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Hospitalization and Cognitive Decline: Can the Nature of the Relationship Be Deciphered?

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Abstract

Background—Evidence for a relationship between hospitalization and incident cognitive decline exists mainly in the literature focusing on critical care hospitalization. Recent studies, however, have also found an association between noncritical care hospitalization and the development of cognitive decline.

Objective—This article will review the literature pertaining to hospitalization and cognitive decline, including hospitalizations for both critical and noncritical care, and in medical and surgical patients. The article will also explore the various factors that have been implicated in the development of cognitive decline and dementia.

Methods—Review of the literature was completed using PubMed and Medline search programs.

Results—Several articles supporting evidence for the association between hospitalization and cognitive decline are available. Evidence for potential mediating factors also does exist.

Conclusions—There is evidence to support an association between hospitalization and development of cognitive decline. Factors that could mediate this association include, but may not be limited to, delirium, medications, stress, and depression. There is a need for further research in this area in order to better understand the underlying pathophysiology involved in the development of cognitive decline and dementia and to determine if preventive measures might be beneficial in decreasing risk for cognitive decline for patients who are hospitalized.

Keywords

Hospitalization; cognitive impairment; cognitive decline; dementia

Hospitals can be dangerous places for older patients, with increased risk of nosocomial infections,[1] medication interactions,[2] delirium,[3] surgical complications,[4] and functional decline.[5] Recent research shows that patients may additionally be at risk for cognitive

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decline after hospitalization.[6–8] This is a significant public health issue, as those over the age of 65 are the most frequently hospitalized and have the longest length of stay. In the United States alone, the number of adults over 65 is expected to reach 79 million by 2030, making up 19% of the population.[9] Hospitalizations will be more numerous, and cost effective risk management even more crucial. The medical community is actively seeking prevention strategies to avoid unnecessary hospitalizations and to reduce hospital-acquired complications. The risk of cognitive sequelae with hospitalization, however, has not been a focus of prevention strategies. The risk for development of cognitive decline is of course concerning due to the morbidity and mortality associated with cognitive impairment and dementia, which leads to functional decline, worsening medical condition, increasing dependency and care needs, and institutionalization.

It has been challenging to design studies that can both establish a relationship between cognitive decline and hospitalization and determine the nature and direction of this relationship. Some researchers have hypothesized that those patients who are very early in the development of a progressive dementing illness may be more at risk for the medical illnesses that precipitate hospitalization.[7] Possibly the patient's cognitive impairment leads to mismanagement of their medical illness. Alternatively, the disease states that cause acute medical issues could also be promoting neurodegeneration or otherwise damaging the brain with resultant cognitive decline. The latter theory is supported by previous studies showing an increased risk for cognitive impairment with specific disease states, such as cardiovascular failure and stroke.[10,11]

There is limited compelling data, however, on the relative contributions of the many possible risk factors associated with cognitive decline, so it becomes even more difficult to distinguish which factors also associated with hospitalization could be contributing to the decline. Observational studies give adequate evidence to support an increased risk for development of dementia in persons with diabetes mellitus, with metabolic syndrome, smokers, those possessing the apolipoprotein E e4 allele, and those with depression.[12] There is some evidence that degree of medical comorbidity, rather than any particular disease state, assessed during hospitalization is associated with cognitive impairment.[13] Alternatively, specific events or syndromes occurring during hospitalization, including surgeries,[14,15] acute respiratory distress syndrome (ARDS),[16,17] or delirium,[18] have been shown to increase one's risk for cognitive decline. Intensive care settings, where these syndromes are common, have been a primary focus of research, and the potential contribution of hyperglycemia, hypoxia, cardiovascular status, and use of anesthetic agents in this setting have been considered.[19,20] There is also recent evidence, however, that even noncritical care hospitalization, usually defined as hospital admissions not involving an illness classified as critical, is associated with cognitive decline,[6] suggesting that in addition to these factors, there may be other contributing factors common to all hospital admissions that contribute to risk for cognitive impairment.

Although an association between hospitalization and cognitive decline has been demonstrated in the literature, at present, the nature of cognitive decline that occurs more frequently in those patients who have been hospitalized remains poorly characterized. The vast majority of the literature relies on retrospective assessment of pre-hospitalization

cognitive function, making it difficult to determine whether cognitive changes are abrupt in onset. Due to lack of long-term follow-up in most studies, it is also not clear whether hospitalization leads to cognitive change that remains static or instead initiates a progressive, neurodegenerative-type cognitive decline. Understanding the nature of the relationship between hospitalization and cognitive decline will not only help in developing preventive measures, but may also aid in our understanding of the pathologies contributing to differing dementia subtypes. A primary goal of this article will be to review the literature pertaining to cognitive decline following hospitalization. Review of the literature was completed using PubMed and Medline search programs. Search terms included *cognitive decline or stress and hospitalization,* and post-operative cognitive dysfunction. Cognitive impairment was cross-referenced with the terms *stress, hospitalization, steroids,* and *depression.* All relevant articles were included in the review. This article will also present possible theories to explain the association between hospitalization and cognitive decline. Specifically, the potential role of stress will be described, because physical and psychological stress are likely present in the majority of hospitalizations, and stress is a known risk factor for the development of cognitive impairment. Other possible factors, such as delirium, common treatments used during hospitalization, and depression, will also be reviewed. Finally, we will highlight the potential for further research in this area.

