Costs of Intravenous Adverse Drug Events in Academic and Nonacademic Intensive Care Units

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Background: Adverse drug events (ADEs), particularly those involving intravenous medications (IV-ADEs), are common among intensive care unit (ICU) patients and may increase hospitalization costs. Precise cost estimates have not been reported for academic ICUs, and no studies have included nonacademic ICUs.

Objectives: To estimate increases in costs and length of stay after IV-ADEs at an academic and a nonacademic hospital.

Research Design: This study reviewed medical records to identify IV-ADEs, and then, using a nested case-control design with propensity-score matching, assessed differences in costs and length of stay between cases and controls.

Subjects: A total of 4604 adult ICU patients in 3 ICUs at an academic hospital and 2 ICUs at a nonacademic hospital in 2003 and 2004.

Measures: Increased cost and length of stay associated with IV-ADEs.

Results: Three hundred ninety-seven IV-ADEs were identified: 79% temporary physical injuries, 0% permanent physical injuries, 20% interventions to sustain life, and 2% in-hospital deaths. In the academic ICUs, patients with IV-ADEs had $6647 greater costs ($P < 0.0001$) and 4.8-day longer stays ($P = 0.0003$) compared with controls. In the nonacademic ICUs, IV-ADEs were not associated with greater costs ($188, $P = 0.4236$) or lengths of stay (−0.3 days, $P = 0.8016$). Cost and length-of-stay differences between the hospitals were statistically significant ($P = 0.0012$). However, there were no differences in IV-ADE severity or preventability, and the characteristics of patients experiencing IV-ADEs differed only modestly.

Conclusions: IV-ADEs substantially increased hospitalization costs and length of stay in ICUs at an academic hospital but not at a nonacademic hospital, likely because of differences in practices after IV-ADEs occurred.

Key Words: critical care, drug therapy: adverse effects, economics, intravenous infusions, intravenous injections

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Injuries caused by medication therapy (adverse drug events or ADEs) occur at a rate of 37.8 per 1000 patient days among adults in US intensive care units (ICUs).[1] In addition to harming patients, ADEs also seem to increase hospitalization costs.[2] However, precise estimates of the costs attributable to ADEs have not been published for academic ICUs, and no studies have included nonacademic ICUs,[2,3] where most care is provided. The effects of ADEs may differ between academic and nonacademic settings because the former generally have more providers involved in each patient's care as well as longer hospitalizations.[4]

Understanding ADE costs is important so that decision makers can weigh them against the potential costs and benefits of prevention strategies. Reducing ADEs may not only protect patients but may also enable hospitals to redirect the money they currently spend responding to ADEs toward more productive endeavors. Hospitals might save money if they implement a prevention strategy that costs less than the ADEs it averts, particularly under prospective and capitated payment mechanisms. If ADEs lengthen hospital stays, prevention might sometimes enhance revenue by making beds available for patients with higher reimbursement rates, for example, if a lack of postoperative ICU beds limits lucrative surgical procedures. Studies are equivocal on whether preventing ADEs might also reduce malpractice costs.[5–7]

The objective of this study was to estimate the additional length of stay and hospitalization costs associated with the ADEs in ICUs that involve intravenous medications (IV-ADEs). A secondary objective was to compare these effects of IV-ADEs in academic and nonacademic settings.

We chose to focus on IV-ADEs for 2 reasons. First, they seem to be the most common, severe, and costly ADEs

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in ICUs. Most medications are administered IV in ICUs, and the error rate is higher for this administration route than others.[3] Many of these IV medications can cause particularly severe injuries, which, in turn, should be associated with higher costs. Pooling IV-ADEs with ADEs involving other administration routes could, therefore, lead to an underestimate of the true costs of the more severe events. Second, certain interventions target preventing IV-ADEs, such as using dedicated infusion nurses, smart IV pumps, or smart IV pumps with embedded bar-code technology (Butterfield R, Cardinal Health, personal communication, January 17, 2007).[8–11]

MATERIALS AND METHODS

We used medical-record review to identify IV-ADEs among study participants, and then, using a case-control design, we compared costs and length of stay for propensity-score-matched participants with and without IV-ADEs. This study was initially designed to examine whether 1 model of smart IV pump would prevent IV-ADEs and thereby reduce IV-ADE costs. Because we found no measurable effect of the pump on preventable IV-ADEs, we chose to report our analysis of IV-ADE costs separately from these clinical findings.

