LOCAL ANESTHETIC SYSTEMIC TOXICITY (LAST)

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INTRODUCTION

Local Anesthetic Systemic Toxicity (LAST) is a rare but life-threatening complication of local anesthetic administration. Excessive plasma levels of local anesthetics may lead to progressive neurologic pathology and cardiovascular collapse [1,2]. LAST may result from rapid absorption of excessive local anesthetic in highly vascularized areas or from accidental intravascular administration. LAST may more likely manifest in patients with reduced local anesthetic clearance, such as hepatic dysfunction, cardiac disease, pregnancy, and other metabolic syndromes. Extreme age may also increase risk due to reduced local anesthetic clearance [3,4].

LAST primarily affects the heart and the brain. Cardiac toxicity is primarily related to inhibition of the voltage-gated sodium channels, leading to conduction disturbances, contractile dysfunction, and ventricular arrhythmias. In the central nervous system (CNS), local anesthetic inhibition of neuronal signaling can lead to excitatory symptoms such as seizures, followed by CNS depression (coma) [4].

While incidence varies, large database studies indicate an incidence of approximately 1 per 1,000 peripheral nerve blocks [5]. However, because of the high likelihood of under-reporting or misdiagnosis, the actual rate may be higher. In fact, one study reported a rate of 1 in 384 among patients undergoing peripheral nerve blocks for perioperative analgesia associated with total joint arthroplasty [6].

The risk of LAST varies by agent due to differences in lipid solubility, potency, and binding affinity. Bupivacaine poses the highest risk of cardiotoxicity due to its avid binding to cardiac muscle sodium channels with slow release [3]. Ropivacaine has reduced lipid solubility and demonstrates a more favorable cardiac safety profile compared to bupivacaine, though it is still capable of inducing systemic toxicity. Lidocaine is generally considered to have a wider therapeutic index, defined as a greater margin between the effective clinical dose and the dose associated with systemic toxicity [7]. To reduce systemic absorption, particularly in high-volume fascial plane blocks, the addition of epinephrine serves as a vasoconstrictor, slowing local anesthetic uptake into the circulation and thereby decreasing peak plasma levels. It may also act as a marker for intravascular injection during test dosing. Numerous studies have shown minimal or only modestly prolonged durations of action when epinephrine is used [8]. Caution is warranted with epinephrine additives in patients with ischemic heart disease or arrhythmias.

TYPICAL PRESENTATION

Case # 1: Neurologic-focused LAST

A 65-year-old, 80kg male with a history of Nonalcoholic Fatty Liver Disease (NAFLD) underwent a bilateral multilevel lumbar medial branch radiofrequency neurotomy without sedation, requiring 30 ml of 0.5% bupivacaine due to periprocedural discomfort. Five minutes following procedural completion, he reported circumoral numbness and tingling and tinnitus, which rapidly progressed to slurred speech and seizure-like activity.

Case #2: Cardiovascular collapse

A 28-year-old, 50 kg female underwent a bilateral transversus abdominis plane (TAP) block under ultrasound guidance for refractory abdominal wall pain with 30 ml of 0.5% ropivacaine per side. Following the injection, she reported lightheadedness and dizziness, and the electrocardiograph (EKG) showed ventricular arrhythmia.

DIAGNOSIS

The diagnosis of LAST should be considered in any patient who has received local anesthesia and presents with new or atypical symptoms, especially if those symptoms are neurological or cardiovascular. The presentation may initially begin with vague symptoms (*e.g.*, tingling, lightheadedness) but rapidly progress to CNS excitation (*e.g.*, agitation, circumoral numbness, tinnitus, seizures), followed by CNS depression and/or cardiovascular arrhythmia and collapse. In patients with sedation or general anesthesia, initial subjective symptomatology could be missed, and seizures or cardiovascular compromise may be the first presenting symptoms.

Recognition of timing following anesthetic administration, along with a high index of suspicion, is key to early detection and treatment [9]. The onset and severity of LAST depend on the degree of systemic absorption (higher in highly vascularized tissue), whether the injection is intravenous or intra-arterial, and on the volume and pharmacology of the injected local anesthetic.

1. Inadvertent Carotid/Vertebral Artery Injection
   - Timeline: Immediate (seconds)
   - Mechanism: Direct arterial injection sends a high local anesthetic concentration to the brain.
   - Presentation: Almost instantaneous neurologic symptoms, including seizures, altered consciousness, and possibly rapid cardiovascular collapse
2. Intravenous (IV) Injection
   - Timeline: Rapid (seconds to minutes)
   - Mechanism: Direct venous entry results in a rapid rise in plasma local anesthetic concentrations.
   - Presentation: Early CNS symptoms (tinnitus, metallic taste, perioral numbness, confusion) and seizures typically precede cardiovascular toxicity (arrhythmias, hypotension, cardiac arrest).
3. Systemic Absorption from Tissue Uptake
   - Timeline: Delayed onset (10-30+ minutes)
   - Mechanism: Gradual absorption from the injection site into systemic circulation
   - Presentation: Slowly progressive symptoms appearing from within 10 minutes to 60 minutes, influenced by dose, site vascularity, and patient factors.

