



ADVERSE DRUG EVENTS IN INTENSIVE CARE UNITS: A CROSS-SECTIONAL STUDY OF PREVALENCE AND RISK FACTORS

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Background Adverse drug events are considered determinants of patient safety and quality of care.

Objective To assess the characteristics of adverse drug events in patients admitted to an intensive care unit and determine the impact of severity of illness and nursing workload on the prevalence of the events.

Methods A cross-sectional survey based on retrospective analysis of a high-quality patient data management system for a university-based intensive care unit was used. The prevalence of adverse drug events was measured by using a validated global trigger tool adapted for the critical care environment. Severity was determined by using a validated algorithm. Disease severity and nursing workload were assessed by using validated scoring systems. An investigator blinded to the study and a panel of experts assessed putative serious adverse drug events for each drug taken. Characteristics of patients with and without adverse drug events were compared by using univariate and stepwise multivariate logistic regression.

Results During 175 of 1009 intensive care unit days screened, 230 adverse drug events occurred in 79 patients. The most common events were hypoglycemia, prolonged activated partial thromboplastin time, and hypokalemia. Of the adverse events, 96% were classified as causing temporary harm and 4% as causing complications. Both mean severity of disease and nursing workload were significantly higher on days when 1 or more adverse drug events occurred.

Conclusion Adverse drug events were common in intensive care unit patients and were associated with illness severity and nursing workload. (*American Journal of Critical Care*. 2011;20:e131-e140)

Although health care personnel are increasingly aware of patient safety,¹ mistakes and errors inevitably occur, particularly in a complex environment such as the intensive care unit (ICU).² These errors have serious implications for patients' well-being, are costly for society, and are a major public motivation to strive for a safer health care system.³

One factor that influences morbidity and mortality is a harmful or unpredicted reaction to a drug, an almost daily occurrence in hospitals. An adverse drug event (ADE) is defined as harm or injury caused by or from the use of a drug.^{3,4} The event can occur at any stage in treatment. Only 25% of ADEs are either unpredictable or caused by an allergic reaction. In most instances (>70%), the ADE is related to the dose of the drug administered.⁴ Because of the severity of their illnesses, which often require administration of drugs with a high risk for adverse reactions, critically ill ICU patients are more vulnerable to ADEs than are other patients. Moreover, administration of multiple drugs, a common event in the ICU, leads to an increased incidence of ADEs.⁵

Many modern ICUs, including ours at Antwerp University Hospital, University of Antwerp, Edegem, Belgium, have implemented use of a patient data management system (PDMS) that allows for electronic prescription and registration of drugs. Despite the introduction of these systems, inconsistencies in drug prescription still occur. Electronic prescription of drugs can limit medication errors,⁶ but use of this technology cannot completely eliminate errors and does not decrease ADEs.

We designed and conducted a study to measure the prevalence and severity of ADEs in a tertiary ICU that uses our PDMS and to investigate the factors that influence the occurrence of ADEs. We also examined the relationships between disease severity and nursing resources with the occurrence and type of ADE.

Methods

Study Population

This cross-sectional study was based on records of patients who were hospitalized in the University

Hospital of Antwerp ICU, which is managed by board-certified ICU physicians. The Antwerp University Hospital is a tertiary referral hospital that treats almost 2300 patients annually in 5 multidisciplinary, but specialized units (39 beds). The survey population was defined as all medical and surgical adult patients admitted to the ICU between November 1, 2008, and March 31, 2009. Patients were randomly selected from a stratified random sample of the adult population. Patients were eligible if they were more than 18 years old and had stayed in the ICU for 2 or more days. The study was approved by the institutional ethical review board. Data were collected by an investigator blinded to the study and then were coded. After the coding, patients for whom an ADE was scored could not be identified.

In addition, neither the physician nor the nurse who had been responsible for treatment of the patient during the observation period or at the moment of the ADE could be identified.

Instruments

All medical and nursing data in the PDMS (Metavision, iMDsoft, Leiden, the Netherlands) collected during the entire stay of the sample patients were reviewed. Data were gathered after each patient was discharged from the ICU. A wide variety of demographic and clinical data were included in the analysis.

The prevalence of ADE, defined as harm or injury caused by or from the use of a drug, was scored by using a specific global trigger tool that has been validated for measuring ADEs.⁷ This practical and efficient method is based on an original method that uses specific events documented in a patient's record as sentinel signals or triggers.⁸ Each patient's file (electronic PDMS) was therefore systematically screened for the mention of predefined triggers or "designations" for an ADE.⁹ This validated scale was applied and adapted to both the local situation and the ICU environment. A focus group (1 ICU physician, 1 ICU pharmacist, and 2 ICU nurses) retained 14 of the 24 initially defined triggers designed for all units for this particular study (Table 1). High-alert drugs were defined as agents that are frequently

In most cases, adverse drug events are related to the dose of the drug administered.

