Medication Safety

The Costs of Adverse Drug Events in Community Hospitals

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Adverse events occur often in hospitals, resulting in high morbidity and financial costs. The single leading cause of adverse events in hospitals in the Medical Practice Study was medications, with 19.4% caused by drugs. The Adverse Drug Event Prevention Study found a rate of 6.5 adverse drug events (ADEs) per 100 nonobstetrical hospitalizations in two tertiary care hospitals. The report *To Err Is Human: Building a Safer Health System* estimated that between 44,000 and 98,000 patients die in the United States annually because of medical errors, with an estimated cost of $17–$29 billion in addition to the human tragedy.

In addition to the harm involved, ADEs create substantial costs for the health care organization or system. They even appear to be sufficiently costly that computerized provider order entry (CPOE) implementation can be justified from the cost perspective alone, although few recent data are available. One study, published in 1997, estimated that the excess costs caused by an ADE in an academic hospital totaled $2,013, with an excess length of stay (LOS) of 1.74 days. Another study published in the same year found that $3,244 of costs were attributable to ADEs, with an excess LOS of 2.2 days. However, both of these studies were performed in tertiary referral hospitals. Information involving community hospitals and ADE costs are scarce; Piontek et al. showed that implementation of an ADE alert system led to a reduction of pharmacy department and drug costs. Measuring the costs of harm is particularly important now, given the US Centers for Medicare & Medicaid Services (CMS) policy of not reimbursing for care of conditions that are undocumented or hospital-acquired, and the movement toward accountable care organizations and bundling, which provide hospitals direct incentives to reduce such costs.

Many strategies have been used to improve medication safety in hospitals, but one of the most effective has been the implementation of CPOE systems. Because CPOE—which primarily affects errors at the prescribing and transcription stages of the medication process—appears effective in decreasing the rates...
of medication errors and ADEs, the state of Massachusetts passed CPOE initiative legislation in 2006 to provide strong incentives to hospitals to implement CPOE applications by 2010.11

To date, few empiric data are available regarding the costs of ADEs in community hospitals, where the bulk of care is delivered, and most available data about ADE costs in any setting are dated.4,5 Costs in community settings are generally lower than in academic hospitals, and the costs of ADEs might be as well. To assess the costs of ADEs in community hospitals, we conducted a retrospective analysis of ADEs in six community hospitals in Massachusetts and assessed the cost and LOS associated with ADEs and estimated the potential savings in preventing them.

Methods

Screening for Adverse Drug Events

We conducted a multicenter, retrospective analysis of ADE cost and LOS after screening for ADEs with a modified version of the Institute for Healthcare Improvement (IHI) 19-item Global Trigger Tool for Measuring Adverse Drug Events. For example, for Trigger 11, International Normalized Ratio (INR) Level > 6, an elevated INR would initiate the search for bleeding for patients receiving warfarin.12,13 One example of a modification was the expansion of ADE Trigger 12, Clostridium difficile Positive Stool to include yeast:

If a patient is on multiple antibiotics, a stool positive for Clostridium difficile or yeast infection related to antibiotics is a likely complication and an indication of an ADE.

The Institutional Review Board of the Brigham and Women’s Hospital, as well as the boards of all the single sites, approved the study.

Study Sites and Patient Selection

Six community hospitals with 100 to 300 beds participated in this study, all of which were planning to implement CPOE in part because of the Massachusetts Hospital CPOE Initiative.11 Between January 2005 and August 2006, 109,641 adult patients > 18 years of age were treated in these hospitals, of which 350 patient charts were selected at each hospital by a random generator and screened for ADEs, as previously described.14,15 In brief, the randomly selected patient charts were screened for ADEs by study nurses in accordance with our adaptation of the IHI trigger tool and consecutively reviewed by two clinicians. Patient charts fulfilling the criteria of an ADE were included in the analysis in the current study. Preventability and severity of ADEs were assessed independently by three physicians [including BLH], two of whom reviewed each case. Severity was categorized as either “significant” (for example, a rash), “serious” (an episode of gastrointestinal bleeding with a need of two erythrocyte units), or life threatening (the need for transfer to an intensive care unit). In cases of disagreement, a third physician was involved for reconciliation.

