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REVIEW ARTICLE



Collaborative Management Strategies for Drug Shortages in Neurocritical Care

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Abstract

Drug shortages have become all too familiar in the health care environment, with over 200 drugs currently on shortage. In the wake of Hurricane Maria in September 2017, hospitals across the USA had to quickly and creatively adjust medication preparation and administration techniques in light of decreased availability of intravenous (IV) bags used for compounding a vast amount of medications. Amino acid preparations, essential for compounding parenteral nutrition, were also directly impacted by the hurricane. Upon realization of the impending drug shortages, hospitals resorted to alternative methods of drug administration, such as IV push routes, formulary substitutions, or alternative drug therapies in hopes of preserving the small supply of IV bags available and prioritizing them for their most critical needs. In some cases, alternative drug therapies were required, which increased the risk of medication errors due to the use of less-familiar treatment options. Clinical pharmacists rounding with medical teams provided essential, patient-specific drug regimen alternatives to help preserve a dwindling supply while ensuring use in the most critical cases. Drug shortages also frequently occur in the setting of manufacturing delays or discontinuation and drug recalls, with potential to negatively impact patient care. The seriousness of the drug shortage crisis reached public attention by December 2017, when political and pharmacy organizations called for response to the national drug shortage crisis. In this article, we review institutional mitigation strategies in response to drug shortages and discuss downstream effects of these shortages, focusing on medications commonly prescribed in neurocritical care patients.

Keywords: Drug shortages, Natural disasters, Medication errors, Patient care, Neurocritical care

Drug shortages continue to affect healthcare services across the nation [1, 2]. On a daily basis, another drug shortage is realized that requires a change in product formulation and dispensing procedures, as well as the need to review alternative therapy options. Recently in the fall of 2017, US hospitals were affected by Hurricane Maria which devastated Puerto Rico, cutting off the supply of small-volume parenteral solutions for intravenous piggyback (IVPB) use nationwide. These solutions are essential to patient care and are used to compound agents ranging from antimicrobials and chemotherapy to

analgesic, sedative, and hemodynamic support in critically ill patients. The hurricane also impaired manufacturing of amino acids, prompting a shift in delivering parenteral nutrition to patients requiring intravenous (IV) nutritional support. Subsequently, hospitals nationwide were affected by the IV opioid shortage in spring 2018. Oftentimes, therapeutic alternatives can be substituted; other times the shortages are more profound and can have drastic consequences. Frequent changes in medication formulations increase the risk of adverse medication events, including medication errors.

The seriousness of the IV fluid shortage reached public attention by fall 2017, when political and pharmacy organizations called for action. In November 2017, the American Society of Health-System Pharmacists (ASHP) hosted a Drug Shortages Roundtable with key

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stakeholders from multiple healthcare disciplines and organizations to review challenges and develop strategies to mitigate drug product shortage concerns [3, 4]. The group recognized improvements in place since the height of the shortage crisis in 2012, during which legislation was enacted requiring drug manufacturers to notify the Food and Drug Administration (FDA) “of any change in production that is reasonably likely to lead to reduction in supply” of a covered drug in the USA. This advanced warning requirement has played a significant role in increasing the awareness of drug shortages, but it has not solved the problem [4–6].

After reviewing the newer trends and previous initiatives, the roundtable provided recommendations unique to natural disasters including: recommending the Federal Trade Commission closely evaluates the potential effects mergers or acquisitions of pharmaceutical companies may have on the drug supply chain; advocating for transparency of manufacturing locations, including detailed information of quality control deficiencies cited during FDA inspections and updated information if problems have been addressed; and proposing the FDA establishes a quality manufacturing initiative to incentivize both contingency plans for interruptions or disasters and redundancy in production. ASHP has recently updated guidelines on the subject as well, suggesting national organizations such as the Centers for Disease Control and Prevention provide guidance on patient prioritization when drug supply is scarce [7]. In spring of 2018, the FDA published several statements and action plans addressing the seriousness of drug shortages caused by manufacturing processes and supply chain availability [8, 9]. The FDA’s involvement has included extending expiration dating for select products, expediting review of new drug applications, and allowing importation from other countries. The FDA has the authority to exercise regulatory discretion to allow manufacturers to import medically necessary drugs following evaluation of foreign firms and drug products for quality control [5].

In wake of Hurricane Maria, national pharmacy and government groups have collaborated on drug shortage mitigation strategies with predictable shortages and opportunities to support manufacturers during unexpected supply shortages. Strategies include developing a critical drug list and promoting manufacture of generic drugs [3, 9]. Unexpected drug shortages can have serious medication safety and cost implications. Unfamiliar alternative therapies could lead to dosing, dispensing, and administration errors, inadequate monitoring of side effects, improper use of a medication altogether, and bypassing technology safeguards such as medication barcode scanning [10]. Having pharmacist presence can help prevent these errors, although smaller, community-based

settings may not have consistent pharmacy services available [11, 12]. Additionally, use of alternative agents may lead to unexpected or unintended drug expenditures.