COGNITIVE IMPAIRMENT AFTER HOSPITALIZATION

Ehlenboch et al.[6] conducted the most recent study exploring the relationship between cognitive decline and hospitalization using a relatively large cohort (N = 2,929) of patients aged 65 and older. The investigators followed subjects prospectively for a mean of 6 years, and monitored various risk factors for dementia. Hospitalizations for any reason during this time period were noted, and diagnosis codes were reviewed to determine if critical illness had been present during the hospitalization. The study subjects did not have a diagnosis of dementia at baseline, but the diagnosis of mild cognitive impairment (MCI) was not determined or used for exclusion. Longitudinal cognitive assessments (the Cognitive Abilities Screening Instrument [CASI]) were performed at evaluations approximately every 2 years. After adjusting for various diseases that could individually be associated with cognitive decline, the investigators found an association between both the development of cognitive decline and the incidence of dementia and admission to the hospital for either critical care or noncritical care illness. Decline in CASI scores from pre- and post-hospitalization were signifi-cant and there was a significantly increased incidence of dementia in patients hospitalized for noncritical care (N = 228) compared with those never hospitalized (N = 146), from 14.6 per thousand per year to 33.6 per thousand per year (adjusted risk of incident dementia with noncritical care hospitalization: 1.4, p = 0.001). The incidence of dementia was also increased to 31.1 per thousand per year in patients hospitalized for critical care (N = 5), but this was not statistically significant probably due to the small number of patients in this group. Interestingly, they found that there was close to no change in cognition in the interval prior to hospitalization, that decline occurred more often during the interval involving hospitalization, and that the slope of decline in the time period following hospitalization showed little additional change. This study provides evidence to refute the assumption made by some that the relationship between cognitive

decline and hospitalization is due primarily to cognitive impairment prior to hospitalization. In addition, it appears that cognitive decline due to hospitalization remains relatively stable in the post-hospitalization period, unlike the progressive decline of other types of dementia. Unfortunately, most commonly affected domains of cognition (e.g., memory, executive function) were not specified, even though these different domains were included in their assessment.

The Ehlenboch et al.[6] study, which is summarized in Table 1 for comparison to other relevant studies discussed here, is important in that it is the first prospective study designed to follow a cohort of older individuals without cognitive impairment at baseline, using an objective measure of cognitive function prior to hospitalization. Previous studies had used family report of patients' normal cognitive status or lack of formal diagnosis of dementia to distinguish those with intact cognitive functioning at baseline.[20] As family members and even providers often miss early signs of cognitive impairment, this method is less than ideal. Without the recognition or exclusion of patients with MCI at baseline, however, it is difficult to determine if those very early in a cognitive disorder who would likely decline, were more likely to be hospitalized or if these individuals might be more vulnerable to the effects of hospitalization.

Another study, in which the investigators accessed objective measures of pre-hospitalization cognitive function and physical well-being, looked at hospitalization utilization in a cohort of patients over the age of 65 who were high functioning at baseline.[7] The cognitive measures (the Short Portable Mental Status Questionnaire [SPMSQ] and tests of delayed verbal recall) were then repeated at the 3-year follow-up evaluation. Again, diagnosis of MCI was not determined for exclusion, and some participants with evidence of mild memory impairments were included. Results demonstrated a strong association between hospital utilization and general cognitive decline over the 3 years, with the adjusted odds ratio for hospitalization for those who declined more than two points on the SPMSQ compared with those with less decline (SPMQ score: 7.8). A particular strength of the study was that the investigators enrolled only high-functioning, physically healthy older adults in order to reduce the confounding effects of chronic medical diseases that put one at risk for both hospitalization and dementia.

Some investigators have attempted to better characterize the nature of cognitive decline with hospitalization based upon the pattern and timing of cognitive change in relation to baseline cognitive functioning. In a sample of 291 medical and surgical patients aged 65 or older without "profound cognitive impairment" at hospital admission based upon a Mini Mental State Examination (MMSE) greater than or equal to 20,[8] cognitive status was assessed at admission and discharge and at 3 and 6 months post-discharge. The investigators distinguished several patterns of cognitive change. Some patients who demonstrated cognitive impairment at the initiation of hospitalization remained consistently impaired or experienced a worsening of cognitive function after discharge (N = 178). Other patients without impairment initially worsened during hospitalization, then showed improvement at follow-up (N = 47). Finally, some patients without impairment during hospitalization showed declined after discharge (N = 66). The authors then hypothesize that those whose cognitive abilities worsened during hospitalization but later improved may represent those

with delirium, as those patients had the highest percentage of surgical procedures. Those showing impairment on admission that persisted or worsened may represent a group of patients already suffering from dementia. The most interesting group for the purposes of this review would be the group without initial impairment who later exhibited a deterioration in cognitive function. Although they showed little acute decline over the course of hospitalization, they overall had a gradual decline over the 6 months following hospitalization, with mean reduction of 1.6 points on the MMSE. This group was actually more likely to have had higher levels of education than the other groups, which may seem at first unusual, but the authors hypothesized that education may delay observable cognitive decline. Age, total education, cardiovascular comorbidities, number of medications, functional and nutritional scores, depressive symptoms, surgical treatment, and low hemoglobin were all significantly associated with cognitive decline. The study was limited due to the lack of prehospitalization cognitive measurement, but provides compelling ideas regarding the possible trajectories of cognitive impairment following hospitalization that merit further study.

There is substantial research focused on the relationship between critical care hospitalizations and cognitive function during and post hospitalization.

