ASRA Practice Advisory on Local Anesthetic Systemic Toxicity

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Abstract: The American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity assimilates and summarizes current knowledge regarding the prevention, diagnosis, and treatment of this potentially fatal complication. It offers evidence-based and/or expert opinion-based recommendations for all physicians and advanced practitioners who routinely administer local anesthetics in potentially toxic doses. The advisory does not address issues related to local anesthetic-related neurotoxicity, allergy, or methemoglobinemia. Recommendations are based primarily on animal and human experimental trials, case series, and case reports. When objective evidence is lacking or incomplete, recommendations are supplemented by expert opinion from the Practice Advisory Panel plus input from other experts, medical specialty groups, and open forum. Specific recommendations are offered for the prevention, diagnosis, and treatment of local anesthetic systemic toxicity.

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Local anesthetics are widely and commonly used throughout medical and dental practice. Although it is rare for patients to manifest serious adverse effects or experience complications secondary to local anesthetic administration, adverse events do occur. These range from the mild symptoms that may follow systemic absorption of local anesthetic from a correctly sited and appropriately dosed regional anesthetic procedure to major central nervous system (CNS) and/or cardiac toxicity (most often from unintentional intravascular injection) that can result in disability or death. A variety of factors influence the likelihood and severity of local anesthetic systemic toxicity (LAST), including individual patient risk factors, concurrent medications, location and technique of block, specific local anesthetic compound, total local anesthetic dose (the product of concentration × volume), timeliness of detection, and adequacy of treatment.

Interest in local anesthetic toxicity has had several peaks, including one that coincided with the initial awareness of local anesthetic toxicities after the introduction of cocaine in 1884, another that followed the linking of fatalities to the use of bupivacaine and etidocaine in the 1970s, and another after the introduction of ropivacaine and levobupivacaine in the late 1980s that continues through the present.[1,2] There is suspicion (but scant evidence) that patients undergoing regional anesthesia are now less likely to have LAST than in earlier decades. On the other hand, improved understanding of LAST pathophysiology and new treatment modalities have emerged in the 2000s. Consequently, the American Society of Regional Anesthesia and Pain Medicine (ASRA) commissioned a panel of experts to update recommendations that came from the 2001 ASRA Conference on Local Anesthetic Toxicity. The current Practice Advisory focuses on LAST, which includes cardiac and CNS toxicity consequent to unintended intravascular injection or delayed tissue uptake. The advisory does not address tissue-related local anesthetic neurotoxicity, allergy, or the production of methemoglobinemia by local anesthetics.

A 2006 survey of US academic anesthesiology departments found no uniform, well-designed, rational approach for management of local anesthetic toxicity.[3] The ASRA Practice Advisory Panel was also formed to correct this deficiency by identifying key practice modifications targeted specifically at improving prevention, diagnosis, and treatment of LAST. Our recommendations reflect our view of the primacy of prevention of LAST as the most effective intervention for enhancing patient safety.

METHODOLOGY

This practice advisory is derived from human and animal experimental studies related to the prevention, diagnosis, and treatment of LAST in adults and children. All available English-, German-, and French-language reports of human and animal scientific inquiry were considered, including randomized controlled trials (RCTs), observational studies, case series, and case reports. Key word literature searches were undertaken using major literature search engines such as the National Library of Medicine's PubMed, Ovid, and Google Search. Article bibliographies were cross-checked for references not identified by search engines.

The ASRA Board of Directors appointed the Panel at their fall 2007 meeting. The Panel consists of recognized experts on local anesthetic toxicity and/or guideline development and includes all authors of this article. This group was responsible

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This study was supported by the American Society of Regional Anesthesia and Pain Medicine (ASRA).
The authors of this document are pleased to announce that their colleagues in the Association of Anaesthetists of Great Britain and Ireland, coincident with this ASRA Practice Advisory, have developed "Guidelines for the Management of Severe Local Anaesthetic Toxicity." Dr. Weinberg contributed to this document. Physicians with particular interest in local anesthetic toxicity may wish to also consult the work of the Association of Anaesthetists of Great Britain and Ireland.
Spencer S. Liu, MD, served as Acting Editor-in-Chief for this article.
Dr. Weinberg was awarded US patent 7,261,903 B1 "Lipid Emulsion in the Treatment of Systemic Poisoning." He does not have equity interest or agreements with any company or commercial entity related to this method. He has never received salary or support from any company. He does not intend to prohibit or restrict the practice of this method on any patient requiring this treatment. Dr. Weinberg also created and maintains www.lipidrescue.org, an educational, noncommercial Web site providing information and a forum for discussing the use of lipid emulsion in treating cardiac toxicity. He derives no salary or support related to this Web site.
Dr. Butterworth served as a consultant to APP Pharmaceuticals, US distributor of ropivacaine in 2008.

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for the initial literature search, assimilation of materials, expert opinion, development of recommendations, and writing the accompanying supporting articles. Individuals neither received direct financial support for their participation nor did any participants other than Drs. Weinberg and Butterworth declare a potential conflict of interest (see appended declaration). The ASRA received no direct financial support from industry or other grants to underwrite expenses (travel support for the panel) related to this initiative.

