

# A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations To Whom It May Concern

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**Abstract:** Local anesthetic systemic toxicity (LAST) occurrence may cross several medical specialties. In 2010, the American Society of Regional Anesthesia and Pain Medicine (ASRA) published the first algorithm on LAST management, introducing the use of lipid emulsion (ILE) treatment. In the present study, we retrieved the cases of LAST published between ASRA guidelines dissemination and March 2014. We analyzed the reported clinical manifestations of LAST, characteristics of affected patients, onset time of toxicity, and clinical setting. We also focused on the treatment measures that were applied in the different cases, especially on the use of ILE and adherence to ASRA recommendations. Despite the limits of a review of case reports, the present study calls attention to the insidious nature of LAST, especially its atypical manifestations, and shows that ILE may currently be underadministered in daily clinical practice, especially in nonanesthesiology practice.

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Local anesthetic systemic toxicity (LAST) is a potentially fatal complication of regional anesthesia affecting primarily the central nervous (CNS) and the cardiovascular (CV) systems. The potential toxicity of local anesthetic (LA) drugs was evident shortly after cocaine was introduced in the second half of the 18th century.<sup>1</sup> The understanding of this phenomenon grew in parallel with the empirical use of new drugs, such as procaine, which were introduced in the effort to mitigate cocaine toxicity as well. More recently, the editorial of Albright<sup>2</sup> in 1979 called attention to the need for study of LAST. In the following decades, awareness of the phenomenon increased as a rising number of clinical cases and laboratory investigations of LAST were reported in the literature. In 2010, the American Society of Regional Anesthesia and Pain Medicine (ASRA) published an algorithm for prevention and treatment of LAST.<sup>3,4</sup> This document focused also on the use of a microemulsion of triglycerides and phospholipids (ILE, most commonly Intralipid) in the management of severe LAST. Indeed, ILE infusion is particularly valuable in severe LAST and has also been proven effective in the treatment of severe poisoning from several lipophilic drugs.<sup>5,6</sup> Available clinical information on LAST is mainly through case reports or series

because randomized trials are not reasonable. Di Gregorio et al<sup>7</sup> first reviewed the cases of LAST published between 1979 and 2009, concluding that 40% of the published cases had clinical features that fell outside the standard description of LAST and that we lack a precise and accurate portrayal of the clinical spectrum of LAST and its optimal treatment.

The latter review provided the basis for comparison with the present work. The aim of the present study was to analyze the impact of ASRA guidelines on the management of LAST, especially in terms of toxicity detection and treatment, particularly focusing on ILE use. Moreover, we wanted to assess the interest in this topic, as reflected in the amount of peer-reviewed clinical cases of LAST recently published.

## METHODS

Reports of LAST published between March 2010 and March 2014 providing clinical data on LAST development and treatment were included in this study. A literature search was performed through PubMed, Scopus, and ScienceDirect. Search terms included the following: *LAST, local anesthetic toxicity, lidocaine, bupivacaine, chirocaine, mepivacaine, ropivacaine, prilocaine, articaine, cardiac arrest, seizures, neurologic toxicity, cardiac toxicity, diagnosis, treatment, lipid emulsion, ILE, resuscitation*. Retrieved articles' references were also searched. Any type of publication was searched in English, French, and German languages because these could be easily accessed by the investigators. Through this search, we retrieved case reports, case series, letters to the editor, and reviews in English and French languages. Reports providing incomplete description of the type of LA, site of administration, timing of LAST, and reported signs and symptoms were excluded, as well as data available only in abstracts. We made no attempt to obtain missing data from authors. The following data were retrieved from the included reports: patient's age and comorbidities, clinical setting, surgical procedure, health care professional administering the LA (anesthesiologist vs nonanesthesiologist), type of anesthetic procedure, administered LA, dosage and concentration, LAST onset time, signs and symptoms of toxicity. Treatment of LAST, ILE use, dosage, time of administration, and outcome of LAST were searched as well.

