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# Pharmacotherapy Pearls for Emergency Neurological Life Support

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**Abstract** The appropriate use of medications during Emergency Neurological Life Support (ENLS) is essential to optimize patient care. Important considerations when choosing the appropriate agent include the patient's organ function and medication allergies, potential adverse drug effects, drug interactions and critical illness and aging pathophysiologic changes. Critical medications used during ENLS include hyperosmolar therapy, anticonvulsants, antithrombotics, anticoagulant reversal and hemostatic agents, anti-shivering agents, neuromuscular blockers, antihypertensive agents, sedatives, vasopressors and inotropes, and antimicrobials. This article focuses on the important pharmacokinetic and pharmacodynamics characteristics, advantages and disadvantages and clinical pearls of these therapies, providing practitioners with essential drug information to optimize pharmacotherapy in acutely ill neurocritical care patients.

**Keywords** ENLS · Pharmacotherapy · Medication · Adverse drug event · Drug interaction

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## Introduction

Neurocritical care patient management is very complicated, especially when trying to optimize therapy during acute injury. Pharmacologic management must be carefully considered in order to minimize cognitive dysfunction and avoid confounding patient evaluations. During emergency neurological life support (ENLS), pharmacotherapy must be individualized for each patient, taking into account their age, comorbidities, and chronic medications. Pharmacokinetic and pharmacodynamic characteristics must be considered as they may change in acute illness and with neurocritical care interventions, such as therapeutic hypothermia. Pharmacokinetic changes may include alterations in medication absorption, distribution, metabolism and elimination; while pharmacodynamics changes could result in loss of drug effect or toxicity. This chapter will focus on pharmacotherapy and clinical pearls that will help the ENLS provider optimize medication management in the acute period of neurological injury.

## Hyperosmolar Therapy

Mannitol and hypertonic saline (HS) are commonly used in neurologically injured patients in the acute setting to treat elevated intracranial pressure (ICP) and cerebral edema. HS is also used in the treatment of hyponatremia. Both agents theoretically work by producing osmotically driven fluid shifts and appear to be equally effective at equal osmolar doses [1]. An online survey of neurointensivists reported that 90% use osmotic agents in the treatment of intracranial hypertension, with a fairly even split in preference for HS (55%) versus mannitol (45%) [2]. It is important to determine which agent would be best in

individual patients based on serum sodium concentrations, plasma osmolality, fluid status, and renal function. A summary of the characteristics of these hyperosmolar agents can be found in Table 1.

Mannitol is an osmotic diuretic that is eliminated by the kidneys. Caution should be used in patients with kidney injury as mannitol may accumulate and worsen cerebral edema; especially in those with BBB disruption due to injury and/or inflammation. An osmolar gap is the most accurate monitoring tool to detect presence of unmeasured osmoles, such as mannitol, and should be used to monitor drug elimination between doses. An osmolar gap of 15–20 mOsm/kg indicates incomplete drug clearance between doses and increases risk of reverse osmotic shift and nephrotoxicity [3–6]. An osmolar gap can be calculated by subtracting the calculated osmolality from the measured osmolality. The laboratories (osmolality, BMP) necessary to calculate an osmolar gap should be drawn as a trough or prior to the mannitol dose. A plasma osmolality of $>320$ mOsm/kg is not a contraindication of ongoing administration of mannitol, as this is not a valid measure of excess mannitol and can also be increased with hyperglycemia. Urine output and electrolyte balances should also be carefully monitored to prevent hypotension, dehydration, and electrolyte imbalances due to excessive diuresis.

Unlike mannitol, HS provides fluid expansion and, therefore, patients with decompensated heart failure or pulmonary edema may be at increased risk of fluid overload. HS may have reduced risk of rebound cerebral edema after discontinuation due to the reflection coefficient of 1 vs 0.9 of mannitol [7, 8]. Caution should be used when administering to patients with chronic hyponatremia as the rapid change in serum sodium may increase the risk of osmotic demyelinating syndrome. Although there are some recommendations to use HS doses equiosmolar to mannitol, there are multiple other studies that show clinical benefit with variable concentrations, doses, and modes of administration of HS. Therefore, at this time, there is no information regarding optimal methods for use of HS. In general, established protocols allow for consistency of care among providers. For that reason, intensivists should work within their institution to come to a consensus regarding treatment goals, develop a protocol, monitor efficacy of the protocol, then re-assess and modify their protocol as needed to achieve the treatment goal. Trough serum sodium levels should be monitored prior to HS administration for HS dose and interval guidance, with the goal to use the lowest dose necessary [9].

**Table 1** Hyperosmolar therapeutic agents for intracranial pressure management [9–12]

| Agent | Dosing | Adverse reactions | Clinical pearls |
|---|---|---|---|
| Mannitol | 0.5–1 g/kg over 5–15 min, can be redosed every 4–6 h | Rebound ICP elevation with abrupt discontinuation (with high, repeated dosing) | Requires in-line filter (precipitates-crystal formation)- may require warming to dissolve crystals before administration |
| | | Acute kidney injury | May be given via peripheral access |
| | | Dehydration | Duration of effect 90 min–6 h |
| | | Hypotension | Monitor trough osmolar gap (Goal $<20$ mOsm/kg) |
| | | Electrolyte imbalances | |
| Hypertonic saline | Concentration dependent (*concentrations listed are approximately equal osmolar to mannitol* 1 g/kg) | Pulmonary edema | Central access required for 23.4% bolus |
| | | Heart failure | Central access for $>2\%$ NaCL if continuous infusion |
| | | Acute kidney injury | |
| | Bolus dosing | Coagulopathy | Duration of effect 90 min–4 h |
| | 3%: 5 ml/kg over 5–20 min (range 2.5–5 ml/kg) | Hypernatremia | Rapid availability via ADC may be limited |
| | | Metabolic acidosis | Controversial if continuous infusion is beneficial for ICP control, but should be used for severe hyponatremia |
| | 5%: 3 ml/kg over 5–20 min (range 2.5–5 ml/kg) | Thrombophlebitis | |
| | 7.5%: 2 ml/kg over 5–20 min (range 1.5–2.5 ml/kg) | Osmotic demyelination syndrome with rapid correction | Monitor serum sodium every 4–6 h (trough), avoid prolonged hypernatremia $>160$ meq/l |
| | 23.4%: 30 ml over 10–20 min | | Decrease chloride and increase acetate content if patients develop metabolic acidosis |
| | Other options: | | |
| | Continuous infusion titrated to a goal Na range | | Use is discouraged in combination with tolvaptan, conivaptan or lithium |

*ICP* intracranial pressure, *ADC* automatic dispensing cabinet

## Anticonvulsant Medications

Drug dosing can be complex when using anticonvulsant agents for status epilepticus (SE), seizure treatment or seizure prophylaxis in select disease states. Agents recommended for SE are given IV over a short period of time, but the choice of agent is mostly dependent on adverse drug reactions (ADRs) and patient stability. Many anticonvulsant agents contain propylene glycol in their intravenous formulation, which can cause hypotension during infusion and may accumulate with prolonged dosing causing metabolic acidosis and neurotoxicity. Anesthetic agents, such as pentobarbital, can cause ileus, immunosuppression, cardiotoxicity and hemodynamic instability and thus need to be monitored closely. Unfortunately, many institutions do not have therapeutic drug concentration monitoring available for pentobarbital and the kinetics are unpredictable; therefore, monitoring the agent's effects with continuous EEG and hemodynamic devices is crucial. When treatment of neurological injury requires therapeutic hypothermia (TH), anticonvulsant agents that are metabolized by the liver will have prolonged duration of action. Careful anticonvulsant concentration monitoring is required and should be done approximately every 48 h over the duration of TH to avoid toxicity and for 3–5 days after rewarming as metabolism increases to baseline to avoid sub-therapeutic concentrations, with doses adjusted based on serum trough concentrations. Traumatic brain injury patients also tend to be hypermetabolic in the acute phase making dosing of anticonvulsant agents, as well as other hepatically metabolized medications, problematic. In these patients, drugs that are metabolized by the liver tend to have lower pharmacodynamics effects due to rapid metabolism and elimination, and higher doses may be required. Lastly, many of the first generation anticonvulsant agents have complex drug interactions that further require therapeutic drug monitoring and frequent assessment of ADRs. A summary of the medications used to treat SE can be found in Table 2.

