Potential adverse drug events: intensive care unit cohort

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ABSTRACT

Introduction: Adverse drug events are associated with morbidity and mortality, high hospital stay rates and high costs. Intensive care unit patients are one of the main risk groups for the occurrence of these events. The use of triggers, which indicate potential events, can simplify detection by systematic screening of medical records and enables continuous measurement. **Objective:** Analyze potential adverse events and correlate their triggers with the length of stay, number of medications, and comorbidities in patients admitted to an adult intensive care unit. **Methods:** A longitudinal study was conducted with patients admitted to intensive care at high complexity hospital in São Paulo, Brazil. A probabilistic sample consisting of medical records of 83 patients hospitalized, for at least 24 hours, for clinical treatment and who received at least one medication. In the identification of the events the adapted instrument of the Institute for Healthcare Improvement was used, which includes drug, biochemical, and clinical triggers. The Pearson's correlation test was used to correlate the number of triggers with the length of stay, the number of medications, and comorbidities, and the significance of $p<0.05$. **Results:** Antihistamines (43.4%), creatinine increase (50.6%), and lethargy (20.5%) were the most frequent triggers for each category. Among the drugs, acetylsalicylic acid (67%) and omeprazole (55%) were prominent. There was a positive correlation between the total number of triggers and time of hospitalization, the number of medications, and comorbidities ($r=0.961$, $r=0.555$, and $r=0,210$ respectively; $p<0.001$). **Conclusions:** Outstanding triggers can be expected for intensive care units' cardiac patients and suggest warning for professionals involved in monitoring these events.

Keywords: Intensive care units, Drugs monitoring, Pharmacovigilance, Patient safety, Nursing.

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INTRODUCTION

In health care services, Adverse Drug Events (ADE) represent a relevant challenge for health care teams and managers. They can be defined as a harmful and unintended harm involving the use of medicines. ADEs may be associated with negative outcomes such as prolonged hospital stay[1], increased morbidity and mortality, and increased costs[2], being one of the main determinants of patient safety and quality of care[3]

Studies have described that between 0.7% and 34.1% of hospitalized patients are affected by ADE[4-14], which is clinically significant or frequent in critically ill patients. In Intensive Care Units (ICUs), the vulnerability of patients to ADE is even higher, especially due to the existence of factors such as severity, organ dysfunctions, comorbidities, the need for numerous therapeutic procedures, and the use of complex polypharmacy[15-16]. Multicenter research has pointed out considerable differences in ADE rates between critically ill and non-critically ill patients. The prevalence of reported medication errors showed a higher rate in critically ill patients (3.7% vs. 1.9%)[17]. Errors that caused permanent damage, required intervention, or resulted in death were two to three times more frequent in ICUs[15-17].

In this context, monitoring potential ADE is of fundamental importance for preventing or reducing patient harm. The IHI trigger Tool is a method for identifying ADEs based on a retrospective review of medical records. This method proposed by the Institute for Healthcare Improvement (IHI) uses triggers that can indicate potential ADEs. Triggers are explicit criteria that, once identified, must be submitted to professional analysis in order to prove or disprove the potential ADE, reduce harm, and implement continuous improvement[18-19].

Previous studies conducted in hospitals have adopted the IHI[6-9,15,20] list, which have contributed to the knowledge about the incidence and factors associated with ADEs. However, aspects related to the correlation of triggers and important clinical variables, in the ICU setting, remain unexplored. Thus, the aim of this study was to analyze potential adverse events and correlate their triggers with the length of stay and number of medications in patients admitted to an adult intensive care unit.

MATERIAL AND METHODS

Ethical aspects

The project was approved by the Research Ethics Committees of the Nursing School and Heart Institute of the University of São Paulo (opinion 759,178) and is in accordance with the National Health Council Resolution - 466/12 of Brazil[21]. Participants were exempted from the Informed Consent Form because there was no contact between the researcher and the participant.

Study design and setting

Retrospective cohort carried out in the ICU of a public hospital of high complexity in the city of São Paulo. This service, specialized in the care of people with cardiopulmonary diseases, is a national reference and participates in the Sentinel Network Hospitals of the Brazilian Health Regulatory Agency - ANVISA, a regulatory agency linked to the Brazilian Ministry of Health. The notifications of ADE are done spontaneously by a digitalized standard instrument and/or online via the institutional intranet. All professionals of the multi-professional team are responsible for AE notifications. The development of this observational study was guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[22].