When a product unexpectedly becomes unavailable, discussing alternative options can lead to cost reduction initiatives, quality improvement endeavors, and opportunities to optimize clinical practice. Creation of a drug shortage committee that meets regularly has allowed an efficient approach to handle all aspects of drug shortage management in preparing for future events. Communication is paramount with dynamic drug availability lists as all involved parties must be aware of issues, ranging from providers, pharmacists, nurses, inventory specialists, medication safety officers, and the pharmacy informatics department. Written notifications, electronic medical record alerts, and e-mail communications are options for relaying information across health systems.

Pharmacists from the Neurocritical Care Society have worked together to review practice and process changes that have resulted from natural disasters and manufacturer shortages. The group discussed the different strategies that institutions have identified to effectively troubleshoot shortages to minimize effects on patient care. Health systems pharmacy departments have altered and created numerous processes in an attempt to minimize impact on patient care. These management strategies on a health system level have included adjustments in staffing models for pharmacists and technicians, implementing restricted use criteria (i.e., by prescriber, unit, diagnosis, and enteral access status), investigating alternative administration strategies, procuring alternative preparations of the same medication, allowing temporary use of non-formulary alternatives, centralizing supply by removing medications from automated dispensing cabinets and code carts, and provision of therapeutic substitution policies. Specific to shortages of products that require IVPB for administration, hospitals have implemented diverse strategies: enabling protocols that allow pharmacists to automatically convert routes of administration, product changes of IVPB using various adapters, use of alternative preparations (i.e., use of pre-mixed products instead of compounding or vice versa), and limiting use of IVPB by allowing nurses to administer select medications as IV push. Herein, we discuss alternative therapeutic management strategies to recent or current shortages within neurocritical care.

Management Strategies for Intensive Care Unit Medication Shortages

Anti-seizure Drugs

Although there are numerous anti-seizure drugs (ASDs), few exist with parenteral formulations used to treat status epilepticus (SE) [13–16]. Benzodiazepines including

diazepam, lorazepam, and midazolam are routinely used first line for seizure cessation and are available in a variety of formulations and routes of administration [17, 18]. As a result of Hurricane Maria in 2017, institutions were challenged with administering IVPB ASDs due to the lack of small-volume IV fluid bags used for dilution. ASDs that can be administered as IV push instead of an intermittent infusion include: fosphenytoin, lacosamide, levetiracetam, and valproic acid. As a result of the IV fluid shortage, institutions preserved supply by switching to IV push administration of these agents. In recent years, there have also been manufacturer shortages with first-line agents, such as lorazepam and diazepam, in addition to maintenance drugs, such as fosphenytoin, levetiracetam, and ketamine. Table 1 lists recommended medications for treating SE by intermittent or continuous infusion based on guideline or package insert recommendations.

Fosphenytoin/Phenytoin

Fosphenytoin is a sodium channel blocker that has been used as a second-line agent for seizure cessation. Fosphenytoin is a pro-drug of phenytoin and has the advantage over IV phenytoin because of its safer medication profile and faster IV push administration rate. Fosphenytoin

can also be administered via intramuscular route when IV access is not available; however, this is not always an appropriate route of administration for status epilepticus. IV phenytoin is a cost-effective option; however, use is associated with serious adverse events, including purple glove syndrome and cardiac abnormalities. In some patients, the large initial loading doses of IV phenytoin or fosphenytoin are associated with cardiovascular adverse effects, including hypotension and bradyarrhythmias. Due to these aforementioned risks, a slow IV infusion is preferred to IV push.

Levetiracetam

IV levetiracetam is an appropriate ASD for patients who are hemodynamically unstable. Levetiracetam loading doses are not associated with the cardiac abnormalities that can be seen with fosphenytoin or phenytoin. Although often given as a short infusion, it can be given via rapid IV push over 5 min without further dilution [19]. Levetiracetam is also available as a ready-to-use bag which can be used as an alternative to a compounded product when IV fluids are in short supply. Some institutions utilized multiple ready-to-use bags for larger doses that are not commercially available (e.g., two 1500 mg