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Table 1
Triggers used^a

| Trigger No. | Definition | Related to |
|-------------|--|--|
| 1 | Serum level of glucose < 50 mg/dL ^b | Intravenous administration of insulin |
| 2 | Activated partial thromboplastin time >100 s | Intravenous administration of heparin |
| 3 | Serum level of potassium <3.0 mmol/L | Intravenous administration of furosemide |
| 4 | Serum level of potassium >5.5 mmol/L | Potassium administration in patients with renal insufficiency Administration of a potassium-sparing diuretic (spironolactone) to a patient without renal insufficiency |
| 5 | International normalized ratio >3 | Over-anticoagulation with coumarin |
| 6 | Vancomycin peak serum level >40 µg/mL | Intravenous administration of vancomycin |
| 7 | Amikacin trough level >8 µg/dL | Intravenous administration of amikacin |
| 8 | Phenytoin sodium serum level >20 µg/mL | Intravenous administration of phenytoin sodium |
| 9 | Tacrolimus serum level >20 ng/ml | Intravenous administration of tacrolimus |
| 10 | Valproate serum level >100 µg/mL | Intravenous administration of valproate |
| 11 | Cyclosporine serum trough level >300 µg/mL | Intravenous administration of cyclosporine |
| 12 | Vitamin K administered | Over-anticoagulation with coumarin |
| 13 | Sodium polystyrene sulfonate (Kayexalate) administered | Hyperkalemia related to intravenous administration of potassium to patients with renal insufficiency or the administration of a potassium-sparing drug to patients without renal insufficiency |
| 14 | 50 mL of glucose 50% + 10E Actrapid (insulin) administered | Hyperkalemia related to intravenous administration of potassium to patients with renal insufficiency or the administration of potassium-sparing drug to patients without renal insufficiency |

^a Based on information from Rozich et al.⁷

^b To convert to millimoles per liter, multiply by 0.0555.

used in critically ill patients and that have a heightened risk for causing harm if used incorrectly. These drugs include heparin and insulin.² Drugs that cause electrolyte abnormalities were also considered important. Hypoglycemia was defined as a blood

glucose level less than 50 mg/dL (to convert to millimoles, multiply by 0.0555), hypokalemia as serum potassium level less than 3.0 mEq/L (normal, 3.5-5 mEq/L). Any activated partial thromboplastin time greater than 100 seconds (>60-90 seconds, the usual therapeutic target if heparin is administered intravenously) was

considered elevated. Some of the original triggers were excluded if the focus group determined they were not applicable to the ICU situation; these included transfer to a higher level of care (ICU is the highest level of care), a toxic lidocaine level (the drug was not used, and serum levels were not measured on a routine basis), and use of sodium polystyrene for hyperkalemia (this treatment is not

used in Belgium). Blood or blood products were not considered medications with this tool. Nurses' notes, physicians' orders and notes, pharmacy records, laboratory values, and vital signs were all collected from the PDMS system. In our unit, adverse events such as hematomas are always noted as "an event." In cases of doubt, the multidisciplinary focus group reviewed the individual observations of the investigator who collected the data.

Classification of ADEs

The trigger tool was used to identify the rate of occurrence of ADEs. Each trigger was noted and classified, and its severity was determined according to criteria of an algorithm¹⁰ established by the National Coordination Council for Medication Error Reporting and Prevention (NCC MERP; Table 2). This logarithm consists of 9 levels of severity, ranging from A to I. Categories A through D represent a potential ADE that is detected before it causes harm or is recognized quickly enough for harm to be averted. Only classes E (harm that contributed to

Electronic prescription of drugs has not decreased adverse drug events.

or resulted in temporary harm that required intervention) through I (most severe event possible) were scored, because they “reach” the patient and might cause harm, either temporary or definite.¹⁰ Both trigger and severity were assessed by the investigator who collected the data.

Disease Severity

Two disease severity scores were calculated. The Acute Physiology and Chronic Health Evaluation (APACHE) II score¹¹ was determined once on the basis of data gathered in the first 24 hours after admission, and the Sepsis-Related Organ Failure Assessment (SOFA) score¹² was determined daily. With these 2 validated measurement tools, disease severity is based on a patient’s age, medical history, physiological parameters, laboratory values, and neurological status. The daily SOFA score is based on the parameters of the preceding scoring period; it therefore gives a clear view of any evolving organ failure as a marker of disease severity. Higher scores in either scoring system reflect worsened disease severity.

Use of Intensive Care Nursing Resources

Nursing activities were inventoried by using the simplified Therapeutic Intervention Scoring System-28 (TISS-28).¹³ Higher scores indicate a greater number of therapeutic interventions. This tool offers a well-recognized system for scoring the difficulty of care or predefined nursing activities during the preceding 24 hours in the ICU.¹⁴ Each of 28 therapeutic interventions is assigned 1 to 8 points; the points are summed daily to obtain the overall score, which ranges from 0 to a maximum of 88, reflecting the nursing workload. Data on the staffing of nurses were taken from the electronic roster planning software (SP Expert; Astrum GmbH, Erlangen, Germany) of the ICU and included the number of nurses per shift (early, late, or night).¹⁵ Nursing students in training were not taken into account because they never execute orders independently.

Statistical Analysis

The data were analyzed by using SPSS, version 17.0 (IBM SPSS Statistics, Armonk, New York). The continuous variables were recorded as the mean, standard deviation, and range; dichotomous and discontinuous variables were recorded as number and percentage. For continuous variables, an independent *t* test was used when 2 groups were taken into account; 1-way analysis of variance was used for analysis of more than 2 groups. The difference between 2 discontinuous variables was calculated by using the χ^2 test. When data were nonnormally

Table 2
The National Coordinating Council for Medication Error Reporting and Prevention index for categorizing medication errors

| Category | Description |
|----------|--|
| A | Circumstances or events that have the capacity to cause error |
| B | An error occurred but the error did not reach the patient (An "error of omission" <i>does</i> reach the patient) |
| C | An error occurred that reached the patient but did not cause the patient harm ^a |
| D | An error occurred that reached the patient and required monitoring ^b to confirm that it resulted in no harm to the patient and/or required intervention ^c to preclude harm |
| E | An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention |
| F | An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization |
| G | An error occurred that may have contributed to or resulted in permanent harm of the patient |
| H | An error occurred that required intervention necessary to sustain life ^d |
| I | An error occurred that may have contributed to or resulted in the patient’s death |

^a Harm: impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.