As suggested by recognized instruments for guideline development such as the Appraisal of Guidelines for Research & Evaluation,[4] every effort was made to ensure the integrity and validity of the process leading to the recommendations made herein. External input, appraisal, and validity were sought using the following mechanisms. The Panel's recommendations were circulated to a separate group of experts selected on the basis of their demonstrated interest and/or expertise in local anesthetic toxicity (Appendix 1). General input was also sought by contacting the Editors-in-Chief of major journals for medical and dental specialties that commonly use local anesthetics (Appendix 2). Comments from these 2 groups were considered and incorporated when appropriate, and particularly as they related to content, interpretation, and clarity of the recommendations. One week before presentation in open forum at the May 3, 2008, ASRA meeting in Cancun, Mexico, meeting registrants were e-mailed a copy of the recommendations. Open comment was solicited primarily with regard to clarity and soundness of the recommendations. After finalizing recommendations, the Practice Advisory summary document and accompanying review articles were submitted to *Regional Anesthesia and Pain Medicine* for publication, where they were subjected to the journal's standard peer-review process. Readers are encouraged to read the accompanying reviews, which provide the details that led to recommendations contained within this summary article.

Grading the Strength of Recommendations

There are no RCTs evaluating serious human LAST; future RCTs are unlikely because of the rarity of these complications and the associated difficulty of obtaining informed consent for medical interventions in critical illness. Common strength-of-evidence schemas that are based on RCT-level evidence are therefore inappropriate for the topic of human LAST but are appropriate for animal studies. Hence, the Practice Advisory's recommendations are based on a modification of a Classification of Recommendations and Levels of Evidence schema that was developed by the American Heart Association (Table 1).[5] The panel wishes to emphasize that assigning a Level of Evidence B or C should not be construed as implying that the associated recommendation is supported by conflicting data or is limited by conflicting interpretations of the available data. Rather, such recommendations reflect our recognition of the importance of the particular question as it relates to LAST, and to the reality that the specific question is either yet to be addressed by a RCT or does not lend itself to experimental inquiry in humans.

Limitations

As with previous ASRA-sponsored practice advisories, our recommendations should be viewed as guidelines that are based on existing literature and expert opinion. The scientific literature that provided the basis for these guidelines and recommendations is imperfect and always evolving. Animal studies should be interpreted with knowledge of species differences, variations in laboratory systems, and differing experimental models. The hypothesis being tested may limit the conclusions one can make, along with extrapolations to the clinical setting. Literature comprising case reports may be biased toward positive outcomes because clinicians are reluctant to present their cases that have poor outcome, and case reports without a "teaching point" will almost never be accepted for publication.[6] Therefore, some local anesthetics, for example, ropivacaine or levobupivacaine, might seem safer than is the case, and specific treatments, for example, lipid emulsion, might fail more often than the literature indicates. Some of our recommendations are based on expert opinion alone. The nature of practice advisories is that they address issues of controversy and uncertainty. We strive to acknowledge these controversies, but then to offer our best advice within the setting of uncertainty. Particularly when addressing more controversial issues, our recommendations tend to err toward conservative management.

Our recommendations are intended to promote quality patient care; nevertheless, rigid observance of our recommendations may not guarantee a specific patient outcome. Our recommendations are not meant to be interpreted as standard of care and they should never supersede sound medical judgment. Those who apply these recommendations will determine their value. As with all practice advisories, these recommendations will be subject to timely revision as warranted by the evolution of technology, scientific evidence, and clinical experience.[7]

TABLE 1. Definitions for Classification of Recommendations and Levels of Evidence

Classification of Recommendations	
Class I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
	IIa. Weight of evidence/opinion is in favor of usefulness/efficacy
	IIb. Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful
Level of Evidence	
Level A	Data derived from randomized clinical trials
Level B	Data derived from nonrandomized or laboratory, eg, animal studies; supported by multiple case reports or case series
Level C	Consensus opinion of experts

The above schema is modified from an American Heart Association schema for developing and grading guidelines.[5]

HISTORY

Local anesthetic systemic toxicity has been recognized and reported since shortly after the introduction of cocaine into clinical practice in the 1880s. From the outset, systemic toxicity was associated with seizures and respiratory failure.[8] It is unclear when direct cardiac toxicity was recognized as a major component of systemic toxicity, rather than an associated adverse effect. The systemic toxic effects of cocaine and cocaine's propensity to cause local tissue toxicity in part led to Einhorn's development of procaine in 1904. Unfortunately, LAST continued to be a major

patient safety concern, so much so that the American Medical Association (AMA) established the Committee for the Study of Toxic Effects of Local Anesthetics in the early 1920s.[9] It became clear that local anesthetics were not only capable of causing death but that cardiac arrest could precede seizures or even occur in the absence of seizures. The AMA Committee stopped short of suggesting a ban on cocaine, but emphasized the primacy of a clear airway to optimize oxygenation and ventilation, a theme that Daniel Moore and Donald Bridenbaugh[10] would continue to stress throughout the mid and late 20th century. The potent lipid-soluble local anesthetics bupivacaine and etidocaine were introduced into clinical practice in the 1960s and 1970s, respectively. By 1969, bupivacaine had been linked to fetal death in 1:900 women who received a paracervical block, admittedly without a clear understanding as to whether bupivacaine itself, the paracervical block technique, or some combination thereof was the responsible etiologic factor. Not until the late 1970s was bupivacaine linked to fatal cardiac arrest in otherwise healthy adult patients. The report of Prentice[11] and Albright's oft-cited editorial[1] set in motion the events that would lead the US Food and Drug Administration and the 3 manufacturers of bupivacaine issuing a "Dear Doctor" letter withdrawing obstetric analgesia as an indication for 0.75% bupivacaine and warning against its further use in paracervical block and intravenous regional anesthesia. Despite the clinical release of the apparently less cardiotoxic single enantiomers ropivacaine and levobupivacaine in the late 1980s, serious morbidity and mortality from cardiac toxicity continued.[2] In the 1990s, animal research gave hope that lipid emulsions might prove to be an antidote for LAST.[12] The first case reports of successful rescue of humans experiencing refractory cardiac toxicity came in the mid 2000s.[13] Today, research is ongoing to refine issues related to lipid emulsion therapy for severe LAST and its prodromes.[14]