Definitions

A medication error is defined as an error anywhere in the process of ordering, delivering, or administering a drug.16 An ADE is defined as a medication error with a drug actually harming the patient. Furthermore, ADEs may be preventable or non-preventable; preventable ADEs were those associated with errors, and an example of a nonpreventable ADE would be an idiosyncratic reaction to a drug.16

Cost Estimation

To estimate the hospitalization costs of a patient with an ADE we included the diagnosis-related group (DRG)–weighted hospitalization cost, as well as the cost of the LOS. Because patients with an ADE had on average of 1.1 events per patient, the cost for a patient with an ADE quite well reflects the cost for an ADE as a single event. We used hospitalization cost and LOS of all patients hospitalized during the study period (N=109,641) as the reference group.

Cost of Illness and Institution-Adjusted Hospitalization. The cost of illness and of institution–adjusted hospitalization was derived according to the following formula:

\[
\text{Hospitalization cost} = \frac{\text{Billed cost}}{\text{Institution-specific Charge-to-cost ratio (CCR)}} \times \text{DRG weight}
\]

Total Cost. The total cost was computed by adding operational and capital cost, as follows:

\[
\text{Total cost} = (\text{Billed cost} \times \text{operating CCR}) + (\text{Billed cost} \times \text{capital CCR})
\]

of each study site

The operating cost reflects the fixed and variable cost for operating a hospital (for example, labor and maintenance), the capital cost the infrastructural cost (buildings, machines). All cost values in cents were rounded off to the next integer and are displayed in 2005/2006 currency (US dollars). A linear regression model was used to perform cost adjustment for age, sex, severity of illness (DRG weights), and the individual hospital settings (CCRs). In contrast to the ADE information, which was available from all six study sites, cost information was available from five of the study sites.
STATISTICAL ANALYSIS

All categorical variables are reported as percentages in summary statistics. For comparison of categorical variables, the chi-square and Fisher’s exact tests were used; the t-test and the ANOVA procedure were used for comparison of means. The threshold of statistical significance was defined at \( p = 0.05 \). Statistical analysis was done with the SAS 9.1 program package (SAS Institute, Inc., Cary, North Carolina).

Results

PATIENT CHARACTERISTICS

Overall, 109,641 patients were hospitalized in all six hospitals during the study period of 20 months (Table 1, above). Of this group, 843 patients (0.008%) were excluded because of missing, no longer valid, or ungroupable DRG weights. None of the randomized and triggered patients were in this group. The mean age was 63.2 years for all centers, with slightly more women (58.1%) than men. The age distribution differed among sites, with more elderly patients in Site 1 (mean age, 72.7 years) and a younger population in Sites 3 and 6 (mean age, 59.6 years in each). Nine out of 10 patients were white.

For computation of cost and LOS we excluded the following patients: 11 patients with no cost data available; 1,370 patients with no DRG weights available (549 missing DRG weights, 821 with a DRG weight of zero because of weight and DRG changes from 2005 to 2006). One site did not provide cost data and was excluded for cost computation. In summary, for cost and LOS computation, 75,353/109,641 (68.7%) of all hospitalized patients with a complete cost data set were available. In 93% of the patients DRG weights were 3 or below; the mean DRG weight was 1.44 for all patients with available data and 2.05 for the patients with an ADE (DRG weights available in 228/230 [99.1%] of ADE patients).

PATIENTS WITH ADVERSE DRUG EVENTS

Overall, the sampling approach identified 230 patients who suffered one or more ADEs (Table 2, page 123). With a mean age of 72.9 years, these patients were significantly older by almost 10 years than the general patient population (\( p < 0.001 \)), had a similar sex distribution, and were more often white (\( p = 0.002 \)). Regarding insurance, almost two thirds were Medicare beneficiaries (64.8%), roughly a third were privately insured (31.3%), and the rest were either paid by Medicaid or self-pay.
RESOURCE USE

As shown in Table 3 (page 124), the resource use of patients suffering one or more ADEs was substantial. In the general population of all hospitalized patients (column A) the average unadjusted hospitalization cost was $6,797, and the average hospitalization cost adjusted for age, sex, DRG weight, and hospital site amounted to $6,910, with a wide range of more than $300,000. The unadjusted average LOS in this population was 4.81 days; the adjusted LOS was 5.01 days. In patients with ADEs (column B), both the adjusted and unadjusted cost and LOS were significantly higher; the average unadjusted hospitalization cost was more expensive by $5,373 ($5,373; p < .001), and the adjusted additional average hospitalization cost was more expensive by $3,420 ($3,420; p < .001). Furthermore, the average unadjusted LOS, as well as the adjusted average LOS, were significantly higher in patients with preventable ADEs (+4.64 days on average for the former and +3.37 days for the latter, both p < .001).

