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Brain Death Determination for Adult and Pediatric Patients

1. Policy Statement:

Criteria for Brain Death Declaration for both Adult and Pediatric patients.

2. Who Should Read This Policy?

Erlanger Health (EH) personnel, both Adult and Pediatrics, Medical Staff and Allied Health Professional Staff

3. Purpose:

Criteria for brain death/death by neurologic criteria in adult; Criteria for brain death/death by neurologic criteria in pediatric patients

4. Definitions:

Whereas, the State of Tennessee has adopted the Uniform Determination of Death Act, which is as follows:

An individual is dead who has sustained either:

I. Permanent cessation of circulatory and respiratory function, or

II. Permanent cessation of all functions of the entire brain, including the brain stem.

5. The Policy:

I. **GENERAL PROCEDURE**

1. When the criteria are met and agreed upon by required physicians, the Brain Death Examination documentation MUST be completed by one attending physician. A second attending physician to confirm is recommended if any question regarding diagnosis remains after required testing or per family request.
2. Brain death declaration is the formal pronouncement of death and the time documented for this declaration is the time of patient death to be used for all legal matters, including

the death certificate issued by the hospital.

3. The pronouncement of death is, by law, a medical act. Therefore, consent is not required, nor can it be requested from the patient's next-of-kin. However, the patient's family must be given full information concerning the brain death determination process by the attending physician or designee, prior to and at all stages during the process.
4. In cases where the Medical Examiner has jurisdiction, the Medical Examiner's permission is not required for the brain death determination process or termination of medical therapy. However, in all such cases where the Medical Examiner has jurisdiction, the Medical Examiner's office shall be immediately notified of the death and the Medical Examiner must be informed before removal of organs.
5. When organs are to be removed from brain dead patients, a declaration of brain death/ death by neurologic criteria (BD/DNC) must be made prior to their removal. Removal of organs must be authorized by the next-of-kin unless the deceased patient had executed a valid organ donation authorization during his/her lifetime. Supportive measures will be continued until the organs have been removed.
6. All hospital rules, policies and procedures concerning matters relevant to any deceased patient (i.e., permission for autopsy, Medical Examiner's jurisdiction, etc.) apply equally to brain dead patients after a declaration of BD/DNC has been made, and all medical therapy or supportive devices have been discontinued.
7. Do not perform BD/DNC evaluation if there is any evidence of consciousness, preservation of any brainstem reflex, motor movement mediated by the brain/brainstem or spontaneous breathing.
8. Conduct further diagnostic testing and do not evaluate for BD/DNC if a patient is comatose, is apneic, or has no brainstem reflexes BUT there is no identified mechanism of brain injury known to lead to BD/DNC.
9. Pregnancy is not a contraindication for BD/DNC examination.

II. **Adult Procedure - For Patients 18 years and older**

I. Criteria for Brain Death

A. Prerequisites

1. Establish that brain injury is present, catastrophic and permanent.
2. Clinical or neuro-imaging (NI) consistent with mechanism and severity of brain injury.
    a. Patient with primary posterior fossa injury: ensure NI shows evidence of supratentorial injury
3. Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base or endocrine disturbance).
4. Exclude pharmacologic paralysis: use train-of-four stimulator or demonstration of deep tendon reflex (DTR).
5. Exclude intoxication by substances that depress CNS. No drug intoxicatin or poisoning. Specific testing should be performed as clinically indicated and recommended by the AAN.

6. Core temperature >36°C (96.8°F).
    a. wait 24 hours after rewarming to 36°C (96.8°F) for patients with core temperature </=35.5°C
7. Absence of hypotension
    a. Blood pressure ≥100mm Hg systolic AND MAP ≥75mm Hg
    b. Target sBP and MAP close to patients baseline for patients whose baseline BP varies significantly from their age based normal

B. The period of observation required to confirm the diagnosis of BD/DNC will vary according to specific clinical circumstances.
    i. Patients with hypoxic ischemic injury observe 24hr before BD/DNC evaluation
    ii. All other injuries including after medical or surgical intervention to treat increased ICP shall be observed for a sufficient amount of time based on pathophysiology of brain injury

C. Neurological Criteria: The three cardinal findings in brain death are coma or unresponsiveness, absence of brain stem reflexes and apnea.
1. Evaluate for unresponsiveness to visual/auditory/tactile stimulation, and lack of motor response to pain in all extremities (nail-bed pressure and supraorbital pressure). Eye opening or eye movement to noxious stimuli is absent. True decerebrate or decorticate posturing or seizures *are inconsistent* with the diagnosis of death.
2. Absence of brainstem reflexes:
    i. Pupils
        1. Absence of papillary response to bright light documented in both eyes.
        2. Size: mid-position (4 mm) to dilated (9 mm)
    ii. Ocular movement (Absence of)
        1. No oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent). - Dolls head phenomenon – if the head is briskly rotated horizontally and vertically, there shall be no movement of the eyes relative to head movement (toward the opposite side). BD/DNC can still be performed without this component in cases of injury
        2. No Oculovestibular reflex - No deviation of the eyes to irrigation in each ear with 50ml of **cold** water (allow 1 minute after injection and at least 5 minutes between testing on each side).
        3. No corneal reflex – Absent of corneal reflex when touching the corneal with a piece of tissue

paper, cotton swab, or squirts of water. No eyelid movement should be seen.