## RESULTS

### Setting of LAST

We identified 67 separate LAST events reported in 54 different articles<sup>8–59</sup> between March 2010 and March 2014. Fifty cases of toxicity occurred after a single injection of LA, whereas in 8 cases, signs and symptoms arose during continuous infusion of LA.<sup>35,38,40,41,54,55,58</sup> In 7 cases, toxicity followed topical administration of LA without needle injection.<sup>26,45,47,48,50,57,59</sup> Finally, in 2 cases, LAST followed direct unintentional LA intravascular injection through a venous cannula.<sup>14,42</sup>

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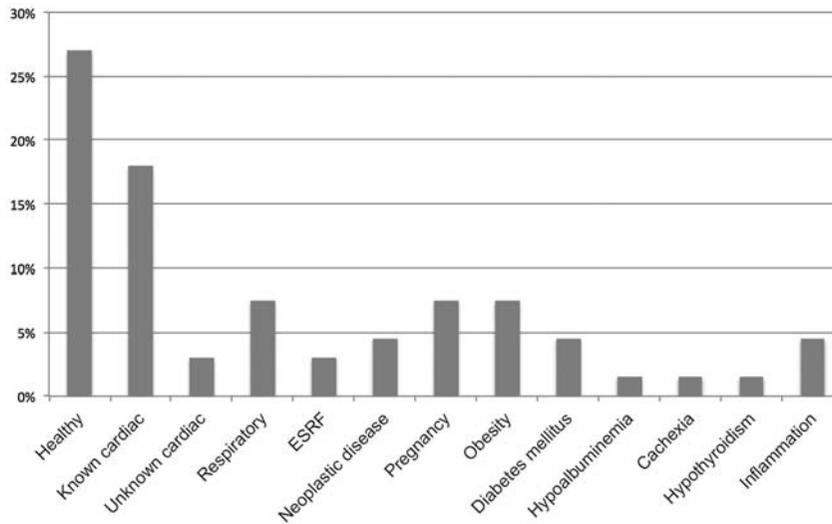


FIGURE 1. Bar chart showing the prevalence of different morbid conditions in the considered patients. ESRF indicates end-stage renal failure.

Proper regional anesthesia was performed in 78% of those 50 patients receiving a single injection of LA. Among these cases, the most frequently reported technique associated with LAST was interscalene block (23%), followed by epidural/caudal block (16%) and dorsal penile block (13%). Instead, the remaining 22% of those cases received a single LA injection for local field infiltration anesthesia, and this was administered by nonanesthesiologists in nearly any case.

In 54 cases, the authors clearly reported the type of practitioner who administered the LA. Anesthesiologists or anesthesiology trainees were involved in most of the cases (65%), whereas the remaining 35% involved dentists (n = 3),<sup>20,23,49</sup> dermatologists (n = 2),<sup>48,50</sup> surgeons (n = 4),<sup>13,51,58,60</sup> general practitioners (n = 2),<sup>30</sup> a nephrologist (n = 1),<sup>46</sup> a pediatrician (n = 1),<sup>39</sup> a nurse (n = 1),<sup>14</sup> a cardiologist (n = 1),<sup>10</sup> or unspecified operators.

With regard to the setting of LAST, 69% of the events occurred in an operating room.<sup>8-10,12-22,24,25,27-29,31-34,36-38,40-43,51-58,60,61</sup> Twelve percent of the cases developed in an office,<sup>30,39,45,46,48-50</sup> whereas another 4% occurred in other locations, including the patient's home. Finally, 15% of the authors did not specify the hospital setting where the LA was administered.

**Patient Characteristics**

Patients' ages ranged between 2 days and 83 years. Twenty percent of the patients were older than 60 years, 30% were younger than 16 years, and 22% were in their first year of life. Approximately 45% of the patients were female.

Twenty-seven percent of the events developed in otherwise healthy individuals. Patients' comorbidities are summarized in Figure 1.

**Local Anesthetics**

Overall, lidocaine and ropivacaine were used in 33% of the cases each (Fig. 2). With regard to regional anesthesia procedures (ie, excluding local field anesthesia), ropivacaine was the most frequent LA (48% of the cases), followed by bupivacaine (23%) and lidocaine (22%). A combination of different LA was reported in 9 cases during single-shot regional anesthesia,<sup>16,19,22,25,34,36,37,44</sup> and lidocaine was included in 8 of these cases. Overall, adrenaline was added to the anesthetic mixture in 8 cases.<sup>8,16,23,27,32,35,37,49</sup>

With regard to local field anesthesia, lidocaine was used in nearly 80% of the cases, occasionally combined with other

LAs. Articaine,<sup>49</sup> propitocaine,<sup>20</sup> and bupivacaine<sup>38</sup> were used alone in 1 case each.