Table 1 Anti-seizure drugs for status epilepticus

	Initial dose	Repeat dose	Administration rate	Adverse effects
Fosphenytoin	20 mg PE/kg	5–10 mg PE/kg in 10 min	150 mg PE/min	Hypotension, arrhythmias
Levetiracetam	60 mg/kg Max 4500 mg	n/a	Infused over 15 min, IV push over 5 min	Sedation, agitation
Valproic acid	20–40 mg/kg Max 3000 mg	20 mg/kg	5–10 mg/kg/min	Hepatotoxicity, transaminitis, hyperammonemia, pancreatitis, thrombocytopenia
Ketamine	1–2 mg/kg	1–2 mg/kg every 3–5 min up to a total dose of 4.5 mg/kg	IV push over 3–5 min; continuous infusion: 2–10 mg/kg/h	Tachycardia, hypertension, increased cardiac output, increased oral secretions
Lacosamide	200–400 mg	n/a	Infused over 15 min; IV push 80 mg/min	PR prolongation, DRESS, hypotension
Phenytoin	20 mg/kg	5–10 mg/kg in 10 min	50 mg/min	Hypotension, arrhythmias, purple glove syndrome
Phenobarbital	15–20 mg/kg	5–10 mg/kg in 10 min	50–100 mg/min	Hypotension, respiratory depression
Diazepam	0.15 mg/kg Max 10 mg	Repeat 0.15 mg/kg (max 10 mg) in 10 min	5 mg/min	Hypotension, respiratory depression
Lorazepam	0.1 mg/kg Max 4 mg	0.1 mg/kg, max dose of 8 mg combined	2 mg/min; dilute 1:1 with normal saline	Hypotension, respiratory depression
Midazolam	10 mg IM	n/a	Continuous infusion: 0.5–2 mg/kg/h	Hypotension, respiratory depression, tachyphylaxis
Pentobarbital	5–15 mg/kg	5–10 mg/kg	50 mg/min; Continuous infusion: 1–5 mg/kg/h	Hypotension, bradycardia, hepatotoxicity, adynamic ileus, respiratory depression
Propofol	1–2 mg/kg		Continuous infusion: 1–5 mg/kg/h	Propofol infusion syndrome, hypotension, hypertriglyceridemia, respiratory depression

DRESS drug reaction with eosinophilia and systemic symptoms, IV intravenous, PE phenytoin equivalents

bags to equal a 3000 mg loading dose); however, this can lead to confusion for nursing staff who may perceive this as a duplicate order.

Intravenous Anesthetic Agents

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that can be used in hemodynamically unstable patients with refractory status epilepticus (RSE). It alternatively can be used as a sedative or adjunctive analgesic. Propofol, midazolam, and pentobarbital continuous infusions are alternatives for RSE. These agents require mechanical ventilation and additional cardiac monitoring, as respiratory depression and hypotension are commonly encountered. Oftentimes, institutions are left with using what is available commercially, including different concentrations and restricting use to specific indications and treatment teams.

Treatment for Intracranial Hypertension

Acute elevations in intracranial pressure (ICP) can be managed with hyperosmolar therapies, such as mannitol or hypertonic saline [20]. Shortages of either agent can severely limit a clinician's ability to quickly and effectively manage ICP crises. Hyperosmolar therapies of mannitol 0.5–1 g/kg, sodium chloride 3% 2.5 mL/kg, or sodium chloride 23.4% 0.687 mL/kg, often administered as a 30 mL dose, are typically utilized. The osmolarities of these products vary significantly [21]. Considerations for choosing between therapies typically center around the type of IV access available, current serum sodium levels, and the patient's osmolar gap. Sodium chloride 23.4% must be administered via a central venous catheter, whereas mannitol and sodium chloride 3% can be administered through peripheral veins. In patients receiving hypertonic saline, most clinicians will attempt to avoid prolonged hypernatremia and subsequent hyperchloremia. Sodium acetate 120 mEq/60 mL given over 30 min may be considered to either prevent hyperchloremic metabolic acidosis secondary to hypertonic saline administration or replace saline during of shortages.

Alternatively, mannitol can generally be administered to patients with an osmolar gap <15–20 mOsm/L. Given the need to compound sodium chloride 2% and 7.5% products using sodium chloride 23.4% vials, these therapies are often unavailable when shortages of sodium chloride 23.4% vials occur. During shortages of standard hyperosmolar therapies, clinicians may consider sodium bicarbonate 8.4% as an alternative or proceed to other measures for ICP control such as burst suppression with propofol or pentobarbital. Table 2 lists different hyperosmolar treatment options for management of intracranial hypertension.

Sodium Bicarbonate 8.4%

Sodium bicarbonate 8.4%, although commonly also on shortage, can be utilized when other hyperosmolar therapies are unavailable [22]. Sodium bicarbonate 8.4% doses of 1 mL/kg have an osmolarity of 2002 mOsm/L and can be given as an IV push over 5–10 min, preferably through a central line, although often being administered via peripheral access. The most commonly available form of sodium bicarbonate 8.4% is a 50 mEq/50 mL vial or injectable syringe, and this dose can be utilized for ease and availability.

Propofol

Propofol bolus doses of 1–3 mg/kg followed by an infusion (max 200 mcg/kg/min) have been recommended for intracranial hypertension management [20]. Patients must have a secure airway and hemodynamic monitoring is required, as hemodynamic instability frequently occurs. Cerebral perfusion pressure should be optimized with the administration of IV fluids and vasopressors. Patients receiving high doses of propofol should be monitored for the development of propofol infusion syndrome, characterized by metabolic acidosis, cardiac dysfunction, hypertriglyceridemia, and rhabdomyolysis. This has historically been described in patients receiving propofol doses >83 mcg/kg/min for greater than 48 h [23].