FREQUENCY, MODELS, AND MECHANISMS

What is known regarding LAST is derived primarily from 3 sources—epidemiologic studies that attempt to define incidence in specific patient populations, case series and case reports that describe clinical manifestations of toxicity and/or treatment,[2] and animal studies that aim to establish relative toxicity, elucidate mechanisms, and identify cofactors that promote or attenuate their occurrence. Epidemiologic studies report statistics that vary widely depending on how toxicity is defined, the clinical scenario in which it occurs, and how the data were collected. For example, death from the application of cocaine or tetracaine to mucous membranes to facilitate otolaryngological procedures was reported in 1951 to occur in 7 of 39,278 patients (1.8:10,000).[15] Seizures associated with brachial plexus blockade, particularly the interscalene and supraclavicular approaches (where local anesthetics may be unintentionally injected into an artery feeding the brain), have been reported in up to 79 in 10,000 patients from a single institutional database.[16] Yet a large surveillance study of French anesthesiologists determined the overall frequency of seizures to be 0 to 25 in 10,000, depending on the type of block performed. Interestingly, there were no cardiac arrests secondary to LAST reported in this series.[17] Information from case reports and series offers insights into clinical scenarios of LAST[2] but is unable to define mechanisms. Human RCTs of local anesthetic toxicity will likely never be performed because of ethical and logistical concerns. Thus, most of what is understood regarding the mechanisms of LAST and its treatment comes from animal studies, yet there is limited consensus among investigations as to which animal model best reflects human toxicity. Even basic mechanistic information is controversial with regard to which anesthetic binding site, ion channel, signaling pathway, or enzyme is most important in CNS or cardiac toxicity or their treatment.

When one interprets animal studies of LAST, it is important to consider the model chosen by the investigators to study their hypothesis and what specific clinical circumstance the model is intended to mimic.[18] Variables include in vivo whole animal models versus in vitro isolated heart versus tissue culture; whole cell, ion channel, or subcellular organelle models; large animal versus small animal; awake versus anesthetized; and bolus dosing versus infusion models. Other important features will influence the interpretation of the findings, including the chosen metrics and parameters of interest, the timing of such measures, or the presence of confounders such as hypoxia. Although each of these approaches provides specific advantage, there is no consensus that any model truly mimics clinical toxicity. For instance, many cases of toxicity occur in patients with underlying ischemic or other cardiac disease, which is not readily modeled in standard experimental animals or preparations. Given that summarizing the mechanisms of LAST assuredly represents an oversimplification, in general, it seems that cardiac toxicity results predominantly from the binding and inhibition of Na channels by local anesthetics. Notably, inhibition of cardiac conduction follows a rank order similar to local anesthetic potency for generating neural blockade.[19] When compared with lidocaine, cardiac conduction channels are bound more rapidly and for longer duration by the more potent local anesthetics bupivacaine, etidocaine, and ropivacaine,[20] albeit less avidly by their *S*(−) isomers.[21] Such evidence notwithstanding, a vast array of other inotropic and metabotropic cell signaling systems are affected by local anesthetics and have been implicated in mediating symptoms and signs of LAST. Furthermore, virtually every component of oxidative phosphorylation is inhibited by potent local anesthetics; this observation provides support for mitochondrial metabolism as an important, potential target of local anesthetics and could help explain why symptoms of LAST include predominantly the organs least tolerant of anaerobic metabolism (heart and brain).

Local anesthetics also differ with regard to their CNS toxicity. The cardiovascular (CV)/CNS ratio describes the dose required to produce CV arrhythmias versus that required to produce seizures. This ratio tends to be lower with bupivacaine compared with lidocaine, which implies a reduced safety margin for the potent compounds when detecting impending cardiac toxicity based on premonitory CNS signs. These more potent local anesthetics indeed generate arrhythmias at lower concentrations compared with lidocaine and mepivacaine. At comparable doses in dogs, bupivacaine and etidocaine caused severe arrhythmias without decreased contractility, while lidocaine caused the opposite, that is, depressed myocardial contractility without arrhythmia.[22–24] However, once plasma concentrations reach higher levels, local anesthetics of all potencies are capable of producing severe myocardial depression.[25]

PREVENTION

This Practice Advisory emphasizes the primacy of prevention in reducing the frequency and severity of LAST, yet no single intervention has been identified that can reliably eliminate risk. Central to prevention is limiting the opportunity for intravascular injection or tissue uptake of local anesthetic, which is best accomplished by early detection of intravascular needle or catheter placement. If an intravascular injection does occur, it should ideally contain the lowest possible dose of local anesthetic. To these ends, various intravascular identification methods have been proposed since the description of the epinephrine test dose by Moore and Batra in 1981.[26] Literature review

suggests that the frequency of LAST associated with epidural anesthesia may have decreased subsequently by 10- to 100-fold.[27] Conversely, actual published reports of LAST have increased recently, most likely because of renewed interest and new information related to the introduction of the less cardiotoxic stereoisomers ropivacaine and levobupivacaine and to clinical experience with successful lipid emulsion rescue.[2]

