) 2013 ²⁵	ANZICS	English	Website
Hungary 2013 ⁴⁰	Debrecen University; Hungarian blood services	Hungarian	Website
Brazil (Westphal) 2011 ^{19–21}	Brazilian Association of Intensive Care Medicine; Brazilian Association of Organ Transplants; Transplantation Centre of Santa Catarina	English and Portuguese	Peer review publication
Canada (Bourret) 2010 ⁸	Transplant Québec	English	Peer review publication (abstract) and website
Chile (Rojas) 2010 ⁴¹	Sociedad Chilena de Trasplante	Spanish	Peer review publication
Canada (Trilium) 2010 ⁴²	Trillium Gift of Life Network	English and French	Website
Cuba (Nodal Arruebarrena) 2009 ⁴³		Spanish	Peer review publication
Australasia 2008 ²⁶	Australasian Transplant Coordinators Association	English	Website
Canada (Shemie) 2006 ⁴⁷	Canadian Critical Care Society; Canadian Association of Transplantation; Société canadienne de transplantation; le Conseil Canadien pour le Don et la Transplantation	English and French	Peer review publication
France (Boulard) 2005 ⁷	Société Française d'Anesthésie et de Réanimation; Société de Réanimation de Langue Française; Agence de la biomédecine	French	Peer review publication

Table 1 continued

Country, (first author/subcategory)Year (reference number)	Organizations	Language	Source
United Kingdom 2005 ³³	Intensive care society UK; British transplant society	English	Website
USA (Powner) 2004 ³¹		English	Peer review publication
Slovenia (Avsec-Letonja) 2003 ⁴⁵		Slovenian	Personal communication
USA(Baldwin) 1993 ²⁸		English	Peer review publication
Argentina ? ²⁴	Institute Nacional Centre unico Coordinator de Ablacion e Implante; Sociedad Argentina de Terapia Intensiva; Sociedad Argentina de Trasplante; Asociacion Argentina de Procuracion de Organos y Tejidos para Transplante; Ministerio de Salud	Spanish	Website
Spain (Escudero) ? ²³	Red/consejo iberoamericano de donacion y trasplante; Servicio de Medicina Intensiva; Coordinación de Trasplantes Hospital Universitario Central de Asturias	Spanish	Website

Table 2 Hemodynamic targets

Country (first author / subcategory) Year (reference number)	Blood pressure targets	Heart rate target	Hemodynamic parameters targets	Echocardiography indication and targets
Ireland (Conrick-Martin) 2019 ³⁵	MAP 60–70 mmHg		CVP 6–10 mmHg PACWP 8–12 mmHg CI > 2.4 L·min ⁻¹ ·m ⁻²	All donors <u>Target:</u> LVEF ≥ 45%
India (Pandit) 2017 ³⁴	SBP >100 mmHg MAP ≥ 60–70 mmHg		CVP 6–8 mmHg PACWP 8–12 mmHg Stroke volume variance < 12% CI 2.4 L·min ⁻¹ ·m ⁻²	All donors (fluid response) Unstable donors <u>Target</u> LVEF ≥ 45%
Australia 2016 ²⁷	SBP > 100 mmHg MAP > 60–80 mmHg	60–120 bpm	CVP 6–10 mmHg CI > 2.5 L·min ⁻¹ ·m ⁻²	Unclear
Austria 2016 ³⁷	MAP 65–75 mmHg	60–120 bpm	CVP 6–12 mmHg	Unstable donors
Germany 2016 ³⁸	MAP 70–100 mmHg		Vascular resistance 2000 +/- 500 dynes·sec ⁻¹ ·cm ⁻⁵ CVP 7–10 mmHg PACWP < 12 mmHg CI 3–5 L·min ⁻¹ ·m ⁻² ITBVI > 850–1000 mL·m ⁻² ELWI 3–7 mL·kg ⁻¹ Stroke volume index 40–60 mL·m ⁻²	Unstable donors
Norway 2016 ⁴⁴	MAP > 65 mmHg	60–120 bpm	CVP 6–10 mmHg	

Table 2 continued

Country (first author / subcategory)Year (reference number)	Blood pressure targets	Heart rate target	Hemodynamic parameters targets	Echocardiography indication and targets
Denmark 2015 ³⁹	MAP > 60–70 mmHg		CVP 6–10 mmHg	All donors
Europe (Eurotransplant) 2015 ²⁹	SBP $\geq$ 90 MAP $\geq$ 70–90 mmHg		CVP 6–10 mmHg PACWP 10–15 mmHg ITBVI 750–1000 mL·m ⁻²	Heart donor
USA (Kotloff) 2015 ³²	MAP $\geq$ 60 mmHg		CVP and/or PAC	Heart donor <u>Target:</u> > 45%
Iran (Firoozifar) 2014 ³⁰	SBP $\geq$ 100 mmHg MAP $\geq$ 60 mmHg, for patients > 60 years old aim for MAP equal to age	70–100 bpm	CVP $\geq$ 12 cmH ₂ O, up to 15 cmH ₂ O if donor > 60 yr old	Heart donor
Switzerland (Haberthur) 2014 ⁴⁶	MAP 65–90 mmHg	60–120 bpm	CVP 8–12 mmHg PACWP 10–15 mmHg GEDVI 680–800 mL·m ⁻² CI > 2.5 L·min ⁻¹ ·m ⁻² EVLWI: < 7 mL·kg ⁻¹ PPV: < 10%	All donors (baseline) Unstable donors
Oceania (ANZICS) 2013 ²⁵	MAP > 70 mmHg			
Hungary 2013 ⁴⁰	MAP 65–75 mmHg		Vascular resistance: $\geq$ 1200 dynes·sec ⁻¹ ·cm ⁻⁵ CVP 6–12 mmHg PACWP 6–12 mmHg CI > 2.5 L·min ⁻¹ ·m ⁻²	
Brazil (Westphal) 2011 ^{19–21}	SBP > 90 mmHg MAP > 65 mmHg			Unstable donors <u>Target:</u> LVEF > 50%
Canada (Bourret) 2010 ⁸	SBP 100–160 mmHg MAP 65–90 mmHg	60–120 bpm	Vascular resistance 800–1200 dynes·sec ⁻¹ ·cm ⁻⁵ CVP 5–10 mmHg,	Heart donors <u>Target:</u> LVEF > 50%
Chile (Rojas) 2010 ⁴¹	MAP $\geq$ 60		CVP 6–10 mmHg (if heart or lungs are not considered, CVP > 10 mmHg is acceptable)	
Canada (Trilium) 2010 ⁴²	SBP 100–160 mmHg MAP 70–90 mmHg	60–120 bpm	Vascular resistance 800–1200 dynes·sec ⁻¹ ·cm ⁻⁵ CVP 6–10 mmHg	Heart donor <u>Target:</u> LVEF > 40%
Cuba (Nodal Arruebarrena) 2009 ⁴³	SBP $\geq$ 100 mmHg	$\leq$ 100 bpm	CVP 10–12 mmHg PACWP 10–12 mmHg	
Australasia 2008 ²⁶	MAP > 70 mmHg			
Canada (Shemie) 2006 ⁴⁷	SBP $\geq$ 100 mmHg MAP $\geq$ 70 mmHg	60–120 bpm	Vascular resistance 800–1200 dynes·sec ⁻¹ ·cm ⁻⁵ CVP 6–10 mmHg PACWP 6–10 mmHg CI > 2.4 L·min ⁻¹ ·m ⁻²	All donors (baseline) Heart donors