## Antithrombotic Agents

Antithrombotic agents may be used for management of acute ischemic stroke (AIS) in the first few hours (e.g. tissue plasminogen activator [tPA], aspirin [ASA], clopidogrel [Plavix]). In addition, patients presenting with intracranial hemorrhage may have be using ASA or Plavix for cardiovascular issues. Knowledge of the characteristics of these agents is important for patient safety. Due to unique mixing instructions (e.g. proper dilution, swirling vs shaking, etc.) of tPA, only those who have been educated on the process should reconstitute the drug. When preparing the appropriate dose of tPA, excess drug should be removed from the bottle before infusion to prevent inadvertent administration of total doses of $>90$ mg and increased risk of intracerebral bleeding. ASA can also be used acutely for patients who are not candidates for tPA; however, other antiplatelet agents, including prasugrel and ticagrelor, have a paucity of data for use acutely after ischemic stroke and prasugrel carries a warning for increased risk of serious bleeding in stroke patients. In patients who are allergic to aspirin and thus not candidates for tPA, clopidogrel can be used. Clopidogrel is commonly administered prior to endovascular procedures as a loading dose and then daily thereafter, and may be used in combination with ASA for 3 months in those who received intracranial stents. It should be noted that approximately 30% of the population have genetic polymorphisms and do not respond to clopidogrel as it is a prodrug that must be converted to its active form. Assays can be used to determine the effectiveness of platelet inhibition with ASA and clopidogrel.

Direct oral anticoagulant (DOACs) are used for stroke prevention in moderate to high risk patients with non-valvular atrial fibrillation. These agents inhibit either thrombin or factor Xa, which are essential for clot formation. DOACs have a significantly lower intracranial bleeding risk than warfarin, but are associated with a risk of gastrointestinal bleeding. When considering tPA for a patient with an AIS, DOAC administration within the last 48 h or any abnormal coagulation tests for these specific agents are a contraindication for receiving tPA. The time of last dose and renal function is essential to know if your institution does not have the specific assays to evaluate each drug class. If the patient requires ASA for AIS and is on a DOAC, there is an increased risk of bleeding and the risk to benefit ratio must be considered until the DOAC has had time to be cleared from the body (i.e. approximately 3–5 half-lives).

The pharmacologic properties of the warfarin, DOACs and antiplatelet agents commonly used in AIS can be found in Tables 3 and 4.

## Anticoagulant/Antiplatelet Reversal and Hemostatic Agents

Reversal of anticoagulants in patients with life threatening bleeding or sustained bleeding is critical. Life threatening bleeding can include intracerebral hemorrhage, gastrointestinal bleeding, uncontrolled retroperitoneal or any hemorrhage into an extremity with risk of compartment syndrome. Reversal may also be necessary when an emergent surgical intervention is required within 6–12 h of presentation. General management strategies to employ when treating major hemorrhages include identifying the cause and source of bleeding, maintaining hemodynamic

**Table 2** Status epilepticus drug dosing recommendations [13, 14]

| Drug name | Dose | Rate | Target serum concentration | Adverse effects | Clinical pearls |
|---|---|---|---|---|---|
| Diazepam (Valium®) | 0.15 mg/kg IV (up to 10 mg per dose); may repeat in 5 min | 5 mg/min (IVP) | N/A | Hypotension, respiratory depression | Rapid redistribution rate; can be given rectally; contains propylene glycol |
| Lorazepam (Ativan®) | 0.1 mg/kg IV (up to 4 mg per dose); repeat in 5–10 min | 2 mg/min (IVP) | N/A | Hypotension, respiratory depression | May be longer-acting for seizure cessation than diazepam, contains propylene glycol |
| Midazolam (Versed®) | 0.2 mg/kg IM up to 10 mg per dose<br>RSE: 0.2 mg/kg (2 mg/min) IV then 0.05–2 mg/kg/h | | N/A | Sedation, respiratory depression | Can also be given buccally, intranasally |
| Phenytoin (Dilantin®) | Load: 20 mg/kg Maintenance dose: 4–6 mg/kg/day divided in 2–3 doses | Up to 50 mg/min | 10–20 mcg/ml Free: 1–2 mcg/ml (an accurate estimate may be obtained 1 h after infusion complete) | Arrhythmias, hypotension, bradycardia | Hypotension (contains propylene glycol), especially in older adults; STRONG CYP inducer with many potential drug interactions |
| Fosphenytoin (Cerebryx®) | Load: 20 mg PE/kg<br>Maintenance dose: 4–6 mg/kg/day divided into 2–3 doses | Up to 150 mg PE/min | Total phenytoin: 10–20 mcg/ml<br>Free phenytoin: 1–2 mcg/ml<br>(an accurate estimate may be obtained 1 h after infusion complete) | Paresthesias, hypotension, bradycardia | Prodrug – converts to phenytoin in 7–15 min after infusion; less thrombophlebitis than phenytoin; same drug interactions and monitoring parameters |
| Phenobarbital | 20 mg/kg<br>1–3 mg/kg/day divided into 1–3 doses | 50–100 mg/min | 15–40 mcg/ml | Hypotension, sedation, respiratory depression | Long-acting; contains propylene glycol; STRONG CYP enzyme inducer with many potential drug interactions |
| Valproate sodium (Depacon®) | Load: 20–40 mg/kg IV<br>Maintenance dose: 10–15 mg/kg/day divided into 2–4 doses | 3–6 mg/kg per minute | 50–150 mcg/ml | Hepatotoxicity, thrombocytopenia, hyperammon-emic encephalopathy, | Less CV side effects than phenytoin<br>CYP enzyme inhibitor with many potential drug interactions<br>Meropenem will significantly reduce VPA levels and should not be used with VPA |
| Levetiracetam (Keppra®) | 1000–3000 mg/day in 2 divided doses<br>IV: administer over 15 min | Over 15 min | 12–46 mcg/ml (not typically monitored) | Dizziness, behavior disturbances (irritability, agitation, aggression) | Reduce dose in renal impairment; few drug interactions |
| Lacosamide (Vimpat®) | 200–400 mg IV<br>Every 12 h | Over 15 min | 2.8–18 mcg/ml (not typically monitored) | PR prolongation, hypotension (rare) | Monitor EKG in patients with underlying cardiac disease; reduce dose in renal impairment; few drug interactions |
| Topiramate (Topamax®) | 200–400 mg NG/PO every 6–12 h | | 2–20 mcg/ml (not typically monitored) | Metabolic acidosis | Weak 2C19 inhibitor |
| Propofol (Diprovan®) | Bolus: 1–2 mg/kg IV<br>RSE: 30–250 mcg/kg/min | | N/A (typically titrated to EEG) | Hypotension, respiratory depression, PRIS | Requires mechanical intubation; often vasopressors are required, hemodynamic monitoring, high lipid load (increased calories; 1.1 kcal/ml) |

**Table 2** continued

| Drug name | Dose | Rate | Target serum concentration | Adverse effects | Clinical pearls |
|---|---|---|---|---|---|
| Pentobarbital (Nembutal®) | Bolus: 10–15 mg/kg IV<br>RSE: 0.5–5 mg/kg/h (may require higher doses to induce burst suppression) | Up to 50 mg/min | 10–20 mcg/ml (typically titrated to EEG) | Hypotension, respiratory depression, cardiac depression, infection, ileus | Requires mechanical intubation, vasopressors, hemodynamic monitoring; STRONG CYP enzyme inducer with many potential drug interactions |
| Ketamine (Ketalar®) | RSE: 0.5–4.5 mg/kg IV bolus, then infusion up to 5 mg/kg/h | | N/A | Hypertension, arrhythmias | Has been associated with cerebral atrophy [15] |

*CV* cardiovascular, *EEG* electroencephalogram, *IM* intramuscular, *IVP* intravenous push, *N/A* not applicable, *NG* nasogastric, *PE* phenytoin equivalents, *PO* by mouth, *PRIS* propofol-related infusion syndrome, *RSE* refractory status epilepticus, *VPA* valproic acid, *CYP* cytochrome P-450 enzyme system

and respiratory stability, maintaining normal body temperature, blood pH and electrolyte balance to facilitate coagulation, application of packing or dressing if applicable, local hemostatic measures or surgical intervention to control bleeding, and lastly identify the anticoagulant and administer an appropriate reversal agent [20].

When reversing an anticoagulant, the risk of continued bleeding to risk of thrombosis is of the utmost importance and should be determined in each case. Second, timing of the last dose of anticoagulant administered and elimination half-life are also necessary to determine if reversal is warranted. If the agent was taken within the 3–5 half-life window, then reversal should be considered in patients with a higher risk of continued bleeding [21]. In medications with longer half-lives (i.e. apixaban) reversal may be considered out to 2–3 days from the last dose. When considering all oral anticoagulants, if the oral agent has been ingested in the previous 2 h, 50 g of oral activated charcoal should be considered. Risks and benefits of this reversal strategy should be considered, especially in patients with gastrointestinal bleeding.

