***Abstract:***

***Introduction:***

Exposures to substances are common but severe clinical outcomes are rare. Of the 2,483,183 calls to Poison Control in the United States in 2022, 2,622 (0.1%) involved a fatality and 38, 739 (1.88%) had a major clinical effect (1). The mortality rate of patients hospitalized for poisoning is 0.6%(2). Approximately 25% of poisoned patients admitted to the hospital for medical treatment require no medical treatment(3). Less than half of poisoned patients admitted to the intensive care unit (ICU) receive ICU level care(4). The rarity of life-threatening ingestions leads to the challenge of how to identify them without subjecting others to unnecessary care, pointlessly consuming resources.

Clinical decision tools for acetaminophen (5), tricyclic antidepressants (6), paraquat (7,8), and bupropion (9,10) identify those at risk for serious clinical outcomes after exposure and improve resource utilization. For example, approximately 2,000 ICU admissions across the United States each year for bupropion ingestion can be avoided by screening for resting tachycardia 8 hours after ingestion(9).

Despite their success, these decision support tools only apply when the xenobiotic ingested is known and it is the only or predominant ingestant. Prior attempts at classifying the severity of an exposure to an unknown agent have had limited prognostic value (11,12). Medical toxicologists in the Netherlands recently derived and internally validated a clinical decision support tool to help physicians determine which patients admitted to the ICU for suspected poisoning could be safely managed on a general medical floor(13). Their tool, INTOXICATE, predicts the need for mechanical ventilation or vasopressors in the first 24 hours of admission, or death at any point during hospitalization, in poisoned patients admitted to the ICU. It requires only readily available clinical data and the class of ingestant.

In their study INTOXICATE would have reduced ICU admissions by 34% if applied. If INTOXICATE generalizes to the American healthcare system, it would prevent unnecessary admissions and increase ICU capacity. INTOXICATE was derived from patients already admitted to the ICU. In the US healthcare system, the Emergency Physician provides a large part of the first 24 hours of care of a poisoned patient, in consultation with Poison Control or a bedside toxicologist, which raises the questions of whether INTOXICATE performs similarly in patients under evaluation in the Emergency Department and to what degree INTOXICATE’s recommendations agree with those of the bedside toxicologist.

The goals of our study were to determine INTOXICATE’s performance in the American healthcare system and to evaluate the agreement between INTOXICATE’s assessment and that of the bedside toxicologist.

***Methods:***

***Setting***

We conducted a retrospective study of toxicology consultations at one urban tertiary care center with a 24/7 bedside toxicology service. We screened all consultations from January 2023 to April 2024 involving patients older than 12. We included patients aged 12-18 even though (14) did not because adolescents comprised 21% (130/605) of toxicology consultations over the last 2 years at the authors’ institution, comprise 31% of nationwide calls for intentional ingestions(15,16), and have cardiovascular and neurological responses comparable to adults. We conducted a planned subgroup analysis of patients aged 12-18.We excluded patients younger than 12 and those with missing data.

***Definitions***

We defined needing ICU care as (14) did, requiring mechanical ventilation or pressors during the first 24 hours after admission, or death during hospitalization. To determine whether a patient requires ICU care, INTOXICATE assigns each patient an INTOXICATE Risk Score (IRS). IRS is calculated by assigning points based on clinical features. For example, a patient receives 1 point if the heart rate is between 75 to 85 beats per minute and 2 points if between 85 to 95 beats per minute. The sum of the scores across all clinical features is the IRS. If the sum exceeds 6, INTOXICATE recommends ICU admission. We refer the reader to (14) for further detail. For the sake of brevity, we use the term “INTOXICATE” to mean the prediction model presented in (14) and derived from patients in the INTOXICATE cohort.

INTOXICATE defined dysrhythmia as tachycardia, second or third-degree AV block, or atrial fibrillation with a ventricular rate greater than 120 beats per minute and hemodynamic instability in the 24 hours before ICU admission. We used the same definition. Their paper did not specify their definition of respiratory insufficiency. We defined it as any need for supplemental oxygen.