Selecting Hospitals and Participants

We selected a 739-bed academic hospital in a medium-sized city in the Northeast and a 566-bed nonacademic hospital in a larger city in the West. The academic hospital is affiliated with a medical school and residency programs; the nonacademic hospital is not.[12] Both provide trauma care, multiorgan transplantation, and other tertiary referral services. The academic hospital payor mix included 95% prospective and 2% capitated payment patients; the nonacademic hospital mix included 28% prospective and 36% capitated payment patients. Our choice of these particular hospitals was based on academic and nonacademic status, geographic diversity, and their having implemented Alaris version 5 intravenous infusion pumps ("smart pumps") in 2003.

We included patients in a 12-bed surgical ICU, 15-bed trauma/burn ICU, and 17-bed medical ICU at the academic hospital; and a 16-bed surgical ICU and 19-bed medical ICU at the nonacademic hospital. Study periods provided 10,000 ICU bed-days at each hospital, with half of the study periods ending 2 weeks before smart-pump implementation and half starting 4 weeks after. We enrolled adults admitted consecutively to the ICUs during the study periods, except we excluded patients with ICU stays that extended 2 weeks or more beyond any study period so that patients admitted before smart-pump implementation would not encounter smart pumps and exclusion criteria would be uniform. However, because smart-pump implementation did not affect IV-ADE rates or severity, this analysis pooled all periods.

We obtained Institutional Review Board approvals; informed consent was not required.

Identifying IV-ADEs

A 3-step process identified participants who had sustained an IV-ADE. First, discharge data identified patients admitted to study ICUs during the study periods. Second, 9 specially trained critical care nurses reviewed medical records, recording (1) dates and times of hospital and ICU admissions and discharges, (2) Acute Physiology and Chronic Health Evaluation (APACHE)-II score on ICU admission (a measure of acute and chronic illness),[13] (3) Charlson Index (a measure of chronic illness),[14] (4) orders to limit care, and (5) reason for ICU admission under APACHE II Then they used manual trigger-tool review (a method that uses key words as sentinels to identify ADEs in medical records) plus implicit review (professional judgment) to identify and summarize suspected ADEs.[15] When they identified one, they documented APACHE-II scores for the 24 hours before the ADE occurred (defined as when its injurious effects were first documented in the medical record). Research nurses worked at the study hospitals but were not involved in caring for patients enrolled in the study.

Third, summaries of suspected ADEs were forwarded to 4 board-certified Internal Medicine physicians unaffiliated with the study hospitals, who rated them individually, then met in pairs to discuss their ratings and reach consensus. Physicians rated (1) whether ADEs had occurred,[16] (2) severity,[17] (3) medication administration routes,[16] (4) whether ADEs prolonged ICU or hospital stay, (5) preventability,[18] and (6) types of errors involved (including failure to intervene errors, defined as failures to modify medication therapy in a timely fashion after a patient started to experience undesirable medication effects).[16]

Matching Cases and Controls

Each participant with an IV-ADE ("case") was matched with a participant at the same hospital without an IV-ADE ("control") using an algorithm with 3 sequential steps.[19,20] First, the total ICU length of stay for the control was equal to or greater than that for the corresponding case at the time the IV-ADE occurred.[16] For example, if a case experienced an IV-ADE on ICU day 3, the control stayed in ICU for 3 or more days. Second, cases and controls had similar reasons for ICU admission (using categories derived from APACHE II). Third, they had similar propensities to experience IV-ADEs. Propensity scores were estimated using generalized nonparametric regression[21] and modeled as functions of age, gender, self-reported race and ethnicity (included in case these affect the risk of IV-ADEs), payment source, estimated household income (derived from zip code),[22] Charlson Index, and APACHE-II score at ICU admission.[23,24] When cases had multiple IV-ADEs, we matched on the first. After matching, study nurses determined controls' APACHE-II scores for the 24-hour period before the point in ICU stay at which the case experienced the IV-ADE.

Estimating Costs

We extracted cost data from internal, resource-based accounting systems. These systems were distinct from charge data, were well-established proprietary systems, listed costs by date and department, and identified costs as variable or fixed. The academic hospital used the McKesson HBOC Trendstar System, whereas the nonacademic hospital used the

Eclipsys/TSI Decision Support version 5.3.01. As is customary, this analysis included only variable costs.