Local anesthetic dose can be limited by several methods. Total dose (the product of volume × concentration) should be tailored to the minimum mass of local anesthetic molecules necessary to achieve the desired clinical effect. Evidence suggests that most peripheral nerve blocks are performed with significantly larger doses than are necessary to achieve desired clinical end points[28]; these data are further supported by ultrasound-guided regional anesthesia (UGRA)[29] and continuous perineural catheter[30] studies that document adequate blockade using exceedingly small doses of properly placed local anesthetic.[31] Dose reduction may be particularly important for those patients thought to be at greater risk of LAST, for example, those patients at extremes of age (<4 months or >70 years) or those with cardiac conduction defect or a history of ischemic heart disease. Neither body weight nor body mass index correlates with local anesthetic plasma levels after a specific dose in adults; the correlation is more accurate in children. Block site, intrinsic vasoactivity of the local anesthetic, use of epinephrine, and patient-related factors such as cardiac, renal, or hepatic dysfunction are more important predictors of local anesthetic plasma levels than either body weight or body mass index.

When the above noted factors that may predispose to LAST are present, reduction of local anesthetic dose is intuitively logical, yet there are no established parameters to guide actual dose reduction.[32] Incremental injection of 3 to 5 mL of local anesthetic with a concomitant pause for at least one circulation time before further injection is a time-honored recommendation with intuitive appeal, but with no objective efficacy data. Practical considerations suggest that the potential benefit from this approach could be outweighed by prolonging overall injection time with an attendant risk of needle movement. Of note, circulation times are increased with lower extremity injection compared with upper extremity injection. Aspiration of needles and catheters, although recommended, may fail to identify intravascular placement in at least 2% of patients.[33] Substituting the less potent levoenantiomers ropivacaine or levobupivacaine might reduce the potential for systemic toxicity Nonetheless, these drugs are potentially toxic and the theoretical benefit of chirality becomes less important with increasing doses, particularly among patients at greater than normal risk for local anesthetic toxicity. It is possible that risk inherent to comorbidities such as ischemic heart disease, conduction defects or low output states far outweighs the potential risk reduction of using levoenantiomers.

How can a clinician reduce the risk of LAST? Although imperfect, intravascular test dosing remains the most reliable marker of intravascular injection. Of the various options described, only fentanyl and epinephrine meet suggested standards for reliability and applicability.[34] Intravenous fentanyl 100 μg has been shown to reliably produce drowsiness or sedation in laboring patients.[27] With regard to epinephrine, 10 to 15 μg/mL epinephrine has a positive predictive value and 80% sensitivity in detecting intravascular injection in adults if heart rate increases by 10 beats per minute or higher or systolic blood pressure increases by 15 mm Hg or higher. For children, intravascular epinephrine 0.5 μg/kg is associated with a 15-mm Hg increase or higher in systolic blood pressure. Nevertheless, epinephrine test doses are unreliable in the elderly, or in patients who are sedated, taking β-blockers, or anesthetized with general or neuraxial anesthesia. Epinephrine is also controversial with regard to its role in nerve injury. Although epinephrine has been shown in animal models to worsen local anesthetic-induced neurotoxicity, it is unclear if the additive injury in humans is clinically relevant over and above that caused primarily by the local anesthetic itself.[35] The frequency of seizures during performance of peripheral nerve block was similar to the frequency of permanent nerve injury in one major study (1.2 versus 2.4 in 10,000, respectively).[36] Notably, severe LAST, but not nerve injury, has the potential to cause death.

Ultrasound guidance may reduce the frequency of vascular puncture, but there are no RCTs that confirm or refute an actual reduction of LAST.[37] Two large case series present conflicting results—one found a statistically significant ($P = 0.001$) reduction in the number of vascular punctures occurring under UGRA versus peripheral nerve stimulation, but no difference in LAST.[38] The other series reported a significant ($P = 0.044$) reduction in seizures with ultrasound-assisted nerve localization versus peripheral nerve stimulation.[39] Although intravascular injection can be observed during UGRA,[40] case reports describe symptomatic intravascular injection despite its use.[41] Whether generation of a hypoechoic region consequent to injected local anesthetic is a sufficient monitor of intravascular injection to warrant omission of epinephrine is the subject of considerable debate, particularly when one considers the frequent needle movements inherent to UGRA techniques versus the generally fixed needle techniques associated with nonultrasound blocks. Thus, prevention of intravascular injection is perhaps best accomplished with a combination of UGRA and epinephrine test dosing. Because the literature offers no firm guidance and no method of detection is perfect, meticulous attention to detail remains the most important asset for prevention. Recommendations for preventing LAST are given in Table 2.

CLINICAL DIAGNOSIS OF SYSTEMIC TOXICITY

The classic description of LAST includes subjective symptoms of CNS excitement such as auditory changes, circumoral numbness, metallic taste, and agitation that then progress to seizures and/or CNS depression (coma, respiratory arrest). In classic descriptions of LAST, cardiac toxicity does not occur without preceding CNS toxicity. When LAST occurs secondary to direct intravascular injection (particularly with injection into the carotid or vertebral arteries), premonitory symptoms can be bypassed and the patient can rapidly develop seizure activity that may progress to cardiac excitation (hypertension, tachycardia, ventricular arrhythmias). With greatly increased blood concentrations, cardiac excitation may be followed by cardiac depression (bradycardia, asystole, decreased contractility, and hypotension). Particularly with the most potent local anesthetics, cardiac toxicity may occur simultaneously with seizure activity or even precede it.