When reversing warfarin the administration of both a rapid reversal agent as well as an agent with sustained effect is crucial since the half-live of warfarin is fundamentally the half-life of factors II (42–72 h), VII (4–6 h), IX (21–30 h), and X (27–48 h). For rapid reversal of warfarin, the Neurocritical Care Society (NCS), American Colleges of Chest Physicians, (CHEST) and American Heart Association/American Stroke Association (AHA/ASA) guidelines suggest use of prothrombin complex concentrate (PCC) agents over fresh frozen plasma (FFP) [22–24]. In addition, a recent study showed 4-Factor PCC to be more likely to achieve a reduction of INR to $<1.3$ in 3 h and was associated with less hematoma expansion than FFP in warfarin-associated ICH patients [25]. PCC's are generally better tolerated than FFP due to lower fluid volumes and decreased risk for transfusion related acute lung injury (TRALI) or circulatory overload (TACO) [26, 27]. There are two types of PCC products available, 4-factor and 3-factor PCC. 4-factor PCC contain all of the vitamin K-dependent coagulation factors, are sufficient to provide immediate warfarin reversal and are the preferred products when available. 3-factor PCC contains only factors II, IX, and X and consideration should be made to supplement with FFP or recombinant factor VIIa to completely reverse anticoagulation. FFP may be a better choice however in patients that require volume resuscitation, and may be used in combination with PCC if reversal is inadequate. When administering PCC for reversal of warfarin, the dose administered is generally based on the clinical scenario and INR (see Table 5). A repeat INR may be checked 30 min after the end of PCC infusion to evaluate if it is within normal range [26, 28–30]. Although limited

**Table 3** Comparison of oral anticoagulant agents [14]

| | Warfarin (Coumadin®) | Dabigatran (Pradaxa®) | Rivaroxaban (Xarelto®) | Apixaban (Eliquis®) | Edoxaban (Savaysa®) |
|---|---|---|---|---|---|
| Mechanism | Vitamin K antagonist (II, VII, IX, X) | Direct thrombin inhibitor | Direct Xa inhibitor | Direct Xa inhibitor | Direct Xa inhibitor |
| Indication | Cardioembolic stroke<br>VTE treatment | Nonvalvular atrial fibrillation<br>VTE treatment | Nonvalvular atrial fibrillation<br>VTE treatment<br>VTE prophylaxis (ortho) | Nonvalvular atrial fibrillation<br>VTE treatment<br>VTE prophylaxis (ortho) | Nonvalvular atrial fibrillation<br>VTE treatment |
| Dose | Variable<br>INR goal is usually 2–3 (goal of 2.5–3.5 with mechanical valves) | **VTE/non valvular afib**<br>150 mg BID (CrCl > 30 ml/min)<br>75 mg twice daily (CrCl 15–30 ml/min)<br>Not recommended in CrCl < 15 ml/min | **VTE**<br>15 mg BID with food for 3 weeks followed by 20 mg once daily<br>**Ortho prophylaxis** 10 mg once daily<br>**Nonvalvular afib***:<br>20 mg once daily with food;<br>15 mg once daily (CrCl 15–50 ml/min) | **VTE**<br>10 mg BID × 7 days followed by 5 mg BID for 6 months<br>**Ortho prophylaxis**<br>2.5 mg BID<br>**Nonvalvular afib**<br>5 mg BID PO;<br>2.5 mg BID if ≥2 of the following: ≥80 yo, ≤60 kg, Cr ≥ 1.5 mg/dl | **VTE**<br>60 mg daily<br>30 mg daily (CrCl 15–50 m/min) |
| Onset | 48–120+ h | 1–2 h | 2–4 h | 3–4 h | 1–2 h |
| Half-life | 20–60 h (variable) | 12–17 h[a] | 5–9 h<br>11–13 elderly | 8–12 h[a] | 10–14 h |
| Drug interactions | ↑ *warfarin effects*<br>Herbals<br>Amiodarone/dronedarone<br>Antibiotics<br>Antifungals<br>HIV medications<br>Phenytoin (acutely)<br>Acute ethanol ingestion<br>↓ *warfarin effects*<br>Phenobarbital<br>Carbamazepine<br>Rifampin<br>Vitamin K (food as well)<br>Chronic ethanol ingestion | ↑ *dabigatran effects (PgP inhibitors)*<br>Dronedarone<br>Ketoconazole<br>↓ *dabigatran effects*<br>Rifampin | ↑ *rivaroxaban effects (PgP and CYP3A4 inhibitors)*<br>Clarithromycin<br>Erythromycin<br>Ketoconazole<br>Fluconazole<br>Ritonavir<br>↓ *rivaroxaban effects (PgP and CYP3A4 inducers)*<br>Phenytoin<br>Phenobarbital<br>Carbamazepine<br>Rifampin | ↑ *apixaban effects(PgP and CYP3A4 inhibitors)*<br>Clarithromycin<br>Erythromycin<br>Ketoconazole<br>Fluconazole<br>Ritonavir<br>↓ *apixiban effects (PgP and CYP3A4 inducers)*<br>Phenytoin<br>Phenobarbital<br>Carbamazepine<br>Rifampin | ↑ *edoxaban effects (PgP inhibitors)*<br>Verapamil<br>Erythromycin<br>Ketoconazole<br>Cyclosporin<br>Amiodarone/dronedarone<br>↓ *apixiban effects (PgP inducers)*<br>Rifampin |
| Contraindications | Child-Pugh C (caution) | CrCl ≤ 15 ml/min | CrCl ≤ 15 ml/min<br>Child-Pugh C | CrCl ≤ 15–25 ml/min<br>Child-Pugh C | CrCl > 95 ml/min (reduced efficacy) |

**Table 3** continued

| | Warfarin (Coumadin®) | Dabigatran (Pradaxa®) | Rivaroxaban (Xarelto®) | Apixaban (Eliquis®) | Edoxaban (Savaysa®) |
|---|---|---|---|---|---|
| Peri-procedural discontinuation | 1–7 days (surgery risk dependent) | 1–7 days (renal function and surgery risk dependent) | 1–5 days (renal function and surgery risk dependent) | 1–5 days (renal function and surgery risk dependent) | 24 h prior (renal and surgery risk dependent) |
| Clinical pearls | Numerous drug–drug-food interactions | Pro-drug-Do not open/crush (~ 75% ↑ in exposure | Can crush and administer via feeding tube (as long as not given post-pyloric); Dose adjustments vary by indications | Can crush 5 or 2.5 mg tabs in 60 ml D5 W and administer via feeding tube; | Consider dose reduction in patient < 60 kg |

*Ortho* orthopedic, *afib* atrial fibrillation, *CrCl* creatinine clearance, *scr* serum creatinine

data is available for recommending a second dose of PCC, if INR remains elevated and risk of continued bleeding is still high, a second dose of PCC may be considered. Of note, factor eight inhibitor bypassing agent (FEIBA®), a 4-factor PCC with activated factor VII, may interfere with INR test resulting in a falsely low INR. Four-factor PCC was recently shown to be more effective than FFP in reversing INR, especially when reversal is emergent [31]. There are no clinical trials combining PCC and factor rVIIa for treatment of life threatening bleeding. It is unknown if combined use increases efficacy or risk of thrombosis. Current recommendation is to not combine factor rVIIa and 4-factor PCC. For sustained reversal, phytonadione (vitamin K) should be simultaneously administered to patients who require rapid reversal. Intravenous and oral vitamin K effectively lowers INR within 12–14 and 24–36 h, respectively [32–34]. Subcutaneous administration is not recommended due to unpredictable absorption and delayed response [35].

Idarucizumab (Praxbind) is a humanized monoclonal antibody fragment that binds dabigatran to neutralize its anticoagulant effects within minutes of administration. The recommended dose of idarucizumab is 5 g intravenously, administered in two 2.5 g doses [36–38]. Each 2.5 g vial should be administered over no longer than 5–10 min and each vial should be given no more than 15 min apart. Idarucizumab must be administered within 1 h after removal from the vial. It has been demonstrated that plasma dabigatran concentrations may rebound 12–24 h after idarucizumab administration, likely due to re-distribution from the extravascular compartment. Safety and effectiveness of repeat treatment with idarucizumab has not been established. Additionally, renal impairment does not impact the reversal effect of idarucizumab and therefore there is no dose adjustment necessary in patients with renal impairment.