**Nerve Localization and Safety Measures**

The adoption of ultrasound guidance (UGRA) and electrical stimulation (ENS) for nerve localization during regional anesthesia is summarized in Figure 3, as well as the use of intermittent aspiration. Eleven (16%) cases reported the use of UGRA.<sup>19,25,29,32,33,35,51,53,55</sup> Fifteen (22%) practitioners adopted ENS,<sup>12,16,22,24,29,31,41,44</sup> whereas intermittent aspiration before injection was reported in 22 cases of LA administration for peripheral nerve block.<sup>8,11,15,16,18,19,22,24,25,27,31-33,36,38,41,43,46,58</sup> Finally, only 1 author reported on the concomitant use of ultrasound, ENS, and intermittent aspiration<sup>29</sup> in a patient who developed toxicity 10 minutes after LA injection.

**Timing of LAST Injection**

Many authors adopted a non-numeric description when addressing the rapid onset of signs and symptoms of toxicity. In case

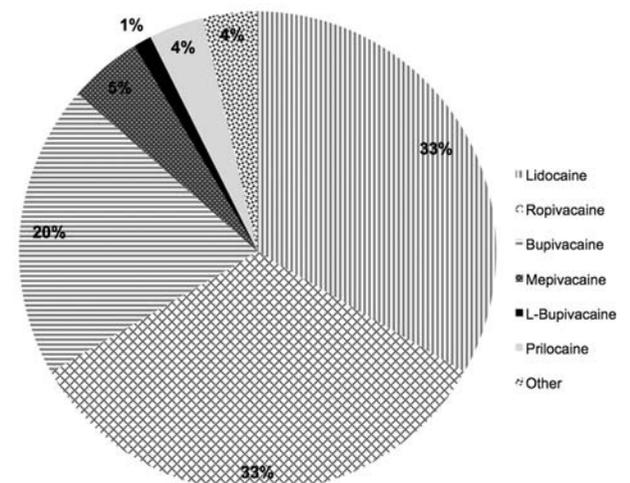
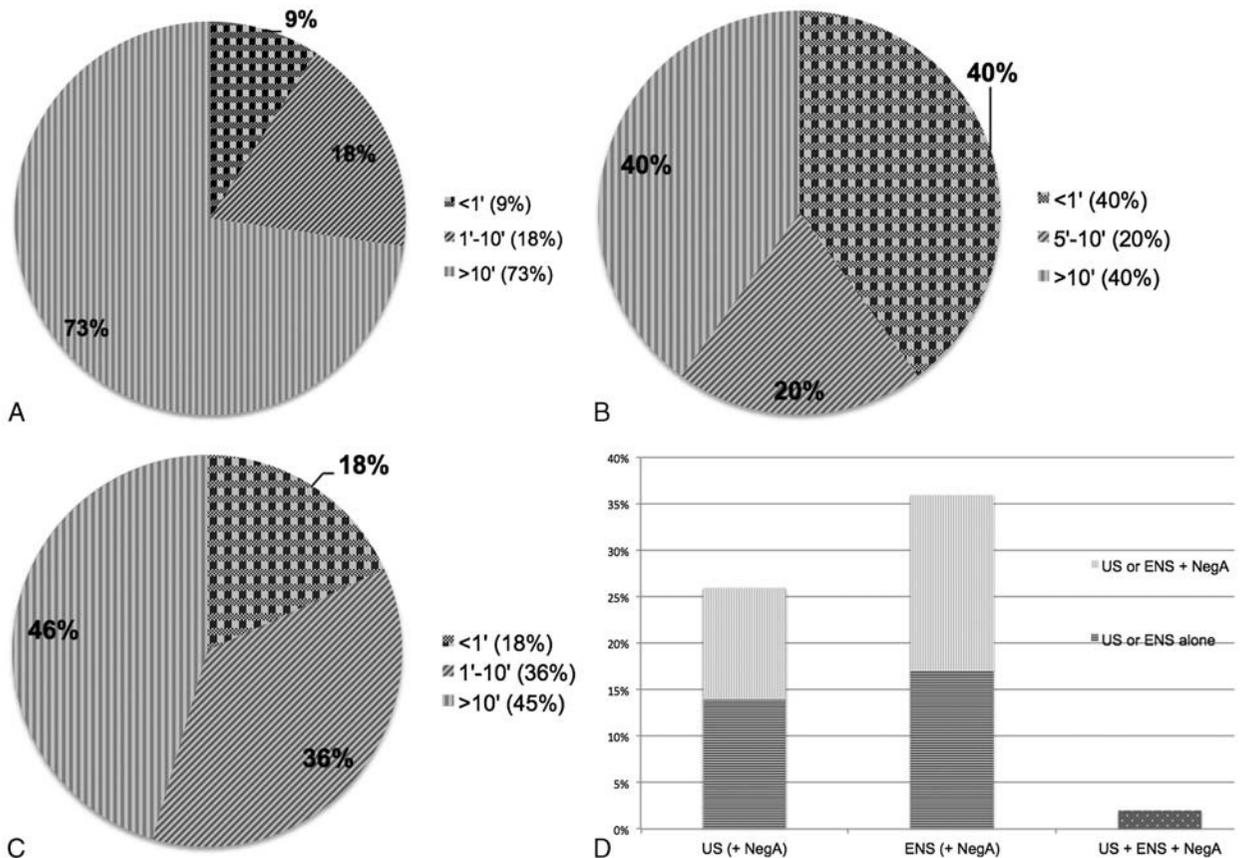