^b Monitoring: to observe or record relevant physiological or psychological signs.

^c Intervention: may include change in therapy or active medical/surgical treatment.

^d Intervention necessary to sustain life: includes cardiovascular and respiratory support (eg, cardiopulmonary resuscitation, defibrillation, intubation).

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distributed, nonparametric testing was used: the Mann-Whitney test was used for 2 groups and the Kruskal-Wallis test for multiple groups. Factors that were statistically significant in univariate analysis were selected for multivariate analysis. Logistic regression was applied by using the presence of an ADE as the outcome. Results were considered significant at $P < .05$.

Results

Demographics and Characteristics

Each trigger was noted and classified according to the NCC MERP criteria. A total of 79 patients were included in the study. The demographic and clinical data are summarized in Table 3. Most patients were women, had undergone surgery (54%), had a mean age of 65.3 years, were in the ICU for a mean of almost 13 days. Of note, 18% of the study patients had underlying type 2 diabetes. The mean SOFA and APACHE II scores were 7.8 and 25.2, respectively, reflecting a high severity of illness.

Adverse drug events were scored based on 14 specific clinical triggers.

Table 3
Demographics of the study population (N = 79)

| Characteristic | % | Mean (SD), range |
|------------------------------|----|--------------------|
| Sex | | |
| Male | 39 | |
| Female | 61 | |
| Type of admission | | |
| Surgical | 54 | |
| Medical | 46 | |
| Diabetes mellitus type 2 | 18 | |
| Age, y | | 65.3 (12.8), 25-90 |
| Days in intensive care unit | | 12.7 (12.9), 2-48 |
| SOFA score ^a | | 7.8 (5.4), 0-24 |
| APACHE II score ^b | | 25.2 (8.2), 9-47 |

^a Sepsis-Related Organ Failure Assessment (SOFA): higher score indicates more failing organs (score range, 0-24).

^b Acute Physiology and Chronic Health Evaluation (APACHE) II: higher score indicates an increased risk of mortality (score range, 0-71).

Table 4
Description of the medical/nursing-related characteristics of the screened patient days (N = 1009)

| Characteristic | % | Mean (SD), range |
|---|----|-------------------|
| Mechanical ventilation ^a | 51 | |
| Renal insufficiency ^b | 33 | |
| Dialysis ^b | 10 | |
| Sedation ^c | 45 | |
| Enteral tube feeding | 53 | |
| Intrahospital transfer ^d | 9 | |
| Number of vasoactive medications ^e | | 1.2 (1.2), 0-8 |
| Nurse staffing | | |
| Morning | | 5.5 (1.0), 4-9 |
| Evening | | 3.4 (0.6), 3-6 |
| Night | | 2.3 (0.5), 2-3 |
| Bed to nurse ratio | | |
| Morning | | 1.4 (0.2), 1-2 |
| Evening | | 2.8 (0.1), 2-3 |
| Night | | 3.3 (0.3), 3-4 |
| Nursing workload | | |
| TISS-28 ^f | | 30.1 (7.1), 12-56 |

^a Invasive mechanical ventilation during the entire day (24 h/d) in the intensive care unit (ICU).

^b Renal insufficiency defined as serum level of creatinine greater than 1.5 mg/dL (133 μmol/L) on a specific ICU day.

^c Sedative administered by continuous intravenous infusion during the entire ICU day (24 h/d).

^d Transportation of an ICU patient within the hospital for the purpose of undergoing a diagnostic or therapeutic procedure on a specific day.

^e All vasoactive medications (inotropic agents and/or vasopressors) administered by continuous intravenous infusion during the entire ICU day (24 h/d).

^f Therapeutic Intervention Scoring System-28: higher score indicates increased workload (score range, 0-78).

A total of 1009 hospital days (3027 shifts) were screened for these 79 patients (Table 4). Of these patient days, 72% were week days; the remaining were weekend days. Patients received invasive mechanical ventilation for 51% of the hospital days and had sufficient caloric intake by oral feeding during 53% of their ICU stay. On 6% of the ventilation days, patients did not receive sedative drugs continuously. A serum creatinine level was greater than 1.5 mg/dL (to convert to micromoles per liter, multiply by 88.4) on 33% of the hospital days, and this event was accompanied by dialysis 10% of the time. The number of continuously intravenously administered vasoactive medications ranged from 0 to 8.

The nursing schedule in the ICU varied by shift. To provide care for 6 to 7 patients, usually 2 nurses worked overnight, 3 nurses worked in the late evening, and 5 to 6 worked during the morning shift. A higher nurse to patient ratio was therefore achieved in the morning hours. The mean TISS-28 score was 30.1 (range, 12-56; Table 4). On 26 days (3% of all patient days), the TISS-28 score per shift was greater than 46, a value recognized as the upper limit for the capability of a typical ICU nurse to perform and deliver work during a shift.¹³

Prevalence of ADEs

A total of 230 ADEs were recorded and occurred on 175 of the 1009 analyzed patient days. Thus, 1 or more ADEs occurred on 17% of all patient days. On 133 of the patient days, only 1 ADE occurred (76% of all days in which an ADE occurred), and on 32 patient days, 2 ADEs were observed. A total of 3 or more ADEs per patient day was rare. In 1 instance, 3 occurred in 7 days; in another instance, 4 ADEs occurred in 3 days.

