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Predictors of agitation in the critically ill

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Predictors of Agitation in the Adult Critically Ill

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Acknowledgment

TABLE OF CONTENTS

List of Tables

List of Figures

ABSTRACT

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By **Ruth Srednicki Burk, PhD**

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BACKGROUND: Agitation is a common complication in the intensive care unit (ICU) manifested in behavior and actions that range from simple apprehension or anxiety to frankly combative behavior.[5] Agitation is associated with significant adverse outcomes.[1-3] Studies report up to 71% of ICU patients have some degree of agitation during their ICU stay and that agitation is observed 32% of the time.[3;4] Potential causes of agitation in critically ill patients are numerous; however, data about factors that predict agitation are limited.

OBJECTIVE: The specific aim of this study was to identify predictors of agitation on admission to the ICU as well as within 24 hours prior to the first agitation event.

DESIGN: Retrospective medical record review.

SETTING: Two adult critical care units, Medical Respiratory ICU (MRICU) and Surgical Trauma ICU (STICU) in an urban university medical center.

SUBJECTS: A convenience sample of 200 critically ill adult patients, all older than 18 years of age, consecutively admitted to a MRICU and STICU, admitted for longer than 24 hours, over a two month period.

METHODS: Risk factors for agitation were identified from literature review as well as from expert consultation. Data were collected during the first 5 days of ICU stay. Agitation was identified using the documented Richmond Agitation-Sedation Scale or notation of "agitation" in the medical record.

RESULTS: Of the sample 56.5% were male, 51.5% Euro-American, with mean age 55.5 years (±16.4). Independent predictors of agitation on admission to the ICU were: past medical history of illicit substance use, height, both the Sequential Organ Failure Assessment respiratory and central nervous system subscores, and use of restraints. Predictors of agitation within 24 hours prior to the first agitation event were: percent of hours using restraints, percent of hours using mechanical ventilation, number of genitourinary catheters, and blood pH and albumin.

CONCLUSIONS: Use of these empirically based data may allow care providers to identify those at risk as well as predict agitation. Elimination or reduction of agitation in the ICU would improve patient safety and reduce hospitalization resulting in significant savings to healthcare costs.

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CHAPTER 1. INTRODUCTION

Care of the critically ill patient in the United States consumes approximately 15% of all healthcare dollars[1] with approximately $80.8 billion spent on intensive care.[2] The cost of complications resulting in an increased intensive care unit (ICU) stay can inflate this amount significantly. One of the more common complications is agitation. Agitation is most often described as excessive restlessness, usually non-purposeful physical activity, associated with internal tension, anxiety, or emotional distress.[3-5] In the ICU, agitation can be manifested in behavior and actions that range from simple apprehension or anxiety, inappropriate self-removal of indwelling tubes and catheters, attempted assault of a care provider, and to frankly combative behavior.[6] Agitation has been shown to extend the length of stay (LOS) in the hospital[7;8] from a median of 5 to 12 days.[7] Studies report up to 71% of ICU patients have some degree of agitation during their ICU stay[9] and that agitation is observed 32% of days.[10]

The management of agitation usually involves increasing sedative medication or the use of patient restraints. Medical treatment of agitation may result in excessive sedation and hemodynamic instability in over 75% of patients,[7] seriously compromising patient safety. Continuous infusion of sedative and analgesic medications is associated with prolonged mechanical ventilation, organ system failure, increased LOS and reintubation, ultimately resulting in higher hospitalization costs.[11] To avoid these problems, sedative and analgesic levels are reduced and may result in under-sedation. Attempts to minimize sedative use may culminate in severe agitation and anxiety with cardiopulmonary instability such as hypertension, tachycardia, tachypnea, ventilator dysynchrony, hypoxemia and unplanned extubations.[12] Sedation of critically ill patients has been shown to result in increased hospital LOS,

1

complications of immobility, and hospital costs – with sedative drugs costing more than $500 per day.[13]

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) 2000 standards acknowledge that the use of restraints poses an inherent risk to the physical safety and psychological well-being of the individual and staff, and therefore, is to be used only in an emergency, when there is an imminent risk of individual harm. These conditions are often present during agitation. Therefore, early identification and optimal management of agitation will likely improve patient safety, which is an important target of the national health care agenda. The Agency for Healthcare Research and Quality (AHRQ), JHACO, and The Centers for Medicare & Medicaid Services (CMS) support measures to reduce patient physical restraints.

Potential causes of agitation in critically ill patients are numerous; however, data about factors that predict agitation are limited. The etiology of agitation is multifactoral and agitation is costly; therefore, management of agitation should be directed at prevention rather than treatment.

The evaluation of agitation and sedation is primarily a nursing responsibility. Surveys indicate that nurses are responsible for administering and titrating sedation for patient comfort in 94% of ICUs.[14] Currently there is no tool or evaluative system to alert health care providers to impending agitation, although scales, such as the Richmond Agitation-Sedation Scale[15] (RASS), evaluate degree of agitation once agitation has been identified. Use of empirically based information would assist care providers to identify those at risk as well as predict agitation. Identification of patients at particularly high risk for developing agitation provides an opportunity to implement preventative strategies to protect patients from self- and iatrogenic-induced injury.

Agitation is considered multifactoral – age, gender, severity of illness, past medical history (PMH)/admitting diagnosis, presence of endotracheal tubes and invasive lines/catheters, use of sedatives and analgesics, use of restraints, hypoxemia, pain, fever, heart rate (HR), and blood pressure (BP) are thought to be significant contributing factors.[4;5] Chapter 2 summarizes

2

a review of the literature of agitation in critical illness – its significance, risk factors, and evaluation. However, few empirical studies have systematically evaluated predisposing factors. An exhaustive review by Fraser et al.[9] in 2000 found no studies that examined the etiology of agitation in patients in the ICU. Since then, there have been 4 studies directed at identifying risk factors.[7;8;10;16]   Most studies have focused on optimizing sedative therapy and quantifying agitation rather than addressing prevention.

A retrospective medical record review was initiated to explore the predictors of agitation in a sample of adult medical and surgical ICU subjects for up to 5 days. This comprehensive investigation of risk factors is presented in Chapter 3. The purpose of this study was to examine the relationship of demographic and clinical characteristics of critically ill patients to the development of agitated behavior. The specific aim of this study was to identify predictors of agitation on admission to the ICU as well as those present 24 hours prior to agitation.

Data from 200 subjects was collected. Agitation was identified using documentation of the RASS[15] using values of +1 (restless – anxious or apprehensive but movements not aggressive or vigorous) through +4 (combative – overtly combative or violent; immediate danger to staff) to identify agitation. The RASS[15] is the standard sedation-agitation tool used in both of the target ICUs and values are routinely obtained every 4 hours and more frequently if needed. Agitation was also documented using the keyword "agitation" (all forms of the word, "agitated", "agitation", "agit") recorded from the medical record using physicians' and nurses' notes in the nursing bedside flowsheet, emergency department documentation, operating room notes, and circle-the-item for reporting agitation in flowsheets.

Risk factors presumed to be associated with agitation, identified from literature review (Chapter 2) as well as from expert consultation, were used for data collection. Information pertaining to preadmission risk factors and baseline demographics as well as clinical factors, theorized and implicated, in the onset of agitation was retrieved from patient medical records.

3

Data were summarized by hour, 4-hour block, and day for each subject and categorized as an agitation or non-agitation hour, block, or day. Documentation of agitation in this manner, with detail not previously presented in other studies, allowed investigation into the onset, frequency, and characteristics of agitation. The summary and discussion of these data are presented in Chapter 3.

Agitation was found in both medical and surgical subjects. Of the 200 subjects, 118 (59%) had at least one episode of agitation during the 5 study days during 319 (31.9%) patient-days. Of the total data hours, the overall agitation rate was 7.8%. The onset of agitation was a median of 2 hours (range 0-114; IQR 0-13.75) from ICU admission.

On admission, univariate factors associated with agitation were determined. Individual demographic and preadmission factors present on ICU admission that were significantly associated with agitation were: male gender, greater body weight, past medical history of illicit substance use, and psychiatric diagnosis. Agitation was associated with higher severity of illness including the total Sequential Organ Failure Assessment[17] (SOFA) score, the SOFA respiratory and central nervous system (CNS) subscores, the Glasgow Coma Score (GCS), and Acute Physiology And Chronic Health Evaluation III[18] (APACHE III). Specific clinical factors associated with agitation were $PaO_2/FiO_2 < 200$ mmHg, FiO_2, serum pH, serum magnesium, serum glucose, use of restraints, use of mechanical ventilation (MV), pain rating, number of total catheters, number of genitourinary (GU) catheters, and number of gastrointestinal (GI) and other catheters. Following, logistic multivariate regression analysis identified predictors of agitation on admission as: past medical history of illicit substance use (p=0.0176), height (p=0.0178), both the SOFA respiratory (p=0.0124) and CNS subscores (p<.0001), and use of restraints (p=0.0125).

Univariate factors associated with agitation, present 24 hours prior to the first agitation event, were determined. Significant individual demographic and preadmission factors as well as severity of illness scores present within 24 hours prior to onset of the first agitation event were

4

the same as the on-admission group. Specific clinical factors prior to the first agitation event associated with agitation were also the same with the exception of total number of catheters and GI and other catheters. Logistic multivariate regression identified predictors of agitation within 24 hours preceding agitation to be: past medical history of psychiatric diagnosis (p=0.015), height (p=0.015), total SOFA score (p=0.012), P/F<200mmHg (p=0.011), serum pH (p=0.026), percent of hours using restraints (p=0.0003), percent of hours using mechanical ventilation (p=0.0004), pain rating (0.0059), and presence of genitourinary catheters (p=0.0264).

This study contributes new knowledge to identification of agitation in the medical and surgical ICU patient populations. This evidence may allow a better understanding of risk factors of agitation and add to empirical data guiding future research direction. After identification of the risk factors and predictors of agitation, an evaluative tool can be developed to alert caretakers to the possibility of agitation, so that interventions can be implemented before agitation occurs. Elimination or reduction of agitation in the ICU would improve patient safety and reduce hospitalization resulting in significant improvement in patient health and safety as well as savings to healthcare costs.

5

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7

Agitation in Adult Critically Ill Patients: Significance, Risk Factors, and Evaluation

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8

Abstract

Agitation in critically ill adults is a frequent complication of hospitalization – up to 71% of intensive care unit (ICU) patients have some degree of agitation during their ICU stay. Agitation can result in life-threatening complications related to hemodynamic instability, unplanned extubation and hypoxia, with injury to the patient or care providers, and has been found to extend the hospital length of stay increasing hospital costs. However, agitation remains incompletely understood with no gold standards for indicators, assessment approaches, evaluative tools, or treatment plans. Despite the need for more information in this area, a consensus has yet to be reached for almost any aspect of agitation. The purpose of this review is to examine agitation in adult critically ill patients – its significance, risk factors, and evaluation.

9

Care of the critically ill patient in the United States consumes roughly 15% of all healthcare dollars[1] with approximately $80.8 billion spent on intensive care.[2] Complications in the intensive care unit (ICU) can inflate this cost significantly. One of the more common complications is agitation which can result in a variety of significant and negative patient outcomes and increased hospital costs. This paper will review the incidence and significance, risk factors, consequences, and evaluation of agitation as well as present suggestions for directions of future research.

Agitation is most often described as excessive restlessness, or non-purposeful physical activity, associated with internal tension, anxiety, or emotional distress.[3-5] Patients appear to be anxious, jittery, and hyperalert. Recently, agitation has also been defined as a nonspecific constellation of relatively unrelated behaviors that can be seen in a number of different clinical conditions, usually presenting a fluctuating course.[6] These behaviors may include nonaggressive and aggressive physical components (i.e. pacing, aimless psychomotor activity vs. fighting, throwing, grabbing) and verbal components (i.e. constant questioning, chatting vs. cursing, screaming). In the ICU, agitation can be manifested in behaviors and actions that range from simple apprehension or anxiety, inappropriate self-removal of indwelling tubes and catheters, attempted assault of a care provider, and to frankly combative behavior.[7;8] There appears to be a growing consensus that agitation exists on a continuum from jitteriness and fidgeting with little or no confusion to overt combativeness with or without delirium.[9] Observed and postulated physiologic manifestations of agitation seen in escalating movement include increased sympathetic nervous system tone as well as increased levels of circulating catecholamines, resulting in palpitations, tachycardia, arrhythmias, increased blood pressure, vasoconstriction of the extremities, myocardial ischemia, infarction and sudden death.[6;10;11]

Agitation has been shown to be associated with longer length of stay in the hospital[12;13] from (a median of) 5 to 12 days.[12] Studies report up to 71% of ICU patients have some degree of agitation during their ICU stay[14] and that agitation has been observed in up to 32% of patient-

10

days.[15] In a prospective evaluation of adult medical ICU patients by Carrion et al.,[16] moderate or severe agitation was observed by bedside nurses in over 20% of patient-shifts, and overt agitation, such as resulting in self-removal of a tube or catheter or aggressive behavior towards a healthcare provider, in 9% of patient-shifts.

Agitation treatment usually involves the increased use of sedation or restraints; however, both have inherent problems. Continuous infusion of sedative and analgesic medications is associated with prolonged mechanical ventilation (MV), organ system failure, and increased length of stay and reintubation, ultimately resulting in higher hospitalization costs.[17] Medical treatment of agitation may result in excessive sedation and hemodynamic instability, impacting over 75% of patients in one study,[12] and potentially seriously compromising patient safety. To avoid these problems, doses of sedative and analgesic medication may be reduced or infusions temporarily stopped – which can then result in under-sedation. Attempts to minimize sedative use may culminate in severe agitation and anxiety with cardiopulmonary instability such as hypertension, tachycardia, tachypnea, and unplanned extubations.[18]

Risk Factors for Agitation

Agitation is poorly understood with no identified gold-standard for indicators, assessment approaches or treatment plans. Few empirical studies have systematically evaluated predisposing risk factors in the ICU environment, although agitation has been identified for over 100 years; reports of observed agitation were present in the early days of ICUs.[19] Thus far, most research has focused on optimizing sedative therapy.

Experts have unanimously theorized that agitation is the result of intrinsic and/or extrinsic factors producing psychological and/or physical stress (Table 1); however, to date, studies have been inconclusive of specifically which factors, or combinations of factors, are involved in agitation. Although critically ill patients suffer both psychological and biological stressors, and these are present and implicated in virtually all cases of agitation, it is not yet understood why some critically ill patients never experience agitation.[3-5]

11

Agitation is also thought to be a result of dysregulation of neurotransmitters. Sachdev and Kruk[20] proposed a model of restlessness in different clinical disorders involving disturbances of the cortico-striatal-thalamic circuits of the brain, explained by increased or decreased levels of dopamine, serotonin, gamma-aminobutyric acid (GABA) and noradrenergic activity.[6;21]

An exhaustive review by Fraser et al.[14] in 2000 found no studies in the previous 30 years with a primary goal to evaluate risk factors for agitation in ICU patients. Their search included a variety of databases: Health Periodicals Database, Cancerlit, Internet, Cinahl, Health Periodicals, MEDLINE, and Psych Info. Since that time only 4 studies have been found to be published.[12-15] (Table 2). It is important to recognize that publication bias in these literature searches may exist in that non-significant or negative results may not have been published. The four studies addressed the etiology of agitation from the context of gaining information for specific populations – the elderly, mechanically ventilated patients, Medical Respiratory ICU (MRICU) patients, and a general mixed medical-surgical ICU population.

