***Abstract:*** *To structure the abstract, use the same terms used to break the text into sections. The Abstract should not include abbreviations.*

***Introduction:*** *This section should state the relevance and background to the study, its rationale and main objectives. Please note that only common abbreviations should be used in the main text, which should be explained at first use.*

A challenge during the initial evaluation of the poisoned patient is to prognosticate the severity of an ingestion from incomplete. poisoned intensive care unit ()of For example, admitting all ingestions of more than 450 mg of bupropion to the ICU for 24 hours to observe for ventricular dysrhythmias, leads to approximately 2,000 unnecessary ICU admissions across the United States each year1. **(place for continued references to all those studies showing high # of admits but low # of deaths; not sure how many to use to make the case).**

A clinical decision support tool would help guide emergency physicians in selecting the level of care for poisoned patients and in standardizing recommendations from medical toxicologists. It is difficult to make one tool that accurately risk-stratifies the variety of physiological derangements that poisoned patients can have. [Poison Severity Score]

**Something here about need for better discrimination.**

Medical toxicologists in the Netherlands developed INTOXICATE, a clinical decision support tool to help physicians determine whether poisoned patients required ICU admission or could be safely managed on a general medical floor2. INTOXICATE identified easily obtainable clinical covariates as predictors of ICU requirement (defined as mechanical ventilation and/or vasopressors in the first 24 hours of ICU stay, or death at any point during hospitalization) in patients who were admitted to the ICU and received a diagnosis of intoxication. INTOXICATE was internally validated by resampling and correctly identified 34% of ICU patients who did not ultimately require ICU-level care. If applying INTOXICATE has a similar effect in the American healthcare system, it would simultaneously improve the care of poisoned patients and increase access to the ICU.

This outcome, however, assumes INTOXICATE would only be applied to patients who would otherwise have been admitted to the ICU. It remains unclear how having access to such a tool would change clinical decision making. For such a tool to have use in reducing ICU admissions, it must not only be externally valid, but also demonstrate sufficient specificity such as to not bias practitioners to admit patients who do not need ICU admission and would not have been admitted in the absence of a positive score.

The goal of this study was to externally validate INTOXICATE in as a clinical decision tool for the emergency physician or bedside toxicologist to use in the initial evaluation of a poisoned patient.

***Methods:***

***Setting***

We conducted a retrospective study of toxicology consultations from January 2023 to April 2024 at one urban tertiary care center with a 24/7 bedside toxicology service. We screened all consultations. We excluded patients younger than 12 years of age. The original study did not include patients younger than 18. We included adolescents because they are an age-group with frequent ingestions and have comparable cardiovascular and neurological responses to xenobiotics.

***Subjects***

***Definitions***

INTOXICATE assigns each patient a score, the INTOXICATE Risk Score (IRS). Each patient receives a score for each value of certain 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. We refer the reader to (1) for further detail on calculating IRS.

***Statistical analyses***

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

***Results:*** *Present your results in logical sequence in the text, tables, and illustrations.*

**Description of Data Set.**

**Insert summary of patient statistics here (with a table): be sure to note that the only intoxication types encountered were *street drug, combination, unknown* and one instance of *sedatives.***

**Performance of INTOXICATE.** Table X shows the performance.

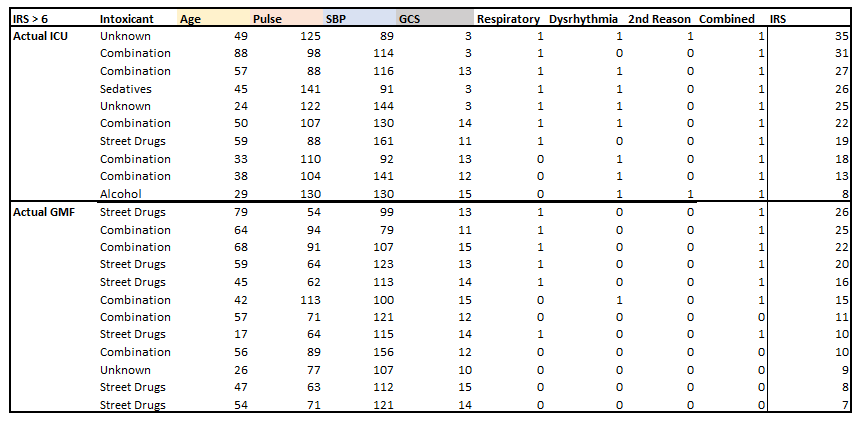
Of the remaining 110 patients, 21 (19%) were admitted to the ICU, 16 (14%) to a general medical floor, and 75 (68%) were discharged or transferred directly to psychiatry. INTOXICATE recommended ICU admission for 14/21 (67%) of patients for whom the toxicologist recommended ICU admission, ICU admission for 12 of the 16 (75%) patients for whom admission the toxicologist recommended a general medical floor, and ICU admission for and 37 of the 44 (84%) patients for whom the toxicologist recommended discharge. 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. The interrater agreement (Cohen's kappa) between INTOXICATE and the actual disposition was 0.045 (p=0.474).

