***Abstract:***

***Introduction:***

Although exposures to substances are prevalent, 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 rarity of life-threatening ingestions leads to the diagnostic challenge of how to identify them without subjecting others to unnecessary care and needlessly consuming resources. Approximately 25% of poisoned patients admitted to the hospital for medical treatment require no medical treatment(2). Less than half of poisoned patients admitted to the intensive care unit (ICU) receive ICU level care(3).

The success of clinical decision tools for acetaminophen (5), tricyclic antidepressants (6), paraquat (7,8), and bupropion (4,9) demonstrate that clinical decision tools can 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(4).

Despite their success, these decision support tools apply only 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 (10,11). Medical toxicologists in the Netherlands recently derived and internally validated a clinical decision support tool to help physicians determine whether poisoned patients required ICU admission or could be safely managed on a general medical floor (12). The 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 the initial derivation study INTOXICATE would have reduced ICU admissions by 34% if applied. INTOXICATE was derived from patients already admitted to the ICU. If INTOXICATE generalizes to the American healthcare system, it would prevent unnecessary admissions and increase ICU capacity. A critical difference between the Dutch and US healthcare systems is that in America, substantial care happens in the Emergency Department, directed by the Emergency Physician in consultation with bedside toxicology or Poison Control rather. This difference raises the question of whether INTOXICATE can be applied to patients in the Emergency Department.

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 the initial derivation study did not because adolescents comprise 130/605 (21%) of our consultations and 31% of nationwide calls for intentional ingestions(13,14). We postulated that INTOXICATE generalizes to adolescents, who 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.  ***[COMMENT: Consider adding stronger justification for including adolescents, as the original study was on adults.]***

***Definitions***

We defined needing ICU care as (15) 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 (16) for further detail. For the sake of brevity we use the term “INTOXICATE” to mean the prediction model presented in (12) and derived from patients in the INTOXICATE cohort.

INTOXICATE defined dysrhythmia as hemodynamic instability in the 24 hours before ICU admission and arrhythmia, tachycardia, second or third-degree AV block, or atrial fibrillation with a ventricular rate greater than 120 beats per minute. We used the same definition.

INTOXICATE considers 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 and did not die during admission.

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

***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 of the adolescents and adults were, 15 [14-16] and 35 [28-50], respectively, expressed as median [interquartile range]. Adults were more likely to be admitted to a general medical floor than adolescents. Adolescents were more likely to be discharged (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. ***[COMMENT: Did you assess whether missing data were random or systematically related to certain patient characteristics?]***

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%) were 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 a lower risk score because it considered the xenobiotic to which exposure was reported to be low 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 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 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 ingestion acetaminophen requiring 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 alcohol intoxication and was hypertensive, tachycardic, with GCS 10 (IRS = 4). In INTOXICATE’s schema, report of alcohol ingestion decreases the need for ICU admission. INTOXICATE recommended the ICU for 9 adolescents for whom Toxicology 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*.*  ***[COMMENT: Acknowledge that this subgroup may be underpowered for robust statistical 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. We found that INTOXICATE had no statistically significant agreement with bedside toxicologists.

Variation in practices across health care systems may contribute to low agreement between INTOXICATE and the bedside toxicologist. In the US healthcare system, the most likely user of INTOXICATE is the Emergency Physician, who determines the initial level of care. At the authors’ institution, all patients receiving hyperbaric treatment are admitted to the ICU because the hyperbaric chamber is in an ICU. The agreement between INTOXICATE and the initial disposition may be different in health care systems that use Poison Control instead of bedside consultation. The toxicologist considers features INTOXICATE does not, such as clonus, abnormal EKG intervals, progressive limb swelling, inability to tolerate food or liquid by mouth, or acidemia. INTOXICATE does not consider trends in vital signs. Some Emergency Departments may be able to observe patients for long enough to discharge what would be an admission in other locales. 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 patients 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 recommended the ICU for all patients with any of the above criteria, suggesting an opportunity to refine criteria, for example considering degrees of respiratory insufficiency. The lack of significant difference in cirrhosis between adolescents and adults in our study is likely an artifact of low sample size. No adolescents were reported as having cirrhosis and only 2/79 (2.5%) of adults. The low prevalence of cirrhosis in adults in our study may reflect how Toxicology is rarely consulted at our institution for alcohol intoxication or alcohol withdrawal.

INTOXICATE uses APACHE IV diagnoses to classify ingestions, which may not agree with the bedside toxicologist’s classification. The APACHE IV category *Antidepressants* groups SSRIs, tricyclic antidepressants, and lithium together. This grouping leads INTOXICATE to treat clinical features in all three types of ingestions the same. Tachycardia has different clinical significance in SSRIs than tricyclic antidepressants. Ingestion of an opioid classified as a *Street Drug* rather than *Analgesic* is more likely to require ICU care. This division doesn’t account for ingesting multiple opioids, like methadone and heroin. The category *Combination of two subtypes of intoxication* groups together all polysubstance intoxications. Brandenburg did not include polysubstance intoxication as a covariate in their model or assign it 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 validity of prognosticating clinical course from this variable.  ***[COMMENT: Since bedside toxicologists do not use APACHE IV, could this classification mismatch contribute to differences in recommendations?]***

***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) | | | | |