The Costs of Adverse Drug Events in Hospitalized Patients

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Objective.—To assess the additional resource utilization associated with an adverse drug event (ADE).

Design.—Nested case-control study within a prospective cohort study.

Participants.—The cohort included 4108 admissions to a stratified random sample of 11 medical and surgical units in 2 tertiary-care hospitals over a 6-month period. Cases were patients with an ADE, and the control for each case was the patient on the same unit as the case with the most similar pre-event length of stay.

Main Outcome Measures.—Postevent length of stay and total costs.

Methods.—Incidents were detected by self-report stimulated by nurses and pharmacists and by daily chart review, and were classified as to whether they represented ADEs. Information on length of stay and charges was obtained from billing data, and costs were estimated by multiplying components of charges times hospital-specific ratios of costs to charges.

Results.—During the study period, there were 247 ADEs among 207 admissions. After outliers and multiple episodes were excluded, there were 190 ADEs, of which 60 were preventable. In paired regression analyses adjusting for multiple factors, including severity, comorbidity, and case mix, the additional length of stay associated with an ADE was 2.2 days (P=.04), and the increase in cost associated with an ADE was $3244 ($P$=.04). For preventable ADEs, the increases were 4.6 days in length of stay (P=.03) and $5857 in total cost ($P$=.07). After adjusting for our sampling strategy, the estimated postevent costs attributable to an ADE were $2595 for all ADEs and $4685 for preventable ADEs. Based on these costs and data about the incidence of ADEs, we estimate that the annual costs attributable to all ADEs and preventable ADEs for a 700-bed teaching hospital are $5.6 million and $2.8 million, respectively.

Conclusions.—The substantial costs of ADEs to hospitals justify investment in efforts to prevent these events. Moreover, these estimates are conservative because they do not include the costs of injuries to patients or malpractice costs.

JAMA. 1997;277:307-311

ADVERSE EVENTS occurring during hospitalization are common: they were identified in 3.7% of patients hospitalized in New York in the Harvard Medical Practice Study.[1] Drugs were the leading cause of adverse events, associated with adverse events in 0.7% of hospitalized patients.[2]

We recently reported results from the Adverse Drug Event (ADE) Prevention Study,[3,4] which was designed to better understand how common ADEs are and why they occur and to develop strategies to prevent them. The overall ADE rate was 6.5 per 100 admissions; of these ADEs, 28% were judged preventable. Preventable ADEs were more likely to be serious. Improving the systems by which drugs are ordered and administered may prevent many of these ADEs.[4]

Despite the widespread impression that ADEs in hospitals are costly,[5,6] few data are available to quantify the additional resource utilization associated with these events. One previous study using data from 1990 through 1992 found 1.9 days of increased length of stay and an attributable difference in hospital costs of $1939, not including malpractice costs or the costs of injuries to patients.[7] Drug injuries frequently result in malpractice claims, and in a large study of closed claims, drug injuries accounted for the highest total expenditure of any type of procedure-related injury.[8] The annual national cost of drug-related morbidity and mortality was recently estimated at $76.6 billion, with the majority ($47 billion) related to hospital admissions associated with drug therapy or the absence of appropriate drug therapy.[9] By comparison, the cost of all diabetes care has been estimated at $45.2 billion.[9]

See also pp 301, 312, and 341.

Because of the current economic crisis within hospitals,[10] only quality improvement efforts that are cost-effective are likely to be pursued. Depending on the costs of ADEs and the costs of system improvements, however, quality improvement might reduce costs in this area.[3]

To better define the costs associated with ADEs, we undertook a prospective study to compare the length of stay and total charges for patients with ADEs vs those for all patients admitted to study units and, using case-control comparisons, to evaluate the increases in length of stay, total charges, and total costs in patients with ADEs and preventable ADEs.

