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Original Contributions

Adverse Drug Events in Hospitalized Patients

Excess Length of Stay, Extra Costs, and Attributable Mortality

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Objective.—To determine the excess length of stay, extra costs, and mortality attributable to adverse drug events (ADEs) in hospitalized patients.

Design.—Matched case-control study.

Setting.—The LDS Hospital, a tertiary care health care institution.

Patients.—All patients admitted to LDS Hospital from January 1, 1990, to December 31, 1993, were eligible. Cases were defined as patients with ADEs that occurred during hospitalization; controls were selected according to matching variables in a stepwise fashion.

Methods.—Controls were matched to cases on primary discharge diagnosis related group (DRG), age, sex, acuity, and year of admission; varying numbers of controls were matched to each case. Matching was successful for 71% of the cases, leading to 1580 cases and 20 197 controls.

Main Outcome Measures.—Crude and attributable mortality, crude and attributable length of stay, and cost of hospitalization.

Results.—ADEs complicated 2.43 per 100 admissions to the LDS Hospital during the study period. The crude mortality rates for the cases and matched controls were 3.5% and 1.05%, respectively ($P<.001$). The mean length of hospital stay significantly differed between the cases and matched controls (7.69 vs 4.46 days; $P<.001$) as did the mean cost of hospitalization ($10 010 vs $5355; $P<.001$). The extra length of hospital stay attributable to an ADE was 1.74 days ($P<.001$). The excess cost of hospitalization attributable to an ADE was $2013 ($P<.001$). A linear regression analysis for length of stay and cost controlling for all matching variables revealed that the occurrence of an ADE was associated with increased length of stay of 1.91 days and an increased cost of $2262 ($P<.001$). In a similar logistic regression analysis for mortality, the increased risk of death among patients experiencing an ADE was 1.88 (95% confidence interval, 1.54-2.22; $P<.001$).

Conclusion.—The attributable lengths of stay and costs of hospitalization for ADEs are substantial. An ADE is associated with a significantly prolonged length of stay, increased economic burden, and an almost 2-fold increased risk of death.

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DRUG-RELATED morbidity and mortality have been estimated to cost more than $136 billion a year in the United States.[1] These estimates are higher than the total cost of cardiovascular care or diabetes care in the United States.[1] A major component of these costs is adverse drug reactions (ADEs).[2] In addition, ADEs may account for up to 140 000 deaths annually in the United States.[3] More than 2 decades ago, seminal work by the Boston Collaborative Drug Surveillance Project estimated that approximately 30% of hospitalized patients experience adverse events attributable to drugs and that from 3% to 28% of all hospital admissions are related to ADEs.[4] Moreover, fatal ADEs are expected in approximately 0.31% of hospitalized patients in the United States.[5-9]

See also pp 307, 312, and 341.

ADEs were the most common type of adverse event experienced by patients in the Harvard Medical Practice Study, a study of over 30 000 inpatient hospitalizations that were intensively reviewed to ascertain the occurrence of adverse events at several hospitals in New York State in the mid 1980s.[10] The study documented that at least 3.7% of all hospitalized patients developed a serious, disabling, and clinically important adverse event during their hospitalizations, of which almost 20% were ADEs. Since that study was not designed to determine the attributable impact of an ADE, the investigators did not specifically evaluate the impact of an ADE on mortality, length of stay, or resource utilization during hospitalization. The exact costs attributed to ADEs are unknown and although several earlier studies attempted to estimate these costs, they were hampered by crude and inadequate methods.[8,9]

We have developed and implemented a hospital-wide surveillance program for the detection and characterization of ADEs in our hospital population that has been ongoing since 1989.[11] In the present study we describe a matched case-control study of hospitalized patients using a severity adjustment system to evaluate the attributable costs, length of stay, and mortality for ADEs in hospitalized patients.