INTOXICATE recommends two levels of care, ICU or not. We captured additional data on disposition including admission to a general medical floor, admission to an intermediate care floor (also called “stepdown”), discharge from the Emergency Department. and transfer to Emergency Psychiatry. We considered admission to ICU or stepdown as “admission to ICU” and all other disposition as “not admission to the ICU”.

***Statistical analyses***

Our outcome measure for INTOXICATE’s performance, was the proportion of patients admitted to the ICU in our cohort for whom INTOXICATE recommended against ICU admission and who did not require mechanical ventilation or vasopressors in the first 24 hours of admission or die during admission.

Our outcome measure for the agreement between INTOXOCATE and physician recommendations was the inter-rater reliability between the INTOXICATE’s predicted disposition and the treating physician's decision. We used Cohen’s κ to quantify inter-rater reliability. We chose this measure instead of overall agreement to capture the degree to which INTOXICATE agrees with toxicologist decision-making beyond chance.

All statistical analyses were performed in R using custom software written by author MC. The computer code with no protected health information is available at the GitHub repository: https://github.com/mac389/INTOXICATE.

***Results:***

**Description of Data Set.** We screened 112 patients. We excluded 7 who were under 12 and 2 who had missing data, ultimately including 103 patients for analysis (Figure 1). The median age [interquartile range] of adolescents was 15 [14-16] and adults 35 [28-50]. Adults were more commonly admitted to a general medical floor than adolescents and adolescents more commonly discharged, but this trend did not reach statistical significance (Table 1). There were no statistically significant differences between adolescents and adults in terms of gender, heart rate, respiratory insufficiency, history of cirrhosis, dysrhythmia, GCS, type of exposure, or other medical reasons for ICU admission. The systolic blood pressure was statistically significantly different, 116 [106-119] for adolescents and 120 [112-140] for adults. This difference is too small to be clinically meaningful.

Of the 103 patients included in the analysis, 20 (19%) were admitted to the ICU, 16 (16%) to a general medical floor, and 75 (73%) discharged or transferred directly to psychiatry. INTOXICATE predicted admitting 61 (59%) patients to the ICU. It recommended ICU admission for 13/20 (65%) of patients for whom the toxicologist recommended ICU admission, for 12/16 (75%) patients for whom admission the toxicologist recommended a general medical floor, and for 36/75 (48%) patients for whom the toxicologist recommended discharge.  ***[COMMENT: Since this is much higher than the toxicologist-recommended 21 ICU admissions, discuss whether the threshold score should be adjusted to reduce over-triage.]***

The inter-rater agreement between INTOXICATE’s predictions and the bedside toxicologists’ recommendations was not statistically significantly different than chance for either adolescents or adults (Table 2). No patients for whom toxicology recommended a floor admission were admitted to a floor and then transferred to the ICU. No patients who were discharged but for whom INTOXICATE recommended admission returned to any hospital in the metropolitan area in 48 hours.  ***[COMMENT: Highlight potential reasons for this poor agreement and whether modifications to INTOXICATE’s scoring might improve alignment.]***

**Adults.** Of the 79 adults, 16 (20%) were admitted to the ICU. Of those 16, INTOXICATE and toxicologist agreed that 11 (69%) required ICU admission. For the remaining 5, INTOXICATE considered them lower risk than the toxicologist did because it considered the reported ingestants lower risk, there was no respiratory insufficiency or dysrhythmia, and their GCS scores were 15. The median (IQR) pulse in those for whom INTOXICATE and Toxicology recommended ICU admission was 87 (76-104) beats per minute. It was 70 (65-74) beats per minute in the patients for whom Toxicology recommended ICU admission but INTOXICATE did not. The median ages were 38 (30-53) and 30 (25-38), respectively. These differences in age and heart rate were not statistically significant. Taking the toxicologist’s recommendation as the gold standard, the sensitivity and specificity of INTOXICATE for patients aged 18-65 were 69% [41-89] and 38% [26-51], respectively, expressed as estimate [95% confidence interval].