METHODS

Patient Population

Study patients included all adults at 2 large tertiary care hospitals in Boston, Mass, Brigham and Women's Hospital (726 beds) and Massachusetts General Hospital (846 beds), admitted to any of 11 units over a 6-month period between February and July 1993, as previously de-

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scribed.[3] Study units were a stratified random sample of medical and surgical units and of intensive and general care units, including 5 intensive care units (ICUs) (3 surgical and 2 medical) and 6 general care units (4 medical and 2 surgical). We intentionally oversampled ICUs and excluded obstetric units because we previously found that ADEs were more common in ICUs than in general care units and because obstetric units had almost no ADEs.[11]

We collected some data on all patients in the study cohort and more detailed information on cases and controls. Analyses were conducted using as cases both patients with an ADE and the subset of patients with a preventable ADE. Controls were selected as the patient on the same unit as the case with the most similar pre-event length of stay. Therefore, cases and controls had the same level of care (ICU vs non-ICU), and almost all were on the same service (medicine vs surgery).

Case Finding and Definitions

We used 3 mechanisms for identifying incidents. First, nurses and pharmacists were asked to report incidents to nurse investigators. Second, a nurse investigator visited each unit at least twice daily on weekdays and solicited information from nurses, pharmacists, and clerical personnel concerning all actual or potential drug-related incidents. Third, the nurse investigator reviewed all charts at least daily on weekdays.

The primary outcome of the study was the ADE, defined as an injury resulting from medical intervention related to a drug. An example would be a patient who received a β-blocker and developed complete heart block requiring temporary pacing. If the patient had already been taking a calcium channel blocker and had first-degree atrioventricular block, the event would be considered a preventable ADE. In previous reports regarding this study we also presented data on potential ADEs, incidents in which an error was made but no harm occurred.[3,4] Although these incidents have the potential to harm and although they create extra work for hospital staff, because they have little direct effect on resource utilization, they were excluded from this analysis.

Classification of Incidents

All incidents were evaluated independently by 2 physician reviewers, who classified them according to whether an ADE was present and, if present, whether it was preventable.[3] The κ statistics for agreement were 0.98 for the presence of an ADE and 0.92 for preventability.[3] When the 2 reviewers disagreed, they met and reached consensus. If consensus could not be reached, a third reviewer evaluated the incident, and that person's decision was used.

Study Variables

Data elements collected for all patients included age, sex, race (by chart review, white vs nonwhite), whether the patient was in an ICU during the hospital stay, primary insurer, diagnosis related group (DRG) weight, and whether the patient was alive at discharge. For cases and controls, additional detailed information was gathered; the severity of illness at the time of the event was measured by the Therapeutic Intervention Scoring System,[12] and comorbidity was assessed using the Charlson Index.[13]

Outcome variables included total length of stay and subcategories of length of stay (ICU, intermediate, and routine care). Total charges and subcategories of charges (ICU, intermediate, and routine care charges and pharmacy, laboratory, and surgery charges) were also gathered and then converted to costs by multiplying times hospital-specific ratios of costs to charges.[14] At 1 hospital, ratios of costs to charges were not available, so we used the other hospital's ratios and varied these in a sensitivity analysis.

Statistical Analysis

Univariate comparisons were made using the χ^2 statistic for categorical variables and the Wilcoxon rank-sum statistic and Kruskal-Wallis comparison as appropriate for nonnormal continuous variables.

The primary analyses were the comparison of postevent resource utilization and length of stay between the cases and controls. These analyses were performed using multiple linear regression, including a dummy variable for pair number, thus retaining the paired design. We refer to these analyses as the paired regression analyses. In these analyses, we controlled for confounding by clinical and nonclinical determinants of resource utilization, including age, sex, race, Therapeutic Intervention Scoring System score for the 24 hours before the event, Charlson Index comorbidity score, whether the patient was alive at discharge, whether the patient was in an ICU, DRG weight at discharge,[15] and primary insurer. Weights are assigned by the Health Care Financing Administration to each DRG and are used to weight reimbursement for a specific DRG, so that they measure the intensity of resource use and, indirectly, severity of illness by diagnosis. Because we were interested only in the incremental increase in resource utilization associated with ADEs, all comparisons were made using 1-sided tests. The adjusted R^2 value is presented for each model. All analyses were performed using the SAS statistical package.[16]

