Emergency Neurological Life Support Pharmacotherapy Protocol Version 5.0

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Pharmacotherapy Protocol: Table of Contents

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Pharmacotherapy Introduction

These protocols were created to highlight the use and dosing of common medications used during neurological emergency resuscitation. Many of these medications are relevant to many ENLS protocols and are cross referenced for ease of access. We have done our best to indicate adult and pediatric dosing of medications but know that these are Western medications primarily so may differ in name from drugs internationally.

Antibiotics and Antiviral Agents

Choosing the appropriate antimicrobial or antiviral agent and dose is essential when treating meningitis and encephalitis. Inflammation of the blood brain barrier allows antimicrobials to penetrate cerebral tissue. Streptococcus pneumonia meningitis should be treated with dexamethasone (10mg IV every 6 hours for 4 days) in conjunction with antibiotics to decrease neurological sequelae. See pediatric considerations. Selection of an appropriate antimicrobial should be based on the local antibiogram, drug resistance patterns, and age of the patient. See the ENLS protocol Meningitis and Encephalitis and Spinal Cord Compression, and Pharmacotherapy for more detail on treating CNS infections.

CNS Pathogen	Recommended Therapy
H. influenzae	Third-generation cephalosporin
S. pneumoniae	Vancomycin (Trough goal: 15-20 mcg/ml) PLUS Third-generation cephalosporin
N. meningitidis	Third-generation cephalosporin
L. monocytogenes	Ampicillin
S. agalactiae	Ampicillin
E. coli	Third-generation cephalosporin
Staphylococci	Vancomycin (Trough goal: 15-20 mcg/ml)
HSV, VZV, CMV	Acyclovir (dosed on IBW), IV: • Infants <3 months: 20 mg/kg/dose every 8 hours (chronic suppressive therapy is needed following any neonatal HSV infection) • Infants and children 3 months to <12 years: 10 to 15 mg/kg/dose every 8 hours • Children ≥12 years and Adolescents: 10 mg/kg/dose IV every 8 hours • Adults: 10 mg/kg/dose IV every 8 hours

Pediatric considerations: Corticosteroids are not recommended in neonates with suspected meningitis due to insufficient data. In infants and children, dexamethasone 0.15 mg/kg/dose (max 10 mg) every 6 hours for 2-4 days has been shown to prevent neurologic sequalae, specifically hearing loss, in the setting of *H. influenzae* type b meningitis when the first dose of dexamethasone was administered immediately prior to or at the same time as the first dose of antibiotics. Avoid steroid therapy when there is a delay in presentation or after antibiotics have

been started. For pneumococcal meningitis, studies have shown variable effects in reducing neurologic sequalae and the use of dexamethasone in pediatric patients for this indication remains controversial, for infants and children older than 6 weeks of age, the use of dexamethasone in pneumococcal meningitis should be evaluated against possible risks of the intervention.

Anticoagulant Reversal

Control the bleeding

When rapid reversal of an anticoagulant is necessary, the risk - benefit ratio of continued bleeding to thrombosis is crucial and must be considered on an individual basis. In all cases that include INR elevation or active bleeding, anticoagulation medication should be stopped. If the last dose of an anticoagulant was taken within the 3-5 half-life window, then reversal should be considered in patients with a high bleeding risk. These agents are relevant for the ENLS protocols Intracerebral Hemorrhage, Subarachnoid Hemorrhage, Traumatic Brain Injury, Traumatic Spine Injury, and Spinal Cord Compression. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Vitamin K Antagonist Reversal