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METHODS

The LDS Hospital is a 520-bed teaching hospital affiliated with the University of Utah School of Medicine in Salt Lake City. The present study was performed using a hospital information system that has a computerized medical record that contains an integrated patient database drawn from numerous sources including pharmacy, laboratory, surgery, radiology, and admitting, among others.[12] In addition to the integrated patient database, an interactive modular knowledge base is used that continually analyzes information contained in the computerized medical record. Criteria-based algorithms for drug usage have been developed and used to improve drug use and the quality of patient care.[11,13-15]

This system has been also been adapted to perform computerized surveillance of hospital patients for ADEs and has been in continuous clinical operation since May 1989.[11,14] These programs allow for voluntary reporting through physician, nurse, or pharmacist entry of potential ADEs from all computer terminals throughout the hospital. Once activated, this program allows easy entry of patient name, type of ADE symptoms, and reporter identification. In addition, algorithms were created within the knowledge base for automated detection of potential ADEs through the use of various automated signals (drug stop orders, antidote orders, abnormal laboratory tests, etc). Then each of these patients was evaluated for a suspected ADE by 1 of us (S.L.P) and confirmed with the attending physician. A comprehensive and consistent protocol has been used for the evaluation, diagnosis, and characterization of all ADEs. For example, all ADEs are scored for severity (mild, moderate, severe), causality (Naranjo algorithm), and allergic or not (type B or A).[11] If an ADE occurred, relevant information was stored in the electronic medical record. A large database of this ADE information has been created and used in this and other studies.[11,14,15]

Study Design

This matched case-control study included all patients admitted to LDS Hospital from January 1, 1990, to December 31, 1993, and who had a confirmed ADE. Patients with ADEs were designated as cases, and selected patients without ADEs from this same time frame were labeled as matched controls. Cases were excluded if they had more than 1 ADE or developed any nosocomial infection.

Case Finding

We defined ADEs based on the World Health Organization definition[11]: an ADE is one that is "noxious and unintended and occurs at doses used in humans for prophylaxis, diagnosis, therapy, or modification of physiologic functions." Furthermore, for the purposes of this investigation, this definition excluded therapeutic failures, poisonings, and intentional overdoses.

Matching and Selection of Matched Controls

Matched controls were selected among all patients admitted to LDS Hospital over the study period according to matching variables. We required that a matched control patient have no evidence of either an ADE or a nosocomial infection.

The matching criteria included admission to LDS Hospital during the study period, sex, age (±10 years), exact primary discharge diagnosis related group (DRG), same calendar year of admission, and same hospital acuity score category (1, 2, 3, or 4). The selection of the matched controls was performed as described in earlier reports in a stepwise manner, first attempting to match on exact discharge DRG, then acuity score category, then year of admission, then age, and finally sex; control patients were included only if successfully matched on all variables. Varying numbers of controls were matched to each case.[15,16] A consistent method has been used to calculate patient acuity based on actual nursing resource use.[17] The method used to calculate these acuity scores involves nurse responses to numerous standardized questions about the care of the patient calculated for every nursing shift of the patient's hospitalization. These questions are based on objective measures of patient care for 10 different clinical care categories for which a predetermined amount of time has been assigned. The 10 clinical care nursing categories are constant time assignment, vital sign measurement, fluid intake/diet, output/drainage tubes, respiratory care on the part of the nurse, medications, turning and/or assisted activity, laboratory work, daily care/cleanliness, and miscellaneous special procedures. Many health service researchers have used similar nursing assessments to measure severity of illness.[18-22] Accordingly, we used the nursing acuity system to create a severity of illness model based on the nursing acuity score and the primary discharge DRG. The mean nursing acuity score for the hospitalization is assigned to 1 of 4 categories (1, 2, 3, or 4) based on increasing acuity (intensity) of care; this category is then combined with the primary discharge DRG to create a severity of illness model. This model was validated by measuring its ability to predict length of stay, cost of hospitalization, and mortality with a large linear regression model for length of stay and cost of hospitalization and a logistic regression model for mortality.[15,16] This model has been found to predict length of stay (R^2=0.56), cost of hospitalization (R^2=0.67), as well as mortality (R^2=0.51). These R^2 values are all higher than a comparative commercially available severity of illness model.[15,16]

Cost outcomes were determined from a transaction-based microcosting system called the standard cost manager (SCM), a microcomputer software system designed and developed by Intermountain Health Care, Inc, and Ernst and Whinney.[23] This system is a cost-based accounting system that uses time and motion studies to estimate the actual costs of all aspects of hospital care, updated each year, and is used widely throughout US hospitals.[15,16]

Study Objectives and Outcomes

The objectives of this study were to examine the crude and attributable excess length of stay, extra costs, and mortality associated with the occurrence of an ADE. Crude excess length of stay was the difference between mean length of stay in cases and mean length of stay in matched controls. Crude extra cost was the difference between mean total hospital costs in cases and mean total hospital costs in matched controls. Crude mortality ratio was the ratio of the mortality rate in cases divided by the mortality rate in matched controls.