Table 2 Hyperosmolar therapies for ICP management

	Equiosmolar dose	Osmolarity	Sodium concentration	Usual dose
2% sodium chloride	3.5 mL/kg	684 mOsm/L	342 mEq/L	250–500 mL
2% sodium chloride/sodium acetate	4.1 mL/kg	588 mOsm/L	294 mEq/L	250–500 mL
3% sodium chloride	2.5 mL/kg	1027 mOsm/L	513 mEq/L	250–500 mL
7.5% sodium chloride/sodium acetate	1 mL/kg	2196 mOsm/L	1283 mEq/L	50–250 mL
8.4% sodium bicarbonate	1 mL/kg	2002 mOsm/L	1000 mEq/L	50–100 mL
23.4% sodium chloride	0.3 mL/kg	8008 mOsm/L	4004 mEq/L	30 mL
Mannitol 20%	0.5–1 g/kg	1098 mOsm/L	n/a	0.5–1 mg/kg

ICP intracranial pressure

Pentobarbital

Pentobarbital boluses are typically administered at a dose of 5–15 mg/kg given over 30 min to 2 h, followed by a maintenance infusion of 1–4 mg/kg/h titrated to ICP goal or burst suppression pattern on electroencephalogram [20]. Patients receiving pentobarbital must have a secure airway and monitoring for hemodynamic instability, cardiac depression, immune suppression, and paralytic ileus [20].

Intravenous Fluids

Shortages of IV fluids were severely exacerbated in the aftermath of Hurricane Maria in 2017 [4, 24]. The shortage extended from the initial small-volume products of 50 mL and 100 mL bags to include larger bag sizes of 500 mL and 1000 mL. Recommendations for alternative medication administration methods for products requiring dilution in 50 mL and 100-mL bags can be found elsewhere in this publication. The main focus of this section will be on the use of IV fluids for fluid resuscitation.

Recommendations for conservation of IV fluids were developed by the ASHP [25]. Those recommendations are as follows:

- Consider using oral hydration whenever possible
- Make policies to allow substitution of products based on product availability at the site. For example, an organization could choose to allow lactated ringers solution to be substituted for 0.9% sodium chloride solution or 5% dextrose with 0.45% sodium chloride to be substituted for 5% dextrose. Special attention is needed for patients at risk for cerebral edema who require isotonic IV fluids. Table 3 provides a comparison of fluid components.
- Evaluate total fluid requirements for surgeries. The American College of Surgeons 2014 Principle and Practice notes total volume replacement needs for elective surgeries are much less (500 mL to 3000 mL

total) than traditionally thought (4500 mL to 6000 mL total) [26].

- Evaluate the clinical need for IV fluid replacement and “keep vein open” orders at every shift change. Consider catheter locks and flushes for eligible patients. Discontinue infusions when appropriate.
- Use smaller bag sizes for low-rate infusion when possible depending on product availability.
- Consider reserving some products for specific clinical situations as outlined in Tables 2 and 3 [25–29].
- Consider using commercially available rather than compounded dialysis solutions whenever possible.

In the absence of IV fluids commonly used for resuscitation, many health systems have resorted to the use of oral rehydration therapy, especially in patients with mild dehydration or those that only need “maintenance” therapy. In a publication from 2018, a group of physicians from the Emergency Department at Brigham and Women’s Hospital developed a protocol for using oral rehydration therapy in patients presenting with mild dehydration from conditions such as pharyngitis, gastroenteritis, pregnancy-related vomiting, and upper respiratory tract infection [30]. Patients deemed to be experiencing severe dehydration or who were unable to take liquids by mouth were excluded from the protocol. The authors administered 500 to 1000 mL of oral fluids, including oral electrolyte solutions, water, dilute juice, or dilute sport drinks. Considerations for use of specific products on the basis of concomitant disease states such as renal disease, diabetes mellitus, or heart failure were recommended. Patients were instructed to drink 30 mL (two large sips) every 3–5 min with specific instructions for drinking goals and the use of tracking sheets. Comfort medications such as analgesics, antipyretics, and anti-emetics were administered as needed. Through the use of this protocol, the authors were able to reduce the use of IV fluids by an estimated 30%. In patients, unable to take medications by mouth but with enteral access via

Table 3 Comparison of selected intravenous fluids

	mOsm/L	Na (mEq/L)	Cl (mEq/L)	Dextrose (g/L)	K (mEq/L)	Ca (mEq/L)	Lactate (mEq/L)
0.9% sodium chloride	308	154	154	–	–	–	–
0.45% sodium chloride	154	77	77	–	–	–	–
5% dextrose plus 0.225% sodium chloride	321	7739	7739	50	–	–	–
5% dextrose plus 0.9% sodium chloride	560	154	154	50	–	–	–
5% dextrose	252	–	–	50	–	–	–
Lactated ringers solution	273	130	109	–	4	2.7	28
Lactated ringers and 5% dextrose solution	525	130	109	50	4	2.7	28
Plasmalyte	294	140	98	–	5	–	–

a nasogastric or orogastric tube, oral rehydration therapies can be administered as needed.