bpm = beats·min⁻¹; CI= cardiac index; CVP = central venous pressure; DBP = diastolic blood pressure; EVLWI = extravascular lung water index; GEDVI = global end-diastolic volume index; ITBVI = intrathoracic blood volume index; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; PAC = pulmonary artery catheter; PACWP = pulmonary artery catheter wedge pressure; PPV = pulse pressure variation; SBP = systolic blood pressure; TTE = transthoracic echocardiogram

Table 3 Hemodynamic therapies

Country, (first author / subcategory) Year (reference number)	Fluid therapy		Vasopressors	Inotropic support
	Therapy	Contraindicated solutions		
Ireland (Conrick-Martin) 2019 ³⁵	RL, NS, or balanced crystalloids 2 nd line: colloid solutions		Vasopressin 0.5–2.5 U·hr ⁻¹ 2 nd line: NE or phenylephrine	Dobutamine or adrenaline Limit dobutamine to 10 µg·kg ⁻¹ ·min ⁻¹
India (Pandit) 2017 ³⁴	½ NS or balanced crystalloid solutions (RL or Plasmalyte-A) 2 nd line: albumin 20% or 4%	Avoid fluid containing D5% Avoid starches	Vasopressin 2.4 U·hr ⁻¹ 2 nd line: norepinephrine, epinephrine, phenylephrine 3 rd line: dopamine	
Australia 2016 ²⁷	Balanced crystalloids 2 nd line: albumin 4%, 20%	Starches Gelatin	NE ad 0.2 µg·kg ⁻¹ ·min ⁻¹ 2 nd line: add vasopressin 1.2–2.4 U·hr ⁻¹	Dobutamine 2 nd line: epinephrine
Austria 2016 ⁷	1 st line: 1/2NS+D5%	Starches	NE, dopamine, phenylephrine, vasopressin	Dobutamine, isoproterenol, levosimendan, milrinone 2 nd line : NE
Germany 2016 ³⁸	RL or NS 2 nd line: albumin 5%	Starches	NE 2 nd line: vasopressin 1 U bolus then 0.5–4 U·hr ⁻¹	Dobutamine, dopamine
Norway 2016 ⁴⁴	Ringer acetate, NS, D5%. 2 nd line: 2:1 mix crystalloids and colloids (albumin 5% or dextran)	Starches	Dopamine, NE, or vasopressin 1 U bolus then 0.5–2.5 U·hr ⁻¹	Dopamine 2–20 µg·kg ⁻¹ ·min ⁻¹
Denmark 2015 ³⁹	Balanced crystalloids and consider blood products	Starches Albumin (caution)	Dopamine up to 10 mg·kg ⁻¹ ·min ⁻¹ 2 nd line: NE ad 0.1 µg·kg ⁻¹ ·min ⁻¹ 3 rd line: add vasopressin 0.4–5 U·hr ⁻¹	Dobutamine, dopamine, or epinephrine
Europe (Eurotransplant) 2015 ²⁹	D5%, NS, D2.5%–0.45 saline, RL 2 nd line: 2:1 mix crystalloid/colloid		Dopamine ad 10 µg·kg ⁻¹ ·min ⁻¹ 2 nd line: NE < 0.2 µg·kg ⁻¹ ·min ⁻¹	
USA (Kotloff) 2015 ³²	NS or RL	Starches	Dopamine up to 10 µg·kg ⁻¹ ·min ⁻¹ 2 nd line: vasopressin 0.01–0.04 U·min ⁻¹	Dopamine, dobutamine, or epinephrine
Iran (Firoozifar) 2014 ³⁰	RL or NS 2 nd line: albumin or gelofusin		Dopamine ad 10 µg·kg ⁻¹ ·min ⁻¹ 2 nd line: NE	Dopamine 2 nd line: epinephrine (congestive heart failure)
Switzerland (Habertur) 2014 ⁴⁶	NS or RL 2 nd line: HES 130/0.4, gelatin	HES 130/0.4 or gelatin (caution if renal failure)	NE 0.5–3 µg·kg ⁻¹ ·min ⁻¹ 2 nd line: vasopressin 0.5–2.4 U·hr ⁻¹	Dobutamine ≤ 5 µg·kg ⁻¹ ·min ⁻¹
Oceania (ANZICS) 2013 ²⁵			NE	
Hungary 2013 ⁴⁰	Maintenance D5%	HES 0.4/6% (caution)	NE 0.01–2.5 µg·kg ⁻¹ ·min ⁻¹ 2 nd line: vasopressin 0.01–0.04 U·min ⁻¹ alone or in combination with NE	Combination dobutamine/NE ad 10 µg·kg ⁻¹ ·min ⁻¹ 2 nd line: dopamine 4–10 µg·min ⁻¹
Brazil (Westphal) 2011 ^{19–21}	Crystalloid solution		NE, epinephrine or dopamine 2 nd line: vasopressin 1 U bolus then 0.5–2.5 U·hr ⁻¹	Dobutamine