Risk factors for agitation are categorized into four groups: patient characteristics, ICU therapies, critical illness, and physiologic instability. The empirical data from these 4 recent studies is reviewed here. While these studies have shown some agreement in risk factors, there are also conflicting results.

12

Table 1. Factors proposed to be involved in the onset of agitation

Physiologic	Environmental	Technological	Pharmacologic	Patient Characteristics
Severity of illness	Noise	Mechanical ventilation	Sedatives	Age
CNS insults	Lack of windows	Restraints	Analgesics	Sex
Dyspnea	Visitation policies	ET/NG/Trach tubes	Anticholinergics	PMH
Nausea	Temperature	Foley catheters	Paralytics	Psychiatric history
Constipation	Light intensity/source	Feeding tubes	Anesthetics	Drug abuse
Thirst	Odors	PA, CV & other arterial lines	Steroids	Alcohol abuse
Organ failure		Radiological tests	Bronchodilators	Allergies
Patient-ventilator dyssynchrony		Laboratory work	Cardiac drugs	Family history/genetics
Fever		Dialysis	Antihistamines	Anxiety/stress
Hypoxemia		Bedside monitors	Antibiotics	
		Diagnostic tools	Drug-drug interactions	
		Hemodynamic monitoring devices	Antipsychotics	

CNS – Central Nervous System
ET – Endotracheal
NG – Nasogastric
Trach - Tracheal
PA – Pulmonary Artery
CV – Central Vein
PMH – Past Medical History

13

Table 2. Empirical studies of factors associated with agitation

Study	Sample, Design and Objective	Inclusion criteria	Agitation evaluation	Factors found associated with agitation
Fraser, et al., 2000, USA	130 patients; Multidisciplinary ICU (Tertiary care center) <u>Prospective observational design:</u> to study the frequency, duration, severity, and treatment of agitation in ICU patients to determine if the elderly represent a distinct population	All patients older than 18 admitted for longer than 24 hours, for a 4 month period	SAS; agitation defined as SAS greater than 4	Anxiety, delirium, drug administration, and pain. 97% of instances of severe agitation were associated with several possible etiologies.
Woods, J.C., et al., 2004, USA	143 patients; Medical ICU (Tertiary care center), <u>Prospective observational design:</u> to determine the frequency, characteristics and outcomes of <u>severe</u> agitation among ventilated ICU patients	All <u>MV</u> patients, 18 or older, admitted for longer than 24 hours, for a 4 month period	MAAS; only evaluated <u>severe</u> agitation (2 or more MAAS scores higher than 4 in a 24 hr period and sedative and/or analgesic agents higher than recommended guideline dosages OR the combination of two sedatives within the same 24 hr period, because maximal doses of one sedative did not achieve adequate sedation)	<u>Severely</u> agitated patients were: younger, more likely to be admitted from an outside hospital ICU, had lower pH, and a PaO_2/FIO_2 less than 200 mmHg.
Jaber, S., et al., 2005, France	182 patients; Medical-surgical ICU; <u>Prospective observational design:</u> to evaluate the incidence, risk factors, and outcomes of agitation	All patients	Modified Ramsay scale; agitation defined as a modified Ramsay score of 1	Sepsis, alcohol abuse, use of sedatives, fever, dysnatremia, and use of psychoactive drugs

14

Gardner, K., Sessler, C.N., Grap, M.J., 2006, USA	83 patients; Medical Respiratory ICU; <u>Retrospective chart review</u>: to examine the relationship of clinical, laboratory, and intervention characteristics of ICU patients to agitation	Patients 18 yo or older, admitted over a one-month period	RASS; agitation defined as a RASS score of 2 or higher	Higher APACHE II scores, daily MODS scores – among the MODS subscores, specifically the pulmonary, cardiovascular, and neurologic components were higher in agitated patients

ICU – Intensive care unit
MV – mechanically ventilated
SAS – Sedation Agitation Scale
MAAS - Motor Activity Assessment Scale
RASS - Richmond Agitation-Sedation Scale
APACHE II - Acute Physiology, Age, Chronic Health Evaluation II
MODS - Multi-Organ Dysfunction Scores

Patient Characteristics. Individual patient characteristics such as demographics, medical history, and admitting status may provide susceptibility to agitation.

Demographics, specifically age and gender, have been thought to be associated with agitation. All studies evaluated the relationship between age and agitation with some inconsistency in the data. No relationship was found between presence of agitation and age in three of the studies[13-15] and it should be noted that the objective of the one by Fraser et al.[14] specifically addressed this possibility. In 2000, Fraser et al.[14] compared agitation in young versus elderly patients related to frequency, severity, onset, and duration, and the choice and route of sedating agent(s), dosing requirements, and adverse effects. This prospective medical record review involved 130 patients older than 18 years of age admitted for longer than 24 hours during a 4-month period. Of the 130 patients, 92 (70.8%) were described as having agitation. Severity of illness was measured using the admission Acute Physiology and Chronic Health Exam (APACHE) II score.[22] Agitation, measured by the Riker Sedation-Agitation Scale[7] (SAS) as a score greater than 4, derived from written descriptions of behaviors in patient documentation, was linked with suspected causes by identifying potential etiologies in medical records. If a caregiver assigned a cause of agitation, it was classified as a probable cause; if none was assigned, all factors present during agitation were classified as possible causes. Additional data collected included laboratory values indicating hepatic or renal dysfunction, need for ventilatory support, and ICU admission information. Analysis involved descriptive statistics and univariate analyses followed by simple regression to determine the association between ICU length of stay and severity of agitation using alpha=0.05 as the level of significance. The study described factors found in the agitated patient, but did not identify predictors of agitation. Although they found no relationship between agitation and age, they did find that the elderly experienced a higher frequency of side effects (55%) than younger patients (33%).

Woods et al.[12] in 2004 studied the frequency, characteristics, and outcomes of severe agitation in mechanically ventilated (MV) medical ICU patients with a prospective medical record

16

review. Of the 143 enrolled patients, 23 (16.1%) exhibited severe agitation. The study lasted approximately 4 months with a patient length of stay in the ICU for a minimum of 24 hours. The main outcome variable, severe agitation, was defined as two or more Motor Activity Assessment Scale (MAAS) scores above 4 in a 24-hour period, and sedative and/or narcotic doses above the established sedation and analgesia protocol, or a combination of two or more sedatives because adequate sedation was not initially achieved. The MAAS was assessed by nursing staff; daily interruption of sedation was not practiced. Data collected included admission information, a severity of illness (APACHE II) score,[22] arterial blood gases with corresponding ventilator settings, laboratory values, nursing interventions, total doses of sedatives, analgesics or neuromuscular blocking agents as well as documented new conditions or adverse events, discharge disposition, length of stay, weaning status, and patient instigated removal of endotracheal (ET) tubes, nasogastric (NG) tubes, or arterial lines. Analysis involved descriptive statistics and time-to-event using Cox-proportional hazards with time-varying covariates comparing the two groups (severely agitated and non-agitated patients); resulting estimates were reported as hazard ratios (95% confidence interval [CI]). The study focused on characteristics and outcomes of severe agitation rather than on factors that may predict earlier levels of agitated behavior. Surprisingly, in this study, one of the four factors in their multivariate analysis found to be correlated to severe agitation in MV patients was *younger* age (50.2 versus 62.6 years, *p*=0.0016). The authors stated that the differences found may be related to: 1) differences in inclusion criteria as only severely agitated patients were studied; 2) the use of an ICU protocol to manage sedative and/or analgesic agents based on the most recent practice guidelines; and 3) relative ratio differences – a lower rate of agitation in patients older than 65 may have made it appear that younger patients had a higher rate.

Jaber et al.,[13] in 2005, used a prospective observational design in a study over 8 months, to evaluate the incidence, risk factors, and outcomes of agitation in 182 medical-surgical ICU patients, both receiving, and not receiving, mechanical ventilation. Agitation was identified in 95

17

(52%) of the 182 patients. Agitation was assessed daily by a clinical pharmacist using a modified Ramsay score (agitation designated as a score of 1) as well as by use of recorded notes from care providers. The evaluation was then confirmed during a daily meeting of ICU physicians and nurses. Data collected included admission and discharge information, severity of illness score (Simplified Acute Physiology Score [SAPS] II)[23], and history of psychoactive drug use or ethanol abuse, characteristics of agitation, laboratory values, temperature, and presence of sepsis. Descriptive statistics were used followed by univariate analysis between the two groups (agitated and nonagitated patients). These univariate predictors were then used to model the risk of agitation by using stepwise block regression. The Hosmer and Lemeshow test was used to determine appropriateness of the model (p=0.053). A p<0.05 was considered significant. They found no relationship between age and agitation.

A study in 2006 conducted by Gardner, Sessler and Grap[15] used a retrospective chart review of 83 subjects over a 2-month period in a Medical Respiratory ICU. Data obtained from this study is limited to a published abstract. Of the 83 patients, 35 (42%) were agitated during at least one day of their ICU stay. Since routine agitation-sedation scoring was not conducted in this unit during the study period, nursing documentation was used to rate the level of agitation. Data collected included admission information, severity of illness (APACHE II[22]) score, daily multi-organ dysfunction scores (MODS), frequency of agitated behavior, and number of tubes and lines pulled. No association between age and agitation was found.

Empirical evidence suggesting a lack of relationship between age and agitation, although not conclusive, is compelling. Comparison of the 4 studies is difficult due to Woods et al.'s[12] narrow spectrum of both population (exclusively MV) and agitation level (specifically severe agitation), while the others used more general criteria. Jaber et al.[13] also commented that the limitations of statistical analysis needs to be considered as the number of severely agitated patients was small (n=23). With respect to an association between gender and agitation, empirical evidence suggests no relationship – all four studies reported no correlation.

18

Medical history, including alcohol or drug use/abuse, use of antipsychotic medications for treatment of psychiatric disorders, admitting diagnosis, and admission from an outside hospital were studied to determine association with agitation. Alcohol use/abuse as a risk factor for agitation was examined in 3 of the studies and an association was found in 1. In 95 agitated general ICU patients, Jaber et al.[13] found history of alcohol use/abuse (n=40 vs 15, p=0.001; odds ratio 3.32, 95% CI [1.12-10.0]) to be one of 7 independent risk factors for agitation. Of the study participants, 30% had a history of alcohol abuse as defined by a frequency of >14 U (units)/week and/or periods of time with >4 U/day. In their study, those with a history of alcohol abuse were three times more likely to become agitated than those who were not. In contrast, both Woods et al.[12] (severe agitation and MV patients) and Gardner et al.,[15] with agitated patients of n=23 and n=35 respectively, found no such relationship. Criteria for determining alcohol dependency or alcohol use was not defined so a comparison of these 2 studies to Jaber et al.'s[13] may be difficult. Also limitations of statistical analyses for small sample sizes should be considered. Thus, empirical evidence is inconclusive with respect to alcohol use/abuse. In the analysis of drug use, 2 studies[12;15] addressed the possible predictor; neither finding a significant relationship in the multivariate analysis. In the univariate analysis marijuana use (Hazard ratio 7.94, 95% CI [1.82-34.73], p=0.007) was significantly associated with the development of severe agitation in 23 MV agitated patients.[12] Neither study described the criteria for determining drug use or types of drugs considered. Considering the limitations of both sample size and narrow limits of population and agitation, empirical evidence is inconclusive regarding the relationship between drug use and agitation. Psychoactive drug use (in the context of regular antipsychotic medications for treatment of a psychiatric disorder) was examined by Jaber et al.[13] in 182 patients (21% used psychoactive drugs before hospitalization), and was found to be a risk factor of agitation in their multivariate model (n=32 vs 6, p=0.001). Additionally, patients who regularly used psychoactive drugs were 5 times more likely to develop agitation than those who did not. The types of drugs were not discussed. The authors

19

commented that the significant relationship may be explained by the characteristics of the study population who were frequent users of psychoactive drugs. Empirical evidence for this factor is inconclusive. Admission status, both admitting diagnoses and origin of admission, were examined in relation to agitation. Admitting diagnosis was examined and was not found to be significant factor in multivariate analyses. Woods et al.[12] and Gardner et al.[15] gathered diagnoses present on admission. Jaber et al.[13] recorded reason for ICU admission for the two distinct populations – surgical and medical patients. In the univariate analysis they found that the incidence of agitation was greater in the medical patients than among the surgical patients (38 of 46 patients, 83%; vs 57 of 136 patients, 42%; p<0.001). With respect to origin of admission, admission from an outside hospital was found to be significantly associated (48% versus 21%; *p*=0.0158) in the multivariate analysis by Woods et al.[12] The authors commented that there was a possibility that the transferred patients were sicker than those admitted in-house, although APACHE II scores did not reflect this. They argued that post-admission developments may not have been reflected in the admission APACHE II ratings, supported by a study that found patients transferred to a tertiary center ICU have a longer hospital stay and higher mortality compared with those admitted directly to an ICU.[24] They also stated that it was unknown to what extent sedation and analgesia protocols were utilized by referring hospitals. The limited sample size and narrow limits of both the population and agitation definition call into question the strength of this association. Empirical evidence is inconclusive with respect to a relationship between admission status and agitation.

ICU Therapies. Treatment of the critically ill patient involves regimens employing the use of invasive lines and pharmacotherapeutics possibly associated with agitation. Endotracheal (ET) tube intubation has been found to be a source of stress and irritation to the critically ill patient[25-27] and, therefore, suspected of contributing to agitation. Two studies[12;13] examined this relationship and found mechanical ventilation to have no relationship to agitation.

20

One study[13] found a univariate but no multivariate association in the incidence of agitation in those with and without MV.

Critically ill patients receive numerous pharmacotherapeutics. Multiple drugs, with appropriate as well as unintended under- and over-medication, may result in significant and unpredictable interactions, and is thought to be one of the more common causes of agitation (Table 3). These therapies can act, and interact, unpredictably. The pharmacological treatment itself may not be associated with agitation; however, the numerous metabolites and their varying elimination rates may contribute to or precipitate agitation. Psychological stress to the patient associated with undersedation and the inadequate treatment of discomfort and pain, as well as physiological stress associated with the critical illness and its pharmaceutic treatment have been thought to be related to the onset of agitation. In particular sedatives, especially the benzodiazepines, most frequently used to treat agitation, and analgesics, specifically opiates, have been studied with relation to agitation.

