Heparin Drug Shortage Conservation Strategies

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Heparin is the anticoagulant of choice when a rapid anticoagulant is indicated: Onset of action is immediate when administered IV as a bolus.[1] The major anticoagulant effect of heparin is mediated by heparin/antithrombin (AT) interaction. Heparin/AT inactivates factor IIa (thrombin) and factors Xa, IXa, XIa, and XIIa. Heparin is approved for multiple indications, such as venous thromboembolism (VTE) treatment and prophylaxis of medical and surgical patients; stroke prevention in atrial fibrillation (AF); acute coronary syndrome (ACS); vascular and cardiac surgeries; and various interventional procedures (eg, diagnostic angiography and percutaneous coronary intervention [PCI]). It also is used as an anticoagulant in blood transfusions, extracorporeal circulation, and for maintaining patency of central vascular access devices (CVADs).

About 60% of the crude heparin used to manufacture heparin in the US originates in China, derived from porcine mucosa. African swine fever, a contagious virus with no cure, has eliminated about 25% to 35% of China's pig population, or about 150 million pigs. In July 2019, members of the US House of Representatives Committee on Energy and Commerce sent a letter to the US Food and Drug Administration asking for details on the potential impact of African swine fever on the supply of heparin.[2]

The US Department of Veterans Affairs (VA) heath care system is currently experiencing a shortage of heparin vials and syringes. It is unclear when resolution of this shortage will occur as it could resolve within several weeks or as late as January 2020.[3] Although vials and syringes are the current products that are affected, it is possible the shortage may eventually include IV heparin bags as well.

Since the foremost objective of VA health care providers is to provide timely access to medications for veterans, strategies to conserve unfractionated heparin (UfH) must be used since it is a first-line therapy where few evidence-based alternatives exist. Conservation strategies may include drug rationing, therapeutic substitution, and compounding of needed products using the limited stock available in the pharmacy.[4] It is important that all staff are educated on facility strategies in order to be familiar with alternatives and limit the potential for near misses, adverse events, and provider frustration.

In shortage situations, the VA-Pharmacy Benefits Management (PBM) defers decisions regarding drug preservation, processes to shift to viable alternatives, and the best practice for safe transitions to local facilities and their subject matter experts.[5] At the VA Tennessee Valley Healthcare System, a 1A, tertiary, dual campus health care system, a pharmacy task force has formed to track drug shortages impacting the facility's efficiencies and budgets. This group communicates with the Pharmacy and Therapeutics committee about potential risks to patient care and develops shortage briefs (following an SBAR [situation, background, assessment, recommendation] design) generally authored and championed by at least 1 clinical pharmacy specialist and supervising physicians who are field experts. Prior to dissemination, the SBAR undergoes a rapid peer-review process.

To date, VA PBM has not issued specific guidance on how pharmacists should proceed in case of a shortage. However, we recommend strategies that may be considered for implementation during a potential UfH shortage. For example, pharmacists can use therapeutic alternatives for which best available evidence suggests no disadvantage.[4] The Table lists alternative agents according to indication and patient-specific considerations that may preclude use. Existing UfH products may also be used for drug compounding (eg, use current stock to provide an indicated aliquot) to meet the need of prioritized patients.[4] In addition, we suggest prioritizing current UfH/heparinized saline for

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TABLE Anticoagulation Therapeutic Substitution by Specific Diagnosis or Procedure

Indications for Use	Substitutions	Recommended Dosing	Comments
Infusion therapy: Flushing and locking (peripheral catheters,[16] midline catheters, PICC, nontunneled CVAD, ports)	Preservative free 0.9% sodium chloride (USP)	Flushing volume: twice internal volume of catheter system Locking volume: internal volume of catheter plus 20%	Use pharmacy-prepared or commercially available prefilled syringes of appropriate IV solution to flush and lock vascular access devices; CAUTION: If bacteriostatic 0.9% sodium chloride is used, limit flush volume to 30 mL in 24 h to reduce the possible toxic effects from the preservative benzyl chloride[16]
Bridging anticoagulation (no history of HIT/HITTS)[18-20]	Enoxaparin	CrCL > 30 mL/min: 1 mg/kg q12h	CAUTION: Only for high-risk patients (eg, mechanical mitral valve)
ACS[21-23]	Bivalirudin (preprocedural, first line in an invasive approach)	Bolus: 0.10 mg/kg then CI: 0.25 mg/kg/h Ward standardized concentration: 250 mg/500 mL or 0.5 mg/mL	CAUTION: Consider dose adjustment for CrCl < 30 mL/min; discuss with cardiology[24]; NOTE: Depending on facility experience, may also consider argatroban
	Enoxaparin (preprocedural, second line in an invasive approach of STEMI)	STEMI, CrCl > 30 mL/min, aged < 75 y: 1 mg/kg SC q12h (maximum: 100 mg SC for first 2 doses only) STEMI, CrCl > 30 mL/min, aged ≥ 75 y: 0.75 mg/kg SC q12 (maximum: 75 mg SC q12h, for the first 2 doses only) NSTE ACS (not preferred for invasive approach): CrCl ≥ 30 mL/min: 1 mg/kg SC q2h NOTE: Bivalirudin is preferred when CrCl is < 60 mL/min	ALERT: Do not use enoxaparin or any low-molecular-weight heparin if patient may proceed to cardiac surgery since the last dose must be given 24 h prior to surgery[25]; CAUTION: Discuss with cardiology if 30 mg IV loading dose is desired in STEMI, for those aged < 75 y; Must know number of doses and timing of last enoxaparin dose before proceeding to LHC/PCI; IV bolus and SC dosing are separated by 15 min
	Fondaparinux (medical management only)	CrCl > 30 mL/min: 2.5 mg daily NOTE: Initial dose is IV; all subsequent are SC	CAUTION: Discuss use with cardiology since patient will require an additional anticoagulant with anti-IIa activity if PCI is performed to avert catheter thrombosis