The differential diagnosis of LAST is broad, but may include:

- Anaphylaxis: May include cardiovascular collapse and hypotension, but often also presents with rash, wheezing, and airway compromise.
- Vasovagal reaction: Typically presents with bradycardia and hypotension but without seizure or other ventricular tachyarrhythmia.
- High spinal anesthesia: May cause hypotension and bradycardia as well as respiratory distress, but without seizure or other ventricular arrhythmia.
- Concomitant cardiac events: May include arrhythmias, heart blocks, and cardiac arrest in patients with concomitant cardiac risk factors and comorbidities.

EMERGENCY PROTOCOL

1. Stop further local anesthetic administration immediately.
2. Call for help.
   - Designate someone to call emergency medical services (EMS, 911, or local equivalent) and initiate the code protocol. Bring in a crash cart and an automated external defibrillator (AED).
3. Airway Management and Seizure Control
   - Provide 100% oxygen via a non-rebreather mask. Ensure airway patency.
   - If seizures occur, administer benzodiazepines.
     - o If IV access is available, consider midazolam 2-5 mg IV, or diazepam 5-10 mg IV.
     - o Intramuscular midazolam is the preferred treatment when IV access is unavailable for emergent benzodiazepine administration.
   - Avoid large doses of propofol for seizure suppression due to risks of worsened cardiac depression.
4. Initiate 20% Lipid Emulsion Therapy (if available)
   - Over 70kg: Bolus 100 ml over 2-3 minutes followed by infusion of 250 ml over 15-20 minutes.
     - o If the patient remains unstable, repeat the bolus and double the infusion.
   - Under 70kg: Bolus 1.5 ml/kg over 2-3 minutes followed by infusion of 0.25 ml/kg/min.
     - o If the patient remains unstable, repeat the bolus and double the infusion.
   - Maximum lipid dose: 12 ml/kg
5. Cardiopulmonary Resuscitation (as needed)
   - Begin Advanced Cardiac Life Support (ACLS) protocol if pulseless.
   - *LAST resuscitation differs from standard ACLS protocols.* Use a smaller-than-normal dose of epinephrine (≤1 mcg/kg) initially, due to arrhythmia concerns. Note that higher doses of epinephrine in the setting of LAST have been associated with severe lactic acidosis, pulmonary edema, and hypoxia [10].
6. Medications to AVOID
   - Further local anesthetics: may worsen LAST
   - Beta-blockers: depress cardiac contractility
   - Calcium channel blockers: depress cardiac contractility
   - Vasopressin: increases afterload alone, undesirable due to contractility concerns
7. Monitor and Transfer
   - Transfer to a higher level of care [emergency department (ED)/intensive care unit (ICU)] after initial stabilization.
   - Monitor for delayed recurrence due to local anesthetic redistribution.
8. Follow-up
   - Notify the patient's emergency contact or family.
   - Consider debriefing the team and reviewing procedures to prevent future occurrences.

RISK MITIGATION/PREVENTION

- Use of appropriate imaging guidance: Ultrasound and real-time or digital subtraction fluoroscopic imaging with contrast medium may reduce the risk of inadvertent intravascular injection and LAST [11].
- Calculate maximum safety dose: adjust for patient weight, age, liver function, and injection site (highly vascular vs. avascular site)
  - NOTE: Dosing should be based on lean body weight (LBW) [12].
- Inject incrementally: Use small aliquots of 3-5 ml, aspirate between injections, and monitor appropriately.
- Use the lowest effective concentration and/or volume to achieve the desired outcome.
- Adding epinephrine to a local anesthetic may increase the maximum allowable local anesthetic dosage (See Table).
- Lipid emulsion therapy should be available if large amounts of local anesthetic are utilized for neural blockade.
- Ensure proper training: regular staff training and updated emergency protocols
- Regardless of the service site, the facility should be appropriately equipped to manage emergencies (see ***Advance Preparation for Emergencies*** [13]).

Local Anesthetic Maximum Doses

Anesthetic	Maximum Dose without Epinephrine (mg/kg)	Maximum Dose with Epinephrine (mg/kg)
Bupivacaine	2-2.5	3
Ropivacaine	3	3.5
Lidocaine	4.5-5	7
Mepivacaine	5	7
Prilocaine	6	8
2-Chloroprocaine	11	14