Table 3 continued

Country, (first author / subcategory)Year (reference number)	Fluid therapy		Vasopressors	Inotropic support
	Therapy	Contraindicated solutions		
Canada (Bourret) 2010 ⁸	D5%-1/2NS maintenance, NS 2 nd line: albumin	Starches (renal failure)	Vasopressin $\leq 2.4 \text{ U}\cdot\text{hr}^{-1}$ 2 nd line : NE $< 0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ 3 rd line: epinephrine $0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or phenylephrine $0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or dopamine $\leq 10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	
Chile (Rojas) 2010 ⁴¹	RL or NS 2 nd line: gelatin (lung donors)		Dopamine ad $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ 2 nd line: add NE	Epinephrine or dobutamine
Canada (Trilium) 2010 ⁴²	Crystalloids		Vasopressin ad to $2.4 \text{ U}\cdot\text{hr}^{-1}$ 2 nd line: dopamine $5\text{--}10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ 3 rd line: NE ad $20 \mu\text{g}\cdot\text{min}^{-1}$, epinephrine up to $20 \mu\text{g}\cdot\text{min}^{-1}$, phenylephrine ad $200 \mu\text{g}\cdot\text{min}^{-1}$	
Cuba (Nodal Arruebarrena) 2009 ⁴³	Mix 65% crystalloids-35% colloids 2 nd line: starches, gelatin		Dopamine ad $3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ 2 nd line: add noradrenaline $0.1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	Dobutamine $5\text{--}15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$
Australasia 2008 ²⁶			NE 2 nd line: vasopressin $0.5\text{--}4 \text{ U}\cdot\text{hr}^{-1}$	Limit use
Canada (Shemie) 2006 ⁴⁷			Vasopressin $2.4 \text{ U}\cdot\text{hr}^{-1}$ 2 nd line: NE, epinephrine and/or phenylephrine max $0.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	Dopamine $\leq 10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$

HES = hydroxyethyl starch; NE = norepinephrine; NS = normal saline; RL = Ringer lactate

Registry in Organ Donation and Transplantation (IRODaT) database.¹⁰ Lastly, we examined the references of each guideline included in this review. This literature search is up to date as of May 2020.¹⁰

Eligibility criteria

This review includes any document endorsed by an organ donation organization (ODO), a professional society, or a government, that aims to direct the medical management of adult, neurologically deceased, multi-organ donors, including clinical goals, therapies, diagnostics, or monitoring. This review excludes recommendations for organ donation following a circulatory determination of death, living organ donation, and paediatric organ donation. We also excluded hospital protocols and checklists, organ-specific recommendations for donor care, and review articles. Organ donor care in the ICU relies mostly on hemodynamic management and interventions that may have multi-organ effects. For this reason, we excluded organ-specific recommendations. Nevertheless, this exclusion criterion was not applied at

the search strategy level to reduce the risk of publication bias. The manual screening permitted us to confirm that organ-specific recommendations pertained to the management of recipients, which was outside the scope of this review. Table 1 presents data for all guidelines, and all other tables present data pertaining to guidelines released after the 2006 Canadian guidelines were published.

Guidelines selection

Two independent reviewers (A.J.F., and one of E.C., D.R.W., K.S., F.D.A., M.W., B.R., D.B., I.B.) screened titles and abstracts generated from the literature search using Covidence® software (Veritas Health Innovation, Melbourne, Australia),¹¹ and reviewed full text reports for all potentially relevant citations. A third independent reviewer resolved disagreements. Where more than one citation reported a guideline for one organization, the most recent version was included.

Table 4 Hormone therapies

Country (first author / subcategory) Year (reference number)	Combined hormone therapy		Additional corticosteroids specific details	Additional thyroid hormones details	Additional insulin details	Additional antidiuretic hormone analogues details
	<i>Components</i>	<i>Indications</i>				
Ireland (Conrick-Martin) 2019 ³⁵	Vasopressin Insulin Thyroid hormones Corticosteroids	Hemodynamic instability, impaired cardiac function in potential heart donor	Specific indication: Shock reversal: MP 1 g <i>iv</i> q24h	Specific indication: Hemodynamic instability: T3 4 µg <i>iv</i> then 3 µg·hr ⁻¹	Specific indication: Glycemic control: <i>iv</i> insulin for glycemia < 10 mmol·L ⁻¹	Specific indication: Hemodynamic instability: vasopressin 1 U <i>iv</i> bolus then 2.4 U·hr ⁻¹ Specific indication: Diabetes insipidus: DDAVP 1–2 µg <i>iv</i> or SC PRN or vasopressin 0.5–2.4 U·hr ⁻¹
India (Pandit) 2017 ³⁴	Vasopressin Insulin Thyroid hormones Corticosteroids	Refractory hemodynamic instability	MP 15 mg·kg ⁻¹ <i>iv</i> q24hr or 250 mg <i>iv</i> then 100 mg·hr ⁻¹	T4 20 µg bolus <i>iv</i> then 10 µg·hr ⁻¹ infusion or T4 300–400 µg PO q8h or T3 (if available)	Specific indication: Glycemic control: Insulin for glycemia 80–150 mg·dL ⁻¹	Vasopressin 0.5–4 U·hr ⁻¹ <i>iv</i> infusion Specific indication: Diabetes insipidus: DDAVP 10 µg intranasal, 1–2 puffs q4h or vasopressin 0.5–2 U·hr ⁻¹ <i>iv</i> infusion
Australia 2016 ²⁷	Unclear	Not formally recommended, consider if LVEF < 45% or heart/lung donors	MP 15 mg·kg ⁻¹ <i>iv</i> x 1	T3 <i>iv</i> 4 µg·hr ⁻¹	Specific indication: Glycemic control: Insulin for glycemia 6–10 mmol·L ⁻¹	Specific indication: Diabetes insipidus: DDAVP 1–4 µg <i>iv</i> q4–8h PRN or vasopressin 0.04–2.4 U·hr ⁻¹ <i>iv</i> infusion
Austria 2016 ³⁷			Specific indication: Persistent hypotension: hydrocortisone 200 mg <i>iv</i> then 200 mg·24 hr ⁻¹		Specific indication: Glycemic control: Insulin <i>iv</i> infusion 5 U·hr ⁻¹ and for glycemia 80–150 mg·dL ⁻¹	Specific indication: Diabetes insipidus: desmopressin <i>iv</i> 1–4 µg q6–8h
Germany 2016 ³⁸	Unclear	Hemodynamic instability	MP 15 mg·kg ⁻¹ Specific indication: All donors			Specific indication: Diabetes insipidus: DDAVP 1–4 µg <i>iv</i> PRN
Norway 2016 ⁴⁴	Unclear	Hemodynamic instability	MP 15 mg·kg ⁻¹ Specific indication: All donors			Specific indication: Diabetes insipidus: DDAVP 1–4 µg <i>iv</i> PRN