A different approach was used to determine attributable length of stay and attributable cost of hospitalization.[24,25] Rather than comparing the mean group values for these variables between all cases and all controls, the attribution method compares the difference between each case and the mean for all controls specifically matched to that case. Then the individual differences are summed for each of the case/matched control sets, and an overall mean difference is calculated for the outcome variable in question.[24,25] Separate analyses using the attribution methods were conducted for selected types of ADEs (itching, nausea and vomiting, diarrhea, arrhythmia, etc).

Statistical Analysis

A *t* test (for independent samples) was used to detect statistically significant differences between the overall groups of cases and matched control patients in hospital length of stay and cost of hospitalization. A paired *t* test was used to look for statistically significant differences in attributable length of stay and cost of hospitalization between cases and matched controls. All *t* tests were 2

tailed. Since the patients in the case group and the matched control group were not randomly assigned with respect to risk of an ADE, we developed stepwise regression models to predict the impact of an ADE on length of stay, cost, and mortality while controlling for other factors that might be confounded with the occurrence of an ADE.[26] A logistic regression model was created for mortality. Linear regression models were created for length of stay and cost of hospitalization, which were continuous variables. Independent variables in the 3 models included all match criteria (age, sex, acuity, exact discharge DRG, and year of admission) as well as the occurrence of an ADE. Independent variables were analyzed as categories using dummy variables for sex, DRG, acuity, and year of admission.[26] Age was handled as a continuous variable. Numerous individual DRGs were found to be significant in the regression models, and they were each treated as a separate category and the remaining DRGs were placed in a single group. Using a backward stepwise method, independent variables remained in the model if found to have a significance level of .10 or less.

RESULTS

Between January 1, 1990, and December 31, 1993, a total of 91 574 patients were admitted to LDS Hospital. A total of 2227 patients developed ADEs during this period, for a rate of 2.43 per 100 admissions. The average time from admission to development of an ADE was 3.67 days, and the average number of different drugs given to patients before they experienced an ADE was 12.52. A mean of 18.39 different drugs were given to patients who experienced an ADE. Overall, 28% of these patients spent time in an intensive care unit, and the average time spent for those patients in an intensive care unit (ICU) was 4.7 days. The leading causal drugs were morphine (patient-controlled infusion, routine intravenous, and epidural), digoxin, meperidine, oxycodone and acetaminophen, imipenem, cefazolin, warfarin, and vancomycin. The leading types of ADEs were itching, nausea/vomiting, rash, dizziness, fever, renal failure, confusion, and arrhythmia (Table 1).

Among the 2227 ADE patients, 1580 cases were matched to a total of 20 197 control patients who were admitted during the 4-year study period (Table 1). A total of 647 unmatched case patients had an average length of stay of 9.17 days and an average cost of hospitalization of $12 252. These patients had a higher mortality, acuity score, more severe ADEs, and more drug exposures, but the causal drugs and types of ADEs did not differ from the cases. The unmatched cases were excluded from further analysis; the following analysis applies only to the 1580 cases that were matched. The case patients had a mean age of 54 years, and the matched control patients had a mean age of 45 years. The matched control patients had a crude mortality rate of 1.05% vs 3.5% ($P<.001$) for the case patients with ADEs. The crude mortality ratio of cases to controls was 3.33 (Table 1). The matched control patients had a mean length of stay of 4.46 vs 7.69 ($P<.001$) days for patients with ADEs, and 16.4% of the matched controls spent time in an ICU with an average ICU length of stay of 3.11 days. The matched controls had a mean total cost of hospitalization of $5355 compared with $10 010 ($P<.001$) for patients with ADEs (Table 1). Attributable excess length of hospital stay was 1.74 days ($P<.001$). Total excess length of stay was 2749 days for the case patients. The mean attributable excess hospital cost for an ADE was $2013 ($P<.001$) (Table 1). Total excess costs for this study were $3 180 540 for the case patients. For the subset of cases with severe ADEs the attributable length of stay was 3.6 days and the attributable cost of hospitalization was $3634.