INR	Clinical Setting	Treatment Options
< 4.5	No bleeding	Hold warfarin until INR in therapeutic range
	Rapid reversal required (<24 hrs)	Hold warfarin Vitamin K 2.5mg PO If urgent reversal needed (≤ 12 hrs) for procedure consider 4PCC 25 IU/kg IV
4.5-10	No bleeding	Hold warfarin until INR in therapeutic range Consider vitamin K 2.5 mg PO if risk factors for bleeding*
	Rapid reversal required (<24 hrs)	Hold warfarin Give vitamin K 5 mg PO If urgent reversal needed (≤ 12 hrs) for procedure consider 4PCC 35 IU/kg IV
>10	No bleeding	Hold warfarin until INR in therapeutic range Give vitamin K 2.5-5 mg PO or 1-2 mg IV* Repeat every 24 hours as necessary
	Rapid reversal required (<24 hrs)	Hold warfarin Give vitamin K 1-2 mg IV Repeat every 6-24 hours as necessary If urgent reversal needed (≤ 12 hrs) for procedure consider 4PCC 50 IU/kg IV
ANY INR	Serious or Life-threatening bleeding	Hold warfarin Give vitamin K 10mg IV over 30minutes If patient volume overloaded give PCC Recheck INR 30 minutes after PCC administered **INR / 4-factor PCC dose / Max dose** 2-3.9 / 25 units/kg / 2500 units 4-6 / 35 units/kg / 3500 units >6 / 50 units/kg / 5000 units If volume resuscitation necessary, consider FFP 15-20 ml/kg Recheck INR after FFP administered

Pediatric considerations:

In children on warfarin where reversal is needed, consider holding warfarin at any INR. For excessively prolonged INRs (usually > 8) and no bleeding, consider administration of intravenous vitamin K (0.03 mg/kg/DOSE, up to 5 mg). In the presence of significant bleeding, immediate reversal with FFP, PCC or factor VII may be needed. There is limited data for use of PCC in pediatric patients for emergent reversal of VKA, data for anticoagulation reversal in pediatric patients is limited to case series and case reports. Usual doses reported for PCC were 25 IU/kg, but doses up to 50 IU/kg have been used. Idarucizumab and Andexanet alfa have not been studied in pediatric patients, while emergent use may be reasonable, no dosing recommendations are possible at this time.

Factor Xa Inhibitors Reversal

Apixaban (Eliquis®)
Rivaroxaban (Xarelto®)

Edoxaban (Savaysa®)

- If ingested within 2 hours, administer activated charcoal 50 g
- Consider time of last dose and $t_{1/2}$ of agent when deciding to reverse agent. Recommend reversal if last dose given within 3-5 elimination $t_{1/2}$ of the drug to ensure hemostasis
- Consider Andexanet-alfa (see dosing)
  Step 1: Determine previous factor Xa agent and dose history
  Only indicated for reversal of rivaroxaban & apixaban

Factor Xa Inhibitor	Factor Xa Inhibitor Last Dose	Timing of Last Dose	
		<8h or unknown	≥8h
Rivaroxaban	≤10 mg	Low dose	Low dose
	>10 mg or unknown	High dose	
Apixaban	≤5 mg	Low dose	
	>5 mg or unknown	High dose	

Step 2: Determine Andexanet-alfa dose

Dose	Initial bolus	Maintenance infusion
Low	400 mg IV over 15 min	4 mg/min for 100 min
High	800 mg IV over 15 min	8 mg/min for 112 min

Effective Alternative Option:

	• Administer PCC 50 units/kg over 10 min ○ If volume needed consider 15-20 ml/kg FFP • .

Direct Thrombin Inhibitors Reversal	

Dabigatran (Pradaxa®)	• If ingested within 2 hours, administer activated charcoal 50g PO/NG
	• Drug of Choice: idarucizumab 5gm IV push (two 2.5 gm vials given back-to-back)
	• Consider the following if idarucizumab not available:
	  ○ Emergent hemodialysis OR
	  ○ Weak evidence for:
	  ▪ FFP 15-20 mL/kg
	  ▪ rFVIIa 20mcg/kg and may repeat x1

Bivalirudin (Angiomax®)	• Turn off infusion • Monitor aPTT to confirm clearance • Supportive measures to control bleeding
Argatroban	• Turn off infusion • Monitor aPTT to confirm clearance • Supportive measures to control bleeding

<table>
<tr><th colspan="2">Unfractionated Heparin and Low Molecular Weight Heparin (LMWH) Reversal</th></tr>
<tr><td>Unfractionated heparin</td><td>

Protamine neutralizes heparin. Dosing is based on time since last dose of heparin.

