

ALLOSTATIC LOAD AND DELIRIUM AMONG HOSPITALIZED ELDERS

by

Theodore Smith Rigney, Jr.

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I end my acknowledgements with an excerpt from Mathew Arnold's poem, *The Scholar Gypsy*, written in 1853, well over a hundred years before the theory of allostatic load described the cumulative pathological effects of exposure to acute and chronic stress.

*"For what wears out the life of mortal men?
'Tis that from change to change their being rolls:
'Tis that repeated shocks again, again,
Exhaust the energy of strongest souls
And numb the elastic powers."*

DEDICATION

To Michael, you have taught me more than any school ever will.

TABLE OF CONTENTS

LIST OF FIGURES.....	10
LIST OF TABLES.....	11
ABSTRACT.....	12
CHAPTER I: INTRODUCTION & CONCEPTUAL FRAMEWORK	14
Introduction	14
Significance	15
Background	18
Delirium	18
Stress Response	19
Allostasis.....	20
Allostatic Load	20
Theoretical Framework	22
Model of Allostatic Load & Delirium in Hospitalized Elderly.....	23
Overview and Purpose of the Study.....	25
Specific Aims	25
Definitions	26
Allostasis.....	26
Allostatic load.....	26
Delirium	27
Homeostenosis.....	27
Primary Mediators.....	28
Secondary Outcomes	28
Stress.....	28
Summary	29
CHAPTER II: BACKGROUND & LITERATURE REVIEW	30
Introduction.....	30
Delirium.....	31
History.....	31
Definition.....	32
Diagnostic Criteria.....	33
Clinical Features.....	35
Delirium sub-types.....	36
Delirium onset.....	37
Delirium duration.....	37
Subsyndromal delirium.....	38
Severity of delirium.....	39
Differential Diagnosis for Delirium	39
Prevalence and Incidence of Delirium.....	40

TABLE OF CONTENTS – *Continued*

Summary on Delirium Occurrence.....	44
Outcomes after Delirium	45
Delirium Risk Factors.....	46
Predisposing factors.....	47
Precipitating factors.....	49
Intensive care unit delirium risk factors.....	50
Risk factors for delirium in surgical patients	51
Delirium Pathophysiology.....	53
Stress.....	57
Stress Physiology.....	59
Allostasis.....	61
Allostatic Load	63
Primary Mediators	65
Primary Effects.....	66
Secondary Outcomes.....	66
Tertiary Outcomes.....	67
Validation of Allostatic Load	67
Allostatic Load Concept Development.....	73
Allostatic Load and Delirium	74
Aging	76
Allostatic Load and Aging.....	77
Homeostenosis.....	77
Model of Allostatic Load & Delirium in Hospitalized Elderly.....	79
Summary.....	80
 CHAPTER III: METHODS	 81
Introduction.....	81
Study Design and Overview.....	81
Setting.....	81
Sample	82
Inclusion/exclusion Criteria	82
Sample Size	82
Sampling Plan	83
Measures	84
Demographic and Medical Variables.....	84
Standardized Mini-Mental Status Exam	85
Summary.....	85
Time limits.....	85
Reliability.....	86
Interpretation of the score	86
Confusion Assessment Method.....	87
Summary.....	87

TABLE OF CONTENTS – *Continued*

Reliability.....	88
Interpretation of the score.....	88
Allostatic Load	89
Summary.....	89
Validity.....	89
Allostatic load components	90
Allostatic load score calculation.....	93
Procedures	94
Overview	94
Access to Potential Participants.....	94
Data Collection.....	96
Standardized Mini-Mental Status Exam.....	96
Confusion Assessment Method.....	96
Allostatic load.....	97
Demographic variables.....	98
Medical variables.....	98
Data Management and Analysis Plan.....	99
Protection of Human Subjects.....	100
Human Subject Involvement and Characteristics.....	100
Security of Materials	101
Potential Risks.....	102
Protection Against Risks.....	103
Potential Benefits of the Proposed Research to the Participants.....	103
Inclusion of Women and Minorities.....	104
Summary.....	104
CHAPTER IV: RESULTS	106
Overview.....	106
Univariate Analysis.....	106
Allostatic Load Scoring	109
Delirium Assessment.....	112
Correlational Analysis	112
Logistic Regression.....	115
Research Question One	117
Research Question Two.....	118
Exploratory Analysis	121
Summary.....	122
CHAPTER V: DISCUSSION	125
Introduction	125
Research Questions	126
Research Question One	126

TABLE OF CONTENTS – *Continued*

Research Question Two	126
Characteristics of the Study Participants	127
Cognitive Screening.....	129
Delirium Screening.....	131
Delirium Incidence	132
Allostatic Load	133
Allostatic Load Score Calculations	134
Conclusions from Additional Analyses	135
Conclusions from Analysis of Delirium Incidence, Age and Individual Variables of Allostatic Load	137
Discussion of Limitations	138
Model Development	138
Sampling	139
Measurement of Allostatic Load	141
Operationalization	141
Changing physiological systems	142
Calculating AL scores	142
Gender differences	143
Measurement of Delirium	144
Future Research	145
Conclusions	146
 APPENDIX A: DATA COLLECTION FORMS	 149
 APPENDIX B: RECRUITMENT SCRIPT	 155
 APPENDIX C: CONSENT FORMS	 158
 APPENDIX D: LETTERS OF APPROVAL	 166
 APPENDIX E. LITERATURE REVIEW OF DELIRIUM MEASURES	 169
 REFERENCES	 175

LIST OF FIGURES

FIGURE 1. Model of Allostatic Load & Delirium in Hospitalized Elderly.....	24
FIGURE 2. Allostatic response patterns.....	64
FIGURE 3. Data collection protocol	95

LIST OF TABLES

TABLE 1. DSM IV-TR Diagnostic Criteria for Delirium	34
TABLE 2. Potential etiologies for delirium	40
TABLE 3. Psychiatric differential diagnosis for delirium	41
TABLE 4. Variables of Allostatic Load	70
TABLE 5. Components of Allostatic Load.....	94
TABLE 6. Demographic Variables.....	107
TABLE 7. Other Variables of Interest.....	108
TABLE 8. Components of Allostatic Load.....	111
TABLE 9. Zero Order Correlations- Variables of Interest.....	113
TABLE 10. Zero Order Correlations- Allostatic Load Parameters.....	114
TABLE 11. Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium	117
TABLE 12. Summary of Logistic Regression Analysis for Alternative Composite Value of Allostatic Load Variable Predicting Delirium.....	118
TABLE 13. Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium	119
TABLE 14. Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium	119
TABLE 15. Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium	120
TABLE 16. Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium.....	121
TABLE 17. Summary of Simultaneous Logistic Regression Analysis for All Allostatic Load Variables Predicting Delirium	122

ABSTRACT

Delirium is a state of acute confusion and is common in hospitalized older adults. Delirium is associated with significant increases in morbidity and mortality, as well as healthcare costs. Delirium also is associated with functional and cognitive decline, as well as need for institutionalization and rehabilitation. Delirium can cause psychosocial distress for patients and families. While much is understood about the epidemiology of delirium, the pathophysiological mechanisms that lead to the development of delirium are less clearly defined.

The purpose of this study was to investigate the relationship of allostatic load (AL), a composite measure of primary (i.e. acute) stress mediators and secondary (i.e. chronic) stress outcomes and delirium in the hospitalized older adult. Development of the Allostatic Load & Delirium in Hospitalized Elderly model provided a theoretical framework for the study.

Forty- four participants, ranging from 66 to 93 years of age ($M = 76$ years of age) were recruited from three intensive care units and enrolled once they were determined not to have a cognitive deficit or prevalent delirium, as assessed by the Standardized Mini-Mental State Examination and Confusion Assessment Method (CAM), respectively. Ten AL components reflective of acute and chronic stress were collected upon admission. Allostatic load was calculated as the sum of the number of components for which the participant was rated in the highest risk quartile. Allostatic load subsets based on acute and chronic components were also calculated. Incident delirium was assessed 48 -72 hours after admission with the CAM.

Findings indicated that the incidence of delirium was 29.2%. The subset AL score based on components considered primary stress mediators was significantly related to delirium; however, no other variables were associated with delirium. Logistic regression modeling indicated that an AL subset of primary stress mediators did predict the incidence of delirium (OR 2.5, 95% CI = 1.12, 5.79; $X^2(1) = 5.668, p < .05$).

The findings from this study exploring the relationship between AL and delirium in the hospitalized older adult suggest that an AL score based on primary mediators may be useful in predicting delirium in the hospitalized older adult.

CHAPTER I: INTRODUCTION & CONCEPTUAL FRAMEWORK

Introduction

Delirium is a state of acute confusion and is common in elderly hospitalized adults. Unrecognized or untreated delirium can have profound effects on the hospitalized older adult. Delirium is associated with significant increases in morbidity and mortality, as well as healthcare costs (as cited in 2004). Delirium is also associated with increased functional and cognitive decline and increased need for institutionalization, rehabilitation, and home care (Duppils & Wikblad, 2007; McAvay et al., 2006; Roberts, Rickard, Rajbhandari, & Reynolds, 2007). Importantly, the experience of delirium can cause significant psychosocial distress for patients and families (Burns, Gallagley, & Byrne, 2004; Moraga & Rodriguez-Pascual, 2007; Ranhoff et al., 2006).

While much is understood about the epidemiology of delirium, including predisposing factors, such as dementia and advanced age, and common precipitating factors, such as infection, drugs and major surgery (Alsop et al., 2006), theoretical approaches to understanding the pathophysiological mechanisms leading to the development of delirium are less clearly defined (Broadhurst & Wilson, 2001; Ebersoldt, Sharshar, & Annane, 2007; Engel & Romano, 1959/2004; McEwen, 2007). Evidence implicating a stress response in delirium (Inouye, 2006; Olsson, 1999; White et al., 2002) suggests that an approach to the study of the mechanisms of delirium in the hospitalized older adult is through understanding the theory of allostatic load.

Significance

The study of older adults is becoming increasingly more important to the care of hospitalized patients. Although adults 65 years of age and older make up only 12.6% of the United States population, they account for approximately 35% of all hospital admissions (Institute of Medicine, 2008). If current trends continue, the number of older adults will reach more than 71 million by the year 2030 (Administration on Aging, 2008) and create unprecedented demands on hospital-based resources (Inouye, 2006).

The problem of delirium in the hospitalized older adult is of particular importance for several reasons. Delirium is associated with an increased risk of mortality. Hospital mortality rates of older adults admitted with delirium range 10% – 24% (Ely, Shintani et al., 2004; McAvay et al., 2006). Elderly intensive care patients with incident delirium have higher 6-month mortality rates than patients who never develop delirium (Kakuma et al., 2003). Elderly delirious patients also have a higher rate of death in the months following discharge (McAvay et al., 2006; Pitkala et al., 2008).

Delirium is associated with increased cognitive and functional decline after hospital discharge (Siddiqi et al., 2006). A common misperception is that delirium is completely reversible when its underlying cause(s) is(are) treated; however, several investigators have demonstrated that a number of delirious older adults never return to their baseline cognitive state, particularly in the presence of an already existing dementia (Lin et al., 2004; Thomason & Ely, 2004). Delirium also negatively affects functional outcomes in older adults admitted to long-term care facilities after acute care

hospitalization and the longer the episode of delirium, the worse the functional outcome (Inouye, 2006; Zakriya, Sieber, Christmas, Wenz, & Franckowiak, 2004).

The consequences of delirium include not only worsening cognitive and functional outcomes, but also lengthier hospital stays and the need for increased services after hospital discharge (van Zyl & Seitz, 2006). Considerable other costs accrue after hospital discharge because of the increased need for institutionalization, rehabilitation, and home care (Kiely, Jones, Bergmann, & Marcantonio, 2007).

Delirium and its adverse effects complicates the hospitalization of many older adults (Inouye, 2006) and, in 2006, accounted for 38% of all hospital days in adults 65 years of age and older (DeFrances, Lucas, Buie, & Golosinskiy, 2008). Increased hospital length of stay is associated with delirium (Milbrandt et al., 2004) and healthcare costs are 31% higher for older adults who were delirious during hospitalization (Leslie, Marcantonio, Zhang, Leo-Summers, & Inouye, 2008).

In the intensive care unit (ICU), where the incidence of delirium can be as high as 82% (Milbrandt et al., 2004), even one episode of delirium has been associated with up to 39% higher costs (Milbrandt et al., 2004). Delirium-related increases in ICU costs have been projected to range between \$6.5 and \$20.4 billion annually (Leslie et al., 2008).

Delirium in the hospitalized elder is of significant concern for additional reasons. Health-related quality of life measures show greater declines in elderly surgical patients (Pitkala et al., 2008) and in elderly medical patients (Breitbart, Gibson, & Tremblay, 2002) who were delirious during their hospitalization.

Delirium can cause significant psychological distress for patients (Duppils & Wikblad, 2007; Roberts, Rickard, Raibhandari, & Reynolds, 2006). A growing body of research suggests that many of those who experience delirium not only recall the delirious episode, but recall it as a distressing event (Andersson, Hallberg, Norberg, & Edberg, 2002; Lof, Berggren, & Ahlstrom, 2006; Roberts et al., 2007). After resolution of the delirious episode, many patients report feeling shame and guilt, humiliation and fear of recurrence (Russell & Kahn, 2007). Many of these negative feelings persist after discharge from the acute care environment (Roberts et al., 2007).

Much of the research investigating delirium recall in hospitalized older adults acknowledges that family members are affected by witnessing delirium episodes and find them to be highly distressing events. The uncharacteristic behavior, whether it is the delirious family member acting aggressively or anxiously, being abusive, or lying lethargically in the hospital bed, is frightening and causes great distress for family members (Burns et al., 2004; Moraga & Rodriguez-Pascual, 2007).

Delirium carries a personal, familial and societal burden that will only increase in magnitude as the population ages. A better understanding of the underlying processes in delirium would assist in the prediction, screening and early intervention for hospitalized older adults. Identification of hospitalized elders at risk for delirium may improve diagnosis and treatment and prevent morbidity and mortality associated with this complex disorder.

Background

Delirium

Delirium is an acute, fluctuating disorder of attention and cognition and may be associated with disturbance of mood. It is a transient, usually reversible, cerebral dysfunction, characterized by confusion and altered mental status. There is a reduced ability to focus or remain attentive to the surrounding environment. Delirium is a syndrome that has been associated with a variety of predisposing factors (e.g., age, dementia) and precipitating factors (e.g., infection, hypoxia) (BaHammam, 2006; Inouye et al., 2007; Meagher, 2001c). Disruption of sleep superimposed on acute disease may precipitate or worsen symptoms of delirium (BaHammam, 2006; Balasundaram & Holmes, 2007).

The prevalence of delirium has been reported to range from 18% – 55% among hospitalized elderly (Fick, Agostini, & Inouye, 2002; Roche, 2003; Siddiqi & House, 2006). An additional 10% – 50% of older adults develop delirium after admission to the hospital (Bergeron, Skrobik, & Dubois, 2002; McNicoll, Pisani, Ely, Gifford, & Inouye, 2005). Delirium has been diagnosed in 41% – 87% of patients admitted to the ICU (Bruce, Ritchie, Blizard, Lai, & Raven, 2007). The incidence of postoperative delirium ranges from 5% – 65% (Lepouse, Lautner, Liu, Gomis, & Leon, 2006; Marcantonio et al., 2003) .

Stress Response

A sizeable body of literature exists describing multiple etiologies for delirium; yet, current understanding of the pathogenesis of delirium is incomplete. Several authors have characterized delirium as a stress response involving the hypothalamic-pituitary-adrenal (HPA) axis, a key element of the neuroendocrine system, and mediated by high levels of circulating glucocorticoids or an increased vulnerability to their effects – or both (Marcantonio et al., 2006b; Olsson, 1999). Hypothalamic-pituitary-adrenal axis overactivity has been observed in those with delirium (Robertsson et al., 2001) and actually may precede episodes of delirium (Warrington & Bostwick, 2006). Patients with Cushing’s syndrome and those treated with large doses of corticosteroids are at risk for delirium, as are those with elevated serum cortisol levels (Ferro, Caeiro, & Verdelho, 2002; Robertsson et al., 2001).

However, researchers have yet to elucidate fully the possible mechanisms of delirium in the elderly. For instance, some researchers believe an age-related loss of cholinergic reserve may be one of the reasons why delirium is more common in the older adult (Heffelfinger & Newcomer, 2001; Hshieh, Fong, Marcantonio, & Inouye, 2008; Olsson, 1999). In addition, many older adults have an impaired HPA axis regulation, leading to high levels of circulating glucocorticoids (O’Keefe & Lavan, 1999) and this impaired regulation of the HPA axis may put older adults at increased risk of developing delirium during an acute illness (Trzepacz, 2000). Furthermore, it has been suggested that the age-related changes in neurotransmission, hormonal regulation, and immune response are all implicated in the differential risk for delirium faced by hospitalized elderly

(Schulkin, 2003a). The complexity of these pathophysiological mechanisms, which includes the involvement of several regulatory systems, supports the idea that the theory of allostasis could be a valuable theoretical framework identifying hospitalized elders at risk for delirium.

Allostasis

The theory of allostasis provides a different understanding of the stress response. Allostasis is a continuous process of physiological adaptation that the body undergoes in the face of potentially stressful challenges (Schulkin, 2003a). The theory of allostasis departs from that of homeostasis and emphasizes that parameters of physiological regulation do not remain constant (they vary widely), and that, rather than a sign of dysfunction, this is an indication of healthy functioning (Clark, Bond, & Hecker, 2007).

Allostatic Load

Allostasis represents an integrated response of multiple interacting physiological systems, such as, but not confined to, the HPA axis and the autonomic nervous system. The theory of allostasis describes regulatory systems for which there is a vulnerability to overload and dysfunction. This state of dysfunction is described as allostatic load (AL) and reflects the cumulative negative effects of adaptation to environmental stressors and psychosocial challenges, all superimposed on an individual's genetic predisposition, development, and learned behavioral or lifestyle factors, including smoking, diet, and physical activity (McEwen & Lasley, 2003; McEwen & Seeman, 1999).

Allostatic load is an aggregate result of the activation of several physiological systems responding to acute and chronic stressors (Hart, Birkas, Lachmann, & Saunders,

2002). These stressors have been conceptualized as primary (i.e. acute) stress mediators and secondary (i.e. chronic) stress outcomes (McEwen, 2007; McEwen & Seeman, 1999). The original operationalization of AL included ten parameters, four primary mediators and six secondary outcomes (McEwen & Wingfield, 2003; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997).

The four primary mediators were cortisol, norepinephrine, epinephrine and dehydroepiandrosterone sulfate (DHEAS) and the six secondary outcomes were systolic and diastolic blood pressure (BP), waist-to-hip ratio (WHR), glycosylated hemoglobin (HgbA_{1c}), high-density lipoprotein (HDL) and the total cholesterol/high-density lipoprotein (TC/HDL) ratio. These 10 parameters have been used either unchanged or with minor variation in the majority of AL studies.

While it has been suggested that an older adult's baseline vulnerability (e.g., sensory deficit), combined with a precipitating risk factor (e.g., hospitalization), contributes to an increased risk for developing delirium (Inouye, Viscoli, Horwitz, Hurst, & Tinetti, 1993; Inouye et al., 2007), it remains unclear why some hospitalized older adults develop delirium and others do not (Karlman, Singer, & Seeman, 2006b). Investigating the proposed relationships between AL and delirium in the hospitalized older adult may increase our understanding of the mechanisms of delirium.

While investigators have not studied the relationship between AL and delirium, previous investigations of AL and its relationship to other health outcomes have provided compelling results that suggest elucidating the relationship between allostasis and delirium may be a fruitful avenue of discovery for understanding the pathophysiological

mechanisms of delirium. Higher AL has been associated with increased mortality (Seeman, McEwen et al., 2001), declines in cognitive and physical functioning (Karlamañgla, Singer, McEwen, Rowe, & Seeman, 2002; McEwen & Lasley, 2003) and frailty among older woman (Szanton, Allen, Seplaki, Bandeen-Roche, & Fried, 2009). Increased AL has been associated with a composite measure of cardiovascular disease events, such as myocardial infarction, hypertension, stroke, and diabetes mellitus (Karlamañgla, et al.), as well as heart disease and periodontal health (Sabbah, Watt, Sheiham, & Tsakos, 2008). Furthermore, AL has been related to mental health disorders, such as depression and anxiety (Goertzel et al., 2006), and chronic fatigue syndrome (Adamis, Treloar, Darwiche et al., 2007; Goertzel et al., 2006; Maloney et al., 2006). Finally, AL has been associated with lower socioeconomic status (Evans, Kim, Ting, Teshler, & Shannis, 2007; Merkin et al., 2009; Sabbah et al., 2008), homelessness (Worthman & Panter-Brick, 2008), caring for a spouse with dementia (Clark, Bond, & Hecker, 2007), and racial background (Geronimus, Hicken, Keene, & Bound, 2006).

Theoretical Framework

A novel approach to the study of the mechanisms of delirium in the hospitalized older adult is through incorporating the theory of AL. A theory driven framework of the underlying processes in delirium would assist in the prediction, screening and early intervention for hospitalized older adults. Identification of hospitalized elders at risk for delirium may improve diagnosis and treatment and prevent the morbidity and mortality associated with this complex disorder.

Model of Allostatic Load & Delirium in Hospitalized Elderly

Development of the theoretical model, Allostatic Load & Delirium in Hospitalized Elderly (ALDHE) is based on empirical investigations in delirium and theories of AL, stress and gerontology (Figure 1). The ALDHE model provides a new theoretical framework for understanding delirium by considering the effect of AL and aging on the development of delirium.

The multi-factorial etiology of delirium is acknowledged in the ALDHE model by incorporating predisposing (e.g., age, cognitive dysfunction) and precipitating (e.g., infection, hypoxia) delirium risk factors as chronic or acute stressors. Also included as chronic or acute stressors are characteristics of the individual older adult (e.g., psychosocial development, learned behavioral or lifestyle factors) and their hospitalization experience (e.g., sleep deprivation, immobilization).

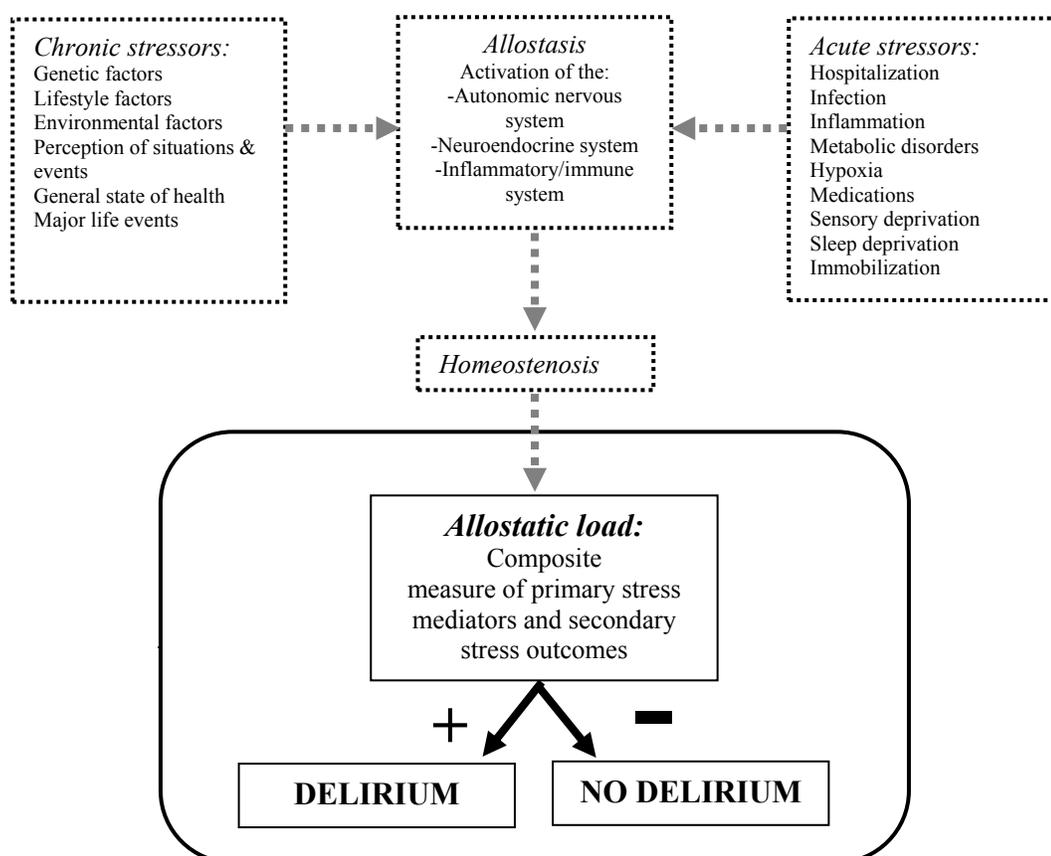
In the ALDHE model, chronic and acute stressors prompt an allostatic response. The allostatic response is a multiple regulatory systems response, including the autonomic, neuroendocrine and inflammatory/immune systems. While the activation of these physiological systems is necessary and adaptive, recurrent, exaggerated, or continual allostatic responses harm the regulatory systems themselves and may lead to tissue and cellular dysfunction and/or damage. In the ALDHE model, this process is moderated by *homeostenosis*, age-related, heterogeneous changes in physiology and functional capacity and a reduced capacity to accommodate change (Resnick, 2001).

According to the ALDHE model, AL should be viewed as a highly individualized process, reflective of an individual's exposure to acute and chronic stressors. It is

important to recognize that the development of AL is not solely an acute process; AL accumulates, in a chronic fashion, over time (Crimmins, Johnston, Hayward, & Seeman, 2003; Stewart, 2006) and it is hypothesized that hospitalization may increase AL further. The continued burden of AL leads ultimately to pathology (McEwen, 2003) and may lead

Figure 1

Model of Allostatic Load & Delirium in Hospitalized Elderly



to delirium. This model demonstrates the complexity of delirium and the vulnerability of hospitalized elders.

This dissertation investigated the relationship between AL and delirium. A worthwhile extension of this work would be to validate the full ALDHE model in future studies.

Overview and Purpose of the Study

The purpose of this research was to investigate the relationship of AL, a composite measure of primary (i.e. acute) stress mediators and secondary (i.e. chronic) stress outcomes, and delirium in the hospitalized older adult. The original operationalization of AL developed by Seeman and colleagues (1997a), which summarizes levels of physiologic activity across a range of regulatory systems (McEwen, 2007b; Singer, Ryff, & Seeman, 2004), was used in this study. This descriptive study examined the ability of AL to predict delirium in hospitalized older adults.

Specific Aims

Aim 1: Determine if AL predicts delirium in hospitalized elders.

Research Question #1: Does the composite value of AL predict delirium in hospitalized elders?

Aim 2: Determine if specific subsets of components that comprise AL predict delirium in hospitalized elders.

Research Question #2a: Does the composite value of the subset of AL components considered primary mediators, urinary cortisol, norepinephrine, and epinephrine and serum dihydroepiandrosterone sulfate (DHEAS), predict delirium in hospitalized elders?

Research Question #2b: Does the composite value of the subset of AL components considered secondary outcomes, systolic and diastolic blood pressure (BP), waist-to-hip ratio (WHR), serum high-density lipoprotein (HDL) and glycosylated hemoglobin (HgbA_{1c}), and the total cholesterol/high-density lipoprotein (TC/HDL) ratio predict delirium in hospitalized elders?”

Definitions

Allostasis

Allostasis is a continuous process of adaptation via physiological or behavioral changes that an individual undergoes in the face of potentially stressful challenges, or in anticipation of potentially stressful challenges, to achieve stability. The regulatory activity of allostasis does not contain specific physiological set points as in homeostasis, rather it provides behavioral and physiological responses in order to anticipate and respond effectively to stressors (Sterling, 2004). Alterations in the HPA axis, the autonomic nervous system, proinflammatory cytokines and/or a number of other hormones and/or systems are responsible for this complex regulatory activity (McEwen, 2007).

Allostatic Load

Allostatic load is the physiological cost of chronic or repetitive exposure to stress. Four conditions that lead to AL are: (1) repeated frequency of stress responses to multiple novel stressors; (2) failure to habituate to repeated stressors of the same kind; (3) failure to turn off each stress response in a timely manner; and (4) inadequate response that leads to compensatory hyperactivity of other mediators (McEwen & Lasley, 2003b).

If the stress response continues, it may lead to a down-regulation of receptors and subsequent tissue damage. AL can be operationalized as a composite index of indicators of cumulative strain on multiple organs and tissues that accumulates, leading to tissue ‘wear and tear’ and is associated with acute and chronic changes in physiologic activity in response to stress (McEwen, 2007).

Delirium

Delirium is a neuropsychiatric syndrome that results from disturbances in central nervous system functioning, encompassing a broad spectrum of psychological, physiological, and behavioral manifestations and characterized by a rapid onset of disordered cognitive function, disturbance of consciousness, and altered psychomotor behavior (Flacker & Lipsitz, 1999a; Gunther, Morandi, & Ely, 2008). There are three variants of delirium: (1) hyperactive delirium, with increased psychomotor activity, and increased responsiveness to the environment; (2) hypoactive delirium, with reduced psychomotor activity and a general picture of withdrawal from the environment; and (3) mixed, which involves behavior that fluctuates between hyperactive and hypoactive delirium (Camus, Gonthier, Dubos, Schwed, & Simeone, 2000).

Homeostenosis

Homeostenosis is a progressive reduction in an organism’s capacity to maintain homeostasis as it ages; it is an age-related restriction in an organism’s physiological reserves, impairing the ability to compensate for physiologic challenges (Resnick, 2000). The loss of functional reserve seen in homeostenosis occurs at different rates in different people and even at different rates within the same person (Resnick, 2001).