Despite this classic description, case reports of LAST emphasize the extreme variability of its presentation, including timing of onset, initial manifestations, and duration. We found an atypical presentation was reported in approximately 40% of published cases of LAST. In these instances, symptoms were delayed by 5 mins or more or occurred with only CV signs of toxicity. The practitioner's vigilance is of critical importance in recognizing these early signs of LAST, appreciating their variable presentation, and having a low threshold for considering LAST in patients that have received potentially toxic doses of local anesthetics and manifest atypical or unexpected signs and symptoms.

TABLE 2. Recommendations for Preventing LAST

- There is no single measure that can prevent LAST in clinical practice.
- Use the lowest effective dose of local anesthetic (dose = product of volume × concentration) (I; C)
- Use incremental injection of local anesthetics—administer 3- to 5-mL aliquots, pausing 15–30 s between each injection. When using a fixed needle approach, eg, landmark, paresthesia-seeking, or electrical stimulation, time between injections should encompass one circulation time (~30–45 s); however, this ideal may be balanced against the risk of needle movement between injections. Circulation time may be increased with lower extremity blocks. Use of larger dosing increments would dictate the need for longer intervals to reduce the cumulative dose from stacked injections before an event of LAST. Incremental injection may be less important with ultrasound guidance, given that frequent needle movement is often used with the technique (I; C).
- Aspirate the needle or catheter before each injection, recognizing that there is an ~2% false-negative rate for this diagnostic intervention (I; C).
- When injecting potentially toxic doses of local anesthetic, use of an intravascular marker is recommended. Although epinephrine is an imperfect maker and its use is open to physician judgment, its benefits likely outweigh its risks in the majority of patients (IIa; B):
  - Intravascular injection of epinephrine 10–15 μg/mL in adults produces a ≥10 beat heart rate increase or a ≥15-mm Hg systolic blood pressure increase in the absence of β-blockade, active labor, advanced age, or general/neuraxial anesthesia.
  - Intravascular injection of epinephrine 0.5 μg/kg in children produces a ≥15-mm Hg increase in systolic blood pressure.
  - Appropriate subtoxic doses of local anesthetic can produce subjective symptoms of mild systemic toxicity (auditory changes, excitation, metallic taste, etc.) in unpremedicated patients.
  - Fentanyl 100 μg produces sedation if injected intravascularly in laboring patients.
- Ultrasound guidance may reduce the frequency of intravascular injection, but actual reduction of LAST remains unproven in humans. Individual reports describe LAST despite the use of UGRA. The overall effectiveness of ultrasound guidance in reducing the frequency of LAST remains to be determined (IIa; C).

The class of recommendation and level of evidence for each intervention are given in parenthesis (Table 1).

Local anesthetic systemic toxicity continues to be a major source of morbidity and mortality in regional anesthesia practice. Recent American Society of Anesthesiologists Closed Claims data note that LAST accounted for one-third of claims for death or brain damage associated with regional anesthesia.[42] Conversely, physicians tend to report and publish their successes rather than their failures—in our review of 93 separate LAST events contained within 74 reports, there was only 1 death. Our review spanned 30 years, yet 65% of the reports were published in the last 10 years. From this review, several patterns emerge. First, two-thirds of patients were female and nearly half the cases were in patients at the extremes of age—16% were younger than 16 years and 30% were older than 60 years. More than 90% of cases involved the most potent local anesthetics, that is, bupivacaine, ropivacaine, and levobupivacaine. Less than 1 in 5 cases involved continuous infusion techniques and half of these were in children. Although analysis of case reports only establishes association rather than cause-and-effect, it is interesting to note that more than one-third of reports of cardiac and CNS toxicity involved patients with underlying cardiac, neurologic, or metabolic disease, for example, diabetes, renal failure, isovaleric academia.

In our reviewed single injection cases, the median time from injection to first symptom was 52.5 seconds (interquartile range, 30–180 seconds), which suggests direct injection into an artery supplying the brain or a large intravascular bolus containing sufficient local anesthetic dose to cause CNS symptoms even after first pass clearance through the lungs. For this same group of cases, the mean time to first symptom was 89 seconds (95% confidence interval, 67–120 seconds). Most other reports noted first symptoms between 1 and 5 mins of injection, suggesting partial intravascular injection, lower extremity injection, and/or tissue uptake. Importantly, approximately 25% of cases described symptoms first appearing more than 5 mins after injection (one report described a 60-min delay), which emphasizes the importance of prolonged observation of patients receiving potentially toxic doses of local anesthetic. Local anesthetic systemic toxicity may occur as frequently as 1:1000 peripheral nerve blocks,[43] but it is likely that most of these cases involve minor subjective symptoms that do not progress to frank CNS or cardiac toxicity. Of those cases serious enough to report and publish, 45% involved only CNS signs and symptoms, whereas 44% involved both CNS and cardiac manifestations. Reported cases rarely presented with only cardiac signs and symptoms.[2]

Our overall analysis of case reports suggests that although LAST tends to follow classic presentations, variations are common. Although seizure was the most common presenting symptom, less than 20% of cases involved any of the classic prodromal symptoms such as auditory changes, metallic taste, or disinhibition. Thus, practitioners are advised to be ever-vigilant of potential LAST, particularly in patients at the extremes of age who may have underlying cardiac, pulmonary, renal, hepatic, metabolic, or neurologic disease. Importantly, LAST does not always manifest itself as obvious seizure or cardiac arrhythmias in close temporal relationship to local anesthetic injection. Practitioners should consider the diagnosis of impending LAST in patients that develop unexplained agitation or CNS depression, or unexplained signs of CV compromise, for example, progressive hypotension, bradycardia, or ventricular arrhythmia, even if more than 15 mins after local anesthetic injection.[2] Recommendations for diagnosing LAST are contained in Table 3.

