

Prognostic Utility of Initial Lactate in Patients With Acute Drug Overdose: A Validation Cohort

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Study objective: Previous studies have suggested that the initial emergency department (ED) lactate concentration may be an important prognostic indicator for in-hospital mortality from acute drug poisoning. We conduct this cohort study to formally validate the prognostic utility of the initial lactate concentration in a larger, distinct patient population with acute drug overdose.

Methods: This observational, prospective, cohort study was conducted during 5 years at 2 urban teaching hospitals. Consecutive adult ED patients with acute drug overdose had serum lactate levels tested as part of clinical care. The primary outcome was inpatient fatality. Receiver operating characteristics were plotted to determine optimal cut points, test characteristics, area under the curve, odds ratios, and 95% confidence intervals (CIs).

Results: Of 3,739 patients screened, 1,406 were analyzed (56% women; mean age 43.1 years) and 24 died (1.7%). The difference in mean initial lactate concentration was 5.9 mmol/L (95% CI 3.4 to 8.1 mmol/L) higher in patients who died compared with survivors. The area under the curve for prediction of fatality was 0.85 (95% CI 0.73 to 0.95). The optimal lactate cut point for fatality was greater than or equal to 5.0 (odds ratio 34.2; 95% CI 13.7 to 84.2; 94.7% specificity). Drug classes for which lactate had the highest utility were salicylates, sympathomimetics, acetaminophen, and opioids (all area under the curve ≥ 0.97); lowest utility was for diuretics and angiotensin-converting enzyme inhibitors.

Conclusion: Initial lactate concentration is a useful biomarker for early clinical decisionmaking in ED patients with acute drug overdose. Studies of lactate-tailored management for these patient populations are warranted. [Ann Emerg Med. 2018;■:1-8.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Importance

Drug poisoning has been the leading cause of injury-related fatality in the United States since 2008.¹ For the first time, drug overdose deaths surpassed 50,000 in a single year in 2015.² There were more than 2.7 million exposures reported to poison control centers in the United States in 2016,³ which substantially underestimates the true exposure prevalence.⁴ Thus, clinical research on drug overdose screening and assessment is necessary to curtail the increasing drug overdose epidemic, especially in frontline health care settings such as the emergency department (ED). There are currently no existing vital sign parameters or clinical risk scores proven to predict in-hospital mortality in poisoned patients. Recently, it was shown that cardiac biomarkers may predict overdose mortality⁵; however, only a limited subset of this population is routinely tested with such biomarkers.

Background

Lactate is a metabolic byproduct of anaerobic metabolism and is therefore produced by most tissues in the human body. Lactate is rapidly cleared by the liver, with some additional clearance by the kidneys under normal conditions.⁶ Elevated concentrations of serum lactate occur in conditions that cause tissue hypoxia or hypoperfusion (type A), as well as other pathophysiologic conditions (type B) not related to tissue hypoxia. Regardless of the cause of elevated serum lactate concentration, it is a useful prognostic indicator in a variety of clinical circumstances.⁷⁻¹⁰ However, there are conflicting reports about the utility of lactate, specifically in the setting of acute drug overdose,^{11,12} which leaves the prognostic indicator utility of lactate an open question. Furthermore, there are no current guidelines for the use of lactate-tailored therapy to guide management of poisoned patients. We conducted a longitudinal analysis on a larger distinct

Editor's Capsule Summary*What is already known on this topic*

Emergency department (ED) lactate concentration may be an important prognostic indicator for in-hospital mortality from acute drug poisoning.

What question this study addressed

Can the lactate concentration obtained at ED presentation identify poisoned patients at higher risk for death?

What this study adds to our knowledge

The optimal lactate cut point to predict death was 5.0 mmol/L and performed best for salicylates, sympathomimetics, acetaminophen, and opioids.

How this is relevant clinical practice

An elevated lactate concentration can identify acutely poisoned patients with increased risk of death, but this study could not determine to what extent lactate concentration improves care.

sample of patients to formally confirm and validate the prognostic utility of the initial lactate concentration in patients with acute drug overdose.

