



# A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients

## Citation

Inouye, Sharon K., Sidney T. Bogardus, Peter A. Charpentier, Linda Leo-Summers, Denise Acampora, Theodore R. Holford, and Leo M. Cooney. 1999. "A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients." *New England Journal of Medicine* 340, no. 9: 669–676.

## Published Version

doi:10.1056/NEJM199903043400901

## Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:13956243>

## Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA>

## Share Your Story

The Harvard community has made this article openly available.  
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

# The New England Journal of Medicine

© Copyright, 1999, by the Massachusetts Medical Society

VOLUME 340

MARCH 4, 1999

NUMBER 9



## A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS

SHARON K. INOUE, M.D., M.P.H., SIDNEY T. BOGARDUS, JR., M.D., PETER A. CHARPENTIER, M.P.H.,  
LINDA LEO-SUMMERS, M.P.H., DENISE ACAMPORA, M.P.H., THEODORE R. HOLFORD, PH.D., AND LEO M. COONEY, JR., M.D.

### ABSTRACT

**Background** Since in hospitalized older patients delirium is associated with poor outcomes, we evaluated the effectiveness of a multicomponent strategy for the prevention of delirium.

**Methods** We studied 852 patients 70 years of age or older who had been admitted to the general-medicine service at a teaching hospital. Patients from one intervention unit and two usual-care units were enrolled by means of a prospective matching strategy. The intervention consisted of standardized protocols for the management of six risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. Delirium, the primary outcome, was assessed daily until discharge.

**Results** Delirium developed in 9.9 percent of the intervention group, as compared with 15.0 percent of the usual-care group (matched odds ratio, 0.60; 95 percent confidence interval, 0.39 to 0.92). The total number of days with delirium (105 vs. 161,  $P=0.02$ ) and the total number of episodes (62 vs. 90,  $P=0.03$ ) were significantly lower in the intervention group. However, the severity of delirium and recurrence rates were not significantly different. The overall rate of adherence to the intervention was 87 percent, and the total number of targeted risk factors per patient was significantly reduced. Intervention was associated with significant improvement in the degree of cognitive impairment among patients with cognitive impairment at admission and with a significant reduction in the rate of use of sleep medications among all patients. Among the other risk factors, there were trends toward improvement in immobility, visual impairment, and hearing impairment.

**Conclusions** The risk-factor intervention strategy that we studied resulted in significant reductions in the number and duration of episodes of delirium in hospitalized older patients. The intervention had no significant effect on the severity of delirium or on recurrence rates; this finding suggests that primary prevention of delirium is probably the most effective treatment strategy. (N Engl J Med 1999;340:669-76.)

©1999, Massachusetts Medical Society.

**D**ELIRIUM, also known as acute confusional state, is a common, serious, and potentially preventable source of morbidity and mortality among hospitalized older patients.<sup>1-3</sup> Delirium has particular importance because patients over 65 years of age account for more than 48 percent of all days of hospital care.<sup>4</sup> Each year, delirium complicates hospital stays for more than 2.3 million older people, involves more than 17.5 million inpatient days, and accounts for more than \$4 billion (in 1994 dollars) of Medicare expenditures.<sup>5</sup> Substantial additional costs accrue after discharge from the hospital, because of the increased need for institutionalization, rehabilitation, and home care.<sup>6,7</sup> Moreover, the incidence of delirium will probably increase with the aging of the population.<sup>8</sup>

Previous interventional studies of delirium have focused on four types of intervention: general geriatric approaches,<sup>9-14</sup> nursing care,<sup>15-19</sup> family interventions,<sup>20</sup> and anesthesia.<sup>21-23</sup> Although in most of the studies there were trends toward a reduction in delirium in the intervention group, in most cases the reduction was not statistically significant. Many studies had methodologic limitations, such as small samples, use of nontargeted interventions, and use of relatively insensitive outcome measures (e.g., screening mental-status tests or confusion checklists). Finally, most previous studies focused on the treatment of delirium rather than on primary prevention, which was the goal of the present study.

Rarely is delirium caused by a single factor; rather, it is a multifactorial syndrome, resulting from the interaction of vulnerability on the part of the patient

From the Departments of Internal Medicine (S.K.I., S.T.B., D.A., L.M.C.) and Epidemiology and Public Health (P.A.C., L.L.-S., T.R.H.), Yale University School of Medicine, New Haven, Conn. Address reprint requests to Dr. Inoue at the Yale University School of Medicine, 20 York St., Tompkins 15, New Haven, CT 06504.

(i.e., the presence of predisposing conditions, such as cognitive impairment, severe illness, or visual impairment) and hospital-related insults (i.e., medications and procedures).<sup>1,24</sup> The risk of delirium increases with the number of risk factors present.<sup>24,25</sup> Therefore, a multicomponent approach targeted to the patient's risk factors is the most clinically relevant and potentially effective intervention for delirium.

We conducted a controlled clinical trial of a multicomponent strategy to reduce the number of risk factors for delirium with the goal of preventing delirium in hospitalized older patients. Our aims were to compare the effectiveness of a multicomponent strategy for reducing the risk of delirium with that of a usual plan of care for hospitalized older patients, to determine the level of adherence to the intervention protocol, and to measure the effect of the intervention on the targeted risk factors.

## METHODS

### Study Design

This controlled clinical trial used prospective, individual matching to compare patients admitted to one intervention and two usual-care (control) units at a teaching hospital. Random assignment of subjects to the intervention or usual-care units was not possible because of the large number of patients in all medical units during the time of the study. A pilot study confirmed that randomization was not feasible, because beds in the units intended for study were often unavailable.

