***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 treatment3. Less than half of poisoned patients admitted to the intensive care unit (ICU) receive ICU level care4. 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 ingestion9.

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 floor13. 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 to the derivation cohort. If INTOXICATE generalizes to the American healthcare system, it would prevent unnecessary admissions and increase ICU capacity. The main goal of our study was to externally validate INTOXICATE. Our secondary goals were to evaluate the agreement between the recommendations of INTOXICATE and those of the bedside toxicologist and to determine the generalizability of INTOXICATE to all patients presenting to the Emergency Department with suspected poisoning. Our motivation for comparing INTOXICATE to bedside toxicologists was to determine whether INTOXICATE’s decision reflected sound medical decision making. Our motivation for determining the generalizability to patients in the Emergency Department is that INTOXICATE will have a greater impact if used to avoid unnecessary ICU admissions rather than downgrade the patient after admission to the ICU.

***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 INTOXICATE’s performance in Emergency Department patients was the same.

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 9 who were under 12, ultimately including 103 patients for analysis (Figure 1). The median age [interquartile range] of adolescents was 15 [14-16] and of adults 35 [28-50]. Adults were more commonly admitted to a general medical floor than adolescents and adolescents more commonly discharged. Neither tendency reached 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 67 (65%) discharged or transferred directly to psychiatry. Of the 20 patients admitted to the ICU, 16 (80%) were older than 18.

**External Validation.** INTOXICATE recommended admission for 11 of the 16 adult patients (69%) that were admitted to the ICU, potentially reducing ICU admissions by 31%. Of the 5 patients for whom INTOXICATE did not recommend ICU admission, 2 needed hyperbaric treatment and 3 []. In the authors’ institution, any patient who receives hyperbaric oxygen is admitted to the ICU. The hyperbaric chamber is in the ICU. 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].

**Performance in the ED poisoned population.** Of the 103 patients included in the analysis, INTOXICATE recommended admitting 61 (59%) 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. 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.

INTOXICATE recommended ICU admission in 39/79 (49%) of adults 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.

**Performance in 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 to make statistically valid conclusions.

**Threshold Adjustment for ED Population.** The threshold in INTOXICATE accounts for how poisoned patients who are not critically ill may still have a concerning exposure and abnormal clinical findings. The numerical value of the threshold expresses the relative prevalence of these concerning clinical features in the critically poisoned patient and non-critically poisoned patient. This ratio may differ in the ED population than in one preselected for the ICU. To determine the impact of adjusting INTOXICATE’s threshold, we performed an ROC analysis to identify the cutoff that maximized sensitivity and specificity in the ED population and then evaluated INTOXICATE’s performance at that threshold. ROC analysis identified 17 as the optimal cutoff in the ED population (Figure 2). The original threshold was 6. If we used the higher cutoff, Cohen’s κ increased from 0.04 [-0.092 to 0.173] (no agreement) to 0.49 [0.263 to 0.718] (fair agreement) and the overall ICU admission rate fell from 49% to 9%. INTOXICATE recommended ICU admission in 8/79 (10%) of adults and 1/24 (4%) of adolescents.

***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 adults in our study for whom toxicology recommended ICU admission, INTOXICATE would have reduced ICU admissions by 32% (5/16), consistent with the effect size in 14. Including adolescents, the reduction becomes 35% (7/20). There were too few adolescents to estimate the effect size in this subgroup.

If directly applied to all Emergency Department patients who received a toxicology consult, INTOXICATE would nearly triple ICU utilization, from 21 ICU admissions to 61 with a rationale that had no statistically significant agreement with the recommendations of bedside toxicologists. If the threshold for admission is increased to 17, INTOXICATE would have reduced ICU admissions by 40% (8/20) with a rationale that had fair agreement with the bedside toxicologist.

Variation in practices across health care systems may contribute to imperfect agreement between INTOXICATE and the bedside toxicologist. At the authors’ institution, all patients receiving hyperbaric treatment are admitted to the ICU because the hyperbaric chamber is in an ICU, which decreases the agreement with INTOXICATE. It is practice at the author’s institution to perform extended observation in the ED. This may not be possible in other healthcare systems. The toxicologist considers features INTOXICATE does not, such as EKG intervals, findings from the physical exam and patient interview and the patient’s course after a period of observation.

The improvement in INTOXICATE’s performance after increasing the threshold for admission demonstrated that INTOXICATE can be applied to poisoned patients under evaluation in the ED. Adjusting the threshold is one way to account for the difference in clinical importance between abnormal vital signs on arrival and sustained vital sign abnormalities, as would occur in patients admitted to the ICU.

The architecture of INTOXICATE may predispose it to disagree with toxicologists. INTOXICATE uses APACHE IV categories for xenobiotics, 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 after ingestion of an SSRI than after a tricyclic antidepressant. An opioid classified as a *Street Drug* is more likely to require ICU care than an opioid classified as an *Analgesic*. It is not clear how to classify diverted opioids used to self-medicate for pain.14 INTOXICATE does consider polysubstance intoxication to contribute to the likelihood of needing ICU level care, leading to the ironic prediction that polysubstance ingestions are lower risk. Polysubstance exposures are implicated in 48-58% of unintentional overdose deaths17,18. In our cohort, 18 out of 28 adult patients (64%), had a polysubstance ingestion.

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, there were no toxicology consults for adults with isolated alcohol intoxication.

***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. Increasing INTOXICATE’s threshold for ICU admission improved its performance in the ED population, leading to 40% fewer admissions and fair agreement with bedside toxicologists.

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**A flowchart of a number of individuals

Description automatically generated**

Figure Screening and Inclusion of Patients.

A graph of a curve

Description automatically generated with medium confidence

Figure ROC

| **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

|  | **Adolescent** | | | | | **Adult** | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Predicted Disposition | |  |  |  | Predicted Disposition | |  |  |  |
| ICU | Not ICU | **Total** | **Cohen’s kappa** | **p-value** | ICU | Not ICU | **Total** | **Cohen’s kappa** | CI |
| **Actual Disposition** |  |  |  |  |  |  |  |  | 0.49 | 0.263 - 0.718 |
| ICU | 1 | 0 | 1 |  |  | 7 | 1 | 8 |  |  |
| Not ICU | 3 | 20 | 23 |  |  | 12 | 59 | 71 |  |  |
| **Total** | 4 | 20 | 24 |  |  | 19 | 60 | 79 |  |  |

|  | **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) | | | | |