Woods et al.[12] measured the daily total dose of sedatives, analgesics or neuromuscular blocking agents and found that both sedatives and analgesics were administered to MV patients experiencing severe agitation more frequently and in greater doses both prior to, or on the day of, agitation onset as well as throughout the ICU stay. Specifically, 96% of severely agitated MV patients received lorazepam at some point during their medical ICU (MICU) stay compared to 75% of those who were non-agitated (p=0.028); midazolam was reported as 70% vs. 39% (p=0.007); propofol was reported as 83% vs. 32% (p<0.0001); continuous IV morphine as 61% vs 18% (p<0.001), total morphine as 83% vs. 59% (p=0.033); and fentanyl as 61% vs 38% (p=0.037). Similarly, Jaber et al.[13] found that use of sedatives was an independent risk factor for agitation (Odds Ratio 4.03, 95% CI [1.62-10.4]). In the univariate analysis a significant association with agitation was found with benzodiazepines (54 of 74 patients, 73%, p=0.001), opioids (46 of 64 patients, 72%, p=0.001), and neuroleptic drugs (17 of 19 patients, 89%, p=0.001); however, in the multivariate analysis there was no increase in agitation based on

21

these specific classes as well as others (propofol, clonidine). They found that the general use of sedatives and/or analgesics in the 48 hours preceding the onset of agitation is more frequent in agitated patients than in patients who are not (72% vs. 36%, p=0.001). They also found that the use of sedatives and/or analgesics increased the risk of agitation by approximately four times. Data regarding specific drugs was not discussed. Fraser et al.,[14] (n=130) in the comparison of young vs. older patients, evaluated sedating medications as defined as benzodiazepines (lorazepam, midazolam), butyrophenones (haloperidol), and barbiturates (phenobarbital) with respect to treatment of agitation. Drugs, dosages, and routes of administration were examined and they found agitated patient-days associated with administration of opiates (72%), benzodiazepines (62%), and haloperidol (29%).[14] The study also reported that drug administration (as well as pain, anxiety, and delirium) accounted for 73% of probable or possible factors attributed to the onset of agitation – but all of these factors were assigned by caregiver judgment, not derived empirically.

It is not surprising that sedatives are associated with agitation – as sedatives are the primary therapy for agitation; however, the increased use of sedatives prior to the onset of agitation raises questions about the involvement of other mechanisms, processes, or paths. Confounding this possible involvement is the simple understanding that healthcare providers, observing restlessness and anxiety and/or a worsening condition, may choose to administer or increase sedatives as a measure to increase patient comfort. As these four studies did not measure anxiety or restlessness as an indication of impending agitation, the increase in medication observed prior to agitation may simply be due to a caregiver response to observed behavior.

Table 3. Medications thought to be associated with agitation or delirium in the Intensive Care Unit[4;31]

Antibiotics	Cardiac Drugs
Acyclovir	Captopril
Amphotericin B	Clonidine
Cephalosporins	Digoxin
Ciprofloxacin	Dopamine
Imipenem – cilastin	Labetalol
Ketoconazole	Lidocaine
Metronidazole	Nifedipine
Penicillin	Nitroprusside
Rifampin	Procainamide
Trimethoprim - sulfamethoxazole	Propranolol
	Quinidine sulfate
Anticonvulsants	**Corticosteroids**
Phenobarbital	Dexamethasone
Phenytoin	Methylprednisolone
Miscellaneous Drugs	**Narcotic Analgesics**
Hydroxyzine	Codeine
Ketamine	Meperidine
Metroclopramide	Morphine sulfate
Theophylline	
Anticholinergics	
Benzodiazepines	
Nonsteroidal anti-inflammatory agents	

23

Critical Illness. Illness severity and the presence of pain have been studied with relationship to agitation in the critically ill patient. Higher severity of illness ratings, reflecting a higher degree of physiological stress, is thought to be related to the onset of agitation as most scoring schemas reflect derangements of different body systems. Jaber et al.[13] (n=182) studied severity of illness with association to agitation and found that patients with agitation had a higher Simplified Acute Physiology Score (SAPS) II score (40 ± 16 vs 33 ± 13, $p<0.01$) on admission than those who did not. The SAPS II tool provides an estimate of the risk of death based on daily physiologic variables rather than on medical history or diagnosis. Significant findings of the Gardner et al.[15] study were that patients with greater levels of illness at admission and during the ICU stay appear to have a greater risk for developing agitation. In their retrospective chart review (n=83) they found that the Acute Physiology And Chronic Health Evaluation (APACHE) II scores, a severity of disease classification system on admission, was significantly greater (23.8 vs 17.5; $p=0.002$) in those subjects who experienced agitation during their ICU stay compared to those who did not. They also found daily multi-organ dysfunction scores (MODS) were also higher (8.2 vs 6.8, $p=0.002$) on days when subjects were noted to exhibit agitated behavior. In contrast, Woods et al.[12] (n=143) reported no significant difference in APACHE II scores in the study of severely agitated MV patients. Jaber et al.[13] found agitation associated with a prolonged ICU stay (16 ± 19 days vs. 6 ± 6 days, $p=0.0001$) while Woods et al.[12] found severe agitation in MV patients to be associated with longer MICU stays (median of 12 vs. 5 days, $p<0.0001$). It would be difficult to determine if the severity of illness or agitation was primarily responsible for the prolonged ICU stay. It is also important to note that complex relationships exist between organ dysfunction, severity of illness, and interventions confounding the determination of agitation risk.

Pain has long been theoretically associated with agitation[3;4] because higher pain ratings may reflect a higher degree of both physiological and psychological stress; however, no studies have reported empirical data supporting the proposition. In the prospective chart review by

24

Fraser et al.[14] (n=130), pain (with anxiety, delirium, and drug administration) accounted for 73% of probable or possible factors attributed to the onset of agitation as determined by written report of caregivers. It is not clear whether presence of pain was assigned by caregiver judgment or patient report.

Physiologic instability. Physiological alterations have been identified as risk factors for agitation (Table 4). Dysregulated physiologic systems, as evidenced by disturbances of oxygenation and electrolyte values, diagnoses of sepsis, and physical manifestations of critical illness, such as fever, have been implicated in the onset of agitation[4;28;29] as all reflect physiological stress.

Hypoxia is commonly associated with agitation. Lowered blood oxygen content stimulates the sympathetic nervous system to release catecholamines with resulting muscle tension and anxiety. Inadequate oxygenation from restricted lung expansion, mechanical ventilator dysynchrony, and disease process may contribute to oxygen saturations below 90% leading to agitation. Woods et al.[12] (n=143) in their study of severely agitated MV patients (n=23) found a PaO_2/FIO_2 below 200 mmHg to be an independent risk factor for severe agitation (Hazard ratio 1.61, 95% CI [1.02 – 2.54], p=0.041). In their univariate analysis an increased FiO_2 (presumably in response to a low PaO_2 but not discussed) was a factor associated with severe agitation.

Electrolyte imbalances have been implicated in the onset of agitation. Jaber et al.[13] (n=182) collected daily documented serum concentration of sodium, potassium, magnesium (as well as urea, creatinine, calcium and phosphorus) to examine the relationship to agitation. In their univariate analysis an association was found with highest sodium (median: 143.0 [140.0-143.0 (25th-75th percentile)] vs. 139.0 [137.0-142.0], p=0.001) and lowest sodium (median: 132.5 [130.0-135.0] vs. 134.5 [131.2-137.0], p=0.016), lowest potassium (median: 3.28 [3.00-3.63] vs. 3.53 [3.20-3.89], p<0.001), and highest magnesium (median: 1.10 [1.00-1.30] vs. 1.05 [0.90-1.20], p<0.01). In the final multivariate analysis they determined dysnatremia (sodium level ≤

25

134 mmol/L or ≥ 143 mmol/L) to be an independent risk factor for agitation (Odds ratio 2.61, 95% CI [1.03-6.58]). Studying pH, Woods et al.[12] (n=143) with MV severely agitated patients (n=23), also collected daily laboratory values and identified a lower pH (minus 0.1 unit) to be a factor associated with severe agitation (Hazard ratio 1.55, 95% CI [1.05-2.31, p= 0.028). The authors commented that the worse acidemia may reflect a greater degree of illness or having received high-dose intravenous lorazepam which can cause hyperosmolar anion gap metabolic acidosis mediated by the large volumes of infused propylene glycol as the carrier molecule for lorazepam.

Sepsis is believed to stress physiological systems and is considered to be associated with agitation. Due to both bacterial load and toxins, sepsis may result in hypotension leading to inadequate oxygenation – an additional stressor. Sepsis disrupts microvascular blood flow and oxygen delivery causing a decrease in tissue oxygen extraction. Jaber et al.[13] found that sepsis was an independent risk factor for the development of agitation (Odds ratio 2.61, 95% CI: 1.03-6.58). The onset of fever is an indication of the body's immune response to infections and inflammation triggered by viruses, bacteria, fungi, drugs, and toxins. These substances and many others are known to be indicative of physiological stress and are thought to precede agitation but only one study supported the association empirically. Jaber et al.[13] used the definition of sepsis according to the criteria of Bone[30] and found body temperature greater than or equal to 38 degrees (100.4° C) to be an independent risk factor for agitation (Odds ratio 4.52, 95% CI: 1.80-11.49).

26

TABLE 4. Physiological alterations proposed to be associated with agitation or delirium[4;28;29]

Acidosis	CNS infection	Tension pneumothorax
Hypoxemia	Cerebral abscess	Intoxication
Hypercarbia	Intracranial hemorrhage	Withdrawal
Electrolyte imbalance	Epidural or subdural hematoma	Myocardial ischemia
Sepsis	Meningitis	Intestinal ischemia
Hypoglycemia	Encephalitis	Cerebral ischemia
Hyperglycemia	Liver encephalopathy	Iatrogenic complications
Tumor	Uremic encephalopathy	
Elevated heavy metals – lead, mercury, and manganese		

Consequences of Agitation

Agitation is not a benign condition and has serious consequences largely related to sedation and restraint use. Eighty-five percent of adult ICU patients receive intravenous (IV) sedation[5;31;32] to ameliorate fear and anxiety, facilitate sleep, and increase tolerance of tubes, lines, and catheters. The goals of sedative use in the critical care setting are to provide physiologic stability and patient comfort; however, with the onset of agitation, patients may experience over-sedation and/or restraints. Historically, at the onset of observed agitation, due to danger to caregivers and patients, both physical restraints and/or increased sedation (pharmacologic restraint) was used. Outcomes of the use of restraints, both pharmacologic and physical, have been shown to be similar and significant – increased danger to patients.[33;34] In recent years, deep or prolonged sedation has been shown to prolong the duration and weaning of MV.[17;35] Lighter and more limited sedation practices with a goal of calm and alert or easily aroused patient state is the present focus to minimize the consequences of prolonged MV.[35-37]

Over- and Under-sedation.

Over-sedation. Over-sedation can result in increased length of time of mechanical ventilation, coma, respiratory depression, hypotension, bradycardia, ileus, renal failure, immunosuppression, and post-traumatic stress syndrome (PTSD)[17;38;38-41] which may include complications of continuous IV sedation including increased length of intensive care stay and hospital stay, acquired organ system derangements, and increased frequency of reintubation.[17]

Extended sedation also has been implicated in increased risks for complications of immobility, such as deep venous thrombosis, decubitus skin ulceration, and pressure-induced peripheral neuropathy.[42-47] Over-sedation also adds to the cost of hospitalization from extended length of stay, sedative expense, and mechanical ventilation.[48] Dasta et al.[49] studied daily ICU cost in 2002 dollars of both MV and non-MV patients. They found average daily ICU costs to be $19,725 (25th percentile $5,613; 75th percentile $21,420). They also estimated a non-mechanical ventilation day today to be $2,880 (95% CI $1,219 - $4,541) in contrast to a

28

mechanical ventilation day of $5,811 (95% CI $5,050 - $11,374). Each additional day of mechanical ventilation cost approximately $5,700 and mechanical ventilation was found to be the greatest independent predictor of cost (p< 0.0001).

The American College of Critical Care Medicine of the Society of Critical Care Medicine's (SCCM) guidelines for the sustained use of sedatives and analgesics in the critically ill adult recommend that sedatives be administered to a defined endpoint with systematic tapering of the dose or daily interruption with retitration to minimize prolonged sedative effects. Although optimal sedative levels are the goal, under-sedation may also occur.

Under-sedation. Under-sedation or inadequate sedation increases the risk of developing anxiety and/or agitation which may lead to serious consequences.[12] Inadequate levels of sedation may place the intubated patient at risk for self-extubation (SE) or removal of therapeutic lines, physical harm or injury due to an agitated state,[12;50] disruption of ICU therapy, and PTSD. Under-sedation and/or agitation can also affect caregiver workloads. In managing an agitated patient, the caregiver's attention can be consumed by one patient, limiting time for other patients or responsibilities.

Care of the critically ill patient often includes the use of numerous indwelling tubes and vascular catheters that may be a source of patient stress and irritation. Their removal by the confused, agitated patient is common and can be life-threatening.[4] Several authors have documented that agitated patients are more likely to remove indwelling tubes or catheters and the incidence was shown to range from 20% to 28%.[18;51] SE of endotracheal tubes occurs much more frequently in agitated patients.[12;52] In a study of unplanned extubations in 426 mechanically ventilated adult patients over a 2-month period, Boulain[18] found that 61% were agitated at the moment of an unplanned extubation. Over a one month period, Fraser et al.[53] found a frequency of patient-initiated device removal of 28% and, significantly, agitation was documented within 2 hours of 74% of the events. Mion et al.[54] studied 49,482 patient-days in 49 randomly selected adult ICUs and found that patients removed 1623 devices on 1097 occasions

29

for an overall rate of 22.1 episodes/1000 patient-days (range 0-102.4). More than half (58%) the patients had documented agitation or anxiety at the time of the episode.

Significant adverse events following SE occur in up to 28% of ventilated patients including bronchospasm, vocal cord damage, and onset of new arrhythmias.[55-57] SE has also been shown to increase ICU and hospital length of stay, duration of MV, and rate of ICU-acquired infections.[58] In addition mortality was found to be higher among patients with unplanned extubation that required reintubation than among those that did not require reintubation.[58] Krinsley and Barone[58] examined 100 patients over a period of 5 months finding 44 instances of unplanned extubation that required reintubation.

There is also significant cost associated with unplanned device removal, which is often associated with agitation. Fraser et al.[53] investigated the frequency and cost of patient-initiated device removal in the ICU. Patients who removed devices had a longer ICU stay – 11.4 vs. 4.7 days – adding to hospitalization expense. Costs associated with device removal in 2001 were estimated to be $7606, and the estimated annual cost was approximately $250,000. Using a conservative estimate of inflation, the cost per episode today would be approximately $10,000, and the estimated annual cost would be approximately $336,000. In a study of unplanned extubations in a surgical ICU by Curry et al.[59] it was reported that the hospital indirectly calculated (from limited data) the cost of intubation of $1000 per reintubation event. The authors state that this estimate could be conservative compared to other hospitals' costs.

Agitation as a result of under-sedation may also result in disruption of treatment regimen as Woods et al.[12] found that 30% of agitated patients versus 8% of non-agitated patients experienced disruption of therapy. Disruption of treatment regimen may lead to poorer outcomes, increased length of stay and higher costs.

Inadequate sedation and analgesia during neuromuscular blockade has been shown to be associated with PTSD.[60;61] Patients report vivid recall under paralysis which may contribute to PTSD symptoms.

30

There are also problems associated with daily sedative interruption to minimize prolonged sedative effects. Kress et al.[62] found that sedative interruption was associated with significant changes in vital signs – heart rate, blood pressure, rate-pressure product, and respiratory rate all increased significantly. Concomitant with these changes in vital signs, epinephrine, norepinephrine, and dopamine levels were markedly increased in a subgroup of patients not receiving exogenous vasoactive drugs.

Restraint use in agitation.