Of the 7/29 patients for whom INTOXICATE did not recommend ICU admission (IRS ≤ 6), none were recommended for ICU admission by toxicology. None had any respiratory distress, dysrhythmias, or second reasons for ICU admission. Compared to patients for whom INTOXICATE recommended ICU admission, these patients were younger (mean age 30 years vs 49 years, *p* = 0.001) and had higher GCS scores (mean GCS 14 vs 11, *p* = 0.03). Heart rate and SBP were not significantly different between these two groups.

We examined the subset of patients for whom INTOXICATE recommended ICU admission, comparing those for whom toxicology agreed with INTOXICATE and admitted the patient to the ICU (IRS(+)/ICU(+), *n* = 10), and those for whom toxicology recommended a floor admission or discharge (IRS(+)/ICU(-), *n* = 12). IRS was higher in the IRS(+)/ICU(-) group, but there was (IRS(+)/ICU(+) IRS = 22.4, 95% CI [16.6, 28.2]; IRS(+)/ICU(-) IRS = 14.9, 95% CI [10.6, 19.2], *p* = 0.03). Patients recommended for ICU by both IRS and toxicology had significantly higher heart rates than those recommended for ICU by IRS but not toxicology (IRS(+)/ICU(+) HR = 111 bpm, 95% CI [99, 124]; IRS(+)/ICU(-) HR = 76 bpm, 95% CI [64, 88], *p* < 0.001). Only 1 of 12 patients in the IRS(+)/ICU(-) group was tachycardic at time of consulation, compared to 7/10 patients in the IRS(+)/ICU(+) group. Presence of one or more comorbidities (respiratory insufficiency, dysrhythmia, second reason for ICU admission) was associated with toxicology recommendation for ICU admission (IRS(+)/ICU(+) = 10/10, IRS(+)/ICU(-) = 7/12, Fisher exact test *p* = 0.04). GCS was lower in the IRS(+)/ICU(+) group (IRS(+)/ICU(+) GCS = 9.0, 95% CI [5.2, 12.8]; IRS(+)/ICU(-) GCS = 13.2, 95% CI [12.0, 14.3], *p* = 0.04). Age, SBP, and intoxication type were not signficiantly different between the two groups.

→ **some spots up here where I reported 95% CI because it seems like the expected thing to do but for which SD may be more informative, as it conveys spread (for example, it’s not much of a shocker that IRS+ICU+ patients have a higher IRS scores than IRS+ICU-, and what I’d rather convey is the degree of overlap between the two). I also don’t want to overwhelm with numbers. I will revisit this later.**

→ **maybe to put in methods; t tests assuming unequal variances were used to compare continuous variables, Fisher exact tests were used to compare incidence of dichotomous variables.**

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*Covariates contributing to IRS for all patients recommended for ICU treatment by a positive IRS score (>6). Dichotomous variables are encoded as 1 = true, 0 = false.*

***Discussion:***

If applied to patients for whom toxicology recommended ICU admission, INTOXICATE would have reduced ICU admissions by 33% (7/21), consistent with the findings of Brandenburg et. al.. We found that in a cohort of ED patients, however, INTOXICATE also recommended ICU admission for 49 of 60 patients for whom toxicology recommended a GMF or discharge. This would have *increased* ICU utilization by around 200% (from 21 to 44). While we expect that the diligent practitioner would not employ INTOXICATE for all patients, instead reserving INTOXICATE as a rule-out tool for patients who would otherwise have been admitted to the ICU, our findings demonstrate a concerningly low threshold for over-utilization that would negate the beneficial effects of INTOXICATE.