Primary Mediators

Primary mediators are physiological agents, such as hormones, neurotransmitters and catecholamines that are released in response to psychological and/or environmental challenges (McEwen, 2000). Primary mediators include, but are not limited to, cortisol, norepinephrine, epinephrine and DHEAS. These primary mediators have widespread influences and are powerful in determining a variety of secondary and tertiary outcomes (McEwen, 2004).

Secondary Outcomes

Secondary outcomes reflect the cumulative impact of primary mediators over time and their effects in a tissue or organ (McEwen & Wingfield, 2003). These outcomes are related to chronic exposure and subsequent abnormal metabolism (McEwen & Seeman, 1999). The first set of secondary outcomes studied were WHR and HgbA_{1c}, reflecting the effects of chronic, sustained elevations in glucose and the development of insulin resistance because of chronic elevations in cortisol and increased sympathetic nervous system activity; systolic and diastolic BP elevation reflecting HPA axis activation and elevated sympathetic nervous system activity; and HDL and the TC/HDL ratio, reflecting elevated glucocorticoid activity and the chronic activation of primary mediators (McEwen & Wingfield, 2003; Seeman, McEwen et al., 2001; Seeman, Singer et al., 1997).

Stress

Stress is a series of physiological and psychological reactions enabling an individual to cope with and adapt to noxious or aversive stimuli (Tsigos & Chrousos,

2002). These reactions include interactions between an individual and the environment, particularly if new and/or challenging situations lead the individual to perceive a discrepancy (real or perceived) between demands of the situation and the individual's physiological or psychological resources (Clark et al., 2007).

Summary

The study of delirium in the hospitalized older adult is of growing significance. There is mounting evidence that delirium leads to a number of poor outcomes; yet, the pathogenesis of delirium remains unclear, and several different hypotheses compete for attention to describe the mechanism of delirium in the hospitalized older adult.

The development of the ALDHE model provides a new theoretical viewpoint for the study of delirium in the hospitalized elder. Developing a theory driven framework of the underlying processes in delirium will assist in the prediction, screening and early intervention of at-risk hospitalized elders, improving diagnosis and treatment, and preventing the morbidity and mortality associated with this complex disorder.

CHAPTER II: BACKGROUND & LITERATURE REVIEW

Introduction

Delirium is a complex clinical syndrome that has held the interest of clinicians and researchers for decades. While a large body of literature exists to describe a growing list of risk factors for delirium in the hospitalized elder and several risk prediction models have been developed to aid the clinician in identifying those older adults most at risk for delirium during hospitalization, the body of research on the pathophysiological processes of delirium is less clearly defined.

The purpose of this research was to investigate the relationship of AL, a composite measure of chronic and acute stress, and delirium in the hospitalized older adult. Earlier research characterizing delirium as a stress response (Engel & Romano, 1959/2004; Olsson, 1999; White, 2002) made use of stress theory, specifically the theory of AL, a fruitful avenue of exploration. The Allostatic Load & Delirium in Hospitalized Elderly (ALDHE) model provides a new theoretical framework for understanding delirium and incorporates factors inherent in the individual older adult and factors inherent in the hospitalization experience.

This chapter will provide further detail on the theories incorporated in the ALDHE model developed for this research, namely, delirium etiology, stress theory and stress physiology, allostasis and AL, aging and the effect of aging on allostasis.

Delirium

History

Scientists have found descriptions of delirium in medical writings from over the past two centuries. Hippocrates used the word *phrenitis* to describe a transient disorder characterized by cognitive and behavioral disturbances, insomnia, restlessness, and agitation (as cited in Adamis, Treloar, Martin, & Macdonald, 2007). *Lethargus*, on the contrary, was described as a condition producing symptoms such as listlessness, sleepiness, inertia, memory impairment, and dulling of the senses. The term *delirium* was first used by Celsius, a Roman physician from the first century AD and derives from *de lira* (off the path) (de Rooij, Schuurmans, van der Mast, & Levi, 2005). Celsius used delirium to describe a state characterized by delusions and perceptual disturbances in association with fever.

The nineteenth century saw the introduction of a number of important concepts. The classic description of a *clouding of consciousness* was used to describe a condition somewhere between wakefulness and coma, and confusion became a synonym for delirium (Adamis, Treloar, Martin et al., 2007). During this same period, physicians were attempting to distinguish delirium caused by alcohol withdrawal as a separate condition. Senile delirium was described as a syndrome separate from dementia that could be reversed if the underlying cause was treated (Adamis, Treloar, Martin et al.).

By the early twentieth century, delirium was characterized as a transient disorder of cognitive function, with many of the same features that are used in the diagnosis today (Adamis, Treloar, Martin et al., 2007). The development of the *Diagnostic and Statistical*

Manual of Mental Disorders (DSM) by the American Psychiatric Association (APA) during the latter part of the twentieth century was an attempt to define delirium more rigorously (along with all mental disturbances) (Granberg-Axell, Malmros, Bergbom, & Lundberg, 2002; Pandharipande, Jackson, & Ely, 2005; Roberts, 2004).

A variety of terms were used to describe the cluster of symptoms we recognize as delirium: acute confusion, acute confusional state, organic brain syndrome, acute brain failure, acute brain syndrome, cerebral insufficiency, metabolic encephalopathy, exogenous psychosis, ICU syndrome or psychosis, toxic psychosis, toxic delirium, postcardiotomy delirium, sundown syndrome, and reversible dementia (Cole, Dendukuri, McCusker, & Han, 2003; Granberg-Axell, Bergbom, & Lundberg, 2001; Meagher, 2001; Roberts, 2004). The complexity of the delirium syndrome itself may explain the lack of consistent and precise terminology and the challenges with terminology may account, in part, for why delirium continues to be under-recognized, under- or misdiagnosed, and undertreated.

Definition

Delirium is a neuropsychiatric syndrome that results from disturbances in central nervous system functioning (Schuurmans, Duursma, & Shortridge-Baggett, 2001).

Delirium encompasses a broad spectrum of psychological, physiological and behavioral manifestations (Inouye et al., 2006), characterized by a rapid onset of disordered cognitive function, disturbance of consciousness and altered psychomotor behavior, oftentimes accompanied by adverse physiologic manifestations and autonomic nervous system instability (Clary & Krishnan, 2001; Lindsay, 1999).

Diagnostic Criteria

Delirium is defined by a set of criteria set forth in the DSM. In the first and second editions of the DSM, vague and nonspecific terms, such as organic brain syndrome and acute brain disorders, described the symptoms of such a cognitive disorder (Clary & Krishnan, 2001; Cook, 2004; Lindsay, 1999). It was not until the third edition (DSM-III; APA, 1980) that criteria that are more specific were put into place to define organic mental disorders, such as delirium.

Using consistent terminology and explicit diagnostic criteria for the first time, the DSM-III (APA, 1980) defined delirium as a mental disorder (with a recognized synonym of acute confusional state), characterized by clouding of consciousness with reduced capacity to shift, focus, or sustain attention, accompanied by disturbances in orientation, memory, perception, speech, sleep-wake cycle, and psychomotor activity (Cook, 2004). The DSM-III also distinguished other types of organic mental disorders, such as dementia, from delirium (Laurila, Pitkala, Strandberg, & Tilvis, 2004).

The DSM-III underwent major modifications (DSM-III-R; APA, 1987) and reduced attentiveness and disorganized thinking became the emphasis of the delirium diagnosis, rather than clouding of consciousness (Cole, Dendukuri et al., 2003; Lipowski, 1991). The operationalization of diagnostic criteria in the DSM-III-R facilitated clinical detection of delirium, delirium research and quickly became the ‘gold standard’ diagnostic criteria for delirium (Cole, Dendukuri et al., 2003).

In the initial version of the DSM-IV (APA, 1994) and in the current version, DSM-IV-text revised (DSM-IV-TR; APA, 2000), specific symptoms were deleted and the focus

was placed on the attentional and cognitive deficits seen in delirium (Table 1; Cole, 2004). Associated features described in the DSM-IV-TR include sleep-wake cycle disturbances and altered psychomotor behavior, both common in delirium (Cole, Dendukuri et al., 2003). With the exception of some limited validation testing on the DSM-IV criteria, the diagnostic criteria for delirium are based on consensus of expert opinion and clinical experience without benefit of more systematic scientific study (Cole, Dendukuri et al., 2003; Laurila et al., 2004; Tucker, 2005). In comparison studies of earlier DSM versions, the DSM-IV found more cases of delirium, especially among acutely ill, hospitalized elderly (Laurila et al., 2004) and the DSM-IV criteria were found to be the most inclusive criteria for hospitalized elderly with or without dementia (Cole, Dendukuri et al., 2003). Conversely, Meagher and Trzepacz have remarked that the

Table 1

DSM IV-TR Diagnostic Criteria for Delirium

-
- A. Disturbance of consciousness with a reduced clarity of awareness of the environment with reduced ability to focus, sustain, or shift attention
 - B. Change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
 - C. Develops over a short period of time (usually hours to days) and tends to fluctuate over the course of the day
 - D. Evidence that the disturbance is caused by direct physiological consequence of a medical condition *OR* substance intoxication *OR* substance withdrawal *OR* medication side effect or toxin exposure *OR* multiple etiologies
-

Note: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). 4th ed. Washington, DC: American Psychiatric Association; 2000.

DSM-IV describes a “circularity in delirium-dementia differentiation,” (2007, p. 468) where delirium is the default diagnosis if the cognitive deficits are not accounted for by dementia and dementia is the suggested diagnosis when the cognitive changes do not occur as part of a delirious episode. Furthermore, Meagher and Trzepacz (2007) comment that the DSM-IV does not recognize subsyndromal delirium (SSD), a more recently recognized condition in which one or more symptoms of delirium are present, but they do not meet the DSM criteria for delirium. Meagher and Trzepacz (2007) call for any subsequent editions of the DSM to provide more clarity in the differential diagnosis of delirium and to highlight those symptoms possibly related to SSD.

Clinical Features

Alterations in consciousness involving both cognition and arousal are characteristic of delirium. Reduced levels of awareness, impaired attention span, fluctuating levels of alertness, impaired orientation and memory, disorganized thinking, and distorted perceptions are clinical features of delirium (Bhat & Rockwood, 2007; Foreman, Wakefield, Culp, & Milisen, 2001). Distractibility and disturbed sleep-wake cycles are key features of delirium. The clinical features of delirium develop abruptly over hours to days and may fluctuate diurnally, often worsening at night (Bhat & Rockwood, 2007). Depending on which symptoms are apparent, delirium may be mistaken for a variety of disorders including dementia, mood disorder and/or a functional psychosis (Meagher, 2001).

Delirium sub-types. The literature contains descriptions of three subtypes of delirium: hyperactive/ hyperalert, hypoactive/hypoalert, and mixed (Camus et al., 2000; Cole, 2004; Lipowski, 1991; Meagher et al., 2008). In order to define these different subtypes of delirium, some studies have focused on differences in psychomotor behavior (Kiely et al., 2007; Leonard et al., 2007; Meagher et al., 2008; Meagher & Trzepacz, 2000), while one study investigated differences in arousal disturbances, i.e. based on level of attention and alertness (Ross, Peyser, Shapiro, & Folstein, 1991). Increased psychomotor activity, sympathetic nervous system overactivity, increased alertness or hypervigilance, psychosis, and labile mood all characterize hyperactive delirium (Stagno, Gibson, & Breitbart, 2004).

In contrast, decreased psychomotor activity, withdrawal, apathy, lethargy, somnolence, and inattention characterize hypoactive delirium (Farrell & Dosa, 2007). Psychotic features, such as delusions and perceptual disturbances, may be present in hypoactive delirium (Farrell & Dosa, 2007).

In the mixed delirium subtype, symptoms associated with hyperactive and hypoactive delirium alternate in the same individual (Cole, 2004; Pandharipande et al., 2005). A small proportion of those who become delirious have no psychomotor disturbances (McCusker, Cole, Dendukuri, Han, & Belzile, 2003).

Delirium subtypes may have different etiologies and pathophysiological foundations (Camus et al., 2000; de Rooij et al., 2005), respond differently to treatment (de Rooij et al., 2005) and may be associated with different outcomes, including mortality (Bellelli & Trabucchi, 2006; Kiely et al., 2007; Marcantonio et al., 2003).

Delirium onset. The majority of delirium cases occur within 48 – 72 hours of a medical hospital admission (Ely, Margolin et al., 2001; Kalisvaart et al., 2006; Korevaar, van Munster, & de Rooij, 2005; Sheng, Shen, Cordato, Zhang, & Chan, 2006). There are similar findings in the surgical population, with the majority of postoperative delirium occurring by post-operative day three (de Jonghe et al., 2007; Duppils & Wikblad, 2000; Lundstrom et al., 2007). In the ICU setting, the average onset of delirium is two to three days (Ely, Siegel, & Inouye, 2001; McNicoll et al., 2003; Pisani, Murphy, Van Ness, Araujo, & Inouye, 2007).

Delirium duration. Researchers and clinicians have long considered delirium a transient and reversible condition that, depending on the underlying cause, most often resolves quickly. However, there is some evidence that delirium may be more persistent than previously thought (Adamis, Treloar, Martin, & Macdonald, 2006; Cole & McCusker, 2002; Kiely et al., 2007). Furthermore, it appears that there is no single pattern of delirium. Some may experience a single day of delirium, while others have delirium on multiple days. For those with delirium on multiple days, it appears that there is no single daily pattern or grouping (Foreman et al., 2001; Marcantonio, Ta, Duthie, & Resnick, 2002).

The literature reports wide variation in the duration of delirium in the hospitalized older adult. While some authors have reported that hospitalized elders have resolution of their delirium within 24 – 48 hours (Duppils & Wikblad, 2000; Pandharipande et al., 2005), several other investigators have described a duration of delirium lasting 7-14 days

(Adamis et al., 2006; Ely, Siegel et al., 2001; Kalisvaart et al., 2006; Lundstrom et al., 2005; Rockwood, 2003).

Delirium may persist for weeks to months after hospital discharge. Reports of continued delirium at discharge range from 5% to 39% in older adults (Marcantonio, Flacker, Michaels, & Resnick, 2000; Marcantonio et al., 2005; Marcantonio et al., 2003; McCusker, Cole, Abrahamowicz et al., 2001) and several authors have reported a persistence of delirium symptoms months after discharge (Marcantonio et al., 2000; McCusker et al., 2003; Rockwood, Goodman, Flynn, & Stolee, 1996).

Subsyndromal delirium. Some hospitalized older adults exhibit two or more of the DSM criteria for delirium (e.g., confusion, inattention), but not all. (Cole, McCusker, Dendukuri, & Han, 2003; Ouimet, Riker et al., 2007). These symptoms may precede or follow an episode of actual delirium or may never progress to delirium (Cole, McCusker et al., 2003).

The clinical profile associated with SSD is similar to that seen with DSM-defined delirium, including older age, cognitive dysfunction, and more comorbidities (McCusker, Cole, Abrahamowicz, Primeau, & Belzile, 2002; Ouimet, Riker et al., 2007). Poorer outcomes are reported for those with SSD, including longer hospital stays, increased mortality and lower cognitive and functional status after hospital discharge (Cole, McCusker et al., 2003; Dosa, Intrator, McNicoll, Cang, & Teno, 2007; Marcantonio et al., 2002a; Marcantonio et al., 2005; Ouimet, Riker et al., 2007).

Severity of delirium. Twenty-two to 51% of hospitalized older adults who develop delirium have an episode that is classified as severe (Kiely et al., 2006; Marcantonio et al., 2002a). Several rating scales have been developed to assess delirium severity (Marcantonio et al., 2002a; Voyer, McCusker, Cole, & Khomenko, 2006). When compared to older adults with mild delirium, older adults with severe delirium had worse outcomes, including functional decline, nursing home placement, and increased mortality (Kelly et al., 2001; Marcantonio et al., 2002; McCusker et al., 2002). Cognitive impairment or dementia has been reported as a risk factor for more severe delirium symptoms (Marcantonio et al., 2002; McCusker et al., 2002).

Differential Diagnosis for Delirium

Delirium is a clinical diagnosis, yet because of its fluctuating nature and heterogeneity in presentation, recognition can be difficult. The medical differential diagnosis of delirium is extensive (Table 2) and in order to treat delirium, a large number of potential etiologies for delirium must be differentiated into usable diagnostic categories and then investigated (Clary & Krishnan, 2001). Differentiation between delirium and dementia may be difficult, as features of the two disorders sometimes overlap (see Table 3; Milisen, Braes, Fick, & Foreman, 2006).

Delirium typically has a rapid onset, while dementia develops slowly (Inouye, 2001). A hallmark sign of delirium is an inability to attend (i.e., pay attention) to the surrounding environment, although attention may be disturbed in the later stages of dementia as well (Cole & McCusker, 2002). While it is common to observe cognitive fluctuations in delirium, in dementia these are far less common and, for the most part, do

Table 2

Potential etiologies for delirium

<i>Central Nervous System</i>	<i>Metabolic Disorder</i>	<i>Cardiopulmonary</i>	<i>Systemic illness</i>
Head trauma	Renal failure	Myocardial infarction	Substance intoxication
Seizures	Hepatic failure	Congestive heart failure	or withdrawal
Postictal state	Anemia	Cardiac arrhythmia	Infection
Vascular disease	Hypoxia	Shock	Neoplasm
Degenerative disease	Hypoglycemia	Respiratory failure	Severe trauma
	Thiamine deficiency		Sensory deprivation
	Endocrinopathy		Temperature
	Fluid or electrolyte		dysregulation
	Imbalance		Postoperative state
	Acid-base imbalance		

Note: Adapted from American Psychiatric Association (2002). Practice Guidelines for the Treatment of Psychiatric Disorders: Compendium 2002. Washington: American Psychiatric Association

not fluctuate (Cole & McCusker). Sleep is usually disturbed in delirium but not in dementia (Cole & McCusker).

Finally, it is important to differentiate between normal cognitive changes and delirium, depression or dementia. Cognitive changes can be attributed to an age-associated cognitive decline or it can be a consequence of delirium, depression, and/or dementia (Insel & Badger, 2002).

Prevalence and Incidence of Delirium

Almost all of the occurrence estimates of delirium are derived from hospitalized patients; however, there are some data available from population-based studies looking at delirium occurrence in other settings. In community-dwelling older adults aged 55 years and over, delirium prevalence ranges from <0.5% (Andrew, Freter, & Rockwood, 2006)

Table 3

Psychiatric differential diagnosis for delirium

	Delirium	Dementia	Depression	Psychosis
<i>Onset</i>	Acute	Insidious	Variable	Slow
<i>Duration</i>	Short	Lengthy	Variable, recurrent	Variable, recurrent
<i>Course</i>	Fluctuating	Progressive	Variable	Variable
<i>Conscious</i>	Clouded	Clear until late phases	Generally unimpaired	Unimpaired
<i>Attention</i>	Poor	Preserved in early stages	Poor	Poor
<i>Cognition</i>	Impaired	Impaired	Variable	Normal
<i>Hallucinations</i>	Common (visual)	Infrequent	Rare	Common (auditory)
<i>Delusions</i>	Unstructured	Uncommon	Paranoid (occasionally)	Maintained
<i>Orientation</i>	Poor	Poor	Usually good	Good
<i>Short-term memory</i>	Reduced	Reduced	Normal	Normal
<i>Speech</i>	Incoherent	Dysphasia	Normal	Normal
<i>Psychomotor behavior</i>	Lethargic, agitated or mixed	Normal	Variable	Variable
<i>Involuntary movements</i>	Present	Absent	Absent	Absent
<i>Physical illness</i>	Present	Absent	Variable	Usually absent

Note: Adapted from Burton (2005), *Psychiatry*, Walden, MA: Blackwell Publishing

to 1.1% (Folstein, Bassett, Romanoski, & Nestadt, 1991). In the oldest-old (aged 85 years and older), the prevalence for delirium varies widely, from <0.5% (Andrew et al., 2006) to 13.6% (Folstein et al.), although in both studies there were small numbers of cases in this sub-sample of the oldest-old (Folstein et al.). In another study of the oldest old, the incidence of delirium in non-demented elders was 10% during a 3-year observation period (Rahkonen et al., 2001).

In other settings, such as skilled nursing facilities and other long-term care settings, delirium prevalence ranges from 0.5 % to 39% (Andrew et al., 2006; Culp et al., 1997; Mentes, Culp, Maas, & Rantz, 1999; Streim, Oslin, Katz, & Parmelee, 1997). Another prevalence study involving frail, older adults receiving healthcare services found a much higher prevalence of delirium: 58% in nursing homes, 35% in assisted living facilities and 35% in elders living in their own homes with home care services (Andrew et al., 2006; Sandberg, Gustafson, Brannstrom, & Bucht, 1998).

Delirium is common in hospitalized older adults. In elders admitted to medical wards, the prevalence of delirium at admission ranges from 5% - 31% (Cole & McCusker, 2002; Lundstrom et al., 2005; Mussi, Ferrari, Ascari, & Salvioli, 1999; O'Keefe & Lavan, 1999) and the subsequent incidence during hospitalization ranges from 3% to 55% (Bourdel-Marchasson et al., 2004; Inouye et al., 1999; Sheng et al., 2006). Studies among elders seen in emergency departments have reported prevalence rates of 5% to 10% (Elie et al., 2000; Lewis, Miller, Morley, Nork, & Lasater, 1995; Naughton, Moran, Kadah, Heman-Ackah, & Longano, 1995).

The incidence of delirium in the ICU setting has been reported as low as 11% to 31% (Aldemir et al., 2001; Balas et al., 2007; Dubois, Bergeron, Dumont, Dial, & Skrobik, 2001; Lin et al., 2004; McNicoll et al., 2003; Ouimet, Kavanagh, Gottfried, & Skrobik, 2007) and as high as 80% (Ely, Gautam et al., 2001; Ely, Shintani et al., 2004) or greater (Ely, Gautam et al., 2001). Delirium may be especially prevalent in patients with long ICU stays or with the use of complex technology (McNicoll et al., 2003).

In a study of elders admitted to a sub-ICU, where the intensity of care was between that offered in a medical ward and that offered in an ICU, investigators detected delirium in 29.2 % of admissions. Of those with delirium, 15.5% had delirium at admission and a further 13.7% developed delirium during their time in the sub-ICU (Ranhoff et al., 2006).

In surgical patients, researchers have reported delirium in 5% - 26% of elective noncardiac surgeries (Franco, Litaker, Locala, & Bronson, 2001; Galanakis, Bickel, Gradinger, Von Gumpfenberg, & Forstl, 2001; Litaker, Locala, Franco, Bronson, & Tannous, 2001; Rudolph et al., 2007). The incidence is higher, 29% - 52.2%, in elective vascular surgery (Benoit et al., 2005; Bohner et al., 2003; Mann et al., 2000; Sasajima et al., 2000; Schneider et al., 2002). In one study of elderly patients undergoing major abdominal surgery the incidence of postoperative delirium was 60% (Ganai et al., 2007).

The incidence of delirium after cardiac surgery ranges from 8% - 50%, depending on the type of procedure performed and the population studied (Bucerius et al., 2004; Eriksson, Samuelsson, Gustafson, Aberg, & Engstrom, 2002; Kazmierski et al., 2006; Kobayashi et al., 2002; Rudolph et al., 2005; Rudolph et al., 2006; Santos, Velasco, & Fraguas, 2004; Veliz-Reissmuller, Agüero Torres, van der Linden, Lindblom, & Eriksdotter Jonhagen, 2007). Although it has been suggested that improved surgical, cardiopulmonary bypass, and anesthesia techniques have lowered the incidence of delirium after cardiac surgery (Taggart & Westaby, 2001), this has not been confirmed (Santos et al., 2004; Sockalingam et al., 2005).

A large body of literature exists that investigates delirium in the elderly hip-fracture surgery population. Higher rates of delirium have been seen in this population; however, the reason for this is not clear (Contin, Perez-Jara, Alonso-Contin, Enguix, & Ramos, 2005), prompting some authors to suggest that delirium in hip fracture patients may be a different syndrome from that observed in medically ill patients (Brauer, Morrison, Silberzweig, & Siu, 2000). Prevalence rates for delirium in elderly surgical patients with hip fracture range from 4.4% - 61% (Brauer et al., 2000; Edlund, Lundstrom, Brannstrom, Bucht, & Gustafson, 2001; Holmes & House, 2000; Kagansky et al., 2004; Morrison et al., 2003). The incidence of postoperative delirium in elderly surgical patients with hip fracture is 4% - 53.3% (Andersson et al., 2002; Bitsch, Foss, Kristensen, & Kehlet, 2004; Brauer et al., 2000; Duppils & Wikblad, 2000; Edlund et al., 2001; Galanakis et al., 2001; Kagansky et al., 2004; Marcantonio, Flacker, Wright, & Resnick, 2001; Morrison et al., 2003; Schuurmans, Deschamps, Markham, Shortridge-Baggett, & Duursma, 2003; Zakriya et al., 2004; Zakriya et al., 2002), while for those undergoing elective hip or knee surgery, the incidence rates are 3.6% - 53.3% (Andersson et al., 2002; Contin et al., 2005; Dai, Lou, Yip, & Huang, 2000; Duppils & Wikblad, 2000; Freter et al., 2005; Galanakis et al., 2001; Kudoh, Takase, Takahira, Katagai, & Takazawa, 2003; Linstedt et al., 2002).

Summary on Delirium Occurrence

The hip fracture surgery population tends to have the highest occurrence of delirium complicating their hospital stay while the medical population has the lowest rates. Other surgical populations appear to have intermediate rates of delirium. There is a

higher occurrence of delirium in elderly admitted to an ICU setting than to a general medical unit. The wide variation in delirium occurrence likely reflects differences in patient population, including potential confounders, such as physiological acuity, medical comorbidities, cognitive function and clinical setting.

Methodologically, the instruments used to screen for and diagnose delirium, as well as the use and frequency of repeated measures for assessing delirium, likely affect the reported occurrences of delirium. The potential for under-diagnosis due to inaccuracies in assessment and missing cases of delirium that present between assessment periods makes it possible for the misclassification of hospitalized elders with delirium as not having delirium. Therefore, the reported frequencies of delirium well may underestimate the true nature of this syndrome in the hospitalized elderly.

Outcomes after Delirium

Delirium has been associated with higher mortality among older adults during hospitalization (Curyto et al., 2001; Laurila, Pitkala, Strandberg, & Tilvis, 2002; McCusker et al., 2002; Pitkala, Laurila, Strandberg, & Tilvis, 2005; Villalpando-Berumen et al., 2003) and after discharge (Edelstein et al., 2004; Rahkonen et al., 2000). Delirium also has been associated with higher morbidity (Cole, 2004; Fick et al., 2002); poor recovery from surgery (Galanakis et al., 2001; Marcantonio et al., 2000), and increased hospital and ICU length of stay (Dolan et al., 2000; Ely, Shintani et al., 2004; McCusker et al., 2003; Uldall, Harris, & Lalonde, 2000). Hospitalized older adults who experience delirium are also at an increased risk of cognitive decline, functional decline, and need for institutionalization, rehabilitation, and home care (Jackson et al., 2004;

Marcantonio et al., 2003; McCusker, Cole, Dendukuri, Belzile, & Primeau, 2001; Siddiqi, Stockdale, Britton, & Holmes, 2007). Additionally, delirium causes significant psychosocial distress for patients and families (Duppils & Wikblad, 2007; Roberts et al., 2007).

The cost of delirium to the health care system is substantial. Delirium has been associated with increased nursing time per patient and higher daily hospital costs (Inouye, 1998, 2006; Milbrandt et al., 2004). Substantial additional costs accrue after hospital discharge because of the increased need for nursing home placement, rehabilitation services, physician visits, home health care and rehospitalization (Inouye, 1998). Inouye and colleagues (1999) estimated that delirium complicates hospital stays for more than 2.3 million older persons each year, involving more than 17.5 million hospital days and accounting for more than \$6.9 billion of Medicare expenditures. A recent study reported that patients with delirium have significantly higher health care costs and estimated that the national burden of delirium on the health care system ranges from \$38 billion to \$152 billion each year (Leslie et al., 2008).

Delirium Risk Factors

There are numerous risk factors associated with the development of delirium in the hospitalized older adult and, generally, clinicians accept that some patients are more vulnerable to developing delirium (Inouye, 1999; Inouye et al., 2006). Risk factors for delirium may be modifiable (e.g., alcohol and/or drug use) or non-modifiable (e.g., gender, age), they may relate to the patient and their condition (e.g., alcohol withdrawal, infection), to the setting (e.g., sleep disturbances), or to a clinical intervention (e.g.,

urinary catheterization) These risk factors may be present on admission or develop during hospitalization (Inouye, 1999).

Inouye and her colleagues (Inouye, 1993; Inouye & Charpentier, 1996) conceptualized risk factors for delirium as belonging to one of two groups: predisposing factors or precipitating factors. Predisposing factors are present at the time of hospital admission and reflect the baseline vulnerability of a patient. Precipitating factors are hospital-related factors that contribute to the development of delirium. Precipitating factors may be noxious stimuli (e.g., urinary catheterization, physical restraint use) or more subtle stressful factors (e.g., eyeglasses left out of reach, no calendar in the hospital room). An older adult with a high vulnerability may develop delirium once exposed to even a 'mild' precipitating factor, while the older adult with low vulnerability would be resistant to the development of delirium, even when exposed to the most noxious of stimuli (Inouye, 2006; Inouye et al., 1999).

Predisposing factors. As mentioned earlier, most of the literature describing the risk for delirium in the elderly is based on hospital studies. Some authors have investigated a general hospital population while others have investigated either a specific population (e.g., hip fracture surgical patients) or specific risk factors (e.g., vascular risk factors) within a general or specific population. Others have investigated the impact of a particular setting (e.g., ICU). Small sample sizes or the failure to control for important confounding variables have limited many investigations; therefore, it is difficult to generalize findings from one study to another or from one population to another.

However, there are several risk factors confirmed in multiple prospective studies that have used a multivariate approach that enabled them to identify independent risk factors.