Goals of This Investigation

We aimed to assess the prognostic utility for the initial serum lactate concentration to predict inpatient mortality in ED patients with acute drug overdose. We anticipated that precise cut points would have clinical utility to provide high predictive value for in-hospital mortality. Furthermore, we hypothesized that initial serum lactate concentration would be significantly higher in patients who died, and would have variable utility with different optimal cut points for specific drug classes.

MATERIALS AND METHODS**Study Design and Setting**

This observational, prospective, cohort study was performed during 5 years (2009 to 2013) at 2 urban teaching hospitals. The EDs at these hospitals have a combined annual visit volume in excess of 150,000 and are staffed 24 hours per day with board-certified emergency physicians and intensivists. The study protocol was approved by the institutional review board for all participating institutions, with a waiver of informed consent.

Selection of Participants

The study population was consecutive adults who present to the ED with acute drug overdose. The screening, inclusion, and exclusion criteria have been previously described.^{13,14} Briefly, patients were included who met both of the following criteria: acute presentation (within 24 hours of exposure) and suspected overdose (ie, drug dose sufficient to cause symptoms or any prescription drug exposure greater than its therapeutic dose). Exclusion criteria were the following: alternative diagnosis (eg, trauma, infection), chronic presentation (ie, not meeting acute criteria above), nondrug overdose (eg, plant), exposures limited to dermal or inhalational routes only (ie, trivial exposures), prisoners, younger than 18 years, anaphylaxis, patients with incomplete data (ie, left against medical advice, transferred to an outside institution, or otherwise eloped from the hospital), out-of-hospital cardiac arrest, and patients with do-not-resuscitate orders. Furthermore, patients without lactate data (ie, for whom clinicians did not test serum lactate as part of routine care) were excluded from data analysis.

Methods of Measurement

Data collection from the medical chart occurred in accordance with accepted guidelines for valid medical chart abstraction, including training of abstractors blinded to study objectives and formal interrater reliability of a random sampling of 10 test charts before mass data abstraction (initial ED lactate concentration and in-hospital mortality assessed; 100% agreement; Cohen's $\kappa=1.0$).¹⁵ Clinical data included demographics, drug exposures involved in overdose, vasopressor administration in-hospital, and initial serum bicarbonate concentration, all of which were obtained from medical records and deidentified. Serum toxicology (acetaminophen, salicylate, ethanol, and, rarely, selected drug concentrations on an individual basis) and urine toxicology screens (most commonly including cannabinoids, amphetamines, opioids, benzodiazepines, cocaine metabolite, barbiturates, phencyclidine, and tricyclics) were performed according to clinician judgment as part of routine clinical management. In addition, exposures were separated into clinically relevant drug classes by 2 of the authors with board certification in medical toxicology (A.M. and R.H.). β -Adrenergic antagonists and calcium channel blockers were consolidated for lactate analysis because the prognosis, antidotal therapy, and lactate pathophysiology are essentially the same for these 2 groups.

Blood for a venous serum lactate concentration was drawn at the bedside for all control patients. The decision to measure serum lactate concentration was made at the discretion of the treating physician as part of clinical care,

and results were readily available to the clinicians in real time. Only the initial ED lactate concentration was used in the analysis for receiver operating characteristics (ROC) analysis; as such, subsequent lactate concentrations, even if changed or abnormal, were not included in the analysis. Serum was analyzed with amperometric electrodes with enzymatic membranes and run with Radiometer ABLTM 700 analyzers (Brønshøj, Denmark). According to the manufacturer, the range of normal values for venous serum lactate concentration is 1.0 to 2.5 mmol/L.

Outcome Measures

The primary outcome was in-hospital (ie, ED or inpatient) all-cause fatality. As outlined above, patients with do-not-resuscitate orders were excluded from analysis. The secondary outcome was the occurrence of shock, defined as treatment with vasopressors (ie, not defined by vital signs) at any point during the ED or hospital stay.

The study protocol was previously described.^{13,14} Briefly, subjects were prospectively followed to hospital discharge with data collection from included electronic medical records, paper medical records, and consultation records. Hospital medical record follow-up for all patients was performed by research assistants trained in medical abstraction and recorded with standardized data collection forms according to established guidelines.¹⁵ Results (from electronic physician notes, laboratory records, and discharge summaries) were prospectively available to the study investigators. Patients discharged from the hospital had no further follow-up.