Patients could be in the study more than once; there were 247 ADEs associated with 207 admissions of 204 patients. When patients had more than 1 ADE, we evaluated only the first episode in that admission. Outliers were identified by examining the Studentized residuals for length of stay; all ADEs with residuals of −2 or lower or 2 or greater were evaluated.[17] Some outlier patients were in the hospital for as long as a year, often awaiting nursing home placement; we judged it unlikely that most ADEs that occurred in such patients influenced length of stay. The same episodes were found to be outliers when total charges and total costs were used as the outcomes. We performed analyses both including and excluding multiple episodes and outliers, but we present here only the analyses in which they were excluded because the outliers unduly influenced the results. If outliers are included, the point estimate of the cost of an ADE is larger. In the first reports from this data set, 4031 admissions were included.[3] Through billing data available now (but not at the time of the original report), we identified another 76 patients at 1 hospital and 1 additional patient at the other hospital who were admitted to study units but were not included in the denominator in the earlier report. Thus, the total number of admissions was 4108.

To estimate the impact of ADEs on a hospital and across the nation, we performed extrapolations. For the main resource utilization outcome, postevent costs, we present a figure that is adjusted for our sampling strategy. We performed unpaired analyses in which we estimated postevent costs by unit type (medical ICU, surgical ICU, general medical, or general surgical), including an interaction term between unit type and presence of an event. These adjusted postevent costs by unit type were used to determine the ratios of cost by unit type to overall cost. These ratios were assumed to hold for costs attributable to ADEs by unit type. We multiplied these ratios by overall cost attributable to an ADE to obtain cost attributable to an ADE by unit type. These figures were then multiplied by the projected number of events per year for a hospital by unit type, which we had previously determined from a study in which rates by unit type were estimated,[3] and summed to obtain a cost per hospital per year. We also performed analyses in which we estimated the postevent costs attributable to ADEs within strata, but so few patients were involved that we were not sure the results were stable. These analyses suggested very high costs for ADEs in ICUs (>$10 000), with al-

most no costs for ADEs in general medical and surgical care units. When we used these results in the extrapolations, they had little effect on the overall estimate of hospital costs (they suggested that the point estimate would be 13% lower); these analyses are not presented.

The national estimates were reached by multiplying the number of admissions to acute care hospitals per year (after excluding obstetric admissions) times the ADE rate we previously estimated of 6.5 per 100 admissions[3] times the cost per ADE estimated in this study, after adjusting for our sampling strategy, as described above. For preventable ADEs, we assumed that the point estimate of costs we reached was accurate and that the proportion of preventable events was similar across unit types.

RESULTS

During the study, there were 247 ADEs, of which 70 (28%) were preventable.[3] Of all ADEs, 57% were judged significant, 30% serious, 12% life-threatening, and 1% fatal. Analgesics (30%) and antibiotics (30%) accounted for the largest percentages of nonpreventable ADEs, followed by antineoplastic agents (8%) and sedatives (7%). The largest percentages of preventable ADEs were caused by analgesics (29%), sedatives (10%), antibiotics (9%), and antipsychotics (7%).

When all ADEs were examined by organ system affected, central nervous system (CNS) complications (18%), gastrointestinal complications (18%), allergic/cutaneous complications (16%), and cardiovascular complications (16%) were most frequent. The gastrointestinal complications were predominantly nausea, vomiting, and antibiotic-associated diarrhea; the allergic/cutaneous complications were largely rashes. Central nervous system and cardiac complications were more often serious; confusion, delirium, and oversedation accounted for 64% of the CNS complications, and hypotension accounted for 79% of the cardiovascular complications. For the preventable ADEs, cardiovascular (21%), CNS (19%), and respiratory (9%) complications were most common; only 7% of the complications were allergic reactions and only 1% were gastrointestinal. In the cardiovascular category, hypotension was again the most frequent complication (73%). To qualify as an ADE, hypotension had to be severe enough to require therapy, often vasopressor agents. In several instances hypotension was associated with respiratory failure requiring intubation. Of the CNS complications, 85% were confusion or delirium.