Patients with nonpreventable ADEs showed even higher cost differences compared with the general patient population (+$5,812 unadjusted and +$4,410 adjusted, both p < .001). Although the additional cost was somewhat higher compared with the patients with preventable ADEs, the average LOS was slightly lower (+4.06 days unadjusted, +2.99 days adjusted, both p < .001) but still clearly longer than the average in the general patient population.

The comparison of cost and LOS between patients with preventable with those with nonpreventable ADEs was essentially similar. The average hospitalization cost was higher and LOS was longer in patients with ADEs than without.

RESOURCE USE OF ADVERSE DRUG EVENTS BY PREVENTABILITY

Table 4 (page 124) shows the resource use of patients with ADEs according to preventability. Patients with preventable ADEs (column B) showed almost double the unadjusted hospitalization cost compared with the general patient population (column A) (+$5,694 per hospitalization; p < .001); the adjusted difference turned out to be slightly smaller (+$3,511; p < .001). Furthermore, the average unadjusted LOS, as well as the adjusted average LOS, were significantly higher in patients with preventable ADEs (+4.64 days on average for the former and +3.37 days for the latter, both p < .001).

Patients with nonpreventable ADEs showed even higher cost differences compared with the general patient population (+$5,812 unadjusted and +$4,410 adjusted, both p < .001). Although the additional cost was somewhat higher compared with the patients with preventable ADEs, the average LOS was slightly lower (+4.06 days unadjusted, +2.99 days adjusted, both p < .001) but still clearly longer than the average in the general patient population.

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RESOURCE USE OF ADVERSE DRUG EVENTS BY SEVERITY

Evaluating the resource use according the severity of the ADEs (Table 5, page 125), we noticed a highly significant and consistent rise of the average hospitalization cost, as well as LOS, according to severity; that is, from patients with significant to life-threatening ADEs. The consistency was noticeable in unadjusted and adjusted data; while the average unadjusted hospitalization cost increased from $12,038 in patients with significant ADEs to $16,316 in patients with life-threatening ADEs (compared with only $6,804 in the general patient population), the adjusted average hospitalization cost was somewhat lower—ranging from $9,768 in patients with significant ADEs to $15,033 in patients with life-threatening ADEs—compared with $6,917 in the general cohort.

The average LOS showed the same effects, with a consistent rise in hospitalization duration according to severity of the ADEs. While the average unadjusted LOS in the general patient cohort was 4.82 days, it increased to 8.82 days in patients with significant ADEs (+4.0 days) and to 12.3 days in patients with life-threatening ADEs (+7.48 days). Again, the adjusted average LOS was somewhat lower in patients with ADEs (significant ADEs: 7.79 days; life-threatening ADEs: 10.56 days, both p < 0.001) than the unadjusted average LOS of patients with ADEs.

Taken together, of the 109,641 patients treated in the ob-
### Table 3. Unadjusted and Adjusted Resource Use Consequences of Adverse Drug Events*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A Hospitalized Patients, All Sites N = 109,641 Reference Mean/Median (Range) [SD]</th>
<th>Difference Mean/Median, P Value (A vs B) (Range) [SD]</th>
<th>B Patients with ADEs, All Sites N = 230† Mean/Median (Range) [SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted Average Hospitalization Cost‡</strong></td>
<td>6,797/4,653 (53–322,030)</td>
<td>+5,373+/3,845 Both p &lt; .001</td>
<td>12,170/8,498 (1,470–78,742)</td>
</tr>
<tr>
<td>[28.9]</td>
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<td>[587]</td>
</tr>
<tr>
<td><strong>Adjusted Average Hospitalization Cost‡</strong></td>
<td>6,910/4,694 (53–322,030)</td>
<td>+3,420+/2,486 Both p &lt; .001</td>
<td>10,330/7,180 (1,470–78,742)</td>
</tr>
<tr>
<td>[25.9]</td>
<td></td>
<td></td>
<td>[463]</td>
</tr>
<tr>
<td><strong>Unadjusted Average LOS Days (Range) [SD]</strong></td>
<td>4.81/3.0 (1–276) [0.02]</td>
<td>+4.36+/3.0 Both p &lt; .001</td>
<td>9.176.0</td>
</tr>
<tr>
<td>[28.9]</td>
<td></td>
<td></td>
<td>(1–49) [0.35]</td>
</tr>
<tr>
<td><strong>Adjusted Average LOS Days†</strong></td>
<td>5.01/3.40 (1–276) [0.02]</td>
<td>+3.15+/2.41 Both p &lt; .001</td>
<td>8.16/5.81</td>
</tr>
<tr>
<td>[25.9]</td>
<td></td>
<td></td>
<td>(1–49) [0.33]</td>
</tr>
</tbody>
</table>