Primary Data Analysis

Sample size was fixed a priori according to previous enrollment of the parent studies.¹³⁻¹⁵ ROC were plotted to determine optimal lactate cut points, along with test characteristics (sensitivity/specificity), area under the curve (AUC), odds ratios (ORs), and 95% confidence intervals (CIs). The AUC of the ROC curve reflects the overall accuracy and the separation performance of lactate as a biomarker, and can be readily used to compare different biomarker combinations or models. When appropriate, χ^2 (with 2-tailed Fisher's exact test when appropriate) and *t* test were calculated for categorical and continuous variables, respectively, with 5% α (2-tailed). Collinearity between bicarbonate and lactate was assessed with the variance inflation factor, with a cutoff greater than 5 signaling multicollinearity. Sensitivity analysis of only single drug exposures was performed in which medians and interquartile range of lactates were compared. All statistical analysis was performed with SPSS (version 22.0; IBM, Chicago, IL).

RESULTS

Characteristics of Study Subjects

Of 3,739 patients screened, 2,333 met exclusion criteria, leaving 1,406 patients for analysis. Patients were excluded for the following reasons: missing lactate level (1,487), younger than 18 years (376), missing outcomes (278), alternate diagnoses (141), nondrugs (37), and out-of-hospital cardiac arrest (14). Patients were predominantly women (56%) with mean age 43.1 years; 58.2% were white, 19.8% black, 6.5% Asian, and 15.5% other; and ethnically, patients were 28.9% Latino or Hispanic. In the 1,406 patients whose data were analyzed, the primary outcome occurred in 24 (1.7%), and the secondary outcome in 54 (3.9%). Of 1,487 patients with missing lactate data, there were 2 primary outcomes (0.13%) and 4 secondary outcomes (0.26%).

Main Results

Of 1,406 patients analyzed, there were 24 fatalities (1.7%). Mean initial lactate concentration was 2.31 mmol/L (SEM 0.09 mmol/L) overall, 8.1 mmol/L (SEM 1.6 mmol/L) in fatalities and 2.21 mmol/L (SEM 0.08 mmol/L) for survivors (*t* test $P < .001$). The ROC curve for prediction of drug overdose fatality using the initial ED lactate concentration is shown in the [Figure](#). The AUC for prediction of fatality was 0.85 (95% CI 0.73 to 0.97). The optimal lactate concentration cut point for fatality was 5.0 mmol/L (OR 34.2; 95% CI 13.7 to 84.2), which was 70.8% sensitive (95% CI 69% to 73%) and 94.7% specific (95% CI 93% to 96%); the optimal cut point for the occurrence of both primary and secondary outcomes combined (ie, shock or death) was 2.7 mmol/L (OR 7.9; 95% CI 4.5 to 13.9). An initial lactate concentration of 7.5 mmol/L or greater had 23.8% positive predictive value (95% CI 14% to 36%) and less than 2.0 mmol/L had 99.5% negative predictive value (95% CI 98.8% to 99.9%). [Table 1](#) outlines the drug exposures and lactate concentrations of all 24 deaths.

Of 1,406 patients analyzed, 715 (51%) had some type of positive drug screen result as confirmation of exposure. There were 3 drug classes that were significantly associated with fatality, in descending order of incidence: digoxin (21.1%; OR 18.2; $P < .001$); diuretics (16.7%; OR 12.4; $P = .02$), and β -adrenergic antagonists and calcium channel blockers combined (11.9%; OR 10.5; $P < .001$). The highest utility for prediction of fatality by the initial lactate concentration occurred in these drug classes: salicylates (AUC=0.98; 95% CI 0.90 to 1.0; cut point=6.0), sympathomimetics (AUC=0.98; 95% CI 0.95 to 0.99; cut point=7.8), acetaminophen (AUC=0.98; 95% CI 0.95 to 1.0; cut point=10.0), opioids (AUC=0.97; 95% CI 0.94