The prospective, individual matching strategy was chosen as an alternative to randomization that would ensure that patients in our study groups were comparable at base line. This strategy has been described in detail previously.<sup>26</sup> In brief, all the subjects in the intervention unit who met the eligibility criteria were enrolled. Concurrently, eligible patients from two usual-care units were identified, so that the subject pool was sufficiently large to permit the use of a computerized algorithm<sup>27</sup> designed to match patients according to age within five years, sex, and base-line risk of delirium (intermediate or high) as defined by our previously developed predictive model.<sup>25</sup> The predictive model included four of the risk factors for delirium: visual impairment, severe illness, cognitive impairment, and a high ratio of blood urea nitrogen to creatinine. Intermediate risk was defined as the presence of one or two risk factors at base line, and high risk as the presence of three or four risk factors at base line. The matching factors were selected because previous work had established them as important predictors of the development of delirium.<sup>25,28</sup> To control for changing patterns of care over time, patients in the intervention group and matched usual-care patients were required to have been admitted within 180 days of each other. The computerized algorithm matched patients prospectively, strictly on the basis of their characteristics at admission.

### Setting and Patients

Potential participants in the study were consecutive patients admitted to the general-medicine service (non-intensive care) at Yale–New Haven Hospital from March 25, 1995, through March 18, 1998. Yale–New Haven Hospital, an 800-bed urban teaching hospital with 200 medical beds, serves a large number of patients from the community as well as a population of referred patients. A total of 2434 patients were potentially eligible to participate: they were admitted to one of three general-medicine units, were at least 70 years old, had no delirium at the time of admission, and were at intermediate or high risk for delirium at base line. Of these, 1265 patients were excluded because of inability to partic-

ipate in interviews (because of profound dementia that precluded verbal communication [154 patients], a language barrier [92], profound aphasia [38], or intubation or respiratory isolation [14]), coma or terminal illness (69 patients), a hospital stay of 48 hours or less (219), prior enrollment in this study (324), or other reasons (e.g., unavailability of an interviewer or unavailability of the patient because of examinations or procedures elsewhere in the hospital) (355). Of the remaining 1169 eligible patients, the patient, family, or physician refused enrollment in 250 cases and a matching patient could not be found in 67 cases. Thus, the final study sample included 852 patients, who were matched as 426 pairs of patients receiving the study intervention and usual care.

The 1265 patients who were excluded did not differ significantly from the 852 patients who were enrolled in terms of age, sex, or base-line risk of delirium; however, a larger proportion of patients receiving usual care were excluded (63 percent, vs. 50 percent in the intervention group;  $P=0.001$ ), mainly because more patients were available for screening in the two usual-care units. The 250 patients who declined to participate did not differ significantly from the 852 who enrolled in terms of age, sex, base-line risk of delirium, or group assignment. Of the 919 qualified patients who agreed to enroll, 67 (7 percent) could not be matched (24 in the intervention group and 43 in the usual-care group). These 67 unmatched patients, as compared with the 852 enrolled patients, were significantly older (mean age, 84 and 80 years, respectively), had a higher risk of delirium at base line (high risk, 42 percent vs. 28 percent), and were more likely to be admitted to a usual-care unit (64 percent vs. 50 percent). These differences were due to the inherent difficulty of finding matches for patients who were at extreme ends of the matching criteria (e.g., extremely old); patients receiving usual care predominated because of the matching algorithm, which kept a pool of unmatched patients receiving usual care available to facilitate subsequent matching.

Informed consent for participation was obtained orally from the patients or, for those with substantial cognitive impairment, from a proxy (usually the closest relative), according to procedures approved by the institutional review board of the Yale University School of Medicine.

### Assessments

All the assessments were carried out by members of a research staff who had no role in the intervention and who were unaware of the nature of the study and of the patients' group assignments. The staff was composed of research nurses and experienced clinical researchers, all of whom underwent intensive training and followed standard procedures outlined in a detailed training and coding manual. At base line, standardization of assessments and measurements of interrater reliability verified the consistency of ratings among all the staff members. Subsequently, researchers met monthly to review procedural and coding issues. Quality checks of interviews and assessments of the interrater reliability with respect to the primary outcomes and targeted risk factors were performed every six months. All the data were collected on standardized, precoded forms, and the data were entered twice into a computerized data base and underwent extensive checks of error and validity.

The screening interview included the Mini–Mental State Examination,<sup>29</sup> the Digit Span Test,<sup>30</sup> evaluation by the Confusion Assessment Method,<sup>31</sup> assessment of Katz's Activities of Daily Living,<sup>32</sup> the standard Jaeger test for vision, and chart review to determine the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) score.<sup>33</sup> The Mini–Mental State Examination measures cognitive functioning on a scale of 0 (poor) to 30 (excellent), with a score of less than 24 indicating cognitive impairment. The orientation score consists of the 10 orientation items on the Mini–Mental State Examination, each scored on a scale of 0 to 10, with a score of less than 8 indicating disorientation. The Digit Span Test measures attention span on a scale of 0 to 7, with lower scores indicating inattention. Evaluation of Katz's

Activities of Daily Living assesses the ability to perform seven basic-care skills (feeding, bathing, grooming, dressing, using the toilet, transferring between bed and chair, and walking) on a scale of 0 to 14, with lower scores indicating functional impairment.

Eligible patients then underwent the base-line assessment, which included the collection of demographic data, assessment of instrumental activities of daily living,<sup>34</sup> the Whisper Test<sup>35</sup> for hearing, and assessment of sleep. Visual impairment was defined as binocular near vision, after correction, worse than 20/70 as measured by the standard Jaeger test. The APACHE II score measures severity of illness on a scale of 0 to 71, with higher scores indicating increased severity. The instrumental Activities of Daily Living scale assesses the ability to perform seven complex activities (using the telephone, grocery shopping, using transportation, cooking, housekeeping, taking medications, and handling finances) on a scale of 0 to 14, with lower scores indicating functional impairment. The Whisper Test measures hearing according to the number of 12 whispers heard, with 6 or fewer indicating hearing impairment. A family member was interviewed at the time of admission and asked to describe the patient's cognitive functioning before admission and any recent cognitive changes and to complete the modified Blessed Dementia Rating Scale,<sup>36,37</sup> an observer-rated score that correlates directly with the number of neuritic plaques found on postmortem examination of the brain. The modified (shortened) version has been tested<sup>37</sup>; scores greater than 2 on the modified Blessed Dementia Rating Scale indicate possible dementia. A ratio of blood urea nitrogen to creatinine (both measured in milligrams per deciliter) of 18 or greater was used as an index of dehydration. Screening and base-line assessments were completed within 48 hours after admission.