Until the release of a specific antidote to reverse factor-Xa inhibitors, administration of a 4-factor PCC should be strongly considered for reversal of life-threatening bleeds in patients taking factor-Xa inhibitors (apixaban, rivaroxaban, edoxaban). There is no standard recommended dose of PCC for treatment of bleeding associated with these agents, but one study demonstrated an improvement in surrogate endpoints, endogenous thrombin potential and PTT, in health individuals who received PCC 50 units/kg to reverse rivaroxaban [39]. Only animal studies have evaluated factor VIIa for treatment of bleeding associated with rivaroxaban. Andexanet alfa is a recombinant, inactive protein analogue of factor-Xa that competitively binds apixaban and rivaroxaban and eliminates the ability of these agents to inhibit endogenous factor-Xa. Andexanet alfa should be available in the United Stated by the end of 2017 and will be the drug of choice for reversal of

**Table 4** Comparison of antiplatelet medications [14, 16–19]

| Indication | Medication | Dose | Interactions | Clinical pearls |
|---|---|---|---|---|
| *AIS primary prevention* | *COX inhibitor*<br>Aspirin | 81–325 mg daily | | Irreversible platelet inhibition (5–7 days)<br>GI bleed is most common complication: Dose dependent risk<br>81 mg vs 325 mg—higher dose may ↑ risk 2×<br>Risk is not decreased with buffered or enteric coated dosage formulations<br>Ibuprofen can inhibit non-enteric coated ASA effects, so must be dosed 8 h before or 30 min after ASA dose |
| *AIS secondary prevention* | Aspirin | 81 mg daily | | See above |
| | *PDE inhibitor*<br>Dipyridamole/aspirin (Aggrenox®) | 200 mg/25 mg BID | No significant drug interactions | Irreversible platelet inhibition (5–7 days)<br>Headache in up to 40% of patients<br>Tolerance often develops within 1–2 weeks |
| | *ADP inhibitors*<br>Clopidogrel (Plavix®) | 75 mg daily; 300–600 mg loading doses prior to endovacular procedures | ↓ *clopidogrel effects*<br>Proton pump inhibitors | Pro-drug—CYP2C19 conversion to active metabolite<br>Impacted by genetic polymorphisms<br>Irreversible platelet inhibition (5–7 days)<br>Hypersensitivity (usually rash)<br>ADR: TTP is rare (ticlopidine > clopidogrel) |
| | Ticlopidine (Ticlid®) | 250 mg BID | Strong inhibitor of CYP2C19, and moderate inhibitor of CYP2D6 | Pro-drug—CYP3A4 conversion to active metabolite<br>Irreversible platelet inhibition (5–7 days)<br>Replaced by clopidogrel-delayed onset and ↑ ADR's<br>ADR's: GI intolerance, neutropenia, aplastic anemia, and TTP |

*COX* cyclooxygenase, *PDE* phosphodiesterase, *ADP* adenosine diphosphate, *BID* twice daily, *NSAIDs* non-steroidal anti-inflammatory drug, *GI* gastrointestinal, *CYP* cytochrome P450, *ADR* adverse drug reaction, *TTP* thrombotic thrombocytopenic purpura

**Table 5** Reversal of vitamin K antagonist

| INR | Clinical setting | Treatment options |
|---|---|---|
| *Vitamin K antagonist reversal* | | |
| <4.5 | No bleeding | Hold warfarin until INR in therapeutic range |
| | Rapid reversal required (<24 h) | Hold warfarin |
| | | Vitamin K 2.5 mg PO |
| | | If urgent reversal needed (≤12 h) for procedure consider 4PCC 25 IU/kg IV or rFVIIa 1 mg 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[a] |
| | Rapid reversal required (<24 h) | Hold warfarin |
| | | Give vitamin K 5 mg PO |
| | | If urgent reversal needed (≤12 h) for procedure consider 4PCC 35 IU/kg IV or rFVIIa 1 mg IV |
| >10 | No bleeding | Hold warfarin until INR in therapeutic range |
| | | Give vitamin K 2.5–5 mg PO or 1–2 mg IV[a] |
| | | Repeat every 24 h as necessary |
| | Rapid reversal required (<24 h) | Hold warfarin |
| | | Give vitamin K 1–2 mg IV |
| | | Repeat every 6–24 h as necessary |
| | | If urgent reversal needed (≤12 h) for procedure consider 4PCC 50 IU/kg IV or rFVIIa 1 mg IV |
| ANY INR | Serious or life threatening bleeding | Hold warfarin |
| | | Give vitamin K 10 mg IV over 30 min |
| | | If patient volume overloaded give PCC |
| | | Recheck INR 30 min after PCC administered[b] |

| INR | 4-factor PCC dose (units/kg) | Max dose (units) |
|---|---|---|
| 2–3.9 | 25 | 2500 |
| 4–6 | 35 | 3500 |
| >6 | 50 | 5000 |

| | | |
|---|---|---|
| | | If volume resuscitation needed give 15–20 ml/kg FFP |
| | | Recheck INR after FFP administered |

[b] Consider second dose of PCC if INR still elevated and patient still bleeding

life threatening bleeding in patients taking factor-Xa inhibitors. Studies have shown the intravenous administration of a bolus of andexanet, followed by 2 h of continuous infusion, restores endogenous factor-Xa function with effective hemostasis in patients with acute major bleeding receiving oral factor-Xa inhibitors [40, 41].

Recombinant activated factor VII (rFVIIa) was shown to decrease hematoma growth in non-coagulopathic ICH patients, however no improvement in mortality was demonstrated in a large randomized trial so it is not recommended in this patient population [42]. The NCS, CHEST and AHA/ASA do not recommend rFVIIa for warfarin reversal although its use to supplement 3-factor PCC in patients with life threatening bleeding on warfarin may be considered [24, 43–45]. The dose of rFVIIa is not well established and generally lower doses (10–20 mcg/kg) are preferred due to risk of thrombosis with higher doses. The duration of INR correction is dose dependent, transient, and does not reflect efficacy. Furthermore, there may be an increased risk of thrombotic complications with the use of rFVIIa and this risk may be increased with concomitant use of PCC although not well established.

Platelet transfusions are used commonly for both prophylactic and therapeutic reversal of antiplatelet therapy in patients taking an antiplatelet agent (Aspirin, clopidogrel, prasugrel, ticagrelor) with acute neurologic injury. Although a paucity in the literature still exists in regards to administration of platelets for an emergent neurosurgical procedure or in patients after TBI or aSAH, recent findings from the PATCH trail demonstrate worse outcomes in

patients that receive platelets for spontaneous ICH when compared to standard care without platelet therapy [46]. However, few patients in PATCH were on clopidogrel and those undergoing neurosurgical procedures were excluded. (Please see ENLS ICH module for further recommendations regarding platelet transfusion) (Tables 6, 7, 8, 9).

## Antifibrinolytic Therapy after Subarachnoid Hemorrhage

Re-hemorrhage is a significant problem in management of patients with aneurysmal subarachnoid hemorrhage (SAH) and contributes to morbidity and mortality in the acute setting. Antifibrinolytics have a role as short term therapy (less than 72 h) to prevent rebleeding in the acute setting while waiting for treatment to secure the aneurysm. Several retrospective and one prospective study have shown that a short course of an antifibrinolytic reduce the rate of re-hemorrhage without an increase in cerebral ischemia, vasospasm, and/or hydrocephalus [49–51].

Tranexamic acid is generally dosed as 1 g IV given over 10 min every 4–6 h and aminocaproic acid (Amicar) as a 5 g IV bolus given over 1 h followed by 1 g/h infusion. Caution must be used when giving concomitantly with nimodipine as both may cause a precipitous decrease in blood pressure. Due to potential risk of ischemic complications in patients undergoing endovascular treatment, one may consider holding antifibinolytic therapy 4–6 h prior to the endovascular procedure to prevent thrombotic complications. Only short-term therapy, generally less than 72 h post bleed, is recommended.

## Shiver Control during Therapeutic Temperature Management

Shivering is a physiologic homeostatic mechanism that helps maintain temperature and is triggered in humans when core temperature falls below 36 degrees Celsius and ceases at temperatures $<34$ Celsius. Elderly patients have approximately a 1-degree Celsius lower shivering threshold than younger patients [52]. Sustained shivering increases the metabolic rate and should be avoided as it counteracts cooling induction, consumes energy, contributes to increased intracranial pressure, and increases brain oxygen consumption [53]. Therefore it is crucial to evaluate and treat shivering in patients who are being treated with therapeutic temperature management (Tables 10, 11; Fig. 1).