Next to increasing *age* (Dai et al., 2000; Eden & Foreman, 1996; Kazmierski et al., 2006; Litaker et al., 2001; Marcantonio, Goldman, Orav, Cook, & Lee, 1998; Martin, Stones, Young, & Bedard, 2000; Santos & Velasco, 2005; Santos, Wahlund, Varli, Tadeu Velasco, & Eriksson Jonhagen, 2005), *preexisting cognitive decline* is probably the most confirmed risk factor for delirium (Dai et al., 2000; Edelstein et al., 2004; Galanakis et al., 2001; Iseli, Brand, Telford, & LoGiudice, 2007; Kagansky et al., 2004; Kazmierski et al., 2006; Korevaar et al., 2005; Litaker et al., 2001; Martin et al., 2000; McNicoll et al., 2003; O'Keeffe, Mulkerrin, Nayeem, Varughese, & Pillay, 2005; Pisani et al., 2007; Rahkonen et al., 2001).

Other factors that put hospitalized elders at risk for delirium include a variety of medical comorbidities, such as *high blood pressure* (Rahkonen et al., 2001; Santos et al., 2004), *nutritional deficiency* (Schuurmans et al., 2001), *dehydration* (Schneider et al., 2002; Schuurmans et al., 2001; Weber, Coverdale, & Kunik, 2004), *alcohol use* (Blondell, Powell, Dodds, Looney, & Lukan, 2004; Litaker et al., 2001), and *benzodiazepine use* (Lepouse et al., 2006; Pisani et al., 2007). Other risk factors for delirium include *male gender* (Edelstein et al., 2004; Fischer, 2001), *vision impairment* (Inouye, 1993), pre-existing *functional impairment* (Schneider et al., 2002; Weber et al., 2004), depression (Kazmierski et al., 2006), and a variety of *metabolic and electrolyte abnormalities*, such as metabolic acidosis, hypocalcemia, hyponatremia, azotemia, transaminitis, hyperamylasemia, hyperbilirubinemia (Aldemir et al., 2001; Korevaar et

al., 2005; Marcantonio et al., 2000; Meagher, 2001; Pisani et al., 2007). An increased risk for delirium also has been found in those with poor cognitive performance on neuropsychological testing (Dasgupta & Dumbrell, 2006), impaired executive function (Rudolph et al., 2006), and a prior history of delirium (Litaker et al., 2001).

Precipitating factors. Investigators have described a number of precipitating factors reported to increase the risk for delirium in the hospitalized elderly, including the use of *physical restraints* and a high number of *invasive procedures*, including *urinary catheterization* (Inouye & Charpentier, 1996; Margiotta, Bianchetti, Ranieri, & Trabucchi, 2006; Martin et al., 2000; Ranhoff et al., 2006; Schuurmans et al., 2001). *Malnutrition, infection and sleep deprivation* once hospitalized increase the risk for the development of delirium (Brown & Boyle, 2002; Martin et al., 2000; Schuurmans et al., 2001).

Environmental factors, such as *frequent location changes* (e.g., medical unit to post-anesthesia care unit to ICU), *lack of windows* in patient rooms, high levels of *ambient noise, absence of a clock or watch*, and the absence of *reading glasses* all have been described as risk factors for the development of delirium (Brown & Boyle, 2002; McCusker, Cole, Abrahamowicz et al., 2001).

The most common factor for delirium occurrence is medication usage, particularly in the hospital setting, contributing to more than one third of all cases of delirium in hospitalized elders (Alagiakrishnan & Wiens, 2004). Although the use of almost any medication may be associated with delirium, medications with anticholinergic properties have a well established mechanism for not only precipitating delirium (Han et

al., 2001; Scott, Pache, Keane, Buckle, & O'Brien, 2007), but also for increasing the severity of delirium symptoms (Han et al., 2001). Benzodiazepines are another common culprit (Martin & Haynes, 2000; Pandharipande et al., 2006). Researchers have implicated several other medication classes in inducing delirium. These include antipsychotics, tricyclic antidepressants, narcotics, anxiolytics, histamine receptor antagonists, anti-hypertensives, and anti-inflammatories (Agostini, Leo-Summers, & Inouye, 2001; Han et al., 2001; Meagher, 2001b; Pandharipande et al., 2006; Pisani et al., 2007; Rahkonen et al., 2001; Santos & Velasco, 2005; van der Mast, van den Broek, Fekkes, Peppinkhuizen, & Habbema, 2000; Voyer, McCusker, Cole, St-Jacques, & Khomenko, 2007). Dopamine, a positive inotropic agent, has been associated with delirium in the ICU (Sommer, Wise, & Kraemer, 2002; Van Rompaey, Bossaert, Shortridge-Bagett, Schuurmans, & Truijen, 2007) and even supposedly benign medications, such as beta blockers, have been found to cause delirium on occasion (Fisher, Davis, & Jeffery, 2002).

Intensive care unit delirium risk factors. Delirium is a common disorder among older patients in the ICU. Likely this is due, in part, to specific factors unique to the ICU patient, such as physiologic instability accompanying critical illness and severe sleep cycle disruptions and the use of invasive treatment and monitoring systems and higher and more frequent doses of multiple medications (Gunther et al., 2008; Pisani et al., 2007).

A recent analysis of six studies evaluating risk factors for delirium in the ICU identified multiple risk factors that proved to be significant for the development of

delirium (Van Rompaey et al., 2007). Predisposing risk factors included age, dementia, respiratory disease and alcohol abuse. Included among the 21 precipitating factors identified were Acute Physiology and Chronic Health Evaluation (APACHE) II scores, hypertension, medication (e.g. morphine), and a variety of abnormal laboratory values (e.g. hyperbilirubinemia, azotemia) (Van Rompaey et al., 2007). Other recent prospective studies have looked at delirium in the ICU and have shown that age, severity of illness, hypertension, alcohol use and sedative and analgesic use were associated with delirium (Ouimet, Kavanagh et al., 2007; Pandharipande et al., 2006; Pisani et al., 2007).

Risk factors for delirium in surgical patients. Older surgical patients are at risk for developing delirium. Preoperative risk factors for delirium in older adults undergoing elective non-cardiac surgery include age, alcoholism, pre-existing cognitive and functional impairment, multiple comorbidities, and markedly abnormal serum sodium, potassium or glucose levels (Dai et al., 2000; Marcantonio et al., 2000; Schuurmans et al., 2001; Yildizeli et al., 2005), as well as sensory impairment, depression, and preoperative psychotropic drug use (Galanakis et al., 2001; Lepouse et al., 2006).

Researchers have described various perioperative factors in the development of delirium in the older surgical patient. Low intraoperative hemoglobin values (Joosten, Lemiengre, Nelis, Verbeke, & Milisen, 2006) and intraoperative blood loss (Norkiene et al., 2007), as well as postoperative blood transfusions (Schneider et al., 2002) and low postoperative hematocrit values (Schuurmans et al., 2001; Wang, Lee, Goh, & Chon, 2004) are associated with the development of postoperative delirium. Duration of surgery (Bucorius et al., 2004; Lepouse et al., 2006) and the type of surgery (Schuurmans et al.,

2003) also are associated with postoperative delirium. Additional precipitating factors that have been identified include prolonged waiting time for surgery, lack of postoperative mobility, infection, bladder catheterization, and inadequate pain management (Edlund et al., 2001; Edlund et al., 2007; Furlaneto & Garcez-Leme, 2006; Schuurmans et al., 2003), as well as benzodiazepine use (Santos & Velasco, 2005) and sleep deprivation (Yildizeli et al., 2005). A recent review of 25 studies of preoperative risk factors associated with delirium following noncardiac surgery demonstrated that the strongest associations were seen between delirium and cognitive impairment or psychotropic drug use (Dasgupta & Dumbrell, 2006).

Atherosclerosis may predispose older surgical patients to delirium (Bucerius et al., 2004; Santos et al., 2004). The incidence of delirium after surgery for atherosclerosis, including aortic aneurysm repair, coronary artery bypass grafting and peripheral vascular bypass is approximately double that of elective orthopedic procedures (Rudolph et al., 2005). Previous studies have identified atherosclerosis burden (the presence of atherosclerotic plaque in the aorta, coronary and carotid arteries) (Rudolph et al., 2005) and vascular risk factors (age, male gender, tobacco use, hypertension, previous myocardial infarction, and prior vascular surgery) as important risk factors for delirium (Benoit et al., 2005; Dubois et al., 2001; Inouye, 2006; Marcantonio et al., 2005; Rudolph et al., 2005). In a large study of noncardiac surgery patients, those with vascular risk factors and mild impairments on cognitive testing were at double the risk for delirium compared to those with either of these risk factors alone (Rudolph et al., 2007).

Delirium Pathophysiology

Although the etiology of delirium is well studied, researchers understand far less about the pathological mechanisms that lead to the development of delirium (Maldonado, 2008). A major challenge to its study has been the heterogeneity of the delirium syndrome and the settings and populations in which it is studied.

In 1959, Engel and Romano presented the most well known theory for the pathophysiology of delirium. Based on diffuse slowing on electroencephalographs of delirious patients, they considered delirium to be a generalized dysfunction of the cerebral cortex, or syndrome of cerebral insufficiency, and theorized that a reduced oxidative metabolism in the brain was the underlying cause (Engel & Romano, 1959/2004; Ferro et al., 2002). Subsequent research suggested that delirium resulted from dysfunction in multiple regions of the brain interacting with various neurotransmitters, rather than a global cerebral dysfunction (Flacker & Lipsitz, 1999; Hshieh et al., 2008; Trzepacz, 2000; van der Mast, van den Broek, Fekkes, Peplinkhuizen, & Roest, 1996).

One of the best-documented mechanisms for delirium is cholinergic deficiency. Acetylcholine is an important central neurotransmitter in regulating arousal, consciousness, attention, and cognitive functions, either via direct stimulation of muscarinic receptors at the brainstem, basal forebrain and neocortex, or by indirect mediation of the effects of other transmitters, such as dopamine (Trzepacz, 2000). Cholinergic deficiency has been described during aging as cholinergic neurons undergo degenerative changes (Mufson, Ginsberg, Ikonomovic, & DeKosky, 2003; Schliebs & Arendt, 2006). Several investigators have postulated that decreased synthesis of cerebral

acetylcholine account for the impaired cognitive and attentional function and slowing of electroencephalographic background activity commonly seen in delirium (Lemstra, Eikelenboom, & van Gool, 2003; Trzepacz, 2000).

The first evidence for the mechanism of cholinergic deficiency came from case reports linking delirium to acute poisoning with anticholinergic drugs and demonstrating reversal of delirium with procholinergic drugs (Beaver & Gavin, 1998; Cheng, Hu, Hung, & Yang, 2002; Trzepacz, 2000). Administration of multiple medications with anticholinergic effects may create an anticholinergic burden, causing a greater risk for delirium in the older adult (Han et al., 2001; Tune & Egeli, 1999) or delirium may be due to endogenous anticholinergic activity in the absence of anticholinergic medications (Flacker & Lipsitz, 1999).

Dopaminergic excess also appears to contribute to delirium, likely due to its regulatory influence on the release of acetylcholine (Lipowski, 1991; Trzepacz, 2000). Based on the reciprocal activity between dopamine and acetylcholine (i.e. increased dopamine leads to decreased acetylcholine), a dopaminergic drug, such as levodopa can precipitate delirium and dopamine antagonists (e.g., antipsychotic agents) can effectively treat delirium (Trzepacz, 2000).

Perturbations of other neurotransmitters, such as serotonin, γ aminobutyric acid, glutamate, melatonin and histamine also may have a role in the pathophysiology of delirium (Cole, 2004; Flacker & Lipsitz, 1999; Shigeta et al., 2001; Trzepacz, 2000; van der Mast et al., 2000). These hormones may exert their influence through interactions

with the cholinergic and dopaminergic neurotransmitter pathways (Gaudreau & Gagnon, 2005; Trzepacz, 2000).

Interestingly, Engel and Romano's theory of a generalized cerebral dysfunction overshadowed earlier work from an early 20th century German psychiatrist, Karl Bonhoeffer, who questioned why seemingly unrelated etiologic causes of delirium could produce a uniform mental syndrome. Bonhoeffer theorized there was a common secondary factor, an 'autotoxin' that explained why different non-neurological diseases induced a specific neurological syndrome (as cited in Eikelenboom, Hoogendijk, Jonker, & van Tilburg, 2002). Bonhoeffer's theory becomes more intriguing if one replaces the term 'autotoxin' with cytokine.

Several investigators have concluded that cytokines, such as interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor (TNF) α , and interferon, play an important role in the pathogenesis of delirium (Cole, 2004; Eikelenboom et al., 2002; Trzepacz, 2000). Cytokines are a large, diverse group of secreted proteins and peptides that mediate and regulate a wide variety of immune and inflammatory processes (Broadhurst & Wilson, 2001; de Rooij, van Munster, Korevaar, & Levi, 2007).

Studies performed in hospitalized elderly admitted to general medical or surgical units have demonstrated that one or more cytokines were elevated more in delirious than in nondelirious patients (de Rooij et al., 2007; Kudoh et al., 2003; Visvanathan, Sundararajan, Pugach, & Zabriskie, 2003). Conversely, insulin-like growth factor-1 (IGF-1) may be neuroprotective, as hospitalized elderly with delirium had lower circulating

IGF-1 levels than did those without delirium (Adamis, Treloar, Finbarr et al., 2007; Wilson, Broadhurst, Diver, Jackson, & Mottram, 2005).

Finally, other researchers have characterized delirium as a stress response involving the HPA axis that is mediated by high levels of circulating glucocorticoids or an increased vulnerability to their effects – or both (Engel & Romano, 1959/2004; Olsson, 1999; White, 2002). Stress is a potent modulator of brain and cognitive function and affects brain function by prompting a rapid response through the sympathetic nervous system and then more slowly via the HPA axis (McEwen & Seeman, 1999). While catecholamines of the sympathetic nervous system have an immediate effect (increasing delivery of glucose and oxygen availability to the brain, thereby, enhancing cognitive function) (Korol, 2002), the HPA axis affects neuronal integrity within hours and produces changes that can last for weeks (McEwen). Excessive or protracted stimulation of the HPA axis results in elevated glucocorticoid levels that have an adverse effect on hippocampal neurons (McEwen), the amygdala and the prefrontal cortex (McEwen; VonDras, Powless, Olson, Wheeler, & Snudden, 2005).

Patients with Cushing's syndrome and those treated with large doses of corticosteroids are at risk for delirium (Flacker & Lipsitz, 1999); however, in studies examining the relationship between serum cortisol levels and delirium in general medical and surgical settings, the results have been equivocal. Several studies have found that delirium in acute stroke patients is associated with persistent elevation in plasma cortisol levels (e.g., Fassbender, Schmidt, Mossner, Daffertshofer, & Hennerici, 1994; Olsson, 1999) and another study of delirious postoperative patients demonstrated these patients

had a prolonged elevation of cortisol levels and a delay in the return of normal circadian variation of cortisol levels (McIntosh et al., 1985). However, a study of postcardiac surgery patients found no association between delirium and pre- or postoperative cortisol levels (van der Mast et al., 1996). More recently, some investigators have suggested that elders have an impaired HPA system and, as a result, a low delirium threshold (Robertsson et al., 2001).

The body of literature describing linkages between stress and delirium are compelling; yet, the conflicting results found in some studies highlight the need for further research. This current research elucidates the relationship between delirium in the hospitalized elder and stress by investigating the incidence of delirium in the hospitalized older adult and the theory of AL. In order to understand the theory of AL, it is necessary to understand the phenomenon of stress and the evolution of stress physiology.

Stress

Stress is an important phenomenon, yet use of the term is challenged by multiple definitions and by the different paradigms in which stress is considered. Stress is a complex response made more so by the simultaneous adaptive nature and potentially maladaptive consequences. Several different approaches have been used to more fully understand stress: stress as stimulus, stress as response and stress as an interactional process involving both stimulus and response.

A stimulus-based conceptualization views stress as a noxious or aversive characteristic of the environment that disturbs the individual (Schulkin, 2003b; Szabo, 1998). Stress, then, consists of those noxious or aversive exposures and if they are intense

or frequent enough, either singly or cumulatively, the individual is likely to be distressed, possibly causing physiological dysfunction and, in some cases, disease (Ursin & Eriksen, 2004).

Another approach is to view stress as a response, where noxious or aversive stimuli prompt a physiological reaction in the individual. In such a case, environmental stimuli are stressors (i.e., noxious or aversive exposures) and characteristics of the individual can moderate the stress response (Schulkin, 2003b; Ursin & Eriksen, 2004).

A third way of conceptualizing stress is to view it as an interaction between the individual and the environment. In this view, rather than seeing stress as either as stimulus or response, stress is viewed as a process of both a precipitating stimulus and an individual's reaction and ability to cope (Lazarus, DeLongis, Folkman, & Gruen, 1985; Ursin & Eriksen, 2004). This approach attempts to account for the wide variability in inter- and intra-individual response to the same stimulus. Coping is both psychological (involving cognitive and behavioral strategies) and physiological (Somerfield & McCrae, 2000; Ursin & Eriksen, 2004). If normal coping is ineffective, stress is prolonged and abnormal responses may occur, leading to distress and possibly dysfunction or disease (Olshansky, Carnes, & Butler, 2003). The progression of these events is subject to great individual variation.

In summary, stress can be thought of as a series of physiological and psychological reactions enabling the individual to cope with and adapt to challenging stimuli- either positive or negative. This could include interactions between an individual and the environment, particularly if new and/or challenging situations lead the individual

to perceive a discrepancy (real or perceived) between demands of the situation and the individual's physiological or psychological resources. Illness, hospitalization, sleep deprivation, invasive procedures and unknown or unclear diagnoses all can be viewed as sources of acute stress, while major life events, general state of health, lifestyle factors, and perception of situations and life events can be viewed as sources of chronic stress. Both acute and chronic stress factors such as those described here have been associated with delirium (Inouye, 2006).

Stress Physiology

Efforts to understand the physiological responses of an organism as it attempts to maintain and defend internal stability characterizes the work of two scientists who laid the foundation for stress theory. Claude Bernard, a 19th century French physician, proposed that the function of physiological processes was to regulate or control the internal environment (*milieu interne*) of the organism (as cited in Chambers & Buchman, 2001). Walter Cannon, an early 20th century physiologist, was famous for describing the "flight or fight" syndrome that linked emotional perceptions such as fear to physiological changes in the organism (1935). Cannon placed an emphasis on the interaction of emotion and physiological regulation, focusing on the activation of the sympathetic adrenal medullary system; specifically the autonomic nervous system and the release of catecholamines, epinephrine and norepinephrine (Cannon, 1935; Chambers & Buchman, 2001). Cannon also coined the term *homeostasis* to describe the maintenance of a stable internal environment through relatively constant, complex, and coordinated changes,

rigorously controlled by interdependent physiological mechanisms (Cannon, 1935). The goal of these feedback mechanisms is to reduce variability and maintain constancy.

Hans Selye, a Canadian endocrinologist, extended Cannon's observations in developing his now classic theory of stress, the "general adaptation syndrome" (GAS; Selye, 1936/1998). Selye theorized that in order to survive, every organism must be able to adapt to environmental and social conditions that are stressful and potentially life threatening (1936/1998). These adaptive responses must be nonspecific in order for the organism to respond to a vast array of stressful conditions, whether it is injury, temperature extremes, lack of food, or psychological conditions, such as fear. The HPA axis plays a central role in Selye's formulation of the GAS, including chemical mediators such as corticotropin-releasing hormone, glucocorticoids, such as cortisol, and catecholamines (e.g., epinephrine and norepinephrine) (Schulkin, Thompson, & Rosen, 2003).

In the GAS, there are three stages in the reaction to a stressor: alarm reaction, resistance and exhaustion (Schulkin et al., 2003; Selye, 1936/1998). Initially, when exposed to a stressor, an alarm reaction phase begins and the organism prepares itself for "fight or flight." If the stress exposure persists, the second phase of resistance begins and adaptation and resistance to the stressor develops. In a sustained stress response, depletion of energy stores will occur and the third phase of the GAS occurs where adaptation ceases and exhaustion follows. Selye believed this could lead to illness and death (1936/1998).

Advances in understanding the stress response have led to a greater appreciation for the complexity of physiological systems and repudiation of Selye's theory that there is a stereotypical, non-specific, response of mediators to all types of stressors. It appears that different patterns of stress response are related to the type of stressor and these differences include not only physiologic variation in the regulation of stress mediators, but also differing perceptions of and different behavioral responses (McEwen, 1998; Schulkin, 2003a; Sterling, 2004). Furthermore, rather than dysfunction being caused by an exhaustion of defense mechanisms (as proposed in the third stage of GAS), it is the stress mediators themselves that can have adverse effects on the organism (McEwen, 1998; McEwen, 2006).

In addition, it was argued that homeostasis alone could not explain the regulation and maintenance of all physiological systems. While adaptation to normal variation in physiological set points was one physiological response (homeostasis), adaptation to unexpected or prolonged changes required a broader, more complex, range of responses (McEwen & Sapolsky, 1995; as cited in Sterling, 2004). A defining feature of healthy functioning, therefore, was the capacity to respond to unpredictable or sustained stressors; i.e., to anticipate stressful challenges (McEwen & Wingfield, 2003; Schulkin, 2003a; Sterling, 2004).

Allostasis

The theory of allostasis, introduced by Sterling and Eyer in the 1980's, refers to the process of "maintaining stability (or homeostasis) through change" (Sterling, 2004, p. 1). Allostasis was described as a continuous process of adaptation that the individual

undergoes in the face of potentially stressful challenges. The concept of allostasis departs from that of homeostasis and emphasizes two key points about physiological regulation: parameters are not constant (they vary widely), and variation, rather than a sign of dysfunction, is an indication of healthy functioning (Sterling, 2004). The regulatory system of allostasis does not contain specific physiological set points as in homeostasis, rather it provides behavioral and physiological responses in order to anticipate and respond effectively to stressors. While homeostasis describes regulation of specific physiological parameters within a precise and narrow range of vital values, such as oxygen content in the blood, allostasis describes an alternative set of adaptive processes to stressors, such as a drop in temperature, exposure to a pathogen, or the sudden reaction to a perceived danger (McEwen & Wingfield, 2003; Schulkin, 2003a; Sterling, 2004). The goal of homeostasis and allostasis is to maintain internal stability, but they meet challenges to internal stability in different ways.

Proponents of the theory of allostasis believed a paradigm shift was necessary in how we view regulatory system adaptation because most physiologic research has been carried out in laboratory settings, studying organs or organ systems as isolated entities, while in reality they are in constant interaction in our environment (McEwen, 2003; Sterling, 2004; Sterling & Eyer, 1988). These authors speculate that an organism actually achieves stability by being able to move easily between various physiologic states, responding to physical stimuli and coping with psychosocial challenges. In addition, the allostatic response is one coordinated by the brain. Because of this coordination, allostasis is a more complex form of regulation than homeostasis (Sterling, 2004) and

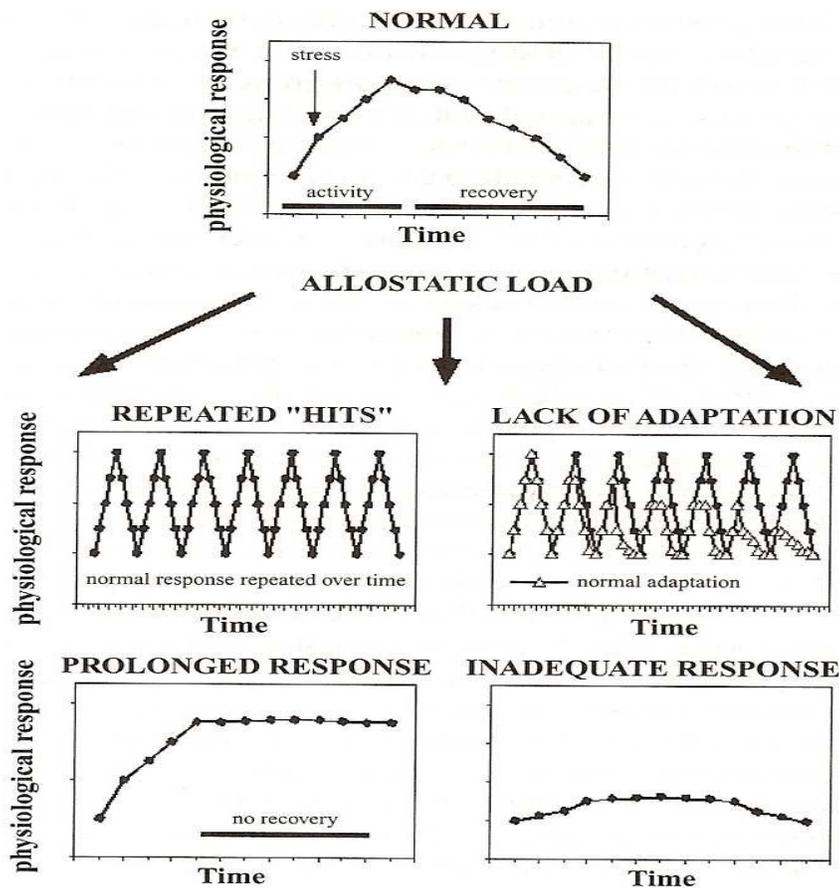
allows the body to anticipate challenge and make necessary adjustments in preparation (Schulkin, 2003a).

Allostatic Load

McEwen and Stellar (1993) developed a framework for understanding the acute and chronic responses to stress and used the concept of *allostatic load* (AL). An acute stress response involves activation of the neuroendocrine, autonomic, and immune systems. This adaptive, i.e. allostatic, response continues for the duration of the stress and then terminates. If the allostatic response continues, it may lead to a down-regulation of receptors and subsequent tissue damage. This damage is termed AL. In other words, AL is the cost of chronic exposure to the mediators of the stress response (McEwen, 1998; McEwen & Stellar, 1993). Furthermore, when unpredictable, repetitive and/or exaggerated stress occur, then AL can increase dramatically, serving no useful purpose and making the individual vulnerable to disease (McEwen, 2004).

McEwen (2006) describes five subtypes of allostatic response patterns that may occur (Figure 2). The first subtype is a ‘normal’ allostatic response to stress that is congruent with the changing circumstance. There is an immediate physiological response to an acute stressor and there is a gradual decline. The “repeated hits” subtype shows continued and/or over-stimulation that elicits a repetitive physiological response. The third subtype is a lack of habituation or adaptation to the same stressor over time, resulting in a continually high response to a stressor that after time begins to elicit less reactivity. The fourth subtype is a prolonged reaction that is due to a failure to terminate the physiological response. Finally, the fifth subtype is an inadequate response,

Figure 2

Allostatic response patterns

Note: From McEwen (1998). Stress, adaptation and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, 840, 33-44.

oftentimes leading to a compensatory hyperactivity of other mediators (McEwen, 2006; Schulkin, 2003a).

A challenge for the first AL researchers was how best to describe and measure the cascade of events that led from allostasis to AL (Seeman, Singer, Rowe, Horwitz, &

McEwen, 1997). There was no organized method for choosing which biological measures would facilitate systematically relating those measures to specific disease outcomes or systematically adding new biological measures. In an attempt to overcome these limitations, McEwen and Seeman (1999b) developed the concept of primary mediators causing primary effects. These primary effects would lead to the development of secondary outcomes. The effects of these secondary outcomes would lead to tertiary outcomes, or actual diseases.

Primary Mediators

McEwen described primary mediators of AL: cortisol (an adrenal steroid) and DHEAS (a cortisol antagonist), both part of HPA axis activity, and epinephrine and norepinephrine, catecholamines involved in autonomic nervous system activation (McEwen & Seeman, 1999). These primary mediators have widespread influences and are very powerful in their impact on a variety of secondary and tertiary outcomes (McEwen & Lasley, 2003).

Other primary mediators of AL have been suggested, but have not been extensively studied. They include prolactin (Schulkin, 2003a), a hormone that reduces HPA axis activity, growth hormones such as insulin-like growth factor-1 and immune system cytokines, such as interleukin-6, that are, in part, inhibited by adrenal steroids (McEwen & Lasley, 2003; McEwen, 2002; Seplaki, Goldman, Weinstein, & Lin, 2004). The chronic dysregulation of these primary mediators leads to primary effects.

Primary Effects

Primary mediators initiate physiologic responses that are termed primary effects. Primary effects defines the mechanisms by which primary mediators exert their influences (McEwen & Seeman, 1999). Primary effects are biochemical changes at the cellular level and represent the link between the dysregulation of primary mediators and the secondary outcomes caused by this dysregulation. Primary effects are often tissue and organ specific and may result from the action of more than one primary mediator (McEwen & Seeman).

Secondary Outcomes

Secondary outcomes are the result of physiological processes that reflect a cumulative, chronic impact of primary mediators on metabolism and tissues or organs (McEwen, 2007; McEwen & Seeman, 1999). For example, increased WHR and Hg_{A1C} reflect the effects of sustained elevations in glucose and the insulin resistance that develop as a result of elevated cortisol and increased sympathetic nervous system activity (McEwen & Seeman).

This is the first study of AL and its relationship with a health outcome, i.e. delirium, in an acutely stressful situation such as acute illness and hospitalization. The theory of AL would suggest that measurement of secondary outcomes is important, even in an acute situation, as secondary outcomes may affect the response of primary mediators and impact AL.

Tertiary Outcomes

The final stage of this pathological pathway is the development of actual disease. Tertiary outcomes are the specific diseases or disorders that are the result of AL and are predicted from the extreme values of the primary mediators and secondary outcomes (McEwen & Seeman, 1999). Delirium can be considered a tertiary outcome.