FIGURE 2. Cake diagram showing the proportion of local anesthetic drugs used in the considered cases.



**FIGURE 3.** Onset time of LAST according to the modality of nerve localization. A, After single-shot ultrasound-guided regional anesthesia. B, After single-shot regional anesthesia performed under electrical nerve stimulation guidance. C, After single-shot regional anesthesia performed with intermittent negative aspiration before injection. D, Bar chart showing the proportion of included cases adopting different methods for nerve localization and intermittent negative aspiration. US indicates ultrasound; ENS, electrical nerve stimulation; NegA, intermittent negative aspiration.

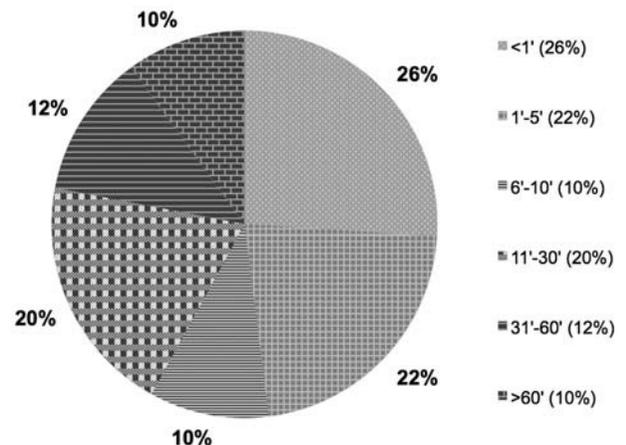
of “immediate” or “rapid” onset, we assumed that it occurred within 1 minute (<1 minute) because direct intravascular injection is the most common cause and 60 seconds is a typical circulation time.<sup>7</sup> The distribution of onset time intervals after a single injection of LA is shown in Figure 4. We did not include in this analysis the 2 cases of direct intravenous injection of LA. We collected 8 cases in which LAST appeared during continuous infusion of LA. In those patients, symptoms developed hours or even days after having commenced the administration.

### Topical Administration of LA

We identified 7 cases of LAST after topical administration of LA, most commonly in nonanesthesia settings. Five of these were pediatric patients, and 4 were younger than 4 years. Two cases followed an overdose of cutaneous lidocaine/prilocaine gel<sup>48,50</sup>; 1 case developed after accidental ingestion of 40 mg/kg of lidocaine in a 2-year-old child, prescribed for a painful stomatitis aphthosa<sup>59</sup>; and another case developed soon after the oral, esophageal, and tracheal administration of almost 500 mg of lidocaine.<sup>45</sup> The latter was the only case in this group where toxicity manifested almost immediately after LA administration. In the remaining cases, signs and symptoms developed at least 20 minutes after exposure.

### Clinical Spectrum of LAST

The most common signs and symptoms of LAST involved the CNS and the CV system. Isolated CNS toxicity occurred in 50% of the cases, combined CNS and CV toxicity were reported in 36% of the cases, and 14% presented isolated CV toxicity.



**FIGURE 4.** Cake diagram showing the included cases according to the onset time of LAST after single-shot regional anesthesia.