To estimate the excess costs associated with each individual type of ADE based on the major symptoms of the ADE, we broke out subsets of ADEs (Table 2). Itching, a common ADE, was associated with an increased cost of $677 and almost 18 hours of excess length of stay, while nausea and vomiting was associated with an increased cost of $1712 and an excess length of stay of 1.37 days. Diarrhea was less common, yet it was associated with an excess cost of $4631. Cardiac arrhythmias were common and associated with an excess cost of $4410 and an excess length of stay of 3.93 days. Drug-induced bleeding and drug-induced fever were quite costly at $6700 and $9022, respectively.

Table 1.—Adverse Drug Events (ADEs): Attributable Length of Stay and Costs*

	Case Patients	Matched Controls*	Attributable Difference
No.	1580	20 197	...
Age, y	54	45	...
Mortality, %	3.5	1.05	...
Acuity category, %			
1	7.3	26	...
2	50	46.6	...
3	32.3	20	...
4	10.4	7.4	...
ADE severity, %			
Mild	2.02	...	...
Moderate	92.1	...	...
Severe	5.79	...	...
Type of ADE	Itching, nausea/vomiting, rash, dizziness, fever, renal failure, confusion, arrhythmia	...	...
Causal drug	Morphine (3 types), digoxin, meperidine, oxycodone, imipenem, cefazolin, warfarin, vancomycin	...	...
No. of drugs given	16.97	10.52	...
Mean length of stay, d	7.69†	4.46†	1.74‡
Mean cost of hospitalization, $	10 010†	5355†	2013.80‡

*These data reflect group comparisons only. Each patient was matched to a variable number of control patients having the same characteristics. The method of analysis compares each case to its matched controls, not overall group mean comparisons.
†$P<.001$, t test for independent samples.
‡$P<.001$, paired t 2-tailed (each case vs specific matched controls).

Regression Models

The stepwise logistic regression model for mortality revealed several variables that were associated with an increased risk of mortality: increased age, higher acuity levels, and DRG 105 (cardiac valve procedure with pump and without cardiac catheterization) and DRG 108 (other cardiovascular or vascular procedure with pump). The occurrence of an ADE was associated with an increased risk of death (odds ratio (OR)=1.88; 95% confidence interval (CI), 1.54-2.22; $P<.001$). The stepwise linear regression model revealed several variables to be associated with prolonged length of stay: higher acuity levels (3 and 4 from a scale of 1 to 4), numerous DRGs, age, sex, and the occurrence of an ADE (Table 3). Increased age and female sex posed slightly increased risks. Certain DRGs (see footnote, Table 3) were associated with an increased risk of an ADE (including DRGs 104, 105, and 108, which were cardiac and other vascular procedures requiring a pump, and 148 [major small and large bowel procedures with complica-

Table 2.—Attributable Costs for Various Types of Adverse Drug Events*

Type of ADE	Total No. of Patients	Attributable Cost, $	Attributable Length of Stay, d
Cardiac arrhythmia	561	4410	3.93
Diarrhea	182	4631	4.40
Fever	26	9022	5.49
Nausea/vomiting	526	712	1.37
Renal failure	324	1371	4.54
Confusion	98	2232	2.50
Rash	108	1868	1.37
Itching	548	677	0.72
Hypotension	75	3563	2.94
Bleeding	26	6702	4.89

*Each patient with the specified adverse drug event (ADE) was compared with his or her matched control (see "Methods").

Table 3.—Length of Stay and Cost (Linear Regression Model) and Mortality (Logistic Regression Model)*

Parameter	Coefficient for Length of Stay, d	Coefficient for Cost of Hospitalization, $	Mortality, OR (95% CI)
Age (continuous)	0.17	−16.5	1.07 (1.06-1.08)
Sex (female)	−0.805	−1884	. . .
Acuity score category 3	1.20	493	. . .
Acuity score category 4	4.51	15 010	. . .
DRG 104	5.00	17 693	. . .
DRG 105	2.32	10 079	3.06 (2.39-3.72)
DRG 108	3.66	9585	8.16 (7.6-8.71)
DRG 148	3.73	2538	. . .
DRG 373	−2.60	−3305	. . .
DRG 112	−2.23	−1951	. . .
DRG 337	−3.60	−3891	. . .
DRG 124	−2.97	−4084	. . .
DRG 198	−2.51	−1751	. . .
DRG 219	−2.03	−1982	. . .
DRG 222	−3.25	−2799	. . .
DRG 127	−1.931	−4031	. . .
Adverse drug event	1.91	2262	1.88 (1.54-2.22)
R^2	0.36	0.51	. . .