In brief, the Joint Commission on Accreditation of Healthcare Organizations 2000 standards acknowledge that the use of restraint poses an inherent risk to the physical safety and psychological well-being of the individual and staff, and are to be used only in an emergency, when there is an imminent risk of individual harm.[63] These conditions are often present during agitation. Therefore, early identification and optimal management of agitation will likely improve patient safety, part of the national health care agenda.[63;64;65] However, use of physical restraints for agitated patients may be necessary to protect both the patient and staff. Harmful consequences may occur, either directly or indirectly, as a result of the use of physical restraints including new onset of bladder and bowel incontinence, new pressure ulcers, and increased rate of nosocomial infections.[66;67] Severe or permanent injuries include brachial plexus nerve injuries from wrist restraints, joint contractures, and hypoxic encephalopathy. The most serious injury is death from strangulation.[34] Although most data about the adverse consequences of physical restraints is from non-ICU settings, in the ICU agitation is common and consequences of uncontrolled agitation are more dangerous (removal of critical lines and catheters) than potential lethal results of device removal. Use of techniques that reduce the likelihood of risk and the use of non-physical interventions is recommended.[33;68]

Evaluation of agitation

Currently there is no gold standard to alert health care providers to impending agitation, although scales exist to evaluate patient state/degree of agitation once agitation has been

31

identified. Most scales currently in use have the same inherent issues – many agitation levels have overlapping criteria and rely on the subjective evaluation of the patient's state. Both have the potential to contribute to inconsistent scoring or identification of the degree of agitation. Despite these shortcomings, systematic evaluation of agitation and pain with rapid-response treatment shows promise in decreasing agitation events. In a study in 2006 by Chanques et al.,[69] an education program for nurses and physicians followed by systematic evaluation of pain and agitation levels by nurses with rapid calls to physicians for treatment decreased the observed incidence and intensity of pain and agitation in ICU patients. The improved pain and agitation management was also associated with a significantly shorter duration of mechanical ventilation (120 vs. 65 hrs., $p = .01$) and lower nosocomial infection rate (17% vs. 8%, $p < .05$).

At present there are no clinically useful, valid and reliable tools for the objective measurement of agitation; however, there are promising avenues of exploration.

Subjective measures of agitation.

Adult subjective sedation-agitation scales are used by healthcare providers to determine the patient's level of sedation and agitation.[70;71] Recommendations for the use of a validated sedation assessment scale[5] and a need for prospective studies to establish and study population-specific, goal-oriented sedation-agitation scales to enhance the consistency of caregiver observations and allow comparison of drug effects in adults[72] have been documented by both national physician and nurse organizations. Although a variety of scales measure sedation, many of these do not also evaluate agitation. Some pain scales such as the Adult Nonverbal Pain Scale (NVPS)[73] (patterned after the face, legs, activity, cry, consolability, and pain assessment tool [FLACC]) and the Critical Care Pain Observation Tool (CPOT)[74] include a movement component (as body movement is considered indicative of pain) but do not specifically rate agitation.

32

The most common and widely used scales measuring agitation in adult ICUs have been well-reviewed in other articles. This review will briefly describe widely used tools that have had studies establishing validity and reliability with a focus specifically on agitation.

The Ramsay Scale.[75]   This is one of the first scales designed for evaluating the level of consciousness during sedation in ICU patients and is still commonly used today. The 6-point scale includes one agitation response option of "patient anxious or agitated or both" (given an assessment value of 1). The tool would be less useful for identification of agitation per se as "anxious", a patient state, is not generally accepted to be synonymous with "agitated", a patient behavior – the category would not be considered discrete.

The Riker Sedation-Agitation Scale (SAS).[7] The SAS was designed to assess agitation and sedation in adult ICU patients. This tool is a 7 point scale with 3 severity levels for agitation: "Agitated", "Very agitated", and "Dangerous agitation". It fulfills some of the criteria for a desirable tool: it was developed from multidisciplinary involvement (nursing, medicine, and clinical pharmacology); it has applicability to diverse ICU patient populations; it is easy to use; each level has multiple patient behavior descriptors; the levels may guide sedation administration; and it has been tested for reliability[7] (r=0.91, p<0.001, weighted kappa 0.92, p<0.001; r=0.98) and validity[7] (validity vs Ramsay scale: r=0.91, p<0.001; validity vs Harris scale: r=0.93, p<0.001).

A potential weakness of this tool is a lack of "specific and discrete criteria for each level". As a previously mentioned problem with the Ramsay Scale, "anxious" is not a specific descriptor for the SAS diagnosis "agitated" (level 5). Considering distinction of criteria, judicious use of physical restraints (in level 6, "Very agitated") at the discretion of the caregiver, may be chosen when the patient begins pulling at the endotracheal tube (in level 7, "Dangerous agitation"); likewise, biting the endotracheal tube (in level 6, "Very agitated") may occur when the patient is attempting to sit up (in level 5, "Agitated"). The categories are not mutually exclusive.

33

The Richmond Agitation Sedation Scale (RASS).[8] The RASS was designed for assessing sedation and agitation in adult ICU patients. This instrument is a 10 point scale with one level for "Restless" (+1) and 3 levels for agitation: "Agitated" (+2), "Very agitated" (+3), and "Combative" (+4). Similar to the SAS, it fulfills criteria for a desirable tool: developed from multidisciplinary involvement (nursing, medicine, and clinical pharmacology), used in diverse patient populations, easy to use, each level has multiple patient behavior descriptors, levels may guide sedation administration, and extensively tested for validity (against the Ramsay [r= -0.78][8] and SAS [r=0.78],[8] and against the BIS [r=0.63],[76] and actigraphy [r=0.58][77]) and reliability (r=0.956; K=0.73 for 5 raters; r=0.964, K=0.80 for nurse educator vs. 27 RNs).[8]

This scale provides greater discrimination between levels of agitation with a total of four categories, versus the SAS's three. The RASS assigns the term "Restless" (+1) as behavior indicative of the patient states of anxiety and apprehension (rather than designate it as "agitation" in the SAS), enhancing specificity. The instrument is easy to administer, recall, and interpret and descriptors are concise. Similar to the SAS, however, is the issue of distinct levels – "Movements not aggressive or vigorous" (Score +1, "Restless") are not mutually exclusive of "Frequent nonpurposeful movement" (Score +2, "Agitated"). In general, however, this instrument can be considered one of the best for evaluation of agitation.

Adaptation to Intensive Care Environment (ATICE).[78] This instrument includes multiple domains for consciousness (with subscales for awakeness and comprehension) and tolerance (with subscales for calmness [agitation], ventilator synchrony, and face relaxation) in evaluating mechanically ventilated adult ICU patients. Low ATICE scores reflect poor adaptation to the ICU environment (altered consciousness, eyes closed, agitation, permanent grimacing); likewise, high scores indicate good adaptation (eyes opening spontaneously, calmness, comprehension, relaxed face). The ATICE was developed from multidisciplinary involvement (nursing and medicine), is easy to use, and was tested for validity (cross-sectional and longitudinal confirmed by strong correlations between ATICE and relevant items/domains of the

34

Ramsay Scale, Riker Scale, Glasgow Coma Scale, Comfort Scale, visual analog scales, and amounts of sedatives and analgesics administered) and reliability (high interrater reliability indicated by high intraclass correlation coefficients [from 0.92 to 0.99]).

It should be recognized that the ATICE was designed to measure adaptation to the ICU environment; the calmness subscore was not intended to be used as a single tool to evaluate agitation. Calmness grading is easily understood; however, use of both a summated scale and Likert scale for ATICE evaluations may be confusing to some. Three levels of agitation rating are used (similar to the SAS), evaluated on a scale from 2 "agitation, responds to verbal order" through 0 "life-threatening agitation". An agitation subscale weakness includes specificity: "life threatening agitation" (0) is not mutually exclusive of "agitation, does not respond to verbal order" (2). Of note is that there are 20 separate steps involved in performing a full ATICE assessment. This tool also lacks applicability to diverse ICU patient populations as it was designed specifically for use in the mechanically ventilated patient.

Objective measures of agitation.

As agitation is associated with excessive restlessness and physical activity, the ability to objectively detect increasing activity, especially continuously, may be an important first step in assessing impending agitation. There are promising directions of inquiry:

Actigraphy. The electronic device, the actigraph, strapped to the wrist or ankle, provides a continuous measure of activity data (expressions of accelerated movement in numerical form) and can continuously sense and record minimal movements. The use of actigraphy as an objective measure of movement has been tested and shows promise;[77] however, at this time, actigraphy has not been fully validated as an appropriate or sensitive measure of agitation.

Heart rate variability (HRV), blood pressure variability (BPV), and systolic BP. Chase et al.[79] investigated decreased heart rate variability (HRV), increased blood pressure variability (BPV), and increased systolic BP (processed by wavelet transforms and autoregressive signal processing) as an objective measure of agitation in 13 normal subjects and 5 ICU patients. The

detected agitation levels showed good correlation with agitation levels provided by trained nursing staff using the modified Riker Sedation-Agitation Scale (SAS).[7] At present this process is not clinically feasible; future studies are required to validate the process on a larger sample. Unoki et al.[80] studied HRV as a marker of the function of the autonomic nervous system in patients receiving MV, and concluded that deep sedation may be associated with depression of parasympathetic function. Future studies are required to establish HRV as an indicator of stress or agitation.

Digitalized images. Facial grimacing and full body movement (as recorded digitalized images) were explored in the context of correlation with agitation by Becouze et al.[81] These methods require further testing and clinical validation; however, they may be useful in the future.

Future directions for research related to agitation

There has been a paucity of research involving agitation; therefore a great number of possibilities for exploration exist:

- The clinical presentation of agitation should be investigated systematically and terms used to describe agitation should be standardized.
    - A gold-standard tool for the identification and evaluation of agitation is needed. Currently, the RASS[8] has a greater number and more discrete levels of agitation than other scales but a consensus is essential for standardization. This would serve to reduce confounding variables related to construct and criterion validity.
- The selection of any of the numerous suspected causative factors of agitation could be studied with correlation to agitation.
- Using greater sample sizes in future studies may assist in clarifying factors.
- One proposed etiology of agitation is enzymatic alteration from a wide variety of physiological and chemical insults resulting in dysregulation of neurotransmitters. Comparisons of neurotransmitter differences between agitated and calm patients may suggest which of these could be responsible.

36

- Animal studies could be initiated to probe the pathophysiological mechanisms of agitation.

- Greater levels of severity of illness have been associated with agitation. Determining the specific level or level range significantly associated with the onset may be key to targeting patients for both inclusion in studies and for proposed interventions.

In summary, a critical barrier to progress in solving the problem of agitation has been the lack of empirical identification of the precursors of agitation which, with the appropriate intervention, could eliminate the need to treat the agitated patient. Use of empirically-based information would assist care providers in identifying those at risk as well as predict agitation. After identification of the risk factors and predictors, an evaluative tool could be developed to alert caretakers to the possibility of agitation – interventions could be implemented well before agitation occurs. Elimination or reduction of agitation in the ICU would significantly improve patient safety, and reduce hospitalization resulting in significant savings to healthcare costs.

37

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Agitation Onset, Frequency, and Associated Temporal Factors in the Adult Critically Ill

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48

ABSTRACT

Background: Agitation in critically ill adults is a frequent complication of hospitalization and can result in life-threatening complications to the patient or care providers, and has been found to extend the hospital length of stay thereby increasing hospital costs.

Objectives: The specific aim of this study was to describe the incidence, onset, and temporal factors related to agitation.

Methods: The sample included all adult patients, consecutively admitted to a medical ICU (MICU) and surgical trauma ICU (STICU), over a two month period. Data were collected during the first 5 days of ICU stay. Agitation was identified using the documented Richmond Agitation-Sedation Scale or notation of "agitation" in the medical record. The hour was used as the documentation epoch and data were summarized by hour, 4-hour block, and day for each subject.

Results: 200 subjects were enrolled, 100 from each ICU. 118 (59%) were agitated at any time during the 5 days. The over-all agitation rate was 7.8% of the hourly. Agitation onset was a mean of 11.6 hours from ICU admission. Of those subjects who were agitated at any time during the study, 86% (n=102) had agitation on day 1. Subjects in the MRICU had a significantly greater number of agitation hours in the first day and first hour of admission and also significantly earlier agitation onset.

Conclusions: Agitation is present in over one-half of ICU patients, typically develops on the first day in the ICU stay, and involves consecutive days. It occurs earlier in medical ICUs.

Agitation is excessive restlessness, or non-purposeful physical activity associated with internal tension, anxiety, or emotional distress.[1-3] These behaviors may include both nonaggressive and aggressive physical components (i.e. aimless psychomotor activity vs. physical altercation/hostility) and verbal components (i.e. persistent questioning, chatting vs. cursing, screaming). Up to 71% of Intensive Care Unit (ICU) patients have some degree of agitation during their ICU stay.[4] Agitation has been shown to extend the length of hospital stay from a median of 5 to 12 days contributing to increased costs and is associated with adverse clinical outcomes.[5;6] Agitation can be manifested in simple apprehension or anxiety, inappropriate self-removal of indwelling tubes and catheters, and/or to attempted assault of a care provider.[7;8]

The Society of Critical Care Medicine's (SCCM) recent sedation and analgesia guidelines now also include agitation, and highlight the need for prompt identification and treatment of possible underlying causes of agitation.[9] Understanding the natural history of agitation may be important for agitation management as the identification of agitation before it is manifested may reduce its adverse effects. Knowledge of agitation onset and course may provide information about timing to encourage enhanced vigilance so interventions can be implemented to prevent or ameliorate the phenomena and its consequences. Early identification of patients at risk may lead to reduction in adverse outcomes and cost associated with sedation and hospitalization. Although agitation is associated with deleterious outcomes, there are few data that describe the frequency, onset, and course of agitation in the critical care environment. Therefore, the specific aim of this study was to describe the frequency, onset and patterns of agitation in the adult critically ill population.

METHODS

Subjects and Setting

The study was conducted in an 865-bed academic medical center which offers a wide range of patient care services including all critical care specialties. Approval was obtained from

50

the Institutional Review Board of the university. The study was conducted in 2 adult units (medical-respiratory ICU [MRICU] and surgical trauma ICU [STICU]). The sample included all adult patients, 18 years of age and older, consecutively admitted to the MRICU and STICU over a two month period using a retrospective medical record review. Patient exclusion criteria were an ICU length of stay less than 24 hours (to omit those who had a short length of ICU for overnight monitoring), those with medical records that were not available, and patients previously admitted during the study duration. Other exclusion criteria were conditions affecting patient movement interfering with sedation scale scoring including administration of paralytics preventing any movement, patients with chronic, persistent neuro-muscular disorders (such as cerebral palsy and Parkinson's disease), and patients with head trauma or stroke.

Documentation of Agitation

Agitation was identified using the documented Richmond Agitation-Sedation Scale (RASS), a 10 point scale, from +4 (combative) through 0 (calm, alert) to -5 (unarousable) assessed at the bedside in 3 steps using discreet criteria, over 30-60 seconds[8] (Table 1). The new 2013 SCCM guidelines endorse the RASS as one of the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients.[9] The RASS has demonstrated excellent interrater reliability and criterion, construct, and face validity across a variety of critical care settings.[8;10-12] The RASS is the standard sedation-agitation tool used in both of the target ICUs. RASS values are routinely obtained every 4 hours in the units and more frequently if needed. A RASS of +1 (restless – anxious or apprehensive but movements not aggressive or vigorous) through +4 (combative – overtly combative or violent; immediate danger to staff) were used to identify agitation. The +1 RASS was accepted as an indicator for agitation as it indicates restlessness, anxiety, or apprehension – qualities not present in a calm and alert patient (RASS = 0) and use of positive numbers in the RASS have been previously documented as agitation.[8]

51

Table 1. The Richmond Agitation-Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Agitation was also documented using the keyword "agitation" (all forms of the word, "agitated", "agitation", "agit") recorded from the medical record using physicians' and nurses' notes in the nursing bedside flowsheet, emergency department documentation, operating room notes, and circle-the-item for reporting agitation in flowsheets.