INTOXICATE recommended ICU admission in 39/79 (49%) of patients whom the bedside toxicologist did not. INTOXICATE considered them higher risk than the toxicologist did because of older age, respiratory insufficiency, most often supplemental oxygen by nasal cannula, and GCS scores lower than 15. The median heart rate and median systolic blood pressure were not significantly different between those for whom INTOXICATE recommended ICU admission and those for whom it did not.

**Adolescents.** Of the 24 adolescents, 4 were admitted to the ICU. INTOXICATE and the bedside toxicologist agreed that two of the four (50%) required ICU admission. These patients presented with GCS 10 and 14, and heart rates 109 and 120, respectively. One presented after ingesting an unknown substance. Of the two patients, for whom INTOXICATE did not recommend ICU admission, one presented with somnolence after ingesting acetaminophen, which required N-acetylcysteine, and diphenhydramine. INTOXICATE assigned a risk score of 3 because the patient was normotensive, not tachycardic, had no cirrhosis, respiratory insufficiency, or cardiac dysrhythmia. The other presented with reported alcohol intoxication and was hypertensive, tachycardic, with GCS 10 (IRS = 4). In INTOXICATE’s schema, isolated alcohol intoxication decreases the need for ICU admission relative to other xenobiotics. INTOXICATE recommended the ICU for 9 adolescents for whom the toxicologist did not. These 9 patients presented with different ingestions, but all were tachycardic with median (IQR) of 114 (106 - 115) bpm. All had a GCS of 15. Taking the toxicologist’s recommendation as the gold standard, the sensitivity and specificity of INTOXICATE were 50% [1-99] and 55% [33-77], respectively, expressed as estimate [95% confidence interval]. The wide confidence intervals reflect the small number of adolescents admitted to the ICU. This subgroup analysis is too underpowered too make statistically valid conclusions.

***Discussion:***

The goals of our study were to determine INTOXICATE’s performance in the American healthcare system and to evaluate the agreement between INTOXICATE’s assessment and that of the bedside toxicologist.

If applied only to patients in our study for whom toxicology recommended ICU admission, INTOXICATE would have reduced ICU admissions by 33% (7/21), consistent with the initial derivation study. If applied to all Emergency Department patients who received a toxicology consult, INTOXICATE nearly tripled ICU utilization, from 21 ICU admissions to 61. INTOXICATE had no statistically significant agreement with the recommendations of bedside toxicologists.

Variation in practices across health care systems may contribute to low agreement between INTOXICATE and the bedside toxicologist. Some Emergency Departments may be able to observe patients for long enough to discharge what would be an admission in other locales. At the authors’ institution, all patients receiving hyperbaric treatment are admitted to the ICU because the hyperbaric chamber is in an ICU. The toxicologist considers features INTOXICATE does not, such as clonus, EKG intervals, findings from the physical exam and patient interview. INTOXICATE does not consider trends in vital signs. The IRS threshold of 6 points that was chosen by Brandenburg et. al. to minimize false negatives and may need adjustment for different healthcare systems. ***[COMMENT: Would adjusting this threshold (e.g., IRS > 7) improve specificity without compromising sensitivity? Consider exploring this in the discussion.]***

Our study did not evaluate all facets of INTOXICATE. INTOXICATE identifies predictors of not needing ICU care, such as acute intoxication with alcohol. In our cohort, Toxicology was not consulted on any adults with isolated alcohol intoxication. INTOXICATE identifies respiratory insufficiency, dysrhythmia, cirrhosis, and a nontoxicological reason for ICU admission as predictors of needing ICU care. In our study, all patients admitted to the ICU had respiratory insufficiency or a dysrhythmia, or both, but 7 of the 19 patients Toxicology recommended discharging had one of those conditions. INTOXICATE recommends the ICU for all patients with respiratory insufficiency or a dysrhythmia, suggesting an opportunity to refine criteria, for example considering degrees of respiratory insufficiency or persistence of tachydysrhythmias.