## Neuromuscular Blocking Agents

Neuromuscular blocking agents are used as an adjunct to general anesthesia to facilitate tracheal intubation, provide skeletal muscle relaxation during surgery, facilitate mechanical ventilation, assist in treatment of malignant ICP, or control refractory shivering during targeted temperature management. Short acting agents are preferred. These agents interrupt signal transmission at the neuromuscular junction, and are categorized as either depolarizing or non-depolarizing agents. Succinylcholine is the only depolarizing paralytic and works by mimicking the action of acetylcholine. All other agents are non-depolarizing, competitive acetylcholine antagonists. Drug Interactions can be seen with drugs that reduce or inhibit plasma cholinesterase activity, and synergistic effects may occur with other neuromuscular blocking agents. Certain medications can increase the duration of neuromuscular blockade. (Paralytics affect all skeletal muscles but have no effect on consciousness, and therefore must be used with proper sedation and analgesia. 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 utilized 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,

**Table 6** Reversal of factor Xa inhibitors

| Generic | Elimination half-life | Remove by HD | Emergent reversal for life-threatening bleeding |
|---|---|---|---|
| *Factor Xa inhibitor reversal* | | | |
| Apixaban (Eliquis) | 8–12 h longer in renal impairment | No | If ingested within 2 h, administer activated charcoal 50 g<br>Administer PCC 25—50 units/kg over 10 min |
| Rivaroxaban (Xarelto) | 5–9 h<br>Elderly: 11–13 h longer in renal impairment | No | If volume needed consider 15–20 ml/kg FFP<br>Consider time of last dose and half-life of agent when deciding to reverse agent |
| Edoxaban (Savaysa®) | 10–14 h longer in renal impairment | No | Recommend reversal if last dose given within 3–5 elimination half-lives of the drug to ensure hemostasis |

**Table 7** Reversal of direct thrombin inhibitors

| Generic | Elimination half-life | Remove by HD | Emergent reversal for life-threatening bleeding |
|---|---|---|---|
| *Direct thrombin inhibitor reversal* | | | |
| Dabigatran (Pradaxa) | 12–17 h up to 34 h in severe renal impairment | 62–68% | If ingested within 2 h, administer activated charcoal 50 g<br>Drug of choice: Idarucizumab 5 g IV push (two 2.5 g vials given back-to-back)<br>Consider the following if Idarucizumab not available:<br>Emergent hemodialysisOR<br>*Weak evidence for*<br>FFP 15–20 ml/kg<br>rFVIIa 20 mcg/kg and may repeat × 1 |
| Bivalirudin (Angiomax) | 25 min up to 1 h in severe renal impairment | 25% | Turn off infusion.<br>Monitor aPTT to confirm clearance<br>Supportive measures to control bleeding |

**Table 8** Reversal of low molecular weight heparin [47, 48]

| Generic | Elimination half-life | Emergent reversal for life-threatening bleeding |
|---|---|---|
| Enoxaparin (Lovenox) | 4–7 h longer in renal impairment | Protamine partially reverses the anticoagulant effect of LMWHs (~60%) |
| Dalteparin (Fragmin) | 3–5 h longer in severe renal impairment | |
| Fondaparinux (Arixtra) | 17–21 h significantly longer in renal impairment | [a] Consider reversal beyond 12 h in patients with renal insufficiency<br>Monitor anti factor Xa activity to confirm reversal<br>**Supportive treatment**<br>*Data weak for reversal effect with the following but may consider*<br>PCC 50 units/kg OR<br>Factor VIIa 20 mcg/kg and may repeat x 1<br>**Protamine does not help reverse bleeding** |

| Time since last dose of LMWH | Dose of protamine |
|---|---|
| <8 h | 1 mg per for each 100 units enoxaparin/dalteparin administered (max 50 mg) |
| 8–12 h | 0.5 mg for each 100 units enoxaparin/dalteparin administered (max 25 mg) |
| >12 h | Not likely to be useful[a] (max 25 mg) |

caution should be exercised when using PNS in the setting of hypothermia (Tables 12, 13).

## Sedation and Analgesia

When using sedative and analgesic agents during ENLS, treatment and monitoring goals must be identified and communicated. Many of these agents will be affected by end organ dysfunction and drug interactions, so choices must be individualized for each patient based on these parameters. The minimum effective dose should be used. When used in combination, many of these agents are synergistic, so lower doses of both agents can be used (e.g. propofol and morphine). Older adult patients may be more sensitive to these agents and have impaired renal and hepatic function that prolongs drug effects, thus lower doses and shorter acting agents are preferred. Sedatives and

**Table 9** Reversal of unfractionated heparin

| Generic | Elimination half-life | Remove by HD | Emergent reversal for life-threatening bleeding |
|---|---|---|---|
| *Heparin reversal* | | | |
| Heparin | 1–2 h (dose-dependent) | Partial | Protamine neutralizes heparin |

| Time since last dose of heparin | Dose of Protamine |
|---|---|
| Immediate | 1 mg for each 100 units of heparin administered (max 50 mg) |
| 30 min | 0.5 mg for each 100 units of heparin administered |
| >2 h | 0.25 mg for each 100 units of heparin administered |

* Risk factors for bleeding: hepatic or renal disease, alcohol abuse, malignancy, >75 years, plts < 75, concomitant ASA, SBP ≥ 160, Hct < 30, excessive fall risk, recent stroke

**Table 10** The Bedside Shivering Assessment Scale [53]

| Score | Description |
|---|---|
| 0 | No shivering |
| 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 |

**Table 11** Anti-shivering medications for therapeutic temperature management [14, 54–57]

| Drug | Dose | Advantages | Disadvantages |
|---|---|---|---|
| Acetaminophen | 650–1000 mg q 4–6 h | No sedative effects | Caution with liver dysfunction |
| | | | Available as both IV and PO/PT |
| Ibuprofen | 400–600 mg q 4–6 h | No sedative effects | Caution with renal dysfunction or recent GI bleed |
| | | | Available as both IV and PO/PT |
| | | | Theoretical platelet dysfunction |
| Buspirone | 20–30 mg q 8 h | Can use in combination with meperidine | Only oral administration available |
| | | Does not decrease seizure threshold | |
| | | Minimally sedative | |
| Dexmedetomidine | 0.2–2 mcg/kg/h | May have additive effects with meperidine | Dose limiting ADRs: Hypotension and bradycardia |
| | | | Bolus dose not recommended |
| | | Short activity | |
| Magnesium | Bolus: 4 g IV q 4 h to maintain goal serum level | Serum Mg+ goal: 3–4 mg/dl | Monitor Ca+, K+, and Phos levels as well and replace to maintain normal serum levels |
| | OR | | |
| | Infusion: 0.5–1 mg/h | | |
| Propofol | 50–75 mcg/kg/min | Short activity | Caution in patients with hypotension |
| | | | Must be intubated |

**Table 11** continued

| Drug | Dose | Advantages | Disadvantages |
|---|---|---|---|
| Benzodiazepine (midazolam, lorazepam) | Bolus: 2–5 mg IV PRN<br>OR<br>Infusion: 1–10 mg/h | Can be used PRN or continuous infusion | Prolonged sedation with continuous infusion |
| Fentanyl | 25–150 mcg/h | Short acting (t 1/2 = 3–4 h)<br>Can be used PRN or continuous infusion | Constipation |
| Remifentanyl | 0.1–1 mcg/kg/min | Short acting (t 1/2 = 5–10 min) | Constipation |
| Meperidine | 25–100 mg IV q 4–6 h PRN | Most effective anti-shiver drug<br>May have additive effects with dexmedetomidine | Accumulation occurs in renal dysfunction<br>Decrease seizure threshold; caution with frequent dosing |
| Dantrolene | 1–2.5 mg/kg IV q 6 h (doses > 100 mg q 6 h are generally not recommended) | Impacts degree of shiver (gain), not shiver threshold<br>Good adjunctive therapy<br>Mild sedative effects | |
| Paralytic:<br>Vecuronium<br>Cisatracurium | Vecuronium:<br>Bolus: 0.05–0.1 mg/kg (duration 30–45 min)<br>Infusion: 0.05–1.5 mcg/kg/min titrate to TOF<br>Cisatracurium:<br>Bolus: 0.1–0.2 mg/kg (duration 45–60 min)<br>Infusion: 2–10 mcg/kg/min | Last line therapy | Patient must be adequately sedation and analgesia prior to paralytic administration<br>Must be intubated<br>EEG recommended during paralysis<br>Vecuronium may have prolonged effect with renal and hepatic dysfunction |

opiates may produce tolerance and dependence, which can result in increasing dose requirements. Withdrawal symptoms can occur with abrupt discontinuation after prolonged use; therefore, it is suggested to down titrate maintenance infusions by not more than 25% daily.

Drug interactions for these agents can lead to further complications, overutilization of monitoring devices and longer intensive care unit (ICU) lengths of stay. Monitoring medications as they are added and discontinued can help prevent unwanted adverse drug reactions. Sedative and analgesic agents commonly used in the ICU can be found in Tables 14 and 15.

### Intravenous Antihypertensive Agents

Intravenous antihypertensive are necessary to mitigate hypertension in many acute neurologic conditions. Blood pressure goals vary dramatically between disease states and controversy surrounds the definition of best practice in many areas. When blood pressure reduction is required the agent of choice should be selected based on the rapidity of control required, underlying cardiovascular function, volume status, organ function, and other hemodynamic parameters (i.e. heart rate) and drug interactions (Table 16).