Abbreviations: ACS, acute coronary syndrome; ACT, activated clotting time; BL, baseline; BMI, body mass index; CCL, cardiac catheterization laboratory; CI, continuous infusion; CrCl, creatinine clearance; CVAD, central vascular access device; HIT, heparin-induced thrombocytopenia; HITTS, heparin-induced thrombocytopenia with thrombosis syndrome; ICU, intensive care unit; IHD; ischemic heart disease (stable and unstable disease); IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; IV, intravenous; LHC, left heart cardiac catheterization; NSTE ACS, Non-ST elevation myocardial infarction/acute coronary syndrome; PCI, percutaneous coronary intervention (eg, stenting); PICC, peripherally inserted central catheter; RAO, radial artery occulsion; RCA, regional citrate anticoagulation; SC, subcutaneous; SQH, subcutaneous heparin; STEMI, ST elevation myocardial infarction; tPA, tissue plasminogen activator; VTE, venous thromboembolism; WT, weight.
[a]Hip arthroplasty or fracture.

use for the following groups of patients[4]:

- Emergent/urgent cardiac surgery[1,6];
- Hemodialysis patients[1,7-9] for which the low-molecular-weight heparin (LMWH) dalteparin is deemed inappropriate **or** the patient is not monitored in the intensive care unit for regional citrate administration;
- VTE prophylaxis for patients with epidurals **or** chest tubes for which urgent invasive management may occur, recent cardiac or neurosurgery, **or** for patients with a creatine clearance < 15 mL/min or receiving hemodialysis[10-12];
- Vascular surgery (eg, limb ischemia) and interventions (eg, carotid stenting, endarterectomy)[13,14];
- Mesenteric ischemia (venous thrombosis) with a potential to proceed to laparotomy[15];
- Critically ill patients with arterial lines

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VTE[26,27]	Enoxaparin	CrCl > 30 mL/min: 1 mg/kg SC q12h (preferred) **or** 1.5 mg/kg SC q24h CrCl 15-30 mL/min: 1 mg/kg q24h	Consider transitioning to an oral agent that does not require initial heparin therapy (eg, apixaban) if patient is appropriate
	Fondaparinux	If CrCl > 50 mL/min and wt is: < 50 kg: 5 mg SC q24h; 50-100 kg: 7.5 mg SC q24h; >100 kg: 10 mg SC q24h	Consider transitioning to an oral agent that does not require initial heparin therapy (eg, apixaban, rivaroxaban; **not** dabigatran) if patient is appropriate; NOTE: Dosing is modified according to wt in kg
VTE prophylaxis in orthopedic surgical inpatients[28,29]	Enoxaparin	Hip[a]: CrCl > 30 mL/min: 30 mg SC q12h **or** 40 mg SC q24h; CrCl 15-30 mL/min: 30 mg SC q24h; Knee: CrCl > 30 mL/min: 30 mg SC q12h; CrCl 15-30 mL/min: 30 mg SC q24h	Start ≥ 12 h postoperatively
	Fondaparinux	CrCl ≥ 30 mL/min, wt > 50 kg: 2.5 mg SC daily	Start 6-8 h postoperatively
	Oral agents	CrCl > 15 mL/min: apixaban 2.5 mg po bid CrCl ≥ 30 mL/min: rivaroxaban 10 mg po q24h CrCl > 30 mL/min: dabigatran 110 mg on day 1, then 220 mg po q24h thereafter	Start apixaban, 12-24 h postoperatively Start rivaroxaban, 6-10 h postoperatively Start dabigatran 1-4 h postoperatively CAUTION: Start only after hemostasis is established
VTE prophylaxis in surgical patients without epidurals, chest tubes, or recent cardiac or neurosurgery[10,11]	Enoxaparin	Calculate Caprini score (use medication if ≥ 3) and assess bleed risk CrCl ≥ 30 mL/min, wt < 100 kg: 40 mg SC q24h CrCl ≥ 30 mL/min, wt > 100 kg: 40 mg SC q12h CrCl 15-30 mL/min: 30 mg SQ q24h	Apply sequential compression devices to all patients with a Caprini score ≥ 5[9]; For thoracic and abdominal/pelvic surgeries with malignancy, consider extended prophylaxis (28-30 d)[10,30]; CAUTION: Start only after hemostasis is established
VTE prophylaxis in medical patients with a Padua score ≥ 4 (high VTE risk) and IMPROVE bleeding risk score < 7[11,12,31]	Enoxaparin	CrCl ≥ 30 mL/min: 40 mg QC q24h CrCl ≥ 30 mL/min and BMI ≥ 40: 30 mg SC q12h CrCl 15-30 mL/min: 30 mg SC q24h	