*$P<.001$ for all parameter values given. OR indicates odds ratio; and CI, confidence interval. Diagnosis related group (DRG) 104, cardiac valve procedure with pump and cardiac catheterization; DRG 105, cardiac valve procedure with pump, without cardiac catheterization; DRG 108, other cardiovascular or vascular procedure with pump; DRG 112, vascular procedures except major reconstruction without pump; DRG 124, circulatory disorders except acute myocardial infarction, with cardiac catheterization and complex diagnosis; DRG 127, heart failure and shock; DRG 148, major small and large bowel procedures with cardiac catheterization; DRG 198, cholecystectomy except by laparoscope without circulatory disorders and without cardiac catheterization; DRG 219, lower extremity and humerus procedures except hip, foot, femur, in patients older than 17 years, without cardiac catheterization; DRG 222, knee procedure without cardiac catheterization; DRG 337, transurethral prostatectomy without cardiac catheterization; and DRG 373, vaginal delivery without complicating diagnosis.

tion]). Other DRGs were associated with a decreased risk (DRGs 337,transurethral prostatectomy without complication, 373, vaginal delivery without complicating diagnosis, 222, knee procedures without complication, and 124 circulatory disorders except acute myocardial infarction (AMI), with cardiac catheterization and complex diagnosis). An ADE was associated with an excess length of stay of 1.91 days (Table 3).

The linear regression model for total cost of hospitalization revealed several variables to be associated with increased costs of hospitalization including severity of illness, several DRGs, sex, age, and the occurrence of an ADE (Table 3). Younger age was associated with a lower cost of hospitalization, as was male sex. Higher acuity levels were associated with higher costs of hospitalization. The same DRGs associated with higher risk for ADEs were associated risk with higher hospital costs (DRGs 104, 105, 108, and 148). Certain DRGs were associated with lower costs (DRGs 373, vaginal delivery without complicating diagnosis; 124, circulatory disorders except AMI, with cardiac catheterization and complex diagnosis; and 127, heart failure and shock). An ADE was associated with a cost of $2262 (Table 3).

COMMENT

This study focused on ADEs in hospital patients because ADEs can cause significant increases in patient mortality and cost of hospitalization, as well significant outpatient disability.[10] Before widespread enthusiasm can develop to prevent these events, further documentation of their impact must be provided. At the LDS Hospital approximately 2.4% of all patients develop an ADE.[11,14] These are not rare and unusual events; indeed, as in the Harvard Medical Practice Study, they are quite common. In a recent study the rate of ADEs was even higher at 6.5%,[27] suggesting that rates may vary depending, in part, on methods of detection (ADE definition, computerized or manual surveillance) and case ascertainment (all hospital patients or focused hospital unit surveillance). These differences may explain differences in rates between institutions that have focused on ADE detection.

The average cost of an ADE at LDS Hospital was $2013 with a range of $677 to $9022 for common types of ADEs. This is similar to what is reported in other studies using cost measurements, although the cost of various types of ADEs has not been previously elucidated.[28,29] For instance, an episode of drug-related itching may increase costs by $677; this may seem high, but the increased costs can be explained by the resulting symptomatic treatment and diagnostic search for the cause, which in our institution can lead to a prolongation of hospital stay of almost 18 hours. A total of 567 ADEs were detected in 1992 at LDS Hospital, and the direct hospital costs were $1 099 413 in that year alone. Over a 4-year period, the excess hospital costs alone were $4 482 951 and the excess hospital days were 3874 days. These do not include liability costs or the costs of injuries to patients. If 50% of these ADEs are potentially preventable, then successfully targeted programs could save more than $500 000 annually and prevent almost 450 extra days of hospitalization annually at LDS Hospital.