INTOXICATE uses APACHE IV categories for, which may not agree with the bedside toxicologist’s grouping. For example, the APACHE IV category *Antidepressants* includes SSRIs, tricyclic antidepressants, and lithium. Grouping them together leads INTOXICATE to consider clinical features in all three types of xenobiotics to have the same meaning. Tachycardia has different clinical significance in SSRIs than tricyclic antidepressants. An opioid classified as a *Street Drug* rather than *Analgesic* is more likely to require ICU care, but it is not clear how to classify diverted opioids used to self-medicate for pain. (14) did not assign polysubstance intoxication a risk score, leading to the ironic prediction that polysubstance ingestions are lower risk. Polysubstance exposures are implicated in 48-58% of unintentional overdose deaths (17,18). For 18 out of 28 adult patients (64%), the intoxication type was *Intoxicant NOS* or *Combination*, highlighting the difficulty of identifying the substances involved in the initial evaluation and raising the question of the utility of prognosticating from this variable.

***Conclusions:***

In a single center retrospective study, INTOXICATE identified 33% of patients admitted to the ICU who could be safely downgraded, an effect size comparable to that previously reported in the Dutch healthcare system. If applied to patients under evaluation in the Emergency Department, instead of the original study population of INTOXICATE triples ICU utilization. INTOXICATE’s recommendations did not significantly agree with those of 4 bedside toxicologists.

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**A flowchart of a number of individuals

Description automatically generated**

Figure 1. Screening and Inclusion of Patients.

| **Characteristic** | **Adolescent**, N = 24*1* | **Adult**, N = 79*1* | **p-value***2* |
| --- | --- | --- | --- |
| **Age** | 15 (14, 16) | 35 (28, 50) | <0.001 |
| **Gender** |  |  | 0.2 |
| F | 13 (54%) | 40 (51%) |  |
| M | 10 (42%) | 39 (49%) |  |
| NB | 1 (4.2%) | 0 (0%) |  |
| **Pulse** | 99 (89, 110) | 90 (72, 107) | 0.071 |
| **SBP** | 116 (106, 119) | 120 (112, 140) | 0.033 |
| **Actual Disposition** |  |  | 0.5 |
| Discharge | 18 (75%) | 49 (62%) |  |
| GMF | 2 (8.3%) | 14 (18%) |  |
| ICU | 4 (17%) | 16 (20%) |  |
| **Respiratory Insufficiency** | 2 (8.3%) | 16 (20%) | 0.2 |
| **Cirrhosis** | 0 (0%) | 2 (2.5%) | >0.9 |
| **Dysrhythmia** | 12 (50%) | 29 (37%) | 0.3 |
| **Secondary Reason for ICU Admission** | 0 (0%) | 1 (1.3%) | >0.9 |
| **GCS** |  |  | 0.024 |
| 3 | 0 (0%) | 3 (3.8%) |  |
| 5 | 0 (0%) | 1 (1.3%) |  |
| 10 | 3 (13%) | 0 (0%) |  |
| 11 | 0 (0%) | 1 (1.3%) |  |
| 12 | 0 (0%) | 1 (1.3%) |  |
| 13 | 0 (0%) | 2 (2.5%) |  |
| 14 | 3 (13%) | 2 (2.5%) |  |
| 15 | 18 (75%) | 69 (87%) |  |
| **Exposure Category** |  |  | 0.11 |
| Alcohol | 2 (8.3%) | 5 (6.3%) |  |
| Analgesic | 6 (25%) | 11 (14%) |  |
| Antidepressants | 5 (21%) | 11 (14%) |  |
| CO, As, CN | 0 (0%) | 9 (11%) |  |
| Combination | 1 (4.2%) | 16 (20%) |  |
| Sedatives | 0 (0%) | 6 (7.6%) |  |
| Street Drugs | 5 (21%) | 10 (13%) |  |
| Unknown | 5 (21%) | 11 (14%) |  |
| *1* Median (IQR); n (%) | | | |
| *2* Wilcoxon rank sum test; Fisher’s exact test; Pearson’s Chi-squared test | | | |

