Medication Management of Patients in the Organ Recovery Center (ORC)

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Objectives

Pharmacists	Technicians
• Identify classes of medications that play a vital role in the management of patients post brain-death until time of organ procurement • Recognize the differences in therapeutic recommendations between living and post brain-death patients • Discuss which physiologic complications are of concern between brain-death and organ procurement	• Discuss the purpose and need for an organ recovery center • Identify common medications that should be available to personnel in an organ recovery center • Recognize medications that may require compounding and would not be stocked in an organ recovery center

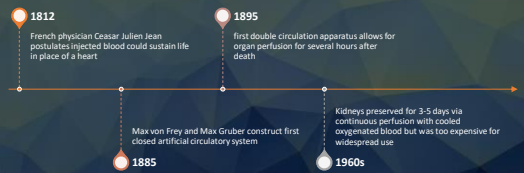
Background

- 12,587 deceased donors provided at least 1 organ for transplant
- 33,309 of 39,719 donated organs for transplant came from deceased donors
- Living donor transplants decreased by 22.6% during the COVID-19 pandemic
- Piedmont Atlanta Hospital's ORC opened in April 2021
- Includes 2 operating rooms and 6 ICU bays

Background

- United Network for Organ Sharing (UNOS) organ transplant timeframes
- Can temporarily maintain organ perfusion in patients after neurological death
- Final stages of brain death characterized by:
  - Total loss of sympathetic tone and circulating catecholamines
  - Profound vasodilation leading to hypotension and hemodynamic instability
  - Sepsis resulting in inflammation, capillary leakage, metabolic acidosis, and pulmonary edema
- Pharmacological management required

History of Organ Preservation



History of Organ Preservation

- 1969 – Static cold storage (SCS)
  - Gold standard
  - Flushing organ with preservation solution at 0-4C and immersing in same solution until time of transplantation
  - Success with kidneys, heart, liver, and lungs
- Future – *ex vivo* machine perfusion
  - Supply oxygen and nutrients
  - Prevent ischemia and reperfusion injury
  - Keep physiological metabolism

Post-brain Death Organ Donors

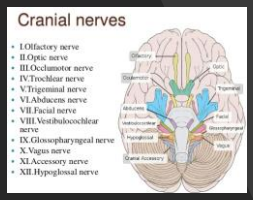
- SCS limited to 4-36 hours depending on organ
- Body can be maintained and perfused for hours to days
- Decreased risk of ischemic injury to organs
- Associated with improved graft function post transplant

Diagnosis of Brain Death

- Irreversible loss of all functions of the brain including brain stem
- 3 essential findings per American Association of Neurology (AAN)
  - Coma
  - Absence of brainstem reflexes
  - Apnea
- Observe patient for 6+ hours after exam for clinical manifestations inconsistent with brain death
- Repeat brainstem reflex exam
- Confirmatory imaging not required but can be used to verify
  - Exception: patients with skull/cervical injuries preventing accurate physical assessment

Assessment of Brainstem Reflexes

- Pupils – Cranial nerves II and III
  - No response to bright light
- Ocular movement – Cranial nerves III, VI, and VIII
  - No oculocephalic reflex
  - No deviation of eyes to irrigation in each ear with 50mL cold water



Assessment of Brainstem Reflexes

- Facial sensation and facial motor response – Cranial nerves V, VII, and IX
  - No corneal reflex
  - No jaw reflex
  - No grimacing to deep pressure on nail bed, supraorbital ridge, or temporo-mandibular joint
- Pharyngeal and tracheal reflexes – Cranial nerves IX and X
  - No response after stimulation of posterior pharynx
  - No cough response to tracheobronchial suctioning

Monitoring

- Temperature
- Blood pressure
- Heart Rate
- Rhythm
- Pulse O2 Saturation
- Urine output

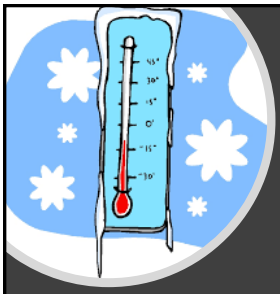
- Arterial line
- Central venous catheter
- Pulmonary arterial catheter
- Renal Function
- Electrolytes
- Acid-base status
- Lactate

Cushing's Reflex

- Medullary ischemia associated with brain death results in reflex hypertension and bradycardia
- Intracranial pressure rises and compresses arterioles cerebellum
- Activation of SNS
  - α1 receptor agonism causes vasoconstriction
  - Body's attempt to rescue blood flow for redirection to the brain
- Increased ICP distorts vagus nerve and results in bradycardia
- Net result = ischemia and organ damage