ADE Characteristics

The 3 most frequently observed ADEs accounted for 78% of all ADEs. Hypoglycemia was the most frequent (33%). The other 2 were hypokalemia and a prolonged activated partial thromboplastin time. The remaining 22% of all ADEs were not related to the 3 most frequently observed (Figure 1).

Scoring the severity of the total number of ADEs (n = 230) according to the NCC MERP severity classification indicated that no ADE was severe enough to be classified G, H, or I; and 96% of ADEs were classified as class E. All class F ADEs (4%) were related to an activated partial thromboplastin time greater than 100 seconds. This "prolonged thromboplastin time" caused an increased incidence of bleeding, apparently leading to a prolonged stay in the ICU.

ADEs and Their Relationship to Disease Severity

The mean SOFA score was significantly higher on days when ADEs occurred than on days without ADEs (10 vs 8; $P < .001$; Figure 2). On patient days with 1 or more ADEs ($n = 175$), the mean SOFA score was highest (13) on days with 4 ADEs (2%) and lowest (9) on days with 2 ADEs (20%).

ADEs and Nursing Resources

The most frequently occurring ADE, hypoglycemia (blood glucose, < 50 mg/dL) was related to nursing staff characteristics (Table 5). Continuous insulin was administered in a comparable manner throughout the different shifts (64% in early shifts and 67% in evening and night shifts). However the number of hypoglycemic episodes was significantly higher during night shifts than during morning shifts (6% vs 3%; $P = .005$) and evening shifts (6% vs 2%; $P = .001$).

Diuretics were administered more often during morning shifts (19% vs 11% in the evening and 9% on the night shift). However, the difference between the incidence of hypokalemia on night shifts (15% vs 14%; $P = .09$) and evening shifts (25% vs 14%; $P = .05$ and 25% vs 15%; $P = .77$) were not significant. In 26% of the morning and night shifts and 27% of the evening shifts, intravenous heparin was administered. Again, the incidence of prolonged activated partial thromboplastin time (> 100 seconds) during night shifts compared with the incidence during morning shifts (10% vs 6%; $P = .77$) and evening shifts (10% vs 7%; $P = .22$) was not significant.

The mean TISS-28 score (33) was significantly higher during patient days with 1 or more ADEs than on patient days when no ADE occurred ($P = .002$; Figure 3). On patient days with 1 or more ADE, the mean TISS-28 score was the highest (38) for patient days when 3 ADEs (4%) occurred. The lowest TISS-28 score (32) occurred on patient days with 2 ADEs (18%).

Univariate analysis of the different factors showed that patients were more likely to have an ADE if they were receiving mechanical ventilation, had renal insufficiency, or were receiving sedative or vasoactive drugs on a continuous basis (for P values, see Table 6). Transport of a patient was associated with diagnostic or surgical intervention outside the ICU and was associated with an increased likelihood of an ADE (74%; $P = .03$; Table 6).

Discussion

Our findings confirm that drugs administered in the ICU may be an important cause of ADEs. ADEs were common; a total of 230 occurred on more than 17% of the screened patient days. The lack of a gold standard for reporting and collecting data on ADEs

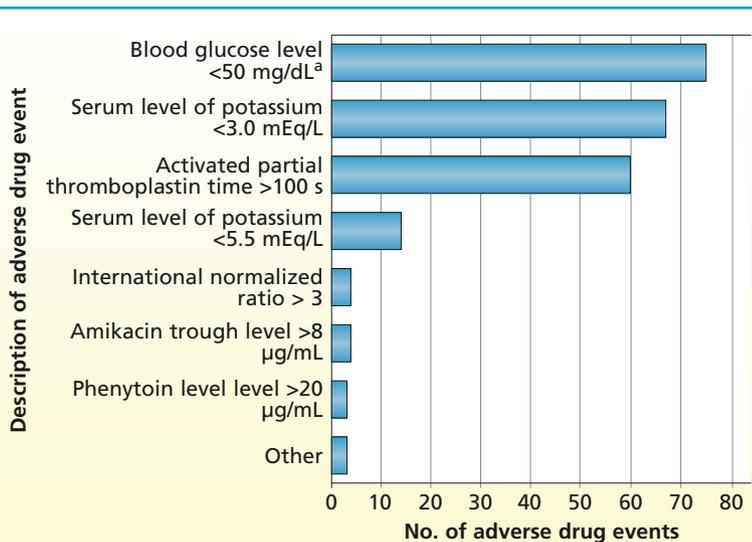


Figure 1 Characteristics and numbers of adverse drug events ($N = 230$). The category Other includes 1 case of vancomycin peak level exceeding 40 μ g/mL, 1 case of tacrolimus level exceeding 20 ng/mL, 1 case of cyclosporine trough level exceeding 300 μ g/mL, and no cases of a valproate level exceeding 100 μ g/mL.

^a To convert to millimoles per liter, multiply by 0.0555.