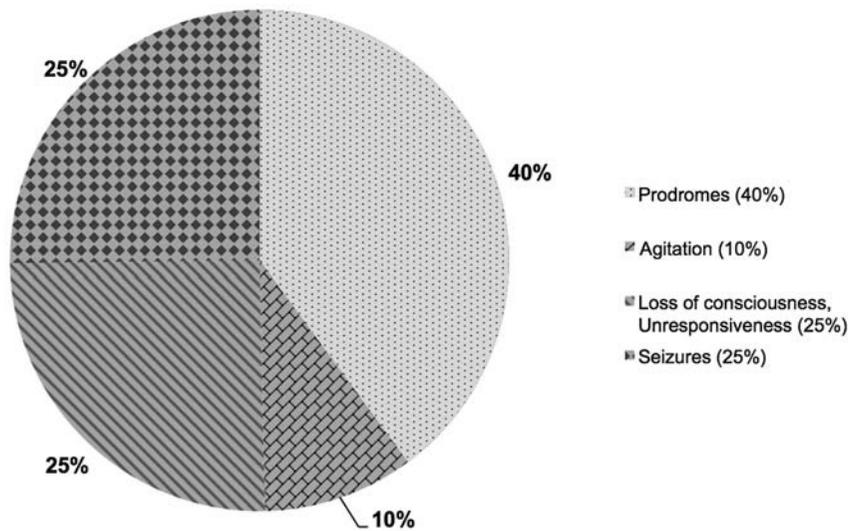


FIGURE 5. Cake diagram showing the prevalence of different neurological manifestations of toxicity in the included cases.

When combined, symptoms progressed from CNS to CV manifestations in 83% of the patients. Conversely, an opposite pattern of toxicity concerned the remaining 17% of the cases. Furthermore, 5 cases presented methemoglobinemia after administration of lidocaine and prilocaine.<sup>9,20,23,48,50</sup>

### Neurologic Signs of Toxicity

The most common sign of CNS toxicity was seizure, which occurred in 36 cases (54%), accounting for 25% of CNS manifestations (Fig. 5). Some minor CNS abnormalities (ie, other than seizure, agitation, and loss of consciousness) such as confusion, dizziness, tinnitus, dysgeusia, hallucinations, slurred speech, gait problems, limb twitching, extremity paresthesia, intention tremor, hypotonia, and facial sensorimotor and eye movement abnormalities were defined as prodromal manifestations of toxicity when they occurred either alone or before major signs of toxicity. Considered together, prodromes were the most frequent CNS manifestation of LAST (40%). In 9 of these cases, there were no further manifestations of LAST, whereas in 19 cases, toxicity progressed to major CNS or CV manifestations, such as seizures, loss of consciousness, arrhythmias, or cardiac arrest.

### CV Signs of Toxicity

Cardiovascular toxicity occurred in 32 (55%) of the patients. Of these cases, 23 were associated with CNS manifestations, whereas isolated CV toxicity occurred in 9 patients. Eight of these patients with isolated CV toxicity developed LAST during general anesthesia or while receiving propofol, fentanyl, or other sedatives. The spectrum of CV signs of toxicity is summarized in Figure 6.

### Treatment of LAST

Conventional treatment was herein defined as any pharmacological treatment other than ILE. Advanced cardiovascular measures were adopted in the case of cardiac arrest or life-threatening ventricular arrhythmias, and they altogether were the most frequent treatment adopted in these patients, accounting for 43% of the therapeutic measures. The spectrum of the adopted therapeutic measures is shown in Figure 7.

Lipid emulsion was used in 23 patients.<sup>8,10,12-17,19,24,25,29,32-35,37,40,45,46,51,59,61</sup> In 13 cases, ILE was used after the conventional treatment was started, whereas in the remaining 10 cases,