After multiple episodes (n=40) and length-of-stay outliers (n=17) were excluded, there were 190 cases, matched for pre-event length of stay with 190 controls (Table 1); 60 of the 190 cases were preventable ADEs. In addition, we obtained demographic data on all patients admitted to study units during the study period (n=4108). The cases and controls were similar with respect to age, sex, race, insurance status, service (medical vs surgical vs gynecologic, and level of care at admission. Charlson Index comorbidity score and DRG weight were higher in controls than in cases, while Therapeutic Intervention Scoring System score was higher in cases than in controls (Table 1); none of these differences was statistically significant.

Table 1. Demographic Characteristics*

	Cases (n=190)	Controls (n=190)	Entire Cohort† (n=4108)
Mean (SD) age, y	55.8 (19.7)	55.6 (18.4)	56.9 (18.8)
Male, No. (%)	98 (51.6)	86 (45.3)	2109 (51.3)
Nonwhite, No. (%)	42 (22.1)	40 (21.1)	855 (20.8)
Uninsured or Medicaid, No. (%)	15 (7.9)	22 (11.6)	444 (10.8)
Hospital service, No. (%)			
Medical	118 (62.1)	119 (62.6)	2460 (59.9)
Surgical	72 (37.9)	71 (37.4)	1601 (39.0)
Gynecologic	0 (0)	0 (0)	47 (1.1)
Charlson Index‡			
Mean (SD)	2.3 (2.5)	2.5 (2.7)	NA
Median [25th, 75th percentile]	2 [0, 3]	2 [0, 4]	
Therapeutic Intervention Scoring System‡			
Mean (SD)	12.2 (12.7)	11.1 (13.0)	NA
Median [25th, 75th percentile]	6 [3, 18]	6 [3, 14]	
DRG weight‡			
Mean (SD)	2.7 (3.3)	3.3 (4.5)	2.1 (2.6)
Median [25th, 75th percentile]	1.7 [1.0, 3.1]	1.8 [1.0, 3.1]	1.2 [0.9, 2.4]

*NA indicates data not available; DRG, diagnosis related group.
†The entire cohort includes the cases and controls as well as the sample population from which they were drawn.
‡A higher score indicates greater severity of illness.

Table 2. Total Resource Utilization*

	Cases (n=190)	Controls (n=190)	Entire Cohort† (n=4108)
Length of stay, d			
Total	20.4 (25.6) 12 [6, 24]	18.2 (16.4) 12 [7, 25]	11.9 (17.5) 7 [3, 13]
In intensive care	6.1 (18.2) 0 [0, 5]	6.2 (13.7) 0 [0, 5]	2.3 (9.6) 0 [0, 1]
In routine care	14.3 (14.7) 10 [6, 17]	12.3 (10.9) 9 [5, 15]	5.4 (9.6) 2 [1, 6]
Hospital charges, $			
Total	51 640 (80 149) 24 209 [12 431, 56 150]	46 467 (57 433) 23 239 [12 822, 64 152]	28 283 (53 030) 12 825 [6315, 28 115]
Intensive care	10 473 (32 404) 0 [0, 9250]	10 399 (23 692) 0 [0, 8750]	3914 (17 137) 0 [0, 1850]
Routine care	9117 (9734) 5940 [3300, 10 560]	7707 (7241) 5280 [3300, 9380]	4510 (6795) 2640 [670, 5280]
Pharmacy	6561 (11 740) 2140 [560, 6201]	5849 (9861) 1635 [515, 6973]	2745 (9623) 467 [135, 1522]
Ancillary	7865 (12 939) 2844 [903, 9734]	7201 (10 308) 2656 [943, 9759]	3561 (8780) 1134 [422, 3130]
Surgery	5214 (7791) 1854 [0, 8650]	4888 (6253) 2389 [0, 7992]	3390 (6032) 0 [0, 4992]
Total costs,‡ $	27 173 (41 263) 13 623 [7529, 28 764]	24 974 (28 722) 13 995 [7691, 33 776]	12 452 (25 427) 5717 [2907, 12 257]

*Values are mean (SD) on the first line, median [25th, 75th percentile] on the second line. All 3-way comparisons between the cases, controls, and remaining patients were significant ($P<.001$, Wilcoxon test).
†The entire cohort includes the cases and controls as well as the remainder of the sample population.
‡Derived by multiplying components of charges times hospital-specific ratios of costs to charges, and summing.

