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PHARMACOTHERAPY

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, medication allergies, potential adverse drug effects, drug interactions, critical illness, and age-related pathophysiologic changes. Medications used during ENLS include hyperosmolar therapy, antiseizures, antithrombotics, anticoagulant reversal hemostatic agents, antishivering agents, neuromuscular blockers, antihypertensive agents, sedatives, vasopressors inotropes, and antimicrobials. This chapter focuses on key pharmacokinetic and pharmacodynamic characteristics, advantages and disadvantages, and clinical pearls of these therapies, thereby providing practitioners with essential drug information to optimize pharmacotherapy in acutely ill neurocritical care patients.

Keywords: ENLS, Pharmacotherapy, Medication, Adverse drug event, Drug interaction

Introduction

Neurocritical care patient management is highly complicated, especially when trying to optimize therapy during the acute injury. Pharmacologic management must be carefully considered in order to minimize cognitive dysfunction and avoid confounding patient neurologic 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. Pharmacokinetic changes may include alterations in medication absorption, distribution, metabolism, and elimination, while pharmacodynamic changes could result in loss of drug effect or an increase in toxicity. This chapter will focus on pharmacotherapy and clinical pearls that will help the ENLS provider optimize medication management in the acute period of neurologic injury.

Chapter Outline

- Hyperosmolar therapy
- Antiseizure medications
- Antithrombotic agents
- Anticoagulant reversal and hemostatic agents
- Antishivering agents
- Neuromuscular blocking agents
- Antihypertensive agents
- Sedation and Analgesia
- Vasopressors and inotropes
- Antimicrobials

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 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% of respondents utilize osmotic agents in the

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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 agent that is eliminated by the kidneys. Caution should be used in patients with renal impairment as mannitol may accumulate and worsen cerebral edema, especially in those with blood brain barrier (BBB) disruption due to injury and/or inflammation. The osmolar gap is the most useful monitoring method to detect the presence of unmeasured osmoles, such as mannitol, and should be used to monitor drug elimination between doses. An osmolar gap of greater than 15–20 mOsm/kg indicates incomplete drug clearance between doses and increases the 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 laboratory tests (osmolality, sodium, glucose, and urea) necessary to calculate an osmolar gap should be obtained 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 be carefully monitored to prevent hypotension, dehydration, and electrolyte imbalances due to excessive diuresis.

Unlike mannitol, HS provides intravascular expansion; therefore, patients with decompensated heart failure or pulmonary edema may be at increased risk of fluid overload. HS may have a lesser risk of rebound cerebral edema after discontinuation due to the differences in the reflection coefficient, which describes the permeability (1 = impermeable) of a substance relative to the BBB (1 for HS vs. 0.9 of mannitol) [7, 8]. Caution should be used when administering HS to patients with chronic hyponatremia, as a rapid change in serum sodium may increase the risk of osmotic demyelination 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. At this time, there is no information regarding an optimal protocol for the use of HS. In general, established protocols allow for consistency of care among providers. For this reason, neurocritical care providers should work within their institution to establish a consensus regarding treatment goals, develop a protocol, monitor efficacy of the protocol, and then reassess and modify their protocol as needed to achieve

Table 1 Hyperosmolar therapeutic agents for management of elevated intracranial pressure [1, 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) Acute kidney injury Dehydration Hypotension Electrolyte imbalances	Requires inline filter (precipitates–crystal formation) May require warming to dissolve crystals before administration May be given via peripheral access Duration of effect 90 min–6 h Monitor trough osmolar gap (goal < 20 mOsm/Kg)
Hypertonic saline	Concentration dependent (concentrations listed are approximately equal osmolar to mannitol 1 g/kg) Bolus dosing 3%: 5 mL/kg over 5–20 min (range 2.5–5 mL/kg) 5%: 3 mL/kg over 5–20 min (range 2.5–5 mL/kg) 7.5%: 2 mL/kg over 5–20 min (range 1.5–2.5 mL/kg) 23.4%: 30 ml over 10–20 min Other options Continuous infusion titrated to a goal Na range	Pulmonary edema Heart failure Acute kidney injury Coagulopathy Hypernatremia Metabolic acidosis Thrombophlebitis Osmotic demyelination syndrome with rapid correction	Central access required for 23.4% bolus Central access for > 2% NaCl–acetate if continuous infusion 3% NaCl boluses may be administered peripherally 5% NaCl may be administered safely in bolus doses for up to 72 h via peripheral line [13] Duration of effect 90 min–4 h Controversial if continuous infusion is beneficial for ICP control, but should be used for severe hyponatremia Monitor serum sodium every 4–6 h (trough), avoid prolonged hypernatremia > 160 mEq/L Decrease chloride and increase acetate content if patients develop metabolic acidosis Use is discouraged in combination with tolvaptan or conivaptan

ICP intracranial pressure

the desired treatment goal. Trough serum sodium levels should be monitored prior to HS administration to guide the HS dose and dosing interval. The goal should be to use the lowest effective dose in order to allow for ongoing drug administration and avoid sustained hypernatremia [9].

Nursing Considerations

Nursing care for patients requiring mannitol and HS includes monitoring patients for side effects and possible adverse reactions to these medications. Nursing assessment should include monitoring of neurologic examination, vital signs, and volume status. Monitoring volume status includes intake and output monitoring along with assessment for dehydration and volume overload. Neurologic examination monitoring should occur frequently including intracranial pressure readings as applicable to determine whether the medication is meeting the desired treatment goal. Vital sign monitoring should include heart rate (HR), blood pressure (BP), respiratory rate, and oxygen saturation. The nurse should monitor for signs of dehydration including low urine output, dry mucous membranes, and complaints of thirst, and for signs of volume overload including shortness of breathe, rales, or crackles on lung auscultation [10].

Adverse reactions to hyperosmolar include phlebitis at intravenous (IV) site and electrolyte imbalances. Nurses should frequently monitor the IV site when administrating these medications and immediately stop the medication if IV infiltration occurs. In addition, the bedside nurse should have knowledge of symptoms of electrolyte imbalances and ensure that serum electrolytes are obtained in a timely manner. Special considerations are needed when administering mannitol including the use of an inline IV filter and assessment of the IV infusion prior to administering to evaluate for the presence of crystals or cloudiness. The medication should not be administered until the crystals are dissolved [10].

Antiseizure Medications

Antiseizure agents are necessary to treat seizures and are commonly prescribed for seizure prophylaxis in select neurologic disease states. Although multiple antiseizure agents have been studied as first-line therapy, evidence supports that benzodiazepines should be the agent of choice for emergent initial treatment of seizures or status epilepticus [14]. The preferred route of administration is IV; however, benzodiazepines can be administered via intramuscular (IM), rectal, nasal, or buccal routes when IV therapy is not feasible. For IV therapy, lorazepam is the preferred agent; midazolam is preferred for IM therapy (and can also be given nasally or buccally); and diazepam is preferred for rectal administration [14]. Clonazepam is an alternative agent but it is infrequently used in the USA due to lack of an IV formulation; however, it is commonly used intravenously in Europe [15]. Randomized controlled studies have evaluated lorazepam versus diazepam, phenobarbital, phenytoin, and IM midazolam [16–19]. Initial treatment with lorazepam followed by phenytoin appeared to be the most effective combination; however, the second-generation antiseizure agents were not available at the time, and many options may also be effective. IM midazolam was found to be at least as effective as IV lorazepam in prehospitalized patients with status epilepticus [19]. While there may be concerns about administering benzodiazepines to non-intubated patients, available data suggest respiratory depression is seen less frequently in those treated with benzodiazepines for generalized convulsive status epilepticus (SE) than those who received placebo [16]. Supportive treatment should be provided in the rare situation where respiratory distress or hypotension occurs after benzodiazepine administration. Following administration of a benzodiazepine as first-line therapy, a second-line (urgent control) antiseizure medication is required if seizures persist, unless the immediate cause of the seizure is known and definitively corrected (e.g., severe hypoglycemia) [14]. First-line urgent control antiseizure agents should be given IV over a short period of time and are often chosen based on adverse drug reaction profile, etiology of seizure, patient organ function, any preexisting antiseizure drugs, and patient hemodynamic stability. A summary of antiseizure medications can be found in Table 2.