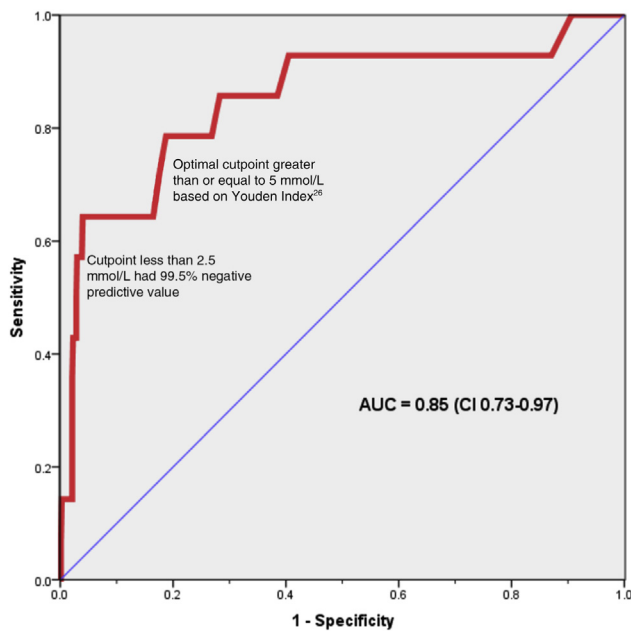


Figure. ROC curve for prediction of drug overdose fatality, using the initial ED lactate concentration. The figure demonstrates the ROC curve of initial ED serum lactate concentration to predict inhospital mortality. The AUC of 0.85 was statistically and clinically significant. This figure demonstrates the ROC curve of initial ED serum lactate concentration to predict in-hospital mortality. The AUC of 0.85 was statistically and clinically significant.

to 0.99; cut point=3.1), digoxin (AUC=0.92; 95% CI 0.78 to 1.0; cut point=2.4), and anticonvulsants (AUC=0.91; 95% CI 0.76 to 1.0; cut point=3.0); lactate concentration had lowest utility for β -adrenergic antagonists and calcium channel blockers (AUC=0.73; 95% CI 0.49 to 0.97; cut point=7.1), diuretics (AUC=0.55; 95% CI 0.20 to 0.89; cut point=1.1), and angiotensin-converting enzyme inhibitors (AUC=0.16; 95% CI 0.01 to 0.31; cut point=0.9). Performing separate analyses for β -adrenergic antagonists (mean lactate difference 2.36; P =NS) and calcium channel blockers (mean lactate difference 4.01; P =NS) separately did not improve utility of lactate in either group (AUC 0.71 and 0.66, respectively). The utility of a lactate concentration could not be assessed for the following drug classes because of absence of deaths in the cohort: lithium, metformin, and statin drugs. The full drug class analysis of the prognostic utility of initial lactate concentration for overdose fatality is summarized in Table 2. A sensitivity analysis of lactate utility among 377 single drug overdoses is included in the Table E1, available online at <http://www.annemergmed.com>.

The incidence of shock was 3.9% ($N=54$) in the cohort. There were 3 drug classes significantly associated with development of shock, in descending order of incidence:

Table 1. Drug exposures and initial lactate level in 24 fatalities.

Fatality*	Decade of Life†	Sex	Lactate (mmol/L)	Drug Exposures	Hospital Day of Death‡
A	2	F	21.0	Flurazepam, diazepam, marijuana, escitalopram	1
B	≥ 7	F	18.3	Nifedipine	1
C	6	F	18.1	Digoxin	3
D	3	F	15.2	APAP, hydromorphone, ibuprofen, pregabalin, benzodiazepines	5
E	3	F	10.3	Oxycodone, APAP, ethanol	8
F	5	F	9.9	Cocaine, heroin, methadone	2
G	≥ 7	M	9.8	Cocaine, benzodiazepines	5
H	5	M	9.7	Methadone, oxycodone, trazodone, benzodiazepines	2
I	6	M	9.4	Methadone	2
J	2	M	9.2	Desomorphine, isopropanol, ethanol	1
K	5	M	8.9	Ethanol, benzodiazepines	9
L	2	F	8.6	Diltiazem	1
M	3	M	7.9	Heroin, cocaine, labetalol	22
N	≥ 7	M	7.7	Bicalutamide, cilostazol, digoxin, salicylates	18
O	≥ 7	F	7.5	Diltiazem, atenolol	6
P	≥ 7	F	6.2	APAP, ethanol, unknown pills	5
Q	6	F	5.0	Digoxin	3
R	4	F	3.2	Oxycodone, benzodiazepines	71
S	5	M	3.1	Valproic acid, escitalopram, sertraline, quetiapine	5
T	≥ 7	M	2.5	Metoprolol, hydrochlorothiazide, digoxin	9
U	3	M	1.9	Unknown pills	53
V	6	F	1.2	Nortriptyline, amlodipine, clonazepam, paroxetine, hydrochlorothiazide	1
W	≥ 7	F	0.9	Amlodipine, carvedilol, olmesartan, ezetimibe	14
X	≥ 7	F	0.3	Lorazepam, ethanol	7