Subsequently, patients were evaluated daily until discharge with a structured interview consisting of the Digit Span Test, Mini-Mental State Examination, and Confusion Assessment Method

rating. On hospital day 5 or at discharge (if discharge was before day 5), patients were reassessed for risk factors for delirium (Table 1). After discharge, medical records were reviewed for evidence of delirium, final diagnoses, medications, laboratory results, and destination after discharge.

## Intervention

The intervention strategy, called the Elder Life Program, was implemented by a trained interdisciplinary team, which consisted of a geriatric nurse-specialist, two specially trained Elder Life specialists, a certified therapeutic-recreation specialist, a physical-therapy consultant, a geriatrician, and trained volunteers. The performance of each staff member, including volunteers, was evaluated quarterly, with completion of checklists to ensure competency and consistent and complete adherence to all intervention protocols.

Six risk factors for delirium were targeted for intervention: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration.<sup>24,25,28,38</sup> These factors were selected on the basis of evidence of their association with the risk of delirium and because they were amenable to intervention strategies considered feasible in the context of current hospital practice. Table 1 describes the risk group that received each intervention, the standardized intervention protocols for each risk factor, and the targeted outcome for each intervention protocol.

## Usual Care

Usual care consisted of standard hospital services provided by physicians, nurses, and support staff (e.g., physical therapists, pharmacists, and nutritionists) in the other general-medicine units. Members of the intervention team did not provide services

TABLE 1. RISK FACTORS FOR DELIRIUM AND INTERVENTION PROTOCOLS.

| TARGETED RISK FACTOR AND ELIGIBLE PATIENTS  | STANDARDIZED INTERVENTION PROTOCOLS  | TARGETED OUTCOME FOR REASSESSMENT                    |
|---|--|--|
| Cognitive impairment*<br>All patients, protocol once daily; patients with base-line MMSE score of <20 or orientation score of <8, protocol three times daily  | Orientation protocol: board with names of care-team members and day's schedule; communication to reorient to surroundings<br>Therapeutic-activities protocol: cognitively stimulating activities three times daily (e.g., discussion of current events, structured reminiscence, or word games)  | Change in orientation score                          |
| Sleep deprivation<br>All patients; need for protocol assessed once daily  | Nonpharmacologic sleep protocol: at bedtime, warm drink (milk or herbal tea), relaxation tapes or music, and back massage<br>Sleep-enhancement protocol: unit-wide noise-reduction strategies (e.g., silent pill crushers, vibrating beepers, and quiet hallways) and schedule adjustments to allow sleep (e.g., rescheduling of medications and procedures) | Change in rate of use of sedative drug for sleep†    |
| Immobility<br>All patients; ambulation whenever possible, and range-of-motion exercises when patients chronically non-ambulatory, bed or wheel-chair bound, immobilized (e.g., because of an extremity fracture or deep venous thrombosis), or when prescribed bed rest | Early-mobilization protocol: ambulation or active range-of-motion exercises three times daily; minimal use of immobilizing equipment (e.g., bladder catheters or physical restraints)  | Change in Activities of Daily Living score           |
| Visual impairment<br>Patients with <20/70 visual acuity on binocular near-vision testing  | Vision protocol: visual aids (e.g., glasses or magnifying lenses) and adaptive equipment (e.g., large illuminated telephone keypads, large-print books, and fluorescent tape on call bell), with daily reinforcement of their use  | Early correction of vision, ≤48 hr after admission   |
| Hearing impairment<br>Patients hearing ≤6 of 12 whispers on Whisper Test  | Hearing protocol: portable amplifying devices, earwax disimpaction, and special communication techniques, with daily reinforcement of these adaptations  | Change in Whisper Test score                         |
| Dehydration<br>Patients with ratio of blood urea nitrogen to creatinine ≥18, screened for protocol by geriatric nurse-specialist  | Dehydration protocol: early recognition of dehydration and volume repletion (i.e., encouragement of oral intake of fluids)   | Change in ratio of blood urea nitrogen to creatinine |

\*The orientation score consisted of results on the first 10 items on the Mini-Mental State Examination (MMSE).

†Sedative drugs included standard hypnotic agents, benzodiazepines, and antihistamines, used as needed for sleep.

to patients assigned to usual care. However, the same attending and resident physicians provided care to patients in both study groups.

### Outcomes

The primary outcome was delirium, defined according to the Confusion Assessment Method criteria,<sup>31</sup> which consisted of acute onset and a fluctuating course of symptoms of delirium, inattention, and either disorganized thinking or an altered level of consciousness. Each of these features was rated by the researchers on the basis of observations made during the daily interviews. The Confusion Assessment Method criteria provided a standardized rating of delirium, which has been validated against geropsychiatric diagnoses, with a sensitivity of 94 to 100 percent, a specificity of 90 to 95 percent, and high interobserver reliability.<sup>31</sup>

For the primary analysis of the effectiveness of the intervention, delirium was considered a binary outcome (present or absent) according to its earliest occurrence, and only one episode of delirium per patient was counted. We also counted the total number of days of delirium (the total person-days of all episodes of delirium) and the number of episodes of delirium in each study group, and we evaluated recurrence (two or more episodes) and severity. The severity of delirium was measured by an additive score for the four designated symptoms (symptom fluctuation, inattention, disorganized thinking, and an altered level of consciousness). Each symptom of delirium except fluctuation was rated by the interviewers as absent (0 points), mild (1 point), or marked (2 points); symptom fluctuation was rated as absent (0 points) or present (1 point). The sum of these ratings yielded a delirium-severity score, ranging from 0 to 7, with higher scores indicating increased severity.