Nursing Considerations

Nursing staff should have knowledge of algorithms for the management of SE in order to be able to anticipate and prepare for what medication may be needed next (see *ENLS Status Epilepticus*). The nurse should be prepared to administer first-line treatment with benzodiazepines immediately when caring for a patient in SE. The nursing assessment should include close monitoring of vital signs including HR, BP, and respiratory status pre- and post-medication administration. It is important to monitor and record any seizure activity pre- and post-benzodiazepine administration to determine medication effectiveness [20]. The IV infusion site should be assessed frequently as some benzodiazepine medications can cause phlebitis. Side effects of phenytoin and fosphenytoin include hypotension and bradycardia; thus, the nursing assessment should include continuous monitoring of HR, rhythm, and BP [10]. If seizures do not subside with first- and second-line antiseizure agents, the nurse should anticipate the need for intubation and need for general anesthetics in order

Table 2 Antiseizure medication dosing recommendations [14, 21]

Generic	Dose	Rate	Target serum concentration	Adverse effects	Clinical pearls
Diazepam	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	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	0.2 mg/kg IM up to 10 mg per dose		N/A	Sedation, respiratory depression Hypotension	Can also be given buccally, intranasally
Phenytoin	Load: 20 mg/kg ADULT/PEDS 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	Load: 20 mg PE/kg ADULT/PEDS maintenance dose: 4- 7 mg/kg/day divided into 2–3 doses	Up to 150 mg PE/min	Total phenytoin: 10–20 mcg/mL Free phenytoin: 1–2 mcg/ml (an accurate estimate may be obtained 1 h after infusion complete)	Arrhythmias, hypotension, bradycardia	Pro-drug–converts to phenytoin in 7–15 min after infusion; less thrombophlebitis than phenytoin; same drug interactions and monitoring parameters
Phenobarbital	20 mg/kg Maintenance dose: 1–3 mg/kg/day divided into 1–3 doses Pediatric dosing: 1–5 mg/kg/day	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	Load: 40 mg/kg IV Maintenance dose: 10–15 mg/kg/day divided into 2–4 doses Pediatric dosing: 20–40 mg/kg/day divided q6 h	3–6 mg/kg per minute	50–150 mcg/mL	Hepatotoxicity, thrombocytopenia, hyperammonemic encephalopathy	Fewer CV side effects than phenytoin CYP enzyme inhibitor with many potential drug interactions meropenem will significantly reduce VPA levels; therefore, caution should be used when combination prescribed
Levetiracetam	Load: 60 mg/kg IV (max: 4500 mg) IV: administer over 15 min Maintenance dose: 1000–3000 mg/day in 2 divided doses Pediatric dosing: 60 mg/kg/day divided q12 h	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	200–400 mg IV Every 12 h Pediatric dosing: 10 mg/kg IV load, then 5–10 mg/kg/day divided q12 h	Over 15 min	2.8–18 mcg/ml (not typically monitored)	PR prolongation, hypotension (rare)	Consider monitor EKG in patients with underlying cardiac disease; reduce dose in renal impairment; few drug interactions
Topiramate	200–400 mg NG/PO every 6–12 h Pediatric dosing: 10 mg/kg PO/NG load followed by 5–10 mg/kg/day divided q12 h		2–20 mcg/mL (not typically monitored)	Metabolic acidosis	Weak 2C19 inhibitor

CV cardiovascular; *CYP* cytochrome P-450 enzyme system; *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

Table 3 Exclusion criteria for alteplase in acute ischemic stroke

Absolute exclusion criteria
No major head trauma, ischemic stroke, intracranial/spinal surgery in the previous 3 months
No history of intracerebral hemorrhage or intracranial neoplasm
No signs and symptoms suggestive of subarachnoid hemorrhage, infective endocarditis, or aortic arch dissection
No GI malignancy or recent bleeding within 21 days
Not taking direct thrombin inhibitors or direct factor Xa inhibitors unless aPTT, INR, platelet count, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or has not received a dose for > 48 h (with normal renal function)
CT shows severe hypoattenuation, hypodensity > 1/3 of cerebral hemisphere, or intracerebral hemorrhage
Additional recommendations
Extended 3–4.5 h is safe in patients > 80 years, patients on warfarin with INR ≤ 1.7, prior stroke with diabetes
IV alteplase is reasonable in patients with early improvement but moderately disabled, seizure at symptom onset if deficits are from stroke, lumbar dural puncture in previous 7 days, major surgery or trauma in previous 14 days, extracranial cervical dissections, unruptured intracranial aneurysm, small number of cerebral microbleeds on MRI, extra-axial intracranial neoplasm, acute or recent MI in past 3 months, acute pericarditis, diabetic retinopathy, sickle cell disease, angiographic procedural stroke, pregnancy, illicit drug use and stroke mimics

to control SE. Nursing staff should anticipate possible abnormal hemodynamics when using continuous infusions and general anesthetics and anticipate the need for possible vasopressors.

Thrombolytic Therapy

Alteplase is the only FDA-approved thrombolytic for use in adult patients with acute ischemic stroke (AIS) who present within 3–4.5 h of initial symptoms. Strict adherence to inclusion and exclusion criteria is essential to minimize hemorrhagic complications (Table 3) [22]. The recommended dose is 0.9 mg/kg with 10% of the dose given as an IV bolus over 1 min with the remainder given as a continuous infusion over 1 h (maximum dose: 90 mg). It is important to use an accurately measured dosing weight and avoid estimations to avoid potential overdosing. Due to unique reconstitution instructions (e.g., proper dilution, swirling vs. shaking, etc.) of alteplase, those who have been trained on the process can expedite preparation and facilitate timely administration. Excess drug should be removed from the vial before infusion to prevent inadvertent administration of total doses of > 90 mg and increased risk of intracerebral bleeding. Systolic blood pressure should be maintained < 180/105 during infusion and for 24 h after treatment.

Symptoms during or after administration of alteplase, such as acute severe headache, nausea/vomiting, acute hypertension, or worsening neurologic examination, may signal intracranial hemorrhage (ICH). The infusion of alteplase should be stopped and a stat head CT should be performed followed by checking laboratories (CBC, PT/INR, fibrinogen), type and cross-match, and consulting neurosurgery (if ICH is confirmed). If available, cryoprecipitate can be administered (10 units infused over 10–30 min) to maintain fibrinogen levels > 200 mg/dL. Tranexamic acid (1000 mg IV over 10 min) or aminocaproic acid (4–5 g IV over 1 h followed by 1 g/h) may be given to control bleeding [23]. Supportive therapy should be provided to manage blood pressure, ICP, cerebral perfusion pressure (CPP), temperature, and glucose.

Angioedema can occur during or after alteplase administration and has been associated with previous angiotensin-converting enzyme (ACE) inhibitor use [24, 25]. Edema limited to the anterior tongue or lips rarely requires intervention, but rapidly progressing edema involving the larynx, oropharynx, palate, or posterior tongue may require emergent oral intubation (nasal intubation may result in epistaxis post-alteplase). Management includes discontinuation of alteplase and any ACE inhibitors followed by the administration of antihistamines (diphenhydramine 50 mg IV, famotidine 20 mg IV) and corticosteroids (methylprednisolone 125 mg IV). If the angioedema continues to progress, subcutaneous 0.1% epinephrine (0.3 mL) can be given [26].

Tenecteplase, another recombinant tissue plasminogen activator that has increased fibrin specificity and longer half-life compared to alteplase, has been studied in AIS as a 0.4 mg/kg single IV bolus. Tenecteplase failed to show superiority over alteplase but has a similar safety profile. Although it is not FDA-approved for acute stroke in the USA, it is recommended as an alternative to alteplase for patients with minor stroke symptoms and no major intracranial occlusion [22].

Nursing Considerations

Thrombolytic medications such as alteplase are high-alert medications. It is important for nursing staff to be familiar with guidelines and protocols in place for administration and monitoring of these medications. Alteplase should be administered as soon as possible by nursing staff once it is ordered by the provider team. Over- and

under-dosage of thrombolytic can cause harm and even death to patients; thus, most institutions require two providers to check medication dosing prior to administering. Complications may include angioedema, ICH, or other bleeding complications. Close monitoring of patients for angioedema is necessary, and nursing staff must consider stopping the infusion with any new lip or tongue swelling or stridor. Close monitoring of neurologic examination during and after administration of alteplase must be performed with immediate discontinuation of the infusion with any decline in neurologic examination. Nursing staff should monitor patients for all types of bleeding complications including gastrointestinal bleeding and bleeding from IV sites. The nurse should ensure that certain invasive procedures are limited and no aspirin or other antiplatelet agents are given 24 h post-alteplase administration [27].