Several studies (reviewed by Hopkins and Jackson[20]) involving various subgroups of critical care patients (either with a defined critical illness, admitted to a medical intensive care unit, or admitted to any intensive care unit), have looked at cognitive decline following critical illness hospitalization.[17,21–30] Subjects in these studies were followed for 1 to 6 years post-discharge, and a risk for decline was observed consistently, with up to 78% of patients developing cognitive decline. There seems to be a trajectory of sub-acute decline, followed by some improvement from 6 months to 1 year post-discharge, and then subsequent decline. Of the relatively few studies that specify the type of cognitive function affected, memory is most commonly reported to be impaired, with executive dysfunction, impaired attention, and slowed mental processing speed also often present.[17,29] Assessment of pre-morbid function (using no pre-hospitalization objective measures), type of neuropsychological testing at follow-up, and disease state of the subjects differed considerably between studies. The majority of the patients included in these studies were relatively young and middle-aged (mean age of 54 [SD: 11]) across studies. Patients over the age of 65 were not excluded due to age, but usually due to pre-existing neurocognitive impairments or significant cardiovascular or neurological disease. Surprisingly, older age was not associated with a higher risk of chronic cognitive impairment in several of the studies. Evidence of hypergylcemia and hypotension during hospitalization and degree of hypoxia were associated with increased risk for cognitive decline in critical care patients.[19,23,24] Duration of mechanical ventilation, and number of days receiving sedative, narcotic, or paralytic medications were not significant contributors to cognitive decline in these studies. Although additional research in primarily geriatric populations is needed to confirm these findings, these data provide evidence that factors associated with critical illness can lead to permanent CNS damage even in relatively young individuals without apparent evidence of pre-existing cognitive disorders. Importantly, there has been evidence of brain atrophy present on imaging in patients with cognitive impairment after discharge from hospitalization for ARDS, described elsewhere.[31]

Surgery, with its suggestion of greater severity of illness, associated need for anesthesia, and heightened risk for infection and other adverse events, is a factor of considerable interest when examining the relationship between hospitalization and cognitive function. Delirium occurs in almost half of surgical patients over the age of 65.[3] Surgery has also been observed to increase risk of persistent and/or progressive cognitive impairment, however. Postoperative Cognitive Dysfunction (POCD) is a syndrome that has been described generally as varying abnormalities on neuropsychological testing following surgery, and includes both delirium and persisting cognitive impairment(15). Research has often focused on the contribution of anesthetics in the development of POCD, and this will be reviewed further in the more general discussion of medication's role in cognitive decline during hospitalization. Considering the vastly differing types of surgery, cognitive dysfunction following coronary bypass graft surgery (CABG) has been most thoroughly studied, as there is an obvious risk of decreased brain perfusion and embolic infarcts that can occur during CABG. The development of dysfunction is commonly thought to be multifactorial in nature, however, and there is conflicting evidence for whether there is a more favorable cognitive outcome for those patients who did not require the cardiopulmonary pump during surgery.[32,33]

Regardless of cause, poor neurologic outcomes are common and concerning. One well-designed study assessed CABG patients pre-operatively and followed them for 5 years after surgery with objective cognitive measures.[14] The study showed evidence for significant immediate decline, then short-term improvement and then later decline. Forty-two percent of patients showed impairment at 5 years, and interestingly those who showed impairment early were more likely to eventually develop dementia. The evidence is not completely consistent, however, with others comparing CABG patients to those with coronary artery disease not receiving surgery finding no difference in cognitive decline between the two groups, and actually little cognitive decline overall.[34]

As mentioned previously, other types of surgeries can put one at risk for delirium and persistent cognitive decline. Investigators have compared cognitive dysfunction after CABG to that following other noncardiac surgeries, and have found comparable incidence of cognitive decline following all type of surgeries.[35,36] One fairly large study of 1,218 noncardiac surgical patients aged 60 years or older found that approximately 10% had neuro-psychological deficits at 3 months postoperatively relative to preoperative cognitive testing.[37] Therefore, factors related to any type of surgery should be explored as potential contributors to cognitive change, including anesthetic and pain medications, immobilization, and physical and psychological stress. Again, anesthesia has been an area of particular interest to researchers, and will be addressed in the context of medication-induced cognitive decline.

As major surgery typically requires inpatient hospitalization, separating the cognitive risks due solely to the surgery itself is a challenge. Interestingly, one study addressed this issue to some degree by examining differences in cognitive function in geriatric patients who underwent relatively minor surgery either as an inpatient or outpatient. Decision for inpatient or outpatient status was not randomized, but guided solely by local practice. Higher rates of cognitive impairment were observed at 1 week and at 3 months following minor

surgery in those who were hospitalized (for a mean of one day) compared with those who had surgery as an outpatient (odds ratio: 2.8).[38] Even hospitalizations that were brief and associated with less serious surgical issues had an almost threefold increased risk for development of cognitive impairment at 3 months. Quite importantly, even though both groups received general anesthesia, the inpatient group had significantly longer duration of use of anesthetic agents. The study authors suggest that factors related to hospitalization may be to blame for the difference and they encourage prevention of hospitalization if possible, but length of anesthesia could also be accounting for their results.

STRESS AND COGNITIVE IMPAIRMENT

As it is apparent that varying hospitalized subgroups of patients are at risk for cognitive decline, it is important to consider which factors common to all hospitalizations might be contributing to this phenomenon. Illnesses requiring hospitalization are typically quite serious and therefore highly stressful for the individual and their loved ones. The relationship between cognition, stress, glucocorticoids, and other stress-response hormones and neuro-chemicals is complicated but worth exploring in this context. Disruption of the stress response may occur naturally with aging and to a greater degree in those who become cognitively impaired.[39] Life-long distress has also been found to be a risk factor for dementia.[40] There are few data, however, on acute stressors, such as those related to illness and/or hospitalization and their possible relationship to cognitive decline. Hospitalization may be a unique type of stressor in that the psychological distress of the hospitalization is compounded by the physical stress of the illness itself.