Immediate: 1mg/100 units of heparin given (max = 50 mg)
30 minutes: 0.5 mg/100 units
> 2 hours: 0.25 mg/100 units

</td></tr>
<tr><td>Enoxaparin
(Lovenox®)

Dalteparin
(Fragmin®)</td><td>

Protamine partially reverses the effect of LMWH (about 60%)
<table>
<tr><th>Time since last dose of LMWH</th><th>Dose of protamine</th></tr>
<tr><td>< 8 hrs</td><td>1mg per for each 1mg enoxaparin/100 units dalteparin administered (max 50mg)</td></tr>
<tr><td>8-12 hrs</td><td>0.5mg for each 1 mg enoxaparin/100 units dalteparin administered (max 25mg)</td></tr>
<tr><td>>12 hrs</td><td>Not likely to be useful* (max 25mg)</td></tr>
</table>
Consider reversal beyond 12 hours in patients with renal insufficiency
Monitor anti-factor Xa activity to confirm reversal

</td></tr>
<tr><td>Fondaparinux
(Arixtra®)</td><td>

Protamine is NOT helpful; supportive care
<u>Weak evidence, but may consider either:</u>

PCC 50 units/kg
rFVIIa 20 mcg/kg (may repeat x 1)

</td></tr>
</table>

Anticonvulsants

Seizures and Status Epilepticus

Status epilepticus is a neurological emergency and warrants rapid treatment using intravenous medications at appropriate doses. See the ENLS protocol Status Epilepticus for timing and choice of medication used in treating unremitting seizures. Choice of agent depends on etiology, patient stability, organ function, adverse drug effects, and consideration of drug interactions. Benzodiazepines should be the first agent, followed quickly by administration of a longer duration agent. Goal therapeutic levels should be established and monitored.

First line / Emergent	Dosing
Lorazepam (Ativan®)	0.1 mg/kg IV up to 4 mg per dose
Midazolam (Versed®)	0.2 mg/kg IM up to 10 mg per dose
Diazepam (Valium®)	0.15 mg/kg IV up to 10 mg per dose
Maintenance / Urgent	
Phenytoin (Dilantin®) OR Fosphenytoin (Cerebyx®)	Load: 20 mg/kg IV (max adult dose: 2000 mg, max pediatric dose: 1500 mg) Maintenance: 4-6 mg/kg/day divided in 2-3 doses (dosing for fosphenytoin is the same, only in phenytoin equivalents (PE))
Valproate sodium (Depacon®)	Load: 40 mg/kg IV (max: 3000 mg) Maintenance: 10-15 mg/kg/day divided into 2-4 doses
Levetiracetam (Keppra®)	Load: 60 mg/kg IV (max: 4500 mg) Maintenance: Adults: 1000-3000 mg/day IV in 2 divided doses Children: 20-55 mg/kg/day divided q12h
Lacosamide (Vimpat®)	Adult Load: 200-400 mg/day IV Adult Maintenance: 200 mg every 12 hours Children: Initial dose: 2 mg/kg/day divided q12h Usual max dose: < 30 kg: 8–12 mg/kg/day 30-50 kg: 6-8 mg/kg/day

Phenobarbital	Load: 20 mg/kg IV Maintenance: Adults:1-3 mg/kg/day divided into 1-3 doses Infants and Children ≤ 5 years: 3-5 mg/kg/day in 1-2 divided doses Children >5 years and adolescents: 2-3 mg/kg/day divided in 1-2 doses

Refractory Status Epilepticus	
Midazolam (Versed®)	Bolus: 0.2 mg/kg IV Infusion: 0.05 - 2 mg/kg/hour
Propofol (Diprivan®)	Bolus: 1-2 mg/kg IV Infusion: 30 - 250 mcg/kg/min
Pentobarbital (Nembutal®)	Bolus: 10-15 mg/kg IV Infusion: 0.5 - 5 mg/kg/hour
Ketamine (Ketalar®)	Bolus: 0.5-4.5 mg/kg IV Infusion: 0.5-10 mg/kg/hour

Pediatric considerations: Routine use of propofol is not recommended due to risk for propofol-related infusion syndrome (PRIS) in children

Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Antithrombotic Agents

Breaking up clots

Antithrombotic agents are used in management of acute ischemic stroke, and the focus of urgent management should be on clot disruption; see ENLS protocol Acute Ischemic Stroke.