Antithrombotic Therapy

For patients who are not candidates for alteplase, acetylsalicylic acid (ASA) should be started immediately. For patients with minor stroke or high-risk transient ischemic attack (TIA), the combination of aspirin (50–325 mg/day) and clopidogrel (600 mg load, then 75 mg/day) may be considered [28]. The combination of extended-release dipyridamole and aspirin can also be started for stroke prevention. Other antiplatelet agents, including prasugrel and ticagrelor, have a paucity of data for acute use after ischemic stroke. Additionally, prasugrel carries a black box warning for increased risk of bleeding in stroke or TIA patients. In patients who are allergic to ASA, 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 receive extra- and intracranial stents. It should be noted that approximately 30–60% of the population have genetic polymorphisms and do not respond to clopidogrel as it is a pro-drug that must be converted by the liver to its active form [28].

In addition to warfarin, direct oral anticoagulants (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 alteplase 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 alteplase. The time of last dose and renal function is essential to know whether 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 4 and 5.

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 ICH, gastrointestinal bleeding, uncontrolled bleeding in the retroperitoneal space, spine hematoma, or any hemorrhage into an extremity with risk of compartment syndrome. Reversal may also be necessary when an emergent surgical intervention is required within 1–12 h of presentation, and the respective anticoagulant has been administered in a timeframe when the agent is effective (depending on time since last dose and drug half-life) (see Tables 6, 7, 8, 9, 10). General management strategies to employ when treating major hemorrhages include identifying the cause and source of bleeding, maintaining hemodynamic 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 identifying the anticoagulant and administering an appropriate reversal agent [32].

When reversing an anticoagulant, the risk of continued bleeding relative to the risk of thrombosis is of the utmost importance and should be determined in each case. The timing of the last dose of anticoagulant administered and elimination half-life are also necessary to determine whether reversal is warranted. If the agent was taken within the 3–5 half-life time window, then reversal should be considered [33]. With medications which have 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-life 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 (ACCP), and American Heart Association/American Stroke Association (AHA/ASA)

Table 4 Comparison of oral anticoagulant agents [21]

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Mechanism	Vitamin K antagonist (II, VII, IX, X)	Direct thrombin inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Dose	Variable INR goal is usually 2–3 (goal of 2.5–3.5 with certain mechanical valves)	**VTE** **Non-valvular afib** 150 mg BID (CrCl > 30 mL/min) 75 mg twice daily (CrCl 15–30 mL/min) Not recommended in CrCl < 15 mL/min	**VTE** 15 mg BID with food for 3 weeks followed by 20 mg once daily (avoid use if CrCl < 30 mL/min **Ortho prophylaxis**: 10 mg once daily **Nonvalvular afib**: 20 mg once daily with food 15 mg once daily CrCl 15–50 mL/min)	**VTE** 10 mg BID X 7 days followed by 5 mg BID for 6 months **Ortho prophylaxis** 2.5 mg BID Non-valvular afib: 5 mg BID PO 2.5 mg BID if ≥ 2 of the following ≥ 80 yo, ≤ 60 kg, Cr ≥ 1.5 mg/dL (0.1326 mmol/L)	**VTE** 60 mg daily 30 mg daily (CrCl 15–50 mL/min)	**VTE prophylaxis**: 160 mg × 1 then 80 mg daily × 35–42 days
Elimination	Hepatic	Renal	Renal	Renal	Renal	Renal
Testing parameter	INR	TT	PT and anti-FXa	Anti-FXa	Anti-FXa	Anti-FXa
Half-life	20–60 h (variable)	12–17 hrs[a]	5–9 h 11–13 elderly	8–12 h[a]	10–14 h	19–27 h
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)	At least 24 h prior (renal and surgery risk dependent)	Unknown
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/G5 and administer via feeding tube	Consider dose reduction in patient < 60 kg	

afib atrial fibrillation; *CrCl* creatinine clearance; *Ortho* orthopedic; *scr* serum creatinine; *TT* thrombin time; *VTE* venous thromboembolism

Table 5 Comparison of antiplatelet medications [21, 28–31]

Indication	Generic name	Dose	Clinical pearls
AIS primary prevention	COX inhibitor Aspirin	75–100 mg Daily	Irreversible platelet inhibition (5–7 days) GI bleed is most common complication: Dose-dependent risk 81 mg versus 325 mg—higher dose may ↑ risk 2× Risk is not decreased with buffered or enteric coated formulations Ibuprofen can inhibit non-enteric coated ASA effects, so must be dosed 8 h before or 30 min after ASA dose Low dose aspirin considered for select adults 40–70 years of age who are considered high risk of stroke without increased bleeding risk; avoid use in adults > 70 years or those at increased risk of bleeding
AIS secondary prevention	Aspirin	81 mg daily	See above
	PDE Inhibitor		
	Extended-release dipyridamole/ Aspirin	200 mg/ 25 mg BID	Irreversible platelet inhibition (5–7 days) Headache in up to 40% of patients Tolerance often develops within 1–2 weeks
	ADP Inhibitors		
	Clopidogrel	300–600 mg loading doses prior to endovascular procedures 75 mg daily	Pro-drug—CYP2C19 conversion to active metabolite Impacted by genetic polymorphisms Irreversible platelet inhibition (5–7 days) Reduced effects with proton pump inhibitors Hypersensitivity (usually rash) ADR: TTP is rare (ticlopidine > clopidogrel)
	Ticlopidine	250 mg BID	Pro-drug—CYP3A4 conversion to active metabolite Irreversible platelet inhibition (5–7 days) Replaced by clopidogrel—delayed onset and ↑ ADRs ADRs: GI intolerance, neutropenia, aplastic anemia, and TTP
	Ticagrelor	180 mg load prior to endovascular procedure 90 mg BID	Active within 2 h of administration Predictable activity Active metabolite Reversibly bound

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

guidelines suggest use of prothrombin complex concentrate (PCC) agents over fresh frozen plasma (FFP) [23, 34, 35]. In addition, a recent study showed four-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 [36]. PCCs are generally better tolerated than FFP due to smaller fluid volumes and less risk for transfusion-related acute lung injury or transfusion-associated circulatory overload [37, 38]. There are two types of PCC products available: four-factor and three-factor PCC. Four-factor PCCs contain all of the vitamin K-dependent coagulation factors, are sufficient to provide immediate warfarin reversal, and are the preferred products when available (see Table 11). Three-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. There are no clinical trials combining three-factor PCC and factor rVIIa or PCC and FFP for treatment of life-threatening bleeding. It is unknown if combining products increases efficacy or risk of thrombosis. FFP may be a better choice initially in patients that require volume resuscitation, and consideration should be made to combine 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 6). A repeat INR may be checked 30 min after the end of PCC infusion to evaluate if it is within normal or desired range [37, 39–42]. Although limited data are available for recommending a second dose of PCC, if the INR remains elevated and bleeding is ongoing, a second dose of PCC may be considered. If repeat doses of PCC are administered, consideration for the increased thrombosis risk must be understood [42]. Of note, FEIBA®, a four-factor PCC with activated factor VII may interfere with the INR test, resulting in a falsely low INR. For sustained warfarin reversal, phytonadione (vitamin K) should be simultaneously administered to patients who require rapid reversal. Intravenous and oral vitamin K (10 mg) effectively lowers INR within 12–14 h and 24–36 h, respectively [43–45]. Subcutaneous administration is not recommended due to unpredictable absorption and delayed response [46] (Table 6).

Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran to neutralize its anticoagulant effects within minutes of administration. The

Table 6 Reversal of vitamin K antagonist

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 4-factor PCC 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 4-factor PCC 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 If urgent reversal needed (≤ 12 hrs) for procedure, consider 4-factor PCC 50 IU/kg IV
ANY INR	Serious or life-threatening bleeding OR Invasive procedure required ≤ 12 hours	Hold warfarin Give vitamin K 10mg IV over 30 minutes Administer 4-factor PCC

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

If volume resuscitation necessary consider FFP 15-20 ml/kg

Recheck INR 30 min after PCC[b] or FFP[#] administered

Vitamin K (phytonadione)		
	Onset of action	Peak Effect
Oral	6-12 hrs	24-48 hrs
IV	1-2 hrs	12-14 hrs
SQ	Not recommend due to unpredictable or delayed response.	