Table 4 continued

Country (first author / subcategory)Year (reference number)	Combined hormone therapy		Additional corticosteroids specific details	Additional thyroid hormones details	Additional insulin details	Additional antidiuretic hormone analogues details
	Components	Indications				
Denmark 2015 ³⁹	Unclear	Hemodynamic instability	MP 15 mg·kg ⁻¹ <i>iv</i> q24h	T3 4 µg <i>iv</i> then 3 µg·hr ⁻¹ infusion or T4 20 µg <i>iv</i> bolus, then 10 µg·hr ⁻¹ infusion or T4 2 µg·kg ⁻¹ tablets PO Specific indication: Unstable donor with LVEF < 45% Not recommended alone	Specific indication: Glycemic control: insulin for glycemia 6–10 mmol·L ⁻¹	Specific indication: Diabetes insipidus: desmopressin 1–2 µg <i>iv</i> q6h PRN or nasal spray 10–20 µg or melting tablet 60–120 µg
Europe (Eurotransplant) 2015 ²⁹					Specific indication: Glycemic control	Specific indication: Diabetes insipidus: DDAVP 2–4 µg <i>iv</i>
USA (Kotloff) 2015 ³²	Thyroid hormones Corticosteroids	LV dysfunction in potential heart donors; unmet hemodynamic goals and/or LVEF < 45% (unclear)	MP 15 mg·kg ⁻¹ , 1g or 250 mg <i>iv</i> then 100 mg·hr ⁻¹ infusion	T4 20 µg <i>iv</i> then 10 µg·hr ⁻¹ OR T3 4 µg <i>iv</i> then 3 µg·hr ⁻¹	Specific indication: Glycemic control: insulin for glycemia < 180 mg·dL ⁻¹	Specific indication: Diabetes insipidus: DDAVP 1–4 µg <i>iv</i> or vasopressin
Iran (Firoozifar) 2014 ³⁰	Unclear	Hemodynamic instability	MP 15 mg·kg ⁻¹ <i>iv</i> q12h	T4 0.6 mg per nasogastric tube x1	Insulin 1 U·hr ⁻¹ and scale adjustment to glycemia < 140	Specific indication: Diabetes insipidus: desmopressin 2–4 µg nasal
Switzerland (Haberthur) 2014 ⁴⁶	Unclear	Hemodynamic instability or cardiac failure	Hydrocortisone 50 mg <i>iv</i> q6h Specific indication: Lung donors: MP 15 mg·kg ⁻¹	T3 4 µg <i>iv</i> then 3 µg·hr ⁻¹ or T4 20 µg <i>v</i> then 10 µg·hr ⁻¹ or TSH 0.1 mg <i>iv</i>	Specific indication: Refractory hemodynamic instability: Glucose 10%-Insulin-Potassium infusion 1 mL·kg ⁻¹ Specific indication: Glycemic control: <i>iv</i> insulin for glycemia 4–8 mmol·L ⁻¹	Specific indication: Diabetes insipidus: desmopressin 0.25–2 µg <i>iv</i> q6h or vasopressin 0.5–2.0 U·hr ⁻¹
Oceania (ANZICS) 2013 ²⁵	Vasopressin Thyroid Corticosteroids	Potential heart donor with LVEF < 45%	MP 15 mg·kg ⁻¹ <i>iv</i> x1	T3 4 µg <i>iv</i> bolus then 3 µg·hr ⁻¹	Specific indication: Glycemic control	Vasopressin 0.5–4.0 U·hr ⁻¹ Specific indication: Diabetes insipidus: DDAVP 2–4 µg <i>iv</i> q2–6 h

Table 4 continued

Country (first author / subcategory) Year (reference number)	Combined hormone therapy		Additional corticosteroids specific details	Additional thyroid hormones details	Additional insulin details	Additional antidiuretic hormone analogues details
	Components	Indications				
Hungary 2013 ⁴⁰	Vasopressin Insulin Thyroid Corticosteroids	Refractory hemodynamic instability	Hydrocortisone 50 mg <i>iv</i> bolus then 50 mg x 4 doses Specific indication: All lung donors: MP 15 mg·kg ⁻¹ q24h	T3 4 µg·kg ⁻¹ <i>iv</i> bolus then 3 µg·hr ⁻¹	10 u bolus then adjust to target glycemia 4.2–8.3 mmol·L ⁻¹ Specific indication: Glycemic control: insulin sliding scale	Vasopressin 1 U bolus then 0.6–2.4 U·hr ⁻¹ Specific indication: Diabetes insipidus: desmopressin 0.6–2 µg <i>iv</i> q6–12h or nasal spray 10–20 µg q12h or vasopressin 0.01–0.04 U·min ⁻¹ <i>iv</i>
Brazil (Westphal) 2011 ^{19–21}	Unclear	All donors	MP 15 mg·kg ⁻¹	T3 4 µg <i>v</i> then 3 µg·hr ⁻¹ OR T4 20 µg <i>iv</i> then by 10 µg·hr ⁻¹ OR T4 1–2 µg·kg ⁻¹ PO	Specific indication: Glycemia control: <i>iv</i> insulin for glycemia < 180 mg·dL ⁻¹	Specific indication: Diabetes insipidus: DDAVP 1–2 µg <i>iv</i> q4h PRN to achieve and/or vasopressin 1 U <i>iv</i> then 0.5–2.4 U·hr ⁻¹
Canada (Bourret) 2010 ⁸	Vasopressin Thyroid hormones Corticosteroids	Refractory hemodynamic instability	MP 15 mg·kg ⁻¹ <i>iv</i> max 1 g q24h Specific indication: Lung donors	T4 20 µg then 10 µg·hr ⁻¹ or 100 µg then 50 µg <i>iv</i> q12h	Specific indication: Glycemic control Specific regimen: <i>iv</i> insulin scale to glycemia 4–8 mmol·L ⁻¹	Specific indication: Diabetes insipidus: DDAVP 1–4 µg <i>iv</i> then 1–2 µg <i>iv</i> q6h PRN
Chile (Rojas) 2010 ⁴¹	Vasopressin Thyroid hormones Corticosteroids	Refractory hemodynamic instability	MP <i>iv</i> 15 mg·kg ⁻¹ x1 Specific indication: Lung donors	T3 4 µg bolus than 3 µg·hr ⁻¹	Specific indication: Glycemic control: <i>iv</i> insulin for glycemia 80–150 mg·dL ⁻¹	Vasopressin 1 U bolus then 0.5–4 U·hr ⁻¹ Specific indication: Diabetes insipidus: Vasopressin 1 U <i>iv</i> then 0.5–4 U·hr ⁻¹ or DDAVP nasal/IM/SC 10–20 µg or DDAVP <i>iv</i> 0.1–0.2 mL q8–12h
Canada (Trilium) 2010 ⁴²	Vasopressin Thyroid hormones Corticosteroids	All donors hemodynamic instability	MP 15 mg·kg ⁻¹ <i>iv</i> bolus (max 1 g) q24h Specific indication: Lung donors	T4 100 µg <i>iv</i> then 50 µg <i>iv</i> q12 or 20 µg <i>iv</i> then 10 µg·hr ⁻¹	Specific indication: Glycemic control: insulin for glycemia 6–10 mmol·L ⁻¹	Vasopressin ≤ 2.4 U·hr ⁻¹ Specific indication: Diabetes insipidus: DDAVP 4 µg <i>iv</i> q6h PRN or vasopressin 0.5–2.4 U·hr ⁻¹
Cuba (Nodal Arruebarrena) 2009 ⁴³	Unclear	Refractory hemodynamic instability			Insulin <i>iv</i> 1 U·hr ⁻¹ adjust to target 120–180 mg·dL ⁻¹ Specific indication: Glycemic control	Specific indication: Diabetes insipidus: DDAVP 0.5–2 µg <i>iv</i> or nasal drops 10–20 µg or inhalation 10 µg q8–12h, or vasopressin
Australasia 2008 ²⁶	Vasopressin Thyroid hormones Corticosteroids	Refractory hemodynamic instability and/or LVEF < 45%	MP 15 mg·kg ⁻¹ <i>iv</i> x1	T3 4 µg <i>iv</i> , then 3 µg·hr ⁻¹	Glycemic control Specific regimen: Insulin for glycemia 5–8 mmol·L ⁻¹	Vasopressin 0.5–4 U·hr ⁻¹ Specific indication: Diabetes insipidus: DDAVP 2–4 µg <i>iv</i> q2–6h or vasopressin 0.5–2 U·hr ⁻¹