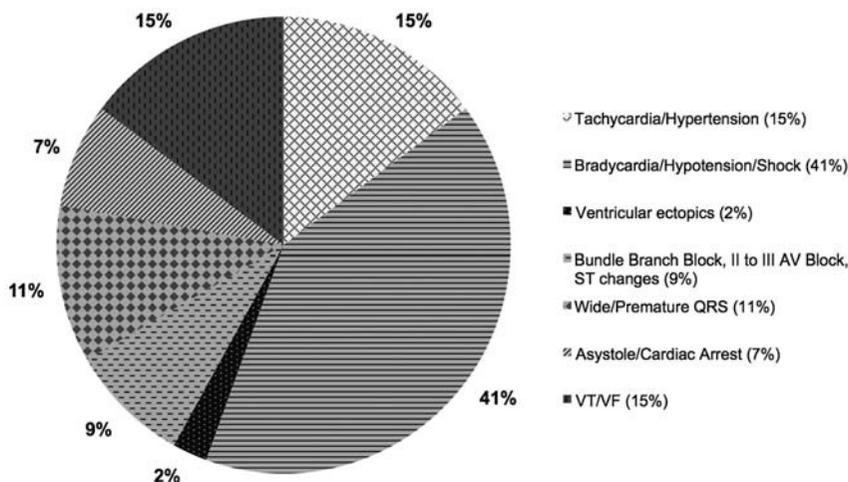
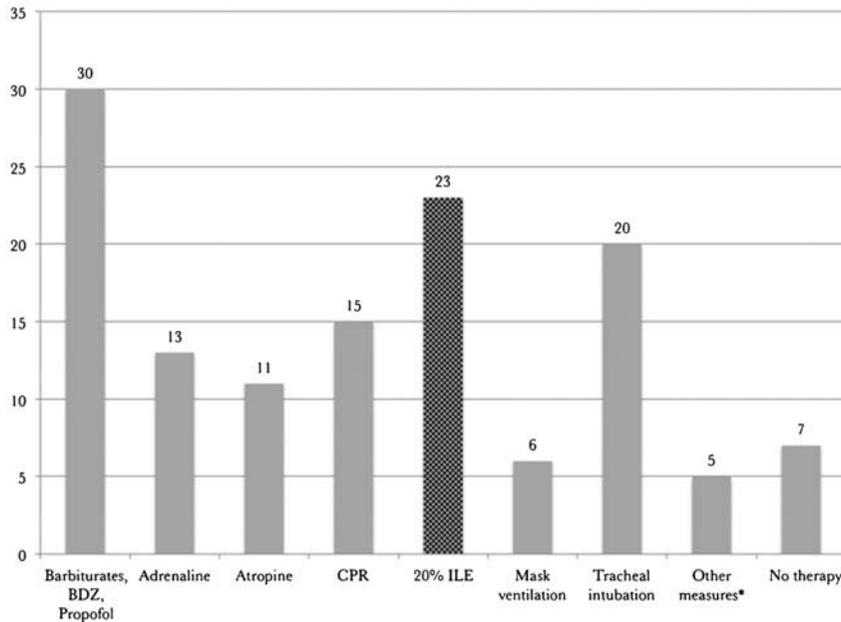


FIGURE 6. Cake diagram showing the prevalence of different cardiovascular manifestations of toxicity in the included cases. AV indicates atrioventricular; ST, ST tract; VT/VF, ventricular tachycardia/ventricular fibrillation.



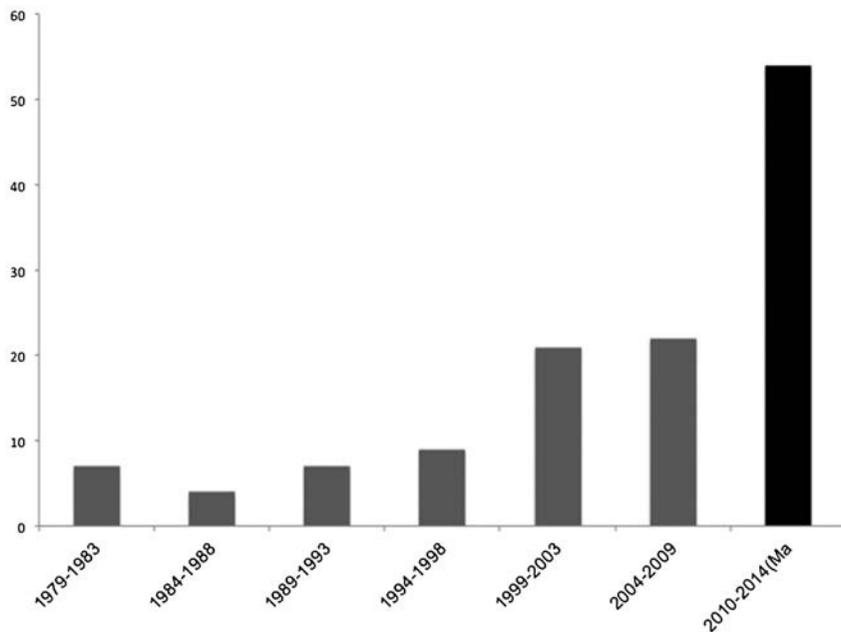
**FIGURE 7.** Bar chart showing the treatment measures adopted in the included cases of LAST. BDZ indicates benzodiazepines; CPR, cardiopulmonary resuscitation. \*Other measures: 3 patients received muscle relaxant to stop convulsions, 1 patient was treated with amiodarone for arrhythmias, and 2 patients needed extracorporeal membrane oxygenation.