If these figures are extrapolated to the United States as a whole, using LDS Hospital ADE occurrence rates and an estimated 32 million yearly hospital visits, then over 770 000 hospital patients in the United States experience an ADE, and the direct hospital costs to treat these events are approximately $1.56 billion annually.[27] If a higher rate of ADEs is assumed, as in the study by Bates et al,[27] then the annual figure for hospital costs alone would be $4.2 billion and the national excess hospital length of stay attributable to ADEs would exceed 1.5 million hospital days. These costs reflect the direct hospital costs to treat ADEs only, and they do not include the costs associated with outpatient treatment or disability, which could raise this estimate by an order of magnitude. Indeed, 1 estimate put the costs of drug misadventures in the United States at $79 billion.[1]

As others have noted, little attention has been focused on the detection and

prevention of ADEs by hospitals, professional organizations, or by the government.[1,27-31] The result is that hospitals detect only about 5% of ongoing ADEs, and the traditional paper-based detection method is far too expensive to be routinely and widely implemented.[27] However, given the frequency of ADEs noted in this and other studies, and the costs of these effects, rigorous tracking of ADEs as an outcome of drug therapy may be wise.[30-35] Failure to track ADEs can be deleterious. As an example, our hospital pharmacy department decided to switch the brand of vancomycin, an antibiotic used in our hospital. This decision resulted in an annual $5000 cost savings to the pharmacy. However, our ADE detection system revealed 25 extra ADEs (rash, fever) related to this new brand of vancomycin with approximately $50 000 in extra costs of care each year (unpublished data). Without rigorously tracking ADEs, the hospital pharmacy decision would have been viewed as a wise and prudent; however, with the perspective of ADE monitoring, the decision actually cost the hospital an extra $45 000. Indeed, Sloan and colleagues have shown that this approach, called component cost management, may save money in the pharmacy budget, but these savings may be more than offset due to greater costs during the course of hospitalization for the treatment of drug-related morbidity.[36] Clearly new methods of detection are needed; as we and others have noted,[11,14,27] computerized identification of ADEs offers great promise in more efficient and effective detection. Our system, based on automated alerts for targeted drug orders and laboratory tests, can be easily implemented at other hospitals through a linkage between laboratory and pharmacy computer systems. Currently several commercial vendors are offering these linkage programs.

Our goal in developing an ADE detection system has always been to develop programs to prevent ADEs. As such, we studied the causes of ADEs in our hospital by tracking all ADEs to their root causes.[37] We have found that almost 50% of all ADEs are potentially preventable. Excessive dosage of a drug for the patient's weight and calculated renal function accounted for 42% of all ADEs in our study and were felt to be potentially preventable. Drug interactions accounted for 4.6% of all ADEs and known drug allergies accounted for 1.5% of all ADEs; both of these categories were felt to be preventable. Finally, medication errors accounted for 1% of all ADEs, including giving the correct drug to the wrong patient, giving the wrong drug to the correct patient, giving the wrong dose (not the ordered dose) to the correct patient, and giving the wrong dosage frequency (not the ordered frequency) to the correct patient.[37] This work has led to a variety of prevention programs, most implemented after the period of this study, that could be easily implemented at other hospitals without sophisticated computer systems. First, we began timely feedback of ongoing ADEs to physicians to prevent progression of ADEs to a more severe form. This intervention resulted in a decline in severe ADEs at our institution.[30] We also began a more effective program for tracking patient drug allergies, and this intervention reduced the occurrence of ADEs due to drug allergies.[30] Next, we began a program that automatically estimates daily renal function of patients (using the patient's age, height, weight, and creatinine to calculate a creatinine clearance) receiving antibiotics eliminated by the kidney, and provided the information, through consultation by a clinical pharmacist with attending physicians. This program resulted in a decline in antibiotic-associated ADEs.[38] Finally, we have developed a computerized disease management program for antibiotic use that has included all of these prior approaches unified in an overall program incorporating physician order entry of all antibiotic orders. This program has been our most effective tool at decreasing the incidence of ADEs, with a 75% decline in ADEs related to antibiotics.[39] We have implemented several different strategies at our hospital to reduce the occurrence of ADEs, most of which can be easily adapted and implemented at other hospitals without highly sophisticated computer systems. However, the most successful approach appears to be computer-based programs that continually monitor drug use for appropriate selection and dosage and intervene through ongoing disease management programs; this is also the most technically challenging approach.