For each case and control, we identified costs incurred during the postevent period (ie, on or after the day of ICU stay on which the case experienced the IV-ADE). For example, if a case experienced an IV-ADE on ICU day 3, we identified costs incurred on or after ICU day 3 for both the case and control.

We determined total postevent costs (costs in postevent period), postevent daily costs (average costs per day during that period), and postevent length of stay (duration of postevent period). To compute costs associated with IV-ADEs, we subtracted total postevent costs for cases from those for controls. We determined changes in postevent daily costs and length of stay similarly.

Analyses

To determine whether the matching algorithm selected controls that were similar to cases, we compared them on the baseline characteristics in Table 1.

Next, at each hospital, we compared total postevent costs between cases and controls. If these costs were significantly different, we compared postevent departmental costs. To determine whether IV-ADEs were associated with greater utilization of services or increased length of stay, we compared postevent daily costs and postevent length of stay between cases and controls. We also examined physicians' judgments about IV-ADEs' effects on length of stay, and examined results by IV-ADE preventability.

Lastly, because changes in costs and length of stay differed between the academic and nonacademic hospitals, we compared them and explored reasons for any dissimilarity, including differences in the IV-ADEs, baseline differences between the 2 case populations, and differences between the 2 control populations. Differences between control populations could exist at baseline or arise during postevent periods; because controls were selected to resemble cases at baseline, we only compared control populations on postevent characteristics. We compared patients' IV-ADE characteristics between the hospitals, including severity, preventability, and failure to intervene errors because these might lead to greater lengths of stay and costs. We did not have other information on patient care practices after IV-ADEs occurred.

Analyses were conducted in SAS Version 9.1.3.[25] We compared categorical variables across nonmatched groups using the χ^2 statistic; when cell sizes were less than 5, we used Fisher exact test. We used McNemar's test to compare categorical variables from case-control pairs. We used the Wilcoxon rank-sum test for continuous variables, with paired tests for all analyses of case-control pairs. Intracluster correlations were calculated for variables rated by study physicians.

We conducted multivariable analyses of total postevent costs and postevent length of stay using generalized linear mixed models that assumed a Gamma error distribution to accommodate right-skewed cost data and used a log link function. We specified random intercepts for the matched case-control pairs to account for nonindependence within

TABLE 1. Baseline Characteristics of Cases Vs. Controls Within Each Hospital

	Academic Hospital			Nonacademic Hospital		
	Cases	**Controls**	***P***	**Cases**	**Controls**	***P***
Demographic characteristics						
Age, mean (SD)	61.6 (18.2)	60.7 (17.8)	0.4800	64.7 (17.7)	65.1 (16.4)	0.9879
Female gender, n (%)	65 (46.8)	59 (42.5)	0.4602	93 (47.9)	82 (42.3)	0.2540
Race/ethnicity			0.9750			0.7149
White, n (%)	112 (80.6)	112 (80.6)		123 (63.4)	119 (61.3)	
Black, n (%)	22 (15.8)	22 (15.8)		6 (3.1)	12 (6.2)	
Hispanic, n (%)	5 (3.6)	4 (2.9)		36 (18.6)	38 (19.6)	
Other race, n (%)	0 (0.0)	1 (0.72)		27 (13.9)	27 (13.9)	
Estimated household income, mean (SD)	$42,444 ($13,847)	$41,258 ($14,886)	0.4678	$49,522 ($18,415)	$47,067 ($14,511)	0.2396
Clinical characteristics						
APACHE II at ICU admission, mean (SD)	14.4 (7.4)	13.1 (6.4)	0.0976	17.9 (7.4)	20.3 (7.0)	0.0006
APACHE II 24 h before IV-ADE, mean (SD)	21.0 (26.1)	12.1 (8.0)	0.0063	25.9 (31.6)	18.0 (7.2)	0.6063
Charlson index, mean (SD)	2.2 (2.1)	2.4 (2.2)	0.3749	2.0 (2.3)	2.1 (2.2)	0.5087
Principal reason for ICU admission			0.7389			0.9473
Operative, n (%)	44 (31.7)	45 (32.4)		82 (42.3)	83 (42.8)	
Nonoperative, n (%)	95 (68.4)	94 (67.6)		112 (57.7)	111 (57.2)	
Unit type			0.1282			0.0641
Surgical/trauma/burn, n (%)*	72 (51.8)	81 (58.3)		102 (52.6)	90 (46.4)	
Medical, n (%)	67 (48.2)	58 (41.7)		92 (47.4)	104 (53.6)	
Baseline economic characteristic						
Pre-event daily costs, mean (SD)†	$3002 ($8081)	$2681 ($6747)	0.5335	$3182 ($3796)	$3124 ($4,386)	0.4199
Total no. participants	139	139		194	194	