Confusion Assessment Method ratings were completed in 4848 of 4857 daily interviews (99.8 percent). Interrater reliability for these ratings was confirmed in 16 paired observations that involved all the members of the research staff (kappa, 1.0). A total of 108 uncertain ratings, ratings with missing Confusion Assessment Method items, or possible episodes of delirium occurring between interviews were assessed for the presence or absence of delirium by two independent reviewers (a geriatrician and a neuropsychologist who were unaware of the patients' study-group assignments) on review of all interview data and medical records.

### Adherence

The level of adherence to the intervention, with reasons for nonadherence, was recorded daily by the intervention staff. Daily adherence was complete if the patient received all parts of the assigned protocol for the total number of times it was to be given. Partial adherence indicated that the patient either received some but not all parts of the protocol or did not receive the protocol for the required number of times that day. Nonadherence indicated that none of the parts of the assigned protocol were received that day.

### Statistical Analysis

Characteristics at admission were compared between patients within matched pairs by matched statistical analyses, either paired t-tests for continuous variables or McNemar's test for binary measures. These results were confirmed with unmatched analyses.

All analyses of the effectiveness of the intervention with regard to the primary outcome used the intention-to-treat approach. The effectiveness of the intervention strategy in reducing the incidence of delirium was evaluated by a method of conditional logistic regression developed by Holford et al.<sup>39</sup> for prospectively sampled, individually matched data. To identify potential confounders, all the base-line characteristics were examined in bivariate analyses, and factors associated at a level of  $P=0.20$  with the type of treatment (intervention or usual care) were further examined. Each potential covariate was added individually to the model and was retained if its presence resulted in a modification of

**TABLE 2. CHARACTERISTICS OF THE PATIENTS ON ADMISSION, ACCORDING TO STUDY GROUP.\***

| CHARACTERISTIC  | INTERVENTION GROUP (N=426) | USUAL-CARE GROUP (N=426) |
|---|----------------------------|--------------------------|
| Age — yr  | 79.6±6.1                   | 79.8±6.2                 |
| Female sex — no. (%)  | 259 (61)                   | 259 (61)                 |
| White race — no. (%)  | 378 (89)                   | 362 (85)                 |
| Married — no. (%)   | 163 (38)                   | 144 (34)                 |
| Residence in nursing home — no. (%)                                 | 24 (6)                     | 27 (6)                   |
| Education — yr  | 11.3±3.3                   | 11.0±3.7                 |
| APACHE II score   | 15.5±4.0                   | 15.6±4.1                 |
| Any impairment in activities of daily living — no. (%)              | 145 (34)                   | 149 (35)                 |
| Any impairment in instrumental activities of daily living — no. (%) | 350 (82)                   | 336 (79)                 |
| MMSE  |                            |                          |
| Mean score  | 23.7±4.6                   | 23.3±4.9                 |
| Patients with score of <24 — no. (%)                                | 175 (41)                   | 192 (45)                 |
| Modified Blessed Dementia Rating Scale                              |                            |                          |
| Mean score  | 0.53±1.2                   | 0.47±1.1                 |
| Patients with score of >2 — no. (%)                                 | 50 (12)                    | 45 (11)                  |
| Base-line risk of delirium  |                            |                          |
| Intermediate — no. (%)  | 307 (72)                   | 307 (72)                 |
| High — no. (%)  | 119 (28)                   | 119 (28)                 |
| Targeted risk factors — no. (%)†                                    |                            |                          |
| Cognitive impairment  | 130 (31)                   | 128 (30)                 |
| Immobility  | 97 (23)                    | 98 (23)                  |
| Visual impairment   | 97 (23)                    | 98 (23)                  |
| Hearing impairment  | 120 (28)                   | 98 (23)                  |
| Dehydration   | 248 (58)                   | 254 (60)                 |
| Total no. of risk factors   | 2.5±1.1                    | 2.5±1.1                  |
| Principal diagnosis — no. (%)                                       |                            |                          |
| Pneumonia   | 51 (12)                    | 46 (11)                  |
| Chronic lung disease  | 41 (10)                    | 54 (13)                  |
| Congestive heart failure  | 43 (10)                    | 48 (11)                  |
| Ischemic heart disease  | 33 (8)                     | 38 (9)                   |
| Gastrointestinal disease  | 65 (15)                    | 46 (11)                  |
| Diabetes mellitus or metabolic disorder                             | 20 (5)                     | 17 (4)                   |
| Cancer  | 12 (3)                     | 12 (3)                   |
| Cerebrovascular disease   | 9 (2)                      | 13 (3)                   |
| Renal failure   | 9 (2)                      | 11 (3)                   |
| Anemia  | 7 (2)                      | 6 (1)                    |
| Other   | 136 (32)                   | 135 (32)                 |

\*Plus-minus values are means ±SD. There were no significant differences in any of these characteristics between the intervention and control groups in matched or unmatched analyses. APACHE II denotes the Acute Physiology, Age, and Chronic Health Evaluation, and MMSE Mini-Mental State Examination. Because of rounding, percentages may not total 100.

†Sleep deprivation is not included here since all the patients were considered to be at risk for this factor. Targeted risk factors were defined as follows: cognitive impairment, orientation score of <8; immobility, Activities of Daily Living score of ≤12; visual impairment, visual acuity of <20/70 on binocular near-vision testing; hearing impairment, score of ≤6 on the Whisper Test; dehydration, ratio of blood urea nitrogen to creatinine of ≥18.

the log-linear parameter for an intervention effect of 10 percent or more.<sup>40,41</sup> Subsequently, unmatched analyses by means of traditional logistic regression for new cases of delirium during the hospital stay and Cox proportional-hazards analysis for the risk of delirium per hospital day, with adjustment for the matching factors, were carried out to provide comparisons and alternatives to the matched analyses, as advocated by previous investigators.<sup>42</sup> Kaplan-Meier analysis and the log-rank test were used to compare the cumulative incidence of delirium, defined as the proba-