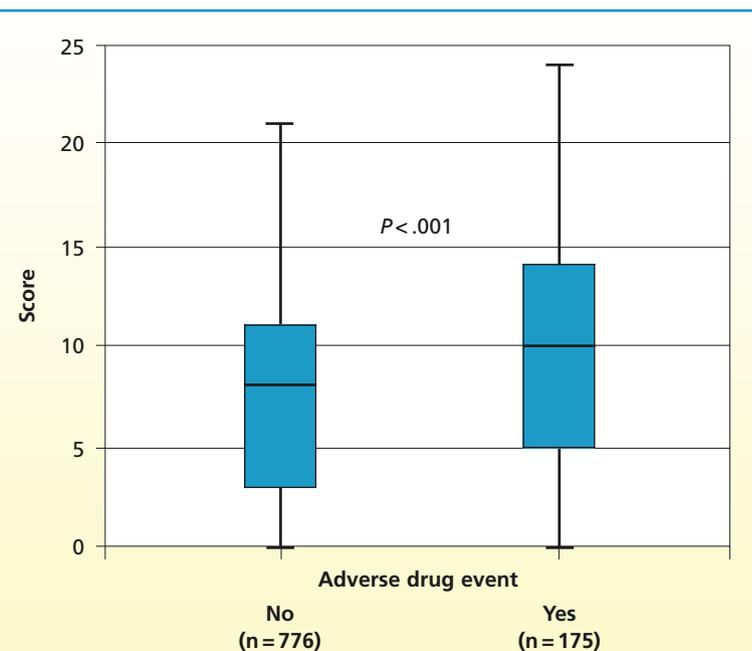


Figure 2 Range of the daily scores on the Sepsis-Related Organ Failure Assessment in relation to the occurrence of an adverse drug event during every separate patient day ($N = 951$).

in general, and in the ICU in particular, excludes a reliable comparison of our study with other studies or validation of the true intrinsic value of the observed incidence.¹⁶ Yet our results clearly show that ICU patients are often exposed to potentially harmful drug events. The prevalence of ADEs in our study is

Table 5
The 3 most prevalent adverse drug events per nursing shift (N = 1009)

| A: Blood glucose level <50 mg/dL ^a | | | | |
|---|---|--------------------------------|-----------------------|------|
| Shift | No. of nursing shifts with intravenous administration of insulin | No. (%) of adverse drug events | <i>p</i> ^b | |
| Morning | 650 | 18/650 (3) | .67 .001 } | |
| Evening | 671 | 16/671 (2) | | |
| Night | 671 | 41/671 (6) | | |
| } | | | | .005 |
| B: Serum level of potassium <3.0 mEq/L | | | | |
| Shift | No. of nursing shifts with intravenous administration of furosemide | No. (%) of adverse drug events | <i>p</i> ^b | |
| Morning | 189 | 26/189 (14) | .05 .77 } | |
| Evening | 109 | 27/109 (25) | | |
| Night | 93 | 14/93 (15) | | |
| } | | | | .09 |
| C: Activated partial thromboplastin time >100 s | | | | |
| Shift | No. of nursing shifts with intravenous administration of heparin | No. (%) of adverse drug events | <i>p</i> ^b | |
| Morning | 266 | 16/266 (6) | .77 .22 } | |
| Evening | 271 | 18/271 (7) | | |
| Night | 266 | 26/266 (10) | | |
| } | | | | .12 |

^a To convert to millimoles per liter, multiply by 0.0555.
^b Significance of difference in the number of adverse drug events between 2 nursing shifts (morning vs evening, evening vs night, or morning vs night).

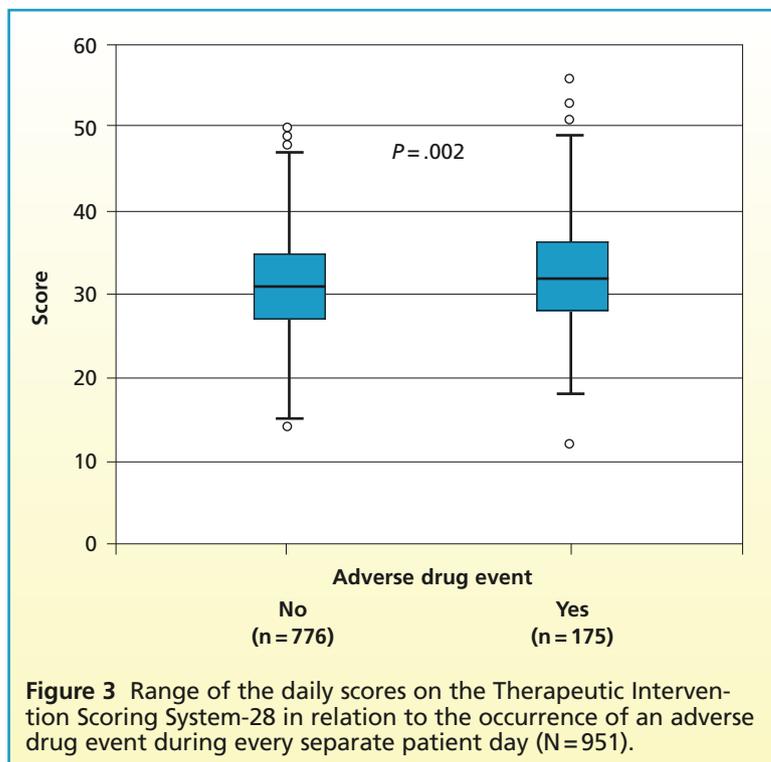


Figure 3 Range of the daily scores on the Therapeutic Intervention Scoring System-28 in relation to the occurrence of an adverse drug event during every separate patient day (N = 951).

slightly greater but well in agreement with that obtained in a few other studies.² Sentinel events

related to medication, indwelling catheters, and airway and equipment failure are common in ICUs. Medication errors occur at a median rate of 106 per 1000 ICU patient days.¹⁷ The proportion of medication errors resulting in true ADEs, however, ranges from 0.6% to 29%.² In one study¹⁸ in which a comparable “low-tech” trigger was used, a retrospective chart review indicated a prevalence of 16.4 adverse events per 100 patient days in the ICU.