4. Absence of facial muscle movement to noxious stimulus. No grimacing or facial muscle movement when deep pressure applied to supraorbital ridge, or deep pressure on the condyles at the level of the temporomandibular joint with no jaw reflex.
5. Absence of the pharyngeal and tracheal reflexes.
    - No pharyngeal or gag reflex after stimulation of the posterior pharynx with tongue blade or suction device (no gag).
    - No cough response to insertion of catheter into trachea, advanced to level of carina, followed by 1 or 2 suctioning passes.

iii. Apnea

1. The Attending physician, and/or their designated physician, who is competent in the application of apnea testing and brain death criteria must be present during the apnea test.
2. Absence of a breathing drive. CO_2 challenge documenting a increase in $PaCO_2$ (above normal levels). Prerequisites for test:
    - Normotension - Systolic blood pressure ≥100 mm Hg and MAP ≥ 75mm Hg
    - Normothermia- Core temperature >36 or 96.8^{oF}
    - Euvolemia - An option is a positive fluid balance in the previous six (6) hours
    - Eucapnia ($PaCO_2$ 35 – 45 mm Hg)
    - Normal pH 7.35-7.45
    - Absence of hypoxia
    - No prior evidence of CO_2 retention (i.e., Chronic Obstructive Pulmonary Disease, Severe Obesity)
3. Adjust vasopressors to a systolic blood pressure ≥100 mm Hg and MAP ≥ 75 mm Hg.
4. Perform Apnea Test

- Have a respiratory therapist at bedside to assist with apnea test.
- Pre-oxygenation for at least 10 minutes with 100% oxygen to obtain arterial PO_2>200 mm Hg.
- Adjust ventilator settings to get eucapnia. Get baseline ABG. (Reduce down to at least 10 breaths per minute and/or < 5 cm H_2O PEEP for eucapnia).
- If pulse oximetry oxygen saturation remains > 95%, obtain a baseline blood gas (PaO_2, $PaCO_2$, pH, bicarbonate, base excess)
- Disconnect from ventilator or place on pressure support ventilation.
- Deliver 100% O_2 into trachea (use cannula or T-tube) to preserve oxygenation
- Look closely for respiratory movements for 8 – 10 minutes (abdominal or chest).
- Abort if systolic blood pressure decreases to < 90 mm Hg
- Abort if oxygen saturation via pulse oximetry is <85% for > 30 seconds
- Abort if cardiac arrhythmias are present, immediately reconnect to ventilator, draw an arterial blood sample and analyze arterial blood gas.
- If no respiratory drive is observed, repeat blood gases (measure arterial PO_2, PCO_2, pH, bicarbonate, base excess) after approximately 8 minutes
- Reconnect the ventilator.
- If respiratory movements are absent and arterial PCO_2 is ≥ 60 mm Hg and ≥ 20mm Hg increase in arterial PCO_2 over baseline normal arterial PCO_2, the apnea test result is positive (supporting the clinical diagnosis of BD/DNC).
- In patients who are suspected to have

chronic CO2 retention, but baseline PaCO2 is unknown, clinicians must conclude that apnea test is consistent with BD/DNC criteria if there are no respirations arterial pH <7.3 and PaCO2 is ≥ 20 mm Hg above patients baseline AND ancillary testing is performed.

- If the test is inconclusive by the patient being hemodynamically stable during the procedure, it may be repeated for a longer period of time (10 – 15 minutes) after the patient is again adequately preoxygenated.
- If ventilator settings were changed for preparation of the apnea test, be sure to return original settings.

iv. Ancillary / Confirmatory Tests
A confirmatory test will be done only on patients for whom specific components of clinical testing cannot be reliably performed or evaluated. The following confirmatory test findings are:

- Cerebral Nuclear Scan – Technetium-99m hexamethylpropylene-amineoxime brain scan. Absence of cerebral blood flow with NO uptake of isotope in brain parenchyma.
- Digital Subtraction Angiography- 4 vessel catheter angiography (DSA)
- Transcranial Doppler Ultrasonography (TCD)

II. Indications for use of ancillary testing:
The following conditions may interfere with the clinical diagnosis of brain death, so that the diagnosis cannot be made with certainty on clinical grounds alone – confirmatory test(s) are recommended. Neurologic testing and apnea test should be performed and consistent with BD/DNC.