Our analysis found a no more than chance agreement between INTOXICATE and the toxicologist at bedside, suggesting that the two approaches use different criteria for ICU admission. These criteria may include components of the patient’s history and physical exam excluded from the INTOXICATE model, such as presence of an intoxicant with known delayed adverse effects, laboratory findings, or concerning trends during the ED observation period. Additionally, these differences can reflect geographic variation in the type of poisoning, and variation in care practices across health care systems, such as routine ICU admission for certain intoxication types or monitoring of medication infusions (e.g., naloxone or NAC).

INTOXICATE does identify particularly strong predictors of an uneventful ICU course, such as acute intoxication with alcohol. We were unable to validate this finding in our cohort, as no patients presented with alcohol intoxication alone. INTOXICATE also strongly weighs the risk associated with respiratory insufficiency, dysrhythmia, cirrhosis, and a second nonintoxication APACHE IV reason for ICU admission. We found that all patients admitted to our ICU had either respiratory insufficiency, dysrhythmia, or both, demonstrating their significance in decision making by toxicologists. Though 7/19 patients safely **(would need to know the actual outcomes of hospital stay to say *safely*, but I’m presuming it at the moment)** recommended for GMF for discharge by toxicology had one of the above comorbidities, INTOXICATE recommended ICU for all patients with any of the above criteria, suggesting that INTOXICATE is not better than toxicology for the purpose of ICU rule-outs in patients with significant comorbidities.

The IRS threshold of >6 points was chosen by Brandenburg et. al. in order to minimize false negatives, given the consequences of withholding or delaying ICU care from patients who require it. As a result, INTOXICATE frequently recommends ICU admission in ED patients who would not have otherwise been admitted to the ICU. Even among Brandenburg’s internal cohort of ICU patients, the IRS had a specificity of 36.2% for requirement of ICU-level care. Though this specificity would be acceptable were it applied to ICU patients, it may not be sufficient for a clinical prediction model recommended for use in the ED given the purpose of the score,which is to reduce ICU admissions before, rather than after, the patients are admitted to the ICU **(sarcastic, I’ll rephrase it later)**.While there have been risk models developed with mortality as an outcome, both for the general patient population and specifically for intoxicated patients **(cite cite cite)**, these have generally been designed as prognostic tools for use in the ICU, and their use as predictors of an uneventful ICU course from the ED has not been evaluated. The strength of INTOXICATE is that it was modelled with ICU requirement, rather than in-hospital mortality, as an outcome, appropriate for resolving the unique issue of disproportionately uneventful ICU courses in intoxicated patients. With this strength, however, there are also weaknesses to a model intended for use in an ED cohort but developed on data from an ICU cohort. **Here I would write something about our results with changing the threshold, and the associated risks of false negatives, though I’ll wait until I have the most up-to-date patient list for this step.**

Intoxication syndromes are highly variable and dependent on the intoxicant. A given clinical finding can often be reassuring in one intoxication, and concerning in another. For certain intoxications, one clinical finding can be particularly predictive of patient outcomes. For example, **Idowu et. al.** found that absence of tachycardia in the first 8 hours of observation following Bupropion overdose had 100% NPV for delayed (>12 hours following ingestion) adverse effects, independent of coingestions, patient characteristics, and other clinical findings. (**can probably find and fit in a few more similar examples for other intoxicants, where a certain clinical finding is particularly predictive of outcome)**.Interestingly, Brandenburg et. al. reported that no interaction terms were found between intoxication type and the other covariates included in their model. Other mortality prediction models have addressed the issue of intoxicant type by additionally categorizing intoxicants according to a mortality index (deaths / exposures), and in cases of polysubstance poisonings, designating the intoxicant with the highest mortality index at a given dosage as the primary intoxicant to be used for risk prediction **(Han et. al.). I think that last bit is worth mentioning but I’m not sure what commentary, if any, to tack on after it.**

Another potential limitation of INTOXICATE is the usage of APACHE IV diagnoses for classification of intoxicant, which was the only indication of intoxication type available to Brandenburg et. al. in their model development cohort. *Antidepressants*, for example, is the diagnosis given to an intoxication with *any* type of antidepressant, including SSRIs, tricyclics, lithium, and others, all of which have potentially different mechanisms of toxicity. A category is given for *analgesics*, presumably pharmaceuticals, however intoxication with opiates produced as drugs of abuse would be classified as a *street drug*, along with cocaine and amphetamines. A category is included for *CO, As, or CN*, but intoxications with other poisons, such as those found in household products or industrial settings, would presumably fall under *toxins not otherwise specified.* The category *combination of two subtypes of intoxication* serves as a catch-all for polysubstance intoxications, however this would fail to identify polysubstance intoxications in patients with two or more mechanistically different intoxicants within the same APACHE IV classification, and Brandenburg **(for reasons unknown and not explained in their paper)** did not include polysubstance intoxication as a covariate in their model or assign it a risk score. This is particularly important given the significant morbidity and mortality associated with polysubstance intoxications, being implicated in 48-58% of overdose deaths **(cited Peppin below, but will find more because that source is specific to unintentional drug overdose and there is definitely plenty more to cite and mention).** Accounting for polysubstance intoxication in clinical prediction models poses the additional challenge of frequently incomplete or inaccurate reporting of intoxicant by patients and collateral sources. **(I’ll try to find a source for how many patients present with unknown intoxication type later)**. We note that for 18/28 of intoxicated patients in our ED cohort, intoxication type was classified as *Intoxicant NOS* or *Combination*, with all but one of the remainder being classified as *Street drug.*