*Trauma/burn and surgical units are pooled because trauma/burn patients were treated in the surgical ICU at the nonacademic hospital.
†Pre-event daily costs = average cost incurred per hospital day before day of IV-ADE.

pairs. These analyses were adjusted for ICU type, gender, age, estimated income, race/ethnicity, payment source, admission and pre-IV-ADE APACHE-II scores, weight, orders to limit care, Charlson Index, pre-event length of stay, and whether smart pumps had been implemented.

RESULTS

Across both hospitals, we identified 477 ADEs among 4604 participants (missing clinical data eliminated 34 eligible participants).

IV-ADEs represented 397 (83%) of the 477 ADEs identified and harmed 347 patients. Of these 347 patients, 35 (10%) experienced more than 1 IV-ADE. Medications most commonly involved were opiates 38%, propofol 14%, benzodiazepines 13%, anticoagulants 17%, and insulin 10%. Severity ratings were as follows: temporary physical injury 79%, permanent physical injury 0%, intervention to sustain life 20%, and in-hospital death 2%. Common examples included vomiting caused by opiates, hypotension caused by sedatives, severe coagulopathy or bleeding caused by anticoagulants, and hypoglycemia caused by insulin. Twenty-six percent were preventable. Intracluster correlations were 0.71 for the presence of an ADE, 0.90 for preventability, and 0.99 for severity.

Of the 397 IV-ADEs, 190 occurred at the academic hospital (21.9 per 1000 patient days) and 207 at the nonacademic hospital (17.4 per 1000 patient days). Missing data or a lack of a suitable control eliminated 12 of 151 cases with IV-ADEs at the academic hospital and 2 of 196 cases at the nonacademic hospital, yielding 139 and 194 matched patient pairs, respectively.

Academic Hospital

Cases and controls were similar at baseline, except that cases' pre-IV-ADE APACHE-II scores were slightly higher, reflecting worse acute illnesses (Table 1). One control (0.7%) experienced an ADE involving a nonintravenous route of administration.

As seen in Table 2, IV-ADEs significantly increased total postevent costs (53% unadjusted, 46% adjusted using the generalized linear mixed models and variables listed above, $t = 3.59$, $P = 0.0005$; eliminating outliers had no effect on results) and postevent length of stay (42% unadjusted, 36% adjusted, $t = 3.03$, $P = 0.03$), but postevent daily costs were similar. However, study physicians judged that only 7 IV-ADEs (5%) prolonged ICU length of stay and 1 (0.7%) prolonged hospitalization after ICU discharge.

Three factors indicate that the increase in total postevent costs was due to the increase in length of stay rather than an increase in per-diem costs after IV-ADEs. First, as noted above, the postevent daily costs were similar between cases and controls. Second, the increase in total postevent costs ($6647) was almost exactly equal to controls postevent daily costs multiplied by the increase in postevent length of stay ($1326/d × 4.8 days = $6365). Third, over half the increase in total postevent costs represented ICU room charges. Cases also had higher costs for diagnostic imaging, respiratory therapy, nutrition, dialysis, pharmacy, and clinical laboratory (Table 3).