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

[#] Consider supplemental dose of PCC if INR still elevated and patient still bleeding

Table 7 Reversal of factor Xa inhibitors(23, 50, 51, 53)

<table>
<tr><th>GENERIC NAME</th><th>ELIMINATION HALF-LIFE</th><th>REMOVAL BY HD</th><th>EMERGENT REVERSAL FOR LIFE-THREATENING BLEEDING</th></tr>
<tr><td>Apixaban</td><td>8-12 hrs

longer in renal impairment</td><td>No</td><td rowspan="2">If ingested within 2 hours, consider administration of activated charcoal 50 g

Consider time of last dose and t ½ of agent when deciding to reverse agent. Recommend reversal if last dose given within 3-5 elimination t ½ 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

<table><tr><th rowspan="2">Factor Xa Inhibitor</th><th rowspan="2">Last Dose of Factor Xa Inhibitor</th><th colspan="2">Timing of Last Dose</th></tr><tr><th>< 8 hrs</th><th>≥ 8 hrs</th></tr><tr><td>Rivaroxaban</td><td>≤ 10 mg</td><td>Low dose</td><td rowspan="4">Low dose</td></tr><tr><td></td><td>>10mg or unknown</td><td>High dose</td></tr><tr><td>Apixaban</td><td>≤ 5mg</td><td>Low dose</td></tr><tr><td></td><td>>5mg</td><td>High dose</td></tr></table>
Step 2: Determine Andexanet-alfa Dose

<table><tr><th>Dose</th><th>Initial bolus</th><th>Maintenance infusion</th></tr><tr><td>Low dose</td><td>400mg IV over 15 min</td><td>4mg/min for 100 min</td></tr><tr><td>High dose</td><td>800mg IV over 15 min</td><td>8 mg/min for 112 min</td></tr></table>
Effective Alternative Option(53):

Administer PCC 50 units/kg over 10 min

If volume needed consider 15-20 ml/kg FFP</td></tr>
<tr><td>Rivaroxaban</td><td>5-9 hrs

Elderly: 11-13 hrs

longer in renal impairment</td><td>No</td></tr>
<tr><td>Edoxaban</td><td>10-14 hrs

Longer in renal impairment</td><td>No</td><td rowspan="2">If ingested within 2 hours, consider administration of activated charcoal 50 g

Consider time of last dose and t ½ of agent when deciding to reverse agent. Recommend reversal if last dose given within 3-5 elimination t ½ of the drug to ensure hemostasis.

Administer PCC 50 units/kg over 10 min

If volume needed, consider 15-20 ml/kg FFP</td></tr>
<tr><td>Betrixiban</td><td>19-27 hrs

Longer in renal impairment</td><td>Unknown</td></tr>
</table>

Table 8 Reversal of direct thrombin inhibitors [23, 47–49]

Generic name	Elimination half-life	Removal by HD	Emergent reversal for life-threatening bleeding
Dabigatran	12–17 h up to 34 h in severe renal impairment	62–68%	If ingested within 2 h, consider administration of activated charcoal 50 g Drug of choice: Idarucizumab 5gm IV push (two 2.5 g vials given back to back) Consider the following if Idarucizumab not available Emergent hemodialysis OR *Weak evidence for* FFP 15–20 ml/kg OR rFVIIa 20 mcg/kg and may repeat × 1
Bivalirudin	25 min up to 1 h in severe renal impairment	25%	Turn off infusion Monitor aPTT to confirm clearance Supportive measures to control bleeding
Argatroban	39–51 min	~ 20%	Turn off infusion. Monitor aPTT to confirm clearance Supportive measures to control bleeding

recommended dose of idarucizumab is 5 g intravenously administered in two 2.5 g doses [47–49]. 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 redistribution from the extravascular compartment. Safety and effectiveness of repeat treatment with idarucizumab have not been established. Additionally, no dose adjustment is necessary in patients with renal impairment (Table 8).

Andexanet alfa is a specific reversal agent for patients taking factor Xa (FXa) inhibitors, apixiban or rivaroxaban, that present with life-threatening bleeding. It is currently not approved for reversal of edoxaban or betrixiban. Andexanet alfa is an inactive protein analogue of FXa that competitively binds apixaban and rivaroxaban and eliminates the ability of these agents to inhibit endogenous FXa. Additionally, andexanet alfa inhibits the activity of tissue factor pathway, increasing tissue factor-initiated thrombin generation. Investigators found andexanet alfa rapidly reversed anti-FXa activity, with a median decrease from baseline of 97% for rivaroxaban and 92% for apixaban in healthy volunteers [50–52]. The dose of andexanet alfa is chosen based on the agent being reversed (apixaban or rivaroxaban), the dose of the FXa inhibitor, and the time the last dose was taken (see Table 7). Caution should be used when administering as the risk of thromboembolic events appears to range from 3 to 6% at day 3 and 11–18% at day 30 [51]. As not all FXa inhibitors are approved for reversal with andexanet alfa, exorbitant cost and limited supply, not all institutions will be able to acquire. Therefore, administration of a four-factor PCC should be strongly considered as a suitable alternative for reversal of life-threatening bleeding in patients taking FXa inhibitors [23]. 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 healthy individuals who received four-factor PCC 50 units/kg to reverse rivaroxaban [53]. Only animal studies have evaluated factor VIIa for treatment of bleeding associated with rivaroxaban (Table 7).

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 [54]. The NCS, ACCP and AHA/ASA do not recommend rFVIIa for warfarin reversal although its use to supplement three-factor PCC in patients with life-threatening bleeding taking warfarin may be considered [23, 55–57]. The dose of rFVIIa is not well established, and lower doses (10–20 mcg/kg) are preferred due to risk of thrombosis with higher doses. Furthermore, there may be an increased thrombotic risk when combined with PCC, although not well established. The duration of coagulopathy correction is dose dependent and transient. Additionally, the INR is not a reliable marker of reversal duration or effect, as rFVIIa may interfere with the INR test causing a falsely low result.

Platelet transfusions are commonly used for both prophylactic and therapeutic reversal of antiplatelet therapy in patients taking an antiplatelet agent (aspirin, clopidogrel, prasugrel, ticagrelor) with an acute neurologic injury. Although there is a paucity of the literature in

Table 9 Reversal of low molecular weight heparin [59, 60]

<table>
<tr><th>GENERIC NAME</th><th>ELIMINATION HALF-LIFE</th><th>EMERGENT REVERSAL FOR LIFE-THREATENING BLEEDING</th></tr>
<tr><td>Enoxaparin</td><td>4-7 hours

Longer in renal impairment</td><td rowspan="2">Protamine partially reverses the anticoagulant effect of LMWHs (~ 60%).

<table><tr><th>Time since last dose of LMWH</th><th>Dose of protamine</th></tr><tr><td>< 8 hrs</td><td>1 mg protamine per each 1 mg enoxaparin

1 mg protamine per each 100 units dalteparin administered

(max 50 mg)</td></tr><tr><td>8-12 hrs</td><td>0.5 mg protamine per each 1mg enoxaparin

0.5 mg protamine per each 100 units dalteparin administered

(max 25mg)</td></tr><tr><td>>12 hrs</td><td>Not likely to be useful* (max 25 mg)</td></tr></table>
*Consider reversal beyond 12 hours in patients with renal insufficiency

Monitor anti-FXa activity to confirm reversal</td></tr>
<tr><td>Dalteparin</td><td>3-5 hours

longer in severe renal impairment</td></tr>
<tr><td>Fondaparinux</td><td>17-21 hrs

significantly longer in renal impairment</td><td>Supportive treatment

<u>Data weak for reversal effect but may consider</u>:

PCC 50 units/kg OR

Factor VIIa 20 mcg/kg and may repeat x 1

Protamine not effective</td></tr>
</table>

regard to administration of platelets for an emergent neurosurgical procedure or in patients after TBI or aSAH, recent findings from the PATCH Trial demonstrate worse outcomes in patients that receive platelets for spontaneous ICH when compared to standard care without platelet therapy [58]. Of note, few patients enrolled in PATCH were receiving clopidogrel, and patients undergoing an emergent neurosurgical procedure were excluded. Therefore, platelet transfusions may be cautiously considered in patients undergoing an emergent neurosurgical procedure and is not recommended for patients presenting with spontaneous ICH at this time (see *ENLS Intracranial Hemorrhage* module for further recommendations regarding platelet transfusion).