Table 4 continued

Country (first author / subcategory)Year (reference number)	Combined hormone therapy		Additional corticosteroids specific details	Additional thyroid hormones details	Additional insulin details	Additional antidiuretic hormone analogues details
	Components	Indications				
Canada (Shemie) 2006 ⁴⁷	Vasopressin Thyroid hormones Corticosteroids	All donors LVEF $\leq$ 40% or hemodynamic instability	MP 15 mg·kg ⁻¹ max 1 g Specific indication: Lung donors	T4 $\mu\text{g iv}$ then 10 $\mu\text{g}\cdot\text{hr}^{-1}$ or T4 100 $\mu\text{g iv}$ then 50 $\mu\text{g iv}$ q12h	Specific indication: Glycemic control: insulin for glycemia 4–8 mmol·L ⁻¹	Vasopressin $\leq$ 2.4 U·hr ⁻¹ Specific indication: Diabetes insipidus: DDAVP 1–4 $\mu\text{g iv}$ then 1–2 $\mu\text{g iv}$ q6h OR vasopressin $\leq$ 2.4 U

DDAVP = 1-desamino-8-d-arginine vasopressin; LVEF = Left ventricle ejection fraction; MP = methylprednisolone; IM = intramuscular; SC = subcutaneous; TSH = thyroid stimulating hormone; T3 = triiodothyronine; T4 = thyroxine

Quality assessments

Four reviewers independently assessed the methodological rigour of every guideline using the validated AGREE-II tool.^{12–14} AGREE-II evaluates the quality of guidelines across six domains: 1) scope and purpose, 2) stakeholder involvement, 3) rigour of development, 4) clarity of presentation, 5) applicability, and 6) editorial independence. Each domain contains specific items^{12–14} that reviewers can assess to rate the domain on a seven-point scale. In reporting the quality of guidelines, we determined the scaled domain score reported as a percentage of the maximum score, across four reviewers for each AGREE-II domain.¹⁵ As suggested by the AGREE-II manual, we created a three-point classification of “low quality” (< 40%), “moderate quality” (40–70%), and “high quality” (> 70%) and transposed the domain scores.¹⁵ We also assessed inter-rater reliability among the four reviewers using two-way random intraclass correlations (ICC), and arbitrarily defined reliability as low (ICC: 0–0.4), moderate (ICC: 0.41–0.79), and high (ICC: 0.8–1.0).¹² These analyses were performed with IBM SPSS Statistics v24.0 2018 (IBM Corp., Armonk, NY, USA).

Data extraction

A pre-tested form was used for data collection. This data collection form was designed and reviewed in collaboration with all the group investigators. The same reviewers, in duplicate, extracted descriptive information and specific donor management recommendations pertaining to six key organ donor care interventions domains: the autonomic storm, hemodynamic instability, hormone supplementation, ventilation, blood product transfusions, and general ICU care.^{16,17}

Information synthesis

We used narrative data synthesis to report guidelines recommendations with the aim of mapping the nature of recommendations as well as describing their frequency among international guidelines. Discrepancies between investigators concerning the interpretation of recommendations were discussed and resolved among the group. Because risks that are inherent to most systematic reviews were not measured, no meta-analysis was possible. We have summarized the information in tables.