Prothrombin Complex Concentrate

In March 2018, CSL Behring recalled select lots of Kcentra[®] (four-factor prothrombin complex concentrate, PCC4) because of a change in packaging that increased the risk of the glass vials breaking in transport [31]. The shortage was exacerbated by increased demand for PCC4 due to the concomitant emergence of synthetic cannabinoids laced with brodifacoum, a long-acting vitamin K antagonist, which were linked to life-threatening bleeding and coagulopathy [32].

During times of shortage, institutions may consider restricting PCC4 to patients requiring reversal of vitamin K antagonists for major bleeding or emergent surgery and using alternative agents for off-label indications (e.g., reversal of direct acting oral anticoagulants, major bleeding during cardiac surgery, and treatment of coagulopathy secondary to liver dysfunction). A prospective blood factor stewardship program has been shown to reduce inappropriate use of PCC4 [33, 34].

Although PCC4 is recommended over three-factor prothrombin complex concentrate (PCC3) for reversal of warfarin-induced coagulopathy, several studies support the off-label use of PCC3 for this indication [35–41]. Activated four-factor prothrombin complex concentrate (aPCC) is given equal weight of recommendation as PCC4 for treatment of factor Xa inhibitor-induced coagulopathy in the Neurocritical Care Society/Society of Critical Care Medicine guidelines for reversal of anti-thrombotics in patients with intracranial hemorrhage, with the caveat that it is associated with a higher risk of thrombotic events compared to PCC4 [35]. Coagulation factor Xa (Andexxa[®]) was approved by the FDA for reversal of apixaban and rivaroxaban and may be used for management of these patients if available.

Several retrospective studies have demonstrated that a fixed dose of 1500 units of PCC4 is effective in correcting international normalized ratio (INR) in patients with warfarin-associated hemorrhage, with up to 100% of patients achieving an INR less than 2 and 75% achieving an INR less than 1.5 [42–45]. Utilizing a fixed-dose strategy may be effective in conserving PCC4 supply rather than using the FDA-approved dose based on weight and initial INR. Recombinant factor VIIa (rFVIIa) is not recommended as first-line treatment for warfarin reversal by the Neurocritical Care Society/Society of Critical Care Medicine guideline for the reversal of anti-thrombotics in intracranial hemorrhage [35]. Additionally, the American Heart Association guideline for the management of spontaneous intracerebral hemorrhage recommends against the administration of rFVIIa because it fails to

replenish all of the vitamin K-dependent clotting factors and does not restore thrombin generation as effectively as PCC [46]. The INR is particularly sensitive to factor VII levels and may decrease despite inadequate levels of factors II, IX, and X that are required for hemostasis [35]. It also has a very short half-life of about 3 h leading to INR rebound [47]. rFVIIa is associated with a high rate of thrombosis (12.8–24%), including a 5% excess risk of arterial thrombosis compared to placebo with intraparenchymal hemorrhage [35, 48].

In summary, strategies for PCC4 conservation include prospective stewardship programs, utilizing alternative agents for non-warfarin-induced coagulopathies, and use of a fixed dose of 1500 units for warfarin reversal. PCC3 may also be considered for warfarin reversal if PCC4 supplies are not able to be sustained.

Antihypertensive Medications

Blood pressure control remains a mainstay of the management of patients presenting with neurologic injuries. In many situations, clinicians must tightly manage hypertension in an attempt to limit secondary injury related to extreme elevations in blood pressure. As such, IV antihypertensive agents are typically utilized in these acute and critical care settings. Over the last several years, intermittent shortages of several IV antihypertensive agents have impacted the choice of agent utilized in neurocritical care. A list of commonly used antihypertensive medications is available in Table 4 [49].

Neurointerventional Medications

Two medications recently on long-term shortage include aminocaproic acid and abciximab, both of which are typically administered in urgent coagulopathic situations following neurointerventional procedures.

Aminocaproic Acid

Aminocaproic acid, an IV anti-fibrinolytic agent, is recommended for the prevention of rebleeding in the setting of aneurysmal subarachnoid hemorrhage, and case reports have supported its consideration for fibrinolytic reversal. Aminocaproic acid was officially documented by the FDA as being on shortage most of 2018 [50]. The only FDA-approved, IV alternative to aminocaproic acid is tranexamic acid. Although data are limited, tranexamic acid, at a dose of 1 g every 6 h, has been used acutely in the management of aneurysmal subarachnoid hemorrhage prior to intervention [51]. Important considerations in using tranexamic acid versus aminocaproic acid include the differences in renal clearance and dosing between the agents as well as the half-lives of the agents.