Intravenous administration of insulin is a common treatment to control hyperglycemia in critically ill patients. Strict glucose control via intravenously administered insulin was used in more than 70% of our patients to achieve target blood glucose levels by using a strategy based on intensive insulin therapy (Leuven protocol)¹⁹ and many other studies.²⁰ Because of the high percentage of patients treated with insulin, our finding that hypoglycemia was the most prevalent ADE was not unexpected. This observation illustrates the clear need for careful monitoring of glucose levels, particularly because insulin-related hypoglycemia has been reported as a marker of poor outcomes.²⁰ The frequency of hypoglycemia in our study (6%) is similar to that of other studies (5%-8%), regardless of whether or not insulin therapy had a favorable or a deleterious effect on mortality and morbidity.^{19,21-23} Reaching

and maintaining normal blood glucose levels requires not only the intravenous administration of insulin but also extensive nursing efforts and frequent glucose monitoring.²⁰

Almost all ADEs were class E, indicating that no serious complications occurred. Only a small fraction of ADEs were class F, and all of these were associated with a markedly prolonged activated partial thromboplastin time. This finding confirms previous assumptions that use of anticoagulants may be associated with serious and frequent ADEs related to the complexity of heparin administration and the interaction of heparin with other drugs.²⁴ Conversely, the ADEs common in our patients did not cause serious harm such as that noted by Grenouillet-Delacret et al²⁵ in prospective 6-month observational study. In that study, 111 of 405 patients (27.4%) had an adverse drug reaction that led to organ failure, and 19% of the reactions contributed to death.

The data on risk factors specifically associated with ICU adverse events, particularly ADEs, are limited. We hypothesized that disease severity is an important risk factor for ADEs. Organ failure (associated with mechanical ventilation, renal insufficiency) and common tasks such as patient transport and the use of sedative and vasoactive medications were additional risk factors. Giraud et al²⁶ reported that a patient's age (≥ 65 years) and increased severity of illness were associated with adverse reactions in the ICU. However, only 11% of the complications experienced by patients in the study²⁶ were medication related. Disease severity was indicated as prognostic factor for ADEs in one other ICU-based study.⁵ Moreover, patients requiring mechanical ventilation also receive sedative agents, which are also a risk factor for ADEs.¹⁷ The use of sedation may not only increase the risk for ADEs but also mask signs and symptoms related to an ADE (eg, dizziness, nausea) and thus impair early detection. In 2 observational studies^{17,27} conducted during a 24-hour period, adverse events (including medication errors) occurred most often in patients who had a higher number of failing organs or were given a higher number of medications parenterally.

Typically in the ICU, drugs are prepared and administered by critical care nurses rather than by physicians. Critical care nurses perform many assessments, measurements, and documentations, and they administer therapy on an ongoing basis. The central role of ICU nurses has been emphasized in the follow-up, dose adjustment, and rate of delivery of medications delivered by intravenous infusion, such as insulin and heparin.^{19,28} Yet, much uncertainty and debate persist about the level of nurse

Table 6
Specific medical characteristics that determine the incidence of adverse drug events^a

| Medical characteristic | Yes (n = 175) | No (n = 776) | P | Odds ratio (95% confidence interval) ^b |
|-------------------------------------|---------------|--------------|------|---|
| Mechanical ventilation ^c | 64 | 51 | .002 | 1.72 (1.22 - 2.41) |
| Renal insufficiency ^d | 42 | 29 | .001 | 1.78 (1.27 - 2.50) |
| Dialysis | 13 | 9 | .09 | 1.55 (0.93 - 2.58) |
| Sedation ^e | 54 | 46 | .04 | 1.41 (1.02 - 1.97) |
| Vasoactive medication ^f | 75 | 63 | .001 | 1.82 (1.25 - 2.65) |
| Intrahospital transfer ^g | 14 | 8 | .03 | 1.74 (1.05 - 2.87) |
| Enteral tube feeding | 51 | 56 | .25 | 0.83 (0.59 - 1.15) |

^a Multiple logistic regression: Nagelkerke $R^2 = 0.038$ ($P < .001$) for the whole model.
^b From univariate analysis.
^c Invasive mechanical ventilation during the entire day (24 h/d) in the intensive care unit (ICU).
^d Renal insufficiency defined as serum level of creatinine greater than 1.5 mg/dL (to convert to micromoles per liter, multiply by 88.4) on a specific ICU day.
^e Sedative administered by continuous intravenous infusion during the entire ICU day (24 h/d).
^f All vasoactive medication (inotropic agents and/or vasopressors) administered by continuous intravenous infusion during the entire ICU day (24 h/d).
^g Transportation of an ICU patient within the hospital for the purpose of a undergoing a diagnostic or therapeutic procedure on a specific ICU day.