This report used a systematic methodology adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).¹⁸ We apply the term “recommend” in this report without distinguishing strong from weak recommendations, since only one of the original guidelines^{19–21} clearly distinguished strong from weak using a grading approach.²²

Results

Description of guidelines

This review includes 27 clinical practice guidelines from 26 countries (Fig. 1). Guidelines were released between 1993 and 2019 (two had no release date)^{23,24} and most were reported in English.^{19–21,25–35} Ten of 27 were published in peer-reviewed journals (Table 1).^{7,8,19–21,28,30–32,34–36}

Quality of guidelines

The quality of guidelines data are presented in Fig. 2. In assessing guideline quality, the inter-rater agreement among four raters varied across domains. Raters achieved

high agreement for domains 1, 2, and 3 in the majority of guidelines. Most guidelines scored moderately well on the clarity of their scope (e.g., specific purpose, target clinicians) (domain 1),^{7,19–21,23,24,26,29,30,37–43} and the clarity of their recommendations (domain 4).^{8,19–21,27,29–31,33,35,37–40,42,44,45} Most guidelines scored low on other domains. Stakeholder involvement (domain 2) was limited: many did not appear to involve members of the public, and/or representatives from all target clinician groups.^{7,8,26,27,29,30,34,35,38–40,42,43,46} Almost all guidelines lacked an explicit and research-based approach for formulating their recommendations (domain 3).^{7,8,23–31,33–35,37–48} For example, only two guidelines mentioned a systematic search of the literature.^{19–21,39} Two guidelines, however, determined the strength of recommendations using a grading approach,^{19–22,34} and one reported the agreement between experts on specific recommendations.⁷ In terms of applicability (domain 5), all guidelines but one⁴⁷ lacked information on facilitators or barriers to their application and no monitoring or auditing criteria were described (domain 5). Finally, only three of 27 reported an approach to conflict of interest in guideline development or presentation (domain 6).^{32,34,47} Although guidelines in this review were released over a 25-year period, we subjectively did not observe a clear improvement in methodological quality in the most recent, except for the purpose and scope (domain 1).

Recommendations

Management of the autonomic storm

The autonomic storm is usually defined as an adrenergic period surrounding brain stem herniation that presents with hypertension, tachycardia, and cardiac dysfunction.^{49,50} Fourteen guidelines (14/27; 51.9%) described the importance of the autonomic storm,^{19–21,23–28,32–35,39,43,44} but less than half provided recommendations about diagnosis^{24,28,32–34,43,44} or treatment strategies.^{23,25,27,28,32–34,44,46} Seventeen guidelines (17/27; 63.0%) recommended specific medications for hypertension and tachycardia^{8,23–29,31,34,37,39,41–43,45–47}; most commonly esmolol^{24–27,34,37,39,41,43,46} and nitroprusside because of their short-acting, titratable effects.^{24–27,34,39,46} Alternatives included various classes of anti-hypertensive agents and remifentanyl. Because of the transient nature of the autonomic storm and the risk of subsequent hypotension, four guidelines recommended not treating hypertension or tachycardia in this setting, or limiting treatment to very severe cases.^{19–21,26,27,34}

Hemodynamic management after the autonomic storm

Recommended targets for mean arterial pressure ranged from 60 mmHg to 100 mmHg (Table 2).^{7,8,19–21,23–27,29–42,44,46,47} As first-line vasopressors, most documents recommended norepinephrine^{7,19–21,23,25–27,38,40,46} and/or dopamine^{19–21,23,24,28–30,32,39,41,43,45} (Table 3). Vasopressin was the preferred agent in Canadian,^{8,36,42,47} Irish,³⁵ Indian,³⁴ and UK guidelines,³³ potentially because of its additional value in the management of diabetes insipidus. Epinephrine was variably suggested as an alternative agent,^{19–21} or as a last choice of vasopressors,^{8,24,34,36,42,45,47} or it was contraindicated altogether.⁴⁰ No clear temporal effect was observed over the years on the choice of vasopressors. Nevertheless, we detected a consistent but nonpersistent recommendation on dopamine as a first-line therapy between 2014 and 2016, potentially in reaction to a trial published in 2009.⁵¹

In terms of fluid management, crystalloids were generally recommended as a first-line solution,^{8,19–21,24,26–33,35,37,38,40–42,46} and some documents recommended colloids along with crystalloids.^{7,23,24,29,39,43,45,46} Four guidelines (4/27; 14.8%) recommended intravenous starches,^{7,40,43,46} and nine (9/27; 33.3%) strongly recommended against starch therapy, particularly for donors with renal failure.^{8,24,26,27,32,34,37–39,44,46} The guidelines recommending starches were all released in 2005–2013, before or in the years surrounding general ICU and organ donor literature studies that changed practice against their use^{52–54}; two of the guidelines identified a maximal dose not to be exceeded, which was related to the risk of acute kidney injury.^{7,40} Three guidelines (3/27; 11.1%) recommended a daily negative or neutral fluid balance to facilitate lung donation.^{24,27,35}

In terms of inotropic agents, dobutamine,^{7,17–19,23,24,27,31,35,37–39,41,45,46} epinephrine,^{7,24,27,32,35,39} and dopamine^{24,31,36,38,39,47} were all recommended most commonly; other agents included isoproterenol,³⁷ levosimendan,³⁷ milrinone,³⁷ and norepinephrine.^{24,37} The inconsistent indications for each related to various clinical measures of impaired cardiac function.^{7,19–21,23,24,27,30–32,34–37,39–41,43,44,46,47} Six guidelines (6/27; 22.2%) made no recommendation on inotropic therapies.^{8,25,28,29,33,42}

Fourteen guidelines (14/27; 51.9%) recommended “usual care” for arrhythmias,^{19–21,23,25–27,32,34,38,40,41,43–46} and amiodarone was the most commonly recommended drug.^{19–21,23,25–27,34,44,46} For bradyarrhythmias, seven reports (7/27; 25.9%) recommended cardiac pacing^{19–21,23,27,40,44,46} or beta-agonist agents,^{19–21,23,27,34,38,40,44,46} citing the lack of effect of

atropine^{19–21,25,27,34,40,44–46} or glycopyrrolate²⁷ after brain death. Seven guidelines (7/27; 25.9%) addressed cardiac arrest among deceased donors, and recommended routine cardiopulmonary resuscitation.^{19–21,23,25,39,41,45,46}

In terms of monitoring, most guidelines recommended central venous pressure (CVP) monitoring, with target ranges from 4 to 15 mmHg.^{8,23,24,27,29–31,33–38^{40–44,46,47}} Guidelines frequently recommended echocardiography to guide hemodynamic therapy,^{7,8,19–21,23,24,27–39,42,46,47} with minimum targets of left ventricular ejection fraction ranging from 40% to 50%.^{8,19–21,24,34,35,38,39,42,46} In addition, 19 documents (19/27; 70.3%) stated various indications for pulmonary artery catheterization, including young donors,⁴¹ potential heart or lung donors,^{24,30} donors with heart dysfunction or pulmonary hypertension,^{17–19,21,31,35,42,46,47} or for all refractory unstable donors.^{8,23,24,34,37,38,42,44,45,47}