Validation of Allostatic Load

Most of the empirical evidence supporting the AL theory stem from analysis of data collected during the MacArthur Studies of Successful Aging, a large, community-based, 7-year longitudinal study of relatively high functioning men and women aged 70–79 at the start of the study in 1988 and followed at baseline, 1991, and 1995 (Berkman, Glass, Brissette, & Seeman, 2000). Seeman and colleagues (1997) developed an operational measure of AL that incorporated physiologic activity across a range of important regulatory systems, including the HPA axis and sympathetic nervous system, as well as the cardiovascular system and various metabolic processes. This AL measure was meant to capture higher levels of physiologic activity reflective of chronic stress or failure to terminate responses to acute stress. Ten variables were selected for this operational measure of AL: WHR (an index of more chronic levels of metabolism and adipose tissue deposition, thought to be influenced by increased glucocorticoid activity), systolic and diastolic BP (indices of cardiovascular activity), serum HDL and TC/HDL ratio (related to long-term atherosclerotic risk), Hg_{A1C} (an integrated measure of glucose metabolism), serum DHEAS (an HPA axis antagonist), 12-hour urinary cortisol excretion (integrated measure of HPA axis activity) and 12-hour urinary norepinephrine and

epinephrine excretion levels (integrated measures of sympathetic nervous system activity).

For each of the 10 variables, participants were grouped into quartiles based on the distribution of all sample values. Seeman and colleagues (1997) then generated AL 'scores' by summing the number of variables for which the participant fell into the highest risk quartile. This was the lowest quartile for HDL and DHEAS, and the top quartile for all other variables. They found that the highest risk quartile cutoff points for each variable held either minimal or no clinical significance when considered individually; yet, by summing the elevated variables, a higher AL score was associated with mortality and cognitive and functional decline (Seeman et al.), as well as an increased incidence of cardiovascular disease (Seeman, McEwen et al., 2001).

The researchers examined several alternative methods for calculating an AL score. One such alternative method used a stricter criterion, generating AL scores based on a sum of the number of variables for which the participant fell into the top (or bottom) 10% of the distribution (i.e., the group at highest risk). Another method for measuring AL was to average the normal scores (z scores) for each of the parameters. Each of the alternative methods yielded essentially the same results as using the risk quartile criteria (Seeman, Singer et al., 1997). These concurrent results suggested to the researchers that their conceptualization of AL was theoretically sound and that disease risks were derived from individuals having relatively greater activity on various measures of physiologic regulation, rather than only at the most extreme levels.

Most investigators studying the relationship between AL and various health-related outcomes have adopted the original operationalization of AL described by Seeman and colleagues (1997) or have used a variant different by one or two variables (Table 4). Other researchers have employed a number of different variables for determining AL. Common to all variants on the operationalization of AL is the recognition that AL reflects the combined consequence of processes across multiple physiological systems; therefore, multiple variables across multiple systems are used.

Allostatic load has been studied in a variety of diverse populations, including community-based, relatively high functioning older American men and women (Karlamanla et al., 2002; Karlamanla et al., 2006; Seeman, Crimmins et al., 2004; Seeman, Lusignolo et al., 2001; Seeman, Singer et al., 1997; Seeman, Singer, Ryff, Dienberg Love, & Levy-Storms, 2002; Singer & Ryff, 1999), a nationally representative sample of American men and women 20 years of age and older (Crimmins, Johnston, Hayward, & Seeman, 2003b; Geronimus et al., 2006; Nelson et al., 2007), Taiwanese men and women 65 years of age and older (Glei et al., 2007; Hu, Wagle, Goldman, Weinstein, & Seeman, 2007; Seplaki et al., 2004; Weinstein et al., 2003), middle-aged men and women (Kinnunen et al., 2005; Lindfors et al., 2006; von Thiele et al., 2006b), mothers of pediatric cancer survivors (Glover, 2006); caregivers of spouses with dementia (Clark et al., 2007), children and adolescents from low-income families (Evans, 2003; Evans et al., 2007), homeless or displaced boys from Nepal (Worthman & Panter-Brick, 2008) and German airline workers (Schnorpfeil et al., 2003). It is noteworthy that AL has yet to be studied in a hospitalized population.

Table 4

Variables of Allostatic Load

<i>First Author (Year)</i>	<i>N</i>	<i>Population</i>	<i>Key Variables</i>
Smith (2009)	182	Chronic fatigue syndrome surveillance study; Wichita, KS	Original 10 ⁺ minus HDL, Hg _{A1C} and TC/HDL ratio plus albumin, aldosterone CRP and IL-6
Evans (2009)	195	Caucasian teenagers, low-income families, from rural upstate New York public schools	Original 10 ⁺ minus DHEAS, HDL, Hg _{A1C} , TC/HDL ratio, and WHR, plus BMI
Merkin (2009)	13,199	National Health and Nutrition Examination Survey, 1988 – 1994 (NHANES III <i>not</i> NHANES IV, no explanation given)	Albumin, CRP, DBP, HDL, Hg _{A1C} , resting heart rate, SBP, TC and WHR
Szanton (2009)	728	Women's Health and Aging Studies	BMI, creatinine clearance, DBP, DHEAS, Hg _{A1C} , IGF, IL-6, SBP, TC/HDL ratio, TG
Worthman (2008)	103	Nepalese boys; 4 groups: homeless, urban squatters, urban middle-class, and rural dwelling	alpha1- antichymotrypsin, cortisol, Epstein-Barr virus, heart rate, height, and weight
Sabbah (2008)	6,847	National Health and Nutrition Examination Survey, 1988 – 1994 (NHANES III)	CRP, DBP, fibrinogen, glucose, HDL, SBP, TG, waist circumference
Glei (2007)	916	Social Environment and Biomarkers of Aging Study (SEBAS); Taiwan	Original 10 ⁺ plus fasting glucose and TG
Nelson (2007)	5,083	National Health and Nutrition Examination Survey, 1999 – 2002 (NHANES IV)	Albumin, BMI, CRP, DBP, GFR, Hg _{A1C} , homocysteine, SBP, TC, TG
Hu (2006)	1,023	Social Environment and Biomarkers of Aging Study (SEBAS); Taiwan	Original 10 ⁺

Note: BMI-body mass index; CRP-C-reactive protein; DBP- diastolic blood pressure; DHEAS- dehydroepiandrosterone sulfate; GFR- glomerular filtration rate; Hg_{A1C} – glycosylated hemoglobin; HDL-high density lipoprotein; insulin-like growth factor- IGF; IL-interleukin; LDL-low density lipoprotein; SBP- systolic blood pressure; TC-total cholesterol; TG- triglycerides; TNF-tissue necrosis factor; and WHR- waist-hip ratio. ⁺ Original 10 variables from Seeman et al., 1997.

Table 4

Variables of Allostatic Load – continued

<i>First Author, Year</i>	<i>N</i>	<i>Population</i>	<i>Key Variables</i>
Maloney (2006)	103	Chronic fatigue syndrome surveillance study; Wichita, KS	Original 10 ⁺ minus HDL, Hg _{A1C} and TC/HDL ratio plus albumin, aldosterone CRP and IL-6
Goertzel (2006)	103	Chronic fatigue syndrome surveillance study; Wichita, KS	Original 10 ⁺ minus HDL, Hg _{A1C} , and TC/HDL ratio plus albumin, aldosterone, CRP and IL-6
Clark (2007a)	260	Caregivers of spouses with Dementia; Australia	Original 10 ⁺
Glover (2006)	28	Mothers of pediatric cancer survivors	Original 10 ⁺
Lindfors (2006)200		Individual Development and Adaptation Study, Sweden	DBP, HDL, Hg _{A1C} , respiratory peak flow, SBP, TC, and WHR
Von Thiele (2006b)	241	Female employees of two public health care organizations	Original 10 ⁺ minus urinary cortisol, epinephrine, and norepinephrine plus glucose, heart rate, LDL, prolactin and TG
Geronimus (2006)	6,586	National Health and Nutrition Examination Survey (NHANES IV)	Albumin, BMI, creatinine clearance, CRP, DBP, Hg _{A1C} , homocysteine, SBP, TC and TG
Karlamangla (2006a)	729	MacArthur Study on Successful Aging	Original 10 ⁺
Kinnunen (2005)	117	Jyväskylä Longitudinal Study of Personality and Social Development; Finland	Original 10 ⁺ minus epinephrine, TC, and TG
Seeman (2004a)	657	MacArthur Study on Successful Aging	Original 10 ⁺ plus albumin creatinine clearance, CRP, fibrinogen, and IL-6
Hellhammer (2004)	76	Two age groups (24-40 and > 60 years of age)	Original 10 ⁺ minus urinary cortisol, epinephrine, and norepinephrine, plus CRP and fibrinogen

Note: BMI-body mass index; CRP-C-reactive protein; DBP- diastolic blood pressure; DHEAS- dehydroepiandrosterone sulfate; GFR- glomerular filtration rate; Hg_{A1C} – glycosylated hemoglobin; HDL-high density lipoprotein; insulin-like growth factor- IGF; IL-interleukin; LDL-low density lipoprotein; SBP- systolic blood pressure; TC-total cholesterol; TG- triglycerides; TNF-tissue necrosis factor; and WHR- waist-hip ratio. ⁺ Original 10 variables from Seeman et al., 1997.

Table 4

Variables of Allostatic Load – continued

<i>First Author, Year</i>	<i>N</i>	<i>Population</i>	<i>Key Variables</i>
Seplaki (2004)	980	Social Environment and Biomarkers of Aging Study (SEBAS); Taiwan	Original 10 ⁺ plus BMI, dopamine, fasting glucose, IGF-1 and IL-6
Crimmins (2003a)	22,221	National Health and Nutrition Examination Survey (NHANES III/IV)	Original 10 ⁺ minus urinary cortisol, epinephrine, and norepinephrine, DHEAS, and WHR, plus albumin, creatinine clearance, CRP, homocysteine, IL-6, respiratory peak flow
Evans (2003)	339	Children, low-income families, from rural upstate New York public schools	Original 10 ⁺ minus DHEAS, HDL, Hg _{A1C} , TC/HDL ratio and WHR, plus BMI
Schnorpfeil (2003)	332	Industrial plant workers; Germany	Original 10 ⁺ plus albumin, BMI, CRP, and TNF-a
Weinstein (2003)	927	Social Environment and Biomarkers of Aging Study (SEBAS); Taiwan	Original 10 ⁺
Karlamangla (2002b)	251	MacArthur Study on Successful Aging	Original 10 ⁺
Seeman (2002b)	871	MacArthur Study on Successful Aging	Original 10 ⁺
Seeman (2001)	720	MacArthur Study on Successful Aging	Original 10 ⁺
Kubzansky (1999)	818	Normative Aging Study	Original 10 ⁺ minus urinary cortisol, DHEAS, Hg _{A1C} , plus postprandial glucose
Singer (1999b)	84	Wisconsin Longitudinal Study	Original 10 ⁺
Seeman (1997b)	765	MacArthur Study on Successful Aging	Original 10: DBP, DHEAS, HDL, Hg _{A1C} , SBP, TC/HDL ratio, urinary cortisol, epinephrine, and norepinephrine, and WHR

Note: BMI-body mass index; CRP-C-reactive protein; DBP- diastolic blood pressure; DHEAS- dehydroepiandrosterone sulfate; GFR- glomerular filtration rate; Hg_{A1C} – glycosylated hemoglobin; HDL-high density lipoprotein; insulin-like growth factor- IGF; IL-interleukin; LDL-low density lipoprotein; SBP- systolic blood pressure; TC-total cholesterol; TG- triglycerides; TNF-tissue necrosis factor; and WHR- waist-hip ratio. ⁺ Original 10 variables from Seeman et al., 1997.

Allostatic load has predicted all cause morbidity and mortality (Karlamanla et al., 2006; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer et al., 1997) and has been associated with lower physical and cognitive functioning (Hu et al., 2006; Seeman, Lusignolo et al., 2001; Seeman, McEwen, Singer, Albert, & Rowe, 1997; Seeman, Singer et al.; Seplaki et al., 2004), functional decline (Karlamanla et al., 2002), frailty in older women (Szanton et al., 2009), decreased working memory in socioeconomically disadvantaged youth (Evans & Schamberg, 2009), and increased age (Crimmins et al., 2003). Allostatic load has been associated with peripheral artery disease (Nelson et al., 2007), chronic fatigue syndrome (Goertzel et al., 2006; Maloney et al., 2006), post-traumatic stress syndrome (Glover, 2006), and heart disease (Karlamanla et al.; Sabbah et al., 2008).

Allostatic load has been associated with lower socioeconomic status (Evans et al., 2007; Merkin et al., 2009; Seeman, Gleib et al., 2004; Singer & Ryff, 1999a), lower education (Kubzansky et al., 1999; Weinstein et al., 2003), higher hostility (Kubzansky et al., 1999), adverse work-related experiences (Kinnunen et al., 2005; Schnorpfeil et al., 2003; von Thiele, Lindfors, & Lundberg, 2006a), poor social experiences (Gleib et al., 2007; Seeman et al., 2002a; Weinstein et al., 2003), psychological stress (Clark et al., 2007b) and self-reports of poor health (Geronimus et al., 2006; Hu et al., 2006).

Allostatic Load Concept Development

Allostatic load provides a comprehensive index of physiological damage that appears to be a more powerful predictor of several adverse health outcomes than any single allostatic measure. In addition, the underlying theory and measurement of AL

provides a valuable framework for future study, allowing researchers to link a number of variables with physiological disturbance and disease. However, not all researchers have agreed on the usefulness of the AL concept. Some have argued that there are conceptual weaknesses in the theory, particularly in regards to energy balance and expenditure and that the theory needs to be broadened, taking additional physiological variables into account (Dallman, 2003; Walsberg, 2003). In addition, it appears that different AL variables may have differential effects on predicting different outcomes, making it difficult to capture with one overarching index (Karlman et al., 2006). In response, McEwen (2003) has noted that the concept of AL is still relatively new and undergoing continued development. Also, Seeman and colleagues (2001) have commented that their original operationalization of AL should be seen as an initial, and only partial, assessment of the concept and, further, that when determining AL, different biological systems might be weighted differently according to the health outcomes to be predicted. Others have defended the concept and suggest that allostasis is a “conceptual advance in understanding whole-body adaptation with an emphasis on cephalic regulation of local systems” (Schulkin, 2003a, p. 26). Furthermore, there is empirical evidence supporting the theory of allostasis. For example, AL, as a composite measure, appears to have more power to predict cognitive and physical functioning, mortality, and a number of disease outcomes than any separate measure alone.

Allostatic Load and Delirium

Evidence implicating a stress response in delirium (Engel & Romano, 1959/2004; McEwen, 2007; White, 2002) suggests that the theory of AL might provide a framework

for modeling the pathophysiological mechanisms of delirium. Delirium is a complex syndrome with a confusing array of etiologic correlates and the historic understandings of stress and homeostasis do not provide a sufficient framework to elucidate the pathophysiological mechanisms that explains delirium in the hospitalized elderly. The notion of AL as a stress response that involves multiple chronic and acute factors along with the coordination of several physiological regulatory systems makes AL a particularly attractive framework for the study of delirium in the hospitalized elder.

While the activation of physiological regulatory systems in response to stress is necessary and adaptive, recurrent, exaggerated, or continual allostatic responses harm the physiological systems themselves and may lead to tissue and cellular dysfunction and/or damage. This continued burden may lead ultimately to the pathology reflected in delirium.

The concept of AL adds a critical component to the understanding of delirium in the hospitalized elder by providing a possible explanation for the heterogeneity seen in delirium occurrence in the hospitalized elder. The theory that AL is an individualized physiological burden, reflective of the specific stressors an older adult is exposed to over a lifetime, as well as acute, repeated or continued stressors, is an explanation for why hospitalized elders exposed to seemingly the same stressors have different responses, with one older adult developing delirium and not the other.

AL is not solely an acute process; AL accumulates, in a chronic fashion, over time. While a probably correct hypothesis is that AL increases as the elder ages, more

important to an explanation for the differences seen in delirium occurrence among the hospitalized elderly, is that the heterogeneity in AL increases as the elder ages.

Aging

Aging is a complex syndrome that many scholars have viewed in different ways. One approach has been to view the aging process as a summation of disease processes ultimately leading to death (Goldsmith, 2007; Hayflick, 2007). Studies of human aging have been hampered by this approach, as discriminating clearly between aging itself and the consequences of age-related disease is more difficult (Goldsmith, 2007; Olshansky et al., 2003).

In contrast, another approach has been to consider that there is no inherent connection between aging and disease, except for the increased risk of disease with advancing age. The increased disease risk is believed to be a result of age-related changes that predispose individuals for disease (Goldsmith, 2007; Olshansky et al., 2003). This view of aging promotes a distinction between healthy and pathological aging and separates the aging process from that of a disease process. Normal aging, then, is considered the accumulation of un-repaired damage, a “wear and tear” that occurs over time, while pathological aging occurs because a disease process leads to aging (Goldsmith; Hayflick, 2007; Kirkwood & Austad, 2000; Olshansky et al.).

There have been numerous theories to explain the aging process and no single theory is entirely satisfactory. Rather, it is suggested that aging might be due to a combination of several theories, the programmed and free radical theories presumably being the most important, while others play a definite, albeit lesser, role (Hayflick, 2007).

In general, theories of aging fall into two major categories (Droge, 2002). Error theories emphasize that aging is the outcome of both random accumulation of error mutations and a general wearing down of tissues and organs during the lifespan of a person. Program theories hold that aging is the result of a sequential switching on and off of particular, predetermined genes. Error theories are built on essentially random, time- and probability-dependent events, whereas program theories of aging include those that propose predetermined mechanisms to explain aging.

Allostatic Load and Aging

It is expected that the AL will increase as one ages (Crimmins et al., 2003). Yet, within any given age cohort there will be a range of variation that is based on genetic predisposition, early life predisposing influences, adaptation to daily life events, and the effects of major life stressors (Lupien & Wan, 2002; McEwen, 2003). It is suspected that the physiological regulatory systems implicated in determining AL play a role in determining the rate of brain and body aging and that they do so by exacerbating processes that can cause damage to tissues and organs (McEwen, 2000). Allostatic load, therefore, is a highly individual matter possibly explaining the heterogeneity in vulnerability to delirium seen in the hospitalized older adult.

Homeostenosis

From a physiologic perspective, one may characterize aging as a progressive reduction in an organ system's capacity to maintain homeostasis. This restriction in an organism's reserves, termed *homeostenosis*, is an important concept in the biology of

aging; it describes a vulnerability to illness and disease due to of a lack of physiological reserve (Resnick, 2000).

Homeostenosis begins in the third decade of life and occurs in each organ system independent of changes in other systems (Resnick, 2000). This decline is influenced by a number of factors, including genetics, personal behavior, and environmental stressors (Miller, 2001). An example of homeostenosis would be the decreased ability to manage fluid and electrolyte derangements as we age, created by a variety of physiological changes, such as diminished thirst perception, changes in the renin-angiotensin-aldosterone system, decreased glomerular filtration, and diminished capacity for urinary concentration (Resnick, 2001).

Heterogeneity is a key characteristic of homeostenosis. The loss of functional reserve seen in homeostenosis occurs at different rates in different people and even at different rates within the same person (Resnick, 2001). People are able to function normally, as homeostenosis results in no overt symptoms or restrictions in activities of daily living at any age, but as people age they may be less likely to be able to withstand any stress that threatens homeostasis (Troncale, 1996). In other words, the typical aging organ does not lose visible function so much as it loses measurable reserve (Taffet, 2008). The older adult attempting to maintain homeostasis requires the use of an ever-increasing amount of compensatory reserve, leaving less of a reserve when responding to threats to homeostasis. This decrease in compensatory reserve will vary person to person, but will determine an older adult's vulnerability to not maintaining homeostasis (Taffet).

Model of Allostatic Load & Delirium in Hospitalized Elderly (ALDHE)

The ALDHE model (Figure 1) provides a new theoretical viewpoint by investigating delirium with the additional consideration of allostasis and aging on the development of delirium. In the model, multiple chronic and acute factors prompt an allostatic response involving several physiological regulatory systems. While the activation of these systems is necessary and adaptive, recurrent, exaggerated, or continual allostatic responses harm the physiological systems themselves and may lead to tissue and cellular dysfunction and/or damage described as AL.

Importantly, AL is individualized, reflective of the specific stressors a person is exposed to and the presence of repeated or continued stressors. It is important to recognize that AL is not solely an acute process; AL accumulates, in a chronic fashion, over time.

In general, the elderly have a higher AL than a younger cohort (Crimmins et al., 2003), and hospitalization may increase it further. When the greater AL found in the elderly is coupled with age-related changes in physiology and functional capacity and a reduced capacity to accommodate change (referred to in this model as homeostenosis), then the risk for delirium may be even greater.

While treatment of the condition or disease state triggering hospitalization likely will decrease AL, the hospitalization experience itself has the potential to increase AL. For example, iatrogenic illness or injury in the hospital environment, use of physical restraints, malnutrition, polypharmacology, pain, and/or fear all prompt stress responses that could be responsible for increasing AL. Additionally, hospitalized elders will show

variability in their AL prior to entering the hospital environment. Theoretically, those with higher AL are at higher risk for delirium. This research predicts who becomes delirious and who does not through evaluation of AL.

Summary

There has been significant progress in understanding the pathophysiological mechanisms for delirium and the theory of a global cerebral impairment is giving way to the hypothesis that disruption of certain neurological pathways and neurotransmitter systems that may lead to delirium. In addition, it is possible that age-related changes in neurotransmitter systems (e.g., loss of cholinergic reserve, impaired regulation of the HPA axis) make the hospitalized older adult more vulnerable to the risk of delirium. Alternatively, there may be no final common pathway and delirium may be a cluster of common symptoms reflective of a variety of situation-specific neurotransmitter abnormalities.

The ALDHE model provides a theoretical framework for understanding relationships between delirium and AL within the context of acute and chronic stress, allostasis and age-related physiological changes. The research questions posed in this study explore delirium pathogenesis in the hospitalized older adult by investigating the relationship between AL, and specific subsets of AL, and delirium.

CHAPTER III: METHODS

Introduction

The purpose of this study was to investigate the relationship of AL, a composite measure of chronic and acute stress, and delirium in the hospitalized elder. This chapter discusses the methods used in the study, including a description of the design, sample, setting, variables measured, instruments used, procedures, data management, data analysis plan and protection of human subjects.

Study Design and Overview

A nonexperimental design was used to answer the research questions. No prior research has investigated AL and delirium in the hospitalized older adult and a descriptive design, which is helpful in describing patterns and connections between variables without making inferences or causal statements (Shadish, Cook, & Campbell, 2002), was appropriate to investigate the ability of AL to predict delirium in the hospitalized older adult.

Once a participant was recruited, they were screened for cognitive dysfunction and prevalent delirium. If cognitively intact and not delirious, they were enrolled in the study. After admission to the ICU, AL measures were collected. Delirium assessment took place 48 – 72 hours after admission.

Setting

The setting for this study was three ICUs in a 365-bed university associated hospital located in the southwestern United States. This hospital has 50 beds across these units, a medical/trauma ICU, a pulmonary ICU and a cardiothoracic surgery ICU. The

hospital admitted 886 men and women sixty-five years of age and older in the 12 months prior to the study period (personal communication, M. Horner, August 1, 2008).

Sample

A convenience sample of men and women sixty-five years of age and older admitted to any one of the three ICU's were recruited. The ICU setting was selected because a higher incidence of delirium (41% – 87%) has been reported in the ICU population (Bergeron et al., 2002; Ely, Inouye et al., 2001; McNicoll et al., 2005). Sampling from a population with a higher incidence of delirium increased the potential for obtaining an adequate number of older adults who experienced delirium during their hospital stay.

Inclusion/Exclusion Criteria

Participants needed to be sixty-five years of age or older and speak and understand English. Exclusion criteria included prevalent delirium, defined as a positive finding on the Confusion Assessment Method (CAM); severe cognitive dysfunction, defined as a Standardized Mini-Mental Status Exam (SMMSE) score of 23 or less; communication deficits, defined as being blind or deaf to the extent that the participant could not participate in the study measures, an inability to speak, due to a condition, such as being mechanically ventilated or aphasic/dysphasic, or dysarthric due to a stroke or other medical condition; anuria; and currently receiving exogenous steroids.

Sample Size

A logistic regression power analysis was performed using the Power Analysis and Sample Size (PASS) software. This calculation demonstrated that a total sample of

37 participants would achieve 80% power at a .05 significance level to detect a change in the probability of delirium occurring as AL increases that corresponded to an odds ratio (OR) of 2.5 (Hsieh, Bloch, & Larsen, 1998; personal communication J. Hepworth, April 9, 2009).

There are no published data regarding AL and delirium; however, limited data from other investigations of AL suggest there would be an increased incidence of delirium associated with increasing AL. Seeman and colleagues demonstrated an increased risk of mortality was associated with increasing AL scores. Older adults with AL scores of 1–2 experienced 1.67 greater mortality compared to those with a zero AL score (95% confidence interval (CI) = 0.71, 4.59); those with AL scores of 3–4 experienced 2.45 times greater mortality (95% CI = 1.04, 6.77); older adults with AL scores of 5-6 experienced 2.79 times greater mortality (CI not reported) and older adults with higher levels of AL (i.e., > 7) experienced the greatest relative risk for mortality (OR = 6.42; 95% CI = 1.36, 32.12) (2001b). Karlamangla and colleagues (2006) demonstrated that for each point increase in an older adult's AL score, there was a 3.33 greater risk for mortality (95% CI = 1.14-9.74).

Sampling Plan

Convenience sampling was used. Nursing staff approached the patient to obtain permission for the researcher to discuss the study. After nursing staff obtained verbal consent from the potential participant, the researcher approached the patient, discussed the study and obtained written informed consent.

Measures

Demographic and Medical Variables

Demographic and medical variables were used to describe characteristics of the study sample. These variables were collected by reviewing the bedside medical record and the electronic medical record. In addition, several demographic and medical variables were collected because of their known status as delirium risk factors.

Demographic variables used to describe characteristics of the study sample included date of admission, date of birth (*age*), gender (*male, female*) and race/ethnic background (*American Indian or Alaskan Native, Asian or Pacific Islander, Black or African American, Hispanic, White or Caucasian*). Two of these demographic variables also were selected because they are known delirium risk factors: increasing age (Santos et al., 2005) and male gender (Edelstein et al., 2004).

Medical variables used to describe characteristics of the study sample included *alcohol use, admitting diagnosis, number of past medical diagnoses, number of outpatient medications* taken and *number of inpatient medications* prescribed. Counts of past medical diagnoses and medications taken have been used in delirium research to describe the comorbid condition of the participants (McAvay et al., 2006; Olofsson, Lundstrom, Borssen, Nyberg, & Gustafson, 2005; Vida et al., 2006). Furthermore, these medical variables were selected because they are known delirium risk factors: the presence of multiple co-morbidities (Rudolph et al., 2007; Yildizeli et al., 2005), polypharmacy (McAvay et al., 2006; Ouimet, Kavanagh et al., 2007), and alcohol use (Van Rompaey et al., 2007).

Standardized Mini-Mental Status Exam (SMMSE)

Summary. The SMMSE, a neuropsychological test used in the clinical evaluation of cognitive function, has been found to be valid in screening for dementia and for documenting changes in cognition (Molloy, Alemayehu, & Roberts, 1991; Vertesi et al., 2001). The SMMSE, a modification of the Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), is an 11-item scale that measures levels of orientation, perception, attention to stimuli, and verbal and motor skills. The same test items are used in the SMMSE as in the MMSE and include orientation to time and place; immediate and delayed recall of 3 items; verbally spelling WORLD backwards; repeating back a phrase; reading and understanding a sentence and performing what is written; following a 3-step command; writing a spontaneous sentence; and copying two intersecting pentagons. However, unlike the MMSE, the SMMSE includes standardized questions and instructions for administration and scoring that allows for variations in wording and make the instrument more resistant to intra- and inter-rater variability (Molloy et al., 1991; Vertesi et al., 2001; See Appendix A for more detail on the SMMSE).

Time limits. The SMMSE imposes standardized time limits for each question (e.g., 10 seconds to respond to a question asking for the present date, 30 seconds to draw a picture, etc.). The total time for administration of the SMMSE was limited to 6 1/2 minutes (Molloy et al., 1991); however, time limits were not adopted in this study because time limits might add unnecessary task complexity for both participant and examiner and falsely overestimate a cognitive impairment. Pangman and colleagues (2000) demonstrated this when comparing MMSE scores with SMMSE scores in older adults

living in long-term care facilities. An older adult's inability to complete certain tasks within time limits imposed by the SMMSE adversely affected scores; however, this was typically a physical limitation, rather than a cognitive impairment (Pangman et al., 2000).

Reliability. Test-retest reliability ($r = .83$ to $.90$) for the MMSE has been documented in different populations (Anthony, LeResche, Niaz, von Korff, & Folstein, 1982). Concurrent validity has been established through correlation with the Wechsler Adult Intelligence Scale (Pearson's $r = .78$ for Verbal IQ and $r = .66$ for Performance IQ) (Folstein et al., 1975).

Comparisons of the SMMSE and the MMSE demonstrated an 86% reduction in intra-rater variance and a 76% reduction in inter-rater variance (Molloy et al., 1991). The intra-class correlation for the SMMSE and the MMSE was $.90$ and $.69$, respectively, even when different raters were involved.

Interpretation of the score. As with the MMSE, SMMSE scores range from zero to 30 (Molloy et al., 1991). When using the MMSE (Folstein et al., 1975), scores of 23 or less were indicative of cognitive impairment, while with the SMMSE scores of 25 or less were indicative of cognitive impairment (Molloy et al., 1991). Scores on the SMMSE considered normal in the general population were between 26 and 30; scores between 20 and 25 indicated mild cognitive impairment; scores between 10 and 20 indicated a moderate cognitive impairment; and a score of less than nine denoted severe cognitive impairment (Molloy et al., 1991; Vertesi et al., 2001).