Table 4 Antihypertensive agents for ICU management

Agent	Onset of action	Half-life	Typical bolus dose	Typical continuous infusion rate	Mechanism of action	Notes
Clevidipine	2–4 min	15 min	n/a	1–2 mg/h may be doubled every 90 s to a maximum of 21 mg/h (may use up to 32 mg/h short term)	Calcium channel blocker (dihydropyridine)	Formulated in 20% lipid emulsion, avoid use with propofol
Diltiazem	3 min	3–5 h	15–25 mg, may repeat in 15 min	5–15 mg/h	Calcium channel blocker (non-dihydropyridine)	Avoid use in patients with heart failure; may cause bradycardia. May accumulate with prolonged continuous infusion
Enalaprilat	< 15 min	35 h	0.625–1.25 mg every 6 h	n/a	ACE inhibitor	Use with caution in renal impairment
Esmolol	2–10 min	9 min	n/a	50–300 mcg/kg/min	Short-acting beta-adrenergic blocker, cardioselective	May load with 500–1000 mcg/kg over 30–60 s. May cause bradycardia
Hydralazine	10–80 min	3–7 h	10–20 mg every 4–6 h	n/a	Arteriolar vasodilator	May cause increased ICP
Labetalol	2–5 min	5.5 h	10–20 mg every 10 min	0.5–10 mg/min	Alpha/beta-adrenergic blocker	May cause bradycardia
Metoprolol	20 min	3–4 h	2.5–10 mg every 5 min, maximum total dose 15 mg	n/a	Beta-adrenergic blocker, cardioselective	May cause bradycardia; may accumulate with prolonged continuous infusion (> 300 mg/day)
Nicardipine	< 5 min	45 min, up to 14 h with long-term infusion	n/a	5 mg/h, titrate by 2.5 mg/h every 5–15 min to a maximum of 15 mg/h	Calcium channel blocker (dihydropyridine)	Consider reducing rate to 3 mg/h when goal achieved to avoid hypotension
Nitroglycerin	1–5 min	2–3 min	n/a	5 mcg/min, titrate by 5 mcg/min every 3–5 min to 20 mcg/min; increase further by 10–20 mcg/min to max 400 mcg/min	Arterial and venous vasodilator	Reserve vials for intra-arterial administration Use caution in patients with cardiac dysfunction
Sodium nitroprusside	Seconds—2 min	1–3 min	n/a	0.25 mcg/kg/min titrate by 0.25–0.5 mcg/kg/min every 5–15 min. Max 10 mcg/kg/min	Arterial and venous vasodilator	Monitor for cyanide toxicity. May cause ICP elevation
Verapamil	3 to 5 min	2–5 h	5–10 mg, may repeat in 15 to 30 min	5 mg/h, titrate to goal heart rate	Calcium channel blocker (non-dihydropyridine)	Avoid use in patients with heart failure; may cause bradycardia

ACE Angiotensin-converting enzyme, ICP intracranial pressure

Abciximab

Abciximab is on worldwide shortage due to an interruption in production from failure to comply with good manufacturing practices at the third party manufacturing site. As the sole supplier of abciximab, the manufacturer has designated abciximab on long-term back order and cannot predict a release date [52]. Neurointerventionalists at many institutions nationwide use abciximab during neurointerventional procedures as rescue therapy for thromboembolism during procedures such as coil embolization or stenting. In the field of cardiology, many providers say that the shortage has gone unnoticed as they were already relying on other GPIIb/IIIa inhibitors and those that were using abciximab have easily made the switch to an alternative agent such as tirofiban [53]. In the neurointerventional field, however, the transition to an alternative GPIIb/IIIa inhibitor is not as straightforward. The indications for these agents in neurointerventional procedures are off-label, and the literature in support of alternative agents is limited to small, non-randomized evaluations with heterogeneous dosing. Anecdotally, many neurointerventionalists with prior experience with intra-arterial abciximab have begun using intra-arterial tirofiban or eptifibatide depending on their institution's formulary.

According to small case series, no significant differences have been demonstrated in recanalization rates or outcomes when intra-arterial versus IV administration of GPIIb/IIIa inhibitors was evaluated. Similarly no significant differences in efficacy were found when abciximab, an irreversible agent, was compared with the reversible agents tirofiban and eptifibatide in these case series [54]. Of note, a limited meta-analysis has demonstrated higher recanalization rates with the reversible GPIIb/IIIa agents compared to abciximab [55]. From a practical standpoint, tirofiban compared to abciximab is less expensive, does not require a filter needle or refrigeration prior to administration, and has a shorter effective half-life of hours compared to days. These practical benefits are tempered by less evidence and less clinical experience by neurointerventionalists. Further, in the setting of bleeding, tirofiban inhibits platelets administered by platelet transfusion until it is eliminated since it reversibly inhibits platelets. Abciximab irreversibly inhibits platelets and will inhibit platelets administered by platelet transfusion up to 30 min after the drug administration. Beyond 30 min, most free drug has been eliminated and the remaining abciximab is unable to release from its binding site. There are no head-to-head studies comparing bleeding risks in the neurointerventional patient population. Providers need to ensure that tirofiban dosing is adjusted in the setting of renal dysfunction ($\text{CrCl} < 60 \text{ mL/min}$).