Alteplase 0.9 mg/kg (not to exceed 90 mg total dose) IV is the only FDA-approved pharmacologic agent available for acute clot disruption in acute ischemic stroke. Drug re-constitution requires special expertise; do not shake the reconstituted infusate, simply swirl the container when reconstituted. Administer 10% of the total dose as an initial IV bolus over 1 minute and infuse the remainder over 60 minutes.

Tenecteplase has also been used as a thrombolytic in acute ischemic stroke (non FDA-approved) at a dose of 0.25mg/kg IV push (max dose 25mg).

Pediatric considerations: Pediatric data is extremely limited. Except for institutions with a previously established pediatric stroke protocol, alteplase should not be routinely used in children with acute ischemic stroke.

Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Hemostatic Agents

Prevent aneurysm re-bleeding

Antifibrinolytics may play a role in preventing re-bleeding of brain aneurysms after subarachnoid hemorrhage prior to definitive treatment to secure the aneurysm. In order to avoid thrombotic complications, doses should be held 4-6 hours prior to any endovascular procedures, and treatment duration should be less than 72 hours. Precipitous drops in blood pressure can be seen if used in conjunction with nimodipine.

Adult Dosing:

- Tranexamic acid 1 g IV over 10 minutes every 4-6 hours
- Aminocaproic acid 5 gram IV over 1 hour followed by 1 gram/hour infusion

These agents are relevant for the ENLS protocol Subarachnoid Hemorrhage. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Hyperosmolar Therapy

Mannitol vs hypertonic saline

Mannitol (0.5 - 1 gm/kg) is an osmotic diuretic, and close monitoring is necessary to avoid hypotension and hypovolemia. Hypertonic saline (HTS) is a volume expander, and can worsen heart failure and pulmonary edema. For emergent use, HTS concentrations greater than 3.0% should be given through a central line, and dosing varies based on concentration:

Concentration	Dose	Infusion duration
3%	5 ml/kg	5-20 min
5%	3 ml/kg	5-20 min
7.5%	2 ml/kg	5-20 min
23.4%	30 ml	10-20 min

Pediatric considerations:

Hypertonic saline 3%: 2-5 mL/kg over 10-20 min
Hypertonic saine 23.4%: 0.5 mL/kg (max dose: 30 mL)

These agents are relevant for the ENLS protocols Intracranial Hypertension and Herniation and Traumatic Brain Injury. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

IV Antihypertensive Medications

Keep blood pressure under control

Blood pressure goals are controversial and vary dramatically between disease states. When blood pressure reduction is required, selection of an agent should be based on rapidity of control, hemodynamic parameters, volume status, organ function, and drug interactions.

Agent	Dose
Continuous Infusions	
Nicardipine (Cardene®)	Adults: Initial dose: 2.5 mg/hour Titration: 2.5mg/hour every 15 minutes to goal BP (max = 15 mg/hour) Children: Initial: 0.5-1mcg/kg/min Titration: 0.5-1 mcg/kg/min every 15 minutes to goal BP (max 5 mcg/kg/min, do not exceed adult max)
Clevidipine (Cleviprex®)	Adult Initial dose: 1-2 mg/hour Adult Titration: increase dose every 90 seconds to goal BP (max = 32 mg/hour)
Esmolol (Brevibloc®)	Adults: 50-300 mcg/kg/min Children: 25-100mcg/kg/min
Intermittent dosing	
Hydralazine	Adults: 10 - 20 mg every 4 - 6 hours Children: 0.1- 0.2 mg/kg/dose (max= 25 mg/dose) every 4-6 hours
Labetalol	Adults: 10 - 80 mg every 10 min up to 300 mg Children: 0.2-1 mg/kg/dose IV bolus (up to 40 mg/dose); use with caution in children