Autonomic Storm

- SNS stimulation from Cushing's reflex can increase catecholamine levels by up to 1000x baseline
- Median duration = 48 hours after brain death
- End results
  - Ischemia
  - Depletion of endogenous catecholamines
  - Profound hypertension followed by profuse hypotension



Core temperature

- Profuse hypotension leads to decrease in core temperature
- Hypothermia occurs in 100% of patients post brain death
- Goal to maintain = 35-37˚C
- Strategies
  - Increased ambient temperature
  - Injection and circulation of warm intravenous fluids
  - Circulate hot air blankets

Anti-Hypertensives

- Short acting agents used to correct elevated blood pressure during autonomic storm immediately following neurologic death
  - Esmolol 100-500 µg/kg bolus followed by infusion of 150 µg/kg/min
  - Other agents: nicardipine
- Late-stage neurologic death hypotension management
  - Goal is to avoid end organ damage and ischemia
  - MAP goal > 60 mmHg
  - Urine output 1-3 mL/kg/hr
  - Cardiac index > 2.4 L/min

Concern for hypotension

- Ischemia of spinal cord results in loss of function of thoracic sympathetic chain
- Reduce in cardiac afterload leads to reduced aortic pressure
- Reduced aortic pressure associated with decreased perfusion of ALL organs
- Other contributing factors:
  - Hyperglycemia-induced osmotic diuresis
  - Central diabetes insipidus
  - Adrenal insufficiency

Fluids/Blood Products

- Volume deficits
  - Replace with 1-2L bolus of NS
  - Maintenance options: D5W, NS, or ½NS at 30-50 mL/hr based on serum electrolyte and glucose needs
- Colloids may be added to prevent tissue edema
  - 5% albumin 12.5-25g as needed
- Packed Red Blood Cells
  - Goal hematocrit > 30% to maintain adequate oxygen delivery

Vasopressors/Inotropic Support

Agent	Starting Dose	Target Receptors	Monitoring Required	Place in Therapy
Dopamine	3–10 μg/kg/min	3–5 μg/kg/min: dopamine 5–10 μg/kg/min: β_1 10–20 μg/kg/min: α_1	Heart rate, blood pressure, electrocardiogram, renal function	Typically first line
Epinephrine	0.05–0.5 μg/kg/min	β_1, β_2, α_1	Heart rate, blood pressure	Second line
Norepinephrine	0.1–2 μg/kg/min	β_1, α_1	Heart rate, blood pressure	Second line
Phenylephrine	0.1–1 μg/kg/min	α_1	Heart rate, blood pressure	Avoid as sole agent due to potent α-adrenergic effects
Isoproterenol	2–10 μg/min	β_1, β_2	Heart rate, blood pressure, electrocardiogram, respiratory rate, serum glucose, potassium, magnesium	May be used for bradyarrhythmia due to vagus nerve disruption in brainstem (typically not responsive to atropine)
Vasopressin	0.03 units/min	V_1	Heart rate, blood pressure, serum and urine sodium, fluid input and output	First line; may allow for dose de-escalation of other vasopressors

- Dopamine associated with beneficial outcomes in organ recipients
- RCT showed reduced need for dialysis in renal transplant patients whose donors underwent dopamine pretreatment
- Excessive alpha-adrenergic stimulation associated with pulmonary edema

Electrolytes

Electrolyte	Goal Concentration	Serum Concentration Before Replacement Therapy	Dose to Administer	Maximum Rate of Administration
Sodium	135–150 meq/dL	Serum osmolality and volume status should be assessed before initiating replacement therapy	…[a]	…[a]
Potassium[c]	4–6 meq/L	2.5–3.4 meq/L <2.5 meq/L	20–40 meq i.v. 40–80 meq i.v.	40 meq/hr
Magnesium[c]	1.7–2.3 mg/dL	1–1.9 mg/dL <1 mg/dL	Magnesium sulfate 1–4 g Magnesium sulfate 4–8 g	Magnesium sulfate 1 g/hr
Calcium (ionized)	>1.1 mmol/L	<0.9 mmol/L	Calcium gluconate 3 g or calcium chloride 1 g	May be given over 10 min if symptomatic (tetany, CNS and cardiovascular symptoms)
Phosphorus[c]	3–4.5 mg/dL	2.3–2.7 mg/dL 1.9–2.2 mg/dL <1.5 mg/dL	0.08–0.16 mmol/kg 0.16–0.32 mmol/kg 0.32–0.64 mmol/kg	Phosphate 7 mmol/hr

[a]Management of sodium disorders is complex and beyond the scope of this article. CNS = central nervous system.
[b]Patients with renal insufficiency should receive 50% of the normal dose.
[c]Replacement dose based on phosphate component. May be given as sodium phosphate or potassium phosphate.