staffing, workload, and range of skills required for patient safety.²⁹ The nursing responsibilities of obtaining blood samples, doing analyses, documenting results, and adjusting the delivery rate of intravenous medications may require up to 2 h/d.³⁰ Quick detection and response are crucial to avoid ADEs. In patients with greater disease severity, samples are obtained more often than in patients with less severe illnesses, a practice that might influence and increase workload.²⁹

Some studies have indicated a relationship between nursing resources and adverse events such as hypotensive incidents and cardiac arrest,²⁶ the duration of weaning,³¹ and length of stay.³² A nurse to patient ratio greater than 1 to 2 has been associated with an increased probability of complications such as infection, longer length of stay, and increased cost.³⁰ Patient outcomes improve if a more optimal nurse to patient ratio is achieved.¹⁵ The mean nursing workload, as indicated by the TISS-28 score, was significantly associated with the incidence of ADEs. In our study, the mean TISS-28 score was significantly higher on days on which more than a single ADE occurred, as previously reported for a hospital-wide study.³³ ADE rates are greater in ICUs with low nurse to patient ratios than in units with higher ratios and in units that have with more admissions.^{17,27} Our findings confirmed this effect on ADEs in the ICU; nursing workload and a lower nurse to patient ratio had a negative influence on the occurrence of ADEs. We are unaware of any

Almost all adverse drug events were class E: no serious complications were seen.

other study that indicated a correlation between the nursing workload, according to the TISS-28 score, and medication safety, as indicated by ADE frequency in the ICU.

Moreover, the 3 most common ADEs occurred most often during the evening and night shifts, when a lower nurse to patient ratio was in effect, but this finding was statistically significant only for ADEs involving hypoglycemia. Other investigators have also reported the relationship between ADEs and the parenteral administration of more than 3 drugs, a process that increases the nursing workload^{25,27} or the nurse to patient ratio.²⁷ Only 2 studies in a total of 15

indicated a significant relationship between nursing resources and both mortality and adverse events.²⁹

West et al²⁹ concluded that although more evidence may be available on a link between ICU nursing resources and complications than on a link between ICU nursing and mortality, evidence for the first link is not yet convincing. Many of the studies were conducted by the same research team, in a single ICU, or only involved a few of the many relationships between nursing resources and complications. Our study has comparable limitations. Although thousands of nursing shifts were studied for ADEs, the analysis was performed retrospectively and the data were for a single ICU. Therefore, the hypothesis that high workload interferes with task performance and contributes to the occurrence of ADEs remains to be established.

The substantial costs incurred by hospitals because of ADEs justifies investments in the prevention of these events.³ Yet, little research has been done to determine which interventions might limit the occurrence of ADEs in the ICU.

An optimized nurse to patient ratio might help reduce the risk of ADEs.¹⁶ Because of the limited resources and the paucity of critical care nurses, other solutions are also necessary. Optimization of medication and care processes by means of technological advancements could help doctors and nurses in daily care responsibilities. Further implementation of a

PDMS, such as the one in our ICU, offers opportunities for electronic prescriptions and may limit the risk for ADEs.¹⁴ Yet, our study shows that even with the use of a high-quality PDMS, critically ill patients remain at high risk for ADEs, the single most frequent source of health care errors.⁷ Whether the

presence of a PDMS in our ICU contributed to the number of (but less severe?) ADEs cannot be determined from our results. Other solutions such as continuous monitoring alarm systems (eg, for measurements of blood glucose levels) are still experimental.²⁰ Finally, augmenting staff knowledge by education on the use, prescription, preparation, and administration of specific drugs and the drugs' respective risk profiles in patients susceptible to ADEs may be worthwhile.¹⁶

Although we studied many nursing shifts, the data were retrospective. Only data that had been put into the system could be produced by the system, and we relied on the quality of the input.

Moreover, the trigger events we studied were chosen from the previously validated list for global trigger tools for ADEs. We did not evaluate new trigger tools or drugs such as continuously infused vasoactive agents, sedatives, or analgesics. Our study was not planned to measure the frequency of ADEs caused by physicians, compared with the registration of medication monitoring loops performed by critical care nurses. Drug-induced acute kidney injury was not assessed, and some ADEs such as hypokalemia might be due to more than simply use of diuretics.

Past research³ has shown that ADEs occur at an overall greater rate in ICUs than in general care units. The reason is multifactorial and involves the increasing complexity of care for critically ill patients. Contributing factors might be the complexity of disease, rapid changes in pharmacotherapy, the complexity of the ICU environment itself, or the complex drug regimens that often include parenteral administration of drugs. Our results clearly indicate the contributions of disease severity, nurse workload, and nurse to patient ratio to the occurrence of ADEs. Our results and previous data provide a new starting point for understanding the incidence of ADEs and indicate the importance of interventional studies to explore whether or not organizational factors may reduce the risk for these costly and potentially harmful errors.

ACKNOWLEDGMENTS

The secretarial aid of Hilde Fleurackers is greatly acknowledged.

FINANCIAL DISCLOSURES

None reported.

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Nursing workload was significantly associated with the incidence of adverse drug events.

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For more about adverse drug events, visit the *Critical Care Nurse* Web site, www.ccnonline.org, and read the article by Anthony et al, "No Interruptions Please: Impact of a No Interruption Zone on Medication Safety in Intensive Care Units" (June 2010).