A. Severe trauma to cervical spine/skull base/orbit/facial injury

B. Inability to determine if limb movements are spinally mediated.

C. Toxic levels of any sedative drugs, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, chemotherapeutic agents, or neuromuscular blocking agents.

D. Sleep apnea or severe pulmonary disease resulting in chronic retention of CO_2 without knowledge of baseline PaCO2

E. Inability to perform apnea test due to risk of cardiopulmonary decompensation, hypoxia, hypotension, cardiac arrhythmia with hemodynamic instability before reaching the arterial pH and PaCO2 target.

III. Clinical observations can be compatible with the diagnosis of brain death. These manifestations are occasionally seen and should not be misinterpreted as evidence for brainstem function.

A. Spontaneous movements of limbs other than pathological flexion or extension response

B. Respiratory-like movements (shoulder elevation and adduction, back arching intercostals expansion without significant tidal volumes)

C. Sweating, blushing, tachycardia

D. Normal blood pressure without pharmacologic support or sudden increases in blood pressure

E. Absence of diabetes insipidus

F. Deep tendon reflexes; superficial abdominal reflexes, triple flexion response

G. Babinski reflex

IV. Guidelines

CIRCULATORY/RESPIRATORY CESSATION

A. In the event of permanent cessation of circulatory/respiratory function, patient will be declared dead by a physician licensed in the State of Tennessee. Time of Death must be recorded on Record of Death.

B. Notification will be made to the Organ Donor Program (Reference the policy Organ/Tissue Recovery).

C. Patients who are pronounced BD/DNC and under consideration for organ donation should not be coded for more than 10 minutes.

BRAIN FUNCTION CESSATION (BRAIN DEATH)

A. Physicians who are active members of the medical staff, and who are skilled in the application of accepted neurological standards based on the neurological criteria to declare brain death, should pronounce brain death.

B. Considering the responsibility entailed in the determination of death based upon neurological criteria, Neurology or Neurosurgery consultation is recommended.

C. Medical record documentation must include Determination of Brain Death Checklist. (see Addendum A) All brain death documentation must be reviewed and attested by at attending.

D. TDS is to be notified of anyone whose death is imminent or a Glasgow Coma score of ≤ 5 or patients eligible for a declaration of death based on irreversible cessation of brain function according to the TCA 68-3-501 (2), within 1 (one) hour of awareness.

E. In the event of organ donation, the patient will be supported by mechanical means, under the care of the organ retrieval team until this is completed.

F. Time of death ***must be*** recorded as the time "Brain Death/Death by Neurologic Criteria" is declared. Record on Record of Death the time the patient is pronounced brain dead.

G. Once the diagnosis of brain death has been established, the patient will be removed from ventilator support within 6 hours unless the family is considering donation.

NOTE: The responsibility for declaring a patient dead based on neurological criteria rests with the physician and he/she is the authority for making this decision. The decision should be based on neurological criteria only. Declaration of death based on the criteria may be a difficult concept for some families to accept. Physicians and nursing staff should be sensitive to this and prepare families accordingly.

V. **ATTACHMENTS**

a. Please see brain death checklist in EPIC

References:

AAN Resources:
https://www.aan.com/Guidelines/Home/GuidelineDetail/1085

AAN Crosswalk:
https://www.neurology.org/doi/full/10.1212/CPJ.0000000000200189

AAN Brain Death Evaluation Tool:
https://www.aan.com/guidelines/bddncPlease see the attached "Addendum: Checklist for Determination of Brain Death"

III. **PEDIATRIC PROCEDURE for Patient less than 18 years of age**

POPULATION – The **criteria *are not applicable* to infants less than corrected gestational age of 37 weeks or older than 18 years of age.**

I. Determination of BD/DNC in neonates, infants, and children relies on a clinical diagnosis that is based on the absence of neurologic function with a known irreversible cause of coma. Coma and apnea must coexist to diagnose BD/DNC. This diagnosis should be made by two attending physicians who have evaluated the history and completed the neurologic examination. The exams should be separated by 12 hours.

II. Prerequisites for initiating a BD/DNC evaluation:

a. For children younger than 24 months, clinicians should wait at least 48 hours after acute brain injury before initiating BD/DNC evaluation.

b. For children older than 2 years with hypoxic ischemic brain injury, clinicians should wait a minimum of 24 hours before initiating BD/DNC evaluation.

c. Hypotension, hypothermia, and metabolic disturbances that could affect the neurologic examination must be corrected before examination for BD/DNC.

i. Ensure systolic and MAP are > 5th percentile for age.

ii. Patients with core body temp <35.5^{O}C should wait a minimum of 24 hours after patient rewarmed to 36^{O}C before evaluation for BD/DNC

d. Sedatives, analgesics, neuromuscular blockers, and anticonvulsant agents

should be discontinued for a reasonable time period based on elimination half-life of the pharmacologic agent to ensure they do not affect the neurologic examination. Knowledge of the total amount of each agent (mg/kg) administered since hospital admission may provide useful information concerning the risk of continued medication effects. Blood or plasma levels to confirm high or supratherapeutic levels of anticonvulsants with sedative effects that are not present should be obtained (if available) and repeated as needed or until the levels are in the low to midtherapeutic range.