Institutions have adopted varying protocols based on the limited literature available for tirofiban intra-arterial and IV dosing in neurointerventional patients. One protocol allows for tirofiban bolus administration up to 25 mcg/kg administered intra-arterially or intravenously. A low-dose infusion of tirofiban 0.08 mcg/kg/min may be used to bridge the patient to a P2Y₁₂ inhibitor and will be continued until the P2Y₁₂ inhibitor loading dose is at maximal efficacy [56]. Another protocol mirrors cardiac bolus dosing for eptifibatide of up to 180 mcg/kg as a loading dose administered intra-arterially [57]. Based on the available evidence and practical application of the reversible GPIIb/IIIa inhibitors, these agents may continue to be utilized during endovascular cases even after the abciximab shortage resolves. At a minimum, providers will be experienced with the use of these agents for rescue therapy during neurointerventional cases, and there will be additional data for their use in this patient population.

Intravenous Opioids

IV opioids may be employed in neurocritical care as adjuncts to sedatives. The most frequently used opioid analgesics are morphine, hydromorphone, and fentanyl. The shortage of these opioids became critical in early 2018 as a result of both manufacturing problems and the Drug Enforcement Administration calling for a reduction in all opioid manufacturing due to the ongoing opioid epidemic [58].

For the management of acute pain, a stepwise approach should be considered. First, providers should switch therapy to oral or enteral opioids whenever possible [59]. Next, multimodal pain management such as non-pharmacologic treatments, peripheral nerve blocks, or other non-opioid adjuncts should also be utilized. Examples of adjuvant analgesics that may be utilized as part of a multimodal pain management strategy include: acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids, muscle relaxants, topical analgesics (e.g., lidocaine and capsaicin), and antidepressants (e.g., duloxetine). Moreover, opioid-sparing infusions (e.g., dexmedetomidine, ketamine, and lidocaine) may also be employed as adjuvants. Non-pharmacologic adjuvants such as integrative medical therapies (e.g., relaxation and acupuncture) and physical therapy should also be optimized.

Also, it is important for anesthesia, pain, and palliative medicine experts from each institution to help provide guidance and develop strategies for handling these shortages. In order to minimize the risk of conversion errors, each institution should utilize a uniform conversion tool that is approved by the Pharmacy and Therapeutics Committee and the anesthesia team. Since

opioid product availability may vary from week-to-week, guidance should be provided to assist clinicians for the purpose of helping to reserve certain opioids for specific patient populations. Furthermore, the electronic health record should be updated to display opioid options that match products currently in stock as well as providing alternative alerts with other options. Inventory control strategies should include reserving supplies of specific IV opioids for specific indications and limiting their placement to those areas with those indications. For example, IV fentanyl may be restricted to areas such as the operating rooms, emergency room, and the intensive care units. Stock of injectable opioids should be optimized in automated dispensing cabinets after reviewing usage patterns. Table 5 provides an example of an institutional plan for navigating through the shortages.

Utilization of Pharmacy Technology

Health information technology can be an invaluable resource to facilitate communication and therapeutic alternative guidance to healthcare providers throughout the medication use process during drug shortages. Effective communication is essential to widespread distribution of information throughout an institution or health care system [7]. Frequent rotation of staff through different shifts and patient care areas make distribution of messages concerning drug shortages challenging. Multiple methods of communication should be utilized and may vary depending on organizational culture. These

methods may include e-mail communication, online dashboards, standing meetings, educational in-services, alerting and clinical decision support upon computerized provider order entry (CPOE), and retrospective chart review of patients actively receiving medications on shortage.

Due to the dynamic nature of drug shortages, technology can be leveraged to provide institutional alerts and monitoring. Several information systems may require updates in the setting of drug shortages including the electronic medical record, clinical decision support systems, CPOE, pharmacy information systems, automated dispensing cabinets, and smart infusion pumps [60]. Updates to technology that normally take weeks to months to implement may be needed within days to weeks in the setting of unanticipated drug shortages. As soon as a drug shortage is identified, surveillance reports can be utilized to identify patients who have active orders for the drug and provide estimations for typical monthly usage to gauge the impact of the drug shortage of in the institution. Pharmacists can work with providers to identify alternative agents or routes of administration (e.g., IV to oral) for patients affected by the drug shortage to ensure continuity of care [61]. Clinical decision support systems within the CPOE system can assist providers with medication ordering. Drug shortage alerts can be incorporated into the CPOE system to communicate restricted use and/or direct providers to an alternative therapy [62]. Once the shortage is resolved, discontinuation of the alert should occur. [61] This strategy allows for

Table 5 Example of institutional opioid shortage mitigation guidance

Patient population	Primary recommendation	Alternative recommendation
OR/IR/other procedural areas	IV fentanyl	IV morphine or fentanyl analogs
Oncology	IV hydromorphone or IV hydromorphone PCA	IV morphine
Sickle cell crisis	IV hydromorphone or IV hydromorphone PCA	IV morphine
ED/ICU patients*	Oral opioid or non-opioid analgesics (if enteral access)	IV morphine (if no enteral access or GI function) or IV fentanyl (if hemodynamically unstable)
Non-ICU patients (e.g., intermediate care/acute care)	Oral opioid or non-opioid analgesics	IV morphine (no GI function)
Opioid tolerant	Oral opioid or non-opioid analgesics	IV morphine (no GI function)
End-of-life/palliative care	Oral opioid options from Comfort Care Order Set (includes oral/sublingual morphine/oxycodone)	IV morphine
Renal dysfunction or hemodynamically unstable	IV hydromorphone or IV fentanyl bolus	