Nursing Considerations

Nursing staff should ensure that anticoagulant reversal and hemostatic agents are given promptly once ordered. During and after administration of these medications, the nurse should closely monitor the neurologic examination and vital signs and alert the provider team with any changes. The nurse should be aware of potential thrombotic complications that can arise from these

Table 10 Reversal of unfractionated heparin

GENERIC NAME	ELIMINATION HALF-LIFE	REMOVAL BY HD	EMERGENT REVERSAL FOR LIFE-THREATENING BLEEDING
Heparin	1-2 hrs (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 minutes	0.5 mg for each 100 units of heparin administered
>2 hrs	0.25 mg for each 100 units of heparin administered

Table 11 Factor product composition per manufacturer label [61]

Product	Clotting factors				Anticoagulant proteins			
	FII	FVII	FIX	FX	Protein C	Protein S	AT	Heparin
Three-factor PCCs								
Bebulin	24–38 IU/ml	<5 IU/ml	24–38 IU/ml	24–38 IU/ml	NA	NA	NA	<0.15 IU/IU of FIX
Profilnine	NMT 150 U/100 FIX units	NMT 35 U/100 FIX units	100 U	100 U/100 FIX units	NA	NA	NA	NA
Four-factor PCCs								
Beriplex	20–48 IU/ml	10–25 IU/ml	30–31 IU/ml	22–60 IU/ml	15–45 IU/ml	12–38 IU/ml	0.2–1.5 IU/ml	0.4–2 IU/ml
Octaplex	14–38 IU/ml	9–24 IU/ml	25 IU/ml	18–30 IU/ml	13–31 IU/ml	12–32 IU/ml	NA	5–12.5 IU/ml
rFVIIa								
NovoSeven	None	0.6 mg/ml	None	None	None	None	None	None
Activated PCC								
FEIBA	1.3 U/U	0.9 U/U	1.4 U/U	1.1 U/U	1.1 U/U	NA	NA	None

medications including ischemic stroke, pulmonary embolism, or myocardial infarction [27].

Attention should be paid to institution-specific guidelines for transfusing blood products including FFP and platelets as well as consent and monitoring protocols. Nursing staff should be aware of potential transfusion-related complications including allergic reactions and volume overload.

Management of Jehovah's Witnesses with Acute Life-Threatening Bleeding

A well-known reason for a patient to decline blood products involves patients who are Jehovah's Witnesses. Among this population are various beliefs as to what blood products are considered acceptable or unacceptable; therefore, it is important to understand the patient's wishes. Attempts must be made to maintain cultural competency with this patient population. Nursing must administer prescriptive medical treatments while assisting with supportive management. Strategies to consider in patients that present with acute life-threatening bleeding include aggressive hemostasis, minimization of blood loss, and hematopoiesis optimization [62, 63]. Hemostasis can be achieved commonly with antifibrinolytics (acceptable to most), prothrombin complex concentrates (acceptable to most), fibrinogen concentrates (acceptable to most), recombinant factor VIIa (acceptable to most), and cryoprecipitate (acceptable to some) [64–67]. Blood loss minimization strategies include using pediatric collection tubes for blood draws and reducing the number of phlebotomies. And lastly optimization of hematopoiesis by providing supplemental intravenous iron, vitamin B12, folic acid and erythropoietin alfa (EPO) 300 units/kg/day × 7 days (if patient will accept albumin) or

Table 12 The Bedside Shivering Assessment Scale [75]

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

darbepoetin alfa 0.45 mcg/kg SQ weekly (if patient will not accept albumin). EPO has been described as a successful treatment for individuals that present with severe bleeding and refuse blood transfusions [68, 69].

Antifibrinolytic Therapy after Subarachnoid Hemorrhage

Rehemorrhage is a significant problem in management of patients with aneurysmal subarachnoid hemorrhage (aSAH) and contributes to morbidity and mortality in the acute setting. Antifibrinolytics have a role as short-term therapy (< 72 h) to prevent rebleeding in the acute setting while waiting for definitive treatments in order to secure the aneurysm. Several retrospective studies and one prospective study have shown that a short course of an antifibrinolytic reduces the rate of rehemorrhage without an increase in cerebral ischemia, vasospasm, and/or hydrocephalus [70–73].

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 these agents 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 antifibrinolytic therapy 4–6 h prior to the endovascular procedure to prevent thrombotic complications. Only short-term use of antifibrinolytics, generally less than 72 h post bleed, is recommended [72].

Nursing Considerations

Nursing care for patients receiving antifibrinolytics includes monitoring patients for signs and symptoms of thrombotic complications, having a knowledge that patients who have a history of hypercoagulable profiles and use of hormonal contraceptives are at higher risk. Side effects include hypotension that may occur from administration via rapid push, hypersensitivity reactions, and rarely seizures [27].

Shiver Control during Therapeutic Temperature Management

Shivering is a physiologic homeostatic mechanism that helps maintain core body temperature and is triggered typically in humans when core temperature falls below 36 °C and ceases at temperatures < 34 °C. Elderly patients have approximately a 1 °C lower shivering threshold than younger patients [74]. Sustained shivering increases the metabolic rate and should be avoided as it counteracts cooling induction, consumes energy, contributes to increased intracranial pressure, increases brain oxygen consumption, and can be deleterious in acute brain injury [75]. Therefore, it is crucial to evaluate and treat shivering in patients who are being treated with targeted temperature management (Tables 12, 13, Fig. 1).

Neuromuscular Blocking Agents

Neuromuscular blocking agents (NMBA) 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 (Table 14). Short acting agents are preferred as all paralytics appear to have prolonged elimination half-lives during hypothermia, and larger acting agents may unnecessarily prolong neuromuscular blockade [80]. 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 may occur that reduce or inhibit plasma cholinesterase activity and/or decrease the sensitivity of endplate acetylcholine thus prolonging the paralytic effects. Conversely drug interaction occurs that may compete for the acetylcholine receptor or upregulate acetylcholine receptors and thus cause the NMBA to appear ineffective (Table 15). Caution should be used in patients with known myasthenia gravis, as this population has a higher sensitivity to the effects of NMBAs and generally require smaller doses. Pediatric dosing (see Table 14) refers to children ≤ 12 years of age or < 40 kg. Paralytics affect all skeletal muscles but have no effect on consciousness and therefore must be used

Table 13 Antishivering medications for therapeutic temperature management [21, 76–79]

Drug	Dose	Advantages	Disadvantages
Acetaminophen/Paracetamol	500/650–1000 mg q 4–6 h	No sedative effects	Caution with liver dysfunction Available as both IV and PO/PT
Metamizol	1000 mg q 4–6 h	No sedative effects	Caution with liver and renal dysfunction Causes hypotension 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 Does not decrease seizure threshold Minimally sedative	Only PO/PT administration available
Dexmedetomidine	0.2–1.4 mcg/kg/h	May have additive effects with meperidine Short activity	Dose-limiting ADRs: hypotension and bradycardia Bolus dose not recommended
Clonidine	Doses studied [80] 75 mcg 1500 mcg 3–9 mcg/kg	Higher doses (6 and 9 mcg/kg) result in hypotension, bradycardia, and sedation	Dose-limiting ADRs Hypotension and bradycardia IV formulations not available in the USA
Magnesium	Bolus: 4gm IV q 4 h to maintain goal serum level OR Infusion: 0.5–1 mg/h	Serum Mg + goal: 3–4 mg/dl	Monitor Ca +, K +, and Phos levels as well and replace to maintain normal serum levels
Propofol	50–75 mcg/kg/min	Short activity	Caution in patients with hypotension Must be intubated
Benzodiazepine (midazolam, lorazepam)	Bolus: 2–5 mg IV PRN OR Infusion: 1–10 mg/h	Can be used PRN or continuous infusion	Prolonged sedation with continuous infusion Continuous Infusion of lorazepam carry increase risk of propylene glycol toxicity
Fentanyl	25–150 mcg/h	Short acting (t ½ = 3–4 h) Can be used PRN or continuous infusion	Constipation
Remifentanil	0.1–1 mcg/kg/min	Short acting (t1/2 = 5–10 min)	Constipation
Meperidine/pethidine	12.5–100 mg IV q 4–6 h PRN	Most effective antishivering drug May have additive effects with dexmedetomidine	Accumulation occurs in renal dysfunction Decreases 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 shivering threshold Good adjunctive therapy Mild sedative effects	Caution in patients with severe liver dysfunction
Paralytic:	Vecuronium Bolus: 0.1 mg/kg (duration 30–45 min)	Last-line therapy	Patient must have adequate continuous sedation and analgesia *prior* to paralytic administration
Vecuronium	Infusion: 0.05–1.5 mcg/kg/min titrate to TOF		Must be intubated EEG recommended during paralysis
Cisatracurium	Cisatracurium: Bolus: 0.15–0.2 mg/kg (duration 45–60 min) Infusion: 2–10 mcg/kg/min		NMBAs may have prolonged effect with hypothermia TOF goal is 1–2 twitches of 4

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 used to evaluate the extent of paralysis. The TOF goal is generally 1–2 responses per 4 stimulations.