**TABLE 3.** DELIRIUM-RELATED OUTCOMES DURING HOSPITALIZATION, ACCORDING TO STUDY GROUP.\*

| OUTCOME   | STUDY GROUP     |                 | STATISTICAL ANALYSIS                  |                                       |
|---|-----------------|-----------------|---------------------------------------|---------------------------------------|
|   | INTERVENTION    | USUAL CARE      | MATCHED                               | UNMATCHED                             |
| All matched patients (n=852)                            |                 |                 |                                       |                                       |
| First episode of delirium — no. of patients (%)         | 42 (9.9)        | 64 (15.0)       | OR, 0.60 (95% CI, 0.39–0.92); P=0.02† | OR, 0.61 (95% CI, 0.40–0.93); P=0.02‡ |
| Total days of delirium§                                 | 105             | 161             | P=0.02¶                               |                                       |
| No. of episodes of delirium                             | 62              | 90              | P=0.03¶                               |                                       |
| Patients with delirium (n=106)                          |                 |                 |                                       |                                       |
| Mean $\pm$ SD delirium-severity score                   | 3.85 $\pm$ 1.27 | 3.52 $\pm$ 1.44 |                                       | P=0.25**                              |
| Recurrence (two or more episodes) — no. of patients (%) | 13 (31.0)       | 17 (26.6)       |                                       | P=0.62††                              |

\*All analyses were based on the intention-to-treat strategy. OR denotes odds ratio, and CI confidence interval.

†This analysis was conducted with conditional logistic-regression models appropriate for matched analyses; 88 discordant pairs were used.

‡This analysis was conducted with unmatched logistic-regression analysis, with control for matching factors.

§For total days of delirium, the mean ( $\pm$ SE) value per patient was 0.25 $\pm$ 0.05 in the intervention group and 0.38 $\pm$ 0.06 in the usual-care group. The mean within-pair difference was 0.13 $\pm$ 0.08 fewer day in the intervention group.

¶For this matched analysis, the sign test was applied on within-pair differences.

||For the number of episodes of delirium, the mean ( $\pm$ SE) value per patient was 0.15 $\pm$ 0.03 in the intervention group and 0.21 $\pm$ 0.03 in the usual-care group. The mean within-pair difference was 0.07 $\pm$ 0.04 fewer episode in the intervention group.

\*\*The delirium-severity score ranged from 0 to 7 according to the presence and severity of four symptoms of delirium; higher scores indicate increased severity. This unmatched comparison was conducted with the t-test.

††This unmatched comparison was conducted with the chi-square test.

bility that delirium would develop by a specified time, between the study groups.

Total days of delirium, defined as the total number of days with delirium among all the patients in each study group, and the number of episodes of delirium in each group were calculated. Statistical comparisons were carried out in the matched analyses with use of the sign test to assess pairwise differences. The severity and rate of recurrence of delirium among patients with delirium were compared between study groups by means of appropriate statistical analyses for unmatched comparisons.

Adherence rates were calculated according to patient-day in the intervention group. Eligible patient-days were defined as those on which patients were assigned to receive the specified part of the intervention protocol. Changes in risk factors or targeted outcomes at the time of reassessment (on day 5 or at discharge, if earlier) were compared between the subgroups of patients in the intervention and usual-care groups who had the risk factor in question at base line by means of unmatched statistical analyses, including chi-square analysis for categorical variables. Adjusted mean scores at reassessment were calculated as least-squares means with use of analysis of covariance with adjustment for the base-line score.

All statistical tests were two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

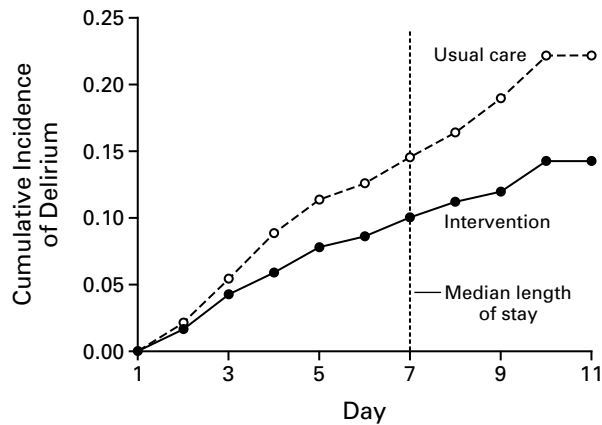
The characteristics of the patients in each study group at the time of admission are shown in Table 2. The intervention and usual-care groups did not differ significantly in terms of any of the characteristics. Many patients with dementia were included in the study; scores on the Mini-Mental State Examination ranged from 7 to 30, with 25 percent of the patients having a score of 20 or less. The mean numbers of risk factors per patient at admission were

similar in the two groups. The median lengths of stay were 7.0 and 6.5 days in the intervention and usual-care groups, respectively (P=0.95). Six patients in the intervention group (1.4 percent) and seven in the usual-care group (1.6 percent) died during hospitalization (P=0.78); complete information on delirium was available for these subjects.

## Overall Effectiveness

The rate of incidence of delirium was significantly lower in the intervention group than in the usual-care group (9.9 percent vs. 15.0 percent, P=0.02). The matched odds ratio of 0.60 (95 percent confidence interval, 0.39 to 0.92) in matched multivariable analyses indicates that a substantial reduction in risk was associated with the intervention (Table 3). After examination of all the potential base-line covariates (Table 2), only a Mini-Mental State Examination score of less than 24 was significantly associated with outcome (P<0.01). Adjustment for the score, however, did not substantially affect the overall results, and thus we did not control for this variable in subsequent models. Unmatched multivariable analyses, including both logistic-regression and Cox proportional-hazards analyses, with adjustment for matching factors, confirmed the matched results. The cumulative incidence of delirium was significantly lower in the intervention group than in the usual-care group (Fig. 1).