Molloy and Standish (1997a) demonstrated that age and level of education affect SMMSE scores. Median scores by age group are 29 for ages 18 to 50 and 28 for ages 51 to

64, while a median score gradually declines from 28 between ages 65 and 74. The SMMSE median score is 27 at age 75 and 26 for ages 80 and over. Median scores by education level (years of formal schooling) are 29 for at least 9 years, 26 for 5 to 8 years, and 22 for 0 to 4 years of education. Molloy and colleagues (2005), as well as others (Vertesi et al., 2001) have suggested that the SMMSE provides a useful overall impression of cognitive ability, but that SMMSE test scores should be considered in the context of a respondent's past history and clinical findings.

Confusion Assessment Method (CAM)

Summary. The CAM is a simple method of identifying features of delirium based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R diagnostic criteria. Developed in 1990, the CAM aimed to improve the identification and recognition of delirium and provide a standardized approach to enable non-psychiatrically trained clinicians to identify delirium quickly and accurately in both clinical and research settings (Inouye et al., 1990).

The CAM is comprised of nine criteria originating from the DSM-III-R: (1) acute onset, (2) inattention, (3) disorganized thinking, (4) altered level of consciousness, (5) disorientation, (6) memory impairment, (7) perceptual disturbances, (8) psychomotor agitation or retardation and (9) altered sleep-wake cycle and the presence of fluctuations in the first four criteria (Inouye et al., 1990). From the CAM criteria, Inouye and colleagues (1990) developed a diagnostic algorithm by using the first four of the nine criteria: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. More specifically, the CAM algorithm required the

presence of the first and second criteria and either the third *or* the fourth criterion for the diagnosis of delirium. The remaining five criteria were not included in the CAM algorithm because the authors anticipated, based on clinical experience and a review of the literature, that these items would not improve the diagnostic sensitivity or specificity (Inouye et al., 1990). The rating takes 5-10 minutes (Inouye et al., 1990).

Since its development, the CAM algorithm has become one of the most widely used instruments for detection of delirium worldwide, both because of its psychometric properties, but also because of its ease of use. The CAM has been used in hundreds of studies and has been translated into over six languages world-wide (Ely, Margolin et al., 2001; Fabbri, Moreira, Garrido, & Almeida; Inouye, 2003).

Reliability. When validated against the ratings of geriatric psychiatrists who have completed a comprehensive psychiatric assessment, the CAM had a sensitivity of 94 – 100%, specificity of 90 – 95%, and high interrater reliability ($\kappa = .81$) (Inouye et al., 1990). In the instrument development study, the authors found that the CAM ratings agreed substantially with other cognitive tests: the MMSE ($\kappa = .64$), the Visual Analogue Scale for Confusion ($\kappa = .82$), Story Recall ($\kappa = .59$), and the Digit Span Test ($\kappa = .66$) (Inouye et al., 1990).

Interpretation of the score. The CAM algorithm has four items that require a yes/no assessment by the rater. The first and second items, as well as either the third *or* fourth items must be scored yes in order to declare a positive diagnosis of delirium (Inouye, 2003; Inouye et al., 1990). The CAM is not a standalone instrument for diagnosing

delirium variant, i.e., hyperactive, hypoactive, or mixed (Peterson et al., 2006); a dichotomous result is obtained, either the respondent is delirious or they are not.

Investigators have not found improvements in the diagnosis of delirium by using additional delirium measures (Smith, Breitbart, & Platt, 1995). Furthermore, after a recent review of 13 delirium assessment instruments, the authors recommended the CAM as the instrument of choice in a research setting (Schuurmans et al., 2003).

Allostatic Load

Summary. Allostatic load is a composite measure of acute and chronic stress activity. The initial operational measure of AL reflected information on levels of physiologic activity across a range of important regulatory systems, including the HPA axis and sympathetic nervous system, as well as the cardiovascular system and metabolic processes (Seeman, Singer et al., 1997b). This composite measure included ten variables, four primary (i.e. acute) mediators (urinary cortisol, norepinephrine and epinephrine, and serum DHEAS) and six secondary (i.e. chronic) outcomes (WHR, systolic BP, diastolic BP and serum Hg_{A1C}, HDL and TC/HDL ratio) (Seeman, Singer et al., 1997b). These 10 variables were used in the current study to measure AL.

Validity. Seeman and colleagues (1997a) tested the construct validity of their measure of AL by comparing the distributions of AL scores in older adults with high levels of cognitive and physical functioning and 2 comparison groups of medium- and low-functioning older adults. The authors note that the groups of medium- and low-functioning older adults were characterized by an increased prevalence of chronic disease and poorer functional health, theoretically resulting in higher AL scores. They found

differential distributions of AL across the three groups with the distribution of AL scores for the medium- and low-functioning groups more heavily distributed toward the higher scores. In contrast, the high functioning group exhibited AL scores more heavily distributed toward the lower scores.

The measure of AL as operationalized by Seeman and colleagues (1997) has been used in several studies with similar results. Higher baseline AL scores has been associated with increased mortality, increased risk for cardiovascular disease, peripheral arterial disease and decline in cognitive and physical functioning (Karlamanla et al., 2002; Karlamanla et al., 2006; Nelson et al., 2007; Seeman, McEwen et al., 2001; Seeman, Singer et al., 1997; Weinstein et al., 2003).

Allostatic load components. *Systolic* and *diastolic BP* was measured by following American Heart Association guidelines for accuracy in blood pressure measurement (Pickering et al., 2005). An automated oscillometric blood pressure device was used. A minimum of two readings was taken at an interval of at least 1 minute, and the average of those readings was used to represent the participant's systolic and diastolic BP. The readings were taken with the participant in the supine position. If the participant could not be placed in the supine position for medical or preferential reasons, the participant was positioned as closely to the supine position as possible and the measurements taken. The blood pressure was measured in a relaxed upper arm. An appropriately sized cuff was used with a bladder length 80% and a width at least 40% of arm circumference (a length-to-width ratio of 2:1). Once the brachial artery in the antecubital fossa was found,

the midline of the bladder of the cuff was placed so that it was over the brachial artery pulsation and the cuff was secured snugly. The researcher obtained all measurements.

The *WHR* was calculated based on waist circumference (at narrowest point between the lowest rib and the iliac crest) and hip circumference (at the maximal buttocks span) (Lohman, Roche, & Martorell, 1988). For both measurements, the participant was placed in a supine position. If the participant could not be placed in the supine position for medical or preferential reasons, the participant was positioned as closely to the supine position as possible and the measurements taken. A single use measuring tape was applied at a 90 degree angle to the midline and was not allowed to be lower on one side of the body. The tape was held snugly, but not tightly enough to indent the skin. This ratio of girth measurements can be reliably and accurately determined (Kushi, Kaye, Folsom, Soler, & Prineas, 1988). In order to employ universal precautions, a single use measuring tape was used for each participant. The researcher obtained all measurements.

Registered Nurses (RNs) in the ICU obtained all 12-hour urine samples for assays of *cortisol*, *epinephrine* and *norepinephrine* with a beginning collection time between 3:00 PM and 7:00 PM. All RNs follow hospital policies and procedures for specimen collection and processing (personal communication, K. Synder, November 15, 2006). The clinical laboratories at the study hospital have established written quality control procedures for monitoring and evaluating the quality of the collection and analytical testing process of each assay method to assure the accuracy and reliability of test results (personal communication, L. Burnham, July 1, 2008).

Twelve-hour urinary samples were used for several reasons. Plasma levels of catecholamines may be influenced by a variety of postural and diurnal related factors, raising concern about the validity and reliability of using plasma biomarkers (Christensen & Jensen, 1995). In contrast, urinary catecholamine excretion over time provides an integrated assessment of adrenomedullary stimulation.

The diurnal rhythm of cortisol is disturbed in ICU patients (Frisk, Olsson, Nylen, & Hahn, 2004), and plasma levels of cortisol are influenced by physical activity as well as other physiological and psychological factors (Cacioppo et al., 1998; Dickerson & Kemeny, 2004). By obtaining twelve hour urine samples with a beginning collection time between 3:00pm and 7:00pm, many factors more frequently seen in the daytime ICU environment (multiple healthcare provider interactions, therapeutic interventions, diagnostic procedures, noise, activities such as ambulation and meals) can be modified and/or avoided, resulting in a more integrated, and hypothetically less varied, measure of adrenal cortex activity. A more standard 24-hour sample was not used because strong correlations have been demonstrated between 12- and 24-hour samples (rank-order correlations: $r = .80$ for norepinephrine; $r = .81$ for cortisol; and $r = .95$ for epinephrine; Seeman, Singer et al., 1997a).

Registered nurses in the ICU obtained all blood samples following hospital policies and procedures for specimen collection and processing. The clinical laboratories have established written quality control procedures for monitoring and evaluating the quality of the collection and analytical testing process of each assay method to assure the accuracy and reliability of test results. Three vials of blood were obtained from each

participant. In order to complete the necessary assays approximately 9 cc's of blood were required from each participant (one lavender top tube, $HgbA_{1c}$ – 3 cc and two gold top tubes, one tube for *DHEAS*- 3 cc and one tube for *TC* and *HDL*- 3 cc; personal communication, L. Burnham, July 1, 2008).

Blood samples were collected within the first 12 hours of hospital admission and in order to limit the number of venipunctures a participant had to undergo, blood specimens were obtained at the same time another specimen was required for the participant's medical care whenever possible. Total cholesterol and HDL can reliably be measured in samples from fasting or non-fasting persons, so fasting was not required prior to obtaining blood samples (Bachorik, Cloey, Finney, Lowry, & Becker, 1991; Craig, Amin, Russell, & Paradise, 2000).

Allostatic load score calculation. Following the methods of Seeman and colleagues (1997a), for each component that a participant was in the highest risk quartile, they received a score of "1." If the participant was in any other quartile for that particular component, they received a score of "0." A participant's AL score, therefore, was the sum of the scores for each component and ranged from 0 to 10.

The reference population used to assign cut-off values in this study for the highest risk quartile for each of the ten components of AL was the same population studied by Seeman and colleagues in the first study investigating AL (1997a). These reference values, either in total or in part, have been used in the majority of studies investigating AL (Table 5).

Table 5

Components of Allostatic Load

Component	Cut point	Component	Cut point
<i>Highest quartile</i>		<i>Lowest quartile</i>	
Systolic BP	≥ 148 mm Hg	HDL	≤ 37 mg/dl
Diastolic BP	≥ 83 mm Hg	DHEAS	≤ 350 ng/ml
WHR	≥ 0.94		
TC/HDL ratio	≥ 5.9		
HgbA _{1c}	$\geq 7.1\%$		
Urinary cortisol	≥ 25.7 ug/g creatinine		
Urinary norepinephrine	≥ 48 ug/g creatinine		
Urinary epinephrine	≥ 5 ug/g creatinine		

Note: Highest quartile cut-off is $>75\%$ percentile. Lowest quartile cut-off is $<25\%$ percentile. Results for the urinary components are reported as milligram per gram of creatinine to adjust for body size. BP = blood pressure, WHR = waist-hip ratio, TC/HDL = total cholesterol/high-density lipoprotein, HgbA_{1c} = glycosolated hemoglobin, HDL = high-density lipoprotein, DHEAS = dehydroepiandrosterone sulfate.

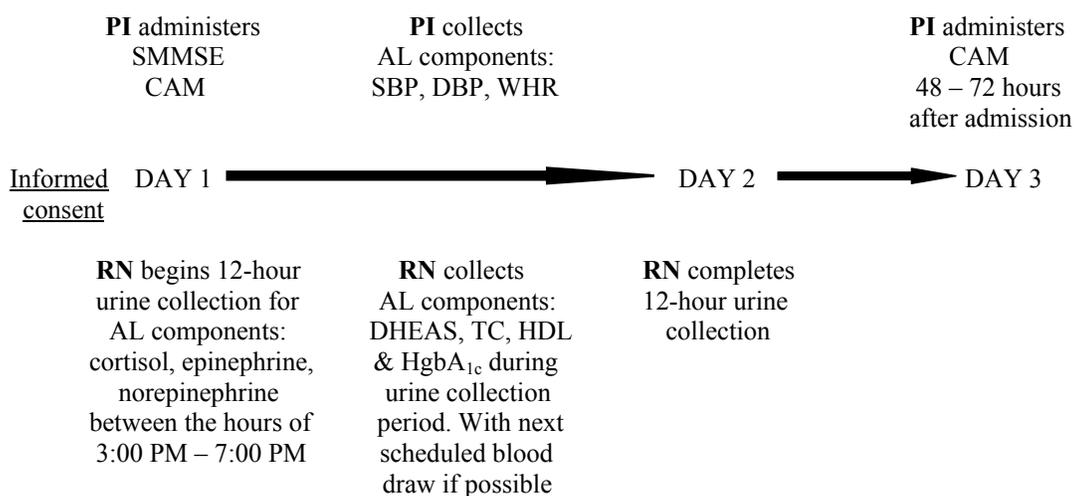
Because the theoretical foundation for AL considers the consequences of actual physiological derangement, participants were coded in terms of the actual physiological values observed for the components of AL (e.g., participants on antihypertensive medication were scored based on their actual BP measurement, not what the BP measurement would have been if the antihypertensive was discontinued) (Seeman, Crimmins et al., 2004b).

Procedures

Overview

A description of the study procedures are in the sections below, including human subject considerations and the method of access to potential participants. Figure 3 summarizes the data collection protocol and the administration (timing and frequency) of the study instruments.

Figure 3

Data collection protocol

Notes: AL- allostatic load, CAM- Confusion Assessment Method, DHEAS- dihydroepiandrosterone sulfate, DBP- diastolic blood pressure, HDL- high density lipoprotein, HgbA_{1c}- glycosylated hemoglobin, PI- Principal Investigator, RN- Registered Nurse, SBP- systolic blood pressure, SMMSE- Standardized Mini-Mental State Exam, TC- total cholesterol, WHR-waist-to-hip ratio.

Access to Potential Participants

The nursing staff contacted the patient to obtain permission for the researcher to discuss the study. After the nursing staff obtained verbal consent from the potential participant to discuss the study, the researcher then met with the potential participant and read aloud a pre-written script about the research project while the potential participant read along (Appendix B). The researcher assured all participants that none of the information gathered would alter his or her care, and that he or she could stop participating or withdraw at any time during the study. If the participant declined to participate in the study, the researcher thanked the participant for his or her time. If the participant agreed,

the researcher then read aloud the consent form while the potential participant read along (Appendix C). If the participant agreed to participate in the study, the participant and researcher signed the written consent form. The researcher then assigned the participant a unique numeric identifier.

Data Collection

Standardized Mini-Mental Status Exam (SMMSE). The researcher administered the SMMSE and recorded the participant's responses on a pre-printed worksheet identified only by the participant's unique numerical identifier (Appendix A). If the participant had a score on the SMMSE of 25 or less (indicating cognitive dysfunction), the participant was excluded from the study. The reason for exclusion was explained to the patient and the patient's RN was informed of the findings.

Confusion Assessment Method (CAM). After enrollment, the researcher administered the CAM to determine if the participant had prevalent delirium (CAM+). The researcher recorded the results on a pre-printed worksheet identified only by the participant's unique numerical identifier (Appendix A). If the participant had a CAM + finding, they were excluded from the study. The reason for exclusion was explained to the patient and the patient's RN was informed of the findings.

The researcher evaluated each participant 48 – 72 hours after admission to determine if the participant had incident delirium (CAM+). This time frame was chosen because it has been demonstrated that a significant percentage of men and women sixty-five years of age and older who become delirious during their ICU stay do so within 48 – 72 hours of admission (Lundstrom et al., 2007; Peterson et al., 2006). The CAM findings

were shared with the participant and the participant's RN. If the participant was delirious, the researcher explained in simple terms that the participant was confused and attempted to reorient the participant to their surroundings.

The researcher recorded the results on a pre-printed worksheet identified only by the participant's unique numerical identifier (Appendix A). If the researcher determined that the participant was delirious (CAM+), the finding was explained to the participant and the participant's RN was informed of the findings.

Allostatic load. The ten components of AL were collected on the day of admission. The researcher collected WHR, SBP and DBP measurements and recorded them on a pre-printed worksheet (Appendix A). The RN initiated, maintained and completed the 12-hour urinary collection, starting between 3:00 PM and 7:00 PM the day of admission to the ICU and ending between 3:00 AM and 7:00 AM the day after admission. Due to the nature of ICU nursing (high acuity, frequent interventions, unexpected events), the RN was allowed to begin the timed urine collection within this four hour window. The urinary sample was maintained on ice throughout the collection period, per hospital policy. The RN collected the blood sample within 12 hours of admission to the ICU. If the participant's RN was not personally going to complete the 12-hour urine collection or obtain the blood samples (going off shift), the researcher requested that the RN include in the nursing report that the participant was enrolled in the study and what the ongoing data collection needs were. Additionally, in the event that a different RN would be completing the blood and/or urine collection, the researcher called the ICU later in the evening to remind the RN and to assure there were no questions.

The researcher brought all supplies to the bedside and personally labeled the three lab tubes and the urine collection container. The researcher also completed all laboratory requisition forms and left them at the participant's bedside. In addition, the researcher inserted a study notice in the nursing careplan with a brief synopsis of the study, the data collection protocol and the researcher's cell phone number (Appendix G).

The researcher obtained the results of all assays from the password-protected participant's electronic medical record. All laboratory results were entered by laboratory personnel into the participant's electronic medical record, but were transcribed by the researcher onto a pre-printed worksheet identified only by the participant's unique numerical identifier (Appendix A). If requested, the results of the various measurements and laboratory tests were shared with the participant.

Demographic variables. The researcher transcribed data from the participant's bedside medical chart and the electronic medical record onto a pre-printed worksheet identified only by the participant's unique numerical identifier (Appendix A). The variables were *age* (date of birth), *gender*, and *racial/ethnic background* (Asian or Pacific Islander, American Indian or Alaskan Native, Black or African American, Hispanic, White or Caucasian).

Medical variables. The researcher transcribed data collected from the participant's bedside medical chart and the electronic medical record onto a pre-printed worksheet identified only by the participant's unique numerical identifier (Appendix A). The variables were *admitting diagnosis*, *past medical history*, *number of outpatient*

medications taken, number of inpatient medication prescribed and the participant's use of alcohol.

Data Management and Analysis Plan

The researcher performed all data entry. Data were collected from participant testing and review of the written medical chart and electronic medical and laboratory records. All data were transcribed onto printed worksheets created *a priori* for individual participant use. All data entry was checked for accuracy by comparing data entries immediately with the written medical chart and electronic medical and laboratory records. The researcher used the completed worksheets for data entry into the Statistical Package for Social Sciences software (SPSS, version 16.0; 2007). All SPSS data entry was checked for accuracy by comparing the completed worksheets and the SPSS database.

Missing data were evaluated for frequency and type. If appropriate, a listwise deletion was used and the complete case was deleted (Field, 2005)

Descriptive statistics (frequency, mean, median, mode, standard deviation) were used to analyze demographic and medical variables. The distribution of each variable was examined using a graphical check (e.g. construction of a histogram) and a test of normality (e.g. Shapiro-Wilk statistic). If the variables seriously deviated from a normal distribution, transformations of the data (e.g. logarithmic, square root) were applied or non-parametric tests appropriate for non-normally distributed variables were used.

Point biserial correlations were used to analyze continuous independent variables and the dichotomous variable of a positive/negative CAM (i.e. determined to be

delirious/not determined to be delirious). The covariance between non-continuous independent variables and the dichotomous variable of a positive/negative CAM was analyzed using the appropriate non-parametric statistic. Chi square statistics were calculated to evaluate the relationship between dichotomous independent variables and the dichotomous variable of a positive/negative CAM.

Logistic regression (LR) was used to model the relationships between AL and delirium and between specific subsets of AL and delirium. Specifically, LR was used to address the following research questions:

#1, “Does the composite value of AL predict delirium in hospitalized elders?”

#2a: “Does the composite value of the subset of AL components that are considered primary mediators, urinary cortisol, norepinephrine and epinephrine and serum dihydroepiandrosterone sulfate (DHEAS)) predict delirium in hospitalized elders?”

#2b: “Does the composite value of the subset of AL components that are considered secondary outcomes, systolic and diastolic blood pressure (BP), waist-to-hip ratio (WHR), serum high-density lipoprotein (HDL) and glycosylated hemoglobin (HgbA_{1c}), and the total cholesterol/high-density lipoprotein (TC/HDL) ratio predict delirium in hospitalized elders?”

Protection of Human Subjects

Human Subject Involvement and Characteristics

The purpose of this study was to describe the relationship between AL and delirium in the hospitalized elder. Hospitalized patients 65 years of age and older were recruited. The nursing staff contacted the patient and/or the patient’s guardian and asked

permission for the researcher to discuss the study. After verbal consent was given by the potential participant, the researcher met with the potential participant and their guardian (if present) to discuss the research project and answer all questions.

Men and women 65 years and older who had been admitted to one of three ICU's were recruited. Criteria for inclusion were men and women sixty-five years of age and older who had been admitted to an ICU who were able to speak and understand English. Exclusion criteria included communication problems (e.g. inability to speak, such as with mechanically ventilated participants, blindness and/or deafness), anuria, and use of exogenous steroids.

Security of Materials

Materials obtained from participants included samples of blood and urine and oral and written paper and pencil measures. Registered nurses in the ICU obtained all blood samples following hospital policies and procedures for specimen collection, processing and transfer to the laboratory. The clinical laboratories at the study hospital have established procedures for monitoring and evaluating the quality and security of the collection and testing process (personal communication, L. Burnham, July 1, 2008). Laboratory personnel entered results of laboratory testing directly into the participant's electronic medical record.

The investigator recorded or transcribed all study data onto pre-printed worksheets identified only with a sequential code number to ensure participant confidentiality. Only the investigator had access to the data. A locked cabinet in the investigator's College of Nursing office held all completed data forms and a backup disk

of the electronic data. A password-protected computer in the same office held all the electronic data. A master list with participants' names and their corresponding code numbers was stored in a different locked file cabinet.

Potential Risks

Participants may be bothered by the discussion of delirium and concerned by their own risk for developing delirium. Participants potentially may feel bothered by responding to the questions asked and by the evaluations that may seem inconvenient or personal in nature.

Venipuncture has minimal risks. To minimize any risk, RNs who were hospital employees, following hospital policies and procedures, performed all venipuncture. Participants had the right to refuse venipuncture. Approximately 9 cc's of blood was obtained from each participant. Participants were sitting or lying down during the procedure. Participants undergoing venipuncture may experience slight discomfort upon needle insertion, drawing of blood and needle withdrawal. Some bleeding at the puncture site may occur. No physical risk to the subject, other than a rare syncopal attack, was contemplated. The rate of syncope after blood donation is less than 3% (Newman, 2002) and may be as low as 1.6% in the general population (Kasprisin, Glynn, Taylor, & Miller, 1993). A small minority of patients may experience symptoms of anxiety associated with venipuncture (Deacon & Abramowitz, 2006). Whenever possible, blood samples were collected when another sample was required in order to limit the number of venipunctures a participant must undergo.

Protection Against Risks

The researcher obtained approval from the Institutional Review Board (IRB) of the University of Arizona and the Nursing Research and Evidence-Based Practice Committee of the study hospital (Appendix D). Additional approval was sought from managers and administrators where appropriate. Data collection was for the exclusive purpose of this research project. Identifying information was not used in the reporting of data. Adverse events were to be reported immediately to the appropriate IRB.

All ICU rooms were single use, allowing for greater privacy. All interviews and assessments were done in private with a door or curtain barrier in place. The participant's call light remained within reach of the participant at all times. At no time was any monitoring equipment or medical devices disconnected during data collection. All medical and nursing prescriptions were complied with, e.g. specific positions, activity level, etc., at all times. The participant's nurse had access to the participant at all times and in the event the participant became distressed or unstable, the researcher notified the nurse assigned to the participant immediately. In the event the participant was determined to be delirious, the investigator notified the nurse assigned to the participant immediately.

Potential Benefits of the Proposed Research to the Participants

This research had no claim of direct potential benefit to any one individual participant. Rather, information and insights gained from this study could lead to a better theoretical understanding of the physiological mechanisms of delirium. This

understanding may lead to better prediction and subsequent screening of those at risk and the development of early interventions to protect hospitalized elderly.

Inclusion of Women and Minorities

Both men and women were recruited. The research included all potential participants who were age 65 and older, limited only by the available population. The proposed gender and ethnic/racial composition of the sample attempted to meet the same gender and ethnic/racial representation seen in the ICU population at the study hospital.

Summary

This descriptive study examined the ability of AL to predict delirium in hospitalized older adults. This study used a nonexperimental design to answer the research questions. The purpose of this study was to determine the relationship between AL and delirium in the hospitalized elder. The purpose of this study was to investigate the relationship of allostatic load (AL), a composite measure of primary (i.e. acute) stress mediators and secondary (i.e. chronic) stress outcomes and delirium in the hospitalized older adult. Development of the Allostatic Load & Delirium in Hospitalized Elderly model provided a theoretical framework for the study.

A nonexperimental design was used to investigate the relationship of AL, a composite measure of primary (i.e. acute) stress mediators and secondary (i.e. chronic) stress outcomes and delirium in the hospitalized older adult. Participants were recruited from three ICUs in a private, nonprofit 365-bed hospital located in a university health sciences center. After recruitment and informed consent, the SMMSE was administered to assess for cognitive dysfunction and the CAM was used to assess for prevalent

delirium. If a participant had an SMMSE score of 25 or less and/or a positive CAM they were excluded from the study. Allostatic load data were collected on the day of admission to the ICU. The CAM was administered 48 – 72 hours after admission to identify incident delirium in the sample.

Descriptive statistics were used to analyze demographic and medical variables. Bivariate statistics were used to describe relationships between variables of interest. Logistic regression was used to answer the research questions. The research procedures and data management plan were described, along with the plan for protection of human subjects.

CHAPTER IV: RESULTS

Overview

The aims of this study were to: (1) determine if AL predicts delirium in hospitalized elders and (2) determine if specific subsets of components that comprise AL predict delirium in hospitalized elders. The Statistical Package for Social Sciences (SPSS, version 16.0; 2007) was used for data analysis. A p-value of < 0.05 was the criterion used to determine statistical significance.

Univariate Analysis

The first phase of the analysis was to examine the baseline characteristics of the sample using descriptive statistics. This univariate analysis included calculating frequencies for categorical variables and the mean, median, range and standard deviation (SD) for continuous variables. The distribution of each variable was examined using a graphical check (e.g. construction of a histogram) and a test of normality (e.g. Shapiro-Wilk statistic). If the variables seriously deviated from a normal distribution, transformations of the data (e.g. logarithmic, square root) were applied or non-parametric tests appropriate for non-normally distributed variables were used.

Forty-eight participants were recruited. The participants consisted of 28 males (58%) and 20 females (42%) between the ages of 66 and 93 years with a mean age of 75.8 years (SD = 6.42). Participants' race/ethnic status included 43 Caucasians (90%), 4 of Hispanic origin (8%), and 1 American Indian (2%) (Table 6). Gender was analyzed as a dichotomous variable (male = 1, female = 2). Age was estimated from date of birth to create a continuous variable for age at admission to the study. Race/ethnic status was

treated as a categorical variable (0 = American Indian/Alaskan native, 1 = Asian/Pacific Islander, 2 = Black/African American, 4 = White/Caucasian, 5 = Other).

There were missing data for 4 participants; 2 were discharged in less than 24 hours (treatment plan was changed from a surgical intervention to a medical intervention), one did not have laboratory data available to complete the calculation of AL due to a collection error, and one had surgery rescheduled to a date outside the study period. Demographic and other relevant variables for the remaining 44 participants are described below (Table 6; Table 7).

There were no significant differences in mean age or SMMSE scores between participants who underwent AL testing and follow-up delirium assessment and those who did not.

Admitting diagnoses included cardiovascular, respiratory and peripheral vascular disease, stroke, subdural hematoma, cancer, spinal stenosis and odontoid fracture. Thirty-seven participants were admitted for surgery and seven were treated medically. Admitting

Table 6

Demographic Variables (N=44)

Variable	N (%)	Mean/Median (SD)	Range
Age		75.70/76 (6.422)	66 – 93
Gender: Male	25 (57%)		
Female	19 (43%)		
Race: Caucasian	40 (91%)		
Hispanic	3 (7%)		
American Indian	1 (2%)		

Note: SD- standard deviation

diagnoses were treated as a categorical variable. Type of admission was treated as a dichotomous variable (medical = 0, surgical = 1).

The majority of participants had comorbid conditions in addition to their admitting diagnosis. The number of comorbid conditions ranged from 0 to 12 with a mean of 5.00 (SD = 2.84). All participants were taking medications prior to admission,

Table 7

Other Variables of Interest (N=44)

Variable	N (%)	Mean/Median (SD)	Range
Admitting Diagnosis:			
Coronary artery disease	11 (25%)		
Lung cancer	7 (16%)		
Spinal stenosis	6 (14%)		
Aortic Aneurysm	4 (9%)		
Pancreatic cancer	4 (9%)		
Valvular disease	4 (9%)		
Peripheral vascular disease	2 (4.5%)		
Subdural hematoma	2 (4.5%)		
Chronic obstructive pulmonary disease	1 (2%)		
Congestive heart failure	1 (2%)		
Pulmonary fibrosis	1 (2%)		
Stroke	1 (2%)		
Odontoid fracture	1 (2%)		
Treatment:			
Surgical	37 (84%)		
Medical	7 (16%)		
Alcohol use:			
No	31 (70%)		
Yes	13 (30%)		
Past medical diagnosis (#)		5.00/4.5 (2.84)	0 – 12
Outpatient medications (#)		5.86/6.0 (2.66)	1 – 12
Inpatient medications (#)		8.34/8.0 (2.89)	4 – 15

Note: SD- standard deviation

ranging from 1-12 medications with a mean of 5.86 (SD = 2.66) and all participants were taking medications after admission to the ICU, ranging from 4 – 15 medications with a mean of 8.34 (SD = 2.89). The number of comorbid conditions, outpatient medications and inpatient medications per participant were analyzed as three separate continuous variables.