As Powe and Griffiths noted, the approaches to formating economic analyses and identifying costs vary substantially.[40] The admittedly complex methods used in the present study, incorporating all drugs and using a sophisticated hospital cost-accounting system, should help to avoid many sources of bias in such studies; nonetheless, our study may still have some bias because the patients were selected nonexperimentally. Although this study was analyzed retrospectively, it does have many features of a cohort control study.[38] The ADEs were, in fact, evaluated prospectively by a member of the study team and validated by the attending physician using an ongoing, longitudinal, comprehensive and consistent protocol that screened all patients admitted to LDS Hospital for ADEs since May 1989. We matched cases and controls on measures of disease severity as well as demographic features and year of hospitalization to attempt to control for confounding in addition to applying regression models to better control for the potential confounding effects of diagnosis, age, sex, year of admission and severity of illness on the outcome variables of cost, length of stay, and mortality. Unfortunately, no measure of disease severity has achieved acceptance as the "gold standard," although there is growing acceptance for the use of nursing assessments as part of severity models.[18-22] In spite of these efforts, the use of severity measures to compare and explain differences in outcomes is fraught with difficulty and remains a potential confounder in this study. In addition, we were unable to find matched controls for 647 cases, primarily because these patients were much more severely ill and the rigor of our matching process prevented us from attaining controls for these patients. Although these patients were more severely ill, they did not differ in types of ADEs or causative drugs from the matched cases, but the inability to include these patients in the analysis clearly limits the generalizability of our results. Another limitation of this study is that the occurrence of ADEs in this study may be much less frequent than at other facilities because of our computerized drug-ordering systems that intercept and prevent many potential ADEs and because certain types of ADEs may not be easily detected by our detection system. Therefore, our ADE database, although large, longitudinal, and consistent, may not represent the universe of ADEs, and thus the total economic consequences of ADEs at other institutions may be substantially greater than at our institution.

We conclude that the occurrence of ADEs significantly prolongs hospital length of stay and increases costs as well as mortality. The potential costs of ADEs both institutionally and nationwide are enormous. Improvements in this area will come from a system-wide approach to improve the process of drug use that includes a monitoring program for the occurrence of ADEs as an important outcome of drug therapy.

References

1. Johnson JA, Bootman JL. Drug-related morbidity and mortality: a cost of illness model. *Arch Intern Med.* 1995;155:1949-1956.
2. Talley RB, Laventurier MF. Drug-induced illness. *JAMA.* 1974;229:1043-1048.
3. Porter J, Jick H. Drug-related deaths among medical inpatients. *JAMA.* 1977;237:879-881.
4. Jick H. Drugs—remarkably non-toxic. *N Engl J Med.* 1974;291:824-828.