Procedure

The medical record was used as the primary source of information and data collection was conducted by a single investigator (RSB). A pilot study was performed, using subjects not part of the study cohort, to systematize data collection and to identify and resolve any ambiguous or conflicting data. Data audits were performed to verify accuracy of information

52

using convenience sampling on approximately 10% of all subjects. The error rate on the data audit was less than 0.03%.

Once admission patterns had been identified our goal was to obtain an equal number of subjects in each unit that would span the majority of the two month period, so that a broad representation of unit admissions would be obtained. Data were collected during the first 5 days of ICU stay as agitation onset and duration has been shown to be 3 to 5 days.[4;6] All data were de-identified and patients were assigned a subject ID number.

For all recurrent data collection, the hour was used as the documentation epoch. Each individual hour was documented as an agitation hour only if the RASS was +1 or above, or the word agitation (or its forms) was found in the medical record during that hour. If any agitation was documented within the hour or there were multiple documented agitation episodes it was considered to be one agitation hour. Subject demographics were also recorded (age, gender, ethnicity, race) as well as admission source (clinic, ED, home, long term care, or outside hospital), admission diagnosis, intubation status, severity of illness score obtained on admission to the ICU using the Acute Physiology And Chronic Health Evaluation III (APACHE III),[13] Charlson Comorbidity Index,[14] ICU length of stay (LOS), hospital LOS, and administration of analgesics and sedatives.

Data Analysis

Data were summarized by hour, 4-hour block, and day for each subject and categorized as an agitation or non-agitation hour, block, or day. Hourly data were condensed into 4-hour blocks as the standard ICU flowsheet contained 4-hour blocks with "agitation" available as a circle-the-item. If any agitation was documented within the 4-hour block or there were multiple documented agitation episodes it was considered to be one agitation block. This consolidation of hours reduced documentation redundancy error while smoothing data peaks. In addition data hours were also condensed into 24-hour periods ("per day"). If any agitation was documented within the 24-hour period it was considered to be one agitation day. Additional data collection

53

included time, ICU day, day of the week, all RASS values, as well as other descriptors of agitated and abnormal behavior. Percent of agitation hours, blocks and days were based on the number of these divided by the number of observed hours, blocks and days throughout the 5 day period, as the number of observed hours, blocks and days varied based on the subject's duration of ICU stay. Agitation reported as "any time" included documentation of any agitation at any time during the study period.   For agitation onset data, only the first agitation hour, block, and day for each subject during the study period was evaluated. To investigate agitation temporal patterns, all agitation blocks were grouped by day of the week, day/night intervals, and time of day.

Descriptive data were expressed as counts and percentages for all nominal and categorical data, and mean, range, and standard deviation (SD) for continuous measures. Univariate analyses were performed between non-agitated and agitated subjects using X^2 and Fisher's Exact Test for categorical data, and Two Sample t Test for continuous data.

RESULTS

Subjects

Over the two month data collection period, 383 potential subjects were reviewed resulting in 200 subjects who qualified by applying inclusion and exclusion criteria and were used for analysis (Figure 1).   Medical record review for up to 5 days of ICU stay for the 200 subjects resulted in 791 patient-days (17,938 hours of data; 4,621 4-hour blocks). Subjects had an average length of ICU stay of 7.9 days (Table 2).

54

Figure 1. Flow diagram of study selection process

Total patients screened
N = 383

MRICU
Screened
N = 179

STICU
Screened
N = 204

MRICU: Did not meet inclusion criteria
N = 79

56 In unit < 24 hours
8 Neuromuscular disorder/paralysis
9 Head trauma/obtunded
6 Readmission

STICU: Did not meet inclusion criteria
N = 104

82 In unit < 24 hours
5 Neuromuscular disorder/paralysis
4 Head trauma/obtunded
12 Readmission
1 Medical record not available

MRICU subjects used in final analysis
N = 100

STICU subjects used in final analysis
N = 100

55

Table 2. Demographics and other descriptors for entire sample and by presence of agitation (at least one observation of agitation per hour)

	Entire sample n = 200	Non-agitated Pts n = 82 (41%)	Agitated Pts n = 118 (59%)
Variable	n (%)	n (%)	n (%)
Gender			
Male	113 (56.5)	42 (51)	73 (62)
Female	87 (43.5)	40 (49)	45 (38)
Ethnicity			
Hispanic or Latino	6 (3)	5 (6)	1 (1)
Not Hispanic or Latino	194 (97)	77 (94)	117 (99)
Race			
Asian	3 (1.5)	2 (2)	1 (1)
Black or African American	94 (47)	39 (48)	55 (47)
White	103 (51.5)	41 (50)	62 (53)
ICU Type			
Medical Respiratory ICU	100 (50)	36 (44)	64 (54)
Surgical Trauma ICU	100 (50)	46 (56)	54 (46)
Admission Source			
Long term care	3 (1.5)	2 (1)	1 (0.5)
Home	16 (8)	4 (2)	12 (6)
Clinic	20 (10)	7 (3.5)	13 (6.5)
Outside hospital	60 (30)	23 (11.5)	37 (18.5)
ED	101 (50.5)	46 (23)	55 (27.5)
Admitting Diagnosis			
Trauma	36 (18)	18 (22)	18 (15)
Sepsis	35 (17.5)	17 (21)	18 (15)
Respiratory failure	27 (13.5)	6 (7)	21 (18)
Hematologic/oncologic problem	27 (13.5)	8 (10)	20 (17)
Other	22 (11)	9 (11)	12 (10)
Renal/GI problem/DKA	28 (14)	15 (19)	13 (11)
Hepatic problem	13 (6.5)	4 (5)	9 (8)
Cardiovascular problem	8 (4)	4 (5)	4 (3)
Drug overdose/poisoning	4 (2)	1 (1)	3 (3)
Intubated	118 (59)	20 (17)	98 (83)
Variable	**Mean (Range, SD)**	**Mean (Range, SD)**	**Mean (Range, SD)**
Age (years)	55.5 (18-89; +/- 16.4)	56 (19-87; +/- 16.4)	55.1 (18-89; +/- 16.5)
ICU length of stay (days)	7.1 (1-99.4; +/- 9.7)	5.9 (1-99.4; +/- 12.1)	7.9 (1.5-36.2; +/- 7.6)
Hospital length of stay (days)	16.6 (1-99.5; +/- 15.3)	15.8 (1-99.5; +/- 16.3)	17.1 (2.2-79; +/- 14.7)
APACHE III score	68 (4-200; +/- 31.9)	57.7 (4-200; +/- 34.3)	74.7 (21-170; +/- 28.2)
SOFA	6.625 (0-18; +/- 3.8)	5.39 (1-17; +/- 3.7)	7.48 (0-18 ; +/- 3.7)
Charlson Comorbidity Index	4.69 (0-17; +/- 3.3)	4.8 (0-13; +/- 3.3)	4.6 (0-17; +/- 3.4)

Abbreviations: patients (pts); intensive care unit (ICU); emergency department (ED); gastrointestingal (GI); Diabetic ketoacidosis(DKA); Acute Physiology And Chronic Health Evaluation (APACHE III); Sequential Organ Failure Assessment (SOFA)
Data are presented as number (%), mean +/- SD, or median (25th – 75th percentiles)

The subjects had a mean age of 55 years and were primarily men, non-Hispanic, and white or African American (Table 2). Mean APACHE III scores, Charlson Comorbidity Index, length of ICU stay, hospital length of stay, and admission source are also shown in Table 2; selected analgesic and sedative medication use is shown in Table 3. During documentation, terms used to describe agitation and their frequencies were recorded (Table 4). The two categories "agitation" and "very agitated, acutely agitated, extremely agitated" included only actual documentation of the keywords indicated. The other categories' notations were behavioral and were only recorded if accompanied by an agitation keyword.

Table 3. Analgesic and sedative medications received at any time for total sample over 5-day data collection period

Medication	Number (%) of pts*
Analgesics	
Fentanyl	117 (58.5)
Morphine	83 (41.5)
Hydromorphone	26 (13)
Sedatives	
Midazolam	95 (47.5)
Propofol	52 (26)
Lorazepam	32 (16)
Haloperidol	24 (12)
Diazepam	2 (1)
Dexmedetomidine	1 (0.5)

*Total is more than 100% as subjects received more than one drug

Table 4. Terms used to describe agitation and their frequencies.

| Term	Frequency
Agitation	301
Very agitated, acutely agitated, extremely agitated	18
Confused/disoriented/AMS*	73
Restless/thrashing/moving around in bed*	41
Pulling clinical tubing/endotracheal tube (ETT)/leads and other items*	27
Aggressive/combative*	14
Biting ETT, attempting to tongue out ETT*	11
Agitation w tactile stimulation/suctioning*	9

*With report of agitation keyword and/or RASS of +1 to +4

57

Agitation Frequency

Of the 200 subjects, 118 (59%) were agitated at any time during the 5 days during 319 (31.9%) patient-days. Approximately one quarter (28.5 %) of the agitation documentation was based on RASS with the balance using an agitation keyword.

Of 17,938 total data hours, the overall agitation rate was 7.8% of the hourly time (1389 hours) and 19.1% of the 4-hour block time (883 blocks).   Of these 4-hour blocks, 36.2% occurred on day 1 (n=102), 20.7% on day 2 (n=71), 16.8% on day 3 (n=60), 14.7% on day 4 (n=50), and 11.7% on day 5 (n=36). Considering the total sample of non-agitated and agitated subjects, percent of agitation was significantly higher on day 1 than other days: 23.3% on day 1, 15.8% on day 2, 16.1% on day 3, 19.3% on day 4, and 20.2% on day 5 (Figure 2).

Figure 2. Percent of time agitated.
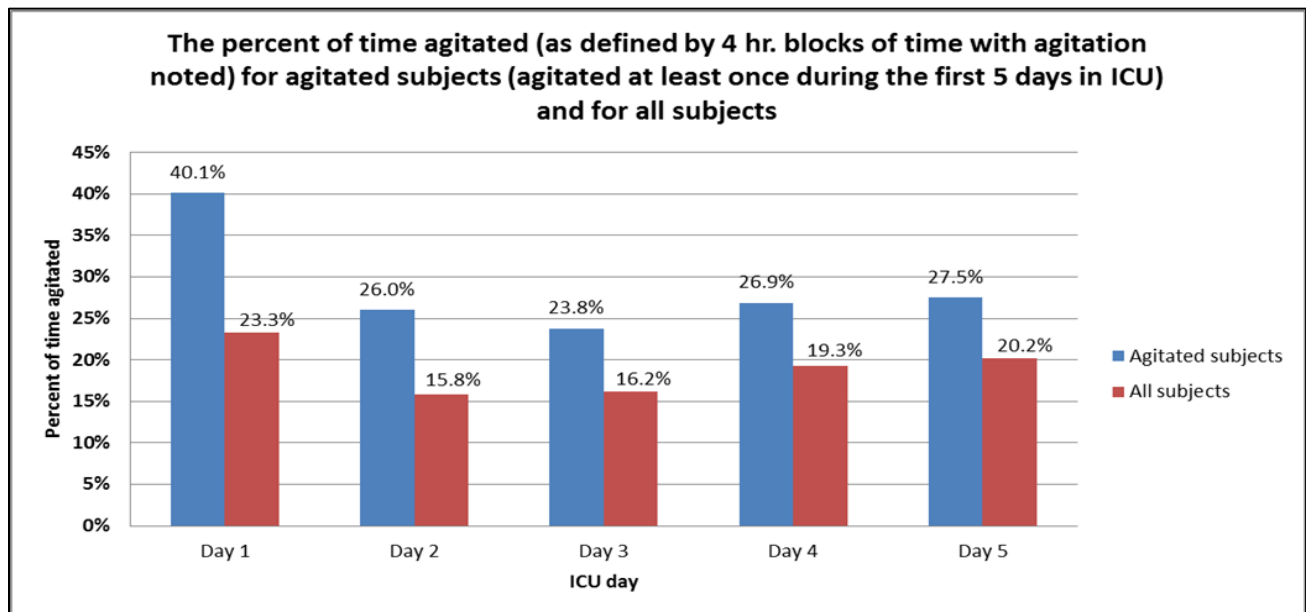
Agitation Onset

The onset of agitation was investigated. The onset of agitation was a mean of 11.6 hours (SD 22.3; Range 0-114; IQR 0-13.75) from ICU admission. Of those subjects who were

58

agitated at any time during the study, 86% (n=102) had agitation on day 1, the remaining 14%

(n=16) had an agitation onset spread out over the next 4 days (Figure 3).

Figure 3. Number of agitated patients who experienced any agitation per day by agitation onset day
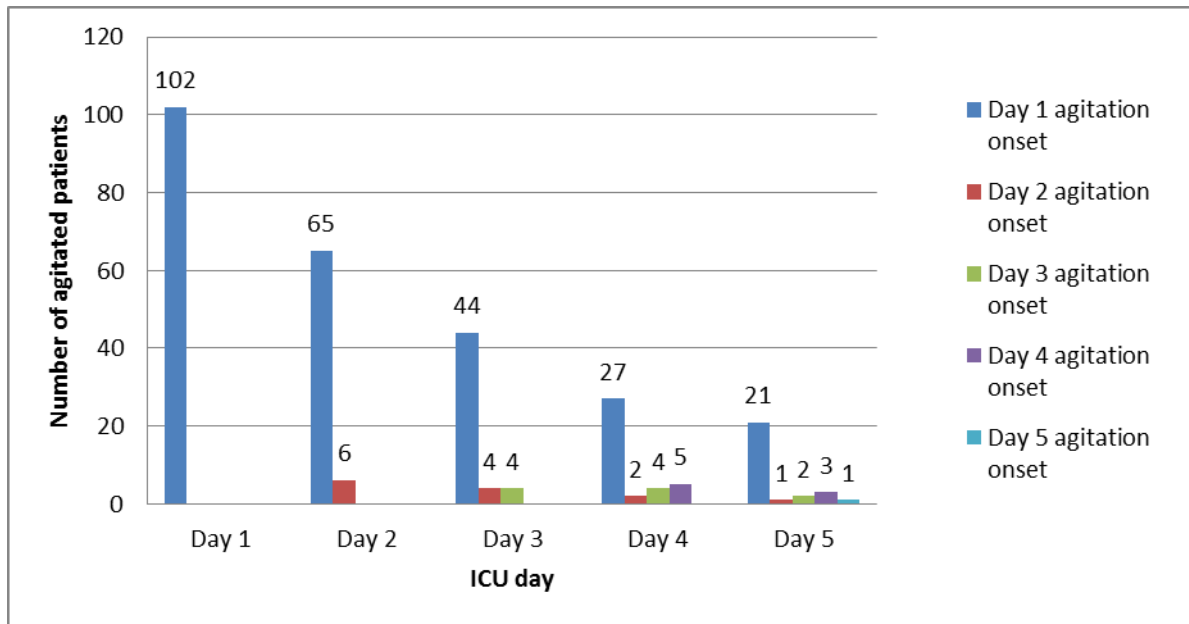
The majority of subjects (n=102; 86%) with first-day agitation continued to have agitation across

other days, while those with later agitation onset had relatively low agitation frequency. Of the

102 subjects with first-day agitation, 44 (43.1%) had agitation reported on ICU admission; 30

more (another 29.4%) had agitation reported from 1 to 4 hours from ICU admission. The mean

onset of agitation for those who had first-day agitation onset was 3.97 hours from admission

(SD 6.4; Range 0-24; IQR 0-5).