TREATMENT

Treatment priorities for LAST include airway management, circulatory support, and promoting the diminution of the systemic effects of local anesthetics. Unlike the case for treatment of "conventional" cardiac arrest, the key to successful care of LAST patients is recognizing the primacy of airway management. As reported by Moore and colleagues a half century ago,[10,44] prevention of hypoxia and acidosis by immediate restoration of oxygenation and ventilation can either halt progression to CV collapse and seizure or facilitate resuscitation. Subsequent laboratory investigations confirm this concept.[45] If seizures occur, they should be rapidly controlled to prevent injury to the patient and acidosis. The Panel recommends that benzodiazepines are the ideal drugs to treat seizures because they have limited potential for cardiac depression. In the absence of readily available benzodiazepine, propofol or thiopental are acceptable alternatives; however, their potential for worsening existing hypotension or cardiac depression requires using the lowest effective dose. The Panel recognizes that further experience with lipid infusion could lead to its use in preference

TABLE 3. Recommendations for Diagnosing LAST

- Classic descriptions of LAST depict a progression of subjective symptoms of CNS excitement (agitation, auditory changes, metallic taste or abrupt onset of psychiatric symptoms), followed by seizures then CNS depression (drowsiness, coma, or respiratory arrest). Near the end of this continuum, initial signs of cardiac toxicity (hypertension, tachycardia, or ventricular arrhythmias) are supplanted by cardiac depression (bradycardia, conduction block, asystole, decreased contractility). However, there is substantial variation in this classic description, including:
  - Simultaneous presentation of CNS and cardiac toxicity
  - Cardiac toxicity without prodromal signs and symptoms of CNS toxicity
  - Thus, the practitioner must be vigilant for atypical or unexpected presentation of LAST (I; B).
- The timing of LAST presentation is variable. Immediate (<60 s) presentation suggests intravascular injection of local anesthetic with direct access to the brain, whereas presentation that is delayed 1–5 mins suggests intermittent intravascular injection, lower extremity injection, or delayed tissue absorption. Because LAST can present >15 mins after injection, patients that receive potentially toxic doses of local anesthetic should be closely monitored for at least 30 mins after injection (I; B).
- Case reports associate LAST with underlying cardiac, neurologic, pulmonary, renal, hepatic, or metabolic disease. Heightened vigilance may be warranted in these patients, particularly if they are at the extremes of age (IIa; B).
- The overall variability of LAST signs and symptoms, timing of onset, and association with various disease states suggests that practitioners should maintain a low threshold for considering the diagnosis of LAST in patients with atypical or unexpected presentation of CNS or cardiac signs and symptoms after receiving more than a minimal dose of local anesthetic (IIa; B).

The class of recommendation and level of evidence for each intervention are given in parenthesis (Table 1).

to benzodiazepines. If tonic-clonic movements persist despite these measures, small doses of succinylcholine may be considered to rapidly stop muscular activity (continued seizure activity exacerbates hypoxia and systemic acidosis), being mindful that seizure activity and acidosis will continue unless interrupted with a sedative hypnotic agent.[46]

Local anesthetic-induced cardiac arrest requires rapid restoration of coronary perfusion pressure to improve myocardial contractility and theoretically to washout local anesthetics from cardiac tissues through improved tissue perfusion. Maintenance of cardiac output and oxygen delivery to tissues is critical for prevention and treatment of acidosis. It is important to recognize that cardiac arrest or arrhythmia associated with LAST represents a substantially different medical problem from the more typical out-of-hospital scenarios addressed by Advanced Cardiac Life Support Guidelines. Although standard dose (1 mg) epinephrine may restore circulation and initially improve blood pressure, it is also highly arrhythmogenic. Furthermore, in animal studies of local anesthetic-induced cardiac arrest, epinephrine resulted in poorer outcomes from bupivacaine-induced asystole than did lipid emulsion,[47] whereas vasopressin also showed very poor outcomes and was associated with pulmonary hemorrhage.[48] Therefore, the Panel advises that if used in treating LAST, lower than "standard" initial doses of epinephrine are suggested (<1 μg/kg). On the basis of animal studies, consideration should be given to avoiding vasopressin. In recalcitrant cases of LAST in which there is inadequate response to epinephrine and other standard therapies, cardiopulmonary bypass should be considered as a bridging therapy until tissue levels of local anesthetic have cleared.