ILE represented the first therapeutic measure, being the sole treatment in 7 patients. With regard to ILE use, 6 patients were given ILE according to ASRA guidelines, whereas a liberal use of lipid was adopted in 9 cases. We defined liberal use of ILE as a range of doses or a mode of administration not included in the recommended limits. In particular, ILE was underdosed in half of these cases, whereas in other cases, the initial lipid bolus was given slowly (ie, in 4–30 minutes). Furthermore, in 8 cases, the authors did not provide any details on the modality of ILE administration. No adverse events were described after lipid administration.

Thirty-eight (66%) of the patients did not receive ILE. Ten of these cases occurred in a non-operating room setting (office, cardiac catheterization laboratory, outpatient clinic), whereas nonanesthesiologists were involved in at least 13 cases.

**Patient Outcomes**

Fifty-three studies reported on the outcome of LAST in 59 patients. Ninety percent of these patients recovered completely, and 6 (10%) died.<sup>28,35,38,41,49,58</sup> Only 1 of these 6 patients was



**FIGURE 8.** Bar chart showing the absolute number of cases on LAST published in different years. Studies published between 1979 and 2009 were retrieved by Di Gregorio et al.<sup>7</sup>

treated with ILE and died because of severe cardiac toxicity that occurred after prolonged and repeated administration of multiple LA.<sup>35</sup>

Among the 6 patients who explicitly received ILE according to guidelines, 4 patients recovered promptly after ILE administration,<sup>8,33,37,61</sup> 1 patient recovered within 30 minutes,<sup>29</sup> and another patient recovered immediately from hazardous cardiac toxicity but experienced neurotoxic recurrences despite continuous ILE infusion.<sup>13</sup> Also those patients treated with ILE at a liberal regimen recovered promptly in the reported cases.

## DISCUSSION

The present review continued previous work by Di Gregorio et al<sup>7</sup> on the study of LAST through the analysis of published clinical cases, with a focus on treatment and patient outcomes. Across time, particularly after dissemination of the ASRA guidelines, publication of LAST cases has grown, despite increasing journal publication biases for case reports (Fig. 8), and this review allows extrapolation of several considerations from the case analysis.

### Patients' Characteristics

Patients' age ranged widely in this review, but 22% of the patients were younger than 1 year, whereas newborns account for only 1% of the western population.<sup>62</sup> There is no evidence on age as an independent risk factor, but this finding suggests a possibly higher incidence of LAST in very young patients. However, these data may be not representative because LAST in pediatric patients might have raised relatively more attention. Nonetheless, deep sedation is common during regional anesthesia in children and may suppress prodromal symptoms of LAST or induce hypoventilation leading to hypoxia and respiratory acidosis, eventually predisposing to toxicity.<sup>63</sup> Muscle tissue is the main site of LA redistribution,<sup>64</sup> and the lower proportion of muscle tissue in pediatric, malnourished, and cachectic patients might reduce their accumulation capacity of LA and their threshold for toxicity.<sup>38,65</sup> Comorbidities such as renal, liver, or heart failure may also play a crucial role in predisposing the patient to LAST.<sup>66</sup> In the present series, though, 27% of the patients were otherwise healthy, confirming that LAST occurs also in patients with few or no comorbidities and the difficulty of predicting a single patient's predisposition to LAST.

### Timing

Interestingly, late-onset toxicity was more frequent than immediate toxicity (Fig. 4). On a temporal basis, Di Gregorio et al<sup>7</sup> defined as *atypical* LAST events arising 5 minutes and more after LA administration, and this regarded 52% of the events in this review compared with the 25% of the previous 30 years.<sup>7</sup> This finding might be explained by the increased attention to LAST, but, importantly, it may reflect the evolution of regional anesthesia practice. The growing use of UGRA may have reduced the rate of vascular puncture, principal cause of immediate toxicity,<sup>65,67</sup> and the increased proportion of delayed toxicity in this review might reflect this trend (Fig. 3). Nonetheless, UGRA is unable to completely prevent LAST because it is operator dependent and several mechanisms are involved in toxicity, such as the injection site, the patient's characteristics, the dose of LA, and its pharmacokinetics, which may play a major role especially in late-onset toxicity.<sup>66,67</sup>