The total number of days of delirium was significantly lower in the intervention group than in the



**Figure 1.** Cumulative Incidence of Delirium According to Study Group.

The cumulative incidence of delirium was defined as the probability of the development of delirium by a specified time. Data on patients were censored at the time of discharge or death. The difference between the groups was significant (chi-square = 4.77;  $P=0.03$  by the log-rank test). Kaplan-Meier estimates of the incidence of delirium at the median length of the hospital stay (seven days, indicated by the dotted line) were 0.100 for the intervention group and 0.145 for the usual-care group.

group that received usual care (105 vs. 161 days,  $P=0.02$ ) (Table 3). The total number of episodes of delirium was also significantly lower in the intervention group (62 episodes, vs. 90 in the usual-care group;  $P=0.03$ ); however, this effect appeared to result primarily from the effects of the intervention on the first episode of delirium rather than on recurrent episodes. Among cases of delirium, severity scores and rates of recurrence did not differ significantly between the two study groups.

In matched-subgroup analyses, the intervention significantly reduced the rate of incidence of delirium in the group at intermediate risk for delirium at base line (odds ratio, 0.52; 95 percent confidence interval, 0.29 to 0.92). In the group at high risk for delirium at base line, the intervention was associated with a reduction in incidence (odds ratio, 0.73; 95 percent confidence interval, 0.38 to 1.38), but the reduction was not statistically significant.

#### Level of Adherence

The overall rate of adherence (complete and partial adherence) to all the intervention protocols was 87 percent (8716 of 10,056 patient-days). The overall adherence rates for the individual protocols were 96 percent for the orientation protocol (2443 of 2534 patient-days), 92 percent for the vision protocol (487 of 531 patient-days), 92 percent for the hearing protocol (514 of 561 patient-days), 86 percent for therapeutic activities (2188 of 2542 patient-days), 84 percent for early mobilization (2054

of 2452 patient-days), 81 percent for volume repletion (68 of 84 patient-days), and 71 percent for the nonpharmacologic sleep protocol (962 of 1352 patient-days). The most common reasons for nonadherence included refusal by the patient, lack of availability of the patient because of procedures elsewhere in the hospital, medical contraindications, and lack of availability of intervention staff members. No adverse effects were associated with the intervention protocols.

#### Effect on Targeted Risk Factors

The change in risk factors or targeted outcomes at the reassessment on day 5 or at discharge is shown in Table 4. At reassessment, there was significant improvement in the orientation score and a significant reduction in the rate of use of sedative drugs for sleep in the intervention group as compared with the usual-care group. The Activities of Daily Living score and the score on the Whisper Test demonstrated trends toward improvement in the intervention group. Receipt of early vision correction was also associated with a trend toward improvement in this group. Overall, there were significantly fewer risk factors present in the intervention group than in the usual-care group at reassessment.

#### Cost of Intervention

The total cost of the intervention, including staff time spent in intervention activities, equipment, supplies, and consultant costs, was \$139,506, or an average of \$327 per patient in the intervention group. The cost of intervention per case of delirium prevented was \$6,341 (\$139,506 for 22 cases prevented [64 cases of delirium occurred in patients receiving usual care, as compared with 42 cases in those receiving the intervention]).

#### DISCUSSION

This controlled clinical trial provides evidence that a multicomponent, targeted intervention strategy, the Elder Life Program, is effective for the prevention of delirium in hospitalized older medical patients. The intervention prevented the initial development of delirium and reduced the total number of days of delirium. It was most effective in patients who were at intermediate risk for delirium at base line. Once an initial episode of delirium had occurred, however, the intervention had no significant effect on the severity of delirium or on the likelihood of recurrence. This finding has an important implication for the treatment of delirium: primary prevention is probably the most effective strategy. Once delirium has occurred, our intervention strategy will be less effective and less efficient.

The strengths of this study include the daily assessment of patients for delirium with a standardized, validated instrument; the completeness of the

**TABLE 4.** CHANGE IN RISK FACTORS OR TARGETED OUTCOMES AT REASSESSMENT, ACCORDING TO STUDY GROUP.\*

| RISK FACTOR   | INTERVENTION | USUAL CARE | P VALUE |
|---|--------------|------------|---------|
| Cognitive impairment  |              |            |         |
| No. (%) of patients assessed  | 128          | 125        |         |
| Improved by 2 points  | 51 (40)      | 33 (26)    | 0.04    |
| Same  | 76 (59)      | 88 (70)    |         |
| Worse by 2 points   | 1 (1)        | 4 (3)      |         |
| Adjusted orientation score at reassessment                          | 7.2±0.2      | 6.8±0.2    | 0.06    |
| Sleep deprivation   |              |            |         |
| No. (%) of patients assessed  | 426          | 426        |         |
| Use of sedative drug for sleep during hospital stay                 | 148 (35)     | 195 (46)   | 0.001   |
| Immobility  |              |            |         |
| No. (%) of patients assessed  | 96           | 98         |         |
| Improved by 2 points  | 6 (6)        | 13 (13)    | 0.06    |
| Same  | 68 (71)      | 54 (55)    |         |
| Worse by 2 points   | 22 (23)      | 31 (32)    |         |
| Adjusted Activities of Daily Living score at reassessment           | 9.7±0.3      | 9.3±0.3    | 0.34    |
| Vision impairment   |              |            |         |
| No. (%) of patients assessed  | 57           | 62         |         |
| Early vision correction   | 21 (37)      | 17 (27)    | 0.27    |
| Hearing impairment  |              |            |         |
| No. (%) of patients assessed  | 120          | 98         |         |
| Improved by 1 point   | 61 (51)      | 39 (40)    | 0.10    |
| Same  | 37 (31)      | 44 (45)    |         |
| Worse by 1 point  | 22 (18)      | 15 (15)    |         |
| Adjusted Whisper Test score at reassessment                         | 5.3±0.3      | 4.5±0.4    | 0.09    |
| Dehydration   |              |            |         |
| No. (%) of patients assessed  | 240          | 254        |         |
| Improved by 5 points  | 107 (45)     | 98 (39)    | 0.40    |
| Same  | 110 (46)     | 127 (50)   |         |
| Worse by 5 points   | 23 (9)       | 29 (11)    |         |
| Adjusted ratio of blood urea nitrogen to creatinine at reassessment | 20.7±0.5     | 20.7±0.5   | 0.22    |
| Total no. of risk factors   |              |            |         |
| No. (%) of patients assessed  | 426          | 426        |         |
| Improved (fewer risk factors)                                       | 272 (64)     | 236 (55)   | 0.02    |
| Same  | 110 (26)     | 124 (29)   |         |
| Worse (more risk factors)   | 44 (10)      | 66 (15)    |         |
| Adjusted no. of risk factors per patient at reassessment            | 1.7±0.1      | 1.9±0.1    | 0.001   |