## Vasopressors and Inotropes

Vasopressor agents induce vasoconstriction and elevation of mean arterial pressure. They are used in the neurological patient in a variety of situations when blood pressure augmentation is desired to treat shock, vasospasm or improve cerebral or spinal perfusion pressure. Vasopressors produce their effects through their actions at adrenergic (alpha and beta), dopamine and vasopressin receptors in the body (Table 17). Alpha-1 adrenergic receptors are located in vascular walls and the heart. Activation of these receptors leads to significant vasoconstriction and increased duration of cardiac contraction. Beta-1 adrenergic receptors are most common in the heart and activation has inotropic and chronotropic effects with minimal vasoconstriction. Beta-2 adrenergic receptors are located in blood vessels, and activation induces

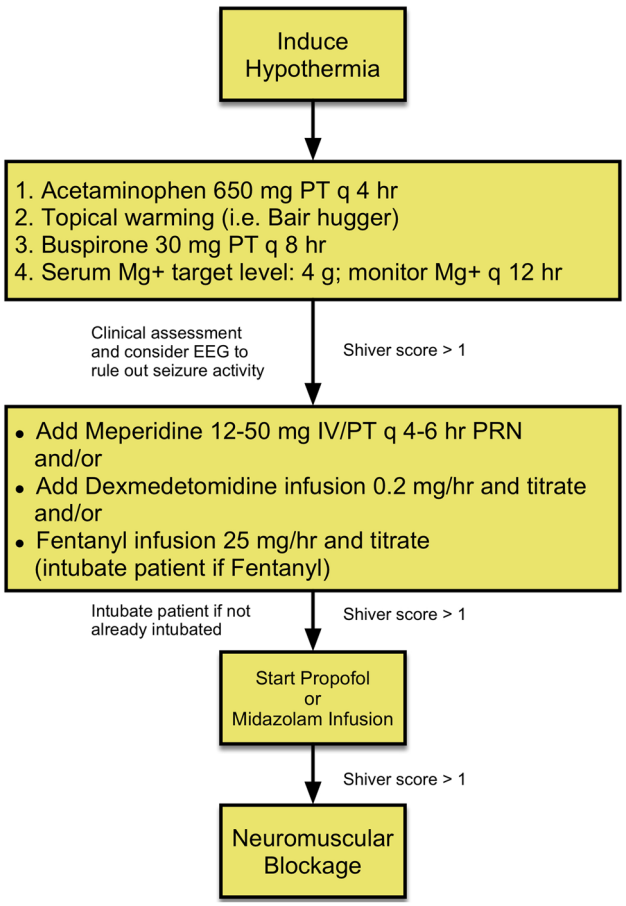


**Fig. 1** Anti-shiver protocol example

vasodilation. Dopamine receptors are present in cerebral, coronary, renal, and mesenteric vascular beds. Activation of these receptors generally leads to vasodilation, although there is a second subtype of dopamine receptors that can cause vasoconstriction through release of norepinephrine as the dose of dopamine increases.

Vasopressin (antidiuretic hormone) is a non-adrenergic vasopressor that is used in diabetes insipidus and as a second-line agent in refractory shock. It may also allow a reduction in the required dose of first-line vasopressors. Adverse effects include hyponatremia, which may worsen cerebral edema, and pulmonary vasoconstriction contributing to hypoxia. Milrinone is another non-adrenergic agent that has both inotropic and vasodilatory effects. It is a phosphodiesterase inhibitor that can be used to provide cardiac support, but its vasodilatory effects may worsen hypotension.

Few comparative studies of these agents have been performed [62, 63], so one vasopressor cannot be recommended over others; thus selection of which agent to use must be based on goals of care and desired physiologic effects.

## Antibiotics

When treating meningitis and encephalitis, choosing an appropriate antimicrobial or antiviral agent and the appropriate dose is essential. Most antibiotics are

**Table 12** Neuromuscular blocking agents [14, 58]

| Medication | Dosing | Onset | Duration | Administration pearls |
|---|---|---|---|---|
| Succinylcholine | Adults:<br>IV<br>0.5–1.1 mg/kg<br>IM<br>2–4 mg/kg<br>Adolescents:<br>1 mg/kg<br>Pediatrics:<br>2 mg/kg | Very rapid<br>IV<br>30–60 s<br>IM<br>240 s | Short<br>Average<br>3–5 min<br>Max<br>7–10 min | Cannot be reversed<br>May cause slight increases in intracranial pressure (ICP; inconsistent data)<br>*Severe hyperkalemia* may occur in patients with burns, severe muscle trauma, neuromuscular diseases, strokes, spinal cord injury, multiple sclerosis, and prolonged immobilization.<br>Contraindicated in patients with<br>Malignant hyperthermia<br>Hyperkalemia (serum potassium > 5.0 mEq/L) |
| Pancuronium | IV<br>Adults and pediatrics<br>0.06–0.1 mg/kg | Intermediate<br>120–180 s | Long<br>35–45 min | Conditions that slow circulation may delay onset<br>Increased effect in patients with myasthenia gravis or Eaton-Lambert disease |

**Table 12** continued

| Medication | Dosing | Onset | Duration | Administration pearls |
|---|---|---|---|---|
| Vecuronium | IV<br>Adults and pediatrics<br>0.1 mg/kg<br>(up to 0.2 mg/kg) | Prolonged<br>180–500 s<br>Faster onset with higher dose (120 s) | Intermediate<br>20–35 min (up to 60 min) | No significant cardiovascular effects<br>No effect on ICP |
| Cisatracurium | IV<br>Adults<br>0.15 mg/kg<br>(up to 0.2 mg/kg)<br>Pediatrics<br>0.1 mg/kg | Fast<br>90–120 s | Prolonged<br>Adults<br>45–75 min<br>Pediatrics<br>20–35 min | Longer half-life in elderly<br>Used as a continuous infusion in ICU during mechanical ventilation<br>Elimination via enzymatic breakdown and does not rely on renal or liver function for clearance |
| Rocuronium | IV<br>Adults<br>0.6 mg/kg<br>(up to 1.2 mg/kg)<br>Pediatrics<br>0.45–0.6 mg/kg | Rapid<br>60–120 s<br>Faster onset with higher dose | Intermediate<br>20–35 min<br>(up to 60 min) | Needs to be refrigerated<br>Prolonged duration in renal failure |

**Table 13** Adverse effects and drug interactions with neuromuscular blocking agents [14, 58]

| Adverse drug effects | Drug interactions (may potentiate effects) |
|---|---|
| Hypersensitivity reactions, including anaphylaxis | Inhalation anesthetics, particularly enflurane and isoflurane |
| Cardiac arrest | Antibiotics |
| Cardiac arrhythmias | Magnesium salts |
| Malignant hyperthermia | Lithium |
| Hypertension or hypotension | Local anesthetics |
| Hyperkalemia | Procainamide |
| Prolonged respiratory depression | Quinidine |
| Jaw rigidity | Drugs that reduce or inhibit plasma cholinesterase activity |
| Rhabdomyolysis | Other neuromuscular blockade agents |
| Myalgias | |
| Skeletal muscle weakness | |

**Table 14** Sedatives [19, 59–61]

| Generic (brand) mechanism of action | Dose | Adverse drug reactions | Drug interactions | Clinical pearls |
|---|---|---|---|---|
| **Propofol (Diprivan®)**<br>GABAa receptor agonist | 5–100 mcg/kg/min | Hypotension, apnea, movement, pain at the injection site, hypertriglyceridemia, pancreatitis, propofol-related infusion syndrome (PRIS) (hyperkalemia, dysrhythmia, lipemia, metabolic acidosis, heart failure, +/− rhabdomyolysis) | Rifampin may enhance hypotensive effects | Contraindications: Allergy to soy or egg<br>Use with caution in patients with cardiovascular disease<br>Rapid onset and offset<br>Lipid vehicle is particularly susceptible to bacterial contamination, Change IV tubing and bottle every 12 h<br>Risk of PRIS is increased in young people and with high doses (>50 mcg/kg/min) for a prolonged duration (>48 h)<br>Blue-green discoloration of urine may occur<br>Propofol delivers 1.1 kcal/ml |
| **Dexmedetomidine (Precedex®)**<br>Alpha-2 agonist | **Loading dose** (1 mcg/kg) NOT recommended (risk of severe bradycardia, hypotension, and sinus arrest)<br>**Maintenance infusion**<br>0.2–0.7<br>mcg/kg/h, some literature supports doses up to 1.4 mcg/kg/h | Hypotension, transient hypertension during loading dose, bradycardia | May enhance beta-blocker induced AV-blockade; beta-blockers may enhance rebound hypertensive effects<br>May ↑ effects/levels of duloxetine, hydrocodone,, antihypertensives | Has analgesic properties<br>Patients arousable with stimulation even during infusion, then return to sedated state without stimulation<br>Does not require mechanical ventilation<br>Use with caution in patients with diabetes mellitus, severe hepatic dysfunction, cardiovascular disease, chronic hypertension or hypovolemia |
| **Lorazepam (Ativan®)**<br>C-IV<br>GABAa receptor agonist | **Loading dose**<br>0.02–0.04 mg/kg<br>**Intermittent dose**<br>0.02–0.06 mg/kg q 2–6 h. (max IV dose 2 mg for agitation—infuse at 2 mg/min)<br>Maintenance infusion<br>0.01–0.1 mg/kg/h | Hypotension, respiratory depression, drowsiness, pain at injection site, akathisia, confusion, anterograde amnesia, visual disturbances, dependency,<br>Paradoxical reactions—hyperactivity and aggressive behavior | Valproic acid can ↑ concentration | IV contains propylene glycol which can accumulate with prolonged infusions and cause a metabolic acidosis<br>Precipitation is possible; an in-line filter is recommended<br>Contraindications: Acute narrow-angle glaucoma |