To further understand how stress could lead to cognitive impairment, investigators have focused primarily on the physiology of the hypothalamic pituitary adrenal axis and the sympathetic nervous system. The stress response involves cortisol release through activation of the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol then binds to both glucorticoid and mineralcorticoid receptors, which are present throughout the central nervous system. Mineralcorticoid receptors have a particularly high affinity for cortisol and are concentrated in the hippocampus, an area of the brain critical to learning and memory. Synthetic corticosteroids also have similar effects on cortisol receptors, with varying potency and duration of action.[41] In animal models, corticosterone has been found to enhance memory consolidation and retrieval at basal levels, but at higher levels these cognitive processes are negatively affected in a dose-dependent fashion.[42] Prolonged hypercortisolemia in rodents has been associated with reduced hippocampal volume.[43] In addition, in patients with Cushing disease or Cushing syndrome, where the adrenal gland produces excessive amounts of glucocorticoids, impairment of verbal learning and delayed recall is often seen, and this improves with cortisol level normalization.[44] There is even evidence of hippocampal atrophy seen on MRI in these patients.[45] Hence, fluctuations in cortisol are critical to behavior and overall health, although excessively high or prolonged exposure to cortisol can have adverse effects on hippocampal cells and function, which may lead to cognitive impairment in humans.

As risk for cognitive impairment increases with age in general, it is also important to review the changes in the stress response that occur with aging. Adequate levels of basal cortisol are

necessary for normal brain function as they play a role in plasticity and survival of neurons. Hippocampal feedback control of the HPA axis decreases in aging, however, producing a steady increase in circulating glucocorticoids. As a cause or consequence, aging is associated with impaired glucocorticoid receptor and intracellular functioning. Neurons may also be more vulnerable to neurotoxicity by high glucocorticoid levels in later life. The hippocampus is particularly vulnerable to these changes, with hippocampal damage resulting in decreased corticosteroid binding sites, and the possibility for persistent, stress-induced HPA activation and hypercortisolemia.

As summarized in Table 2, there is substantial evidence of a higher cortisol response to stress in older patients, possibly more so in women than men.[46] Compared with healthy young controls, elderly patients have been found to have elevated cortisol levels, and those patients with Alzheimer disease had even higher cortisol levels.[47] There is also more recent evidence of a negative correlation between cortisol level and both MMSE score and hippocampal volume measured by magnetic resonance imaging (MRI).[48] In animal models, aging rats and those with neurodegeneration are more likely to show cognitive deficits with acute stressors than younger healthy controls.[49,50] Perhaps there are changes in the stress response that occur with age that lead to increasing vulnerability for hippocampal atrophy and cognitive impairment, particularly when acute stressors are present. Type, severity, duration, and frequency of stressors might be expected to affect the degree and persistence of cognitive changes. The effects of exogenous steroids on cognition will also be addressed more specifically later with a review of medication's possible contribution to cognitive decline.

There are substantial data to support a positive correlation between serum cortisol and severity of stress in patients undergoing surgery,[51] those with stroke,[52] myocardial infarction,[53] and critically ill patients in general.[54,55] Fewer studies have looked at cortisol levels during hospital admissions for general noncritical illness. In one study of 252 adults admitted for noncritical illness, older age, sepsis, prolonged duration of fever, higher comorbidity score, and higher serum creatinine were associated with higher serum cortisol and this was associated with longer hospitalization stay and higher hospital mortality rate.[56] Almost half of the patients had elevated morning cortisol levels, with a mean of 541 nmol/L, and 48% with values between 416 and 690 nmol/L (normal range: 80–330 nmol/L). Patients over the age of 80 had the highest levels. There is also relatively little research looking at cortisol levels in patients who develop delirium, but some have found elevated levels in these patients.[57,58] Some have proposed a hypothesis that delirium is actually a result of an aberrant stress response, with systemic inflammation and an impairment of the HPA axis.[59] This hypothesis focuses on underlying dementia as key however, with prior pathology plus systemic insults interacting to produce delirium.

DELIRIUM AND COGNITIVE IMPAIRMENT

Long-term cognitive effects of delirium in the critical and noncritical care settings have also been of significant interest and are the focus of several comprehensive reviews.[18,60,61] This syndrome is often multifactorial in nature, and it remains unclear whether it is an early sign of an underlying cognitive disorder or a syndrome that produces (or is a result of) a

neurotoxic insult. And of course, stress may play a large role in the development of delirium. Certainly, delirium is an important area of research due to other associated adverse outcomes, with increased mortality and functional decline. It is particularly difficult to study, however, as it has varying presentations, and occurs in multiple medical situations. As discussed previously, this syndrome is common following surgery, but also can occur in up to 42% of medically ill, nonsurgical patients.[3] Moreover, it is unlikely that there is a unifying etiologic explanation for the syndrome. Some propose that delirium serves as a marker of reduced brain capacity. Others explain that delirium involves neuropathologic processes that could result in permanent brain injury in vulnerable individuals. Theories involving dysfunctional stress response, and overactivity of the dopaminergic system or underactivity of the cholinergic system, have also been implicated in delirium.[62]