Univariate Analyses

For all the total resource utilization comparisons (Table 2), the cases and controls were generally similar and were markedly different from the remainder of the cohort ($P<.001$ for 3-way comparison, Wilcoxon test). For example, the mean total length of stay was 20.4 days for cases and 18.2 days for controls, compared with 11.9 days for the entire cohort. The lengths of stay in both the ICUs and the routine care units were also longer for cases and controls. Correspondingly, total charges were much higher for the cases and controls ($51 640

Table 3.—Unadjusted Resource Utilization After the Adverse Drug Event (ADE)*

	Cases (n=190)	Controls (n=190)
Length of stay after ADE, d		
Total (P=.75)	11.9 (15.8) 6 [4, 14]	11.0 (12.0) 6 [3, 15]
In intensive care	3.7 (11.6) 0 [0, 2]	3.3 (8.4) 0 [0, 2]
In routine care	8.5 (9.1) 6 [3, 10]	8.3 (8.3) 5 [3, 11]
Hospital charges after ADE, $		
Total (P=.97)	29 335 (51 663) 10 691 [4447, 33 034]	26 188 (39 084) 10 997 [4200, 32 024]
Intensive care	6323 (20 865) 0 [0, 3700]	5506 (14 563) 0 [0, 3500]
Routine care	5486 (6372) 3300 [1890, 6700]	5123 (5606) 3300 [1340, 6600]
Pharmacy	5500 (11 171) 754 [181, 4829]	4763 (9484) 643 [137, 5356]
Ancillary	4139 (8135) 1144 [425, 4239]	3638 (6470) 1090 [292, 3799]
Surgical	1131 (3304) 0 [0, 0]	1206 (2765) 0 [0, 0]
Total costs after ADE, †$	15 701 (26 926) 5908 [3174, 17 702]	14 214 (19 100) 6545 [2912, 17 636]

*Values are mean (SD) on the first line, median [25th, 75th percentile] on the second line. None of these differences was statistically significant.
†Derived by multiplying components of charges times hospital-specific ratios of costs to charges, and summing.

Table 4.—Adjusted Paired Analysis, Excluding Outliers and Multiple Adverse Drug Events (ADEs)*

	Cases	Controls	Difference	R^2	P
Total ADEs					
No. of events	190	190	...	...	...
Length of stay after ADE, d	12.6 (0.83)	10.4 (0.83)	2.2	0.69	.04
Total hospital charges after ADE, $	30 932 (2464)	24 591 (2464)	6341	0.74	.04
Total costs after ADE,† $	16 580 (1258)	13 336 (1258)	3244	0.74	.04
Preventable ADEs					
No. of events	60	60	...	...	...
Length of stay after ADE, d	15.8 (1.7)	11.2 (1.7)	4.6	0.71	.03
Total hospital charges after ADE, $	42 686 (4891)	31 162 (4891)	11 524	0.77	.06
Total costs after ADE,† $	22 792 (2632)	16 935 (2632)	5857	0.77	.07

*Values are mean (SE) and are adjusted for age, sex, race, primary insurer, diagnosis related group weight, Therapeutic Intervention Scoring System score, and Charlson Index score. The SEs are constrained to be the same for cases and controls in the paired regression analyses. All P values are 1-sided.
†Derived by multiplying components of charges times hospital-specific ratios of costs to charges, and summing.

