

## EDITORIAL

# The story of the broken soul that ultimately breaks the heart? Parallels and crossroads in a complex clinical scenario

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In 2017, the 55 U.S. poison control centers provided telephone guidance for nearly 2.12 million human poison exposures that is about 1 poison exposure reported to U.S. poison control centers every 14.9 seconds. There is a greater proportion of males in poison exposures occurring in children younger than 13 years and a female predominance in teens and adults. Across all ages, only 18.9% were intentional and 2.4% were adverse reactions<sup>1-3</sup>. The majority of poison exposures reported to U.S. poison centers (84%) were non- or minimally toxic and had at most a minor effect, and approximately half of adult cases were managed at the exposure site without medical intervention. Unintentional poisoning has surpassed motor vehicle traffic fatalities as the leading cause of injury death in the U.S. since 2008. Intentional exposures are significantly more serious, with a thirty-one fold increase in morbidity and mortality when compared to unintentional exposures<sup>4</sup>.

Pain medications lead the list of the most common substances involved in adult poison exposures in 2017 (129,917 patients; 11.2%), followed by sedatives/sleeping medications (114,212 patients; 9.8%), antidepressants (83,753; 7.2%), cardiovascular medications (74,293; 6.4%), cleaning substances (63,329; 5.5%), alcohol (55,752; 4.8%), anticonvulsants (49,298; 4.2%), pesticides (41,807; 3.6%) stimulants and street drugs (41,266; 3.6%), and antihistamines (38,228; 3.3%), most often intentional<sup>3</sup>.

The continuous rise in the prescribing, usage, and abuse of opioid drugs, and the subsequent increase in opioid-related deaths has come to be known as the “opioid epidemic” and made president’s Trump administration to declare it a national emergency. Opioid overdoses claimed nearly 50,000 American lives in 2017 alone, more than 9/11 and the wars in Iraq and Afghanistan combined.

The sharpest rise in drug-related fatalities was seen in 2016 and was associated with use of fentanyl and fentanyl analogs, with over 20,000 deaths occurring that year<sup>5</sup>. The substantial increase in fentanyl deaths has been linked to illicitly manufactured fentanyl<sup>6</sup>. The potency of these synthetic opioids can range from approximately 3-10,000 times the strength of morphine by weight and the adulteration of heroin being sold in the U.S. with synthetic opioids has led to alarming medical consequences like naloxone resistance<sup>7</sup>.

U.S. poison centers collect data in real time and upload those data every 9.5 minutes (median time to upload) that is used to find hazardous products quickly, detect chemical/bioterrorism incidents and also follow substance abuse trends. Alerts are sent when there are an unexpectedly large number of cases in an hour, when there is an unexpectedly high frequency of a specific symptom, or when there are cases with combinations of clinical effects suggestive of specific poisonings that might require a rapid public health response. The toxicologists investigate these

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alerts and inform public health officials if outliers are suspicious for events or products of concern<sup>8</sup>.

In this context, the Lionte et al. study "Parameters influencing in-hospital mortality in acutely poisoned patients hospitalized in a medical or ICU ward: is there an influence of toxin-induced myocardial injury?" reflects the current global importance of this issue and similarities across borders. As someone who has practiced medicine on both sides of the Atlantic, it is hard not to acknowledge that the study has a local flavor with the "regional pattern of intoxication" (toxic gases mainly being carbon monoxide, toxic alcohols, vegetal toxin exposure). The authors provide a risk stratification that transcends the geographic barriers and a combined analysis using troponin I (TnI), electrocardiogram (ECG), and transthoracic echocardiography (TTE) parameters in acute poisoning of the sickest subgroup that requires admission in a medical or intensive care unit (ICU) ward.

The limited literature with patients requiring higher level of care is in part provided by this team's previous experience "Usefulness of Transthoracic Echocardiography Parameters and Brain Natriuretic Peptide as Mortality Predictors in Hospitalized Acutely Poisoned Patients: A Prospective Observational Study", but an easy parallel would be with "sepsis-induced myocardial dysfunction (SIMD)" where peak high-sensitive troponin I (hs-TnI) and ST-T change correlate with transthoracic echocardiogram (TTE) derived data and where in about two-thirds of patients with an elevated hs-TnI level cardiac dysfunction was noted by TTE<sup>9-11</sup>.

In the Lionte et al. study, 169 patients of the entire cohort (76.2%) developed complications, while 35 patients had multiple complications, involving at least two major organs or systems, and cardiovascular complications were recorded in 15.76% patients. There was no significant statistical difference in TnI level within age and gender groups, while the mean initial levels of TnI were higher in non-survivor group. The positive troponin is a marker of severity and opens a broad differential diagnosis including direct acute cardiac toxicity, type 2 myocardial infarction (mismatch between supply/demand), stress-induced cardiomyopathy through either increase in catecholamine versus endothelial dysfunction or vasospasm, or even type I MI, with limited options to clarify through additional testing due to patient instability. Multi-organ failure, fast clinical deterioration, lactic acidosis can also be associated with depressed ejection fraction, ECG distortion and positive cardiac biomarkers.

When analyzing ECGs, 40% subjects had an abnormal rhythm with atrial fibrillation being a marker of disease severity, at the time of the TTE, 8 subjects (3.6%) were in atrial fibrillation, and as in our experience with hematological malignancies undergoing stem cell transplant, when present in the setting of multi-organ failure predicts worse outcomes<sup>12</sup>.