For the purposes of this article, it is important to review evidence for a relationship between delirium and persisting cognitive impairment as this may play a key role in cognitive decline following hospitalization. Articles addressing this topic are summarized in Table 3. Again, most studies do not have pre-hospitalization assessments of baseline cognitive function, limiting any conclusions about delirium as an etiologic factor in cognitive decline. In a thorough review of the literature,[60] nine studies were identi-fied that gave evidence for an association between delirium and persisting cognitive decline.[26,63–70] The studies reviewed generally found either statistically significant deficits on follow-up cognitive measures or a higher incidence of dementia in those patients who had episodes of delirium during hospitalization as compared with those who did not. Patients were followed for variable lengths of time and came from varying populations, both medical and surgical, with the majority being geriatric. Only one of the studies objectively assessed pre-hospitalization baseline cognitive function in a cohort of nursing home patients, and found that delirium during hospitalization predicted cognitive decline, whereas pre-hospitalization MMSE scores did not.[70] Those with existing cognitive impairment were also not more likely to develop delirium than those who were cognitively intact. The authors concluded that medical events and the vulnerability of the brain to effects of the medical illness precipitating hospitalization were better predictors of cognitive deterioration over time than baseline cognitive impairment.

A recent comprehensive review[18] focusing on surgical, mostly geriatric patients provides further evidence for a relationship between delirium and cognitive decline in the surgical patient population.[71–79] Pre- or postoperative delirium was associated with persisting cognitive impairment at 1 year in 40% of patients in one study.[71] Another study demonstrated a 3.5 times risk for the development of dementia at 5 years after the surgical procedure in those with delirium,[72] highlighting the risk of cognitive decline after an episode of delirium. As delirium present prior to surgery was also associated with risk for cognitive decline, processes related to delirium rather than factors directly related to the surgery are likely more important to the development of chronic cognitive dysfunction.

Critical care units are also an area of investigation as patients in such units are more severely ill, have longer hospitalizations, receive more medical treatments, and are highly likely to experience delirium, with a prevalence rate of up to 80%.[60] Duration of delirium was predictive of cognitive decline in this seriously ill population.[61] Another study, however,

using a slightly younger cohort with mean age of 54.2 years (compared with 61 years in the previous study) failed to show significant evidence for an association between duration of delirium and cognitive decline.[26] Although the preponderance of the evidence provides compelling support for a relationship between delirium and persistent cognitive dysfunction, a causal relationship cannot be assumed, particularly as in most studies there have been no predelirium objective assessments of cognitive function.

Less is known about the potential for "subsyndromal delirium," a syndrome involving the presence of some symptoms and signs of delirium, to result in cognitive impairment. Compared with those patients without any symptoms of delirium during inpatient admission, elderly patients with any symptoms of delirium were more likely to be cognitively impaired up to 1 year after discharge.[80] In another study, a younger cohort of critical care patients (median age: 54 years) who did not develop delirium but demonstrated impaired memory and problem-solving during the hospitalization, showed the same impairments at the 2-month post-discharge follow-up.[27] If "subsyndromal delirium" is included in future studies of delirium and cognitive decline, the association may be even stronger. Of course it remains unclear whether this syndrome represents a less severe episode of delirium or should be classi-fied as a separate disorder. "Recoverable cognitive dysfunction," which is impairment that does not reach criteria for delirium and improves by discharge, has also been described.[81] Even with improvement to baseline initially, this syndrome is also associated with cognitive decline in approximately 40% of patients 1 year from discharge.

Although these data suggest that delirium is associated with persistent cognitive impairment, it is not the only factor contributing to the relationship between hospitalization and cognitive decline. Clearly only a proportion of patients who had an episode of delirium (up to one third in studies reviewed earlier) go on to experience cognitive decline. There may be common factors that lead to varying clinical scenarios based upon individual vulnerability. We should consider that some causes of delirium, such as hypoxia, metabolic abnormalities, anesthetics, sedative hypnotics, narcotics, and other psychoactive medications could be neurotoxic and put one at higher risk for brain injury and later cognitive impairment and dementia. Additionally, some have proposed that delirium is a result of an aberrant stress response, and stress, as mentioned previously, could play a role in the development of both delirium and cognitive impairment.[59] Hence, delirium may serve as a marker for the ill effects of stress during hospitalization.

MEDICATION AND COGNITIVE IMPAIRMENT

During hospitalization, patients often receive treatments that can adversely affect the central nervous system. Geriatric patients in particular are at risk for the dangers of polypharmacy and are often started on new medications during hospitalization. Simply taking an increased number of medications during hospital admissions is associated with cognitive decline.[8] Specific types of medications may also affect patients' cognitive status both acutely and over time, whether or not patients continue on these treatments. Some common medications used during hospitalization known to cause acute changes in mental status are anesthetics, narcotics, benzodiazepines, anticholinergic medications, and steroid medications. These types of medications are used in multiple different medical situations and are not specific to

any particularly disease state. Overall, there is very limited literature on these medications and their relationship to cognitive decline. There may be some evidence for an association between anesthesia and cognitive impairment, however, and steroids have been shown to possibly contribute to cognitive impairment even months after discontinuation of the medication. Both of these types of medication will therefore be reviewed further.