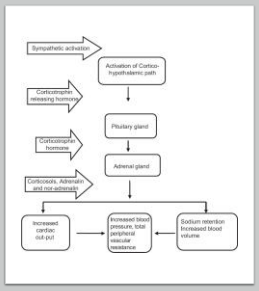
- Body enters hyperglycemic state after brain death
- Creates hyperosmolar state shifting electrolytes
- Electrolyte imbalance associated with graft loss after transplant

Oxygenation/Ventilation

- Maintain tissue oxygenation
- Protect lungs for transplantation
- Nebulized albuterol
  - 1 randomized trial of albuterol 5 mg q4h vs. saline
  - No statistical benefit in decreasing pulmonary edema or improved alveolar function in donor recipients
  - Only use in organ donors with approved indication for bronchodilation
- Low Tidal Volume Ventilation settings
  - Tidal Volume = 6-8 mL/kg ideal body weight
  - RR = 8-16 breaths per min
  - PEEP = 5-10 cm H2O
  - Initial FiO2 = 100%

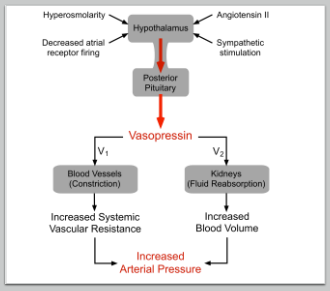
Hormone Replacement

- Used when volume replacement and vasopressors fail to achieve hemodynamic stability
- Hypothalamic-pituitary-adrenal axis fails with neurologic death
- Result of decreased blood supply following Cushing's reflex and autonomic storm
- Estimated 50% drop in thyroid hormones within 24 hours after brain death
- Levothyroxine
  - 20 μg bolus followed by 10 μg/hr continuous infusion
- Other hormones: corticosteroids, triiodothyronine



Central diabetes insipidus

- Lack of vasopressin release due to damage or loss of function to pituitary gland
- Lack of vasopressin synthesis due to failure of production in the hypothalamus
- Observed in >90% of brain-dead donors
- Desmopressin
  - 0.5-2 μg/hr every 2-3 hours to achieve 1-3 mL/kg/hr UOP



Glycemic Control

- Target blood glucose 120-180 mg/dL
- Hyperglycemia can result in further osmotic diuresis
- Create electrolyte imbalances
- Recommend using continuous insulin infusion

Impact of bacteremia

- Active infections in donors associated with adverse outcomes in donor recipients
- Estimated 5% of organ donors bacteremic at time of procurement
- Gram-negative bacilli associated with higher risk of transmission and worse outcomes relative to gram-positives
  - Between 60-80% mortality in recipients if untreated
- Bacteremia of donor did not increase risk of recipient when properly managed

Anti-infective Agents

- Blood and urine cultures should be collected from all potential donors
- Recommended screening: HIV, Hepatitis, EBV, CMV, syphilis, sputum gram stain (lung donor)
- Infected donors to receive minimum 24-48 hours of antimicrobial therapy
- Recommended abx: broad-spectrum
  - Vancomycin, piperacillin-tazobactam, Cefepime, and/or Meropenem
- Not recommended if no infection present at time of death
- Prophylactic cefazolin at time of organ procurement

Anticoagulation

- High risk for thrombosis
- Thrombosis associated with graft failure/dysfunction
- IV heparin recommended before aortic cross-clamping
  - 30,000-40,000 unit bolus recommended
- Heparin Induced Thrombocytopenia (HIT)
  - Argatroban 200 mg over 15 minutes before cross-clamping
  - Limited data from two case studies

Paralytics

- Brain dead patients may still exhibit spinal cord reflexes
- Titrate to goal 2 twitches
- Peripheral nerve stimulation monitoring via ulnar, facial or post tibial nerve
- No specific agent recommended