Sample, inclusion and exclusion criteria

The probabilistic sample was composed of adults (age 18 years or older), admitted to the ICUs, who presented in their medical records at least one trigger during their stay in the unit. Patients whose medical records were not found at the service, with incomplete or illegible records, and those admitted for less than 24 hours were excluded. The patient was followed from the day of admission until discharge from the ICU - by discharge or death. For sample calculation, we used the total number of ICU admissions in the last twelve months, a frequency of occurrence of ADE of approximately 13%[4,7,16,20,23,24], losses of 10% and 5% error; thus, the calculation indicated a minimum sample size of 83 participants.

Data extraction

The medical records review for data extraction was based on the reading of medical prescriptions, laboratory tests, medical evolution, notes, and nursing evolution. For data extraction, we used an instrument composed of admission demographic and clinical variables (gender, age, unit of origin, length of stay, diagnosis on admission, and comorbidities); variables related to drug therapy (drug, route, day, and time of administration), triggers (drug, biochemical, and clinical), and ICU discharge status (survivor, death).

Definitions and list of triggers criteria

Potential ADE was defined as the possibility of occurrence of an ADE related to the medication identified in the prescription, measured through the identification of triggers - drug, biochemical or clinical[19]. Polypharmacy was defined as the use of five or more drugs[16,17].

The IHI methodology was used in the identification of the triggers. The original IHI list includes 19 triggers, among which seven are drugs used as antidotes to adverse reactions, eight are biochemical parameters, and four are information about the care and clinical evolution of the patient. In 2003, the list of triggers was expanded from 19 to 24, and the last trigger can be customized according to the needs of the institution[19]. In this study, 22 triggers were used, which were grouped into 12 drugs, five of them used as antidotes to adverse reactions, seven were biochemical parameters, and three were information about the care and clinical evolution of the patient, as shown in Chart 1.

The trigger "protamine sulfate" was added as specific to the institution where the study took place. This trigger aims to detect events related to altered coagulation due to the use of heparin during invasive procedures for diagnosis and treatment of coronary artery disease.

Triggers whose purpose was to detect changes in serum levels of aminoglycosides and digoxin were changed to "use of aminoglycosides" and "use

Chart 1

Triggers of adverse drug events used.

Trigger	Identification Process
• T1 - Antihistamine (hydroxyzine, loratadine, diphenhydramine, ranitidine)	• Hypersensitivity reaction or effect of the drug
• T2 - Vitamin K	•
• T3 - Flumazenil	• Excess warfarin anticoagulation
• T4 - Antiemetics (ondansetron, bromopride, metoclopramide, domperidone, dimenhydrinate, promethazine)	• Excessive sedation by benzodiazepines • Nausea/vomiting related to the use of the medication
• T5 - Naloxone	
• T6 - Antidiarrheal	• Excessive sedation by narcotic
• T7 - Ion exchange resins (calcium polystyrene, calcium gluconate)	• ADE • Hyperkalemia related to renal injury or drug effect
• T8 - Glucose 50%.	• Hypoglycemia related to insulin use
• T9 - Use of digoxin	• Toxic level of digoxin
• T10 - Use of aminoglycosides (amikacin, gentamicin, streptomycin)	• Toxic levels of antibiotics
• T11 - Vancomycin use	• Toxic levels of antibiotics
• T12 - APTT > 100 seconds	• Excess heparin anticoagulation
• T13 - INR > 6	• Excess warfarin anticoagulation
• T14 - Leukocyte count < 3,000 mm3	• Drug-Related Leukopenia
• T15 - Serum or capillary glucose < 50 mg/dl	• Hypoglycemia related to insulin use
• T16 - Serum creatinine > 1.5 mg/dl	• Drug-related kidney injury
• T17 - Platelets < 50.000 mm3	• Drug-Related Thrombocytopenia
• T18 - Vancomycin level > 26 µg/ml	• Toxic levels of antibiotics
• T19 - Excessive sedation, lethargy, falling	• Related to excessive use of medication
• T20 - Skin rash	• Usage/ADE Related
• T21 - Abrupt withdrawal of medication	• Adverse drug event
• T22 - Protamine sulfate (institution-specific)	• Excess heparin anticoagulation

Adapted from Rosich[19].

of digoxin" due to the non-existence of routine collection of these tests in the study setting. The sodium polystyrene trigger, which may indicate hyperkalemia related to the renal injury is not used in the institution and for this reason, was replaced by ion exchange resins (calcium polystyrene, calcium gluconate, and polarizing solution).