\*Plus-minus values are means ±SD. These results are based on unmatched analyses. All the adjusted scores were calculated at reassessment (on day 5 or at discharge, if earlier). These scores were calculated as least-squares means with use of analysis of covariance with adjustment for the base-line score. Targeted risk factors were defined as follows: cognitive impairment, orientation score of <8; immobility, Activities of Daily Living score of ≤12; vision impairment, visual acuity of <20/70 on binocular near-vision testing; hearing impairment, score of ≤6 on the Whisper Test; and dehydration, ratio of blood urea nitrogen to creatinine of ≥18.

outcome data, with no losses to follow-up; the targeting of at-risk patients for intervention, an approach that maximizes the efficiency and clinical relevance of the intervention; and the detailed tracking of adherence to the intervention protocols. Moreover, the practical, realistic nature of the intervention protocols, designed to target well-documented risk factors for delirium, enhances their feasibility and the extent to which they can be applied in other settings.

These findings lend strong support to the use of a multicomponent intervention to prevent delirium. The positive trends in the reduction of risk factors at the time of reassessment validate the effectiveness of each intervention protocol. The significant reduction in the total number of risk factors with intervention as compared with usual care suggests that risk-factor reduction contributed at least in part to the effectiveness of the intervention strategy.

Several important limitations of this study deserve comment. Logistic constraints precluded random assignment of the patients to the two treatment groups. However, the prospective, individual-matching strategy allowed balanced assignment of the patients to the two groups. Furthermore, a contamination effect in the usual-care group probably decreased the overall rates of delirium. Contamination was evident in the rates of delirium, which were substantially lower than anticipated on the basis of earlier studies in the same study population,<sup>24,25</sup> and it was also evident in the substantial reduction in risk factors that occurred in the usual-care group. Although efforts were made to avoid contamination, some intervention protocols were disseminated by word of mouth to staff members in usual-care units. Moreover, although the intervention strategies most often involved the nursing staff, the physicians rotated on all hospital floors and carried over some intervention protocols to the usual-care group. Despite these contamination effects, which would have tended to bias the results toward the null hypothesis, the significant overall results substantiate the robustness of the effects of the intervention.

The estimated cost of \$6,341 per case of delirium prevented compares favorably with the estimated costs in other studies of \$7,727 to \$11,834 (in 1996 dollars) per fall prevented<sup>43</sup> and \$19,800 to \$42,900 (in 1993 dollars) per myocardial infarction prevented.<sup>44</sup> Although a formal cost-effectiveness analysis was beyond the scope of this study, a complete analysis of health care costs related to delirium may demonstrate that the intervention yields a net savings.

This trial holds substantial promise for the prevention of delirium in hospitalized older patients. Further evaluation is needed to determine the cost effectiveness of the intervention; its effects on related outcomes, such as mortality, rehospitalization, institutionalization, use of home health care, and long-term cognitive functioning; and its effectiveness in other settings.

Supported in part by grants from the National Institute on Aging (R01 AG12551), the Commonwealth Fund (95-47 and 94-90), the Retirement Research Foundation (94-71), the Community Foundation for Greater New Haven (940862/SF, 950775/SF, 961081/SF, and 970342/SF), and the Patrick and Catherine Weldon Donaghue Medical Research Foundation (DF98-105).



We are indebted to the patients, families, nurses, and volunteers at Yale-New Haven Hospital who participated in the study; to the Project Recovery research staff (Annette Hopkins, Andrea Benjamin, Jean Bonyai, Wanda Carr, Sandra Ginter, Geraldine Hawthorne, Bernie Hebert, Lynne Iannone, Linda Johnson, Alice Kosack, Nancy Votto, Alice Van Wie, and Karen Wu); to the Elder Life Program intervention and development staff (Leslie Hurst, Jane McDowell, Dana Kalina, Diane Carroll, Kurt Acker, Sandra Alfano, Steve Allegretto, Richard Beattie, Lynn Chapman-Adler, Bea Clary, Eileen Coppola, Pam Corbett, Howard Goldberg, Jean Granata, Derek Heard, Jeannette Hodge, Stephanie Johnson, Joanne Lamb, Steven Leder, Dixie Losey, Courtney Lyder, Thomas Lydon, Lisa Mastroianni, Denna Niedzwiecki, Sally Palumbo, Michael Parisi, Valentine Pascale, Meg Pechar, Janet Shen, and Stephen Zink); to the Elder Life Program Community Advisory Board (Patricia Anderson, Dorothy Baker, Edith Berrios, Edward Dobihal, Margaret Edgerly, Dorothy Giannini-Meyers, Thomas Hardin, Carla Hayes, William Heinrichs, Cynthia Matthews, Paula Milone-Nuzzo, Robert Morgan, Cheryl Pierson, Judy Rolnick, Sam Slie, Agnes Timpson, Hattie Turner, and Edith Wilson); to the Elder Life Program Executive Committee (Dr. Edwin Cadman, Brian Condon, Donna Ukanowicz, and Laura Walsh); to the executive committee for the research project (Drs. Ralph Horwitz, Lorraine Mion, Robert Makuch, and Mary Tinetti); to Dr. Emily Richardson for adjudication of delirium outcomes; to Dr. Richard Marottoli, Dr. Mary Tinetti, and Christianna Williams for helpful review of the manuscript; and especially to Robbin Bonanno and Stephen Helfand.