ED emergency department, GI gastrointestinal, ICU intensive care unit, IR interventional radiology, OR operating room, PCA patient-controlled analgesia

*Criteria for fentanyl boluses: acute neurologically injured patients (e.g., traumatic brain injury, ischemic stroke, or intracranial bleeding); trauma patients age ≥ 65 , SBP < 110 mm Hg or high risk for hemorrhagic shock; trauma patients age < 65 , SBP < 90 mm Hg or high risk for hemorrhagic shock; procedural sedation if morphine is contraindicated (e.g., concerns for histamine release, due to hemodynamic instability); mechanically ventilated with hemodynamic instability (SBP < 110 or MAP < 65) to facilitate analgesedation when morphine is contraindicated; targeted temperature management; contact pain service or clinical pharmacist for concerns or recommendations; utilize oral therapy and multimodal therapy for pain management as much as possible

For post-op patients: If patients have enteral access, utilize around-the-clock oral non-opioid analgesics if possible; use IV morphine or hydromorphone only for breakthrough pain if necessary; for patients with renal insufficiency, doses and frequencies of morphine, tramadol and nonsteroidal anti-inflammatory drugs (NSAIDs) should be adjusted. Consult a clinical pharmacist for recommendations

real-time proactive communication for providers considering initiating a therapy on shortage [7].

As product availability can vary frequently, automated dispensing cabinet and CPOE systems should be updated accordingly. Initial strategies for drug shortages may include adjusting par levels of medications stocked in the automatic dispensing cabinets [7]. Prioritizing distribution of short-dated (i.e., soon-to-expire) medications allows for increased time of drug utilization, less inventory required to order, and decreased waste [63]. Throughout the process, it is essential that the CPOE and pharmacy system product preference list is updated accordingly. Medication package selection (e.g., a 2 mL vial of diazepam 5 mg/mL versus 10 mL vial of diazepam 5 mg/mL) may prefer products stocked on the unit in the automated dispensing cabinet over those distributed from central pharmacy. As such, manipulation of inventory available in the automated dispensing cabinet can facilitate correct product selection on order verification [7]. If a shortage becomes significant enough to deplete central pharmacy supply, centralization of inventory may be required to allow for distribution of medication to patients throughout the hospital. If unit-dosed medications are on shortage, purchasing of bulk bottles and repacking into smaller dosage units may help mitigate the impact of drug shortages until resolution.

Validation of barcoding in the pharmacy informatics system as new product National Drug Codes are purchased or medications repackaged should occur prior to distribution of the medication to the floor to ensure barcode medication administration systems recognize the product as the nurse attempts to scan the medication for administration [60]. Informatics pharmacists can assist in performing modification to information systems to include new product packages, barcode validation, and preference lists for product selection.

Updates to smart infusion pump inventory libraries are necessary as new products or preparations become available for use to ensure safe and standardized administration of unfamiliar medication preparations [64]. Smart infusion pumps increase patient safety through customized drug libraries with ability to generate alerts, alarms for out of range doses and rates, automated pump programming via Wi-Fi interoperability and communication with the medical record, and advisories such as the need for central line administration. With each smart pump library change, nursing communication should be distributed to inform bedside nurses of the update [64].

Outcomes

Despite the prevalence of drug shortages over the past decade that have led to the use of the use of

non-preferred treatment strategies, there are few studies assessing the impact of drug shortages on patient outcomes. One retrospective study of 26 US hospitals showed that among patients with septic shock, a nor-epinephrine shortage was associated with an absolute increase in in-hospital mortality of 3.7% (adjusted odds ratio 1.15, 95% CI 1.01–1.30) [65]. The authors hypothesized that the increase in mortality was due to a combination of the use of potentially inferior vasopressors for septic shock such as phenylephrine and dopamine, lack of familiarity with alternative options, and inadequate optimization of supply management during the shortage. Another retrospective study of three intensive care units (ICUs) in Vienna in which remifentanyl was the continuous infusion analgesic of choice demonstrated a longer duration of mechanical ventilation and ICU and hospital length of stay associated with a remifentanyl shortage [66]. The authors postulated that the use of unfamiliar and longer-acting alternatives may have led to suboptimal dosage adjustments and prolonged respiratory depression, impairing ventilator weaning. Additional studies are needed to assess the impact of drug shortages on patient outcomes.

Despite various strategies that can be implemented by hospital clinicians to overcome challenges, shortages of medications for the neurocritical care patient population can be detrimental to the provision of optimal patient care. Mitigation strategies are necessary and should be determined in advance of a shortage impacting an institution whenever possible [67]. Resources are available on the internet for monitoring and planning for drug shortages. These resources help institutions manage inventory during shortages and include web sites from ASHP, The Society of Critical Care Medicine, and the FDA drug shortages.

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