Statistical analysis

The collected data were entered into a spreadsheet (Excel Software, 2003) and transferred to the Statistical Package for Social Sciences (SPSS) program, version 20.0, for the following analyses:

- Descriptive with the preparation of frequency tables, measures of position (mean, median, minimum, and maximum), and dispersion (standard deviation and interquartile range) for quantitative variables.

- Correlation test: Pearson's coefficient was used after performing the Kolmogorov Smirnov normality test. For r values between 0.10 and 0.30, we considered a weak correlation; r between 0.40 and 0.60, moderate correlation; and r between 0.70 and 1.00, strong correlation[25].

RESULTS

Sample characteristics

Figure 1 illustrates the flow chart of the sample and the distribution of patients in the respective categories of triggers.

The mean age of the patients was 65.2 years (±16.0), the mean length of stay was 15.6 days (±23.2), and the mean number of comorbidities was 3.2 (±1.7). Other characteristics of the sample are illustrated in Table 1.

Most patients underwent polypharmacy (73.0%), and more than half of these were elderly (59.0%). The mean number of medications during the ICU stay was 9.4 (±4.2). Ninety-one distinct medications were identified; acetylsalicylic acid (67.0%), omeprazole (54.9%), enoxaparin (53.8%), atorvastatin (43.9%), and clopidogrel (43.9%) were the five most frequent medications.

Table 1

Demographic and clinical characteristics of the patients.

Variables	Patients n=83	%
Gender		
Male	43	51.8
Female	40	48.2
Group age		
< 60 years old	29	39.4
≥ 60 years old	54	65.1
Source Unit		
Emergency Room	79	95.2
Admission Unit	4	4.8
Admission Diagnosis		
Myocardial Infarction	30	36.1
Unstable Angina	18	21.7
Heart Failure	16	19.3
Pulmonary Disorders	7	8.4
Myocardiopathies	4	4.8
Arrhythmias	4	4.8
Valvopathies	3	3.6
Acute Cell Rejection	1	1.3
Hospitalization time		
<15 days	59	71.1
≥15 days	24	28.9
Number of comorbidities		
Up to two	12	34.9
Three or more	54	65.1
ICU Death		
No	71	85.5
Yes	12	14.5

Source: Own elaboration.

ADE triggers

A total of 2,463 triggers were identified during 1,448 inpatient days analyzed, with an average of 1.7 trackers per inpatient day and 29.7 tracers per medical record. "Medication" triggers (78.3%) were the most frequent, followed by "biochemical" (63.9%) and "clinical" (26.5%). A maximum of five triggers per patient were identified.

In the category of drug triggers, antihistamines (43.4%), ion exchange resin (34.9%), and

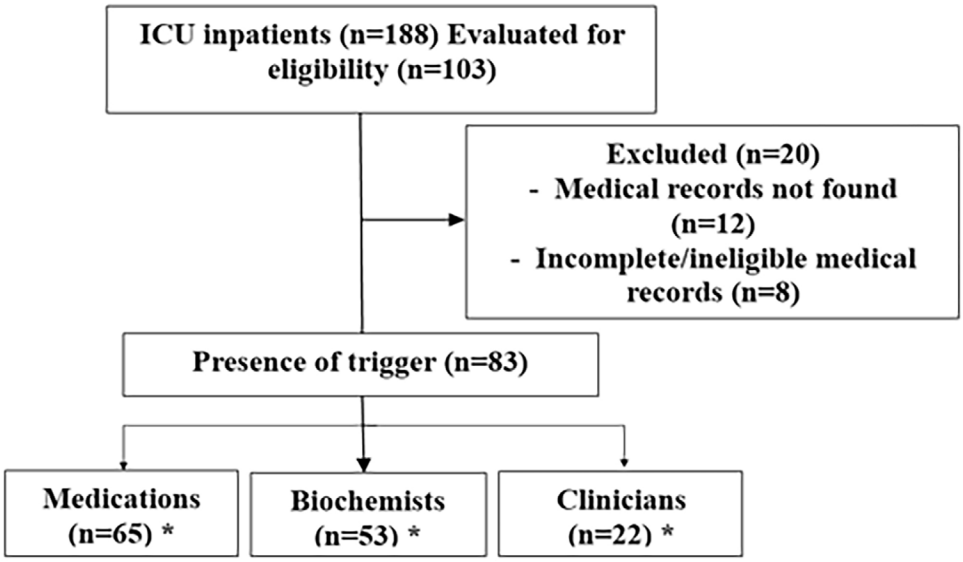

Figure 1: Flowchart of the sample and distribution of patients by type of trigger.
Note: The number of patients in the respective triggers is larger than the sample. Many patients have different triggers at the same time.