Postoperative cognitive decline, described previously, can be seen in patients undergoing various types of surgery, therefore widely used general anesthetic agents have been considered as a possible contributing factor for this syndrome. Evidence to support this comes mainly from animal studies that have shown abnormally increased production of beta-amyloid after prolonged exposure to anesthetics, which also underlies the progression of Alzheimer disease.[82] Possessing the apolipoprotein E gene 4 allele is also a risk factor for both Alzheimer disease and POCD, as is aberrant cholinergic function.[82] No clinical studies have supported this idea however. Actually, medication type and duration of anesthesia have not been associated with risk for cognitive impairment in the majority of studies.[83] Anesthetic medications are also often used in critically ill patients placed under sedation, and duration of sedation has not been associated with increased risk for impairment in this group either.[16] Medications in the sedative hypnotic class are also often used during noncritical care medical admissions in lower doses to aid with insomnia, agitation, or anxiety, but their relationship to persisting cognitive decline in this setting has not been studied. Given the clinical evidence currently available, anesthetic agents are unlikely to be a main factor in the development of cognitive decline after hospitalization.

As stress may be playing a causal role in the development of cognitive decline following hospitalization, the all too common exogenous administration of synthetic glucocorticoids during hospitalizations is concerning (Table 4). Corticosteroids are often used to treat inflammatory, immunologic, and allergic disorders affecting various body systems, such as the pulmonary, neurological, and rheumatologic systems. They are also commonly used in intensive care settings, frequently in the treatment of ARDS and septic shock. There is some research showing that steroids prescribed for medical purposes can lead to cognitive impairment, though it is unclear whether these impairments are persistent.[41] In humans, acute high-dose hydrocortisone can transiently impair declarative memory, and this is not necessarily more prominent in older subjects.[84] Others have found though that both short-term and long-term use of oral corticosteroids can impair declarative memory (hippocampal-mediated) and working memory (frontal lobeemediated), with elderly patients being more at risk.[41,85] For those patients on long-term therapy, cognitive impairment that was seen at baseline after already starting treatment remained evident when tested after 4 years of continued treatment but was found to be stable over that time, not showing further decline.[86] Hippocampal volume also remained decreased on MRI during the 4-year period. Acute high-dose corticosteroid administration, which would more likely occur during a hospitalization, may more likely lead to changes in cognition that are reversible, although several case studies and series demonstrate cognitive decline that is longer-lasting.[87–90] One of these case series showed that cognitive effects remained present 3–11 months after discontinuation of the steroid medication that was used acutely in high doses.[87] In one study, however, chronic low-dose prednisone treatment was not associated with cognitive impairment or decrease in hippocampal volume.[91] There have been no longitudinal cohort

studies looking at incidence of dementia or persisting cognitive decline after discontinuation of corticosteroids.

Interestingly, treatment for steroid-induced cognitive impairment has also been considered. Studies include patients needing chronic corticosteroids for management of medical illness. Of course reduction of steroid dose or discontinuation of the steroid is recommended if possible. Memantine and lamotrigine, however, have demonstrated ameliorating effects on steroid-induced cognitive declines, and are proposed to work through inhibitory effects on glutamate in the hippocampus, as corticosteroids lead to increased glutamate release in this brain region.[92,93] Further evidence of their efficacy as well as investigation of the mechanism by which these pharmacologic agents improve cognition in steroid-treated individuals is needed. Conversely, steroids have been studied as potential treatment for Alzheimer disease given their anti-inflammatory properties. A large study in patients with Alzheimer disease, treated with low dose prednisone for 1 year, showed no benefit in cognitive measures and worsening on behavioral measures.[94]

DEPRESSION AND COGNITIVE IMPAIRMENT

Depression is another factor often considered in the development of cognitive impairment that could play an intermediary role in those patients who have been hospitalized (Table 5). Unfortunately, the relationship between depression and cognitive impairment is already very complicated, before adding the variables of hospitalization. Cognitive impairment, particularly in attention and concentration, can be a symptom of depression. Additionally, symptoms of depression may represent the early stages of dementia. Similar neuropathologic changes may contribute to both cognitive impairment and depression, although there is substantial evidence that depression is an independent risk factor for cognitive decline.[95–99] One very recent study, following a cohort for a mean of 8 years, found that those who had symptoms of depression at baseline had a 50% increased risk for developing dementia, regardless of treatment with antidepressants.[100] Another group of investigators following older adults for a median 23.1 years discovered that having one episode of significant depressive symptoms increased risk for dementia by 87%–92%, and having two or more episodes almost doubled the risk.[101] Hospitalizations were not recorded as a study variable in either of these studies, but likely occurred and could have been important as a mediating factor.

It may be possible that those patients with medical illness with comorbid depressive symptoms are more likely to develop cognitive impairment. One study that supports this idea followed medical inpatients with minor or major depression at hospital admission, finding an association with depression diagnosis and subsequent cognitive changes at 1 year.[102] In another study of patients hospitalized with ARDS, those with cognitive sequelae at 1 year after discharge were also more likely to be depressed.[23] Evidence thus far does not clarify the question of whether the depression occurring during or following hospitalization could be a causal factor in the development of cognitive impairment or a result of the same processes that lead to cognitive impairment.

SUMMARY AND DIRECTIONS OF FUTURE RESEARCH

Though the relationship between hospitalization and cognitive decline is complex and at this point circumstantial, there is sufficient evidence of association to warrant further investigation. Based upon the literature reviewed herein, examining the stress response occurring during hospitalization and its relationship with cognitive function may be most important. Additionally, the effects of delirium, medication exposures, and depression during hospitalization on cognitive function are likely to be fruitful lines of investigation. HPA axis activation is common to each of these other potential contributors to the relationship between hospitalization and cognitive decline and should be considered when possible.