Patterns of Agitation – Onset and Frequency

Patterns of agitation frequency and onset were investigated for day of the week,

day/night intervals, and 4-hour block of day. For day of the week, Tuesdays had the highest

number of agitation hours (253) with the lowest on Friday (157). Considering only first-time agitation hours, Monday was highest (26) closely followed by Tuesday (23), with Sunday the lowest (11). Frequency of agitation during the day (7A-7P) versus the night (7P-7A) showed almost equal number of hours – day (n=679), night (n=710). First-event agitation hours during the day were 63 vs. 55 during the night. For 4-hour blocks, the pattern of agitation onset from 8PM to midnight was higher than others (Figure 4).

Figure 4. Agitation hours per 4-hour block
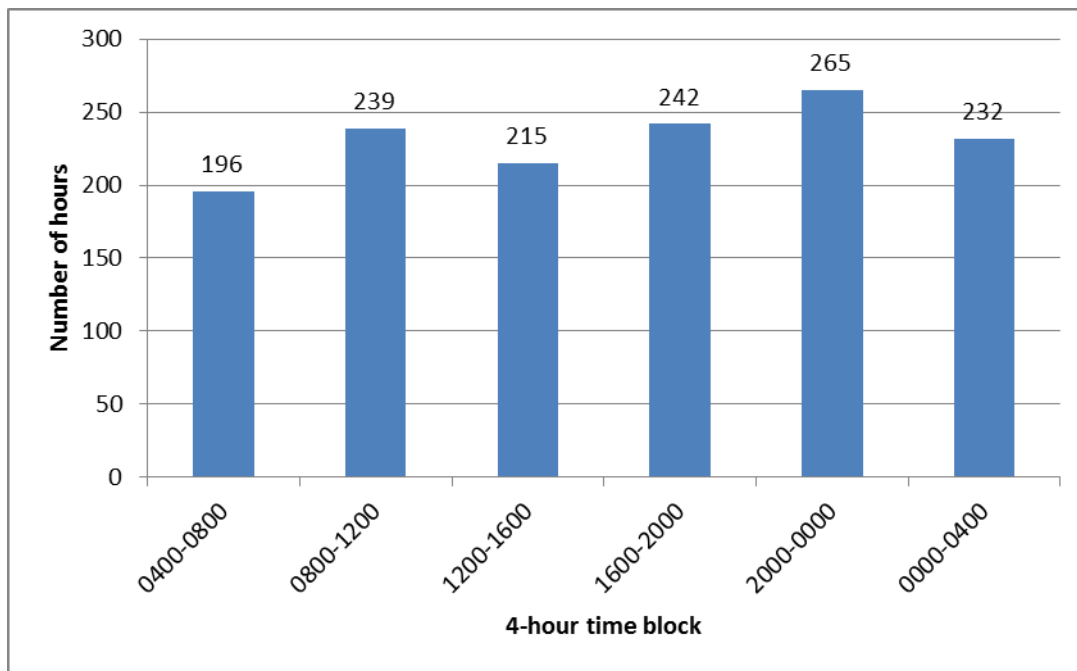
Considering the agitation pattern from a day perspective, of the 118 subjects with agitation at any time, 88 (74.6%) had multiple days of agitation including both those with intermittent and consecutive days of agitation (Figure 5). It is notable that the majority of patterns of consecutive, intermittent, and single day agitation involved day 1 agitation.

Figure 5. Day patterns of agitation depicting the significant portion of agitation that occurs on day 1
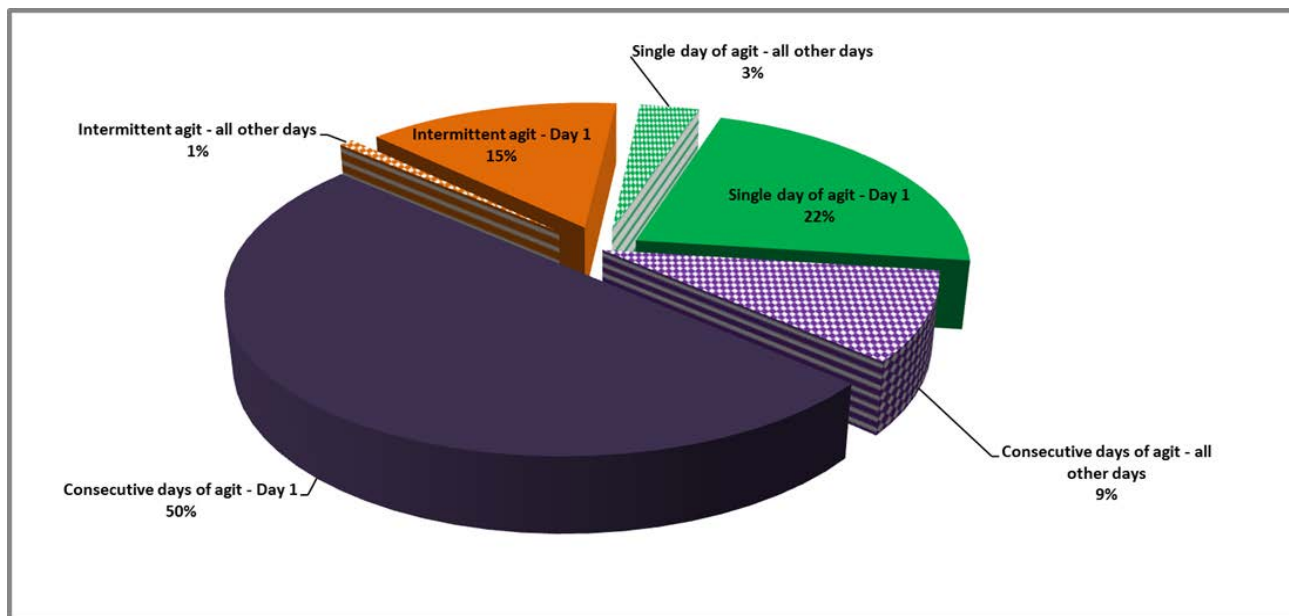
- Intermittent agitation – day 1: The percent of total agitation of all patients that had intermittent agitation on day 1
- Intermittent agitation – all other days: The percent of total agitation of all patients that had intermittent agitation on any day other than day 1
- Single day of agitation – day 1: The percent of total agitation of all patients that had a single day of agitation on day 1
- Single day of agitation – all other days: The percent of total agitation of all patients that had a single day of agitation on any day other than day 1
- Consecutive days of agitation – day 1: The percent of total agitation of all patients that had consecutive days of agitation beginning on day 1
- Consecutive days of agitation – all other days: The percent of total agitation of all patients that had consecutive days of agitation beginning on any day other than day 1

Agitation Patterns by Unit

Unit comparisons were conducted to determine differences in agitation between the MRICU and STICU subjects. Univariate analyses were performed between non-agitated and agitated subjects in the two units using X^2, Fisher's Exact Test, and Two Sample Test for Proportions for categorical data, and Two Sample t Test for continuous data.

61

There was no difference between the MRICU and the STICU in subject age, ethnicity, race, admitting diagnosis, as well as ICU and hospital LOS (Table 5). The MRICU subjects had a greater number of total documentation hours than the STICU although not different between the units. The two units were not different in the number of patients with first day, hour or block agitation. APACHE III, SOFA, and Charlson Comorbidity Index scores on admission to the ICUs were significantly higher for MRICU subjects than for STICU subjects. Subjects in the MRICU had a significantly higher percent of agitated patients on day 1 and 2 although there was no difference between the two units in mean agitation hour onset.

62

Table 5. Comparison of agitated patients between MRICU vs. STICU.

Unit Variable	MRICU (n =100) n (%)		STICU (n =100) n (%)		p value
Total documentation hours	9228 (51.4)		8710 (48.6)		
Total agitation hours	931		458		
Total documentation blocks	2399 (51.9)		2222 (48.1)		
Total agitation blocks	560 (23.3)		323 (14.5)		
*Agitated patients	64 (54)		54 (46)		0.20
Agitation hours in first day of admission	354		139		
Agitation blocks in first day of admission	207		101		
Patients agitated in first day of admission	57 (89.1)		45 (83.3)		0.12
Patients agitated in first hour of admission	26 (48.1)		18 (33.3)		0.23
Patients agitated in first block of admission	36 (56.3)		24 (44.4)		0.09
Patient Level Data	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**p value**
Percent agitation by hour	9.2 (9.5)	0-43	4.7 (6.8)	0-29	<.0001
Percent agitation by block	21.7 (21.4)	0-68	12.6 (16.4)	0-77	0.001
Percent agitation by day					
Day 1	31.9 (32.8)	0-100	15.4 (21.6)	0-100	<.0001
Day 2	21.4 (26.7)	0-100	9.2 (19.6)	0-100	0.0003
Day 3	15.1 (24.2)	0-100	10.3 (24.8)	0-100	0.17
Day 4	12.4 (24.6)	0-100	9.5 (19.9)	0-83	0.36
Day 5	8.9 (20.6)	0-83	8.5 (22.9)	0-100	0.88
Mean agitation onset hour from admission	8.4 (17.2)	0-85	15.5 (26.9)	0-114	0.09
Age (years)	56.7 (16.1)	18-89	53.3 (16.8)	18-82	0.27
ICU length of stay (days)	7.9 (7.5)	1.5-36.2	7.9 (7.9)	1.7-34.1	0.97
Hospital length of stay (days)	15.8 (13.1)	2.2-66.8	18.6 (16.3)	2.8-78.9	0.31
APACHE III score on admission to the ICU	81.2 (27.2)	23-170	66.9 (27.7)	21-132	0.0056
SOFA	7.6 (3.9)	0-18	5.6 (3.5)	1-16	<.0001
Charlson Comorbidity Index	5.5 (3.3)	0-17	3.8 (3.1)	0-13	0.0084

Abbreviations: intensive care unit (ICU); Acute Physiology And Chronic Health Evaluation (APACHE III); Sequential Organ Failure Assessment (SOFA)

DISCUSSION

Agitation Frequency

Agitation is common in the critically ill. In this study the majority of the sample (59%) was agitated at any time during the first 5 days of their ICU stay. Our high frequency of agitation is generally similar to previous studies' agitation rates. Jaber et al.[6] studied 182 medical-surgical ICU subjects over 8 months and found an agitation frequency of 52%. Despite differences in inclusion criteria (our study excluded patients in the unit less than 24 hours and

63

Jaber's did not) and identification of agitation (our RASS and keyword use vs. Ramsay score), the frequency of agitation was similar. Gardner et al.[4] studied 83 medical respiratory ICU patients over a 2-month period and found an agitation frequency of 42% using nursing documentation to rate the level of agitation. Although the study had a smaller sample, they also used a 2 month period with similar agitation rates. Fraser et al.[15] studied 130 medical and surgical ICU patients over a 4 month period and found an agitation frequency of 70.8%. Their exclusion criteria were similar to ours; however, their identification of agitation differed and may explain their higher agitation frequency. They used medical record narratives describing agitated behavior to quantify agitation using the Sedation Agitation Scale (SAS), identifying agitation with SAS scores of 5-7 ("agitated", "very agitated", and "dangerously agitated"). The SAS 5 description includes "anxious", a descriptor not used as indicative of agitation in our study. Interestingly, using SAS 6 or 7 only, they reported an any-day agitation frequency of 46.1% – similar to what we report here. Woods et al.[5] studied 143 medical ICU patients over a 5 month period and reported any-day agitation of 16.1%. This may be explained by the differences in inclusion criteria (ventilated patients, medical ICU, severity and definition of agitation) as well as the use of a sedative/analgesic protocol.

There were also similar findings between this study and others regarding patient-days of agitation. Ours (31.9%) were generally similar those of Gardner et al.'s[4] 32% and Fraser et al.'s[15] 46.1% to 54%. These findings of generally similar agitation frequency suggest that agitation is consistently pervasive. Our hourly and block agitation rates are unique in that this level of detail has not been found previously in the literature. The higher rates of block-time may be due to variations in documentation but may also be more accurate due to the ability of documentation at the end of the 4-hour block. Agitation is generally not a quickly resolving issue and the use of the circle-the-item for a 4-hour block may have been used as an efficient indicator. However, due to individual documentation variation in healthcare providers, the per-day agitation rates may allow a more consistent comparison between studies.

64

Agitation Onset

We found the onset of agitation occurs early in the ICU stay. This is generally consistent with the literature. The vast majority of our sample had agitation onset very early the first day of their ICU stay – considerably earlier than found in previous studies. Fraser et al.[15] found the mean onset time from ICU admission to maximum agitation to be 2.4 days. The differences may be due to definition of agitation onset. We computed the mean of all subjects' agitation onset hours while Fraser reported hours to maximum agitation – however no description of the method for determining maximum agitation was included. Jaber et al.[6] found agitation onset to be 4.4 ± 5.6 days, more than four times longer; however they stated that most of the patients became agitated in less than 3 to 5 days. Their data describe early onset of agitation from several aspects: cumulative distributions of onset and duration of agitation, correlation between duration of agitation and onset of agitation, and correlation between duration of stay in the ICU and duration of agitation.

The causes of such early agitation trends remain unclear. Early agitation onset findings in studies has been thought to be linked to sedative use as the majority of agitated subjects received sedatives. Use of sedatives has been associated with agitation in several studies;[5;6;15] more studies are needed to determine if or what dose of sedative use precipitates agitation or is involved in neurotransmitter imbalance. Severity of disease has also been suggested to be associated with early agitation onset. This appears unlikely as, although we used the APACHE III rather than APACHE II or SAPS, our scores are generally comparable to other studies.[5;6;15]

First-day agitation is common in the critically ill. We found significantly higher first-day rates (86%) compared to Woods et al.[5] who found 7%. This difference may be attributed partially to the dissimilar populations and outcome measurement discussed earlier. Interestingly their subjects actually had higher sedative use (75% - 96%) than ours which seems to contradict the premise of sedative use as a factor influencing this study's increased agitation. In addition to very high first-day agitation rates, over half of our sample had identified agitation in the first

65

hour of ICU admission. This suggests that subjects were admitted in an agitated state –
different from other studies. It is unclear to what this can be attributed. The admission source
and location might be thought to influence this finding but no statistical significance or trend was
found.

Patterns of Agitation – Onset and Frequency

The hourly patterns of agitation onset and frequency for day of the week, day/night, or 4-
hour block intervals were similar. Anecdotally, agitation has been thought to occur more
frequently during the evening/night hours. We found agitation frequency to be higher in the day.
Jaber et al.'s[6] study did not find a significant difference in day/night agitation. These results
suggest that agitation is heterogeneous with little diurnal fluctuation.

Agitation patterns over time revealed that day 1 agitation is implicated in all trends but
more significantly in consecutive days.

Agitation Patterns by Unit

In comparing the two subject populations (MRICU and STICU) with regard to agitated
patients, our findings did not reach statistical significance; however Jaber et al.[6] found agitation
rates higher in medical subjects. Day 1 and 2 percent patient agitation rates found significantly
higher in the MRICU may reflect higher severity of disease. If agitation or acute brain
dysfunction is a result of dysregulation of neurotransmitters, medical ICU patients may have
greater comorbidities and severity of disease that may contribute to the higher agitation rate and
earlier onset. In support of this supposition, we found the APACHE III and SOFA scores, as
well as the Charlson index significantly higher in the MRICU subjects; Jaber and colleagues[6]
also found a significantly higher Simplified Acute Physiology Score (SAPS) II in medical
subjects.