antiemetics (22.9%) were the most frequent. Regarding biochemical triggers, the most frequent were serum creatinine level >1.5 mg/dl (50.6%), serum vancomycin level >26 ngl (19.3%), and WBC <3,000mm^3 (15.7%). Clinical triggers were less frequent, with lethargy being the main one (20.5 %). Naloxone, flumazenil, protamine, INR > 6, falling and excessive sedation were not identified. Table 2 presents the distribution of patients according to the identified AMS trigger categories.

There were strong correlations between the total number of triggers and length of hospitalization (r=0.961); moderate with the number of medications (r=0.555) and weak (r=0.210) with the presence of comorbidities; all with statistical significance (p<0.001) (Figure 2).

DISCUSSION

In the hospital setting, the identification of potential ADEs represents fundamental information to assess the quality of care and patient safety. In this study, whose analysis included 1448 days of ICU stay in a hospital specialized in cardio pneumology, it was evident that most of the identified triggers involved medications (78.3%) and biochemical alterations (63.9%). The mean number of triggers was considerably higher (29.7%) when compared to multicenter research conducted in general hospitals (1.5%)[23] and represented more than twice the Brazilian study conducted in an ICU in a teaching hospital (13.3%)[15]. This difference can be explained by the operational diversity in the clinical judgment of the triggers (forms of notification and classification of the event) and by the severity of the patients in this study, admitted to a highly complex hospital.

Consistent with the previous investigations[15,16,26], we observed the participation of the variable's hospitalization time, comorbidities, and number of medications as important contributors to the occurrence of ADE. In patients hospitalized for long periods, the opportunities of exposure to adverse situations are greater[7,23]. The large number of diagnostic and therapeutic interventions combined with the severity of the clinical condition are attributes that favor the occurrence of ADE, especially in teaching hospitals[4,15]. The high turnover of future professionals (physicians, nurses, pharmacists), superimposed on the inherent differences in academic training, contributes to the increase in the number of these adversities. Additionally, in the context of ICUs, patients who present ADE remain hospitalized for longer, which in turn, predisposes to the occurrence of more ADE and increased costs for the institution[7,15,17,27]. Thus, although the triggers express potential ADEs, the findings of this study indicate that this variable shows a behavior like real

Table 2

Distribution of patients according to categories of adverse drug event triggers.

Trigger Category	n	%
Medications		
Antihistamine	36	43.4
Ion Exchange Resins	29	34.9
Antiemetic	19	22.9
Vancomycin	18	21.6
Glucose 50%	9	10.8
Vitamin K	4	4.8
Antidiarrheal	3	3.6
Digoxin	2	2.4
Aminoglycosides	2	2.4
Biochemicals		
Creatinine	42	50.6
Vancomycin level	16	19.3
Leukocytes	13	15.7
Platelets	6	7.2
APTT	3	3.6
Capillary/serum blood glucose	2	2.4
Clinical		
Excessive sedation, lethargy, falling	17	20.5
Abrupt discontinuation of medication	4	4.8
Skin rash	3	3.8

Source: Elaborated by the author. Legend: APTT - Activated Partial Thromboplastin Time.

ADEs, especially regarding the relationships between variables related to the ICU patient's clinical condition.

The identification of the correlation between triggers and the number of medications and the presence of comorbidities, even if moderate and weak, respectively, can be derived from the overlapping of factors inherent to the clinical condition and the consequences of potential ADE[16] and, therefore, requires joint interpretation. Patients with cardiovascular diseases often have associated comorbidities[24], which require the use of medications, usually of continuous use - catecholamines, diuretics, and antiarrhythmics - an aspect that leads to polypharmacy, which was evidenced in the sample. Moreover, a significant part of these drugs belongs to the high-risk group of pharmacological surveillance,