Hormone therapy

Every guideline addressed hormone supplementation (Table 4). Nineteen (19/27; 70.4%) recommended corticosteroid therapy.^{7,8,19–21,24–27,30,32,34,35,39–44,46,47,49} Four (4/27; 14.8%) recommended steroids for all donors^{32,38,39,44}; three (3/27; 11.1%) recommended steroids for hemodynamically unstable donors,^{23,35,37} and others recommended steroids only if there was the potential for donation of the lungs,^{8,23,24,27,40–42,46,47} heart,²⁷ or liver.⁴⁶ The most common dosing strategy was high-dose methylprednisolone.^{8,19–21,23–27,30,32,34,35,37–42,44,46,47} The recommendation of high-dose corticosteroids was consistent over time and did not seem to be affected by the publication of two systematic reviews questioning their use.^{48,55}

Eighteen guidelines (18/27; 66.7%) recommended thyroid hormone supplementation.^{7,8,19–21,24–27,30,32,34,35,39–43,46,47}

Indications included all donors³⁴ or those with hemodynamic instability.^{27,31,35,39,46} Suggested agents included triiodothyronine (T3; six guidelines),^{25–27,39–41} thyroxine (T4; four guidelines),^{8,30,42,47} or either (six guidelines).^{19–21,24,32,34,38,46} Three guidelines (3/27; 11.1%) did not recommend routine thyroid supplementation based on the lack of supporting evidence.^{23,28,45} Two of them^{26,45} were published before a systematic review showing the lack of evidence for the use of thyroid hormone supplementation⁵⁶; the publication date of the third guideline is unknown.²⁴

Nine guidelines (9/27; 33.3%) addressed insulin therapy for organ donors.^{24,27,30,34,35,39,40,43} Some recommended insulin for all donors,^{30,40,43} potentially for its possible inotropic effect, while others recommended insulin as needed for glycemic control, similarly to ICU general care

practice.^{8,19–21,23,25–27,29,31–35,37–42,46,47} For the latter, dosing ranges and glycemic targets varied. One guideline recommended a mixed infusion of glucose, insulin, and potassium (GIK) for donors with refractory hemodynamic instability.⁴⁶

Vasopressin was suggested as a component of a hormone therapy bundle in 13 guidelines (13/27; 48.1%),^{7,8,24–26,34,35,39–43,47} in doses ranging from 0.4 to 5 U·hr⁻¹.^{19–21,23–27,33,34,40–42,47} Desmopressin, a synthetic analogue of vasopressin that lacks the vasopressor properties, was recommended as first-line therapy for diabetes insipidus in 23 guidelines (23/27; 85.2%), with or without combined vasopressin infusion.^{7,8,19–21,23–27,30–32,34,35,37–40,42–47}

Lung protective mechanical ventilation

All but three (24/27; 88.8%)^{25,26,28} reports provided recommendations on ventilation parameters and/or arterial blood gas targets (Table 5). Recommended tidal volume ranges were from 4–12 mL·kg⁻¹.^{8,19–21,24,27,29–31,35,38–42,46,47} Eleven guidelines (11/27; 40.7%) recommended low tidal volumes (4–8 mL·kg⁻¹) for all donors,^{8,19–21,27,29,35,38,40–42,44,46} and four (4/27; 14.8%) specifically for lung donors.^{19–21,23,24,39}

Almost all guidelines that recommended lung protective strategy in donors^{19–21,27,29,30,35,39,40,44,46} were released after the publication of a lung protective strategy trial in lung donors.⁵ Earlier, a trial on lung protective strategy in general ICU ARDS patients⁵⁷ might also have influenced the recommendations of previous guidelines.^{8,29,41,42,47}

Recommendations on maximal peak airway pressures ranged from 30 cmH₂O to 47 cmH₂O,^{8,29–31,36,38,40–43,46,47} maximal plateau airway pressures ranged from 30 to 35 cmH₂O,^{19–21,23,24,27,31,35,38,46} and eight guidelines (8/27; 29.6%) made recommendations about recruitment maneuvers.^{7,8,19–21,23,24,27,31,32,35,38,42,47} Only the Brazilian guideline recommended advanced ventilation strategies in cases of respiratory failure.^{19–21}

Blood product transfusions

All but one guideline²⁵ made recommendations about blood product transfusion. Hemoglobin transfusion thresholds varied from 70 to 100 g·L⁻¹.^{7,8,19–21,23,24,26,27,29,30,32–34,37,42–47} and some guidelines provided hematocrit thresholds, which ranged from 20% to 30%.^{24,28–31,34,38,40,41,44–46} Only a few guidelines distinguished stable from unstable donors in making these recommendations.^{19–21,23,27}

Recommendations for platelet and coagulation factor transfusions appeared in nine guidelines (9/27;

33.3%).^{7,19–21,24,27,31,38,40,41,43,46} Threshold platelet levels varied from 20 to 150 x 10⁹g·L⁻¹.^{7,19–21,24,27,31,40,41,46} Recommendations for plasma or fibrinogen transfusions were inconsistent; some required active bleeding,^{8,19–21,29,35,42,43,47} while others required only coagulopathy.^{8,19–21,23–25,27,31,33,34,38,41,43} Fibrinolytic therapy (with tranexamic acid, aprotinin, or aminocaproic acid) was recommended in one guideline⁴⁶ and not recommended in another because of potential thrombosis risk.³³

General ICU care

Twenty-three reports (23/27; 85.2%) addressed body temperature, with recommended ranges falling between 35 and 38°C.^{7,8,19–21,23,26,27,29–31,34,35,37–43,46} Recommendations for the management of hyperthermia included antibiotics,^{27,31,39,42} antipyretics (acetaminophen),^{27,31,39} and external cooling.^{27,28,31,39,42} Recommendations for preventing or treating hypothermia included various warming strategies.^{8,19–21,23,25,26,29–31,33–35,37,38,40–46} No guideline, including those released after the 2015 study suggesting protective results of mild hypothermia on recipients renal outcomes,⁴ clearly recommended its use.