**Table 14** continued

| Generic (brand) mechanism of action | Dose | Adverse drug reactions | Drug interactions | Clinical pearls |
|---|---|---|---|---|
| **Midazolam (Versed®)**<br>C-IV<br>GABAa receptor agonist | Loading dose 0.01–0.05 mg/kg<br>Maintenance infusion<br>0.01–0.1 mg/kg/h | Similar to lorazepam | ↑ *midazolam concentration*:<br>grapefruit juice<br>azole antifungals chloramphenicol clarithromycin, diltiazem erythromycin, nefazodone nicardipine, verapamil<br>↓ *midazolam concentration*<br>carbamazepine dexamethasone fosphenytoin oxcarbazepine pentobarbital phenobarbital, phenytoin primidone, rifampin | Rapid onset and short duration, however prolonged infusions may result in accumulation in lipid tissues<br>Active metabolites which may accumulate in renal dysfunction<br>Contraindications: efavirenz, ketoconazole, itraconazole, protease inhibitors |

*CNS* central nervous system, *ICP* intracranial pressure, *GABA* gamma-aminobutyric acid

**Table 15** Analgesics [14]

| Drug class<br>Generic (brand)<br>Schedule<br>formulations | Usual dose | Adverse drug reactions | Drug interactions | Clinical pearls |
|---|---|---|---|---|
| **Fentanyl (Duragesic®)**<br>C-II<br>Buccal "lollipop", transdermal patch, lozenge, sublingual spray, nasal spray, sublingual tablet, injection | Bolus<br>12.5–100 mcg or 1–2 mcg/kg IVP<br>Maintenance IV infusion<br>0.7–10 mcg/kg/h or 25–700 mcg/h | Nausea, vomiting, respiratory depression, bradycardia, edema, confusion, headache, sedation, mood changes, constipation, miosis, chest wall rigidity, diaphoresis, xerostomia, myoclonus, dependency | ↑ *fentanyl concentration (CYP3A4 substrate)*<br>grapefruit juice, amiodarone, azole antifungals, cimetidine, clarithromycin, cyclosporine, desipramine, diltiazem, dronedarone, erythromycin, haloperidol, metronidazole, nefazodone, nicardipine, protease inhibitors, sertraline, verapamil | Use caution in renal or hepatic impairment.<br>Accumulation in lipid tissues is possible with prolonged infusions or repeated bolus doses.<br>The fentanyl patch cannot be rapidly titrated as it has a delayed onset (6–24 h, longest with first dose) and prolonged duration of action even if patch is removed; the transdermal route should be avoided in patients with significant edema or undergoing therapeutic hypothermia due to erratic absorption.<br>Transmucosal, immediate-release products are approved for use in opiate-tolerant patients and are only available through a restricted access program |
| **Hydromorphone (Dilaudid®)**<br>C-II<br>Tablet, extended-release tablet, oral solution, injection, rectal suppository | Oral:<br>2–4 mg every 4–6 h<br>IV:<br>0.2–1 mg every 4–6 h | Nausea, vomiting, respiratory depression, bradycardia, edema, confusion, headache, sedation, mood changes, constipation, miosis, diaphoresis, xerostomia, myoclonus, dependency | | Use caution in patients with inflammatory or obstructive bowel disorder, cardiovascular disease, renal or hepatic impairment |

**Table 15** continued

| Drug class<br>Generic (brand)<br>Schedule<br>formulations | Usual dose | Adverse drug reactions | Drug interactions | Clinical pearls |
|---|---|---|---|---|
| **Morphine**<br>**(Duramorph®, MS Contin®)**<br>C-II<br>Tablet, extended-release tablet, oral solution, injection | Bolus<br>2–10 mg IVP<br>Intermittent dose<br>2–8 mg every 3–4 h<br>Maintenance infusion<br>0.8–30 mg/h | Itching, nausea, vomiting, respiratory depression, sedation, hypotension, mood changes, xerostomia, constipation, pruritis, urinary retention, pain at injection site, dizziness, fever, myoclonus, dependency, may elevate ICP due to hypercarbia | | Active metabolites may accumulate in renal dysfunction; reduced dose recommended<br>Can induce a histamine release that causes itching. |
| **Oxycodone**<br>**(Roxicodone®, Oxycontin®)**<br>C-II<br>Oral tablet, extended-release tablet, oral solution | Usual immediate-release oral dose<br>5–20 mg every 4–6 h | Nausea, vomiting, respiratory depression, dizziness, somnolence, mood changes, constipation, xerostomia, confusion, orthostatic hypotension, diaphoresis, myoclonus, dependency | ↓ *oxycodone concentration* carbamazepine, dexamethasone, efavirenz, fosphenytoin, oxcarbazepine, pentobarbital, phenobarbital, phenytoin, primidone, rifampin<br>↑ *oxycodone concentration* azole antifungals, chloramphenicol, clarithromycin, protease inhibitors, nefazodone, nicardipine | Active metabolites may accumulate in renal dysfunction<br>Often co-formulated with acetaminophen |
| **Hydrocodone/acetaminophen (Vicodin®, Lortab®)**<br>C-II<br>Tablet, oral solution | 5–10 mg of hydrocodone component every 4–6 h, not to exceed 4 g of acetaminophen in 24 h | Bradycardia, hypotension, hypersensitivity reactions, mood changes, sedation, respiratory depression, dependency, diaphoresis, dyspepsia, rare myelosuppression, hepatotoxicity (due to acetaminophen component) | CYP3A4 inhibitors and inducers will change the concentration of hydrocodone | Acetaminophen content varies<br>Use caution in patients with G6PD deficiency, renal or hepatic impairment<br>Hydromorphone is an active metabolite of hydrocodone |

*IVP* intravenous push, *CNS* central nervous system, *MAOI* monoamine oxidase inhibitor, *ICP* intracranial pressure

**Table 16** Intravenous antihypertensive agents [14]

| Agent | Onset (min) | Duration | Half-life | Dosing | Clinical pearls |
|---|---|---|---|---|---|
| *Vasodilators* | | | | | |
| Nicardipine | 5–15 | 0.5–2 h | 2 h | Initial dose: 2.5 mg/h and titrate up by 2.5 mg/h every 15 min until goal BP achieved or max 15 mg/h | Contraindications: severe aortic stenosis<br>Use caution with rapid titration as dose stacking may occur and prolonged hypotension<br>Adverse effects: reflex tachycardia, nausea, vomiting, headache, flushing<br>Available in peripheral and central intravenous concentrations<br>Utilize the peripheral concentration with caution in patients with volume overload (i.e.: pulmonary edema) due to the high volume delivered |