e. The diagnosis of brain death based on neurologic examination alone should not be made if supratherapeutic or high therapeutic levels of sedative agents are present. When levels are in the low or in the midtherapeutic range, medication effects sufficient to affect the results of the neurologic examination are unlikely. If uncertainty remains, an ancillary study should be performed.

f. Assessment of neurologic function may be unreliable immediately after cardiopulmonary resuscitation or other severe acute brain injuries and evaluation for brain death should be deferred for ≥24-48 hours if there are concerns or inconsistencies in the examination.

III. Number of examinations, examiners, and observation periods:

a. Two examinations including apnea testing with each examination separated by a 12hr observation period are required for infants and children 31 days old to 18 years of age and separated by 24hr observation period for term newborns 37 weeks gestational age to 30 days of life.

b. The examinations must be performed by two different attending physicians involved in the care of the child.

c. Recommended observation periods:

1. For children younger than 24 months, clinicians should wait at least 48 hours after acute brain injury before initiating BD/DNC evaluation.

2. For children greater than 24 months, clinicians should wait a minimum of 24 hours before initiating BD/DNC evaluation.

d. The first examination determines the child has met neurologic examination criteria for brain death. The second examination, performed by a different attending physician, confirms that the child has fulfilled criteria for BD/DNC.

e. Assessment of neurologic function may be unreliable immediately after cardiopulmonary resuscitation or other severe acute brain injuries and evaluation for brain death should be deferred for ≥24-48 hours if there are concerns or inconsistencies in the examination.

IV. Neurologic criteria: The three cardinal findings in BD/DNC are coma or unresponsiveness, absence of brain stem reflexes and apnea.

a. Evaluate for unresponsiveness to visual/auditory/tactile stimulation, and lack of motor response to pain in all extremities (nail-bed pressure and supraorbital pressure). Eye opening or eye movement to noxious stimuli is absent. True decerebrate or decorticate posturing or seizures *are inconsistent* with the diagnosis of death.

b. Absence of brain stem reflexes:
    i. Pupils
        a. Absence of papillary response to bright light documented in both eyes
        b. Size: mid-position (4mm) to dilated (9mm)
    ii. Ocular movement (absence of)
        a. No oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent). - Dolls eye phenomenon- if the head is briskly rotated horizontally and vertically, there shall be no movement of the eyes relative to head movement (toward the opposite side). BD/DNC may still be determined without ancillary testing provided that the occulovestibular reflex can be tested and is absent bilaterally and all other criteria are satisfied.
        b. No occulovestibular reflex- no deviation of the eyes to irrigation in each ear with 50mL of cold water (allow 1 minute after injection and at least 5 minutes between testing on each side).
        c. No corneal reflex- Absent of corneal reflex when touching of the corneal with a piece of tissue paper cotton swab, or squirts of water. No eyelid movement should be seen.
        d. Absence of facial muscle movement to noxious stimulus. No grimacing or facial muscle movement when deep pressure applied to supraorbital ridge, or deep pressure on the condyles at the level of the temporomandibular joint with no jaw reflex.
        e. Absence of the pharyngeal and tracheal reflexes.
            i. No pharyngeal or gag reflex after stimulation of the posterior pharynx with tongue blade or suction device (no gag).
            ii. No cough response to insertion of catheter into trachea, advanced to level of carina, followed by 1 or 2 suctioning passes.
            iii. Assess for absence of sucking and rooting reflexes (pts <6 months of age)

c. Apnea testing:
    i. Apnea testing must be performed safely (see guidance below). Requires documentation of an arterial $PaCO_2$ 20mm Hg above the baseline $PACO_2$ and ≥ 60 mm Hg with no respiratory effort during the testing period to support th diagnosis of BD/DNC. Some infants and children with chronic respiratory disease or insufficiency may only be responsive to supranormal $PaCO_2$ levels. In this instance, the $PaCO_2$ level should increase to ≥ 20 mm Hg above the baseline $PaCO_2$ level.

ii. If apnea test cannot be performed as a result of a medical contraindication or cannot be completed because of a hemodynamic instability, desaturation to <85% or an inability to reach a $PaCO_2$ of ≥60 mm Hg, an ancillary study should be performed.

iii. Apnea testing procedure:

a. The patient must have the complete absence of documented respiratory effort (if feasible) by formal apnea testing demonstrating a $PaCO_2$ ≥60 mm Hg and ≥20 mm Hg increase above baseline.