Most guidelines recommended continuation of previously initiated enteral^{8,19–21,25,32,34,35,39,42,46,47} or parenteral nutrition,^{8,32,35,42,46,47} and five guidelines (5/27; 18.5%) suggested initiating enteral nutrition.^{8,19–21,35,42,47} One guideline recommended discontinuation of all nutritional support in potential donors, but did not explain why.⁴⁴

Three reports (3/27; 11.1%) addressed stress ulcer prophylaxis,^{31,39,40} one recommending daily intravenous pantoprazole.³¹ Mechanical and/or pharmacological thromboprophylaxis was recommended by two guidelines (2/27; 7.4%).^{27,35} Eight guidelines (8/27; 29.6%) suggested antimicrobial prophylaxis, including eight different agents or classes.^{7,22,24,28,29,32,39,44} Six other guidelines (6/27; 22.2%) strongly recommended against routine antimicrobial prophylaxis.^{27,34,43,46,47}

Discussion

This systematic review uniquely summarizes 27 guidelines for the management of neurologically deceased organ donors. The results summarize the most recent versions of clinical practice guidelines endorsed by organ donation organizations, medical societies, and governments around the world, whether published in peer-reviewed sources or not. A vast majority originated from Europe, North America, and Australia. Striking observations from this

review include the inconsistency of recommendations across guidelines, the low uptake of evidence-based literature, the lack of systematic updating processes, and most importantly, the absence of rigorous methodology. With a paucity of clinical research in this field, and particularly randomized trials,^{4,5,51} medical guidelines tend to emphasize physiologic reasoning and expert opinion,^{58,59} an approach that lends itself to subjectivity and selective reporting.^{58,60}

With the assessment of potential benefits and risks, guidelines are first meant to help clinicians choose the best options for their patients.⁶¹ Secondly, guidelines help to nuance certainty around clinical decisions by incorporating an evaluation of the quality of the evidence.^{22,62} Our systematic review clearly showed that because of their poor methodology, the available guidelines for the care of organ donors around the world fail to achieve both these goals. First, to choose the best option for a donor, bedside clinicians need to evaluate the whole body of literature in a glimpse, and to summarize the effect of interventions, a heavy task that guidelines can facilitate. Nevertheless, the vast majority of available guidelines on organ donor care do not base their recommendations on systematic reviews of the literature, so do not draw a clear picture of available options and their impact. As a consequence of an arbitrary selection of the evidence, recommendations vary largely around the world, and sometimes fail to integrate the most recent trials. As an example, actual best evidence supports the use of moderate hypothermia in donors to improve kidney recipient outcomes.⁴ Nevertheless, none of the guidelines released after this randomized-controlled study was published incorporated this information in their recommendations. Whether the study was not identified, its results were deliberately ignored, or its results were judged as irrelevant or biased is unknown. The counter-example is the immediate adoption of the lung protective ventilation strategy emanating from an underpowered randomized-controlled trial by the majority of guidelines.⁵

Conversely, interventions such as corticosteroid supplementation are widely recommended in the guidelines, although not supported by published literature.⁵⁵ In this situation, actual guidelines fail to indicate to clinicians the level of certainty surrounding the recommendation, and do not acknowledge potential theoretical but unstudied risks related to corticosteroids (e.g., hyperglycemia or infection in donors). We believe that not grading the evidence and not evaluating the internal and external validity of studies supporting the recommendations could lead to overconfidence in futile interventions, to variability in practices, and to misses in research opportunities.⁶³

The quality of guidelines in the organ donation field can be improved through a systematic validated methodology

along with a grading of the evidence. In a recent joint effort of the *Society of Critical Care Medicine*, the *American College of Chest Physicians*, and the *American Association of Organ Procurement Organizations* to produce evidence-based guidelines for deceased donor care, authors reasoned that because “...the available literature was overwhelmingly composed of observational studies and case series, ... a decision was made that the document would assume the form of a consensus statement rather than a formally graded guideline.”³² Following the present systematic review, where we observed inconsistent recommendations and persistent lack of rigorous methodology over more than 20 years, our group supported the need for an evidence-based Canadian guideline for the management of organ donors. To fulfill its mandate, the group for the Canadian guidelines for the management of organ donors conducted systematic reviews of the literature on every pre-identified PICO (patient, intervention, comparator, outcome) question.⁹ When possible, estimates were pooled and calculated, and recommendations were based on the known benefit or harm. The group who developed the Canadian guidelines for the management of organ donors accompanied every recommendation with its level of certainty, as recommended by GRADE methodology.^{9,22}

In clinical fields such as cardiology and oncology, adherence to guidelines has shown a potential to improve clinical decision processes and clinical outcomes.^{64–66} Guideline adherence in organ donation was not extensively studied, but was reported as low to moderate.⁶⁷ Given our observations, we believe that asking if inconsistent recommendations and poor methodological quality of guidelines have an influenced adherence is a legitimate question. Now that the Canadian guidelines for the management of organ donors are published, research groups should evaluate their acceptance and compliance by clinicians. Then, studies can evaluate the direct impact of guidelines on donors and recipients’ outcomes. Well conducted guidelines should also encourage and trigger randomized studies in nested areas, studies that would then systematically be incorporated in future guidelines through a standardized audit and update mechanism. Although we should be careful not to fall into self-fulfilling prophecy, we believe that, informed by this systematic review, the Canadian guidelines for the care of organ donors have succeeded in their mission.

We have to acknowledge a few limitations to our work. First, we did not evaluate if each guideline’s recommendation was scientifically sound or clinically appropriate; an assessment of the content validity of current guideline individual recommendations was beyond the scope of this review. It is also possible that individual hospitals have developed their own documents to supplant the relatively older guidelines included in this

review. In addition, although we thoroughly searched for the international guidelines, some areas of the globe where organ donor care could take place are underrepresented (Asia, Africa). Finally, although the AGREE-II is the most frequently recommended validated tool to evaluate the quality of reporting for guidelines, we could not overcome its intrinsic limitations.^{12–14}

The strengths of this review include the broad search for relevant guidelines, the systematic assessment of guideline quality using a validated instrument, and duplicate independent data abstraction. To date, this is the only systematic review of guidelines for organ donation, and the findings highlight important opportunities to advance deceased donor care through improved guideline methodology that will incorporate emerging high-quality research.

Conclusion

This systematic review highlighted that existing guidelines for the management of organ donors suffer from inconsistent recommendations and poor methodological quality. It achieved its goal in informing and supporting the Canadian guidelines for the management of organ donors. In this new age of randomized trials in deceased donor care, we can look forward to more frequent guideline updates, stronger recommendations, and stronger justification for the standardization of care. An agenda establishing priorities for research could lead to the development of high-quality guidelines to improve transplant outcomes, as shown in other fields of healthcare.^{68–70}

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