TABLE 2. Postevent Costs and Length of Stay of Cases Vs. Controls Within Each Hospital

	Academic Hospital					Nonacademic Hospital				
	Cases	Controls	Difference (Increment)	Change	*P*	Cases	Controls	Difference (Increment)	Change	*P*
Total postevent costs, mean (SD)*	$19,176 ($20,062)	$12,529 ($13,215)	$6647 ($22,507)	53%	<0.0001	$17,528 ($22,296)	$17,340 ($21,949)	$188 ($28,885)	1%	0.4236
Postevent daily costs, mean (SD)†	$1156 ($660)	$1326 ($1272)	−$170 ($1285)	−13%	0.5622	$1547 ($1361)	$1697 ($1803)	−$150 ($2061)	−9%	0.6966
Postevent length of stay, in days, mean (SD)‡	16.0 (14.7)	11.3 (11.5)	4.8 (17.8)	42%	0.0003	10.2 (10.4)	10.5 (11.4)	−0.3 d (14.1)	−3%	0.8016
Total no. participants	139	139				194	194			

*Total postevent costs = total hospitalization costs incurred on or after the day of the IV-ADE.
†Postevent daily costs = average cost incurred per hospital day on or after the day of the IV-ADE.
‡Postevent length of stay = length of stay in hospital including and after the day of the IV-ADE.

TABLE 3. Postevent Departmental Costs* for Cases Vs. Controls at the Academic Hospital

Department	Cases	Controls	Difference	*P*
Intensive care	$7075	$3501	$3574	<0.0001
Stepdown unit care	$1321	$1087	$234	0.3256
Acute (floor unit) care	$1872	$1734	$138	0.8986
Clinical laboratory	$1319	$895	$424	0.0549
Diagnostic imaging	$653	$418	$235	0.0015
Noninvasive diagnostic testing	$17	$5	$12	0.1413
Pharmacy	$3473	$2115	$1358	0.0004
Respiratory therapy	$664	$400	$264	<0.0001
Nutrition	$42	$24	$18	0.0002
Dialysis	$118	$49	$69	0.0298
Surgery	$807	$562	$245	0.2651
Procedures	$622	$225	$397	0.3038
Anesthesia	$116	$107	$9	0.3021
Physical therapy	$126	$110	$16	0.2074
Orthopedic equipment	$146	$83	$63	0.4582

Values given are mean values.
*Postevent departmental costs = costs incurred on or after the day of the IV-ADE, by department.

The mean total hospitalization costs (including both pre-event and postevent periods) were $34,815 among cases and $26,052 among controls, which means that the costs associated with IV-ADEs represented 55% of control's total hospitalization costs.

Total postevent costs were $8413 higher (SD, $28,103; $P = 0.02$) for the 43 patients with any preventable IV-ADEs and $5856 higher (SD, $19,613; $P = 0.0006$) for the 96 patients with only nonpreventable IV-ADEs than for their matched controls.

Nonacademic Hospital

Cases and controls were similar at baseline, except that controls' admission APACHE-II scores were slightly higher (Table 1). Five controls (2.5%) experienced an ADE involving a nonintravenous route of administration.

Table 2 shows that IV-ADEs did not significantly increase total postevent costs (1% unadjusted, 3% adjusted, $t = 0.33$, $P = 0.74$; eliminating outliers had no effect on results), postevent length of stay, or postevent daily costs. Study physicians judged that 23 IV-ADEs (12%) prolonged ICU length of stay and 2 (1%) prolonged hospitalization after ICU discharge.

The mean total hospitalization costs (including both pre-event and postevent periods) were $31,187 among cases and $31,274 among controls.

Total postevent costs were not significantly different for the 51 patients with any preventable IV-ADEs ($5790; SD, $27,928; $P = 0.25$) and the 143 patients with only nonpreventable IV-ADEs (−$1809; SD, $29,053; $P = 0.49$) than for their matched controls.

Differences Between Hospitals

Patients' IV-ADE characteristics were similar at the 2 hospitals (Table 4). Nevertheless, the increases in total postevent costs and length of stay associated with IV-ADEs were significantly greater at the academic hospital than at the nonacademic hospital ($P = 0.0012$ for both comparisons). Examining the median and the upper percentiles of total postevent costs for cases and controls at each hospital confirmed that higher cost patients contribute to but are not the principal explanation for these findings (Table 5).

Compared with cases at the academic hospital, those at the nonacademic hospital were older, were more likely to be nonwhite, had higher estimated household incomes, had higher admission and pre-IV-ADE APACHE-II scores, and were more frequently admitted after operations. However, pre-event daily costs were similar (Table 4).

Control patients at the nonacademic hospital had slightly higher total postevent costs than those at the academic hospital ($P = 0.1562$) but postevent length of stay was similar ($P = 0.3317$; Table 2).