Lipid emulsion therapy can be instrumental in facilitating resuscitation, most probably by acting as a "lipid sink" that draws down the content of lipid-soluble local anesthetics from within cardiac tissue, thereby improving cardiac conduction, contractility, and coronary perfusion.[49] We recommend an initial bolus of 1.5 mL/kg (lean body mass) 20% lipid emulsion, followed by an infusion of 0.25 mL/kg per minute continued for 10 mins after hemodynamic stability is attained. Failure to achieve stability should prompt an additional bolus and increase of infusion rate to 0.5 mL/kg per minute . Approximately 10 mL/kg lipid emulsion for 30 mins is recommended as an upper limit for initial administration.[46]

There are several as yet unanswered questions regarding lipid emulsion therapy. Initial recommendations conservatively suggested that it be used only after standard resuscitative

TABLE 4. Recommendations for Treatment of LAST

- If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are known to potentiate LAST (I; B).
- If seizures occur, they should be rapidly halted with benzodiazepines. If benzodiazepines are not readily available, small doses of propofol or thiopental are acceptable. Future data may support the early use of lipid emulsion for treating seizures (I; B).
- Although propofol can stop seizures, large doses further depress cardiac function; propofol should be avoided when there are signs of CV compromise (III; B). If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia (I; C).
- If cardiac arrest occurs, we recommend standard Advanced Cardiac Life Support with the following modifications:
  - If epinephrine is used, small initial doses (10–100 μg boluses in the adult) are preferred (IIa; C)
  - Vasopressin is not recommended (III; B)
  - Avoid calcium channel blockers and β-adrenergic receptor blockers (III; C)
  - If ventricular arrhythmias develop, amiodarone is preferred (IIa; B); treatment with local anesthetics (lidocaine or procainamide) is *not* recommended (III; C)
- Lipid emulsion therapy (IIa; B):
  - Consider administering at the first signs of LAST, after airway management
  - Dosing:
    - 1.5 mL/kg 20% lipid emulsion bolus
    - 0.25 mL/kg per minute of infusion, continued for at least 10 mins after circulatory stability is attained
    - If circulatory stability is not attained, consider rebolus and increasing infusion to 0.5 mL/kg per minute
    - Approximately 10 mL/kg lipid emulsion for 30 mins is recommended as the upper limit for initial dosing
- Propofol is not a substitute for lipid emulsion (III; C).
- Failure to respond to lipid emulsion and vasopressor therapy should prompt institution of cardiopulmonary bypass (CPB) (IIa; B). Because there can be considerable lag in beginning CPB, it is reasonable to notify the closest facility capable of providing it when CV compromise is first identified during an episode of LAST.

The class of recommendation and level of evidence for each intervention are given in parenthesis (Table 1).

attempts had failed, but recent case reports[6,50–52] support the early use of lipid emulsion at the first sign of arrhythmia from suspected LAST, prolonged seizure activity, or rapid progression of the toxic event. Because tissue depots of local anesthetic can redistribute to the circulation over time and delayed recurrence of severe toxicity has been reported, we recommend that any patient with significant LAST be observed for at least 12 hrs. There is no evidence that one formulation of lipid emulsion is superior to another for the treatment of LAST. However, it is important to note that *propofol is not a substitute for lipid emulsion therapy* because of its low lipid content (10%), the large volumes required for the benefit of lipid in resuscitation (hundreds of milliliters) and the direct cardiac depressant effects of propofol. Our recommendations for the treatment of LAST are presented in Table 4. Those recommendations are summarized in Appendix 3, which is available online in two sizes and can be printed and laminated for display in areas where potentially toxic doses of local anesthetics are used. (See Supplemental Digital Content 1, http://links.lww.com/AAP/A17, for a condensed version of Appendix 3, and Supplemental Digital Content 2, http://links.lww.com/AAP/A18, for a full-size version).

FUTURE DIRECTIONS

It is apparent that continued investigation is needed to guide future methods for preventing and treating LAST. Improved, less toxic, longer-acting local anesthetics are desired. Novel delivery methods may reduce the dose required to achieve clinical anesthesia and analgesia. Examples include both current technology (UGRA) and delivery methods in development, such as capsaicin coinjection[53] and sustained release microspheres or liposomes.[54] We hope that continued laboratory investigation will lead to improved resuscitation methods. Alternative formulations of lipid emulsion or new agents designed to increase partitioning, binding, capture, or otherwise neutralizing local anesthetic molecules hold the promise of a rapid, effective antidote to LAST. Further refinement is needed with regard to the ideal timing of lipid emulsion therapy, along with identification of potential toxicities or adverse effects.

Our understanding of the mechanisms of LAST, although incomplete, has increased significantly since local anesthesia was introduced more than a century ago. Stepwise improvements in our knowledge regarding prevention, diagnosis, and treatment have likely led to a reduction in fatalities associated with LAST; it is less certain whether the frequency of nonfatal seizures and cardiac events has also declined, particularly those events associated with peripheral nerve block (as opposed to epidural techniques). Although probably linked to the recent development of UGRA and lipid emulsion therapy, the resurgence of published reports of LAST, (particularly involving successful resuscitation) suggests that LAST remains a significant clinical problem. Considering (1) the extensive use of local anesthetics, (2) the frequent use of doses sufficient to cause significant morbidity or mortality, and (3) the imperfect nature of our ability to prevent, detect, and treat these complications, it remains the responsibility of all clinicians using local anesthetics to understand their potential for severe systemic toxicity and to be prepared to respond immediately to these events when they occur.