* ADE, adverse drug event; CCR, hospital-specific charge-to-cost ratio; DRG, diagnosis-related group; LOS, length of stay; SD, standard deviation.
† 230 patients suffered 270 ADEs (1.17 ADEs/patient).
‡ Cost information was provided from five sites only. Hospitalization cost equals billed cost x CCR. All cost values in cents are rounded off to next integer.
§ Adjustment for age, sex, diagnosis-related group (DRG) weight, and hospital site.

### Table 4. Resource Use Consequences of Adverse Drug Events by Preventability*

<table>
<thead>
<tr>
<th>A All Hospitalized Patients N = 109,451 Reference Mean/Median (Range) [SD]</th>
<th>B Patients with Preventable ADE N = 190‡ Mean/Median (Range) [SD]</th>
<th>Difference Mean/Median, P Value (A vs. B) (Range) [SD]</th>
<th>A All Hospitalized Patients N = 109,591 Reference Mean/Median (Range) [SD]</th>
<th>C Patients with Nonpreventable ADE N = 50‖ Mean/Median (Range) [SD]</th>
<th>Difference Mean/Median, P Value (A vs. C) (Range) [SD]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted average hospitalization cost $ (Range) [SD]</strong></td>
<td>6,799/4,653 (53–322,030)</td>
<td>+5,694+/4,125 Both p &lt; .001</td>
<td>6,806/4,657 (53–322,030)</td>
<td>12,618/9,634 (2,987–44,789)</td>
<td>+5,812+/4,977 Both p &lt; .001</td>
</tr>
<tr>
<td>[28.9]</td>
<td></td>
<td></td>
<td>[28.9]</td>
<td>[1,191]</td>
<td></td>
</tr>
<tr>
<td><strong>Adjusted average cost‡ $ (Range) [SD]</strong></td>
<td>6,912/4,695 (53–322,030)</td>
<td>+3,511+/2,402 Both p &lt; .001</td>
<td>6,917/4,695 (53–322,030)</td>
<td>11,327/8,275 (2,987–44,789)</td>
<td>+4,410+/3,580 Both p &lt; .001</td>
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<tr>
<td>[25.9]</td>
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<td></td>
<td>[25.9]</td>
<td>[932.5]</td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted average LOS days (Range) [SD]</strong></td>
<td>4.81/3.0 (1–276) [0.02]</td>
<td>+4.64+/4.0 Both p &lt; .001</td>
<td>4.82/3.0 (1–276) [0.02]</td>
<td>8.88/6.0</td>
<td>+4.06+/3.0 Both p &lt; .001</td>
</tr>
<tr>
<td>[28.9]</td>
<td></td>
<td></td>
<td>[0.75]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjusted average LOS days§ (Range) [SD]</strong></td>
<td>5.01/3.40 (1–276) [0.02]</td>
<td>+3.37+/2.36 Both p &lt; .001</td>
<td>5.02/3.40 (1–276) [0.02]</td>
<td>8.00/6.54</td>
<td>+2.99+/3.14 Both p &lt; .001</td>
</tr>
<tr>
<td>[25.9]</td>
<td></td>
<td></td>
<td>[0.70]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ADE, adverse drug event; LOS, length of stay; SD, standard deviation.
‡ Total minus patients with preventable ADEs (109,641 – 190).
§ Total minus patients with nonpreventable ADEs (109,641 – 50).
‖ Total minus patients with nonpreventable ADEs (109,641 – 50).
# Adjustment for age, gender, diagnosis-related group (DRG) weight, and hospital site.
served time window of 20 months, 15% (n = 16,446) were estimated to have suffered an ADE in our earlier evaluation, 15 of which 76% were preventable ADEs (Table 4), suggesting there were 12,499 preventable events in the population. With an average adjusted additional cost of $3,511 per preventable ADE, this amounts to $43.9 million preventable cost for all six sites or $7.3 million on average for each site ($4.6 million/year and site).

Discussion

We found that ADEs in community hospitals cost more than $3,000 dollars on average and an average increase of LOS of 3.1 days. Both these figures are similar to those in academic institutions, and the LOS increase was actually greater, suggesting that community hospitals may also benefit from investing in interventions to prevent ADEs if they are effective.