## REFERENCES

- Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. *Am J Med* 1994;97:278-88.
- Rummans TA, Evans JM, Krahn LE, Fleming KC. Delirium in elderly patients: evaluation and management. *Mayo Clin Proc* 1995;70:989-98.
- Francis J, Kapoor WN. Delirium in hospitalized elderly. *J Gen Intern Med* 1990;5:65-79.
- The Administration on Aging. A profile of older Americans. Washington, D.C.: American Association of Retired Persons, 1995.
- Statistical abstract of the United States. Washington, D.C.: Bureau of the Census, 1996:116.
- Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *J Gen Intern Med* 1998;13:234-42.
- Cole MG, Primeau FJ. Prognosis of delirium in elderly hospital patients. *CMAJ* 1993;149:41-6.
- Hobbs FB, Damon BL. Special studies, 65+ in the United States. Current population reports. Series P23. No. 190. Washington, D.C.: Bureau of the Census, 1996.
- Hogan DB, Fox RA, Gadley BWD, Mann OE. Effect of a geriatric consultation service on management of patients in an acute care hospital. *CMAJ* 1984;136:713-7.
- Cole MG, Fenton FR, Englesmann F, Mansouri I. Effectiveness of geriatric psychiatry consultation in an acute care hospital: a randomized clinical trial. *J Am Geriatr Soc* 1991;39:1183-8.
- Layne OL Jr, Yudofsky SC. Postoperative psychosis in cardiectomy patients: the role of organic and psychiatric factors. *N Engl J Med* 1971;284:518-20.
- Schindler JA, Shook J, Schwartz GM. Beneficial effects of psychiatric intervention on recovery after coronary artery bypass graft surgery. *Gen Hosp Psychiatry* 1989;11:358-64.
- Cole MG, Primeau FJ, Bailey RE, et al. Systematic intervention for elderly inpatients with delirium: a randomized trial. *CMAJ* 1994;151:965-70.
- Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL. Effectiveness of a geriatric evaluation unit: a randomized clinical trial. *N Engl J Med* 1984;311:1664-70.
- Wanich CK, Sullivan-Marx EM, Gottlieb GL, Johnson JC. Functional status outcomes of a nursing intervention in hospitalized elderly. *Image J Nurs Sch* 1992;24:201-7.
- Nagley SJ. Predicting and preventing confusion in your patients. *J Gerontol Nurs* 1986;12:27-31.
- Williams MA, Campbell EB, Raynor WJ, Mlynarczyk SM, Ward SE. Reducing acute confusional states in elderly patients with hip fractures. *Res Nurs Health* 1985;8:329-37.
- Budd S, Brown W. Effect of a reorientation technique on postcardiotomy delirium. *Nurs Res* 1974;23:341-8.
- Owens JF, Hutelmyer CM. The effect of preoperative intervention on delirium in cardiac surgical patients. *Nurs Res* 1982;31:60-2.
- Chatham MA. The effect of family involvement on patients' manifestations of postcardiotomy psychosis. *Heart Lung* 1978;7:995-9.
- Riis J, Lomholt B, Haxholdt O, et al. Immediate and long-term mental recovery from general versus epidural anesthesia in elderly patients. *Acta Anaesthesiol Scand* 1983;27:44-9.
- Williams-Russo P, Urquhart RN, Sharrock NE, Charlson ME. Postoperative delirium: predictors and prognosis in elderly orthopedic patients. *J Am Geriatr Soc* 1992;40:759-67.
- Gustafson Y, Brannstrom B, Berggren D, et al. A geriatric-anesthesiology program to reduce acute confusional states in elderly patients treated for femoral neck fractures. *J Am Geriatr Soc* 1991;39:655-62.
- Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. *JAMA* 1996;275:852-7.
- Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med* 1993;119:474-81.
- Makuch RW, Zhang Z, Charpentier PA, Inouye SK. Prospective individual matching: covariate balance and power in a comparative study. *Stat Med* 1998;17:1517-26.
- Charpentier PA, Inouye SK. Prospective individualized matching in a non-randomized geriatric intervention trial. *Gerontologist* 1995;35(Special Issue 1):181.
- Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med* 1998;13:204-12.
- Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.
- Cummings JL. Clinical neuropsychiatry. Orlando, Fla.: Grune & Stratton, 1985:9.
- Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the Confusion Assessment Method: a new method for detection of delirium. *Ann Intern Med* 1990;113:941-8.
- Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL, a standardized measure of biological and psychosocial function. *JAMA* 1963;185:914-9.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818-29.
- Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179-86.
- MacPhee GJ, Crowther JA, McAlpine CH. A simple screening test for hearing impairment in elderly patients. *Age Ageing* 1988;17:347-51.
- Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968;114:797-811.
- Uhlmann RF, Larson EB, Buchner DM. Correlations of Mini-Mental State and modified Dementia Rating Scale to measures of transitional health status in dementia. *J Gerontol* 1987;42:33-6.
- Beresin EV. Delirium in the elderly. *J Geriatr Psychiatry Neurol* 1988;1:127-43.
- Holford TR, Bracken MB, Eskenazi B. Log-linear models for the analysis of matched cohort studies. *Am J Epidemiol* 1989;130:1247-53.
- Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989;79:340-9.
- Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol* 1989;129:125-37. [Erratum, *Am J Epidemiol* 1989;130:1066.]
- Lynn HS, McCulloch CE. When does it pay to break the matches for analysis of a matched-pairs design? *Biometrics* 1992;48:397-409.
- Rizzo JA, Baker DI, McAvay G, Tinetti ME. The cost-effectiveness of a multifactorial targeted prevention program for falls among community elderly persons. *Med Care* 1996;34:954-69.
- Hall JP, Heller RF, Dobson AJ, Lloyd DM, Sanson-Fisher RW, Leeder SR. A cost-effectiveness analysis of alternative strategies for the prevention of heart disease. *Med J Aust* 1988;148:273-7.