Seventy percent of the participants drank alcohol regularly. Alcohol use was treated as a dichotomous variable (0 = No, 1 = Yes).

The mean score on the SMMSE was 28.8 (SD = 1.41) with scores ranging from 25 to 30. For those participants found to be delirious 48 -72 hours after admission, the mean SMMSE score was 28.4 (SD = 1.59) and in those participants found not to be delirious the mean SMMSE score was 28.9 (SD = 1.35). The difference in SMMSE scores by delirium status was not significant ($U = 198.5, p = .759, r = -.007$). Scores on the SMMSE were analyzed as a continuous variable. This variable had a negatively skewed distribution. Therefore, non-parametric statistics were used.

Allostatic Load Scoring

The mean AL score was 3.64 (SD = 1.08) ($n = 44$) and ranged from 1 to 5 with a median of 4. The mean AL score based on primary mediators was 2.25 (SD = .92) and ranged from 0 to 4 with a median score of 2. The mean AL score based on components secondary outcomes was 1.39 (SD = .92) and ranged from 0 to 3 with a median score of 1.5. The AL score, as well as the subset scores, were treated as continuous variables.

In the original studies, the AL score was calculated in community-dwelling older adults by summing the number of parameters for which the older adult fell into the high-

risk quartile (Seeman, Crimmins et al., 2004a; Seeman, Singer et al., 1997a; e.g., Seeman, Unger, McAvay, & Mendes de Leon, 1999). High-risk quartiles were determined by analyzing the distribution of values in the sample studied..

The researcher considered that older adults who have been hospitalized in an ICU are exposed to different levels of stress than the older community-dwelling adults studied by Seeman and colleagues and using the same cut-off points to determine highest risk quartile may not be appropriate. Therefore, using the same AL data, high-risk quartiles were redefined using the distribution of scores for each parameter in the study sample.

For each of the 10 AL indicators, study participants were classified into quartiles based on the distribution of values. Allostatic load was measured by summing the number of parameters for which the participant fell into the highest-risk quartile (i.e. highest quartile for all parameters, except HDL and DHEAS for which membership in the lowest quartile corresponded to highest risk). The high-risk quartiles for all 10 AL parameters in this sample were different from the high-risk quartiles used in original studies (Table 8).

The recalculated mean AL score based on the sample in this study, was 2.48 (SD = 1.29) and ranged from 0 to 6 with a median of 2.5. The mean AL subset score based on primary mediators was 0.98 (SD = .89) and ranged from 0 to 3 with a median score of 1. The mean AL subset score based on secondary outcomes was 1.48 (SD = 1.19) and ranged from 0 to 5 with a median score of 1.5. The recalculated AL score, as well as the recalculated subset scores, were treated as continuous variables.

Each of the ten parameters of AL (SBP, DBP, WHR, HgbA_{1c}, TC/HDL ratio, HDL, serum DHEAs, and urinary cortisol, epinephrine and norepinephrine) were treated

Table 8

Components of Allostatic Load

Component	Community-dwelling elders*	Elders Admitted to the ICU	
<i>Highest quartile</i>			
Systolic BP	≥ 148 mm Hg	Systolic BP	≥ 144 mm Hg
Diastolic BP	≥ 83 mm Hg	Diastolic BP	≥ 81 mm Hg
WHR	≥ 0.94	WHR	≥ 1.07
TC/HDL ratio	≥ 5.90	TC/HDL ratio	≥ 3.92
HgbA _{1c}	$\geq 7.1\%$	HgbA _{1c}	$\geq 5.9\%$
Urinary cortisol	≥ 25.7 ug/g creatinine	Urinary cortisol	≥ 134.1 ug/g cre
Urinary norepinephrine	≥ 48 ug/g creatinine	Urinary norepinephrine	≥ 76.5 ug/g cre
Urinary epinephrine	≥ 5 ug/g creatinine	Urinary epinephrine	≥ 19.8 ug/g cre
<i>Lowest quartile</i>			
HDL	≤ 37 mg/dl	HDL	≤ 27 mg/dl
DHEA-s	≤ 35 ug/dl	DHEA-S	≤ 43 ug/dl

Note: * (Seeman, Singer et al., 1997a). cre = creatinine, ICU = Intensive care unit. Highest quartile cut-off is $>75\%$ percentile. Lowest quartile cut-off is $<25\%$ percentile. Results for the urinary components are reported as milligram per gram of creatinine to adjust for body size.

as continuous variables. Five of these variables were not normally distributed (HgbA_{1c}, serum DHEAs, and urinary cortisol, epinephrine and norepinephrine). Review of the data revealed several outliers in the distribution of these five variables. The outliers were not removed as they were valid values in the sample and were considered to indicate the range of findings under study. However, logarithmic transformation resulted in a normal distribution for serum DHEA-S, and urinary epinephrine and norepinephrine.

Logarithmic transformation can be used to normalize skewed data and stabilize the variance of a sample (Field, 2003). Logarithmic transformation consists of taking the log of each observation in the data set (in this analysis, log to the base 10). Urinary

cortisol and HgbA_{1c} were resistant to transformation and non-parametric statistics were used as appropriate.

Delirium Assessment

The CAM diagnostic algorithm was used to identify prevalent delirium at admission (exclusion criterion). Reassessment with the CAM diagnostic algorithm was conducted 48 to 72 hours after admission to assess for incident delirium. The CAM findings were treated as a dichotomous variable (1 = no delirium, 2 = delirium). No prevalent cases of delirium were discovered. Fourteen participants were determined to have delirium 48 to 72 hours after admission. The overall incidence of delirium was 29.2% (95% CI = 15.3 - 42.7%). The remaining 31 participants were not confirmed to have delirium during the 48 – 72 hour study period. The 37 participants admitted for a surgical procedure had a higher incidence of delirium than did the seven participants admitted for medical reasons (32.4% vs. 28.6%).

Correlational Analysis

In the second phase of the analysis the covariance between variables was examined. The bivariate analysis included calculating point biserial correlations between continuous variables and the dichotomous variable of a positive/negative CAM finding (i.e. determined to be delirious/not determined to be delirious). The covariances between non-continuous variables and the categorical variable of a positive CAM finding were analyzed using the appropriate non-parametric statistic.

A correlation matrix of all continuous variables and delirium was constructed (Table 9). The matrix was examined for expected and unexpected covariances. Zero-order

Table 9

Zero Order Correlations- Variables of Interest

Variables	Delirium	SMMSE	AL	AL chronic	AL acute	AL2	AL2 chronic	AL2 acute	Age	PMH	Outpt meds
SMMSE	-.04+										
AL	.04	.22									
AL-chronic	-.13	.21	.59**								
AL-acute	.13	.05	.59**	-.31*							
AL2	.11	.21	.38**	.35*	.09						
AL2- chro	-.10	.21	.27*	.63**	.32*	.76**					
AL2- -acute	.31*	.00	.16	-.36**	.56**	.47**	-.21				
Age	.14	-.25*+	-.12	-.13	-.02	-.18	-.18	-.02			
PMH	.01	-.16+	-.06	-.10	.03	-.04	-.01	-.05	.41**		
Outpt Meds	.15	-.09	-.13	-.07	-.08	-.05	.06	-.09	.11	.40**	
Inpt Meds	.06	-.19	.01	-.14	.15	-.14	-.11	-.07	-.17	.25	.40**

Note: AL- allostatic load, AL2 – recalculated allostatic load, inpt- inpatient, meds- medications, outpt- outpatient, PMH- past medical history, SMMSE- Standardized Mini-Mental Status Examination, + Kendall's tau, * $p < .05$, ** $p < .01$

correlations demonstrated that the recalculated subset AL score based on components considered primary stress mediators was significantly related to delirium ($rpb = .31, p < .05$). No other continuous variables were associated with delirium. Age and PMH demonstrated a significant relationship ($r = .41, p < .01$), as did age and SMMSE scores ($\tau = -.25, p < .05$). Past medical history and outpatient medications demonstrated a significant relationship ($r = .40, p < .01$), as did outpatient medications and inpatient medications ($r = .40, p < .01$). As would be expected, the subset scores of AL were significantly related to the overall AL score.

A second correlation matrix of the continuous variables that made up the composite AL score, age and the dependent variable was constructed (Table 10). The matrix was examined for expected and unexpected covariances. The zero-order correlations revealed that none of the individual AL variables were significantly related to delirium. The WHR was

Table 10

Zero Order Correlations- Allostatic Load Parameters

	Delirium	SBP	DBP	WHR	DHEAS	TC/HDL	HDL	HgBA _{1c}	UNorepi	UEpi	UCort
SBP	.119										
DBP	.239	.202									
WHR	-.237	.010	.076								
DHEAS	.098	.140	.005	.027							
TC/HDL	-.015	.170	.187	.348*	.111						
HDL	.138	.160	-.285	-.339*	-.119	-.435**					
HgBA _{1c}	.046+	.127+	-.020+	.128+	-.090+	.132+	.008+				
UNorepi	.019	-.023	.017	.057	.121	-.231	.021	.100+			
UEpi	-.043	-.229	.160	.105	.180	.103	.354*	-.106+	.106		
UCort	.238+	.117+	.002+	-.277**+	.055+	-.149+	.154+	-.100+	.176+	.058+	
Age	.162	-.040	-.098	-.266	-.201	-.093	-.151	-.187+	-.007	-.009	.212*+

Note: DBP- diastolic blood pressure, DHEAS- dihydroepiandrosterone sulfate, HDL- High density lipoprotein, HgBA_{1c}- glycosylated hemoglobin, SBP- systolic blood pressure, TC/HDL- total cholesterol/high density lipoprotein ratio, UNorepi- urinary norepinephrine, UEpi- urinary epinephrine, UCort- urinary cortisol, WHR- waist-hip ratio. + Kendall's tau, * p<.05, **p<.01.

significantly related to TC/HDL ratio ($\tau = .35, p < .05$) and inversely related to HDL ($\tau = -.34, p < .05$). The WHR also had a significant inverse relationship with urinary cortisol ($\tau = .28, p < .05$), as did urinary cortisol and age ($\tau = -.21, p < .05$). High-density lipoprotein had a significant relationship with urinary epinephrine ($\tau = .35, p < .05$) and, as anticipated, TC/HDL ratio had a significant relationship with HDL ($\tau = -.44, p < .05$).

When calculating numerous correlations, the general nature of statistical significance dictate that significant results will be found due to chance (Field, 2003). For example, by definition, a coefficient significant at the .05 level will occur by chance once in every 20 coefficients. Thus, all results not predicted or planned should be interpreted with particular caution and consistency with other results sought.

Chi square statistics were calculated when both variables were dichotomous.

There was no significant difference in expected frequencies between gender and delirium ($X^2 = .50, df = 1, p = .48$) or alcohol use and delirium ($X^2 = 1.31, df = 1, p = .25$).

A dummy variable was created for race (0 = White or Caucasian, 1 = not White or Caucasian). There was no significant difference in expected frequencies between these two groups and delirium ($X^2 = .32, df = 1, p = .57$), although due to a small number of participants in the *not White or Caucasian* group (< 5 participants in each cell), this group comparison should be considered suspect as there is a probability of erroneous results (Field, 2003).

Logistic Regression

The final phase of data analysis consisted of modeling the relationship between delirium and a set of covariates, as well as addressing the research aims. Logistic regression (LR) is a statistical model appropriate for dichotomous outcomes (Peng, Lee & Ingersoll, 2003). Logistic regression does not assume linearity of relationship between the independent variables and the dependent variable, does not require normally distributed variables, does not assume homoscedasticity, and in general has less stringent requirements than other models, such as discriminant function analysis or ordinary least squares regression (Field, 2003; Peng & So, 2002). Instead, LR assumes that the binomial distribution describes the same probability across the range of predictor values (Peng & So). The binomial assumption is known to be robust as long as the sample is random and observations are independent from each other.

In this study, LR modeling provided an estimate of the probability of delirium occurring given particular predictor (i.e., independent) variables. Specifically, the dependent variable (in this case delirium) is defined as the natural logarithm of the odds of disease, or the logit (Peng, et al., 2002). The coefficients obtained through LR denote the magnitude of the increase or decrease in the log odds produced by one unit of change in the value of an predictor variable, while controlling for the effects of the other variables in the model (Peng, et al.).

An odds ratio can be calculated by exponentiating the beta coefficients (Field, 2003). An odds ratio (OR) of 1.0 indicates that there is no association between the predictor variable and the incidence of delirium. A value greater than 1.0 indicates a positive association or increased risk of delirium. Conversely, an OR less than 1.0 means there is an inverse association or a decreased risk. Odds ratios provide a valid estimate of relative risk and confidence limits around this estimate of relative risk can be obtained using the beta coefficient and its related standard error (Field). Unadjusted ORs were calculated as the ratio of number of incident cases of delirium when the AL parameter was present versus the number when the parameter was absent.

The use of R^2 , the coefficient of determination, is well established in linear regression. It is defined as the proportion of variance in the dependent variable that can be explained by predictors in the model (Field, 2003). While there is no true equivalent for this concept in the LR model, several analogues have been proposed. Hosmer and Lemeshow's R^2 is calculated by dividing the model chi-square by the original log-likelihood of the model before any predictors are entered (Peng & So, 2002). Cox and

Snell's R^2 is based on the log-likelihood of the new model, the log-likelihood of the original model and the sample size (Peng & So). Nagelkerke's R^2 amends Cox and Snell's R^2 so that the statistic reaches its theoretical maximum of 1 (Field, 2003).

Collectively these R^2 statistics provide some insight into the substantive significance of the model being evaluated (Field, 2003), although it is recommended these statistics be treated as supplementary to other, more useful indices of evaluation, such as overall evaluation of the model and the tests of individual regression coefficients (Peng & So).

Research Question One

Research question one, "Does the composite value of AL predict delirium in hospitalized elders?" was examined by logistic regression. Delirium was regressed on the predictor variable of the composite AL score. Overall, the logistic regression model did not demonstrate an improvement over the intercept-only model (Table 11). The individual regression coefficient was not a significant predictor of delirium.

Table 11

Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium (N = 44)

Variable	β (SE)	Wald's X^2 (df)	p	e^{β} (odds ratio)
Constant	-.793 (1.151)	.474(1)	.49	NA
AL	.008 (.303)	.001(1)	.98	1.008

Note. $R^2 = .00$ (Hosmer & Lemeshow), $.00$ (Cox & Snell), $.30$ (Nagelkerke). Model X^2 (1) = $.001$, $p = .98$. AL- allostatic load.

As an alternative, delirium was regressed on the composite value of the AL score calculated specifically in this sample of hospitalized older adults. Overall, the logistic regression model did not demonstrate an improvement over the intercept-only model (Table 12). The individual regression coefficient was not a significant predictor of delirium.

Table 12

Summary of Logistic Regression Analysis for Alternative Composite Value of Allostatic Load Variable Predicting Delirium (N = 44)

Variable	β (SE)	Wald's χ^2 (df)	p	e^β (odds ratio)
Constant	-1.876 (.815)	5.303(1)	<.05	NA
AL	.429 (.275)	2.430(1)	.12	1.536

Note. $R^2 = .05$ (Hosmer & Lemeshow), $.06$ (Cox & Snell), $.08$ (Nagelkerke). Model χ^2 (1) = 2.642, $p = .10$. AL- allostatic load.

Research Question Two

Research question 2a, “Does the composite value of AL components considered primary mediators, urinary cortisol, norepinephrine, and epinephrine and serum dihydroepiandrosterone sulfate (DHEA), predict delirium in hospitalized elders?” was examined by logistic regression. Delirium was regressed on the predictor variable of the AL subset score based on primary mediators. The AL subset score based on primary mediators was calculated using the criterion cutoff points described in the original study. Overall, the logistic regression model did not demonstrate an improvement over the intercept-only model (Table 13). The individual regression coefficient was not a significant predictor of delirium.

Table 13

*Summary of Logistic Regression Analysis for Composite Value of Allostatic Load
Variable Predicting Delirium (N = 44)*

Variable	β (SE)	Wald's X^2 (df)	p	e^β (odds ratio)
Constant	-1.511 (.924)	2.672(1)	.10	NA
AL	.326 (.369)	.782(1)	.37	1.385

Note. $R^2 = .01$ (Hosmer & Lemeshow), $.02$ (Cox & Snell), $.03$ (Nagelkerke). Model $X^2(1) = .806, p = .37$. AL- allostatic load.

As an alternative, delirium was regressed on the AL subset score based on primary mediators calculated specifically in this sample of hospitalized older adults. Overall, the logistic regression model demonstrated significant improvement over the intercept-only model (Table 14). The individual regression coefficient was a significant predictor of delirium and correctly predicted 73.4% of the total cases of delirium. For every unit that the AL subset score based on primary mediators increased, there was a 2.54 (95% CI = 1.12, 5.79) relative risk for developing delirium.

Table 14

*Summary of Logistic Regression Analysis for Composite Value of Allostatic Load
Variable Predicting Delirium (N = 44)*

Variable	β (SE)	Wald's X^2 (df)	p	e^β (odds ratio)
Constant	-1.774 (.601)	8.709(1)	<.05	NA
AL	.933 (.420)	4.938(1)	<.05	2.543

Note. $R^2 = .11$ (Hosmer & Lemeshow), $.12$ (Cox & Snell), $.17$ (Nagelkerke). Model $X^2(1) = 5.668, p < .05$. AL- allostatic load.

Research question 2b, “Does the composite value of AL components considered secondary outcomes, SBP, DBP, WHR, HDL, TC/HDL ratio, and HgbA_{1c}, predict delirium in hospitalized elders?” was examined by logistic regression. Delirium was regressed on the predictor variable of the AL subset score based on secondary outcomes. The AL subset score based on secondary outcomes was calculated using the criterion cutoff points described in the original study. Overall, the logistic regression model did not demonstrate an improvement over the intercept-only model (Table 15). The individual regression coefficient was not a significant predictor of delirium.

Table 15

Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium (N = 44)

Variable	β (SE)	Wald's X^2 (df)	<i>p</i>	e^{β} (odds ratio)
Constant	-.350 (.570)	.378(1)	.54	NA
AL	-.307 (.361)	.725(1)	.40	.736

Note. $R^2 = .01$ (Hosmer & Lemeshow), $.02$ (Cox & Snell), $.02$ (Nagelkerke). Model $X^2(1) = .736, p = .39$. AL- allostatic load.

As an alternative, delirium was regressed on the composite value of the AL subset score based on secondary outcomes calculated specifically in this sample of hospitalized older adults. Overall, the logistic regression model did not demonstrate an improvement over the intercept-only model (Table 16). The individual regression coefficient was not a significant predictor of delirium.

Table 16

Summary of Logistic Regression Analysis for Composite Value of Allostatic Load Variable Predicting Delirium (N = 44)

Variable	β (SE)	Wald's X^2 (df)	p	e^β (odds ratio)
Constant	-.798 (.521)	2.344(1)	.13	NA
AL	.024 (.274)	.008(1)	.93	1.024

Note. $R^2 = .01$ (Hosmer & Lemeshow), .01 (Cox & Snell), .02 (Nagelkerke). Model X^2 (1) = .008, $p = .93$. AL- allostatic load.

Exploratory Analysis

Logistic regression then was used to evaluate the relationship between delirium as the dependent variable and the ten continuous variables that make up AL. The predictor variables entered into the regression model were SBP, DBP, WHR, DHEAS, TC/HDL ratio, HDL, HbG_{A1c}, and urinary epinephrine, norepinephrine and cortisol. The logistic regression model did not demonstrate an improvement over the intercept-only model (Table 17). None of the individual regression coefficients were significant predictors of delirium when entered simultaneously. Another analysis was performed where the predictor variables were entered in a backward stepwise fashion. There was no significant change in results.

A second analysis was performed adding SMMSE, age, gender, a dummy variable for race (0 = White; 1 = Not White), alcohol use (0 = No, 1 = Yes), number of past medical diagnoses, number of outpatient medications, and number of inpatient medications. Although the second analysis provided a better fit to the data ($\Delta R_L^2 = .31$, Analysis 2: -2 Log Likelihood=36.20 compared to Analysis 1: -2 Log

Table 17

Summary of Simultaneous Logistic Regression Analysis for All Allostatic Load Variables Predicting Delirium (N = 44)

Variable	β (SE)	Wald's X^2 (df)	p	e^β (odds ratio)
Constant	.225 (6.136)	.001(1)	.97	NA
SBP	.004 (.023)	.023(1)	.88	1.004
DBP	.060 (.038)	2.511(1)	.11	1.062
WHR	-6.081 (3.847)	2.498(1)	.11	.002
DHEAS	-.005 (.007)	.538(1)	.46	.995
TC/HDL	.335 (.536)	.390(1)	.53	1.397
HDL	.041 (.038)	1.178(1)	.28	1.042
HgbA _{1c}	-.455 (.687)	.438(1)	.51	.635
UEpi	.034 (.026)	1.624(1)	.20	1.034
UNorepi	.001 (.006)	.033(1)	.86	1.001
UCort	-.001 (.001)	1.033(1)	.31	.999

Note. $R^2 = .21$ (Hosmer & Lemeshow), $.23$ (Cox & Snell), $.32$ (Nagelkerke). Model X^2 (10) = 11.32, $p = .33$. DBP- diastolic blood pressure, DHEAS- dihydroepiandrosterone sulfate, HDL- High density lipoprotein, HgbA_{1c}- glycosylated hemoglobin, SBP- systolic blood pressure, TC/HDL- total cholesterol/high density lipoprotein ratio, UNorepi- urinary norepinephrine, UEpi- urinary epinephrine, UCort- urinary cortisol, WHR- waist-hip ratio.

Likelihood=47.73), this difference was not significant ($X^2(18) = 18.844, p = .40$). None of the individual regression coefficients were significant predictors of delirium.

Summary

Results from the analysis of data collected in a sample of older adults hospitalized in an ICU were presented in this chapter. Descriptive statistics were used to characterize the sample. Correlational analyses were used to explore the relationships between variables. Finally, LR was used to address the research questions and to conduct an exploratory analysis of the data.

Logistic regression modeling was used to address research question one, “Does the composite value of AL predict delirium in hospitalized elders?” Allostatic load was not a significant predictor of delirium. The use of an alternative scoring of AL calculated specifically in this sample of hospitalized older adults did not aid in the prediction of delirium.

Logistic regression modeling was used to address research question 2a, “Does the composite value of the subset of AL components considered primary mediators, urinary cortisol, norepinephrine, and epinephrine and serum dihydroepiandrosterone sulfate (DHEAS), predict delirium in hospitalized elders?” This AL subset score was not a significant predictor of delirium.

The use of an alternative scoring of the AL subset based on primary mediators calculated specifically in this sample of hospitalized older adults did aid in the prediction of delirium. The AL subset score based on primary mediators was a significant predictor of delirium and correctly predicted 73.4% of the total cases of delirium. As the value of this AL subset score based on primary mediators increased, so did the odds of developing delirium.

Logistic regression modeling was used to address research question 2b, “Does the composite value of the subset of AL components considered secondary outcomes, systolic and diastolic blood pressure (BP), waist-to-hip ratio (WHR), serum high-density lipoprotein (HDL) and glycosylated hemoglobin (HgbA_{1c}), and the total cholesterol/high-density lipoprotein (TC/HDL) ratio predict delirium in hospitalized elders?” The AL subset score based on secondary outcomes was not a significant predictor of delirium.

The use of an alternative scoring of the AL subset based on secondary outcomes calculated specifically in this sample of hospitalized older adults did not aid in the prediction of delirium.

CHAPTER V: DISCUSSION

Introduction

In this chapter, each research question is addressed and study findings are discussed. Implications of the study for both the AL and delirium literature are presented. This is followed by a discussion of the limitations of this study. The chapter concludes with discussion of topics for further study.

This study examined the ability of AL, and subsets of AL, to predict delirium in hospitalized older adults. The results showed that the AL subset score based on primary mediators calculated specifically in this sample of hospitalized older adults predicted delirium. This was the first study to explore the relationship between AL, and subsets of AL, and delirium in the hospitalized older adult.

Conclusions from additional analyses showed that age was related to PMH, as was PMH and outpatient medications and inpatient and outpatient medications ($p < .01$). When the individual parameters of AL were analyzed, significant relationships were seen between WHR and TC/HDL ratio ($p < .05$), WHR and HDL ($p < .05$), WHR and urinary cortisol ($p < .01$), and HDL and urinary epinephrine ($p < .05$). Another analysis demonstrated that urinary cortisol was related to age ($p < .05$). The results of this study offer support for the importance of a multi-system stress response comprised of an AL measure of primary (i.e. acute) stress mediators, in the consideration of delirium in the hospitalized older adult.

Research Questions

Research Question One

Research question one: “Does AL predict delirium in hospitalized elders?” was examined by logistic regression modeling. To address this question, delirium was regressed on the composite AL score. Model analysis results indicated no improvement in predicting delirium over the null model, that is, the model with no predictor factors or covariates included. Similarly, there was no improvement over the null model when logistic regression was used to model the relationship between delirium and the composite AL score as calculated specifically for this sample.

Research Question Two

The first part of research question two: “Does the composite value of the subset of AL components considered primary mediators, urinary cortisol, norepinephrine, and epinephrine and serum dihydroepiandrosterone sulfate (DHEAS), predict delirium in hospitalized elders? was examined by logistic regression. When delirium was regressed on the AL subset score based on primary mediators, there was no improvement over the null model. However, when delirium was regressed on the AL subset score based on primary mediators calculated specifically for this sample, the logistic regression model demonstrated improvement over the null model. The regression coefficient for this particular AL subset score (i.e., primary mediators) was a significant predictor of delirium and correctly predicted 73.4% of the total cases of delirium.

The second part of research question two, Does the composite value of the subset of AL components considered secondary outcomes, systolic and diastolic blood pressure

(BP), waist-to-hip ratio (WHR), serum high-density lipoprotein (HDL) and glycosylated hemoglobin (HgbA_{1c}), and the total cholesterol/high-density lipoprotein (TC/HDL) ratio predict delirium in hospitalized elders?" was examined by logistic regression. Delirium was regressed on the predictor variable of the AL subset score based on secondary outcomes. Delirium was also regressed on the AL subset score based on secondary outcomes calculated specifically for this sample. Neither model showed any improvement over the null model.

Characteristics of the Study Participants

Adults 65 years of age and older were recruited. The mean age of participants was 75.8, with ages ranging from 66 to 93. Other studies of delirium in hospitalized older adults greater than 65 years of age report mean ages of 75.2 to 85.4 (Duppils & Wikblad, 2004; 1994, p. 211). Prior studies of delirium in the ICU patient did not restrict enrollment to older adults greater than 65 years of age, rather, all ICU patients were included in the investigations (e.g., Ely, Shintani et al., 2004; Granberg-Axell, Malmros, Bergbom, & Lundberg, 2002).

Fifty-seven percent of the participants were male. Other studies of delirium have reported gender composition ranging from 10% to 86% men (Granberg Axell et al., 2002; Rahkonen et al., 2001).

In this study, 90% of the participants were White or Caucasian, 8% were Hispanic and 2% were American Indian. The few delirium studies that did present race or ethnic background data (e.g., Ely, Shintani et al., 2004; Ely, Stephens et al., 2004), reported that 79 – 84% of the sample was White or Caucasian. A comparison with nonpublished data

from the study hospital found that the race or ethnic background of participants in this study differed from those admitted to the same ICUs in the 12 months prior to this study. In that time period, 69.2% of patients admitted to these ICUs were White or Caucasian, 17.4% were Hispanic, 5.4% were American Indian, 2.5% were Black American, 0.9% were Asian-American and 4.6% were unclassified (personal communication, M. Horner, August 1, 2008). There was no differentiation between opportunities for subjects to participate based on ethnic/racial status. Recruiting a larger sample from this hospital population might have attenuated these differences.

Participants had an average of five comorbid conditions and were taking an average of six medications on an outpatient basis. General health status is described in a number of ways in the delirium literature, making comparison difficult. Researchers have used the Charlson comorbidity scale, a summary measure of 19 categories of comorbidity (Charlson, Pompei, Ales, & MacKenzie, 1987); the Acute Physiology & Chronic Health Evaluation, which is based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease (Knaus, Draper, Wagner, & Zimmerman, 1985); the American Society of Anesthesiology classification, an index of physical status used as a means to stratify a patient's systemic illness (Wolters, Wolf, Stutzwe, & Schroder, 1996); and/or, as in this study, counting comorbid conditions and the number of medications being taken at admission (Olofsson et al., 2005; Vida et al., 2006).

Once the participant was admitted to the hospital, an average of 8.34 medications was prescribed. A variety of admitting diagnoses were seen and the majority of

participants entered the hospital for a surgical procedure. All patients admitted for surgery, as well as participants admitted with a medical diagnosis, had multiple comorbidities, a common finding for older adults admitted to the hospital (Marcantonio et al., 2005; Vida et al., 2006).

Seventy percent of the participants reported they did not drink alcohol. Although delirium is a complication of alcohol withdrawal, the mechanism of this syndrome is likely different than the delirium more commonly seen in medical or surgical ICU patients (Marcantonio et al., 2006), which was the focus of this study. Whether or not a participant drank alcohol was distributed almost evenly between the groups of participants with delirium and participants not discovered to have delirium.

In summary, although the characteristics of the sample in this study are comparable to sample characteristics found in other delirium studies, it is apparent there is a great deal of heterogeneity when comparing sample characteristics across studies, limiting the generalizability of all study findings. The variability in sample composition likely reflects the setting from which older adults are admitted to the hospital (e.g., community, assisted living, long-term care settings), the reasons for admission (e.g., medical, surgical, psychiatric), and the hospital settings older adults are admitted to (e.g., hospital ward, ICU, emergency department).