These agents are relevant for the ENLS protocols Acute Ischemic Stroke, Intracerebral Hemorrhage and Subarachnoid Hemorrhage. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Neuromuscular Blockade

Rapid sequence intubation, refractory ICP elevations, shivering

Neuromuscular blocking agents are used primarily to facilitate tracheal intubation or provide skeletal muscle relaxation during surgery, to facilitate mechanical ventilation, or assist in treatment of malignant ICP or refractory shivering during targeted temperature management. Short acting agents are preferred, and concomitant sedation is necessary. Monitoring the train-of-four (TOF) with a peripheral nerve stimulator (PNS) in conjunction with the clinical assessment (vital signs, synchrony with the mechanical ventilator) should always be used to evaluate the extent of paralysis. The TOF goal is generally 1-2 responses per 4 stimulations. Caution should be used when using a PNS in hypothermic patients as the TOF may be unreliable and misleading. Therefore, caution should be exercised when using PNS in the setting of hypothermia. Preferred agents are:

Agent	Dosing	Precautions / Comments
Succinylcholine (Anectine®)	• Adults: 0.5-1.1 mg/kg IV • 2-4 mg/kg IM • Adolescents: 1-1.5 mg/kg IV 3-4 mg/kg IM • Children: 1-2 mg/kg IV • 3-4 mg/kg IM • Infants: 2-3 mg/kg IV 4-5 mg/kg IM	Severe hyperkalemia may occur in muscle trauma, burns, neuromuscular disease, spinal cord injury, and stroke
Cisatracurium (Nimbex®)	Adults 0.15 mg/kg IV (up to 0.2 mg/kg) Children: 0.1-0.15 mg/kg IV	Longer half-life in elderly Can be used as continuous infusion Eliminated via enzymatic pathway
Rocuronium (Zemuron®)	Adults and children: 0.6 mg/kg IV (up to 1.2 mg/kg)	Prolonged duration in renal failure
Vecuronium	Adults and children: 0.1 mg/kg/dose (up to 0.2 mg/kg)	

These agents are relevant for the ENLS protocols Intracranial Hypertension and Herniation, Resuscitation following Cardiac Arrest, and Traumatic Brain Injury. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Sedation and Analgesia

Treat pain and agitation

Sedation and analgesia treatment goals must be identified and communicated clearly. These agents are affected by end organ dysfunction and drug interactions, so choices must be individualized. The minimum effective dose should be used, and many of these agents are synergistic when used together, so lower doses of both agents can be used to achieve the desired effect.

Benzodiazepines are well tolerated as are opiates. These agents are relevant for the ENLS protocols Intracranial Hypertension and Herniation, Resuscitation after Cardiac Arrest, and Traumatic Brain Injury. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Sedatives	Dose
Propofol (Diprivan®)	• Maintenance infusion: 50-100 mcg/kg/min

Dexmedetomidine (Precedex®)	• Loading dose is NOT recommended
	• Maintenance infusion:
	  ○ Adults: 0.2-1.4 mcg/kg/hour
	  ○ Children: 0.2-0.7 mcg/kg/hour. Doses up 2.5 mcg/kg/hour have been reported

Lorazepam (Ativan®)	• Loading: 0.02-0.04 mg/kg
	• Intermittent: 0.02-0.06 mg/kg every 2-6 hour
	• Maintenance infusion:
	  ○ Adults: 0.01-0.1 mg/kg/hour
	  ○ Children: 0.05 mg/kg/hour, rarely used due to concern for propylene glycol toxicity

Midazolam (Versed®)	Adults • Loading: 0.01-0.05 mg/kg • Maintenance infusion: 0.01-0.1 mg/kg/hour Children • Loading: 0.05-0.1mg/kg • Maintenance infusion • Initial: 0.03-0.12mg/kg/h. • Usual range: 0.024 to 0.36mg/kg/hour • Whenever possible, use preservative free product for continuous infusions •