5. Caranasos GJ, Stewart RB, Cluff LE. Drug-induced illness leading to hospitalization. *JAMA.* 1974;228:713-717.
6. Miller RR. Hospital admissions due to adverse drug reactions: a report from the Boston Collaborative Drug Surveillance Program. *Arch Intern Med.* 1974;134:219-223.
7. Melmon KL. Preventable drug reactions: causes and cures. *N Engl J Med.* 1971;284:1361-1368.
8. Karch FE, Lasagna L. Adverse drug reactions: a critical review. *JAMA.* 1975;234:1236-1241.
9. Cluff LE, Caranasos GJ, Stewart RB. Clinical problems with drugs. In: Smith LH, ed. *Major Problems in Internal Medicine.* Philadelphia, Pa: WB Saunders Co; 1975:vol 5.
10. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study. *N Engl J Med.* 1991;324:377-384.
11. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA.* 1991;266:2847-2851.
12. Kuperman G, Gardner RM, Pryor TA. *The HELP System: A Dynamic Hospital Information System.* New York, NY: Springer Verlag; 1990.
13. Evans RS, Larsen RA, Burke JP, et al. Computer surveillance of hospital-acquired infections and antibiotic use. *JAMA.* 1986;256:1007-1011.
14. Classen DC, Pestotnik SL, Evans RS, Burke JP. Description of a computerized adverse drug event monitor using a hospital information system. *Hosp Pharm.* 1992;27:774, 776-779, 783.
15. Evans RS, Classen DC, Stevens LE, et al. Using a hospital information system to assess the effects of adverse drug events.In: Safran C, ed. *Proceedings From the Seventeenth Annual Symposium on Computer Applications in Medical Care.* New York, NY: McGraw-Hill Inc; 1993:161-165.
16. Classen DC. *Assessing the Impact of Adverse Hospital Events on the Cost of Hospitalization and Other Patient Outcomes.* Salt Lake City: University of Utah; 1993. Thesis.
17. The LDS Hospital nurse acuity system. In: *Nursing Care Manual.* Salt Lake City, Utah: LDS Hospital; 1990.
18. Davis RB, Iezzoni LI, Phillips RS, et al. Predicting in-hospital mortality: the importance of functional status information. *Med Care.* 1995;33:906-921.
19. Van Ruiswyk J, Hartz A, Guse C, Sigmann P, Porth C, Buck K. Nursing assessments: patient severity of illness. *Nurs Manag.* 1990;23:44-48.
20. Whalen KL. Level of nursing care required by the unstable angina patient. *Crit Care Med.* 1990; 18:505-508.
21. Lovett RB, Wagner L, McMillan S. Validity and reliability of a pediatric hematology oncology patient acuity tool. *J Pediatr Oncol Nurs.* 1991;8: 122-130.
22. Meyer D. *GRASP: A Patient Information and Workload Management System.* Morgantown, NC: MCS; 1978.
23. *Standard Cost Manager: User's Guide.* Cleveland, Ohio: Ernst and Whinney, Intermountain Health Care Inc; 1987.
24. Haley RW. Measuring the cost of nosocomial infections: methods for estimating the economic burden on the hospital. *Am J Med.* 1991;91:32S-38S.
25. Haley RW. Cost benefit analysis of infection control programs. In: Bennett JV, Brachman PS, eds. *Hospital Infections.* 3rd ed. Boston, Mass: Little Brown & Co; 1992:507-532.
26. Polissar L, Diehr P. Regression analysis in health services research: the use of dummy variables. *Med Care.* 1982;20:959-966.
27. Bates DW, Cullen DJ, Laird N, et al, for the ADE Prevention Study Group. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA.* 1995;274:29-34.
28. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. *Ann Intern Med.* 1992;117:634-640.
29. Schneider PJ, Gift MG, Lee YP, Rothermich EA, Sill BE. Cost of medication related problems at a university hospital. *Am J Health Syst Pharm.* 1995;52:2415-2418.
30. Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. *Ann Pharmacother.* 1994;28:523-527.
31. Colley CA, Lucas LM. Polypharmacy: the cure becomes the disease. *J Gen Intern Med.* 1993;8: 278-283.
32. Berwick DM. Eleven worthy aims for clinical leadership of health system reform. *JAMA.* 1994; 272:797-802.
33. Knox RA, Mooney BC. Hospital dosage mistakes not rare: past cases reveal medication errors. *Boston Globe.* April 16, 1995:1.
34. Prince BS, Goetz CM, Rihn TL, Olsky M. Drug-related emergency department visits and hospital admissions. *Am J Hosp Pharm.* 1992;49:1696-1700.
35. Bloom BS. Direct medical costs of disease and gastrointestinal side effects during treatment for arthritis. *Am J Med.* 1988;84:20-24.
36. Sloan FA, Gordon GS, Cocks DL. Hospital drug formularies and the use of hospital services. *Med Care.* 1993;31:851-867.
37. Evans RS, Pestotnik SL, Classen DC, Bass SB, Burke JP. Prevention of adverse drug events through computerized surveillance. In: Frisse ME, ed. *Proceedings From the Sixteenth Annual Symposium on Computer Applications in Medical Care.* New York, NY: McGraw-Hill Inc; 1992:437-441.
38. Pestotnik SL, Classen DC, Evans RS, Stevens LE, Burke JP. Prospective surveillance of imipenem/cilastatin use and associated seizures using a hospital information system. *Ann Pharmacother.* 1993; 27:497-501.
39. Evans RS, Classen DC, Pestotnik SL, Clemmer TP, Weaver LK, Burke JP. A decision support tool for antibiotic therapy. In: Gardner RM, ed. *Proceedings From the Nineteenth Annual Symposium on Computer Applications in Medical Care.* Philadelphia, Pa: Hanley & Belfus; 1995:651-655.
40. Powe NR, Griffiths RI. The clinical-economic trial: promise, problems, and challenges. *Control Clin Trials.* 1995;16:377-394.

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