DISCUSSION

This study assessed the increases in hospitalization costs and length of stay associated with IV-ADEs that occurred among 4604 adults in ICUs at an academic and a nonacademic hospital. At the academic hospital, patients with IV-ADEs had over $6000 higher costs and 5-day longer stays than matched controls. Surprisingly, IV-ADEs were not associated with greater costs or stays at the nonacademic hospital.

Three prior studies have examined ADE costs at a total of 3 hospitals, including IV and non-IV routes of administration. At 2 academic hospitals, ADEs among adults in ICUs and floor units increased length of stay by 2.2 days and hospitalization costs by $3244 (1993 dollars) relative to matched controls. The researchers could not generate stable cost estimates for ADEs in ICUs; therefore, they estimated costs using ratios of total postevent costs for ICU patients relative to floor patients, finding that ADEs in medical ICUs cost $3369 and those in surgical ICUs cost $5097.[2] A second study at the same hospitals compared hospitalization costs after ADEs in ICU versus floor settings and found a nonsignificant difference of $5691 ($P = 0.16$).[26] The third study found that ADEs among all inpatients at a tertiary nonacademic hospital increased costs by $2013 (1993 dollars).[27]

Our findings at an academic hospital are consistent with these studies' estimates, despite differences in temporal and geographic settings, the fact that we restricted our analysis to IV-ADEs, and our methodological refinements. Applying the consumer price index for hospital and related services to the 1993 ADE cost estimates for surgical and medical ICUs yields $5746 and $8693 in 2003, respectively.[2,28] Because the scope of the available literature on the cost of ADEs in ICUs is so limited, our including 2 previously unexamined hospitals and a nonacademic setting represents an important contribution.[3] Also, because our sample size was larger and we matched cases and controls on pre-event length of stay, principal reason for ICU admission, and propensity to experience an IV-ADE, our analysis has produced the most precise cost estimates currently feasible.

The surprising question posed by our results is why IV-ADEs might increase length of stay and costs at the

TABLE 4. Characteristics of Case Patients and Their IV-ADEs at Each Hospital

	Academic Hospital	Nonacademic Hospital	*P*
Demographic characteristics			
Age, mean (SD)	61.6 (18.2)	64.7 (17.7)	0.0997
Female gender, n (%)	65 (46.8)	93 (47.9)	0.8322
Race/ethnicity			<0.0001
White, n (%)	112 (80.6)	123 (63.4)	
Black, n (%)	22 (15.8)	6 (3.1)	
Hispanic, n (%)	5 (3.6)	36 (18.6)	
Other race, n (%)	0 (0.0)	27 (13.9)	
Estimated household income, mean (SD)	$42,444 ($13,847)	$49,522 ($18,415)	<0.0001
Clinical characteristics			
APACHE II at ICU admission, mean (SD)	14.4 (7.4)	17.9 (7.4)	<0.0001
APACHE II 24 h before IV-ADE, mean (SD)	21.0 (26.1)	25.9 (31.6)	<0.0001
Charlson index, mean (SD)	2.2 (2.1)	2.0 (2.3)	0.2054
Principal reason for ICU admission			0.0489
Operative, n (%)	44 (31.7)	82 (42.3)	
Nonoperative, n (%)	95 (68.4)	112 (57.7)	
Unit type			0.8884
Surgical/trauma/burn, n (%)*	72 (51.8)	102 (52.6)	
Medical, n (%)	67 (48.2)	92 (47.4)	
Baseline economic characteristic			
Pre-event daily costs, mean (SD)†	$3002 ($8081)	$3182 ($3796)	0.1159
Case patients' IV-ADE characteristics			
Most severe IV-ADEs experienced by patients†			0.8730
Temporary injury, n (%)	106 (76.3)	150 (77.3)	
Permanent injury, n (%)	0 (0)	0 (0)	
Intervention to save life, n (%)	31 (22.3)	40 (20.6)	
Death, n (%)	2 (1.4)	4 (2.1)	
Patients experiencing any preventable IV-ADEs, n (%)	43 (30.9)	51 (26.3)	0.3882
Patients experiencing any IV-ADEs involving failure to intervene errors, n (%)	14 (7.2)	21 (10.8)	0.3394
Total no. participants	139	194	

*Pre-event daily costs = average cost incurred per hospital day before the day of the IV-ADE.
†When 1 patient experienced more than 1 IV-ADE, this analysis refers to only the most severe IV-ADE.