F, Female; APAP, acetaminophen; M, male.

*Fatalities are organized in descending order of initial lactate measurement.

†Decade of life greater than 7 was grouped as greater than or equal to 7 to preserve patient confidentiality.

‡The date of ED presentation was defined as hospital day 1.

digoxin (36.8%; OR 16.6; $P<.001$), diuretics (33%; OR 13.4; $P<.001$), and β -adrenergic antagonists or calcium channel blockers (27.1%; OR 12.8; $P<.001$).

Sympathomimetics had a significant association with lower incidence of shock (1.6%; OR 0.33; $P<.01$). The mean lactate concentration was significantly higher in patients who developed shock (6.6 versus 2.3; t test $P<.001$). The AUC overall for lactate to predict occurrence of shock was 0.77. Test characteristics of an abnormal lactate concentration (defined as >2.5 mmol/L) was 68.5% sensitive and 76.3%

Table 2. Prognostic utility of the initial lactate concentration for overdose fatality, based on drug class.

Drug Class*	AUC [†] (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Optimal Cut Point [‡] (mmol/L)	N (Death/Total)
Acetaminophen	0.98 (0.95–1.0)	100 (29–100)	95.3 (90–98)	10.0	3/131
Salicylates	0.98 (0.90–1.0)	100 (3–100)	96.7 (83–100)	6.0	1/31
Sympathomimetics	0.98 (0.95–0.99)	100 (29–100)	96.3 (94–98)	7.8	3/381
Opioids	0.97 (0.94–0.99)	100 (63–100)	86.5 (81–88)	3.1	8/392
Digoxin/cardioactive steroids	0.92 (0.78–1.0)	100 (40–100)	86.7 (66–100)	2.4	4/19
Anticonvulsants	0.91 (0.76–1.0)	100 (16–100)	80.4 (69–87)	3.0	2/94
Antipsychotics	0.83 (0.77–0.90)	100 (3–100)	83.2 (76–89)	3.0	1/132
Antidepressants	0.79 (0.52–1.0)	75 (19–99)	80.9 (72–86)	3.0	4/140
Benzodiazepines	0.78 (0.53–1.0)	62.5 (24–91)	98.5 (97–100)	8.7	8/348
BB/CCB	0.73 (0.49–0.97)	57.1 (16–84)	94.2 (84–99)	7.1	7/59
Diuretics	0.55 (0.20–0.89)	100 (16–100)	40.0 (12–74)	1.1	2/12
ACE inhibitor or ARB	0.16 (0.01–0.31)	100 (3–100)	12.0 (3–31)	0.9	1/26
Total combined	0.85	70.8	93.3	5.0	24/1,406 [§]

BB/CCB, β -Adrenergic antagonists and calcium channel blockers; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

*Drug class is arranged in descending order of AUC. Clinically relevant drug classes were determined by 2 board-certified medical toxicologists. Drug classes without any primary outcomes (eg, biguanides/metformin, lithium, statins) are not listed.

[†]Based on ROC analysis.

[‡]Defined by the Youden Index as the concentration that maximizes the sum of sensitivity plus specificity. Listed sensitivities and specificities are at the optimal cutpoints.²⁶

[§]Column totals add up to much greater than 1,406 because of drug class coexposures.

specific, and an initial lactate concentration greater than 5.0 mmol/L was 46.3% sensitive and 93.9% specific.