Analgesics	Dose
Fentanyl (Duragesic®)	Adults • Bolus: 12.5-100 mcg or 1-2 mcg/kg IVP • Maintenance infusion: 0.7-10 mcg/kg/hour or 25-700 mcg/hour Children • Bolus: 1-2 mcg/kg • Maintenance infusion Initial: 1 mcg/kg/hour
Hydromorphone (Dilaudid®)	Adults • Oral: 2-4 mg every 4-6 hours • Intermittent dose: 0.2-1 mg every 4-6 hours Children: • Oral: 0.03- 0.08 mg/kg/dose every 3-4 hours • IV: 0.01-0.015 mg/kg every 3-8 hours • Maintenance infusion: 0.003-0.005 mg/kg/hour
Morphine (Duramorph®)	Adults • Bolus: 2-10 mg IVP • Intermittent dose: 2-8 mg every 3-4 hours • Maintenance infusion: 0.8-30 mg/hour Children • Bolus 0.1-0.2mg/kg IV over 5min • Intermittent dose: 0.05-0.1 mg/kg every 3-4 hours • Maintenance infusion: Initial 0.01 mg/kg/h – titrate up as required (usual range: 0.01-0.04 mg/kg/hour)

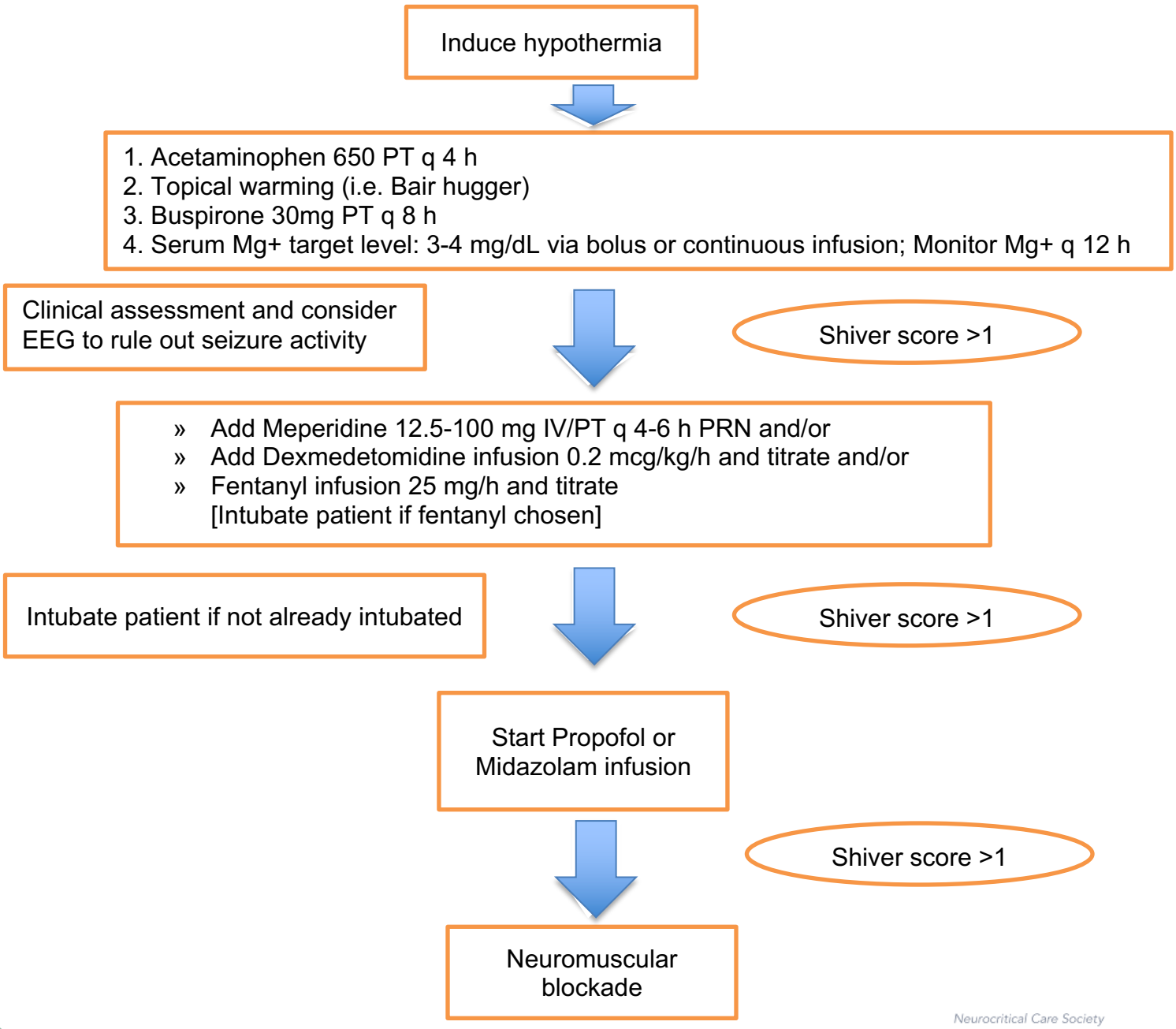
Pediatric considerations: In general, pediatric doses should not exceed adult doses. Routine use of propofol is not recommended due to risk for propofol- related infusion syndrome (PRIS) in children.