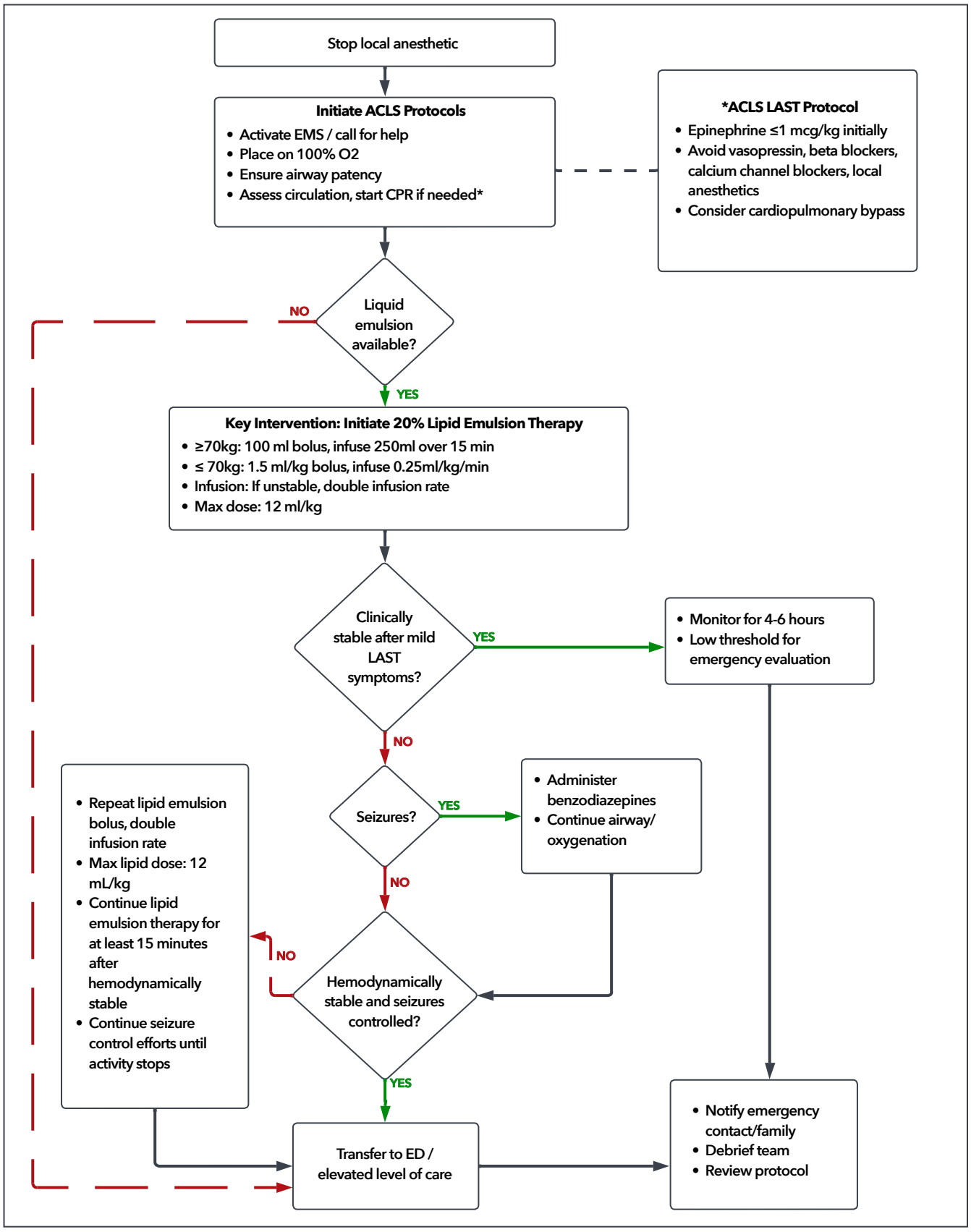
This table lists maximum local anesthetic doses, which generally refer to subcutaneous (subQ) or intradermal injections - that is, injections into soft tissue, not into vascular spaces or confined compartments [14-18].

If injected into more vascular areas (*e.g.*, near major blood vessels) or confined spaces (*e.g.*, spinal/epidural), systemic absorption may be quicker with a higher risk of toxicity. Lower doses may be required for highly vascular sites or patients at increased risk (*e.g.*, elderly, children, pregnancy, hepatic dysfunction) [12].

KEY CONSIDERATIONS/TAKEAWAYS

- LAST is life-threatening, but preventable. LAST can progress to seizures and/or cardiovascular collapse, especially following inadvertent intravascular injection. Early recognition and administration of lipid emulsion therapy, along with adherence to emergency protocols, can improve outcomes.
- Lipid emulsion therapy is the key to management. Lipid rescue should be initiated immediately in any suspected case of LAST, with careful monitoring during and after administration.
- Cardiotoxicity varies by agent. Bupivacaine carries the highest risk for cardiotoxicity, while lidocaine has a wider therapeutic index. Ropivacaine offers a safer cardiac profile than bupivacaine, though it is not without risk.
- Epinephrine can aid detection and reduce risk. Epinephrine may slow systemic absorption and serve as a marker for intravascular injection. However, it should be used cautiously in patients with cardiovascular disease.
- Escalating local anesthetic requirements should prompt reassessment of procedural technique and block efficacy. Consideration should be given to aborting the procedure rather than continuing toward maximal dosing thresholds.
- Prevention requires vigilance and preparedness. Strict adherence to safe dosing, incremental injections, use of imaging guidance, and staff preparedness are essential to minimize the risk of LAST.

SUSPECTED LOCAL ANESTHETIC SYSTEMIC TOXICITY



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DISCLAIMER

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