### Setting of LAST

Even topical application of LA can lead to severe toxicity. Most of these case types followed overdose of transcutaneous or

oral LA formulations, whereas 1 case occurred after lidocaine gables for throat inflammation, emphasizing the role of local inflammation in increased LA absorption. Therefore, any scenario in which LA is used is a potential setting for LAST. Indeed, nearly 35% of the cases referred to LAST in nonanesthesia practice probably also because these cases raised relatively more attention than LAST in anesthesia, which may be underreported and unpublished. Nonetheless, nonanesthesiologists might be unfamiliar with LA use, LAST, and ASRA guidelines and thus deserve better education on this topic. It is the anesthesiologist's task to provide clear information and education on LAST and its management.

### LAST in Regional Anesthesia

Central block was the most common technique involved in LAST in the period 1979–2009,<sup>7</sup> whereas in this review, interscalene block prevailed. This could simply reflect the frequency of this block in clinical practice; conversely, this procedure could be considered a relative risk for developing toxicity because of the rich vasculature of the interscalene groove.<sup>41</sup>

Ropivacaine, first choice in clinical practice,<sup>68</sup> was the LA most frequently associated with LAST after single-shot injection, whereas lidocaine, alone or combined with other LAs, was the second most common, pointing out that none of these drugs is completely safe and that attention must be paid with all LAs.

### Clinical Manifestations

Central nervous system symptoms dominated the spectrum of LAST manifestations. Overall, seizures and loss of consciousness were the most frequent CNS manifestations, and these findings are consistent with the data from the past 3 decades.<sup>7</sup> Interestingly, reports of prodromal neurological symptoms increased from 18% (1979–2009) to 40% (past 4 years) probably because of increased attention to early detection and diagnosis of LAST after ASRA guidelines publication.

When CNS and CV symptoms were combined, they most commonly progressed from CNS to CV abnormalities, but this was not the rule, confirming that toxicity may take different forms.

Di Gregorio et al defined isolated CV manifestations of LAST as clinically *atypical*. Most of these cases had a delayed onset and, importantly, most of them occurred during or immediately after general anesthesia. This aspect may explain the lack of neurological manifestations, possibly unnoticed or covered by CNS depressor medications.<sup>69</sup>

Unfortunately, there was lack of data on the monitoring established during block performance. Without monitoring, early manifestations of toxicity (eg, hemodynamic signs) might go unnoticed.

### Treatment

Supportive conventional treatment prevailed across the studies. Lipid was underadministered in the reported cases, often not adhering to ASRA recommendations. Nonetheless, ILE was effective and its increasing use in the literature likely reflects clinical trends. Several practitioners administered ILE as rescue medication after failure of conventional treatment or patient deterioration, whereas others adopted it as first-choice medication, probably considering it a mechanisms-based treatment. Fetiplace et al<sup>64</sup> recently showed that treatment with ILE in a rat model of LAST exerts a greater binding effect on LA at a higher blood concentration of LA and at earlier time points. These results comport the presumed importance of prompt ILE administration when LAST occurs.

## Limitations

The most important limitation of this review is reliance solely on case reports, which are unstylish but still useful sources of clinical information.<sup>70</sup> Nonetheless, these reports are heterogeneous and hardly comparable, baseline values are often missing, clinical settings are always different, and the reports' reliability remains suspect. Publication bias is certainly a strong factor in these data because authors preferably publish cases with positive outcomes and unusual characteristics and minor manifestations are probably less recognized and reported. Furthermore, perception of LAST as something “normal”—especially in anesthesia practice—may lead to a publishing fatigue in which authors do not write and editors do not publish LAST cases, eventually inducing a “reverse publication bias.”

## CONCLUSIONS

The unpredictability of LAST mandates mindful practice establishing the entire preventive measures available to reduce the likelihood of LAST and for vigilance to detect signs of toxicity. Unfortunately, case reports will most likely continue to be the main source of clinical information on LAST, and it is important that authors keep sharing their experience on this matter. Although LAST is an issue not only in anesthesia, the anesthesiologist must promote education on the topic. Dedicated ASRA guidelines are available<sup>3</sup> but may remain unknown to many nonanesthesiologists.<sup>71</sup> Last, ILE and a plan for LAST management should be promptly available in any facility where LAs are used.

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