To determine the relative prognostic value of lactate level versus serum bicarbonate level, a more routinely ordered laboratory test, we compared the AUC and diagnostic test characteristics for the initial bicarbonate level versus the initial lactate level. The AUC for bicarbonate (0.83; 95% CI 0.73 to 0.94) was lower than that of lactate, and the optimal bicarbonate cut point (≥ 22.9 mmol/L) based on ROC analysis was less specific (78.3%) than that of lactate (94.7%). In addition, post hoc testing result for collinearity between lactate and bicarbonate level was negative (variance inflation factor < 5).

LIMITATIONS

Many patients were excluded because of absence of an ED serum lactate concentration, which may have biased the lactate cut point data; however, this would probably bias toward the null hypothesis because clinicians are typically more likely to test lactate level in more severely ill patients. Another consideration is the study setting because the study was performed at 2 urban tertiary referral centers in a single region. The bicarbonate subgroup analysis may be limited if laboratory testing measures bicarbonate as a calculated value from the Henderson-Hasselbalch equation, rather than the true serum bicarbonate concentration by the photometric enzymatic method with measurement of the rate reaction; however, given that the value used in this study was generally used by the clinician, it probably represents the actual scenario. From a statistical standpoint,

the infrequency of the primary outcome may have inflated the calculated specificities and AUCs. And finally, time to the obtaining of serum lactate concentration was not recorded, which may limit interpretation of our data.

DISCUSSION

In this large prospective validation cohort of patients with acute drug overdose, we found that the initial ED lactate concentration had excellent prognostic utility for the in-hospital occurrence of both shock and fatality. The optimal lactate cut point for fatality was 5.0 mmol/L, which may allow lactate to be used as a biomarker for early decisionmaking in ED patients with acute drug overdose even if specific drug exposures are unknown. Additionally, prognostic utility of lactate level was highly drug specific such that in cases with known exposures, drug-specific lactate cut points were calculated and should be used. Drug classes for which lactate had the highest prognostic utility (ie, highest area under the ROC curve) were salicylates, sympathomimetics, acetaminophen, and opioids. Conversely, lactate level had minimal to no utility for drug overdoses involving β -adrenergic antagonist and calcium channel blockers, diuretics, and angiotensin-converting enzyme inhibitors.

This study successfully validates our previous report that the initial ED lactate concentration has prognostic utility for in-hospital mortality from acute drug poisoning. In that retrospective case-control study, the optimal lactate cut point was 3.0 mmol/L (84% sensitivity, 75% specificity), which conferred a 15.8-fold increase in odds of fatality.¹¹

However, the previous study was limited by smaller sample size, validity of poison control center telephone data collection, and inability to perform drug class subgroup analysis.

To our knowledge, no previous study has specifically shown the prognostic utility of lactate in the setting of drug poisoning from either opioid or sympathomimetic drug overdose. The association of hyperlactatemia and acidosis with sympathomimetic poisoning likely represents a pathophysiologic response to catecholamines, which may be similar to that during exercise and therapeutic infusion in shock states^{16,17} and likely reflects the transition from oxidative to partially anaerobic metabolism. Similarly, hyperlactatemia in the setting of opioid poisoning may represent type A hyperlactatemia caused by tissue hypoxia and subsequent anaerobic metabolism. Patients with opioid or sympathomimetic poisoning may have added prognostic utility with a lactate concentration sent as part of the routine ED evaluation to aid medical decisionmaking.

These data are consistent with those of previous studies examining the utility of lactate level as a biomarker for the management of β -adrenergic antagonist poisoning. It was previously shown in β -adrenergic antagonist poisoning that lactate concentration increases only modestly despite the presence of significant hypotension and shock on admission. Mégarbane et al¹² found that 4 of 9 patients with fatal β -adrenergic antagonist poisoning had lactate concentrations below 3.0 mmol/L. Similarly, in the present study, β -adrenergic antagonist poisoning was significantly associated with shock and fatality; however, the prognostic utility of the lactate concentration was poor for both β -adrenergic antagonist and calcium channel blockers. However, in the sensitivity analysis (Table E1, available online at <http://www.annemergmed.com>) there was clearly elevated lactate in deaths (median 13.3; interquartile range 8.6 to 13.3) compared with that in survivors (median 1.5; interquartile range 0.8 to 2.8). Thus, the initial lactate concentration may still be useful for clinical decisionmaking to guide therapy of patients with isolated β -adrenergic antagonist or calcium channel blocker poisoning. Clinicians should be aware that its utility diminishes in polydrug overdoses with this drug class in particular.