In our previous work, we showed that in these six community hospitals, ADEs occurred in 15% of admissions and in patients with renal insufficiency 10% of admissions.14,15 Patients with ADEs have a much higher hospitalization cost than those without. In comparison, Bates et al., reporting a nested prospective case-control study in a tertiary referral hospital, found an additional cost of $3,244 and an additional LOS of 2.2 days associated with ADEs—that is, a similar cost increase in patients with ADEs with a somewhat lower LOS than in the current study ($1 US in 1997 = $1.10 in 2006).5 Classen et al. found a somewhat lower additional cost of $2,262 and a fairly similar additional LOS of +1.91 days per ADE,4 also in a tertiary referral hospital. After adjusting for inflation, the costs appear slightly higher in tertiary hospitals, while the additional LOS appears moderately longer in community hospitals, although these differences might also derive from methodological differences in the way the different studies were conducted, specifically regarding adjustment for comorbidities and severity of illness. In a review, the additional LOS in patients with adverse drug reactions according to World Health Organization definition was 3.4 days with a range of 1.2 to 8.5 days.17

Furthermore, our analysis showed in regard to preventability that, although differences compared to the general patient population are substantial, patients with preventable and non-preventable ADEs had similar hospitalization costs and LOS, in contrast to the prior study by Bates et al., which found that preventable ADEs were moderately more costly.

As might be expected, severity of ADEs played an important

| Table 5. Resource Use Consequences of Adverse Drug Events by Severity* |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                  | A                | B                | C                | D                |                  |
|                  | All Hospitalized | Patients with   | Patients with   | Patients with   |                  |
|                  | Patients       | Significant      | Serious         | Life-Threatening|
|                  | N = 109,641    | ADEs             | ADEs             | ADEs             |                  |
|                  | Reference      | N = 105†        | N = 126‡        | N = 23§          |                  |
|                  | Mean/Median    | Mean/Median     | Mean/Median     | Mean/Median     |                  |
|                  | (Range) [SD]   | (Range) [SD]    | (Range) [SD]    | (Range) [SD]    |                  |
| Unadjusted       | 6,804/4,656    | 12,038/8,320     | 12,154/9,361    | 16,316/10,140   |                  |
| average hospitalization cost $ (Range) [SD] | (53–322,030) | (2,256–78,742) | (1,470–77,130) | (3,665–50,347) |                  |
| Adjusted         | 6,917/4,694    | 9,768/7,078      | 10,567/7,395    | 15,033/10,484   |                  |
| average cost $ (Range) [SD] | (53–322,030) | (2,256–78,742) | (1,470–77,130) | (3,665–50,347) |                  |
| Unadjusted       | 4.82/3.0       | 8.82/6.0         | 9.28/7.0        | 12.3/11.0       |                  |
| average LOS Days (Range) [SD] | (1–276) | (1–49) | (1–46.0) | (1–40) |                  |
| Adjusted         | 5.02/3.40      | 7.79/5.78        | 8.47/6.03       | 10.56/10.1      |                  |
| average LOS Days (Range) [SD] | (1–276) | (1–49) | (1–46.0) | (1–40) |                  |

*ADE, adverse drug event; DRG, diagnosis-related group; LOS, length of stay; SD, standard deviation.
† 105 patients suffered 109 ADEs (1.04 ADEs/patient).
‡ 126 patients suffered 135 ADEs (1.07 ADEs/patient).
§ 23 patients with 26 ADEs (1.13 ADEs/patient).
‖ Adjustment for DRG weight, sex, age, and hospital site.

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role regarding excess cost and LOS in patients with ADEs. Our observations showed consistent incremental cost and LOS according to increasing severity of the incidents.

**Limitations**

Because the study was conducted only in Massachusetts, the results may not be generalizable to other states or countries due to differences in patient population, infrastructure and case mix. Also, hospitals of greater or lesser size may show different outcomes compared to the middle-sized community hospitals, although these account for a large proportion of the beds in the United States. Furthermore, although we used a well-standardized ADE screening technique, our results may differ from study sites using other ADE screening and evaluation procedures. Finally, co-morbidities may be quite influential regarding cost and LOS in patient outcomes, and we may not have fully accounted for underlying confounders.

**Conclusion**

ADEs in middle-sized hospitals caused considerable cost and additional LOS, and more severe ADEs had higher associated resource utilization. A number of approaches, including CPOE and bar coding, have the potential to improve medication safety. These data provide helpful information for hospitals considering investments in this area to improve the safety of their care.

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References