Limitations of this study warrant mention. As this was a retrospective chart review,
findings are dependent on data completeness and quality – the data was not originally recorded
for research purposes and may lack in quantity and quality. In an effort to mitigate some of

66

these disadvantages, we used a more stringent definition of agitation – documentation of the word "agitation" or the RASS tool – not relying solely on behavioral cues. Strengths of retrospective reviews exist: they are reflective of usual care and allow investigators to examine processes and outcomes as they occur, void of the Hawthorne effect, and they monitor in real time integrating multiple data sources. We currently lack a continuous method of measuring agitation over time. Without this, the best alternative is hourly documentation. Differences in unit samples could be due to differences in unit documentation norms.

Regardless of the evaluation of agitation, whether frequency, onset, or pattern, our data show agitation in the critically ill is a very early phenomenon involving consecutive days. These findings have clinical and resource allocation implications. Focusing efforts, resources and implementing protocols very early in the ICU stay (or before) may prevent the poor outcomes and dangerous sequellae of agitation as well as reduce ICU costs. In addition, interrupting the trend of consecutive days of agitation may have an equal impact in lowering overall agitation frequency.

CONCLUSION

Agitation affects over half of ICU patients, largely occurs the first day in the ICU stay, and involves consecutive days. Patients in the MRICU have a higher severity of illness than the STICU and have higher day 1 and 2 rates of patient agitation. Other studies are needed to clarify patient risk factors and identify strategies (both pharmacological and nonpharmacological) to prevent, ameliorate, or treat the condition.

67

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Predictors of Agitation in the Adult Critically Ill

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69

Abstract

Background:
Agitation in critically ill adults is a frequent complication of hospitalization resulting in multiple adverse outcomes. Studies show from 42-71% of critically ill patients experience agitation and agitation is observed in up to 32% of patient days.

Objectives:
Potential causes of agitation in critically ill patients are numerous; however, data about factors that predict agitation are limited. The purpose of this study is to identify predictors of agitation by investigating demographic and clinical characteristics of critically ill patients.

Methods:
A retrospective medical record review was performed identifying agitation using the Richmond Agitation-Sedation Scale or the use of an "agitation" keyword. A total of 200 patients were studied from a medical and surgical ICU. Two models were examined: 1) on admission and 2) 24 hours prior to the first agitation event. Data pertaining to baseline demographics and preadmission risk factors as well as clinical data were collected and evaluated by logistic multivariable regression to determine predictors of agitation.

Results:
Predictors of agitation on admission to the ICU were: past medical history of illicit substance use, height, both the Sequential Organ Failure Assessment (SOFA) respiratory and central nervous system subscores, and use of restraints. Predictors of agitation identified from data gathered within 24 hours prior to agitation were: past medical history of psychiatric diagnosis, height, SOFA score, P/F<200mmHg, serum pH, percent of hours using restraints, percent of hours using mechanical ventilation, pain, and presence of genitourinary catheters.

Conclusions:
In this study predictors of agitation on admission and within 24 hours prior to agitation onset were primarily clinical variables. This allows considerable opportunity for intervention to ameliorate or prevent agitation.

70

One of the more frequent complications in the intensive care unit (ICU) is agitation. Agitation is associated with adverse clinical outcomes: longer ICU stay, longer duration of mechanical ventilation, a higher rate of self-extubation, unplanned catheter removal, excessive sedation, increased utilization of resources, and increased ICU costs.[1-3] Studies show that from 42-71% of critically ill patients experience agitation.[2-5] Recognizing the impact of agitation, The Society of Critical Care Medicine's (SCCM) recently updated sedation and analgesia guidelines now also include agitation, indicating the need to focus on this significant issue.[6] The guidelines highlight the need for prompt identification and treatment of possible underlying causes of agitation and recommend use of an interdisciplinary team to improve patient management.

Potential causes of agitation in critically ill patients are numerous; however, data about factors that predict agitation are limited. As agitation is often identified after overtly agitated behavior is observed, a critical barrier to progress in the field has been the lack of identification of the precursors of agitation. In order to develop an agitation risk profile for critically ill adults, identification of risk factors on admission and prior to an agitation event is important. Empirically based information would therefore assist care providers to identify those at risk as well as predict agitation. Identification of patients at particularly high risk for developing agitation provides an opportunity to implement preventative strategies to protect patients from self- and iatrogenic-induced injury. Therefore the purpose of this study was to examine the relationship of demographic and clinical characteristics of critically ill patients in the development of agitation.

METHODS

Subjects and Setting

The study was conducted in an 865-bed academic, Level I Trauma Center which offers all critical care specialties, using two adult units (medical-respiratory ICU [MRICU] and surgical trauma ICU [STICU]). All adult patients, 18 years of age and older, consecutively admitted to the MRICU and STICU over a two month period were evaluated for inclusion using a medical

71

record review. The MRICU is a 20 bed medical ICU with approximately 1000 yearly admissions

while the STICU is a 24 bed surgical ICU with approximately 1400 yearly admissions. Approval

was obtained from the University/hospital Institutional Review Board. Patient exclusion criteria

were an ICU length of stay (LOS) less than 24 hours in order to exclude those who were

admitted for short-term/overnight monitoring, those with medical records that were not available,

and patients previously admitted during the study duration. Other exclusion criteria were

conditions affecting patient movement interfering with sedation scale scoring including:

administration of paralytics preventing any movement; patients with chronic, persistent

neuromuscular disorders (such as cerebral palsy and Parkinson's disease); and patients with

head trauma or stroke.

Measures

Agitation

Agitation was identified using medical record documentation of the Richmond Agitation-

Sedation Scale (RASS), which is a 10 point scale, from +4 (combative) through 0 (calm, alert) to

-5 (unarousable) assessed at the bedside in 3 steps using discrete criteria, over a time of 30-60

seconds.[7] The SCCM has identified the RASS as one of the most valid and reliable sedation

assessment tools for measuring quality and depth of sedation in adult ICU patients.[6]   The

RASS has demonstrated excellent interrater reliability and criterion, construct, and face validity

across a variety of critical care settings.[7-11] The RASS was the standard sedation-agitation tool

used in both of the target ICUs and at the time of data collection, no delirium tools were

routinely used. RASS values were routinely obtained every 4 hours in the units and more

frequently if needed. A RASS of +1 (restless – anxious or apprehensive but movements not

aggressive or vigorous) through +4 (combative – overtly combative or violent; immediate danger

to staff) were used to identify agitation. The +1 RASS was accepted as an indicator for agitation

as it indicates restlessness, anxiety, or apprehension – qualities not present in a calm and alert

72

patient (RASS = 0); use of positive numbers in the RASS have been previously documented as an agitation scale.[7]

Agitation was also identified using the keyword "agitation" (all forms of the word, "agitated", "agitation", "agit") recorded from the medical record using physicians' and nurses' notes in the nursing bedside flowsheet, emergency department documentation, operating room notes, and circle-the-item for reporting agitation in flowsheets.

Predictors of Agitation

Demographics and Preadmission Risk Factors. Information pertaining to baseline demographics and preadmission risk factors for agitation were retrieved from admission summaries. Risk factors previously associated with agitation in the critically ill were identified from the literature as well as from expert consultation. These data, collected on admission to the ICU, included demographic characteristics (age, gender, ethnicity, race), marital status, weight, height, Body Mass Index (BMI), hospital admission source (clinic, emergency department [ED], home, long term care, or outside hospital), ICU admission source (operating room, general hospital floor, ED, outside hospital), admitting diagnosis category, and severity of illness data for the Acute Physiology And Chronic Health Evaluation III (APACHE III),[12] the Sequential Organ Failure Assessment (SOFA),[13] as well as the Charlson Age-Comorbidity Index.[14] The APACHE III was also collected on the day of the first agitation event; SOFA scores were collected daily. A past medical history of specific medical issues was also retrieved and included a history of diabetes, alcohol abuse, illicit substance use, tobacco use, psychiatric diagnosis, as well as overuse/abuse and prescribed use of psychiatric medications.

Clinical Risk Factors. Measurable clinical factors were also identified from the literature. Clinical data collected on admission and 24 hours prior to the first agitation event were worst daily values (defined as most extreme or farthest from the normal laboratory mean value) for: creatinine, blood urea nitrogen, daily urine output, bilirubin, hematocrit, and glucose, as well as Glasgow Coma Score (GCS), PaO_2, heart rate, mean arterial pressure, respiration rate, FiO_2,

73

and temperature. Data collected hourly included: pain rating (Numerical Rating Scale), RASS score, use of restraints and type of restraints, use of mechanical ventilation (MV), total number of all catheters as well as number and specific category of invasive lines and catheters (peripherally inserted, centrally inserted, genitourinary [GU], and gastrointestinal [GI]), use of dialysis, presence of sepsis (using Criteria of Bone[15]) and nosocomial infections (hospital-acquired pneumonia, by documentation), as well as community-acquired pneumonia (by documentation). For variables that occurred continuously (e.g. mechanical ventilation, use of restraints), use was calculated by hourly percent of time used. For acute renal failure the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease)[16] classification system rating was collected. All laboratory values for the 5 study days for the following blood tests were recorded on the reporting hour: pH, sodium, potassium, albumin, magnesium, white blood count (WBC), and hemoglobin.

Clinical Outcomes

To fully describe the sample, data were also collected related to ICU and hospital length of stay (LOS), discharge destination or outcome (long term care or other facility, home/prior living arrangement, or death), and adverse events.

Procedure

All data were collected from the medical record by a single investigator (RSB). A pilot study was performed, using subjects not part of the study cohort, to organize and streamline data collection and to identify and resolve any ambiguous or conflicting procedure or data. Data audits were performed to verify accuracy of information using convenience sampling on approximately 10% of all subjects. The error rate on the data audit was less than 0.03%.

To ensure that a broad representation of unit admissions would be obtained our goal was to obtain an equal number of subjects in each of the two study units that would span the majority of a two month period. Data were collected during the first 5 days of ICU stay as

74

agitation onset and duration is highest in the first 3 to 5 days.[2;4] All data were de-identified and patients were assigned a subject ID number.

The hour was used as the documentation epoch for all recurrent data collection. The hour was considered an agitation hour only if the RASS was +1 or above, or the keyword agitation (or its forms) was found in the medical record during that hour. If any agitation was documented within the hour or there were multiple documented agitation episodes, it was considered to be one agitation hour. For each patient only the first admission to the ICU was included in data collection and analysis. Data collection included ICU location (MRICU or STICU) and the ICU hour from admission for up to 5 days.

DATA ANALYSIS

Descriptive statistics were computed on patients' baseline demographic and clinical variables. Based on the data structure, categorical data was described as number (percent), normally distributed continuous data was described as mean ± standard deviation, and non-normal continuous data was described as the median with interquartile range (25th - 75th percentile). For every subject only the first reported occurrence of agitation during the study period was examined. Thus, any report of agitation during the five study days was used to identify two study groups (agitated subjects versus nonagitated subjects). For the GU catheter variable, subjects had either 0 or 1 catheter so the variable was converted to a nominal (yes/no) response.

We examined developing two separate models to identify predictors of agitation. The first model focused on factors on admission to the ICU that might predict agitation. The second model primarily considered factors within 24 hours prior to the first episode of agitation. The time period of 24 hours was chosen to capture both slower-responding physiologic changes (i.e. renal or hematologic indices) as well as those with a more rapid rate (i.e. oxygenation or mental status indices).

75

For both scenarios (factors on admission and factors within 24 hours of first agitation episode), each potential risk factor was examined univariately in simple logistic models to determine its relationship to agitation. Here, the response variable was agitated or not agitated. As a screening tool for risk factors, the alpha level for significance was set to 0.10. Next, logistic regression models were constructed using all significant variables of the univariate analysis and then using subsets of the significant variables from the univariate analysis. For each subset considered, backward elimination was used to select the significant predictors of agitation. In these models, the alpha level was changed to a 0.05 level of significance. Testing for the significant parameters was conducted using the Likelihood Ratio (LR). Alternative models were compared in terms of statistical significance of each predictor, goodness-of-fit statistics (AICc, BIC and R^2 values), and predictive power (e.g. area under the curve [AUC] of the ROC curve and percent correct classification) in order to determine the best model for predicting agitation for both scenarios: on admission and within 24 hours prior to the first episode of agitation. Statistical analysis was performed using SAS JMPvPro10.0 (Cary, NC).

RESULTS

Subjects

Three hundred and eighty three patients, sequentially admitted into the ICUs, were screened, 179 from the MRICU and 204 from the STICU. There were 79 MRICU subjects not meeting inclusion criteria: 56 were in the unit less than 24 hours, 8 had neuromuscular disorders or paralysis, 9 were obtunded or suffered head trauma, and 6 were readmitted. There were 104 STICU subjects not meeting inclusion criteria: 82 were in the unit less than 24 hours, 5 had neuromuscular disorders or paralysis, 4 were obtunded or suffered head trauma, 12 were readmitted, and 1 had no medical record available. In all, 200 subjects, 100 from each ICU, were included in the final analyses. A more detailed, full report of the sample was described in a companion paper that included agitation onset, frequency, and associated temporal factors.[17]

76

Overall the sample subjects had a mean age of 55 years and were primarily men, non-Hispanic, and white or African-American (Table 1). Approximately one quarter (28.5 %) of the agitation documentation was based on RASS with the balance using an agitation keyword. Of the 200 subjects, 118 (59%) were agitated at some point over the 5 day study period and comprised the agitated group for this analysis. Of these 118 agitated subjects, 102 (86%) had agitation on day 1. Of the 102 that were agitated on day 1, 44 (43%) had agitation reported on ICU admission.

Predictors of agitation on ICU admission

In the univariate analysis, individual demographic and preadmission factors present on ICU admission that were significantly associated with agitation were male gender, greater weight, past medical history of illicit substance use and psychiatric diagnosis (Table 2). Severity of illness scores associated with agitation were the total SOFA score, the SOFA respiratory and CNS subscores, the GCS, and APACHE III. Specific clinical factors associated with agitation were P/F < 200 mmHg, FiO_2, serum pH, serum magnesium, serum glucose, use of restraints, use of MV, pain rating, number of total catheters, presence of GU catheters, and number of GI and other catheters (Table 2).

Logistic regression analysis showed that the majority of variables remaining in the final model were clinical factors. The model was statistically significant, indicating that the predictors as a set reliably distinguished between subjects with and without agitation (chi square = 68.071, p<.0001 with df = 5). The AUC for the receiver operating characteristic (ROC) was 0.85. Prediction success overall was 75% (79.3% for subjects with agitation and 69.1% for subjects without agitation). Predictors of agitation were identified as past medical history of illicit substance use, height, both the SOFA respiratory and CNS subscores, and use of restraints (Table 3).