Table 1. GMF, general medical floor.

|  | **Adolescent** | | | | | **Adult** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Predicted Disposition | |  |  |  | Predicted Disposition | |  |  |  |
| ICU | Not ICU | **Total** | **Cohen’s kappa** | **p-value** | ICU | Not ICU | **Total** | **Cohen’s kappa** | **p-value** |
| **Actual Disposition** |  |  |  | 0.029 | 0.89 |  |  |  | 0.038 | 0.69 |
| ICU | 2 | 2 | 4 |  |  | 11 | 5 | 16 |  |  |
| Not ICU | 9 | 11 | 20 |  |  | 39 | 24 | 63 |  |  |
| **Total** | 11 | 13 | 24 | 0.029 |  | 50 | 29 | 79 | 0.038 | 0.050 |

Table 2. Cohen’s

|  | **Toxicologist’s Recommendations** | | | |
| --- | --- | --- | --- | --- |
|  | **ICU** | | **Not ICU** | |
| **INTOXICATE’s Recommendations** | | **INTOXICATE’s Recommendations** | |
| **ICU**, N = 11*1* | **Not ICU**, N = 5*1* | **ICU**, N = 39*1* | **Not ICU**, N = 24*1* |
| **Respiratory Insufficiency** | 6 (55%) | 2 (40%) | 7 (18%) | 1 (4.2%) |
| **Cirrhosis** |  |  |  |  |
| Yes | 0 | 0 | 2 (5.1%) | 0 |
| **Dysrhythmia** | 5 (50%) | 1 (20%) | 22 (56%) | 1 (4.2%) |
| **Secondary Reason for ICU Admission** |  |  |  |  |
| Yes | 1 (9.1%) | 0 |  |  |
| No |  |  | 39 (100%) | 24 (100%) |
| **GCS** |  |  |  |  |
| 3 | 3 (27%) | 0 | 0 (0%) | 0 (0%) |
| 5 | 1 (9.1%) | 0 | 0 (0%) | 0 (0%) |
| 11 | 0 (0%) | 0 | 1 (2.6%) | 0 (0%) |
| 12 | 1 (9.1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 13 | 2 (18%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 14 | 0 (0%) | 0 (0%) | 2 (5.1%) | 0 (0%) |
| 15 | 4 (36%) | 5 (100%) | 36 (92%) | 24 (100%) |
| **Exposure Category** |  |  |  |  |
| Alcohol | 0 (0%) | 1 (20%) | 1 (2.6%) | 3 (13%) |
| Analgesic | 1 (9.1%) | 2 (40%) | 2 (5.1%) | 6 (25%) |
| CO, As, CN | 1 (9.1%) | 2 (40%) | 5 (13%) | 1 (4.2%) |
| Combination | 3 (27%) | 0 (0%) | 8 (21%) | 5 (21%) |
| Street Drugs | 3 (27%) | 0 (0%) | 5 (13%) | 2 (8.3%) |
| Unknown | 3 (27%) | 0 (0%) | 7 (18%) | 1 (4.2%) |
| Antidepressants |  |  | 6 (15%) | 5 (21%) |
| Sedatives |  |  | 5 (13%) | 1 (4.2%) |
| **Pulse** | 87 (76, 104) | 70 (65, 74) | 101 (80, 115) | 85 (73, 91) |
| **SBP** | 113 (91, 149) | 112 (105, 130) | 120 (114, 146) | 123 (115, 129) |
| **Age** | 38 (30, 53) | 30 (25, 38) | 47 (34, 59) | 27 (20, 32) |
| *1* n (%); Median (IQR) | | | | |