Table 5.—Projected Hospital Costs of Adverse Drug Events (ADEs) for 1 Year*

Unit Type	All Patient-Days in the Hospital, %	Patient-Days in This Unit Type Included in the Sample, %	Estimated No. of Events per Hospital per Year†	Estimated Costs per Event,‡ $	Estimated Total Costs per Year, §$
Medical ICU	3.2	11.4	133	3369	449 209
Surgical ICU	9.1	14.6	204	5097	1 038 256
General medical	40.4	53.7	919	2738	2 515 185
General surgical	47.3	20.3	904	1772	1 601 153
Total	**100.0**	**100.0**	**2159**‖	2595	5 603 803

*The purpose of this table is to account for oversampling of intensive care units (ICUs) and medical units and to show how estimated costs were derived.
†Based on site-specific event rates, as previously described[3]; these values are means for the 2 hospitals.
‡Assumes that overall costs per event were $3244 (see Table 4) and that differences in post-ADE costs by unit type were proportional to differences in adjusted total post-ADE costs for patients on these units; these costs were $19 702 for the medical ICU, $29 803 for the surgical ICU, $16 009 for the general medical unit, and $10 359 for the general surgical unit.
§Because of rounding, multiplying the estimated number of events per hospital per year times the estimated costs per patient does not yield the exact values given for estimated total costs per year.
‖The estimated number of events per hospital per year does not add to the total because of rounding.

and $46 467, respectively) than for the entire cohort ($28 283).

The crude mean (SD) postevent length of stay was 1 day longer for cases than for controls (11.9 [15.8] vs 11.0 [12.0] days), but this difference was not significant (P=.75, Wilcoxon test, Table 3). Mean postevent charges were $3147 higher for cases than for controls, again nonsignificant (P=.86). Subcategories of mean charges that were higher in the case group included ICU charges ($817), routine care charges ($363), pharmacy charges ($737), and ancillary charges ($501), while surgical charges were slightly higher in controls ($75); none of these differences was significant. Crude mean total costs after an event were $1487 higher in cases than in controls ($15 701 vs $14 245), again not significant (P=.97, Wilcoxon test).

Multivariate Analyses

In multiple linear regression analyses, controlling for pair, age, sex, race, Charlson Index comorbidity score, Therapeutic Intervention Scoring System score, insurance status, and DRG weight, and comparing all patients who had ADEs with controls, length of stay was 2.2 days longer for patients (P=.04), total charges were $6341 higher for patients (P=.04), and total costs were $3244 higher for patients (P=.04) (Table 4). For the cost analyses, because we did not have the ratios of costs to charges from 1 of the hospitals, we performed a sensitivity analysis in which the ratios were increased and decreased by 20%. This analysis changed the point estimate only from $3380 to $3107, suggesting that the difference between cases and controls was not sensitive to the ratios of costs to charges at that hospital. Differences were even greater for patients with preventable ADEs compared with controls: length of stay was 4.6 days longer for patients (P=.03), total charges were $11 524 higher for patients (P=.06), and total costs were $5857 higher for patients (P=.07).

Projected Hospital Costs

To estimate the total costs per year for a hospital, we performed extrapolations (as described in the "Methods" section) to adjust for our sampling strategy (Table 5). The overall costs to a hospital are approximately $5.6 million per year. For preventable ADEs, this figure is approximately $2.8 million per year. For individual events, after adjusting for the sampling strategy, we reached an estimate for postevent costs of $2595 for an ADE and $4685 for a preventable ADE.

COMMENT

We found that an ADE was associated with $2595 of additional costs to the hospital; for preventable ADEs this figure was almost twice as high. These estimates do not include the costs of injuries to patients or malpractice costs. Thus, ADEs are costly, and interventions to reduce their frequency can be justified economically as well as justified to improve the quality of care.

We did not expect to find such a large difference in length of stay and resource utilization between preventable ADEs and nonpreventable ADEs; this prob-

ably was the case in part because preventable ADEs were more severe than nonpreventable ADEs.[3] Both cases and controls had markedly longer overall lengths of stay than the cohort as a whole, demonstrating the need to adjust for pre-event length of stay when evaluating the resource utilization associated with an ADE. Patients with long stays tend to be sicker and receive more medications and therefore had substantially greater rates of exposure per admission than other patients.