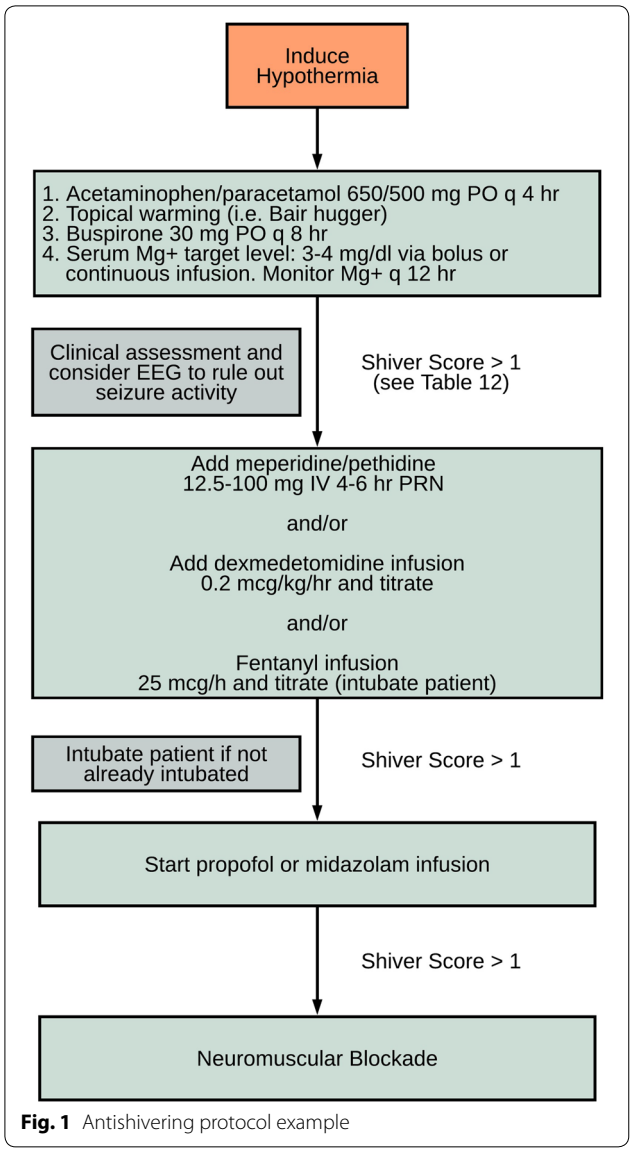

Fig. 1 Antishivering protocol example

Caution should be used when using a PNS in hypothermic patients as the TOF may be unreliable and misleading [81]. Non-depolarizing agents may be reversed with neostigmine or sugammadex. Sugammadex is a selective neuromuscular reversal drug that binds to the neuromuscular agent specifically to reverse aminosteroid neuromuscular blocking agents (rocuronium and vecuronium). Table 16 lists common adverse effects associated with NMBAs.

Nursing Considerations

Nursing care for the patient requiring NMBAs includes special considerations and precautions as these are a high-alert medication. The nurse should ensure that the patient has a secure airway and adequate ventilation and sedation/analgesia prior to administering the medication. The nursing assessment should include vital signs including HR, BP, ventilator synchrony, respiratory rate, and oxygenation, paying special focus to respiratory mechanics to determine effectiveness of paralysis. Nursing staff should ensure that the patient has adequate sedation during the neuromuscular blockade. Staff caring for patients requiring neuromuscular blockage should have special training to be able to perform monitoring of TOF with a PNS with titration of the medication according to institution guidelines. The nurse should anticipate possible abnormal hemodynamics including bradycardia and hypotension and be prepared to administer vasopressors as ordered [27]. It is important for the nursing staff to alter the typical neurologic monitoring in patients who are receiving neuromuscular blockage. These patients should not have noxious stimuli or oculovestibular response performed as they will be unable to elicit a motor response due to muscle paralysis [10].

Sedation and Analgesia

When using sedative and analgesic agents, 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, and 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. Sedative and analgesic agents commonly used in the ICU can be found in Tables 17 and 18.

As opioid overdoses are a worldwide problem, understanding how to recognize and treat intoxications and overdoses is critical. Common manifestations of opioid intoxication include constricted pupils, respiratory depression, and somnolence. Naloxone is a pure competitive antagonist of opioid receptors and can be given via IV, IM, ET, SQ, or nasal route [89]. The onset of action is approximately 1–2 min, and subsequent doses can be repeated every 2–3 min until the desired degree of opioid reversal is achieved. Higher doses may be necessary to reverse methadone, designer drugs, sustained release products, or veterinary tranquilizers.

Nursing Considerations

Nursing care for patients requiring sedation includes establishing clear guidelines between the nurse and

Table 14 Neuromuscular blocking agents [21, 88]

Medication	Dosing	Onset	Duration	Administration pearls
Succinylcholine	Adults IV 0.5 to 1.1 mg/kg IM 2–4 mg/kg Adolescents 1 mg/kg Pediatrics 2 mg/kg	Very Rapid IV 30–60 s IM 4 min	Short Average 3–5 min Max 7–10 min	Cannot be reversed May cause slight increases in ICP (inconsistent data) Severe hyperkalemia may occur in patients with burns, severe muscle trauma, neuromuscular diseases, strokes, spinal cord injury, multiple sclerosis, and prolonged immobilization Contraindicated in patients with Malignant hyperthermia Hyperkalemia (serum potassium > 5.0 mEq/L)
Pancuronium	IV Adults and pediatrics 0.05–0.1 mg/kg	Intermediate 2–3 min	Long 90–100 min	Conditions that slow circulation may delay onset
Vecuronium	IV Adults and pediatrics 0.1 mg/kg (up to 0.2 mg/kg)	Prolonged 3–9 min Faster onset with higher dose (2 min)	Intermediate 35–45 min (up to 60 min)	No significant cardiovascular effects No effect on ICP
Cisatracurium	IV Adults 0.15 mg/kg (up to 0.2 mg/kg) Pediatrics 0.15 mg/kg	Fast 1.5–2 min	Prolonged Adults 45–75 min Pediatrics 20–35 min	Longer half-life in elderly Elimination via enzymatic breakdown and does not rely on renal or liver function for clearance
Rocuronium	IV Adults 0.6 mg/kg (up to 1.2 mg/kg) Pediatrics 0.45–0.6 mg/kg	Rapid 1–2 min Faster onset with higher dose	Intermediate 20–35 min (up to 60 min)	Prolonged duration in renal failure

Table 15 Common drug interactions with neuromuscular blocking agents [82–86]

Drug	Interaction	Effect
Antibiotics (aminoglycoside, tetracycline, clindamycin, vancomycin)	Reduces prejunctional ACh release, decreases postjunctional receptor sensitivity to ACh, blocks ACh receptors or disrupts ion channels	Prolong duration of NMBA
Carbamazepine	Competes for ACh receptor	Causes NMBA resistance
Corticosteroids [82–84]	May decrease sensitivity of endplate to ACh	Prolong duration of NMBA
Cyclosporin	May inhibit NMBA metabolism	Prolong duration of NMBA
Lithium	Activate K + channel presynaptically	Prolong duration of NMBA
Magnesium	Competes with Ca + presynaptically	Prolong duration of NMBA
Phenytoin [85–87]	Upregulation of ACh receptors	Causes NMBA resistance
Theophylline	Unknown	Causes NMBA resistance

provider team on the level of sedation. The nurse should coordinate with the provider team to determine how often interruption of sedation is needed for neurologic examination. The Richmond Agitation Sedation Scale (RASS) scale has been shown to be a reliable and well validated tool to measure the level of sedation in patients in the intensive care unit. Current recommendations call for a RASS goal of 0 to -2. It is important to have clear orders between providers and nurses to ensure the goal of the level of sedation [10].