**Table 16** continued

| Agent | Onset (min) | Duration | Half-life | Dosing | Clinical pearls |
|---|---|---|---|---|---|
| Clevidipine | 2 | 90 s | 1 min | 1–2 mg/h initially, may increase dose every 90 s to a maximum of 32 mg/h | Preferred agent in patients with labile blood pressure or need for rapid control of BP |
| | | | | | Contraindications: Soy/egg product allergy (formulated in a lipid compound), severe aortic stenosis |
| | | | | | Caution: reflex tachycardia |
| Sodium nitroprusside | <2 | 1–2 min | 3–4 min | 0.3–0.5 mcg/kg/min initially, may increase by 0.5 mcg/kg/min every few min to achieve desired effect, maximum 3 mcg/kg/min | Caution in patients with coronary artery disease due to coronary steal |
| | | | | | Avoid in patients with elevated intracranial pressures (ICP) and acute kidney injury (AKI) |
| | | | | | Sodium nitroprusside induced elevations in ICP have never been observed in human subjects, although the potential should be considered. |
| | | | | | Sodium nitroprusside should be avoided in patients with AKI due to the risk of thiocyanate toxicity |
| | | | | | If doses between 3 and 10 mcg/kg/min are indicated, the patient should be monitored for signs of cyanide toxicity (metabolic acidosis, decreased oxygen saturation, bradycardia, confusion and/or convulsions) |
| | | | | | Although not routinely administered, sodium thiosulfate has been coadministered with sodium nitroprusside using a 10:1 ratio of sodium thiosulfate to sodium nitroprusside to prevent cyanide toxicity |
| | | | | | Adverse effects: cyanide/thiocyanate toxicity, nausea, vomiting, methemoglobinemia |
| | | | | | Expensive |
| Hydralazine | 5–20 | 2–12 h | 2–8 h | 10–20 mg every 4–6 h | Adverse effects: reflex tachycardia, headache, flushing |
| | | | | | Ensure adequate volume resuscitation to avoid hypotension |
| *Adrenergic agents* | | | | | |
| Esmolol | 1–2 | 10–30 min | 9 min | 250–400 mcg/kg/min | Contraindicated in bradycardia, heart block, cardiogenic shock, decompensated heart failure |
| | | | | | Avoid loading doses |
| | | | | | Adverse effects: reflex tachycardia, headache, flushing |
| Labetalol | 2–5 | 2–4 h | 4–8 h | 20–80 mg every 10 min up to 300 mg | Use caution with rapid IV titration as dose stacking may occur and prolonged hypotension |
| | | | | | Continuous infusion difficult to titrate due to long duration of activity. Infusion should be reserved for refractory hypertension uncontrolled by bolus doses and/or other medications. Titrate with caution to avoid prolonged hypotension. |
| | | | | | Adverse effects: bronchospasm, HF exacerbation, bradycardia/heart block |

**Table 17** Vasopressors and Inotropes [14]

| Medication | Adrenergic receptor activation | Initial dosing | Indications | Advantages | Disadvantages |
|---|---|---|---|---|---|
| *Vasopressors* | | | | | |
| Norepinephrine | α, β1 | 2–5 mcg/min<br>OR<br>0.02–0.06 mcg/kg/min | Septic shock with low SVR<br>Can be used in anaphylactic shock | Great for increasing SVR and MAP while preserving CO<br>First line agent for septic shock | May increase oxygen consumption<br>Risk of dysrhythmias and myocardial ischemia<br>May decrease intestinal perfusion and increase lactate levels |
| Dopamine | α, β1Δ | Dopa- 1–3 mcg/kg/min<br>α: 3–10 mcg/kg/min<br>β: 10–20 mcg/kg/min | Poor cardiac function with poor perfusion<br>Hypotension with bradycardia | Effective at multiple receptors | Highest risk of dysrhythmias (esp at higher doses) |
| Epinephrine | α, β1, β2 | 0.02–0.05 mcg/kg/min | Septic shock with low SVR and/or low CO<br>Anaphylactic shock | Less need for adequate volume resuscitation for initial response<br>First line agent for septic shock | Risk of dysrhythmias and myocardial ischemia<br>Adverse effects: tachyarrhythmias, hyperglycemia, lactic acidosis, hypokalemia |
| Ephedrine | α, β1, β2 | IV: 5–25 mg slow IV push, may repeat after 5–10 min<br>Oral: 25–50 mg every 8–12 h | IV: Post anesthesia induced hypotension<br>Oral: orthostatic hypotension in spinal cord injury | Can stimulate release of endogenous norepinephrine | Less potent than epinephrine |
| Phenylephrine | α | 10–200 mcg/min<br>OR<br>0.1–1 mcg/kg/min | Rapid MAP increases → post-sedation, etc.<br>↓ outflow tract gradient in patients with obstructive hypertrophic cardiomyopathy | No β effects therefore less arrthymogenic | May decrease CO<br>May cause reflex bradycardia<br>Not indicated for septic shock |
| Vasopressin | 0 | 0.04–0.08 units/min | Refractory hypotension in septic shock<br>Diabetes insipidus | May reduce the dose of other vasopressors when added in refractory hypotension | Not first line agent in shock<br>May decrease splanchnic perfusion and increase gut ischemia |
| *Inotropes* | | | | | |
| Dobutamine | α, β1, β2 | 2.5–10 mcg/kg/min | Acute decompensated heart failure, cardiogenic shock, septic shock with depressed cardiac function | Good to improve CO in decompensated heart failure and | Can decrease SVR and provoke hypotension<br>Tolerance may occur with prolonged administration |
| Milrinone | 0 | 0.25–0.75 mcg/kg/min<br>Reduce dose if CrCl < 50 ml/min | Inotropic agent to increase CO in decompensated heart failure | Useful if adrenergic receptors are downregulated or desensitized in the setting of chronic HF | Elimination reduced in patients with renal dysfunction<br>Adverse effects: hypotension, arrhythmias, thrombocytopenia |

*SVR* systemic vascular resistance, *CO* cardiac output

**Table 18** Antimicrobial recommendations for meningitis and encephalitis [14, 65]

| CNS pathogen | Recommended therapy | Alternative therapies | Clinical pearls |
|---|---|---|---|
| *H. influenzae* | Third-generation cephalosporin (e.g. ceftriaxone 2 g intravenously every 12 h) | Cefepime, ceftaroline, meropenem, fluoroquinolone, chloramphenicol | Meropenem—contraindicated with VPA (significantly decreases VPA serum concentrations) |
| *S. pneumoniae* | Vancomycin + third-generation cephalosporin (e.g. ceftriaxone 2 g intravenously every 12 h) | Meropenem, fluoroquinolone | Vancomycin trough goal: 15–20 mcg/ml<br>Adjust fluroquinolones and meropenem dose for renal dysfunction—can induce seizures |
| *N. meningitidis* | Third-generation cephalosporin (e.g. ceftriaxone 2 g intravenously every 12 h) | Penicillin G, ampicillin, fluoroquinolone, aztreonam, chloramphenicol | |
| *L. monocytogenes* | Ampicillin | Penicillin G, SMX/TMP, meropenem | SMX/TMP is dosed base on SMX component |
| *S. agalactiae* | Ampicillin | Penicillin G, third-generation cephalosporin | |
| *Escherichia coli* | Third-generation cephalosporin (e.g. ceftriaxone 2 g intravenously every 12 h) | Cefepime, ceftaroline, meropenem, aztreonam, fluoroquinolone, SMX/TMP | |
| Staphylococci | Vancomycin | Nafcillin (MSSA only), linezolid, SMX/TMP | Vancomycin trough goal: 15–20 mcg/ml |
| HSV, VZV, CMV | Acyclovir (10 mg/kg/dose every 8 h based on IBW) | Ganciclovir, foscarnet | Adjust for renal dysfunction |

*CMV* cytomegalovirus, *HSV* herpes simplex virus, *IBW* ideal body weight, *MSSA* methicillin-susceptible *S. aureus*, *SMX/TMP* sulfamethoxazole/trimethoprim, *VZV* varicella zoster virus

hydrophilic and do not cross the blood–brain-barrier (BBB) well. However, when the meninges are inflamed, penetration increases and allows drug to reach the site of action. Antibiotics and their microbial targets are listed in Table 18. Steroids (e.g. dexamethasone) are sometimes used in conjunction with antibiotics for S. pneumonia meningitis to decrease neurological sequelae [64]. If used, dexamethasone 10 mg intravenously every 6 h × 4 days is recommended and should be given before or at the same time as the first antibiotic dose.

## Conclusion

Pharmacologic management in patients undergoing ENLS is very challenging, especially while attempting to minimize further cognitive dysfunction and worse outcomes. Medication choices and doses must be individualized for each patient, taking into account their medical history, comorbidities, pharmacokinetic and pharmacodynamic changes due to age, critical illness, and neurocritical care interventions; potential adverse drug effects, and drug interactions. Appropriate pharmacotherapy is essential in optimizing care in the patients with neurological emergencies.

**Compliance with Ethical Standards**

**Conflict of interest** Dr. Gretchen Brophy is an advisory board member/consultant/speaker for UCB, Edge Therapeutics, Chiesi, Sage and Mallinckrodt; has received research funding from Mallinckrodt; and is an executive officer for the Neurocritical Care Society. Dr. Theresa Human is an advisory board member/consultant/speaker for Cumberland Pharmacueticals, UCB, and is a Member of the Board of Directors and Co-Chair of the Educational Products Committee for the Neurocritical Care Society.

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