It has previously been shown that for patients with acetaminophen poisoning, the lactate concentration has prognostic utility for outcome.¹⁸ The data from the present study demonstrate prognostic utility for prediction of fatality after acetaminophen overdose, with an optimal cut point of 10.0 mmol/L. Because circulating lactate is metabolized mainly by the liver, hyperlactatemia may reflect decreases in clearance as a result of impaired hepatic

function.¹⁹ The injured liver may itself act as a source of lactate.²⁰

Recently, an association was found between the initial ED lactate concentration and severe outcome in patients with acute salicylate poisoning.²¹ The data from the present study demonstrate prognostic utility for fatality after salicylate overdose, with an optimal cut point of 6.0 mmol/L. This may be representative of the toxicity exerted by uncoupled oxidative phosphorylation, as well as increased work of breathing.

Despite the well-documented association between metformin or biguanide poisoning and hyperlactatemia,²² the present study was unable to demonstrate an association in this subgroup because of the absence of deaths from metformin poisoning. For the same reason, no conclusions can be drawn about the utility of the initial lactate concentration for the prediction of fatality because of lithium or statin drug poisoning. This underscores the lack of utility for routine lactate measurement in these patients and for patients with good prognosis in general.

Clinically, the results of the present study suggest that the initial serum lactate concentration in selected patients with acute drug overdose may aid medical decisionmaking for the initial disposition from the ED. Although we did not test whether routine testing of lactate concentration in overdose patients will improve care, potential merits of testing may extend most highly to those with limited exposure information and lack of other available testing (eg, no serum drug concentration available, inability to apply a particular nomogram). Additionally, hyperlactatemia in patients with acute drug overdose may warrant bedside medical toxicology consultation, if available.

One group of authors recommended that the routine approach to a patient with an unknown overdose not include measuring serum lactate concentration.²³ However, if the initial lactate concentration can predict mortality early in the patient's course, it may be crucial for the direction of patient care. Given that the optimal lactate cut point for fatality is 5.0 mmol/L, this threshold identifies patients for whom ICU admission is warranted or should at least be seriously considered, unless application of a drug-specific cut point is possible. Furthermore, a lactate concentration less than 2.0 mmol/L has outstanding negative predictive value for mortality and may identify a low-risk subset of patients for medical clearance in the absence of a clinical toxidrome or other concerning clinical findings. Given the drug-specific prognostic utility for lactate level, this biomarker should be interpreted with the aid of medical toxicology consultation. Conversely, lactate level does not appear to be useful for medical decisionmaking for patients with isolated drug

poisoning from a diuretic or angiotensin-converting enzyme inhibitor.

Although drug-specific causes of fatality cannot be proven by this study, there was an association found between diuretics and 12-fold increased odds of mortality (OR 12.4; $P=.02$). The explanation for the diuretic phenomenon observed in this study is likely that association does not prove causation (ie, that diuretic overdose itself was the cause of death). Presumably, diuretics are a confounder in the relationship between a patient's overdose and resultant fatality. The data corroborate this interpretation because lactate was not a useful biomarker in patients with diuretic overdose.

Further study should evaluate lactate-tailored management. In critically ill patients, lactate-guided therapy and early lactate clearance has been associated with improved outcome.^{24,25} Early lactate clearance may indicate a reduction in overall injury caused by prolonged hypoperfusion or hypoxia. Threshold lactate concentrations may aid providers in decisions to administer more aggressive extracorporeal therapies or antidotes, and may provide better ability to gauge response to therapeutic interventions. Additionally, multibiomarker approaches may have incremental value over lactate alone for the assessment of acute drug overdose.

In conclusion, the initial ED lactate concentration may have prognostic utility for in-hospital fatality from acute drug overdose. These data demonstrate that the initial ED lactate concentration might be used as a biomarker that can aid early decisionmaking. According to the variable utility of the initial lactate concentration for specific poisonings, studies of lactate-tailored management for specific drug classes are warranted.

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work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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