Cognitive Screening

Adults 65 years of age and older admitted to an ICU were recruited. After recruitment, the SMMSE was used to evaluate participants' cognitive function. The SMMSE, a modification of the MMSE (Folstein et al., 1975), imposes guidelines for

administration and scoring that improve the reliability of the instrument (Molloy et al., 1991). No delirium studies were found using the SMMSE to evaluate cognitive function; however, the MMSE is used frequently. The psychometrics of both instruments have been tested and compared. High positive correlations between scores on the MMSE and the SMMSE, as well as high test-retest reliability, suggest that both instruments can be used interchangeably and that other considerations may determine the choice of assessment tool (Pangman et al., 2000). The SMMSE may be more appropriate for the hospitalized elder who has been hospitalized for several days and moved between different units or transferred to a hospital outside his usual locale. Scores on the MMSE and the SMMSE can range from 0 to 30 with a score of 25 or lower indicating some degree of cognitive impairment (Folstein et al.; Pangman et al.).

In this study, the mean SMMSE score of 28.9 (SD = 1.35) in participants found to be delirious (n = 14) and the mean SMMSE score of 28.4 (SD = 1.59) in participants not found to be delirious were different from other studies where mean MMSE scores of delirious and not delirious participants ranged from 23 – 27. Differences in these scores from the current study and other studies could be related to the different populations sampled. In two studies of older adults admitted with a hip fracture, mean MMSE scores were 22 and 23 for delirious participants and 26 and 27 for participants not found to be delirious (Dupplis & Wikblad, 2004; Kalisvaart et al., 2006). Another study of medical inpatients over 65 years of age found a mean MMSE score of 24 for delirious participants and 28 for participants not determined to be delirious (McCusker, Cole, Dendukuri et al.,

2001). Differences in mean scores could be related to the different populations sampled. Certainly, the small sample size in this study should be taken into consideration.

There could have been methodological differences between the two assessment instruments that affected scores. Molloy and colleagues found reduced inter- and intrarater variability and higher intraclass correlation for the SMMSE when compared to the MMSE (Molloy & Standish, 1997b). These differences have been attributed to enhanced guidelines for application, administration and scoring of the SMMSE (Molloy et al., 1991; Pangman et al., 2000). However, other authors have reported strong, significant correlations between the MMSE and the SMMSE, to the point of “near redundancy” (Pangman et al., p. 211). Given these correlations, it is unlikely the differences in mean scores are due to differences between the cognitive screening measures used.

Delirium Screening

A positive finding of delirium by using the CAM at admission was an exclusion criterion for this study. This study explored the relationship between delirium incidence in hospitalized elderly and AL. Daily rounds with the ICU charge nurses would uncover patients that the nurses characterized as confused, agitated or delirious and they were excluded from recruitment. No data were maintained on how many potential participants were excluded from the study because of a potential delirium diagnosis. Anecdotally, the few ICU participants thought to be delirious prior to potential recruitment were also mechanically ventilated, another exclusion criteria.

For general interest, the prevalence of delirium in older adults at the time of admission to a medical unit has been reported to range from 5% – 31% (Bergeron et al., 2002; McNicoll et al., 2005). The prevalence of delirium in older adults admitted to an ICU has been reported to range from 31 – 40% (Bergeron et al., 2002; McNicoll et al., 2005; Skrobik & Skrobik, 2007).

Delirium Incidence

It is difficult to evaluate the true incidence of delirium in the hospitalized older adult. The wide variation in delirium occurrence reflects differences in sample characteristics. Timing of delirium assessment varies widely. The potential for under-diagnosis due to inaccuracies in assessment and missing cases of delirium that present between assessment periods makes it possible for the misclassification of delirium in hospitalized elders.

Fourteen participants were determined to be delirious during the study period. The overall incidence of delirium was 29.2% (95% CI = 15.3 - 42.7%). The remaining 31 participants were not confirmed to have delirium during the study period. The incidence of delirium in this study is in keeping with the reported rates of delirium in this population. The incidence of delirium has been reported to range from 3% – 55% among hospitalized elderly (Bourdel-Marchasson et al., 2004; Fick et al., 2002; Roche, 2003; Siddiqi & House, 2006). Delirium has been diagnosed in 11% – 80% of patients admitted to intensive care unit (Bruce et al., 2007). The incidence of postoperative delirium ranges from 5% – 65% (Lepouse et al., 2006).

Allostatic Load

Allostasis represents an integrated response of multiple interacting physiological systems that adapt to environmental and psychosocial stressors (McEwen & Lasley, 2003). Allostatic load is a state of dysfunction and reflects the cumulative negative effects of adaptation to environmental and psychosocial stressors, all superimposed on an individual's genetic predisposition, development, and learned behavioral or lifestyle factors, including smoking, diet, and physical activity (McEwen & Lasley, 2003; McEwen & Seeman, 1999).

Comparison of AL between studies is challenging due to the variety of settings participants are recruited from, as well as age and wellness factors. Furthermore, it is becoming more common in studies of AL to incorporate other biomarkers or possible mediators in an attempt to more completely describe AL (Szanton, Gill, & Allen, 2005), making the comparison of numerical AL scores meaningless when comparing findings between studies. The studies described in the following section all operationalized AL using the same parameters, which facilitated comparison.

The mean AL score in this sample of hospitalized older adults was 3.64 (SD = 1.08). No other studies of AL in hospitalized older adults were found. Seeman and colleagues reported a mean AL of 2.68 (SD = 1.58) in a community-based population of adults 70 years of age and older (Seeman, Singer et al., 1997). In that same study, participants were divided into 3 groups based on a summary measure of physical performance (high, middle and low functioning) and AL scores then were reported for each sub-group. Allostatic load scores ranged from a mean of 2.58 in the high-

functioning group to a mean of 3.10 in the low-functioning group. The medium-functioning group had a mean AL score of 3.14. Hu and colleagues reported a mean AL score of 2.5 (SD = 1.6) in a sample of community-dwelling Taiwanese nationals 65 years of age and older (Hu et al., 2007). In an Australian study investigating the relationship between AL and chronic care giving of spouses with dementia (Clark et al., 2007), the AL score of 3.2 (SD = 1.7).

Clark and colleagues (2007) were the only investigators to report primary mediator and secondary outcome AL subset scores as reported in this study. In this study, the mean AL subset score based on primary mediators was 2.25 (SD = .92), while the Clark study reported a mean AL subset score based on primary mediators of 1.6 (SD =1.0) in their control group. In this study, the mean AL subset score based secondary outcomes was 1.39 (SD = .92), while the Clark study reported a mean AL subset score based secondary outcomes of 1.7 (SD = 1.4) in their control group.

Allostatic Load Score Calculations

Allostatic load was measured by summing the number of parameters for which the participant fell into the high-risk quartile (i.e. highest quartile for all parameters, except HDL and DHEAS for which membership in the lowest quartile corresponded to highest risk). The cut-off points for determining highest risk were those used by Seeman and colleagues in their first investigations of AL.

The same method used by Seeman and colleagues (1997) for partitioning the AL data was used in this sample. The researcher considered that older adults who have been hospitalized in an ICU are exposed to different levels of stress than the older community-

dwelling adults studied by Seeman and colleagues and using the same cut-off points to determine highest risk quartile may not be appropriate. Therefore, using the same AL data, high-risk quartiles were redefined using the distribution of scores for each parameter in this sample.

This resulted in different cut-off points to determine high-risk quartiles in all 10 AL parameters, suggesting there were differences between this sample and the sample studied by Seeman and colleagues. Differences were most pronounced in the primary mediators and in the lipid parameters (HDL; TC/HDL ratio) known to be affected by acute stress (Grant, Hamer, & Steptoe, 2009; Roy, Kirschbaum, & Steptoe, 2001).

The different cut-off points to determine high-risk quartiles for AL resulted in different mean AL scores and mean subset AL scores. The recalculated subset AL score based on primary mediators was the only score to be a significant predictor of delirium. This finding suggests that calculating AL scores based on the sample under study, rather than using normative values from investigations in other populations, may provide a more useful measure of risk for negative health outcomes.

Conclusions from Additional Analyses

An examination of covariances among variables demonstrated some expected relationships. The recalculated subset AL score based on components considered primary stress mediators was related significantly to delirium ($p < .05$); however, no other continuous variables were associated with delirium.

Age and SMMSE scores demonstrated an expected and significant inverse relationship ($p < .05$); as age increased, SMMSE scores decreased. Age and PMH

demonstrated a significant relationship ($p < .01$); increasing age was associated with an increasing number of medical diagnoses. Past medical history and outpatient medications demonstrated a significant relationship ($p < .01$), as did outpatient medications and inpatient medications ($p < .01$). As the number of past medical diagnoses increased, the number of outpatient medications being taken by the participant increased. Similarly, the number of outpatient medications was associated with the number of inpatient medications prescribed.

Age and AL did not demonstrate a significant relationship. Crimmins and colleagues analyzed data from the third National Health and Nutrition Examination Survey, a survey and examination that involved the collection of data over the 1988–94 period from about 18,000 persons 20 years of age or older in a nationally representative sample of the United States noninstitutional population (as cited in Crimmins et al., 2003). They reported that while there was a sharp increase in AL in adults 20 – 60 years of age, AL remained remarkably constant in adults greater than 60 years of age. These authors had the unique perspective of studying AL across the adult lifespan and suggested this finding represented a mortality selectivity; that mortality associated with AL in earlier decades kept AL more constant in the surviving older population. Karlamanga and colleagues (2006), in a longitudinal analysis found that AL scores measured 2.5 years later in community-dwelling adults, 70 to 79 years of age at baseline demonstrated a mean change of .11 (SD = .46). Of note, 63 of the 171 participants studied at the 2.5-year mark had decreases in their AL scores, prompting these researchers to comment that even at older ages, risk factor modification can be beneficial.

Unexpectedly, age and delirium were not significantly related. This finding is in contrast to multiple studies reporting a relationship between age and delirium occurrence (e.g., Koebrugge, Koek, van Wensen, Dautzenberg, & Bosscha, 2009; Morimoto et al., 2009; Santos & Velasco, 2005). Small sample size, differences in sample composition, including restricted age range of participants (65 years of age and older), setting and frequency of delirium assessment may explain this finding.

Conclusions from Analysis of Delirium Incidence, Age and Individual Variables of Allostatic Load

Analysis of covariances among delirium incidence, age and the variables that made up the composite AL score demonstrated expected results. None of the individual AL variables was related significantly to delirium. This finding supports the theory of AL; that the physiological processes defining AL are, by definition, an aggregation of the consequences of mechanisms spanning several physiological systems; that AL is reflected in the cumulative total of physiological dysregulation across multiple physiologic regulatory systems rather than in the measure of an individual component (McEwen, 2007).

Urinary cortisol was the only individual AL variable to have a significant relationship with age ($p < .05$). This finding is in keeping with other research suggesting older adults have impaired HPA axis regulation, leading to high levels of circulating glucocorticoids (Ferrari et al., 2001; Heffelfinger & Newcomer, 2001; Magri et al., 2006).

Several individual variables of AL were significantly associated. Waist-hip ratio was significantly related to TC/HDL ratio ($p < .05$) and inversely related to HDL ($p < .05$). As the WHR increased, HDL decreased and the TC/HDL ratio increased. These covariances have been reported previously, abdominal obesity (e.g., increased WHR) and dyslipidemia (e.g., increased TC/HDL ratio and decreased HDL) are seen together commonly in disorders, such as metabolic syndrome (Bellingrath, Weigl, & Kudielka, 2009). High-density lipoprotein was significantly related to urinary epinephrine ($p < .05$), in contrast to findings in another study investigating these biomarkers (Lee et al., 2001).

Waist-hip ratio demonstrated a significant negative relationship with urinary cortisol ($p < .01$). This relationship has been reported in studies investigating the relationship between cortisol activity and abdominal obesity (Power 2006; Vicennati 2000); however, there are conflicting reports that suggest a positive relationship between abdominal obesity and cortisol (Pasquali, Vicennati, Cacciari, & Pagotto, 2006). Researchers investigating the role of the HPA axis, including cortisol, and abdominal obesity acknowledge the difficulty in examining this complex physiological system.

Discussion of Limitations

Model Development

In this descriptive study, a theory driven framework was applied as a necessary step in generating testable hypotheses. Allostatic load is a complicated, far-reaching construct and delirium is a condition with seemingly multiple pathophysiological origins. The Allostatic Load & Delirium in Hospitalized Elderly (ALDHE) model explores processes that are grounded in theory and empirical investigation and describes

relationships between stress and mechanisms of delirium in the hospitalized elderly. The study of both stress and delirium are theoretically and methodologically complex. The ALDHE model acknowledges this complexity by incorporating a multi-factorial etiology of delirium with physiological and psychological factors inherent in the individual older adult and factors in the hospitalization experience.

This descriptive study was the first to incorporate the ALDHE model and should be considered a first step in the validation of the model. Many of the variables used in the model to describe acute and chronic stressors were not operationalized, a limitation that should be addressed in subsequent model development. While the descriptive design allowed for the describing of relationships between model concepts, no conclusions can be made regarding causality. This should be addressed in subsequent research.

Sampling

A convenience sample of all adults 65 years of age and older admitted to an ICU was used. In order to facilitate consent, assess global cognitive status and exclude prevalent delirium, participants mechanically ventilated or otherwise unable to communicate verbally were excluded from the study. Preliminary investigation and interviews with hospital staff suggested that, even with this exclusion criterion, a large enough sample still could be obtained.

Within the first month of data collection, it became clear that additional sampling methods would be necessary. Many more potential participants were mechanically ventilated than previously suggested and therefore were unable to communicate verbally. In addition, several potential participants refused participation, mostly due to fatigue or feeling unwell.

In order to improve the opportunity for increased recruitment and enrollment while maintaining the integrity of the study design, the sampling pool was expanded to include participants who were to undergo major surgery requiring immediate post-surgical ICU admission. These participants were recruited and enrolled in a pre-operative clinic. The data collection protocol described in Chapter 3 was maintained for all participants, that is, all AL parameter data was collected upon ICU admission after surgery and all participants had repeat delirium assessment within 48 to 72 hours of ICU admission.

While this change in sampling improved the number of participants, recruitment and enrollment remained a greater challenge than expected. Many potential participants were unwilling to participate, even after understanding the particular nature of the study. Difficulty in recruitment among older adults is well known (Blanch, Rudd, Wright, Gall, & Katz, 2008); however, this remained a greater challenge than expected. Depending on the availability of potential participants, data collection continued almost daily from August, 2008 through January, 2009.

The small sample size limits the generalizability of the findings; however, power analysis performed *a priori* suggests that the sample was large enough to demonstrate a moderate effect of AL on the incidence of delirium. The power analysis performed *a priori*, and based on data in prior AL research, used an odds ratio of 2.5 in calculating the needed sample size. A significant finding in this research was that for every unit increase in the subset AL score based on parameters considered primary stress mediators and calculated specifically in this sample, the relative risk for developing delirium was 2.54 (95% CI = 1.12, 5.79). Additionally, many of the bivariate analyses offer evidence for the

validity of the study findings since several components of AL were significantly associated in the expected direction.

Measurement of Allostatic Load

Operationalization. A number of issues related to the measurement of AL require discussion. The original operationalization of AL is well described and represents one picture of comprehensive physiological functioning (Seeman, Singer et al., 1997). Allostatic load has been operationalized differently in most subsequent studies (Table 4), however, there is no one accepted set of parameters to measure AL. While incorporating different combinations of parameters to assess AL is a fruitful avenue of discovery, one that Seeman and colleagues have encouraged and participated in (Seeman, Crimmins et al., 2004; Seeman, Singer et al.), justification for inclusion of different parameters has been weak or even missing. For example, indicators of inflammation have been included in AL studies, but the proposed value of incorporating multiple inflammatory indicators in determining AL is unclear (Schnorpfeil et al., 2003; Seeman, Crimmins et al., 2004). Other authors have included measures of organ dysfunction (e.g., creatinine clearance, respiratory peak flow) that have no conceptual connection to the current understanding of AL (Crimmins et al., 2003). There may be other relevant aspects of the physiological stress response that should be included in our understanding of AL, such as immune or parasympathetic system parameters. Better theoretical justification for inclusion of different parameters would advance our understanding of AL.

Changing physiological systems. Measurement of AL is constrained by the cross-sectional nature of most AL research. Even the few longitudinal studies used only two different measurement points (Karlamañgla et al., 2002; Seeman & Crimmins, 2001; Seeman, Crimmins et al., 2004). The current understanding of AL is based on physiological activity representing a single measure of cumulative physiological response, rather than an assessment of how these systems respond dynamically in response to stress. This limitation can be reduced by measuring AL parameters (one example would be cortisol) throughout the day or in response to a challenge. Adding dynamic measures would be conceptually appropriate as AL theory is based on adaptation to challenge (McEwen, 2006). While adding such measures might be constrained by financial cost and/or resource availability, consideration should be given to other methods for characterizing this dynamic response (Loucks, Juster, & Pruessner, 2008).

Calculating AL scores. The best manner for calculating AL scores is not clear. With rare exception, researchers have calculated a participant's AL score by summing the parameters in the high-risk quartile for each parameter. Additional methods for determining AL scores have been explored using the data collected by Seeman and colleagues in their first study reported in 1997. Seplaki and colleagues (2004) summed the parameters of AL that were in the highest or lowest 10% on any of the AL parameters and found that *both* high and low values of parameters that comprised AL were associated with functional impairment.

A limitation of using high-risk zone methods of scoring is that they do not take full advantage of the measured values of each parameter and they weight each parameter equally (Singer et al., 2004). Karlamangla and colleagues (2002) used canonical correlation to determine the linear combination of biological measures maximally correlated with declines in functional status. Interestingly, when analyzing the original Seeman and colleagues data, the canonical correlation analysis, using only the 4 primary stress mediators (urinary epinephrine, norepinephrine and cortisol and serum DHEAS), proved superior to the 10-item AL score in identifying subsequent functional decline. Given the findings in this study, this is of particular interest.

Singer and colleagues (2004) used recursive partitioning to classify persons into categories by successively identifying the biological measure (and accompanying cutpoint) that best differentiated mortality within 7 years. Although all 10 parameters were *a priori* candidates to enter into the recursive partitioning, only five parameters were used for predicting mortality (DBP, HDL, urinary cortisol, SBP, and HgbA_{1c}). The authors hypothesized that different combinations of biomarkers would be associated with different outcomes.

Gender differences. There are gender differences in the distributions of each of the 10 parameters used in Seeman and colleagues original work (Seeman, Singer, Wilkinson, & McEwen, 2001). It is reasonable to question whether AL scoring schemes should be created on a gender-specific basis, or whether there are gender differences in the distribution of AL scores using the current scoring methods.

Measurement of Delirium

There are factors that make the measurement of delirium in the hospitalized elder difficult, most notably the potential for missed diagnosis due to inaccuracies in assessment and missing cases of delirium that present between assessment periods.

Delirium can vary widely in its clinical presentation and may cycle between hyperactive and hypoactive forms. The clinical features of delirium may develop abruptly over hours to days and may resolve just as rapidly. Symptoms may fluctuate diurnally, often worsening at night (Foreman et al., 2001; Meagher, 2001a) and depending on which symptoms are apparent, may be mistaken for dementia, a mood disorder and/or a functional psychoses, particularly in the elderly (Meagher, 2001b).

A large number of instruments in use are designed to assist in the measurement of delirium (Appendix E). The CAM, used in this study, is a simple algorithm for identifying features of delirium based on DSM criteria (Inouye et al., 1990). Since its development, the CAM has become one of the most widely used instruments for detection of delirium worldwide, both because of its psychometric properties, but also because of its ease of use. The shortened version of the CAM focuses on four key features: (1) acute change in mental status with a fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. The first and the second features, as well as either one of the third or fourth features must be present simultaneously in order to declare a positive diagnosis of delirium (Inouye, 2003). A dichotomous response is obtained, either the respondent is delirious or they are not.

All delirium assessments were carried out by the researcher, an experienced acute care nurse practitioner with experience in the assessment of delirium; however, no reliability testing was conducted on the researcher's precision in assessing delirium. Additionally, although the majority of delirium cases present within 48 -72 hours, it is possible that extending the study period would have captured other cases of delirium.

Future Research

Numerous studies demonstrate that delirium in the hospitalized elderly has a negative impact on morbidity and mortality. Research is needed to investigate delirium psychomotor type, persistence, severity and associations with outcomes of interest, such as cognitive and functional decline. Delirium is not a simple dichotomous state, rather a dynamic condition that often fluctuates between hypoactive and hyperactive expressions. Delirium may have different levels of severity and may persist for a longer period than is currently recognized. For example, absence of agitation (i.e., hypoactive delirium) has been associated with poor outcome at hospital discharge (Andrew, Freter, Rockwood et al., 2005; Kelly et al., 2001), while others have reported equivalent (Camus, Gonthier, Dubos, Schwed, & Simeone, 2000) or better (Marcantonio et al., 2002) outcomes in patients with hypoactive delirium. Regarding the persistence of delirium, several investigators have found that a longer duration of delirium symptoms is associated with worse functional outcomes (Marcantonio, Ta, Duthie, & Resnick, 2002; McCusker et al., 2003; Sheng et al., 2006); however, Andrew and colleagues (2005) found that neither the duration of the delirium episode, nor the length of hospital stay, was associated with functional recovery. Marcantonio and colleagues (2002) found that severe delirium was

associated with worse functional outcomes than mild delirium, particularly at 6 months after discharge. Furthermore, these same authors found that patients who demonstrated some symptoms of delirium, but did not fulfill all CAM criteria for delirium, did worse than patients with few or no delirium symptoms (Marcantonio et al.).

Allostatic load has been shown to be an increasingly important construct in the early identification of physiological dysfunction related to exposure to psychosocial and environmental stress. Research to date has demonstrated that physiological responses to psychosocial and environmental stress and the development of AL are more complicated and nuanced than previously thought. Continued research is needed to define the optimal operationalization of AL. Further, a limitation of using the highest risk quartiles method for AL scoring is that it does not take full advantage of the measured values of each parameter and each parameter is weighted equally. This measurement issue is one that warrants further investigation.

Based on the findings in this study, it is apparent that highest risk quartiles for calculating AL should be based on values in the sample under study rather than cut-off points used in other populations. Further, primary mediators and secondary outcomes should be distinguished analytically when considering negative health outcomes, such as delirium, in hospitalized elders.

Conclusions

The study of delirium in the hospitalized older adult is of growing significance. There is mounting evidence that delirium leads to a number of poor outcomes and questions remain unanswered regarding the pathogenesis of delirium. The theory of AL

considers the additive physiological dysfunction that can occur because of exposure to psychosocial and environmental stress. The idea that such stress may cause a differential risk for delirium in the hospitalized older adult suggests additional avenues of research that may ultimately lead to improved prevention of delirium in this vulnerable population. Furthermore, a better understanding of the causes of AL may lead to earlier interventions focused on behavior modification that can reduce the impact of AL on the older adult's physiological function, decreasing their risk of delirium if hospitalized.

This study demonstrated an association between delirium and an AL subset score based on primary mediators. The highest risk quartiles for all components of AL were based on cut-off points specified by Seeman et al. (1997a); however, when highest risk quartiles for components of AL were based on the distribution of values in the study sample, substantial differences were observed, specifically in the primary mediator components. A majority of the sample had higher values for most of the primary mediators, indicating an acute physiological response to hospitalization and acute illness. The AL subset score based on primary mediators in the study sample significantly predicted delirium incidence while the original AL subset score based on primary mediators using cut-off points specified by Seeman et al. did not. Identification of sample-dependent highest risk quartiles for calculating the AL subset score based on primary mediators more accurately identified those patients responding to the stress of hospitalization and acute illness with a greater increase in primary mediator activity.

This finding has implications for the continued elucidation of AL theory. In a population of older adults exposed to the physiological and psychological stress of

hospitalization and acute illness, a composite measure of AL consisting of primary mediators *and* secondary outcomes may be unnecessary for the prediction of negative health outcomes such as delirium in the hospital setting. Further, calculating AL subset scores based on primary mediator activity in the sample under study, rather than using normative values from investigations in other populations, may provide a more useful measure of risk for negative health outcomes.

APPENDIX A. DATA COLLECTION FORMS

- A1. Patient Demographic Data Collection Form
- A2. Standardized Mini-Mental State Examination (SMMSE)
- A3. Confusion Assessment Method (CAM)
- A4. Allostatic Load Scoring Form

Appendix A1. Patient Demographic Data Collection Form Participant # _____

Date of data collection from medical record: _____

Date of participant admission: _____

Date of Birth (MM/DD/ YYYY)			Outpatient Medications
Gender (circle one)	Male	Female	
Current alcohol use (circle one)	Yes	No	
Racial/ethnic background (select primary)			
American Indian or Alaskan Native			
Asian or Pacific Islander			
Black or African American			
Hispanic			
White or Caucasian			
Other			
Medical History (check all that apply)	Admit	PMH	Inpatient Medications
Diabetes Mellitus, type 1			
Diabetes Mellitus, type 2			
Hypertension			
Hypercholesterolemia			
Chronic Obstructive Airway Disease			
Coronary artery disease			
Myocardial infarction			
Stroke			
Chronic Renal Failure			
Other:			
Other:			

Appendix A2. Standardized Mini-Mental State Examination (SMMSE)

Participant # _____

Date of SMMSE administration: _____

Date participant admission: _____

*Standardized Mini-Mental State Exam	Score	Max score	Score	Score	Max score
Orientation			Language & Praxis		
<i>What is the (year) (season) (date**) (month) (day)?</i>		5	<i>Show a pencil and watch, and ask subject to name them both.</i>		2
<i>Where are we (city) (state) (county***) (hospital⁺) (floor⁺⁺)?</i>		5	<i>Ask the patient to repeat the following: "No ifs, ands, or buts."</i>		1
Registration					
<i>Name three objects: one second to say each. Ask the patient for all three after you have said them. Give one point for each correct answer. Repeat them all until all three are learned. Count trials and record number.</i>		3	<i>(Three-stage command): "Take this paper in your right hand, fold it in half, and put it on the floor."</i>		3
Attention & Calculation			<i>"Read and obey the following: Close your eyes."</i>		1
<i>Spell WORLD backward.</i>		5	<i>Write a sentence."</i>		1
Recall			<i>"Copy this design" (interlocking pentagons)</i>		1
<i>Ask for the three objects repeated above. Give one point for each correct answer.</i>		3	Total Score		30

Appendix A2. Standardized Mini-Mental State Examination – *continued*

Standardized Mini-Mental State Examination instruction comments

- * There is no time limit in responding to any question or activity request in the SMMSE.
- ** An error by one day is acceptable for date and day (e.g., if it is the 11th, the 10th or 13th are acceptable, as is Wednesday or Friday if the day is actually Thursday).
- *** Accept correct country as well as correct county.
The county question may have less relevance to participants if they live outside of the study hospital's county and simply do not know in which county the hospital is located. The intent of replacing the question of county with that of country is to use locations that are relevant to participants in order to carry out a valid cognitive assessment.
- + Accept the word “hospital” without the specific hospital’s name.
Transfer from a number of different facilities or settings within the same hospital may precede admission to the ICU and such circumstances may easily confuse participants, even if they are cognitively intact.
- ++ Accept “the ICU,” the floor the ICU is on, or the ICU designation, e.g. “4NW.”
Acceptable responses include those that are judged meaningful to the participant. For example, if a participant is on “4NW,” a cardiovascular surgical ICU located on the 4th floor, acceptable responses to the question include “4NW,” “surgical unit,” “ICU,” or “4th floor.”

Note: Vertesi, A., Lever, J.A., Molloy, W., Sanderson, B., Tuttle, I., Pokoradi, L., & Principi, E. (2011) Standardized Mini-Mental State Examination Use and interpretation. *Canadian Family Physician*, 47, 2018 – 2023.

Appendix A3. Confusion Assessment Method (CAM)

Participant # _____

Date of administration: _____

Date of participant admission: _____

<p>1. Acute onset and/or fluctuating course?</p> <p>- Is there evidence of an acute change in mental status from the patient's baseline?</p> <p style="text-align: center;">~and/or~</p> <p>- Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity?</p>	<p>yes or no</p> <p>(circle response)</p>
<p>2. Inattentive/easily distractable?</p> <p>- Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?</p>	<p>yes or no</p> <p>(circle response)</p>
<p>3. Thinking disorganized or incoherent?</p> <p>- Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?</p>	<p>yes or no</p> <p>(circle response)</p>
<p>4. Altered level of consciousness?</p> <p>- Overall, how would you rate the patient's level of consciousness? For any answer other than "alert," select "yes."</p> <ul style="list-style-type: none"> - Alert - Vigilant (hyperalert) - Lethargic (drowsy, easily aroused) - Stupor (difficult to arouse) - Coma (unarousable) 	<p>yes or no</p> <p>(circle response)</p>
<p style="text-align: center;">Delirious?</p> <p style="text-align: center;">(requires a yes on #1 and 2 plus either 3 or 4)</p>	<p>yes or no</p> <p>(circle response)</p>

Note: Inouye et al. (1990). Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Annals of Internal Medicine*, 113, 941 – 8.

Appendix A4. Allostatic Load Scoring

Participant # _____

Date and time of participant admission: _____

Components	Value	Score	Date of collection
Systolic blood pressure	#1 mm Hg	0 or 1 (circle response)	
	#2 mm Hg		
	Average:		
Diastolic blood pressure	#1 mm Hg	0 or 1 (circle response)	
	#2 mm Hg		
	Average:		
Waist-to-hip ratio	Waist: cm	0 or 1 (circle response)	
	Hip: cm		
	Ratio:		
DHEA	ng/ml	0 or 1 (circle response)	
Total cholesterol	mg/dl	0 or 1 (circle response)	
High density lipoprotein	mg/dl	0 or 1 (circle response)	
Glycosylated hemoglobin	%	0 or 1 (circle response)	
Urinary epinephrine	ug/g creatinine	0 or 1 (circle response)	Start: Stop:
Urinary norepinephrine	ug/g creatinine	0 or 1 (circle response)	Start: Stop:
Urinary cortisol	ug/g creatinine	0 or 1 (circle response)	Start: Stop:
Allostatic Load Total (0-10):			

Note: Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation allostatic load and its health consequences. MacArthur studies of successful aging. *Archives of Internal Medicine*, 157 (19), 2259-2268.