TABLE 5. Total Postevent Costs for Cases and Controls at Each Hospital (Median and Upper Percentiles)

	Median	75th Percentile	95th Percentile	99th Percentile
Academic hospital				
Controls	$8352	$16,582	$39,035	$66,918
Cases	$12,801	$27,086	$56,733	$104,397
Nonacademic hospital				
Controls	$9063	$19,967	$62,156	$97,232
Cases	$10,327	$21,451	$60,427	$82,449

academic hospital but not at the nonacademic hospital. We detected no differences in IV-ADEs that explain this finding, and differences in patient characteristics seem too modest to fully account for it. Therefore, dissimilar practice patterns in response to IV-ADEs seem likely. Most IV-ADEs caused relatively minor injuries, which may be subject to greater practice variations than severe injuries or deaths. Indeed, our physician reviewers judged that the IV-ADEs would rarely have prolonged length of stay at either hospital, yet we measured a 5-day increase at the academic hospital. Whereas the nonacademic hospital may have shifted some care for these less severe IV-ADEs to the outpatient setting, such injuries may have delayed floor transfers or discharges at the academic hospital. Hospitalizations tend to be longer at academic than nonacademic hospitals,[4] differences that may be magnified by ADEs. Having several trainee physicians involved in each patient's care may create discontinuities and other inefficiencies in responding to IV-ADEs. Regional

practice patterns also influence length of stay, and stays are slightly longer in the academic hospital's state.[29] Payor mix at the 2 hospitals would not explain the length-of-stay differences, given the academic hospital had more prospective plus capitated payment patients and, therefore, greater incentives to shorten stays. Our data, unfortunately, do not provide more specific insights into practices after IV-ADEs occurred.

Given the likelihood of different practice patterns, our findings emphasize the importance of studying nonacademic settings as well as academic ones when estimating ADE costs. Although several studies have compared rates of ADEs and other adverse events between academic and nonacademic hospitals,[30,31] no studies have compared costs. Of the small number of studies on ADE costs, most have been done in the same few academic hospitals, and our data suggest that ADEs might cost substantially less in nonacademic settings. Future studies should examine the costs of ADEs in a variety of nonacademic hospitals. If our findings are replicated, this would call into question the Institute of Medicine's recent estimate that ADEs in hospitals cost $2.3–$3.5 billion per year nationwide.[3]

If our findings do prove representative of nonacademic hospitals, a second key implication would be that, under capitated and prospective payment mechanisms, adopting innovations to prevent IV-ADEs might improve patient outcomes but may be less likely to save these hospitals' money. Several prevention strategies applicable to IV-ADEs have been evaluated, including computerized physician order entry, bar-coding, pharmacist participation in daily rounds, smart pumps, and dedicated medication administration nurses. Of these, computerized physician order entry and pharmacist participation in rounds have been shown to prevent ADEs, and early generation smart pumps have been shown to intercept certain errors but not to affect ADEs.[8–11,32,33] If nonacademic hospitals cannot recover the cost of implementing innovations to prevent IV-ADEs, they may need to redirect resources away from other valuable activities.

Several limitations must be acknowledged. We included only 2 hospitals, selected because they had implemented smart pumps; therefore, our findings may not be representative. Further, medical record review is an imperfect means of identifying ADEs, although it is the main basis for most published analyses.[3]

We did not consider certain IV-ADE costs also omitted from prior studies, including unbilled labor, fixed costs, malpractice claims, physician care, and postdischarge costs, which would underestimate IV-ADE costs at both hospitals. We did not assess effects on quality of life. Case-mix variables, such as the APACHE II, may inadequately adjust for differences between cases and controls. Our comparison of the nonacademic and academic hospitals was limited by being a post hoc analysis; the hospitals were quite different and factors other than academic status may partially explain these results, such as regional or case-mix differences (particularly operative versus nonoperative reasons for ICU admission). The use of different accounting systems by the 2 hospitals is unlikely to explain the differences in IV-ADE costs: first, because cases were matched with controls at the same hospital, and second, because differences in length of stay mirror differences in costs.

In summary, ADEs involving IV medications substantially increased critically ill patients' lengths of stay and hospitalization costs at an academic hospital but not at a nonacademic hospital in a different geographic region. This suggests that the economic effects of ADEs can differ between academic and nonacademic settings.

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