Variable	Pancuronium	Vecuronium	Rocuronium	Atracurium	Cisatracurium
Loading dose[a]	0.08 mg/kg	0.1 mg/kg	0.6 mg/kg[b]	0.4 mg/kg	0.1 mg/kg
Maintenance dose	0.02–0.04 mg/kg/hr	0.02–0.04 mg/kg/hr	0.01–0.012 mg/kg/min	0.4 mg/kg/hr	2–10 µg/kg/min
Prolonged elimination in renal failure	Yes	Yes	Yes	No	No
Onset of action	2–3 min	3–5 min	1–2 min	2–3 min	2–3 min
Half-life	110 min	65–75 min	66–144 min	20 min	22–29 min
Prolonged elimination in hepatic failure	Yes	Yes	Yes	No	No
Adverse reactions	Tachycardia, hypotension	Bradycardia, flushing	Tachycardia, hypertension	Histamine release, flushing	Bradycardia, hypotension

Outcomes

- Deceased donor organs still associated with increased risk of poor allograft function
- Gap has closed with medical management of decreased donors
  - Single-center retrospective review of 320 patients
    - Kidney 1-year allograft survival rate: 91 vs. 87%
    - 5-year: 86 vs. 82%
- Liver deceased vs. living donor comparison inconclusive

Summary

- Increased demand for deceased donor organs
- Physiologic changes after neurological death requires medication management to preserve organs
- Pharmacological intervention associated with improved outcomes in transplant patients

Questions?

References

- *Organ Procurement and Transplantation Network*. OPTN. (n.d.). Retrieved October 29, 2021, from https://optn.transplant.hrsa.gov/news/annual-record-trend-continues-for-deceased-organ-donation-deceased-donor-transplants/.
- *What is the time frame for transplanting organs?* Donor Alliance. (2021, August 26). Retrieved October 28, 2021, from https://www.donoralliance.org/newsroom/donation-essentials/what-is-the-time-frame-for-transplanting-organs/.
- Jing, L., Yao, L., Zhao, M., Peng, L.-ping, & Liu, M. (2018). Organ preservation: From the past to the future. *Acta Pharmacologica Sinica*, *39*(5), 845–857. https://doi.org/10.1038/aps.2017.182
- Aan clinician summary. (2015). *CONTINUUM: Lifelong Learning in Neurology*, *21*, 1461–1462. https://doi.org/10.1212/con.0000000000000228
- Korte, C., Garber, J. L., Descourouez, J. L., Richards, K. R., & Hardinger, K. (2016). Pharmacists' Guide to the management of organ donors after Brain Death. *American Journal of Health-System Pharmacy*, *73*(22), 1829–1839. https://doi.org/10.2146/ajhp150956
- Rosendale, J. D., Chabalewski, F. L., McBride, M. A., Garrity, E. R., Rosengard, B. R., Delmonico, F. L., & Kauffman, H. M. (2002). Increased transplanted organs from the use of a standardized Donor Management Protocol. *American Journal of Transplantation*, *2*(8), 761–768. https://doi.org/10.1034/j.1600-6143.2002.20810.x
- de Vries, D. K., Wijermars, L. G., Reinders, M. E., Lindeman, J. H., & Schaapherder, A. F. (2013). Donor pre-treatment in clinical kidney transplantation: A critical appraisal. *Clinical Transplantation*, *27*(6), 799–808. https://doi.org/10.1111/ctr.12261
- Kaczmarek, I. (2013). Norepinephrine versus dopamine pretreatment of potential heart donors – impact on long-term outcome. *Annals of Transplantation*, *18*, 320–326. https://doi.org/10.12659/aot.883960
- McKeown, D. W., Bonser, R. S., & Kellum, J. A. (2012). Management of the heartbeating brain-dead organ donor. *British Journal of Anaesthesia*, *108*, i96–i107. https://doi.org/10.1093/bja/aer351
- Bajwa, S. J. S., & Haldar, R. (2014). Brain death in ICU patients: Clinical significance of endocrine changes. *Indian Journal of Endocrinology and Metabolism*, *18*(2), 229. https://doi.org/10.4103/2230-8210.129118
- Singh, N. (2002). Impact of donor bacteremia on outcome in organ transplant recipients. *Liver Transplantation*, *8*(10), 975–976. https://doi.org/10.1053/jlts.2002.0080975
- Victims of cardiac arrest occurring outside the hospital: a source of transplantable kidneys. Sanchez-Fructuoso AI, Marques M, Prats D, Conesa J, Calvo N, Perez-Contin MJ, Blazquez J, Fernandez C, Corral E, Del Rio F, Nunez JR, Barrientos A. Ann Intern Med. 2006; 145(3):157.