Future research focused on the relationship between cognitive decline and hospitalization needs to include adequate assessment of several variables. First, adequate assessment of baseline cognitive status prior to hospitalization requires objective measures of a range of cognitive domains. Relying on patient and/or family member report of cognitive function is insufficient. Studies should also focus on individuals who are determined to be completely cognitively intact based upon standard neuro-psychological testing. As cognitive impairment has been also seen in younger individuals following hospitalization, including a sample beyond geriatric patients would be informative as well. Long-term follow-up with frequent cognitive assessment to better assess rate of decline would also be important. Although subjects would have multiple different medical illnesses for which they are being admitted to the hospital, duration of illness, medications used, and whether there were adverse events should be taken into consideration. The presence of different markers of illness, including hypotension, glucose dysregulation, and hypoxemia should be identified. At baseline, during hospitalization, and at follow-up, evaluation with psychiatric interview and measures of subjective stress and depression are important. Neuroimaging studies and other biomarkers of stress and dementia (cerebrospinal fluid, apolipoprotein E allele, cortisol levels) as well as measurement of patients' perceived stress are also worthwhile lines of investigation.

An example of a population of interest for study would be patients with ARDS as they seem to have an increased risk for cognitive decline. In particular, understanding the contribution of steroid medications used during hospitalization for cognitive decline in these patients would be useful. ARDS inevitably occurs or results in hospitalization, and treatment with steroids is common but controversial, hence not all patients receive corticosteroids.[103] Exploration of the long-term cognitive effects of ARDS patients receiving corticosteroids compared with those who do not would be informative, although confounding effects of hypoxemia may make this challenging. It would also be helpful to investigate cognitive effects of corticosteroids in patients with chronic obstructive pulmonary disease (COPD) as they often receive chronic and acute steroids in varying doses. This population has been found to have an increased risk of cognitive decline, but most literature focuses on the possibility of hypoxemia being a key factor, with conflicting results.[104] The role of cortiscosteroids, whether used acutely during hospitalizations or chronically, has not been explored in COPD patients. Following a cohort of individuals with COPD, comparing the cognitive function of those more often hospitalized to those not hospitalized, paying

attention to the possible mitigating factors such as levels and duration of hypoxemia and corticosteroid treatment, would likely be beneficial.

Although this review has focused on the risk of cognitive decline with hospitalization and its related events, clearly many individuals experience hospitalization, medication treatments, and even delirium and remain cognitively intact. Few studies have examined sources of individual resilience. We might hypothesize that factors considered protective for dementia may also lead to decreased risk for cognitive decline following hospitalization. Higher education level, adequate treatment of medical issues, with good compliance, lack of history of substance use, healthy diet, regular exercise, cognitively stimulating leisure activities, and regular social engagement could be some factors related to resilience. These factors are important as they are often changeable through education and proper medical management of patients. Genetic factors are likely to be very important, however. Careful, prospective research incorporating knowledge gained from previous studies will enable future investigations to more clearly delineate the relevant factors contributing to the observed relationship between cognitive decline and hospitalization as well as the factors protecting against it in order to inform the development of appropriate preventive measures.

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TABLE 1

Cognitive Impairment After Hospitalization

Study	Study Design	Population or Exposure	Sample Size	Pre-Hospital Objective Measure	Outcome Measure	Findings/Comments
Ehlenbach 2010[6]	Prospective (followed a mean of 6 years)	Hospitalization for critical illness or noncritical illness (>age 65 years)	2,929	Yes	Cognitive Abilities Screening Instrument	- Noncritical and critical care hospitalizations were associated with cognitive decline - Noncritical care hospitalization was associated with development of dementia
Chen 2010[8]	Prospective (followed 6 months)	Hospitalization to medical or surgical unit, not intubated (>age 65 years)	291	No	Mini-Mental State Examin-ation	- Four patterns of cognitive decline occurred - High functioning patients showed gradual cognitive decline at 6 months, but little acute decline during hospitalization
Hopkins 2006[20]	Review —10 studies (followed 1 —6 years)	Critical care hospitalization — critical illness or to intensive care unit (mean age 54 years [SD: 11])	455	No	Various cognitive tests	- 25%—78% of ICU patients developed cognitive impairment - At 6 years, short-term memory was the cognitive domain most often impaired
Chodosh 2004[7]	Retrospective (over 3 years)	Any hospitalization (>age 65 years)	598	Yes	Short Portable Mental-Status Questionnaire, delayed verbal recall	- Overall decline in cognitive functioning was associated with hospitalizations
Raeder 2003[38]	Prospective (followed for 3 months)	Inpatient versus outpatient surgery (>age 60 years)	372	Yes	Delayed recall, Concept Shifting, Stroop, Letter Coding tests	- Patients who were hospitalized (according to local practice) for minor surgery were more likely to develop cognitive impairment than those having minor surgery on an outpatient basis
Newman 2001[14]	Prospective (followed for 5 years)	CABG surgery (mean age 60.9 years [SD: 10.6])	261	Yes	Short story memory, Trails, Wechsler IQ, Benton Visual Retention tests	- Patients showed early decline, with short-term improvement then later decline (42% at 5 years) - Those with more impairment early were more likely to eventually develop dementia
Moller 1998[37]	Prospective (followed 3 months)	Noncardiac surgery (>age 60)	1,218	No	Stroop, Trails, verbal memory list, Shifting, and Letter Coding tests	- 10% of patients demonstrated neuropsychological deficits at 3 months

Study	Study Design	Population or Exposure	Sample Size	Pre-Hospital Objective Measure	Outcome Measure	Findings/Comments
						- Advanced age was only risk factor associated with late impairment

Notes: CABG: coronary bypass graft surgery.