Shivering Management

Follow a protocol

During therapeutic temperature management, shivering counteracts attempts to set body temperature. Sustained shivering should be avoided as it counteracts cooling induction, increases metabolic rate and may contribute to ICP elevations and increased brain oxygen consumption. The Adult ENLS anti-shivering protocol is shown in the figure below.

Sample Shivering Protocol for Adult Patients



The Bedside Shivering Assessment Scale

0	
1	Shivering localized to the neck and/or thorax only
2	Shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Shivering involves gross movements of the trunk, upper and lower extremities

These agents are relevant for the ENLS protocols Intracranial Hypertension and Herniation and Resuscitation after Cardiac Arrest. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.

Vasopressors and Inotropes

Augment blood pressure and provide cardiac support

Vasopressor agents are used in a variety of situations when blood pressure augmentation is desired to treat shock, vasospasm or improve cerebral or spinal perfusion pressure. Their effects are produced through actions at adrenergic (alpha and beta), dopamine, and vasopressin receptors. Vasopressin is a nonadrenergic vasopressor used in diabetes insipidus and as a second-line agent in refractory shock. Dobutamine and milrinone function primarily as inotropes. The selection of a vasopressor or inotrope should be based on goals of care and desired physiologic effects.

Category / Drug	Initial Dose	Comments
Mixed α / β receptor agonists		
Norepinephrine	2-5 mcg/min, or 0.02-0.06 mcg/kg/min Pediatric dosing: initial 0.1 mcg/kg/min (range: 0.05-2 mcg/kg/min)	First line agent for septic shock
Epinephrine	0.02-0.05 mcg/kg/min Pediatric dosing: 0.1-1 mcg/kg/min	First line agent for septic shock
Dopamine	Dopa: 1-3 mcg/kg/min β: 3-10 mcg/kg/min α: 10-20 mcg/kg/min	Effective at multiple receptors
Ephedrine	5-25 mg slow IVP, may repeat in 5-10 minutes Pediatric dosing: 0.1-0.3 mg/kg/dose (max 25 mg); not routinely used	Oral formulation, dose at 25-50 mg every 8-12 hours
Pure α receptor agonist		
Phenylephrine	10-200 mcg/min, or 0.1-1 mcg/kg/min Pediatric dosing: 0.1 to 0.5 mcg/kg/min	May cause reflex bradycardia

Non-adrenergic		
Vasopressin	0.04-0.08 units/min Pediatric dosing: 0.03-0.12 units/kg/hour	May demonstrate synergistic effect with other vasopressors
Inotropes		
Dobutamine (mixed α / β)	2.5-10 mcg/kg/min Pediatric dosing: 1-20 mcg/kg/min	Good in decompensated heart failure
Milrinone (non-adrenergic)	0.25-0.75 mcg/kg/min	Reduce dose in renal dysfunction

These agents are relevant for the ENLS protocols Intracranial Hypertension and Herniation, Resuscitation after Cardiac Arrest, Subarachnoid Hemorrhage and Traumatic Brain Injury. Detailed drug information can be found in the Pharmacotherapy ENLS chapter.