REFERENCES

1. Stump LS. Re-engineering the medication error-reporting process: removing the blame and improving the system. *Am J Health Syst Pharm*. 2000;57(suppl 4):S10-S17.
2. Kane-Gill SL, Jacobi J, Rothschild JM. Adverse drug events in intensive care units: risk factors, impact, and the role of team care. *Crit Care Med*. 2010;38(6 suppl):S83-S89.
3. Bates DW, Spell N, Cullen DJ, et al; Adverse Drug Events Prevention Study Group. The costs of adverse drug events in hospitalized patients. *JAMA*. 1997;277(4):307-311.
4. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med*. 2004;140(10):795-801.
5. Rothschild JM, Landrigan CP, Cronin JW, et al. The Critical Care Safety Study: the incidence and nature of adverse events and serious medical errors in intensive care. *Crit Care Med*. 2005;33(8):1694-1700.
6. Shamliyan TA, Duval S, Du J, Kane RL. Just what the doctor ordered: review of the evidence of the impact of computerized physician order entry system on medication errors. *Health Serv Res*. 2008;43(1 pt 1):32-53.
7. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care*. 2003;12(3):194-200.
8. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA*. 1991;266(20):2847-2851.
9. Griffin FA, Resar RK. *IHI Global Trigger Tool for Measuring Adverse Events*. IHI innovation series white paper. Cambridge, MA: Institute for Healthcare Improvement; 2007.
10. National Coordinating Council for Medication Error Reporting and Prevention. Taxonomy of medication errors. 2001. <http://www.nccmerp.org/pdf/indexBW2001-06-12.pdf>.
11. Knaus WA, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med*. 1981;9(8):591-597.
12. Vincent JL, Moreno R, Takala J, et al; on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-Related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22(7):707-710.
13. Miranda DR, de Rijk A, Schaufeli W. Simplified Therapeutic Intervention Scoring System: the TISS-28 items—results from a multicenter study. *Crit Care Med*. 1996;24(1):64-73.
14. Moreno R, Morais P. Validation of the Simplified Therapeutic Intervention Scoring System on an independent database. *Intensive Care Med*. 1997;23(6):640-644.
15. Jakob SM, Rothen HU. Intensive care 1980-1995: change in patient characteristics, nursing workload and outcome. *Intensive Care Med*. 1997;23(11):1165-1170.
16. Cullen DJ, Bates DW, Leape LL. Prevention of adverse drug events: a decade of progress in patient safety. *J Clin Anesth*. 2000;12(8):600-614.
17. Valentin A, Capuzzo M, Guidet B, et al. Patient safety in intensive care: results from the multinational Sentinel Events Evaluation (SEE) study. *Intensive Care Med*. 2006;32(10):1591-1598.
18. Resar RK, Rozich JD, Simmonds T, Haraden CR. A trigger tool to identify adverse events in the intensive care unit. *Jt Comm J Qual Patient Saf*. 2006;32(10):585-590.
19. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.
20. De Block C, Manuel-y-Keenoy B, Rogiers P, Jorens P, Van Gaal L. Glucose control and use of continuous glucose monitoring in the intensive care unit: a critical review. *Curr Diabetes Rev*. 2008;4(3):234-244.
21. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
22. Vriesendorp TM, van Santen S, DeVries JH, et al. Predisposing factors for hypoglycemia in the intensive care unit. *Crit Care Med*. 2006;34(1):96-101.
23. Azevedo JR, Lima ER, Cossetti RJ, Azevedo RP. Intensive insulin therapy versus conventional glycemic control in patients with acute neurological injury: a prospective controlled trial. *Arq Neuropsiquiatr*. 2007;65(3B):733-738.
24. Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. *Am J Health Syst Pharm*. 2003;60(17):1750-1759.
25. Grenouillet-Delacré M, Verdoux H, Moore N, et al. Life-threatening adverse drug reactions at admission to medical intensive care: a prospective study in a teaching hospital. *Intensive Care Med*. 2007;33(12):2150-2157.
26. Giraud T, Dhainaut JF, Vaxelaire JF, et al. Iatrogenic complications in adult intensive care units: a prospective two-center study. *Crit Care Med*. 1993;21(1):40-51.
27. Valentin A, Capuzzo M, Guidet B, et al; Research Group on Quality Improvement of the European Society of Intensive Care Medicine (ESICM); Sentinel Events Evaluation (SEE) Study Investigators. Errors in administration of parenteral drugs in intensive care units: multinational prospective study. *BMJ*. 2009;338:b814.
28. Aragon D. Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. *Am J Crit Care*. 2006;15(4):370-377.
29. West E, Mays N, Rafferty AM, Rowan K, Sanderson C. Nursing resources and patient outcomes in intensive care: a systematic review of the literature. *Int J Nurs Stud*. 2009;46(7):993-1011.
30. Amaravadi RK, Dimick JB, Pronovost PJ, Lipsett PA. ICU nurse-to-patient ratio is associated with complications and resource use after esophagectomy. *Intensive Care Med*. 2000;26(12):1857-1862.
31. Thorens JB, Kaelin RM, Jolliet P, Chevrolet JC. Influence of the quality of nursing on the duration of weaning from mechanical ventilation in patients with chronic obstructive pulmonary disease. *Crit Care Med*. 1995;23(11):1807-1815.
32. Pronovost PJ, Jenckes MW, Dorman T, et al. Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. *JAMA*. 1999;281(14):1310-1317.
33. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA*. 2002;288(16):1987-1993.

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