A previous case-control study performed by Evans et al[7] at LDS Hospital in Salt Lake City, Utah, that also measured the increase in utilization associated with ADEs found an attributable increase in length of stay of 1.9 days and increased costs of $1939. However, the authors did not adjust for pre-event length of stay, which appears to be an important confounder. Adjusting for pre-event length of stay in the Utah study would have resulted in a lower estimate of costs, and thus the difference in cost estimates between the 2 studies would have been greater. However, the additional length of stay identified in the 2 studies was similar. Given the differences in costs between the 2 regions, the cost estimates were also similar. The costs of ADEs in other parts of the country and in settings such as community hospitals may vary substantially.

Based on the cost figures and ADE incidence data, we estimate that the annual costs of ADEs for our teaching hospitals are $5.6 million. Because they were associated with higher costs, preventable ADEs accounted for $2.8 million, about half the total, even though they represent fewer than one third of the ADEs. In 1993, there were approximately 25 million nonobstetrical admissions to short-term hospitals in the United States.[18] If the ADE and preventable ADE rates and associated costs we found are representative of those among the nation's acute care hospitals, the total hospital costs of ADEs occurring during hospitalization would be $4 billion. The hospital costs of preventable ADEs alone would be $2 billion. However, these extrapolations to the country as a whole must be viewed with great caution. We evaluated only 2 tertiary care hospitals in 1 region. Because patients in tertiary care centers tend to be sicker than patients in other hospitals, both the numbers and costs of these events are probably overestimated. On the other hand, these 2 hospitals are perceived as 2 of the country's leading hospitals[19] and may have lower event rates than other hospitals. It is not possible to determine the net effect of these countervailing biases.

Our study addressed only the costs of ADEs occurring after patients have been hospitalized, not the costs associated with admissions related to ADEs. The proportion of admissions caused by drug-related issues has ranged from 2.3% to 27.3% in a variety of reports[20]; a meta-analysis arrived at a weighted estimate of 5.1%, including both ADEs and noncompliance with drug therapy.[21] Thus, the costs of ADEs in patients already hospitalized, which we report here, represent only part of the overall costs of medication-related complications. Johnson and Bootman[9] recently used a decision-modeling approach to estimate the cost of drug-related outpatient morbidity to a managed care provider and projected that these costs are $76.6 billion nationwide.

Our study has other limitations besides generalizability. Despite the intensive nature of case identification and the number of units surveyed, we identified only 247 events. Thus, despite the magnitude of the difference found, statistically, the results are only marginally significant. However, patients experiencing an adverse event would be expected to have increased resource utilization, so that the main question is the validity of our estimate of the amount of increase. Because of the large variance of length of stay and charges, the confidence intervals around our point estimates are large. Also, we oversampled ICUs and the medical services but adjusted for this in the estimates for hospitals. Another issue is that the cost data were derived using hospital-specific ratios of costs to charges, a technique that has limitations because of the vagaries of hospital accounting.[22,23] In addition, we had to apply ratios from 1 hospital to the other. However, the results changed little when we varied these ratios in the sensitivity analysis. Finally, since we relied on record review and provider reporting to find events, we undoubtedly missed some events.

The costs of ADEs and preventable ADEs are substantial. We estimated that the annual additional costs associated with preventable ADEs occurring in a large tertiary care hospital were $2.8 million and that the costs associated with all ADEs were $5.6 million. Moreover, these estimates do not include costs of injuries to patients, malpractice costs, or the costs of less serious medication errors or admissions related to ADEs. These results suggest that hospitals can justify devoting additional resources to develop systems that reduce the number of preventable ADEs not only to improve patient care but also to reduce ADE-related expenses.

This study was supported by research grant R01-HS07107-01 from the Agency for Health Care Policy and Research, Washington, DC, and by a grant from the Risk Management Foundation of the Harvard Medical Institutions, Cambridge, Mass.

We thank Anthony Komaroff, MD, and David Meltzer, MD, PhD, for comments on an earlier version of the manuscript.

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