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APPENDIX I

External Expert Appraisers

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APPENDIX 2

Professional Societies Invited to Comment on Draft Guidelines

American Academy of Family Medicine
American Academy of Orthopedic Surgeons
American College of Emergency Physicians
American College of Surgeons
American Dental Association
American Podiatric Medicine Association
American Society of Plastic Surgeons
Anesthesia Patient Safety Foundation

APPENDIX 3

AMERICAN SOCIETY OF
REGIONAL ANESTHESIA AND PAIN MEDICINE

Practice Advisory on Treatment of Local Anesthetic Systemic Toxicity

For Patients Experiencing Signs or Symptoms of Local Anesthetic Systemic Toxicity (LAST)

- **Get Help**
- **Initial Focus**
  - o ***Airway management:*** ventilate with 100% oxygen
  - o ***Seizure suppression:*** benzodiazepines are preferred
  - o ***Basic and Advanced Cardiac Life Support (BLS/ACLS)*** may require prolonged effort
- **Infuse 20% Lipid Emulsion (values in parenthesis are for a 70 kg patient)**
  - o ***Bolus 1.5 mL/kg*** (lean body mass) intravenously over 1 min (~100 mL)
  - o ***Continuous infusion at 0.25 mL/kg/min*** (~18 mL/min; adjust by roller clamp)
  - o Repeat bolus once or twice for persistent cardiovascular collapse
  - o Double the infusion rate to 0.5 mL/kg per minute if blood pressure remains low
  - o ***Continue infusion*** for at least 10 mins after attaining circulatory stability
  - o Recommended upper limit: approximately 10 mL/kg lipid emulsion over the first 30 mins
- **Avoid** vasopressin, calcium channel blockers, β-blockers, or local anesthetic
- **Alert** the nearest facility having cardiopulmonary bypass capability
- **Avoid propofol** in patients having signs of cardiovascular instability
- **Post LAST events** at www.lipidrescue.org and report use of lipid to www.lipidregistry.org

BE PREPARED

- We strongly advise that those using local anesthetics (LAs) in doses sufficient to produce systemic toxicity (LAST) establish a plan for managing this complication. Making a local anesthetic toxicity kit and posting instructions for its use are encouraged.

RISK REDUCTION (BE SENSIBLE)

- Use the least dose of LA necessary to achieve the desired extent and duration of block.
- Local anesthetic blood levels are influenced by site of injection and dose. Factors that can increase the likelihood of LAST include: advanced age, heart failure, ischemic heart disease, conduction abnormalities, metabolic (eg, mitochondrial) disease, liver disease, low plasma protein concentration, metabolic or respiratory acidosis, and medications that inhibit sodium channels. Patients with severe cardiac dysfunction, particularly very low ejection fraction, are more sensitive to LAST and also more prone to receive 'stacked' injections (with resulting elevated LA tissue concentrations) because of slowed circulation time.
- Consider using a pharmacologic marker and/or test dose, for example, epinephrine 5 μg/mL of LA. Know the expected response, onset, duration, and limitations of a "test dose" in identifying intravascular injection.
- Aspirate the syringe prior to each injection while observing for blood.
- Inject incrementally, observing for signs and querying frequently for symptoms of toxicity between each injection.

DETECTION (BE VIGILANT)

- Use standard American Society of Anesthesiologists (ASA) monitors.
- Monitor the patient during and after completing the injection, as clinical toxicity can be delayed up to 30 mins (or longer after tumescent procedures).
- Consider LAST in any patient with altered mental status, neurologic symptoms, or cardiovascular instability following a regional anesthetic.
- Central nervous system signs (may be subtle or absent)
  - Excitation (agitation, confusion, muscle twitching, seizure)
  - Depression (drowsiness, obtundation, coma, apnea)
  - Nonspecific (metallic taste, circumoral numbness, diplopia, tinnitus, dizziness)
- Cardiovascular signs (often the only manifestation of severe LAST)
- Initially may be hyperdynamic (hypertension, tachycardia, ventricular arrhythmias), then
  - Progressive hypotension
  - Conduction block, bradycardia, or asystole
  - Ventricular arrhythmia (ventricular tachycardia, torsades de pointes, ventricular fibrillation)
- Sedative hypnotic drugs reduce seizure risk, but even light sedation may abolish the patient's ability to recognize or report symptoms of rising LA concentrations.

TREATMENT

- Timing of lipid infusion in LAST is controversial. The most conservative approach, waiting until after ACLS has proven unsuccessful, is unreasonable because early treatment can prevent cardiovascular collapse. Infusing lipid at the earliest sign of LAST can result in unnecessary treatment because only a fraction of patients will progress to severe toxicity. The most reasonable approach is to implement lipid therapy on the basis of clinical severity and rate of progression of LAST.
- There is laboratory evidence that epinephrine can impair resuscitation from LAST and reduce the efficacy of lipid rescue. Therefore it is recommended to avoid high doses of epinephrine and use smaller doses, for example, 1 μg/kg, for treating hypotension.
- Propofol should not be used when there are signs of cardiovascular instability. Propofol is a cardiovascular depressant with lipid content too low to provide benefit. Its use is discouraged when there is a risk of progression to cardiovascular collapse.
- Prolonged monitoring ($\geq$ 12 hrs) is recommended after any signs of cardiac toxicity because cardiovascular depression due to LAs can persist or recur after treatment.

The ASRA Practice Advisory on Local Anesthetic Toxicity is published in the society's official publication *Regional Anesthesia and Pain Medicine*, and can be downloaded from the journal Web site at www.rapm.org:

Neal JM, Weinberg GL, Bernards CM, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med* 2010;35:152-161.