**It may be worth finding out what happened to the 7/21 patients who were admitted to the ICU but for whom INTOXICATE recommended GMF, particularly whether they ultimately required ICU-level care. It would be concerning if INTOXICATE was ruling out the wrong patients.**

***Conclusions:*** *This must summarize the main paper. Ensure that extrapolations are reasonable and that conclusions are justified by the data presented, and indicate if the study design can be generalized to a broader study population.*

A clinical prediction model may demonstrate excellent performance in retrospective validation, but the impact it will have on clinical practice is dependent on when it is chosen for use, how its results are interpreted, and whether its recommendations are accepted. Without instruction, it is unlikely that a practitioner will use a model exclusively or inclusively for patients that would have been selected for inclusion in model development, it is unlikely that all practitioners will place equal weight on the results of a given score, and practitioners may be biased to defer to (and document) the results a clinical prediction model only when it agrees with their own judgement. At this stage, INTOXICATE lacks necessary inclusion and exclusion criteria that would guide its use.

This brings up important questions on the role of clinical decision rules in ICU admission for intoxicated patients. Other commonly used clinical decision rules that recommend some course of action (e.g., Ottawa Knee/Ankle, Wells’ DVT/PE, Canadian Head CT, PECARN) were created to help identify patients who would benefit from an action in cases where the risks associated with the action are low (e.g., diagnostic imaging) and the consequences of a false negative are high (e.g., untreated fracture, thromboembolism, or ICH). When these rules are appropriately applied to patients with reasonable pre-test probability of disease based on H&P, just one or two points are sufficient to communicate sufficiently high risk of an outcome to indicate intervention. In contrast, for INTOXICATE, the problem being addressed by the decision rule is the outcome of the decision rule itself - ICU admission - and a slew of non-specific clinical covariates found to have independent (but not independently sufficient!) associations with the outcome are assessed. At this time, INTOXICATE is an arithmetical substitute for the physician’s gauge of pre-test probability, but is not the test itself. In that way, INTOXICATE is more closely related to a mortality prediction score, such as APACHE, and mortality prediction scores are not clinical decision rules. **There’s a lot left that could be written for the conclusion, but I think it’s best to shape up the rest of the paper before I conclude it.**

**Other points to work in**

* **This paper is totally not finished**
* **Not yet known whether a mortality prediction score, developed for intoxicated patients or the general population, at a certain threshold is an equal or better predictor of ICU requirement than a model developed on ICU patients with known outcomes**

**References**

1. Simpson, M. et al. Clinical and electrocardiographic factors associated with adverse cardiovascular events in bupropion exposures. *Clin Toxicol* **61**, 529–535 (2023).
2. Brandenburg, R. et al. The need for ICU admission in intoxicated patients: a prediction model. *Clin Toxicol* **55**, 4–11 (2017).
3. Han, K. S., Kim, S. J., Lee, E. J., Shin, J. H., Lee, J. S., & Lee, S. W. (2021). Development and validation of new poisoning mortality score system for patients with acute poisoning at the emergency department. *Critical care (London, England)*, *25*(1), 29. <https://doi.org/10.1186/s13054-020-03408-1>
4. Idowu, D., Ezema, K., Corcoran, J., & Farkas, A. (2024). The predictive value of heart rate in determining clinical course after a bupropion overdose. Clinical Toxicology, 1–7. <https://doi.org/10.1080/15563650.2024.2347514>
5. Peppin, J. F., Raffa, R. B., & Schatman, M. E. (2020). The Polysubstance Overdose-Death Crisis. Journal of pain research, 13, 3405–3408. https://doi.org/10.2147/JPR.S295715