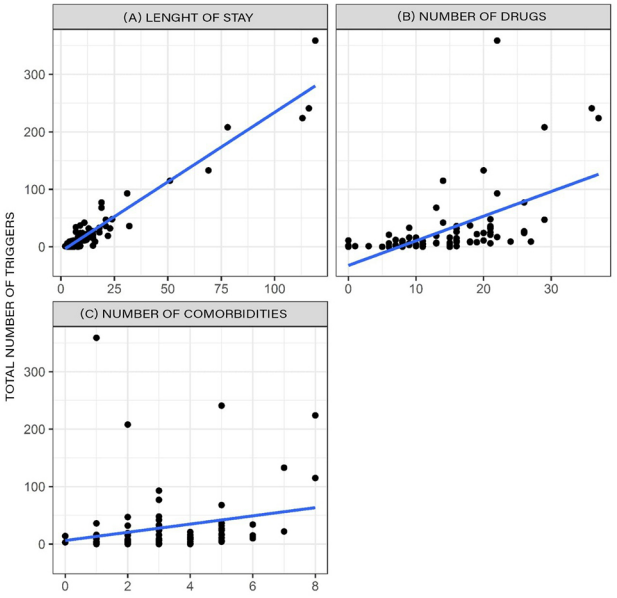

Figure 2: Scatter plots of the analyses between the total number of triggers and the variables length of stay and number of medications.

which increases the risk of potential ADEs[16] and reinforces the advantage of the drug category triggers (78.3%) over the others.

Therapeutic classes of drugs strongly associated with the occurrence of ADE were frequently prescribed in the sample in similarity to a previous study with triggers in a Brazilian hospital[7]. Anticoagulants, antibiotics, cardiovascular agents, hypoglycemic agents, analgesics, and those involved in the treatment of gastrointestinal tract disorders. This aspect precipitated the wide use of antihistamines - H2 antagonists, which were the most frequent triggers (43.4%). The prescription of these drugs had a prophylactic purpose of bleeding related to stress ulcer, a practice that seems to be common in critically ill patients, although it should be used with caution because concomitant use with broad-spectrum antibiotics may increase the risk of *Clostridium difficile* infection[28]. In the present study, identification of this trigger did not indicate a problem caused by prior use of other drugs.

Antiemetics were triggers identified in about a quarter of patients (22.9%). The presence of these agents points to an emphatic concern with preventing stress ulcers, like H2 antagonists, in critically ill patients, especially those undergoing enteral diet

and mechanical ventilation, although this practice is controversial[28,29].

The frequent triggers "increased serum creatinine" (50.6%) and "ion exchange resins" (34.9%) in the sample may indicate the presence of acute renal injury (ARI or AKI) associated or not with hyperkalemia secondary to the use of medications. ICU patients are at high risk of developing ARI (or AKI) due to factors such as comorbidities, sepsis, hypotension, and polypharmacy, more specifically, the use of antimicrobial agents, antihypertensive and chemotherapy drugs, conditions in which avoiding or reducing the prescription of potentially nephrotoxic drugs seems to be the main protection measure[30,31].

As limitations, clinical triggers, "excessive sedation/lethargy", could not be properly judged because sedation assessment scores were rarely found in the records. The detection of potential ADE through retrospective analysis of medical records is conditioned to the quality of registration, which in some situations compromised the search for information. Potential ADEs were not judged in order to evidence their actual occurrence, an aspect that would certainly bring more subsidies for discussion about the prevention and management of ADE in the analyzed service. However, the findings may contribute to expanding triggering strategies for events, with a consequent reduction in the length of hospital stay and costs associated with morbidities and medications.

CONCLUSIONS

The findings allow us to conclude that antihistamines and antiemetics, although discriminated as triggers, in the sample analyzed did not have the character of triggers since they were used to prevent or treat an existing clinical condition and not to indicate adverse effects resulting from previous use of other drugs.

Additionally, the positive correlation between the number of triggers and indirect predictor variables of ADE (length of stay, number of medications, and comorbidities) points out that the severity of the patient may represent one of the main indicators of potential ADE. Thus, the use of triggers represents an essential tool in the identification and monitoring of ADE, especially in high complexity settings, besides encouraging actions to improve the quality of care and patient safety.

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Authors' contributions
VNG worked on data collection and tabulation and article writing; VNG, DDT and SRS: worked on study conception and design and performed data analysis; VNG, DDT and SRS: worked on writing and critical revision of the manuscript. All authors read and approved the final version submitted.

Conflicts of interest
None.

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