b. Normalization of the pH and $PaCO_2$ measured by arterial blood gas analysis, maintenance of core temperature >35^{O}C, normalization of blood pressure appropriate for the age of the child and correcting for factors that could affect respiratory efforts are a prerequisite to testing.

c. The patient should be preoxygenated using 100% oxygen for 5-10 minutes before initiating this test.

d. Intermittent mandatory mechanical ventilation should be discontinued once the patient is well oxygenated and a normal $PaCO_2$ has been achieved.

e. Clinician must ensure adequate oxygenation during apnea testing. This can be accomplished through:

i. stopping intermittent mandatory ventilation and delivering 100% oxygen through CPAP on the ventilator **OR**

ii. stopping intermittent mandatory ventilation and disconnecting the ventilator from the patient's ETT/tracheostomy and delivering 100% oxygen through a flow inflating resuscitation bag with functioning PEEP valve.

f. The patient's heart rate, blood pressure, and oxygen saturation should be continuously monitored while observing for spontaneous respiratory effort throughout the entire procedure.

g. Follow-up blood gases should be obtained to monitor the rise in $PaCO_2$ while the patient remains disconnected from mechanical ventilation.

h. If no respiratory effort is observed from the initiation of the apnea test to the time the measured $PaCO_2$ ≥60 mm Hg and ≥20 mm Hg above the baseline level, the apnea test is consistent with BD/DNC.

i. The patient should be placed back on mechanical ventilator support and medical management should continue until the second neurologic examination and apnea test confirming BD/DNC is completed.

j. If oxygen saturations fall <95%, hemodynamic instability limits completion of apnea testing, or a $PaCO_2$ level of ≥60 mm Hg cannot be achieved, the infant or child should be placed back on ventilator support with appropriate treatment to restore normal oxygen saturations, normocarbia, and hemodynamic parameters. Another attempt to test for apnea may be performed at a later time or an ancillary study may be pursued to assist with determination of brain death.

k. Evidence of any respiratory effort is inconsistent with brain death and the apnea test should be terminated.

V. Ancillary studies:

a. Ancillary studies are not required to establish brain death unless the clinical examination or apnea test cannot be completed.

b. Clinicians should only perform ancillary testing to assist with the diagnosis of BD/DNC when the BD/DNC neurologic examinations or apnea test cannot be completed or the findings cannot be adequately interpreted.

c. Ancillary studies are not a substitute for the neurologic examination.

d. Only 4 vessel catheter angiography or radionuclide cerebral perfusion scintigraphy (RCPS) may be used in children.

e. For all age groups, ancillary studies can be used to assist the clinician in making the diagnosis of brain death or when 1) components of the examination or apnea testing cannot be completed safely as a result of the underlying medical condition of the patient; 2) if there is uncertainty about the results of the neurologic examination; or 3)metabolic derangements that are unable to be adequately corrected

f. When an ancillary study is used because there are inherent examination limitations (i.e., 1-3 in 5e, then components of the examination done initially should be completed and documented prior to ancillary testing.

g. If the ancillary study is equivocal or if there is concern about the validity of the ancillary study, the patient cannot be pronounced dead. The patient should continue to be observed until BD/DNC can be declared on clinical examination criteria and apnea testing or a follow-up ancillary study can be performed to assist with the determination of BD/DNC. A waiting period of 24 hours is recommended before further clinical re-evaluation or repeat ancillary study is performed. Supportive patient care should continue during this time period.

VI. Declaration of death:

a. Death is declared after confirmation and completion of the second clinical examination and apnea test.

b. When ancillary studies are used, documentation of components from the second clinical examination and apnea test that can be completed must remain consistent with BD/DNC. All aspects of the clinical examination, including the apnea test, or ancillary studies must be appropriately documented.

c. The clinical examination should be carried out by experienced clinicians who are familiar with infants and children and have specific training in neurocritical care.

Please see attached tables:

A. Avoiding Inaccurate Determination of BD/DNC Caused by Drugs/Medications and Metabolic Derangements

B. Child Evaluation Pathway

2023 BRAIN DEATH GUIDELINE

AMERICAN ACADEMY OF NEUROLOGY

eTABLE 1. METABOLIC DERANGEMENTS THAT MAY CONFOUND BD/DNC EVALUATION

Laboratory Result	Value[a]
Metabolic	
Ammonia[b]	>75 µmol/L
Blood urea nitrogen	>75 mg/dL
Calcium (or ionized calcium)	<7 mg/dL or >11 mg/dL (or <1 mmol/L or >1.3 mmol/L)
Glucose	<70 mg/dL or >300 mg/dL
Magnesium	<1.5 mg/dL or >4 mg/dL
Potassium	<3 mmol/L or >6 mmol/L
Sodium	<130 mmol/L or >160 mmol/L
Acid-Base	
pH	<7.3 or >7.5
Endocrine	
Total T4	<3 mg/dL or >30 mg/dL
Free T4[b]	≤0.4 ng/dL or >5 ng/dL

[a]The exact values at which the laboratory abnormality could affect the clinical evaluation are uncertain, and the values listed in this table are practical thresholds based on consensus only.