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TABLE 2

Stress and Cognitive Impairment

Study	Study Design	Population or Exposure	Sample Size	Findings/Comments
Wilson 2007[40]	Prospective	Catholic clergy members (hospitalization not study variable)	219	- Chronic distress was associated with development of dementia
				- Chronic distress was not associated with any particular type of neuropathology
Rotman-Pikielny 2006[56]	Cross-sectional	Hospitalized medical inpatients/noncritcal illness	252	- Older age, sepsis, prolonged duration of fever, higher comorbidity score, and higher serum creatinine were associated with higher serum cortisol and this was associated with longer hospitalization stay and higher hospital mortality rate
Otte 2005[46]	Meta-analysis	Young vs. older (hospitalization was not a study variable)	1,295	- Compared with younger subjects, older subjects had a larger cortisol response to dexamethasone challenge
				- The effect of age on cortisol response was three times stronger in women than in men
Ferrari 2000[47]	Case-control	Young vs. older vs. dementia (not hospitalized)	116	- Older age and presence of dementia was associated with higher baseline morning cortisol levels

TABLE 3

Delirium and Cognitive Impairment

Study	Study Design (Length of Follow-up)	Population or Exposure	Sample Size	Findings/Comments
Girard 2010[61]	Prospective (1 yr)	Critical care, delirium	77	- 71% of patients had cognitive impairment at 1 yr - Delirium duration was independent risk factor for persisting decline
MacLullich 2009[18]	Literature Review (3 mos to 5 yrs)	Surgery, delirium	34-674	- Nine studies confirming association between delirium and worsening cognitive impairment
Jones 2006[27]	Prospective (2 mos)	Critical care, without delirium	30	- Nondelirious patients showed evidence of impaired memory (31%) and problem solving (50%) at 2 months
Jackson 2004[60]	Literature Review (6 mos to 3 yrs)	Geripsych patients, general medical patients, surgical patients	34-682	- Nine studies supporting association between delirium and subsequent cognitive impairment - Higher incidence of dementia in patients with a history of delirium
Gruber-Baldini 2003[71],[a]	Prospective (1 yr)	Hip fracture, delirium	674	- Cognitive impairment first detected in hospital persisted in over 40% of individuals at 1 year follow-up
Lundstrom, 2003[72]	Prospective (5 yrs)	Hip fracture, delirium	78	- Patients with delirium were 3.5 times more likely to develop dementia over 5 years
Jackson 2003[26]	Prospective (6 mos)	Critical care, delirium	34	- 32% of patients cognitively impaired at 6 months - Cognitively impaired were more likely to be depressed - Delirium duration was not associated with cognitive decline
Cole 2003[80]	Prospective (1 yr)	Medical inpatients, “ subsyndromal delirium”	164	- Patients with subsyndromal delirium had decreased functional and cognitive status than those without any symptoms of delirium
Katz 2001[70],[b]	Prospective (1 yr)	Hospitalization for any acute illness, nursing home patients, delirium	102	- Delirium and baseline cognitive impairment were associated with cognitive decline - Hospitalization was not independently associated with cognitive decline

Notes: All patients were hospitalized.

[a] Included in Jackson et al. 2004. [b] Included in MacLullich et al. 2009.[59]

TABLE 4

Medications and Cognitive Impairment

Study	Study Design	Population or Exposure	Sample Size	Findings/Comments
Coluccia 2008[91]	Placebo-controlled, crossover	Chronic prednisone vs. controls	24	-Chronic low dose prednisone treatment did not lead to significant memory impairment compared to controls -Patients with acute administration of steroid medication did have memory impairment
Brown 2007[86]	Prospective	Chronic prednisone vs. controls	13	- Cognitive impairment occurring after initiation of prednisone did not lead to further decline over 4 years
Wolf 2001[84]	Placebo-controlled, crossover	Young vs. older	20	- Both young and elderly subjects had transient impairments in short term recall with high dose hydrocortisone
Keenan 1996[85]	Cross-sectional (1) and prospective (2)	Chronic predisone vs. controls	50 (1) and 25 (2)	- Patients on chronic prednisone had more impairments in explicit memory and this was even more significant in elderly subjects - After 3 months, of acute prednisone therapy months, there were significant changes in short-term memory from baseline
Varney 1984[87]	Case series	Acute prednisone	6	- Patients developed cognitive impairment after treatment with prednisone that persisted three to eleven months after discontinuation

TABLE 5

Depression and Cognitive Impairment

Study	Study Design (Length of Follow-up)	Population or Exposure	Sample Size	Findings/Comments
Saczynkski 2010[100]	Prospective (mean of 8 years)	Older adults (hospitalization not study variable)	949	- Those who had symptoms of depression at baseline had a 50% increased risk for developing dementia
Dotson 2010[101]	Prospective (median of 23.1 years)	Older adults (hospitalization not study variable)	1,239	- One episode of significant depressive symptoms increased risk for dementia by 87%—92% - Two or more episodes almost doubled the risk of dementia
Han 2008[102]	Prospective (1 year)	Geriatric medical inpatients	281	- Minor or major depression diagnosis at hospital admission was associated with depression diagnosis and subsequent cognitive changes at one year
Hopkins 1999[23]	Prospective (1 year)	ARDS (hospitalized)	55	- Those with cognitive sequelae at one year after discharge were also more likely to be depressed - Hypoxemia was also associated with risk for cognitive impairment