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for which normal saline is deemed inappropriate for line flushing[16];
- Electrophysiology procedures (eg, AF ablation)[17]; and
- Contraindication to use of a long-acting alternative listed in the table **or** a medical necessity exists for using a rapidly reversible agent. Examples for this category include but are not limited to recent gastrointestinal bleeding, central nervous system lesion, and select neurologic diagnoses (eg, cerebral venous sinus thrombosis with hemorrhage, thrombus in vertebral basilar system or anterior circulation, intraparenchymal hemorrhage plus mechanical valve, medium to large cardioembolic stroke with intracardiac thrombus).

CONCLUSION

The UfH drug shortage represents a significant threat to public health and is a major challenge for US health care systems, including the Veterans Health Administration. Overreliance on a predominant source of crude

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Indications for Use	Substitutions	Recommended Dosing	Comments
IHD with PCI in the CCL[21-23]	Bivalirudin	Bivalirudin initiated preprocedural: Bolus: 0.5 mg/kg; CI: 1.75 mg/kg/h Transition from heparin: Hold heparin x 30 min, then give: Bolus: 0.75 mg/kg; CI, 1.75 mg/kg/h No anticoagulation preprocedure: Bolus: 0.5-0.75 mg/kg; CI: 1.75 mg/kg/h NOTE: May be used in hemodialysis—adjust rate to 0.25 mg/kg/h	NOTE: rate is per hour and concentration used on the wards commonly differs from that used in the CCL; CAUTION: For femoral access,[32] sheath removal and manual compression can occur at 2 h following completion of the infusion in patients with normal renal function. In patients with a CrCl < 30 mL/min or those on dialysis, the ACT should be checked, and sheaths removed once the value is < 180 sec (conservatively < 150 sec)[33]
Radial access for LHC (to prevent RAO)[34,35]	Bivalirudin	Bolus in LHC (no PCI, diagnostic only): 0.75 mg/kg CI in LHC with PCI: see ACS dosing guide for bolus and CI	CAUTION: For use in the CCL only; unlike for heparin, there are no bivalirudin dose-ranging studies for RAO prevention
STEMI, undergoing PCI and received enoxaparin as initial anticoagulant[22]	Enoxaparin	0.3 mg/kg IV supplement if PCI occurs 8-12 h after last enoxaparin SC dose if treated with multiple doses **or** has received only 1 therapeutic dose (1 mg/kg)	CAUTION: For use in the CCL only CAUTION: For femoral access, removal of sheaths can occur 8-12 h after the last dose of therapeutic enoxaparin[32]
Cardiac surgery[6]	Bivalirudin	Bolus: 1 mg/kg on-pump, 0.75 mg/kg off-pump; If transitions to on pump, administer additional 0.25 mg/kg bolus **and** change the CI rate; CI: 2.5 mg/kg/h on-pump, 1.75 mg/kg/h off-pump; prn boluses to keep ACT at target; Pump priming solution: **add** 50 mg	CAUTION: For use in the operating room only; NOTE: Rate is per hour
Hemodialysis[7-9]	RCA in ICU **or** dalteparin	Dalteparin 5000 units, adjustable in increments or decrements of 500 or 1000 units[6]	CAUTION: Will need to monitor for metabolic abnormalities with RCA, best reserved for ICU
Hemodialysis (tunneled) CVAD[16,36]	Trisodium citrate 4% lock		CAUTION: Use pharmacy-prepared or commercially available prefilled syringes of appropriate IV solution to flush and lock vascular access devices; NOTE: tPA is used once weekly for partially or completely occluded catheters; tPA 2 mg/2 mL in lumen for 30 min to 2 h and repeated once if indicated
Apheresis CVAD[16]	Trisodium citrate 4% lock **or** acid-citrate-dextrose formula A (ACD-A, which contains 3% citrate)		CAUTION: Use pharmacy-prepared or commercially available prefilled syringes of appropriate IV solution to flush and lock vascular access devices

heparin has affected multiple UfH manufacturers and products. Current alternatives to UfH include low-molecular-weight heparins, IV direct thrombin inhibitors, and SC fondaparinux, with selection supported by guidelines or evolving literature. However, the shortage has the potential to expand to other injectables, such as dalteparin and enoxaparin, and severely limit care for veterans. It is vital that clinicians rapidly address the current shortage by creating a plan to develop efficient and equitable access to UfH, continue to assess supply and update stakeholders, and select evidence-based alternatives while maintaining focus on efficacy and safety.

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