[b]Routine measuring of these values may not be necessary unless clinically indicated.

eTABLE 2. COMMON MEDICATIONS ADMINISTERED TO CRITICALLY ILL PATIENTS AND ESTIMATED HALF-LIVES[a]

Drug	Pharmacokinetics			Comments
Intravenous sedatives				
Dexmedetomidine[e32]	$t_{1/2}$	Infant ≤28d	3.2 hours	**Hepatic impairment** Compared to a baseline half-life of 2.5 hours in healthy adult patients, clearance in mild, moderate, and severe hepatic impairment was 3.9, 5.4, and 7.4 hours, respectively.[e33] Consider tapering rather than abrupt cessation for patients on >24 hours of therapy to avoid hemodynamic changes.
		Pediatric	<2 years: 2.3 hours 2–11 years: 1.6 hours	
		Adult	~3 hours	
	Metabolism		Hepatic	
	Excretion		Urine (95%)	
Etomidate[e34]	$t_{1/2}$	Infant ≤28d Pediatric Adult	2.6–3.5 hours	**Continuous infusion:** Plasma terminal half-life was found to be ~5.5 hours when administered as a continuous infusion.[e35] **Hepatic impairment:** In patients with cirrhosis, the terminal half-life of continuous infusion can be prolonged up to 2-fold (~9 hours).[e36]
	Metabolism		Hepatic; plasma esterases	
	Excretion		Urine (~75%), bile (10%)	
Ketamine[e37, e38]	$t_{1/2}$	Infant ≤28d Pediatric[e39] Adult	~2.5 hours	
	Metabolism		Hepatic	
	Excretion		Urine (91%)	
Midazolam[e40,b]	$t_{1/2}$	Infant ≤28d	4–12 hours	**Renal impairment:** With continuous infusions, half-life of the parent compound can increase up to 2-fold. Half-life of the active metabolite can increase significantly compared to control group.[e41] **Special populations with prolonged half-lives**: • Elderly: Increased 2-fold • Heart failure: Increased 2-fold • Hepatic impairment: Increased 2.5-fold • Obesity: increased 2-fold
		Pediatric	2.9–4.5 hours	
		Adult	~3 hours	
	Metabolism		Hepatic	
	Excretion		Urine (90%)	
Propofol[e42]	$t_{1/2}$	Infant ≤28d Pediatric Adult	Initial: 40 minutes Terminal: 4–7 hours	**Context sensitive half-time**: Prolonged infusions (>10 days) have been associated with a drug half-life of 1-3 days. **Elderly:** Clearance may be decreased.[e43]
	Metabolism		Hepatic	
	Excretion		Urine (90%)	

Intravenous narcotics				
Fentanyl[e44,b]	$t_{1/2}$	Infant ≤28d	5.5 ± 1.2 hours[e45]	**Continuous infusion:** Half-life prolongs with infusion duration. In children aged 6 months to 14 years, half-life reported as ~21 hours in long-term continuous infusions. **Special populations with prolonged half-lives:** • Infants: half-life inversely proportional to gestational age • Elderly: Increased 5-fold[e44] • Transdermal route: 20-27 hours
		Pediatric	5 months-4.5 years: 2.4 hours	
		Adult	2-4 hours	
	Metabolism		Hepatic	
	Excretion		Urine (75%)	
Hydromorphone[e47,b]	$t_{1/2}$	Infant ≤28d Pediatric Adult	2.3 hours	**Renal impairment:** Increased terminal half-life seen in patients with severe renal impairment compared to controls after oral administration immediate release hydromorphone (40 vs 15 hours).
	Metabolism		Hepatic	
	Excretion		Urine	
Morphine[e48, e49,b]	$t_{1/2}$	Infant ≤28d[e50]	6.5 ± 2.8 hours	**Hepatic impairment:** 1. Children: extrahepatic metabolism may occur, minimal half-life changes 2. Adults with cirrhosis: delayed clearance **Elderly:** Reduced clearance
		Pediatric[e50]	2 ± 1.8 hours	
		Adult	2 hours	
	Metabolism		Hepatic	
	Excretion		Urine (90%)	
Remifentanil[e51, e52]	$t_{1/2}$	≤2 months	5.4 minutes	
		Pediatric	>2 months to <2 years: 3.4 minutes 2–6 years: 3.6 minutes 7–2 years: 5.3 minutes 13 to <16 years: 3.7 minutes 16–18 years: 5.7 minutes	
		Adult	10–20 minutes	
	Metabolism		**Blood and tissue esterases**	
	Excretion		Urine (90%)	