APPENDIX B. RECRUITMENT SCRIPT

Allostatic Load and Delirium Among Hospitalized Elderly

Hello. I am a doctoral student in the College of Nursing. I would be grateful if you would consider participating in my research project. I am studying the experiences older adults have in the hospital.

Older adults sometimes may become temporarily confused when in the hospital. I am interested in trying to understand why some older adults become confused and some do not. I have a hunch that stress may have something to do with it. Stressful experiences, both now and in the past, may have a physical effect on the body. Stress may be related to becoming confused. The purpose of this study is to see if stress is involved with becoming confused when in the hospital.

I am looking for 66 people to participate. You must be at least 65 years of age and speak, read and understand English.

If you choose to join this study, I will ask you to answer some questions about your thought processes. At the same time I will be observing your mental alertness. I may also ask your nurses about your mental alertness. This will take about 10 – 15 minutes of your time.

I will review your medical record to obtain information. I will collect your date of birth, gender and racial/ethnic background. I also will collect your admitting diagnosis, past medical history, history of alcohol or illicit drug use, and the medications you were taking before admission.

After you've been in the hospital for 2 – 3 days, I will visit you again. I will observe your mental alertness. I may also ask your nurses about your mental alertness.

The measure of stress that I am using has many parts because it looks at current and past stress. I will ask you to participate in several assessments. These will involve a few simple measurements taken by me: your blood pressure and your waist and hip measurements. These will take only a few minutes to complete.

Then I will ask you to cooperate with your nurse, as she/he is going to collect your urine for the next 12 hours. The reason for collecting your urine is to measure levels of stress.

At some point during these 12 hours a blood sample will be collected. The reason for collecting your blood is to measure levels of stress. If your healthcare team has ordered a blood test during this same time, the sample for this study will be obtained then. That way there will be no need for a separate collection. However, if no blood test is ordered by your healthcare team during those 12 hours, then a separate collection will be necessary. In either case, an employee at the hospital trained to draw blood will collect the sample.

Your healthcare team and I will be the only people allowed to see the results of these tests.

Your participation in this study is voluntary. You may decide not to begin or to stop the study at any time. Your refusing to participate will have no effect on the care you receive at this hospital or by your healthcare team. You may stop your participation with no effect on the care provided to you at this hospital or by your healthcare team.

Thank you for considering participation in this study.

Ted Rigney, MSN, RN, RNP
Principal Investigator
College of Nursing, University of Arizona
(520) 401-2779

APPENDIX C: CONSENT FORMS

APPROVED BY UNIVERSITY OF AZ IRB
 THIS STAMP MUST APPEAR ON ALL
 DOCUMENTS USED TO CONSENT SUBJECTS.
 DATE: 06-02-08 EXPIRATION: 06-02-09

Informed Consent

Allostatic Load and Delirium Among Hospitalized Elderly

Introduction

You are being invited to take part in a research study. The information in this form is provided to help you decide whether or not to take part. Study personnel will be available to answer your questions and provide additional information. If you decide to take part in the study, you will be asked to sign this consent form. A copy of this form will be given to you.

What is the purpose of this research study?

The purpose of this study is to gain a better understanding of why some older adults may become temporarily confused while in the hospital. It may be that stressful experiences, both now and in the past, have a physical impact on the body. This effect of stress on the body may be related to why some older adults become temporarily confused when in the hospital.

Why are you being asked to participate?

You are being invited to join this study because you are 65 years of age or older, you can speak and read English and you have been admitted to the hospital.

How many people will be asked to participate in this study?

Approximately 66 persons will be asked to participate in this study.

What will happen during this study?

- I will ask you questions about how you think and remember. This will take about 5 – 10 minutes. Because I am interested in confusion, I will observe while we talk.
- If I am concerned about how you are thinking and remembering, I will tell your nurse and your nurse will follow up.

- I will review your medical record to obtain information about your date of birth, gender and racial or ethnic background. I also will collect information about why you came into the hospital, any past medical problems, medications you were taking before coming to the hospital and medications you are taking now.
- After you have been in the hospital for 2 – 3 days, I will return to visit you. I will review your medical record and ask some of the same questions I ask you today. I may also ask your nurse how you have been doing. If I am concerned about you, I will tell your nurse.
- Then, I will take your blood pressure and your waist and hip measurements.
- Next, I will ask you to collect your urine for the next 12 hours. That means you should use whatever collection container I give you. Your nurse will be able to help you collect your urine. The reason for collecting your urine is to measure levels of stress. It is important that all the urine you produce over the 12-hour period be collected in the container. That will give results that are accurate.
- Finally, I will need about one tablespoon of blood that can be collected when someone on your healthcare team is getting blood already for a test needed for your care. This way, we will not have to stick you with a needle to draw the blood. However, if your healthcare team does not need a blood sample during the time you are collecting your urine, we will need to draw a blood sample. The reason for collecting a blood sample is to get information on some things that may change if you are stressed.

How long will I be in this study?

About one hour will be needed to complete this study. You will be involved in the study for about 30 minutes on the first day we meet. Then, in 2 to 3 days, I will return to talk with you for 15 minutes.

Are there any risks to me?

There is the risk that drawing blood may result in temporary discomfort from the needle stick and occasionally there is bruising. Rarely a needle stick could result in infection. We will use sterile technique and trained personnel to obtain the blood samples.

Are there any benefits to me?

You may not receive any benefit from taking part in this study. However, some older adults enjoy talking with people when they are in the hospital and, if after talking with you I am concerned that you may be confused, I will notify your nurse. This may benefit you because finding out early if someone is confused helps the health care team. Then they can identify and treat the possible reason for the confusion.

Will there be any costs to me?

Aside from your time, there are no costs for taking part in the study.

Will the information that is obtained from me be kept confidential?

The only persons who will know that you participated in this study will be me and the members of your healthcare team. If I become concerned about how you are thinking and remembering or that you may be confused, I will notify your nurse.

Your records will be confidential. You will not be identified in any reports or publications resulting from the study. It is possible that representatives of the sponsor that supports the research study will want to come to The University of Arizona to review your information. Representatives of regulatory agencies (including The University of Arizona Human Subjects Protection Program) may access your records.

May I change my mind about participating?

Your participation in this study is voluntary. You may decide to not begin or to stop the study at any time. Your refusing to participate will have no effect on the care or services you receive. You can discontinue your participation with no effect on the care or services you receive from this hospital or your healthcare team. In addition, any new information discovered about the research will be provided to you. This information could affect your willingness to continue your participation.

Whom can I contact for additional information?

You can obtain further information about the research or voice concerns or complaints about the research by calling the Principal Investigator Ted Rigney, PhD (c) at (520) 626-7058. If you have questions concerning your rights as a research participant, have general questions, concerns or complaints or would like to give input about the research and can't reach the research team, or want to talk to someone other than the research team, you may call the University of Arizona Human Subjects Protection Program office at (520) 626-6721. (If out of state use the toll-free number 1-866-278-1455.) If you would like to contact the Human Subjects Protection Program via the web, please visit the following website:
<http://www.irb.arizona.edu/contact/>.

Your Signature

By signing this form, I affirm that I have read the information contained in the form, that the study has been explained to me, that my questions have been answered and that I agree to take part in this study. I do not give up any of my legal rights by signing this form.

 Name (Printed)

 Participant's Signature

 Date signed

Statement by person obtaining consent

I certify that I have explained the research study to the person who has agreed to participate, and that he or she has been informed of the purpose, the procedures, the possible risks and potential benefits associated with participation in this study. Any questions raised have been answered to the participant's satisfaction.

Name of study personnel

Study personnel Signature

Date signed

APPROVED BY UNIVERSITY OF AZ IRB.
THIS STAMP MUST APPEAR ON ALL
DOCUMENTS USED TO CONSENT SUBJECTS.
DATE: 06-02-08 EXPIRATION: 06-02-09

Authorization Form for Use and Disclosure of Protected Health Information for Research

Project Title: Allostatic Load and Delirium Among Hospitalized Elderly

The United States government has issued a new privacy rule to protect the privacy rights of individuals enrolled in research. The Privacy Rule is designed to protect the confidentiality of an individual's health information. This document hereafter known as an "Authorization for Use and Disclosure of Protected Health Information for Research" describes your rights and explains how your health information will be used and disclosed for this study.

PURPOSE

You are being invited to participate voluntarily in the above-titled research project. The purpose of this project is to gain a better understanding of why some older adults may become temporarily confused while in the hospital.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

The University Medical Center will provide the Principal Investigator and the research team access to your medical record. Your medical record will be accessed for the following information:

- date of birth
- gender
- racial/ethnic background
- why you were admitted to the hospital
- history of medical problems or other conditions
- medications you were taking when you were admitted to the hospital
- current medications you are taking in the hospital
- review of progress notes for descriptions of behavior

This information will be used to describe you in the study, as well as identify possible alternative reasons for why some older adults may become temporarily confused while in the hospital.

The information collected will be linked to your identifying information for 5 years and then the link will be destroyed. You have the right to access your Protected Health Information (PHI) that may be created during this study as it relates to your treatment or payment at any time.

CONTACTS

You can obtain further information from the Principal Investigator Ted Rigney, PhD(c) at (520) 626-7058. If you have questions concerning your rights as a research subject, you may call the Human Subjects Protection Program office at (520) 626-6721.

AUTHORIZATION

I hereby authorize the use or disclosure of my individually identifiable health information. I may withdraw this authorization at any time by notifying the Principal Investigator in writing. The address for the Principal Investigator is P.O. Box 210203, Tucson, AZ 85721. If I do withdraw my authorization, any information previously disclosed cannot be withdrawn and may continue to be used. Once information about me is disclosed in accordance with this authorization, the individual or organization that receives this may redisclose it and my information may no longer be protected by Federal Privacy Regulations. I may refuse to sign this authorization form. If I choose not to sign this form, I cannot participate in the research study. *Refusing to sign will not affect my present or future medical care and will not cause any loss of benefits to which I am otherwise entitled.* This authorization will expire on the date the research study ends.

 Subject's Signature

 Date

 Printed Name of Subject

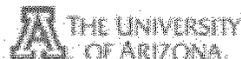
 Signature of Subject's Legal Representative (if necessary)

 Date

 Printed Name of Subject's Legal Representative

 Relationship to the Subject

APPENDIX D: LETTERS OF APPROVAL



Human Subjects
Protection Program

1215 N. Mountain Ave.
P.O. Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
<http://irb.arizona.edu>

2 June 2008

Ted Rigney, MSN, Doctoral Student
Advisor: Kathie Insel, PhD
College of Nursing
PO Box 210203

RE: PROJECT NO 08-0504-02 ALLOSTATIC LOAD AND DELIRIUM AMONG HOSPITALIZED ELDERLY

Dear Mr. Rigney:

We received your research proposal as cited above. The procedures to be followed in this study pose no more than minimal risk to participating subjects and have been reviewed by the Institutional Review Board (IRB) through an Expedited Review procedure as cited in the regulations issued by the U.S. Department of Health and Human Services [45 CFR Part 46.110(h)(1)] based on their inclusion under *research categories 5 and 7*. As this is not a treatment intervention study, the IRB has waived the statement of Alternative Treatments in the consent form as allowed by 45 CFR 46.116(d)(2). Please make copies of the attached IRB stamped consent documents to consent your subjects.

Although full Committee review is not required, notification of the study is submitted to the Committee for their endorsement and/or comment, if any, after administrative approval is granted. This project is approved with an expiration date of 2 June 2009.

The Institutional Review Board (IRB) of the University of Arizona has a current *Federalwide Assurance* of compliance, *FW400004218*, which is on file with the Department of Health and Human Services and covers this activity.

Approval is granted with the understanding that no further changes or additions will be made to the procedures followed without the knowledge and approval of the Human Subjects Committee (IRB) and your College or Departmental Review Committee. Any research related physical or psychological harm to any subject must also be reported to each committee.

A university policy requires that all signed subject consent forms be kept in a permanent file in an area designated for that purpose by the Department Head or comparable authority. This will assure their accessibility in the event that university officials require the information and the principal investigator is unavailable for some reason.

Sincerely yours,

Elaine G. Jones, PhD, RN, FNAP
Chair, Social and Behavioral Sciences Human Subjects Committee

EGJ/mm
cc: Departmental/College Review Committee





UNIVERSITY MEDICAL CENTER

1501 North Campbell Avenue
Tucson, Arizona 85724

April 23, 2008

Ted Rigney, MS, RNP, CCRN, ACNP, FAANP
Doctoral Candidate
University of Arizona
College of Nursing
1305 N. Martin Avenue, Room 311
P.O. Box 210203
Tucson, AZ 85721-0203

Re: Dissertation Proposal "Allostasis and Delirium in Hospitalized Elderly Model"

Dear Mr. Rigney:

The Nursing Research and Evidence-Based Practice Committee has reviewed your proposal and have granted access to University Medical Center to conduct your study because we find your topic timely and of great significance. Your research could be the grounding for addressing a growing national problem in health care and your novel approach has implications for delirium in general and for elder delirium in particular, specifically as it relates to the National Patient Safety Goal addressing falls reduction. The opportunity to provide a theoretical genesis for this problem will positively impact health professionals' abilities to care for their clients.

As per your proposal, our staff will be only minimally involved and it will be important to contact me once you gain IRB approval so that I can assist you in contacting the patient care manager/s to inform them of your purpose. As per HIPAA regulations, you will need to sign a UMC confidentiality agreement with regard to patient information if you have not done so already and you will need to wear either your CON student badge or a visitor badge from the Security Department which you can obtain at our front desk. Also please forward a copy of the IRB approval letter for our records.

We are glad to assist you in the important research work that you are doing for health care and will help you in any way we can. You can contact me at (520) 694-6427 or e-mail me at acrockett@umcaz.edu.

Sincerely,

A handwritten signature in cursive script that reads "Anita B. Crockett".

Anita B. Crockett, RN, PhD
Director, Nursing Research



APPENDIX E. LITERATURE REVIEW OF DELIRIUM MEASURES

Appendix E. Literature Review Of Delirium Measures

Test (Author/Year)	Description	Comment
Screening Instruments		
Clinical Assessment of Confusion-A (CAC-A) (Vermeersch, 92)	<p>A nurse-developed scale derived from the <i>Clinical Assessment of Confusion-B</i>, a larger observational scale, to evaluate cognition, behavior, motor activity, orientation, self-destructiveness, and ability to interact.</p> <p>Psychometrics reported: inter-rater reliability (IRR) ($r = .88$), internal consistency ($r = .80$), and concurrent validity with the Visual Analogue Scale of Confusion ($r = .81$).</p>	The CAC-A cannot distinguish dementia from delirium and, therefore, necessitates the concurrent use of other sources of information if the CAC-A is used in studies of delirium.
Clinical Assessment of Confusion-B (CAC-B) (Vermeersch, 97)	<p>The CAC-B is a modified version of the CAC-A with an additional number of items.</p> <p>Psychometrics reported: internal consistency ($r = .95$) and IRR ($r = .69$) in an acute care setting.</p>	Similar to the CAC-A, certain items in the CAC-B may not be specific to patients with delirium; these items may also be applicable to "confusional" or "delirious" behaviors of patients with dementia or other psychiatric conditions.
Delirium Observation Screening Scale (DOSS) (Schumman 03)	<p>Developed for screening by nursing observations. The DOSS is an observational scale of verbal and nonverbal behavior based on DMS-IV criteria.</p>	Psychometrics were reported regarding two studies, one with geriatric medicine patients and the other with elderly hip fracture patients, demonstrating satisfactory validity and reliability
Intensive Care Delirium Screening Checklist (ICDSC) (Bergeron 01)	<p>The ICDSC was developed to provide ICU clinicians with an easy to use bedside screening tool that incorporates data gathered during routine patient care, and circumvents communication limitations often found in the ICU setting.</p> <p>The checklist is an eight-item list based on DSM-IV criteria and other features of delirium: altered level of consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and overall symptom fluctuation.</p>	<p>One point is given towards each domain that is present, with a score of 4 or higher out of 8 denoting the presence of delirium.</p> <p>With a cut-off score of 4 points or more, sensitivity was 99% and specificity was 64%; reported IRR .94.</p>
NEECHAM Confusion Scale (Neelon 96)	<p>Developed for rapid bedside assessment of delirium, both hyper- and hypoactive subtypes, as well as for early cues of incident delirium. Domains include information processing (attention, command, orientation), behavior (appearance, motor, and verbal), and physiological stability (vital signs, oxygen saturation, and urinary continence).</p> <p>Psychometrics reported: IRR ($r = .96$ to $.99$), internal consistency ($r = .85$ to $.90$), sensitivity of 95% and a specificity of 78% when compared with a composite index of MMSE results, nurses' report of confusion and a patients' self-report of confusion.</p>	<p>In a comparison of the NEECHAM and the CAM-ICU in the ICU setting, all positive CAM-ICU patients were detected by the NEECHAM; however, 21% of the CAM-ICU negative patients had a NEECHAM value diagnostic for delirium (van Rompaey, 07). In another study, the NEECHAM and the DOS were compared in assessing general medical patients with both scales, demonstrating sensitivity of 0.89-1.00 & specificity of 0.86-0.88 (Gemert 07).</p>
Nursing Delirium Screening Scale (Nu-DESC) (Gaudreau 05)	<p>An observational instrument derived from the CRS to assess delirium status on a continuous basis. The Nu-DESC is a five-item scale, each item assessing a symptom potentially indicative of delirium according to DSM-IV criteria. It uses the four items of the CRS and a fifth item rating: unusual physical/mental retardation, thus taking into account hypoactive delirium. Maximum score is 10.</p>	<p>DSM-IV criteria and the MDAS were rated along with CAM assessments: the Nu-DESC had a sensitivity and specificity of 85.7% and 86.8%, respectively.</p>

Appendix E. (continued)		
Test (Author/Year)	Description	Comment
Diagnostic Instruments		
Cognitive Test for Delirium (Hart 96)	<p>A nine item scale for use in the ICU requiring only nonverbal responses (pointing, nodding head, and raising hand). The CTD consists of five subtests assessing orientation, attention span, memory for words and pictures of objects, comprehension, and vigilance. The scores for each subtest range from 0 to 6 and are summed to produce a maximum score of 30.</p> <p>The optimal cut-off score of ≤ 18 yielded a sensitivity of 100% and a specificity of 95% for identification of delirium.</p>	<p>Reliably identifies delirium and discriminates delirium from dementia, depression, and schizophrenia.</p> <p>An "abbreviated CTD" has been developed by the same authors when the assessment of only two content areas (i.e., visual attention span and recognition memory for pictures) was found to maintain good reliability and discriminate delirium from other disorders affecting cognition (e.g., dementia, schizophrenia) (Hart 97).</p>
Confusion Assessment Method (CAM) (Inouye 90)	Two-part measure that screens for overall cognitive impairment and diagnoses delirium. Part two includes only those four features found to have the greatest ability to distinguish delirium from other types of cognitive impairment.	<p>Psychometrics reported: sensitivity of 94-100%, specificity of 90-95%, and IRR (k = 1.0 with 10-item part one and k = .93 with the 4-item part two).</p> <p>The CAM identifies the presence or absence of delirium, but does not assess severity, making it less useful to detect clinical improvement or deterioration.</p>
Confusion Assessment Method – Intensive Care Unit (CAM-ICU) (Ely 99)	<p>A modified version of the CAM intended for use in the ICU. The CAM was modified by incorporating nonverbal, objective assessment instruments for use with nonverbal mechanically ventilated and non-ventilated patients.</p> <p>The CAM-ICU includes a subset of visual and auditory attention screening tests (Attention Screening Examinations, Cognitive Test for Delirium, and the Vigilance A Random Letter Test for the visually impaired) that is useful for obtaining nonverbal responses from patients who are intubated or unable to assume an upright position to complete the psychomotor tasks required in the MMSE</p>	The CAM-ICU, in two studies, was administered by nurses and intensivists and compared to the DSM-IV criteria as administered by either a psychiatrist or geriatrician and reported a sensitivity of 93-100%, a specificity of 89-100%, and a high IRR (k=0.79-0.96). (Ely 01a; Ely 01b)
Delirium Detection Score (Otter 06)	The DDS was developed for use with the critically ill and is composed of eight criteria (orientation, hallucination, agitation, anxiety, seizures, tremor, paroxysmal sweating, and altered sleep- wake rhythm). The DDS score increased with the severity of delirium.	Psychometrics reported: sensitivity 69% specificity 75%, and intraclass correlation between 0.642 and 0.758.
Delirium Scale (Dscale) (Lowy 73)	Includes 53 items in 13 categories for the assessment of cognitive function. Categories include consciousness, orientation, memory-remote, perception, attention, speech, thinking, affect, mood, behavior, rapport, insight, and variability.	The D-Scale was one of the first attempts to develop a more systematic evaluation of delirium, however, the complex design limits use in a clinical setting (Trepazc 94).
Diagnostic and Statistical Manual of Mental Disorders (DSM III, 1980; DSM III R, text revision, 1987; DSM IV, 1994; DSM IV text revision, 2000, American Psychiatric Association)	The standard classification of mental disorders used in the United States; a set of diagnostic criteria that indicate inclusion and exclusion criteria for a particular diagnosis.	The DSM III was published in 1980, DSM III-R in 1987, the DSM-IV in 1994, and the DSM IV in 2000.

Appendix E. (continued)		
Test (Author/Year)	Description	Comment
Diagnostic Instruments		
Global Accessibility Rating Scale (GARS) (Anthony 85)	A visual analog scale for assessing disturbance of consciousness. The rating was based on how well the participant was able to remain focused during an interaction with the researcher. A rating closer to 10 meant the participant remained engaged throughout the interview; however, a rating closer to 0 meant the participant could not remain engaged. Scores < 7.9 were considered consistent with impairment of consciousness and detected impairment in 9 out of 10 participants with a delirium diagnosis, as well as participants with dementia and other psychological disorders.	GARS scores had a low level of agreement with MMSE scores ($k = 0.39$) (Anthony, 85) and use of the GARS to assess delirium has not been recommended because of its lack of specificity and lack of breadth for symptom assessment (Trepacz 94).
Organic Brain Syndrome (OBS) Scale (Gustafson 85, 95)	Developed to evaluate disturbances of awareness and orientation, together with other signs of confusion. The OBS consists of two subscales, one for "disorientation," and a second subscale for "confusion."	The OBS scale has been used in a modified (shortened) fashion where the only psychometric data reported was IRR > 90% (Berggren 87). A recent review of the OBS scale reported that while it can be considered a valid clinical instrument, further evaluation should be carried out (Bjorkelund 06).
Saskatoon Delirium Checklist (SDC) (Miller 88)	The SDC is a checklist based on DSM III criteria to quantify delirium. The checklist consists of 10 symptoms that are rated on a 0-4 point scale with a maximum total score of 40 points, indicative of no impairment. The 10 items are reduced clarity of consciousness, perceptual disturbances, incoherent speech, sleep disturbance, slowing in motor behavior, agitation, disorientation, other memory problems, fluctuation of symptoms, and physical cause.	Developed for a study on the effects of serum anticholinergic levels on cognitive impairment in elderly participants. The SDC has been criticized because no psychometric data are reported in the original study, nor is there support for how symptoms were operationalized for rating, e.g., "reduced clarity of consciousness" (Trepacz, 94).
Delirium Rating Scales		
Confusion Rating Scale (CRS) (Williams 86)	Developed for use by nurses for nurses in clinical settings and does not require patient participation. It has four dimensions: disorientation, inappropriate behavior, inappropriate communication, and illusions/hallucinations. Each dimension is rated as "none" (= 0 points), "mild" (= 1 point), and "pronounced" (= 2 points). The maximum score is 8 points, with a score of zero being normal; scores ≥ 1 are reported to be consistent with confusion.	It has been suggested that the criteria be operationalized and based on DSM criteria to increase its specificity for delirium (Trzeczacz, 94).
Confusional State Evaluation (CSE) (Robertsson, 97)	Developed to measure severity of delirium, to follow changes of symptoms over time, and to evaluate treatment efficacy. The CSE is an observer's rating scale with 22 items. Scores on 12 of the items are summarized to a "confusion score." This score represents delirium severity.	Psychometrics reported: IRR (K-R 20 = .38-.93) and correlation between the "confusion score" of the CSE scale and the global rating of confusion by a psychogeriatrician was $r = 0.79$.
Delirium Assessment Scale (DAS) (O'Keefe 93)	Developed to determine severity of delirium symptoms. Used operationalized DSM-III criteria to compare delirious, delirious-demented, demented, and not cognitively impaired groups.	Sensitivity (83% to 88%) and specificity (79% to 88%) were reported for delirium diagnosis, and IRR for the individual symptoms of the DAS ranged from 0.66 to 0.99.

Appendix E. (continued)		
Test (Author/Year)	Description	Comment
Delirium Rating Scales		
Delirium Index (DI) (McCusker,98)	A measure of the severity of symptoms of delirium based on clinical observation only. Seven domains (attention, thought, consciousness, orientation, memory, perception, and psychomotor activity) are rated on a 4-point scale. The DI is used in conjunction with the MMSE.	Psychometrics reported: IRR (.78 - .88), criterion validity (.84, assessed by repeated measures with the DI and the DRS), and construct validity was assessed by correlating DI ratings with measures of cognition and ADL before admission and during admission. May be used in patients with or without dementia (McCusker 04).
Delirium Rating Scale (DRS) (Trzepacz 88)	A symptom rating scale for assessment of delirium severity over a 24 hour period. Clinician-rated, using all available data: patient interview, family interview, nurse report, and medical record. The DRS is a 10-item scale of symptoms characteristic of delirium: temporal onset of symptoms, perceptual disturbances, hallucinations, delusions, sleep-wake cycle disturbance, cognitive status, psychomotor behavior, lability of mood, physical disorder, and variability of symptoms. The rating scale has 10 items and each item is scored from 0 to a maximum either of 2, 3, or 4 points, depending on the item. The maximum possible score is 32 points.	Although the DRS is quick to complete, data collection involves extensive psychiatric and physical examination of patients, which may be time consuming. The DRS was originally developed to rate the severity of symptoms of delirium,; however, several authors have found that using a DRS threshold score of ≥ 10 correctly identified delirious patients with a sensitivity of 82-94% and a specificity of 82-94% (Burnham 94, Rockwood 96).
Delirium Rating Scale-Revised (DRS-R 98) (Trzepacz 01)	The revised scale used 16 symptom-related items derived from the <i>DSM-III-R</i> and the International Classification of Diseases (ICD – 10) from the World Health Organization. Three diagnostic-related items were added (acute onset, symptom fluctuation, and etiologic factors), which were derived from the DSM-IV.	Psychometrics reported: IRR and internal consistency for the total score of the DRS-R-98 ($r = .98$ and $.90$, respectively) and sensitivity and specificity of the total score ranged from 91% to 100% and 85% to 100%, respectively, depending on the cutoff scores or comparison groups selected.
Delirium Severity Scale (DSS) (Bettin 98)	The DSS was developed to measure delirium severity over time and is a combination of two standard cognitive tests, the Forward Digit Span of the Wechsler Memory Scale-Revised and Similarities. The score is the sum of the raw scores for these two tests, with higher scores reflecting less delirium symptom severity.	The scale was shown to be valid and sensitive to change.
Delirium Symptom Interview (Albert 92)(Albert et al., 1992)	Uses a structured interview and clinical observation for diagnosing the presence of specific symptoms of delirium based on seven symptom domains (disorientation, disturbance of sleep, perceptual disturbance, disturbance of consciousness, incoherent speech, level of psychomotor activity, and fluctuating behavior disorientation).	In the original study describing the DSI, three symptoms were identified by consensus as being “critical” to the diagnosis of delirium: disorientation, disturbance of consciousness, and perceptual disturbance; delirium was diagnosed when any one of these domains was rated positive. Sensitivity was 0.90 and specificity was 0.80 when compared with a physician’s diagnoses.
MCV Nursing Delirium Rating Scale (MCV-NDRS) (Rutherford 91)	The MCV-NDRS is a modified version of the DRS, designed for ICU nurses’ ratings of symptom severity. The scale has 7 items: 4 items from the DRS were deleted (temporal onset of symptoms, physical disorder, perceptual disturbances, and delusions) and the psychomotor behavior item was divided into two items in order to simplify the scale. The 7 items are hallucinations, agitation, withdrawal, cognitive deficits, sleep-wake cycle, lability of mood, and variability of symptoms.	Each item is scored from 0 to a maximum either of 2, 3, or 4 points, depending on the item. The maximum possible score is 20 points.

Appendix E. <i>(continued)</i>		
Test (Author/Year)	Description	Comment
Delirium Rating Scales		
Memorial Delirium Assessment Scale (MDAS) (Breitbart 97)	<p>Designed to measure changes in delirium severity with repeated measures within the same 24-hour period.</p> <p>Items reflect DSM criteria with emphasis on attentional ability and disorganization of thought. Six items reflect current performance, and four rate both current and recent symptoms.</p>	<p>Psychometrics reported: MDAS ratings correlate with ratings on the DRS ($r = .88$) and the MMSE ($r = .91$); IRR ($r = .89$ to $.92$). A cut-off score of 7 gave a sensitivity of 98% and a specificity of 96%.</p> <p>The MDAS allows for prorating scores when a patient cannot actively participate in the assessment (Lawlor 00).</p>
Visual analogue scale for confusion (VASC) (Nagley, 1984)	A 10-cm horizontal line with anchors of "No confusion," and "Severe confusion." Nurses place a mark through the line indicating their perception of the patient's degree of confusion	Psychometrics reported: VASC ratings correlate with the Short Portable Mental Status Questionnaire ($r = .63$). Interrater reliability was reported as $.98$ (Nagley, 1984).

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