Intravenous Antihypertensive Agents

Intravenous antihypertensive agents are necessary to mitigate hypertension in many acute neurologic conditions. BP goals vary dramatically between disease states and controversy surrounds the definition of best practice in many areas. When BP reduction is required the agent

Table 16 Adverse effects with neuromuscular blocking agents [21, 88]

Adverse drug effects
Hypersensitivity reactions, including anaphylaxis
Cardiac arrest
Cardiac arrhythmias
Malignant hyperthermia
Hypertension or hypotension
Hyperkalemia
Prolonged respiratory depression
Jaw rigidity
Rhabdomyolysis
Myalgias
Skeletal muscle weakness

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., HR) and drug interactions (Table 19).

Nursing Considerations

It is important for nurses caring for critically ill neurologic patients to have an understanding of medications used to treat hypertension and specifically how these medications can affect the disease process. It is important for the nurse to have knowledge of side effects and adverse effects to ensure proper titration of the various IV antihypertensive medications. Nicardipine is an IV medication that requires special considerations by nursing staff. This medication should only be administered through a large peripheral IV or via central access in order to prevent phlebitis or local irritation. The infusion site should be changed every 12 h in order to minimize peripheral venous irritation [10].

Vasopressors and Inotropes

Vasopressor agents induce vasoconstriction and elevate mean arterial pressure and CPP. They are used in the neurologic patient in a variety of situations when BP augmentation is desired to treat shock, symptomatic vasospasm, or improve cerebral or spinal perfusion pressure. Vasopressors produce their effects through their actions at adrenergic (alpha and beta), dopamine, or vasopressin receptors in the body (Table 20). Alpha-1 adrenergic receptors are located in vascular walls and in 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 both inotropic and chronotropic effects with minimal vasoconstriction. Beta-2 adrenergic receptors are located on blood vessels, and activation induces 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 [93, 94], 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. Therefore, nursing considerations for drip titration are dependent on provider orders for hemodynamic status goals (i.e., MAP > 65 mmHg).

Nursing Considerations

Prior to starting vasopressors or inotropes, it is important for the nursing staff to establish blood pressure or MAP goals with the provider team. The nurse should closely monitor the HR, rhythm, and BP during initiation and titration [10].

Antibiotics

When treating meningitis, encephalitis, cerebral abscesses, and other CNS infections, choosing an appropriate antimicrobial or antiviral agent and the appropriate dose is essential. Most antibiotics are hydrophilic and do not cross the BBB well; however, when the meninges are inflamed, penetration increases and allows drug to reach the site of action. Avoidance of delay in the administration of antimicrobial therapy, along with adjunctive dexamethasone when indicated, is key to improving outcomes [95–99]. Dexamethasone is only indicated in patients with suspected bacterial meningitis, with further data

Table 17 Sedatives [31, 90–92]

Generic name Mechanism of action	Dose	Adverse drug reactions	Clinical pearls
Propofol GABAa receptor agonist	50–100 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) Risk of PRIS is increased in young people and with high doses (> 70 mcg/kg/min) for a prolonged duration (> 48 h)	Contraindications: Allergy to soy or egg Use with caution in patients with cardiovascular disease Rapid onset and offset Lipid vehicle is particularly susceptible to bacterial contamination, change IV tubing and bottle every 12 h Blue-green discoloration of urine may occur Propofol delivers 1.1 kcal/ml
Dexmedetomidine Alpha-2 agonist	*Loading dose* (1 mcg/kg) NOT recommended (risk of severe bradycardia, hypotension, and sinus arrest) *Maintenance infusion* 0.2–1.4 mcg/kg/h	Hypotension, transient hypertension during loading dose, bradycardia	Has analgesic properties Goal is patient is arousable with stimulation and return to sedate state when stimulation removed Does not require mechanical ventilation
Lorazepam GABAa receptor agonist	*Loading dose* 0.02–0.04 mg/kg *Intermittent dose* 0.02–0.06 mg/kg q2–6 h (max IV dose 2 mg for agitation—infuse at 2 mg/min) Maintenance infusion 0.01–0.1 mg/kg/h	Hypotension, respiratory depression, drowsiness, pain at injection site, akathisia, confusion, anterograde amnesia, visual disturbances Paradoxical reactions—hyperactivity and aggressive behavior	IV contains propylene glycol, which can accumulate with prolonged infusions and cause a metabolic acidosis Precipitation is possible; an inline filter is recommended for infusions
Midazolam GABAa receptor agonist	Loading dose 0.01–0.05 mg/kg Maintenance infusion 0.01–0.1 mg/kg/h	Similar to lorazepam	Rapid onset and short duration Active metabolites which may accumulate in renal dysfunction

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

Table 18 Opioid agonists and antagonists [21]

Generic name	Usual dose	Adverse drug reactions	Clinical pearls
Fentanyl (opioid agonist)	Bolus 12.5–100 mcg or 1–2 mcg/kg IVP Maintenance IV infusion 0.7–10 mcg/kg/h or 25–700 mcg/h	Respiratory depression, bradycardia, edema, confusion, sedation, mood changes, constipation, miosis, chest wall rigidity, diaphoresis, myoclonus	May be alternative in patients with morphine allergy Do not use transdermal formulation in acute setting due to delayed onset (6–24 h)
Hydromorphone (opioid agonist)	Oral 2–4 mg every 4–6 h IV 0.2–1 mg every 4–6 h	Respiratory depression, bradycardia, edema, confusion, sedation, mood changes, constipation, miosis, diaphoresis, myoclonus	May be alternative in patients with morphine allergy
Morphine (opioid agonist)	Bolus 2–10 mg IVP Intermittent dose 2–8 mg every 3–4 h Maintenance infusion 0.8–30 mg/h Pediatric dosing: 0.1–0.2 mg/kg IV over 5 min; maintenance infusion: 0.02–0.03 mg/kg/h—titrate up as required	Itching, respiratory depression, sedation, hypotension, mood changes, xerostomia, constipation, pruritus, urinary retention, pain at injection site, dizziness, fever, myoclonus may elevate ICP due to hypercarbia	Active metabolites may accumulate in renal dysfunction; reduced dose recommended Can induce a histamine release that causes itching
Naloxone (opioid antagonist)	0.04–0.4 mg IV/IM or 1–2 mg per nare into both nares, can be repeated every 2–3 min for desired degree of counteraction. If initial use intranasal, switch to IV/IM when possible	Tachycardia, hypertension, nausea, vomiting, tremor, diaphoresis, dyspnea, withdrawal symptoms	Due to short half-life, effects may wear off before opioid is cleared from the system, resulting in renarcotization

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

Table 19 Intravenous antihypertensive agents [21]