Antiseizure Medications				
Clonazepam[e53,b]	$t_{1/2}$	Infant ≤28d	22–81 hours	**Hepatic impairment:** Clearance may be decreased **Elderly:** Hepatic clearance may be decreased
		Pediatric	28.7 hours	
		Adulte54	17–56 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Diazepam[e55,b]	$t_{1/2}$	Infant ≤28d	Parent: 33–45 hours Active metabolite: 87 hours	Terminal half-life prolonged with repeated dosing. **Hepatic impairment:** In mild and moderate cirrhosis, diazepam half-life is increased by 2-5 fold.[e56] **Elderly:** In healthy patients >60 years, half-life of parent compound was ~79 hours.[e57]
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	
Levetiracetam	$t_{1/2}$	Infant ≤28d[e58]	8.9 hours	**Renal impairment:** Renal clearance is directly proportional to creatinine clearance, reported half-lives[e59]: • Mild impairment: 10.4 hours • Severe impairment: 24.1 hours **Elderly:** Renal clearance may be decreased. • Reported increases in half-life by 2.5 hours.
		Pediatric	<4 years: 5.3 ± 1.3 hours 4–12 years: 6 ± 1.1 hours	
		Adult	6–8 hours	
	Metabolism		Plasma hydrolysis (~24%)	
	Excretion		Urine	
Lorazepam[e60,b]	$t_{1/2}$	Infant ≤28d	40.2 ± 16.5 hours	**Renal impairment**: Half-life slightly prolonged in end stage renal disease (~18 hours).[e61]
		Pediatric	5 months to <3 years: 15.8 hours 3 to <13 years: 16.9 hours 13 to <18 years: 17.8 hours	
		Adult	~14 hours	
	Metabolism		Hepatic	
	Excretion		Urine (88%)	
Pentobarbital[e62]	$t_{1/2}$	Infant ≤28d	26 ± 16 hours	
		Pediatric		
		Adult	22 hours	
	Metabolism		Hepatic	
	Excretion		Urine	

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Antiseizure Medications				
Phenobarbital[e63]	$t_{1/2}$	Infant ≤28d	<10 days: 114.2 ± 43 hours 11-30 days: 73.19 ± 24.17 hours	**Hepatic impairment:** Small changes in half-life are seen in patients with cirrhosis (130 ± 15 hours) compared with the control group (86 ± 3 hours). There is large interpatient variability seen in hepatic impairment.[e64] **Therapeutic Range:** 10–40 mcg/mL
		Pediatric	2-3 months: 62.9 ± 5.2 hours 4-12 months: 63.2 ± 4.2 hours 1-5 years: 68.5 ± 3.2 hours	
		Adult	~79 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Phenytoin[e65] and fosphenytoin[e66, e67]	$t_{1/2}$	Infant ≤28d	0–2 days: 80 hours 3–14 days: 15 hours 15–150 days: 6 hours[e68]	**Michaelis-Menten**: Half-life increases with increasing phenytoin concentrations. **Hepatic impairment:** Active metabolite undergoes enterohepatic circulation and may prolong duration of action.[e69, e70] **Renal impairment:** Total phenytoin serum concentrations should be interpreted with caution. If available, recommend the use of free phenytoin concentrations.[e65] **Obesity:** Half-life may be prolonged in obese patients compared to controls (19.9 vs 12 hours, respectively).[e71] **Elderly:** Clearance decreases with increasing age **Therapeutic Range:** Total Phenytoin 10-20mcg/mL; Free Phenytoin 1-2 mcg/mL
		Pediatric	10–12 hours	
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	
Valproic acid[e72, e73]	$t_{1/2}$	Infant ≤28d	First week of life: 40–45 hours <10 days: 10–67 hours	**Liver impairment:** 18 hours[e73] **Elderly:** 15 hours[e74] **Therapeutic Range:** 50–100 mcg/mL
		Pediatric	>2 months: 7–13 hours 2-14 years: 9 hours	
		Adult	9–19 hours	
	Metabolism		Hepatic	
	Excretion		Urine	

Neuromuscular blocker agents				
Atracurium[e75, e76]	$t_{1/2}$	Infant ≤28d	Infants: 20 minutes Children: 17 minutes	
		Pediatric		
		Adult	20 minutes	
	Metabolism		Hofmann elimination and ester hydrolysis	
	Excretion		Urine (<5%)	
Cisatracurium[e77, e78]	$t_{1/2}$	Infant ≤28d	22-29 minutes	
		Pediatric		
		Adult		
	Metabolism		Hoffman elimination	
	Excretion		Urine (95%)	
Pancuronium[e79,b]	$t_{1/2}$	Infant ≤28d	89–140 min	**Renal impairment:** 257 minutes **Biliary obstruction:** 270 minutes **Hepatic cirrhosis:** 208 minutes **Hypothermia:** May prolong duration
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine (40%), Bile (11%)	
Rocuronium[e80,b]	$t_{1/2}$	Infant ≤28d	3–12 months: 1.3 ± 0.5 hours	**Hepatic impairment:** 4.3 hours **Renal impairment:** 2.4 hours **Elderly:** Duration prolonged in elderly patients compared with young adults (110 vs 78 minutes, respectively)[e81]
		Pediatric	1 to <3 years: 1.1 ± 0.7 hours 3 to <8 years: 0.8 ± 0.3 hours	
		Adult	1.4–2.4 hours	
	Metabolism		Minimally hepatic	
	Excretion		Urine (26%)	
Succinylcholine[e82]	$t_{1/2}$	Infant ≤28d	<1 minute	**Pseudocholinesterase deficiency:** Prolonged clearance[e83]
		Pediatric		
		Adults		
	Metabolism		Plasma pseudocholinesterases	
	Excretion		Urine (10%)	