QTc prolongation was reported as being independently associated with intubation and death in a retrospective study of methadone intoxication<sup>13</sup> and was significantly prolonged in patients with the poor outcome in Lionte et al. study. There were no significant differences in PR intervals and QRS complex width within the outcome groups. ST-T segment changes were common in acidosis, while multi-organ failure was seen in 36.8% patients; both were predictive for a poor outcome. There were no significant differences in the ECG parameters among poison groups.

Myocardial damage, including necrosis, is commonly seen at necropsy after fatal carbon monoxide poisoning. The subendocardial and papillary muscle areas of the left ventricle are most frequently involved, the lesion resembling those of severe hypoxia which carbon monoxide can produce<sup>14</sup>. A retrospective study of 626 consecutive patients over a five year period has identified 19 patients with abnormal initial echocardiography with various patterns: global hypokinesia/akinesia, regional wall hypokinesia/akinesia (Takotsubo type, reverse Takotsubo type, non-specific type). The baseline ejection fraction (EF) was  $36.3 \pm 13.5\%$  (from 15% to 55%), with the majority of abnormal EF recovering to normal (i.e.,  $EF \geq 50\%$ ) at the follow-up echocardiography performed within 12 days after the initial testing<sup>15</sup>.

In a similar study including 147 patients, 16 patients were identified with abnormal echocardiographic findings, with overall incidence of Takotsubo cardiomyopathy in 7.5% (11/147). Levels of cardiac enzymes (CK-MB, Troponin T) were higher in the global hypokinesia and Takotsubo cardiomyopathy groups when compared with the non-cardiomyopathy group. In the Takotsubo cardiomyopathy group, the most commonly consumed poison was organophosphate<sup>16</sup>.

Non-ST elevation myocardial infarction can be a complication of carbon monoxide poisoning,<sup>17,18</sup> further emphasizing the complexity of the clinical picture in acute intoxications. While one could think that established coronary artery disease could decrease patients' resilience in this critical clinical situation, a recent study/animal model suggested another "para-

dox", where acute and chronic remote ischemic conditioning attenuated septic cardiomyopathy, improves cardiac output, protects systemic organs, and improves mortality in a lipopolysaccharide-induced sepsis model<sup>19</sup>.

A similar experience was reported by Gupta et al. when they queried the 2002-2010 Nationwide Inpatient Sample databases to examine the effect of opioid abuse/dependence on outcomes in patients hospitalized with heart failure. Of 9,993,240 patients with heart failure, 29,014 had a history of opioid abuse or dependence, they were likely to be younger men of poor socioeconomic background, lower prevalence of dyslipidemia, diabetes mellitus, coronary artery disease, prior myocardial infarction, and peripheral vascular disease ( $p < 0.001$  for all) and were more likely to be smokers and have chronic pulmonary disease, depression, liver disease, and obesity ( $p < 0.001$  for all). Patients with a history of opioid abuse/dependence had lower incidence of hospital acquired conditions (14.8% vs. 16.5%, adjusted odds ratio: 0.71,  $p < 0.001$ ) and lower in-hospital mortality (1.3% vs. 3.6%, adjusted odds ratio: 0.64,  $p < 0.001$ ) when compared with patients without prior opioid abuse/dependence<sup>20</sup>.

Profound circulatory shock following heroin overdose was reported and while the mechanism of shock is not completely understood, severe depression of left ventricular contractility seems to be the predominant reason, although acute right heart failure with decreased pulmonary capillary wedge pressure and arterial vasodilatation resulting in maldistribution of cardiac output can be a possible contributing factor. The profound hemodynamic shock from heroin overdose results in severe but usually fully reversible depression of myocardial contractility<sup>21</sup>.

There are similarities in the pathogenesis of the drop in ejection fraction with sepsis including increase in inflammatory mediators like tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, and IL-6, increase in damage-associated molecular patterns (DAMPs) like circulating extracellular histones that contribute to endothelial dysfunction, organ failure, and death in experimental sepsis, heat shock proteins (HSPs) produced by cells in reaction to stress, nitric oxide<sup>23,24</sup>, mitochondrial dysfunction through non-competitive inhibition of cytochrome C oxidase leading to sepsis-associated myocardial depression<sup>25</sup>, and autonomic dysregulation, with a state of catecholamine resistance.<sup>26,27</sup>

In a small study (48 patients), sepsis induced cardiac dysfunction assessed by echocardiography showed

mitral annular plane systolic excursion (MAPSE) alone was a good predictor of mortality when combined with APACHE II<sup>28</sup>, and might be a consideration for the authors in their further studies.

Different than in the sepsis clinical scenario, patients with a poor outcome did not have a significantly prolonged hospitalization, suggesting a more abrupt deterioration from the acute intoxication.

Various societal guidelines focus on recognition, risk assessment, resuscitation and emergent management A (airway), B (Breathing) C (Circulation) and D (disability) including treatment of seizures, drug-induced syndromes (malignant hyperthermia, serotonin syndrome, neuroleptic malignant syndrome), decontamination and drug antidotes, emphasize work on E elimination through urine alkalinization, use of activated charcoal and dialysis but they fail to provide details on the ICU care and risk stratification needed for the highest complexity patients. The study by Lionte et al. brings valuable information to fill this gap.

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