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 Pediatric dose: 1–3 mcg/kg/min	Contraindications: Severe aortic stenosis Use caution with rapid titration as dose stacking may occur and prolonged hypotension Adverse effects: Reflex tachycardia, headache, flushing; thrombophlebitis Available in peripheral and central IV concentration
Clevidipine	2	90 s	1 min	1–2 mg/h initially, may increase dose every 90 s to a max of 21 mg/h (32 mg/h max reported for short-term use)	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 Provides 2 kcal/mL—adjust nutritional intake as needed Adverse effects: 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 minutes to achieve desired effect, maximum 3 mcg/kg/min Pediatric dosing: 0.3–4 mcg/kg/min	Avoid in patients with acute kidney injury (AKI) Caution in patients with elevated ICP Sodium nitroprusside-induced elevations in ICP have never been observed in human subjects, although the potential should be considered. Caution in patients with coronary artery disease due to coronary steal Doses of 3–10 mcg/kg/min and/or renal dysfunction present, monitor for signs of cyanide toxicity (metabolic acidosis, decreased oxygen saturation, bradycardia, confusion and/or convulsions) Adverse effects: cyanide/thiocyanate toxicity, methemoglobinemia Expensive
Hydralazine	5–20	2–12 h	2–8 h	10–20 mg IV every 4–6 h Pediatric dosing: 0.2–0.6 mg/kg/dose up to 25 mg/dose every 4 h	Adverse effects: reflex tachycardia, headache, flushing Ensure adequate volume resuscitation to avoid hypotension
Adrenergic agents					
Esmolol	1–2	10–30 min	9 min	Avoid loading dose 50–300 mcg/kg/min	Contraindicated in bradycardia, heart block, cardiogenic shock, decompensated heart failure Adverse effects: Bradycardia/heart block, headache, flushing
Labetalol	2–5	2–4 h	4–8 h	20–80 mg IV every 10 min up to 300 mg Pediatric dosing: 0.2–1 mg/kg/dose IV bolus (up to 40 mg/dose)	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. Adverse effects: Bronchospasm, HF exacerbation, bradycardia/heart block
Urapidil	3–5	4–6 h	3 h	Bolus of 25 mg (may repeat in 2 min if no response; if still no response may give 50 mg) followed by continuous infusion at a rate of 4–24 mg/h	Not available in the USA Adverse effects: dizziness, headache, irregular heartbeat, chest pain, nausea, vomiting, fatigue
Clonidine	10–15	6–10 h	5–25.5 h	75 mcg bolus followed by 0.2 mcg/kg/min infusion (max: 0.5 mcg/kg/min) Avoid > 0.15 mg/infusion or > 0.9 mg/day	Not available for IV infusion in the USA Adverse effects: dizziness, headache, bradycardia, hypotension, dry mouth, constipation, nausea, vomiting, fatigue

Table 20 Vasopressors and inotropes [21]

Drug name	Adrenergic receptor activation	Initial dosing	Indications	Advantages	Disadvantages
Vasopressors					
Norepinephrine	α, β1	2–5 mcg/min OR 0.02–0.06 mcg/kg/min Pediatric dosing: Initiate at 0.1 mcg/kg/min	Septic shock with low SVR Can be used in anaphylactic shock	Great for increasing SVR and MAP while preserving CO First-line agent for septic shock	May increase oxygen consumption Risk of dysrhythmias and myocardial ischemia May decrease intestinal perfusion and increase lactate levels
Dopamine	α, β1	Dopa—1–3 mcg/kg/min α: 3–10 mcg/kg/min β: 10–20 mcg/kg/min	Poor cardiac function with poor perfusion Hypotension with bradycardia	Effective at multiple receptors	Highest risk of dysrhythmias (especially at higher doses)
Epinephrine	α, β1, β2	0.02–0.05 mcg/kg/min Pediatric dosing: 0.1 to 1 mcg/kg/min	Septic shock with low SVR and/or low CO Anaphylactic shock	Less need for adequate volume resuscitation for initial response First-line agent for septic shock	Risk of dysrhythmias and myocardial ischemia Adverse effects: tachyarrhythmias, hyperglycemia, lactic acidosis, hypokalemia
Ephedrine	α, β1, β2	IV: 5 to 25 mg slow IV push, may repeat after 5 to 10 min Oral: 25–50 mg every 8–12 h	IV: Post anesthesia induced hypotension Oral: orthostatic hypotension in spinal cord injury	Can stimulate release of endogenous norepinephrine	Less potent than epinephrine
Phenylephrine	A	10–200 mcg/min OR 0.1–1 mcg/kg/min	Rapid MAP increases → post-sedation, etc.	No β effects therefore less arrhythmogenic	May decrease CO May cause reflex bradycardia Not indicated for septic shock
Vasopressin	0	0.04–0.08 units/min Pediatric dosing: 0.03 -0.12 units/kg/h	Refractory hypotension in septic shock Diabetes insipidus	May reduce the dose of other vasopressors when added in refractory hypotension	Not first-line agent in shock May decrease splanchnic perfusion and increase gut ischemia
Angiotensin II (Giapreza)	AT-1	10 ng/kg/min (ACTUAL body wt) and may titrate by 5 ng/kg/min every 5 min until goal MAP Max 20 ng/kg/min	Refractory septic or distributive shock Not first-line agent	The short t ½ (< 5 min) and clearance independent of renal and hepatic function	Adverse effects: delirium, thrombosis, thrombocytopenia tachycardia, acidosis, hyperglycemia Limited data; no outcome data Expensive
Inotropes					
Dobutamine	α, β1, β2	2.5–10 mcg/kg/min Pediatric dosing: 1–20 mcg/kg/min	Acute decompensated HF, cardiogenic shock, septic shock with decreased CO	Good to improve CO in decompensated HF	Can decrease SVR and provoke hypotension
Milrinone	0	0.25–0.75 mcg/kg/min Reduce dose if CrCl < 50 ml/min	Inotropic agent to increase CO in decompensated HF	Useful if adrenergic receptors are downregulated or desensitized in the setting of chronic HF	Renal elimination Adverse effects: hypotension, arrhythmias, thrombocytopenia

CO cardiac output, *CrCl* creatinine clearance; *HR* heart failure; *MAP* mean arterial pressure; *SVR* systemic vascular resistance

indicating best results in patients with *S. pneumoniae* as the etiology [99]. Delayed administration of antibiotics by more than 3 h after hospital admission has been shown to be a strong, independent risk factor for mortality [100]. Common causes of delayed administration include atypical clinical presentation and necessary imaging required prior to performing a lumbar puncture (LP) [96]. It is important to understand that therapy should not be delayed in either situation but rather efforts should be made to obtain blood cultures followed by rapid antimicrobial administration [101, 102]. Although the use of antimicrobials prior to LP has an adverse impact on the yield of CSF gram stain and culture, a pathogen may still be identified in the CSF in the majority of patients up to several hours after the administration of antimicrobial agents [102]. Antibiotics, dosing, and their microbial targets are discussed in further detail in *ENLS Encephalitis and Meningitis*.

Nursing Considerations

Nursing responsibilities in the event of a neurologic emergency necessitates focused neuroassessments, monitoring of laboratory values, changes in patient neurologic status, and critical evaluation of administration and titration of medications to meet goals of treatments. Frequent assessments should consist of vital signs, the presence of changes in neurologic status, respiratory/oxygenation status, fluid/hydration status, and invasive neurospecific hemodynamic monitoring such as ICP and CPP. The primary nurse must additionally anticipate appropriate medications based on patient condition. Administration of medications must be timely to ensure optimal patient outcomes and caution should be noted when giving high-alert medications. Nursing staff must be aware of adverse effects of medications administered and patient response.

Conclusion

Pharmacologic management in patients is very challenging, especially while attempting to minimize secondary brain injury. 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 neurologic emergencies.

Clinical pearls

- First-line antiseizure agents, administered after benzodiazepines for treatment of status epilepticus, should be given intravenously over a short period of time. The appropriate agent should be chosen based on the medication's adverse drug reaction profile, etiology of seizure, patient organ function, preexisting antiseizure drugs, and the patient hemodynamic stability
- When reversing an anticoagulant, the risk of continued bleeding relative to the risk of thrombosis is of the utmost importance and should be determined in each case. The timing of the last dose of anticoagulant administered and elimination half-life is necessary to determine whether reversal is warranted. In the case of life-threatening bleeding, reversal should be considered if the anticoagulant was taken within 3–5 half-lives and may be necessary out to 2–3 days from the last dose with anticoagulants with long half-lives and/or in patients with acute renal dysfunction
- For rapid reversal of warfarin, guidelines suggest use of prothrombin complex concentrate (PCC) agents over fresh frozen plasma (FFP)
- Shivering is crucial to identify and treat in patients treated with targeted temperature management. Shivering increases the metabolic rate and counteracts cooling induction, consumes energy, contributes to increased intracranial pressure, increases brain oxygen consumption, and can be deleterious in acute brain injury
- When administering neuromuscular blocking agents, it is vital that adequate sedation and analgesia be administered prior to neuromuscular blocking agent. Additionally, 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. Patients should not have noxious stimuli or oculovestibular response performed as they will be unable to elicit a motor response due to muscle paralysis
- When BP 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, and drug interactions
- Selection of appropriate vasopressor must be based on goals of care and desired physiologic effects

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Publisher's Note

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* Important papers
** Landmark papers

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