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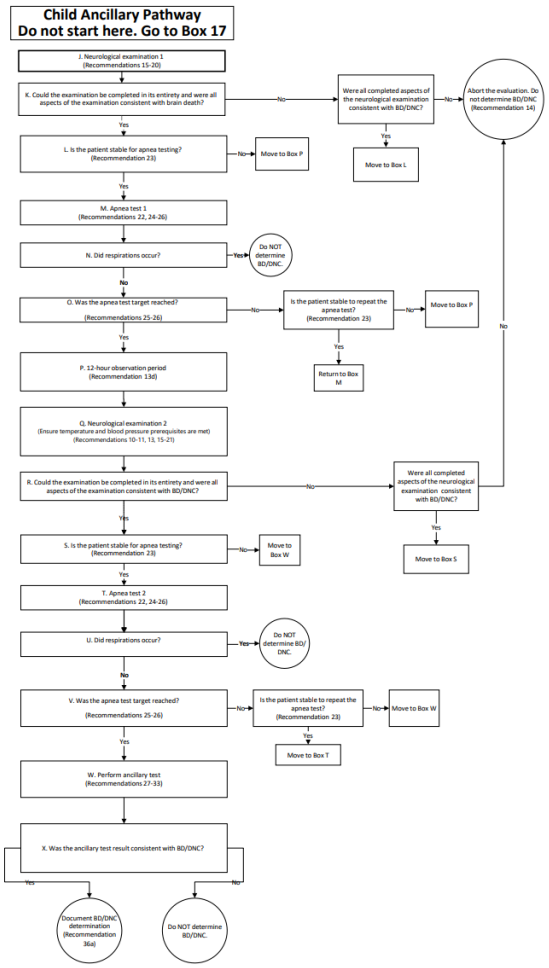
Neuromuscular blocker agents				
Vecuronium[e76, e84,b]	$t_{1/2}$	Infant ≤28d	Infants: 65 minutes	**Hepatic impairment:** Half-life is prolonged in patients with cholestasis compared to controls (58 vs 98 minutes, respectively)[e85] **Hypothermia:** Clearance may be reduced[e86]
		Pediatric	Children: 41 minutes	
		Adult	65–75 minutes	
	Metabolism		Hepatic	
	Excretion		Urine (30%)	

[a]The duration of time that medications should be held before neurologic examination to determine brain death is patient and medication specific. Providers should be aware that the metabolism and clearance of pharmacologic agents can be affected by patient-specific factors, including but not limited to hypothermia, organ dysfunction, obesity, and concomitant drug therapies. Typically, 3 to 5 half-lives will allow for adequate clearance of pharmacologic therapy; however, elimination half-life does not guarantee clearance of medications with active metabolites or enterohepatic recirculation. This table includes terminal half-life, which takes into account both volume of distribution and elimination rate, as well as information on specific populations that experience deviations in standard clearance when clinically significant data are available. Context-sensitive half-time was included when shown to be prolonged compared with reported half-life values. Whenever possible, providers should obtain drug levels to ensure that the levels are in a low to mild therapeutic range before neurologic examination.

[b]Reversal agents can be considered after evaluating the risk vs benefit of their use.



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AAN Crosswalk:

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AAN Brain Death Evaluation Tool:

https://www.aan.com/guidelines/bddnc

Approval Signatures

Step Description	Approver	Date
CNO	Rachel Harris: Exec VP & Chief Nursing Officer	06/2024
Clinical Effectiveness	Carrie Burton: Executive Asst-Chief	06/2024
Medical Executive Committee	Alisa Bolt: Medical Affairs	06/2024
Adult Critical Care Committee	Sara Bacon: Nurse Director	06/2024
	Sara Bacon: Nurse Director	06/2024

Applicability

Erlanger Health - All Search, Erlanger Health - Baroness, Erlanger Health - Bledsoe, Erlanger Health - Children's, Erlanger Health - EMG, Erlanger Health - East, Erlanger Health - North, Erlanger Health - System, Erlanger Health - Western Carolina, Erlanger Health - Western Carolina EMG