Table 1. Demographics and other descriptors for entire sample and by presence of agitation (at least one observation of agitation)

Variable	Entire sample n = 200	Non-agitated Pts n = 82 (41%)	Agitated[a] Pts n = 118 (59%)
Gender			
Male	113 (56.5)	42 (51)	73 (62)
Female	87 (43.5)	40 (49)	45 (38)
Ethnicity			
Hispanic or Latino	6 (3)	5 (6)	1 (1)
Not Hispanic or Latino	194 (97)	77 (94)	117 (99)
Race			
Asian	3 (1.5)	2 (2)	1 (1)
Black or African-American	94 (47)	39 (48)	55 (47)
White	103 (51.5)	41 (50)	62 (53)
ICU Type			
Medical Respiratory ICU	100 (50)	36 (44)	64 (54)
Surgical Trauma ICU	100 (50)	46 (56)	54 (46)
Admission Source			
Long term care	3 (1.5)	2 (1)	1 (0.5)
Home	16 (8)	4 (2)	12 (6)
Clinic	20 (10)	7 (3.5)	13 (6.5)
Outside hospital	60 (30)	23 (11.5)	37 (18.5)
ED	101 (50.5)	46 (23)	55 (27.5)
Admitting Diagnosis			
Trauma	36 (18)	18 (22)	18 (15)
Sepsis	35 (17.5)	17 (21)	18 (15)
Respiratory failure	27 (13.5)	6 (7)	21 (18)
Hematologic/oncologic problem	27 (13.5)	8 (10)	20 (17)
Other	22 (11)	9 (11)	12 (10)
Renal/GI problem/DKA	28 (14)	15 (19)	13 (11)
Hepatic problem	13 (6.5)	4 (5)	9 (8)
Cardiovascular problem	8 (4)	4 (5)	4 (3)
Drug overdose/poisoning	4 (2)	1 (1)	3 (3)
Age (years)	55.5 (+/- 16.4)	56 (+/- 16.4)	55.1 (+/- 16.5)
Total ICU length of stay (days)	3.9 (2.5-8)	2.7 (2-8)	4.8 (3-9.4)
Total hospital length of stay (days)	11.1 (6.3-21.6)	9.1 (6-19.4)	12.8 (6.9-21.8)
APACHE III score	68 (+/- 31.9)	57.7 (+/- 34.3)	74.7 (+/- 28.2)
SOFA	6.625 (+/- 3.8)	5.39 (+/- 3.7)	7.48 (+/- 3.7)
Charlson Comorbidity Index	4.69 (+/- 3.3)	4.8 (+/- 3.3)	4.6 (+/- 3.4)

[a]At least one documented observation of agitation during the 5-day study time

Abbreviations: patients (pts); intenstive care unit (ICU); emergency department (ED); gastrointestingal (GI); Diabetic ketoacidosis(DKA); Acute Physiology And Chronic Health Evaluation (APACHE III); Sequential Organ Failure Assessment (SOFA)

Data are presented as number (%), mean +/- SD, or median (25th – 75th percentiles)

Table 2. Demographic, preadmission and clinical risk factors with univariate significance

Demographic and Preadmission Risk Factors				
Variable	At admission		24 hrs prior to onset of Agitation	
	Non-agitated	Agitated[a]	Non-agitated	Agitated[a]
Gender				
Male	42 (51)	73 (62)*	----	----
Female	40 (49)	45 (38)*	----	----
Height in cm	167.3 (10.3)	172.1 (10.7)**	----	----
Weight in kg	77.1 (22.5)	83.9 (26.1)*	----	----
Subject PMH				
Illicit substance use	26 (32)	55 (47)**	----	----
Psychiatric diagnosis	10 (12)	28 (24)**	----	----
Severity of Illness Scores				
Variable	At admission		24 hrs. prior to onset of Agitation	
	Non-agitated	Agitated[a]	Non-agitated	Agitated[a]
Total SOFA score	6.6 (3.8)	5.4 (3.7)**	5.9 (4.1)	7.4 (3.7)**
Respiratory subscore	0.8 (0.9)	1.3 (1.1)**	0.9 (1)	1.2 (1.1)*
CNS subscore	1.2 (1.3)	2.5 (1.2)**	1.3 (1.3)	2.5 (1.1)*
GCS	12.3 (3.8)	8.6 (3.6)**	12.3 (3.8)	8.6 (3.6)**
APACHE III score	57.7 (34.3)	74.7 (28.2)**	57.7 (34.3)	73.7 (29.3)**
Clinical Risk Factors				
Variable	At admission		24 hrs. prior to onset of Agitation	
	Non-agitated	Agitated[a]	Non-agitated	Agitated[a]
P/F < 200 mmHg	1 (1)	12 (10)**	8 (4)	23 (11.5)*
FiO_2	0.36 (0.21-0.53)	0.5 (0.4-0.7)**	0.36 (0.21-0.53)	0.5 (0.4-0.7)**
Serum pH	7.39 (+/- 0.07)	7.36 (+/- 0.095)**	7.39 (+/- 0.09)	7.36 (+/- 0.09)**
Serum magnesium	1.89 (+/- 0.32)	1.99 (+/- 0.47)*	1.85 (+/- 0.39)	1.98 (+/- 0.45)*
Serum hemoglobin	10.3 (+/- 2.5)	10.3 (+/- 2.2)	9.1 (+/- 2.3)	10.1 (+/- 2.2)**
Serum glucose	146 (+/- 66)	168 (+/- 84)*	146 (+/- 66)	165 (+/- 84)*
Abnormal Temp ≥ 38	12 (15)	35 (30)**	12 (15)	37 (31)**
Abnormal Temp ≥ 38, <36	19 (23)	47 (40)**	19 (23)	49 (42)**
Use of restraints (and percent of time)	6 (7)	40 (34)**	12 (15)	63 (53)**
Use of MV (and percent of time)	15 (8)	70 (35)**	18 (9)	80 (40)**
Highest pain rating	0 (0-5.25)	0 (0-2.25)**	6 (2-8.25)	0 (0-4)**
Total number of catheters	3.2 (+/- 1.8)	4.1 (+/- 2.1)**	4.1 (+/- 1.9)	4.5 (+/- 2)
Presence of GU catheters	44 (54)	90 (76)**	52 (63)	97 (82)**
GI & other catheters	0 (0-1)	1 (0-1)**	1 (0-1)	1 (0-1.25)

Data are presented as number (%), mean +/- SD, or median (25th – 75th percentiles)

Abbreviations: centimeter (cm); kilogram (kg); MRICU (Medical Respiratory ICU); STICU (Surgical Trauma ICU); past medical history (PMH); Sequential Organ Failure Assessment (SOFA); central nervous system (CNS); Acute Physiology And Chronic Health Evaluation (APACHE III); PaO_2/FiO_2 (P/F); mechanically ventilated (MV); Glasgow Coma Score (GCS); Genitourinary (GU); Gastrointestinal (GI)

[a]At least one documented observation of agitation during the 5-day study time

*p 0.05<.01; **p ≤ 0.05

Table 3. Predictors of agitation[a]

Variable:	Odds ratios	95% CI	LR p value
On admission to the ICU			
Past medical history of illicit substance use	2.43	1.18 - 5.15	0.015
Height	1.04	1.01 – 1.08	0.016
SOFA respiratory subscore	1.58	1.11 - 2.28	0.0097
SOFA CNS subscore	1.90	1.45 – 2.54	<.0001
Use of restraints	3.77	1.39 - 11.53	0.008
24 hrs prior to onset of first agitation event			
Past medical history of psychiatric diagnosis	6.24	1.4 – 32.4	0.015
Height	1.06	1.01 – 1.12	0.015
SOFA score	2.3	2.1 – 2.6	0.012
P/F <200 mmHg	4.7	1.4 – 17.9	0.011
Serum pH	1.3[b]	1.02[b] – 1.75[b]	0.026
Restraints (1% of time)	1.04	1.01 – 1.08	0.0003
Mechanical ventilation (1% of time)	1.03	1.01 – 1.04	0.0004
Pain	1.2	1.05 – 1.4	0.0059
Presence of GU catheters	3.8	1.2 – 12.98	0.0264

[a]At least one observation of agitation during the study time
Abbrev: Sequential Organ Failure Assessment (SOFA); central nervous system (CNS); PaO_2/FiO_2 (P/F); Likelihood Ratio (LR)
[b]for each 0.05 increase in pH

Predictors of agitation within 24 hours prior to agitation

In the univariate analysis, significant individual demographic and preadmission factors present within 24 hours prior to onset of the first agitation event were the same as the on-admission group (Table 2). Severity of illness scores significantly associated with agitation on admission were also associated with agitation within 24 hours prior to agitation (SOFA total, SOFA Respiratory subscore, SOFA CNS subscore, APACHE III total, and GCS) (Table 2). Of the factors that were significantly associated with agitation on admission, only total number of catheters, number of GI catheters, and hemoglobin were not significantly associated with agitation within 24 hours prior to agitation onset (Table 2).

Initially all variables that were significantly associated with agitation were used in the model describing predictors of agitation within 24 hours of the event. We also evaluated additional models using subsets of the original variables in order to reduce multicollinearity

80

which was generated by constructing models that included more than one measure of severity of illness (i.e. models considered used only total SOFA, or only SOFA subscores, only total APACHE III, or only APACHE III subscores). After comparison of these models based upon AIC, BIC, R^2 and ROC and predictive ability, the final model was determined.

Similar to predicting upon admission, logistic regression analysis showed that the majority of the variables remaining in the model for predicting within 24 hours of the agitation event were also clinical factors. The model was statistically significant, (chi square = 94.4, p<.0001 with df = 9) and its associated AUC for the ROC was 0.92. Prediction success overall was 83% (85% for subjects with agitation and 79% for subjects without agitation). Predictors of agitation were identified as height, past medical history of psychiatric diagnosis, SOFA score, P/F < 200, serum pH, percent of hours using restraints, percent of hours using mechanical ventilation, pain rating, and presence of GU catheters (Table 3). Predictors of agitation similar for on admission and within 24 hours prior to first agitation event were height and restraints.

Clinical Outcomes

Patient outcomes (length of stay, discharge status and mortality) were also compared between those who experienced agitation and those who did not. There was no difference between agitated and nonagitated patients with respect to number of hospital days prior to ICU admission (p=0.21), ICU length of stay (p=0.12), number of hospital days after ICU discharge (p=0.89), total hospital length of stay (p=0.56) or in-hospital mortality (19%) (p=0.11). Discharge destination was significantly different between the two groups (p=.02); non-agitated subjects were more likely to be discharged to home or prior living arrangement.

Because adverse events are commonly associated with agitation, the number of documented adverse events (self-removal of tubes or lines, falls, and restraint damage) was also recorded. In the total sample (n=200), 33 experienced 50 adverse events. In the sample of 118 agitated subjects, 32 (27%) had 49 adverse events compared to 1 (1%) in 82 nonagitated subjects (p<.0001). Of the 50 adverse events in agitated subjects, 45 (90%) were

81

reported concurrent with agitation during the hour, 4 were reported within 2 hours of documented agitation, and 1 occurred 4 hours from documented intermittent agitation. There were 28 events in the MRICU and 22 in the STICU. Of the 33 subjects with adverse events, 5 (15%) self-extubated, 3 (9%) pulled out critical catheters or tubes (central line, epidural catheter, NG tube sutured to nare), 1 (3%) fell out of bed, 1 (3%) tore restraints off, and 30 (91%) pulled out non-critical catheter/tubes/leads.

DISCUSSION

Agitation is a common and hazardous complication of critical illness. In this study predictors of agitation on admission and within 24 hours prior to agitation onset were primarily clinical variables and, except for use of restraints, may represent the severity of the disease process. Similar to the studies of Fraser et al.[3] and Jaber et al.,[2] age was not associated with agitation, although Woods et al.[1] found that severely agitated subjects were younger (less than 10 years, $p<.04$). Agitation was not associated with a longer ICU or hospital stay but was associated with multiple clinically significant adverse events.

Predictors of agitation on ICU admission

Demographics and Preadmission Risk Factors

Of the preadmission risk factors only past medical history of illicit drug use and height were predictive of agitation. A record of illicit drug use increased the odds of having agitation almost 2.5 times, although others have not reported illicit drug use as a predictor of agitation. Woods[1] reported a univariate association with agitation based on marijuana use only, while Gardner et al.[4] evaluated drug and alcohol abuse but did not find them to be a significant predictor. However, their sample was small (n=83) which may have limited their ability to detect significance. Alcohol abuse was not associated with agitation; however, Jaber et al.[2] reported that alcohol abuse increased the risk of agitation three-fold. They explained that their study population may account for this difference as their ICU is associated with the Institute of Liver and Gastroenterology Disease which treats many alcoholic patients.

82

Height predicted agitation but no other study has reported similar results. This was true on admission as well as for models evaluating 24 hour data prior to agitation and the explanation for this relationship is unclear. This result is further confounded since factors associated with height were not predictors, such as weight or body mass index.

Severity of Illness

Although none of the total severity of illness measures predicted agitation, two SOFA subscores did: respiratory and CNS. The SOFA respiratory subscore uses PaO_2/FiO_2 mmHg (P/F); the SOFA CNS subscore is a categorized GCS. The GCS was only significant in the univariate analysis although it is the basis for the SOFA CNS subscore. The odds of having agitation increased over 1½ times for every point increase in the SOFA respiratory subscore. The odds of having agitation increased almost two-fold for every point increase in the SOFA CNS subscore. Oxygenation level and neurologic condition have been shown to be associated with agitation.[1;4] Impaired oxygenation may result in neurologic deterioration, and the converse can also be true, in cases where neurologic deterioration leads to inadequate ventilation. Pulmonary and neurologic subscores of the Multiple Organ Dysfunction Score[18] (MODS) also have been associated with agitation[4] – the MODS subscores use the same factors as the SOFA (P/F and GCS). Therefore patients who have respiratory or neurologic compromise may be at most risk for agitation on admission.

Clinical Risk Factors

Only use of restraints at admission was predictive of agitation increasing the odds of having agitation over 3.5 times. Restraint use has been reported in 34% of agitated subjects and 50% of episodes of agitation.[2] Although it is difficult to determine whether restraint use causes agitation or restraints are used because patients are already agitated, the association of restraints and agitation is clear. In an observational study by Werner et al.,[19] nursing home residents exhibited either the same amount or more agitated behaviors when they were restrained than when they were not restrained, suggesting that the act of restraining may itself

83

contribute to manifestations of agitation. Werner and colleagues suggest that restriction of movement, particularly through the use of physical restraints, produces an increase in stress which may increase agitation.

Predictors of agitation within 24 hours prior to agitation

While we examined data gathered within 24 hours prior to agitation, other investigators have examined risk factors for agitation at varying time points before the event, including use of daily data with time-varying covariates[1] and data collected within 48 hours prior to agitation[1,2] with some comparable predictors. Risk factors for agitation in other studies similar to those in ours included 1 preadmission risk factor, 1 severity of illness factor, and 3 clinical factors – it is possible that the large number of first-day agitation could have influenced our findings.

Demographics and Preadmission Risk Factors

Of the preadmission risk factors, height was again predictive of agitation; however, past medical history of psychiatric diagnosis was identified as a risk factor in this second model. There was a univariate association with psychiatric diagnosis and agitation on admission but it was not a predictor in the final model. Our study showed medical history of psychiatric diagnosis increased the risk of agitation 6 times. In addition to our study, Jaber et al.[2] also described a correlation between psychiatric history and agitation using data collected on regular use of antipsychotic medications as an indicator of psychiatric disorder. They reported regular use of psychoactive drugs increased the risk of agitation five times.

Severity of Illness

Increasing severity of illness was a predictor of agitation using the total SOFA score. An increase in one point on the SOFA score was associated with more than a two-fold increase in the risk of agitation. An association between agitation and severity of illness was also reported by Gardner et al.[4] They found significantly greater APACHE II scores (23.8 versus 17.5; $p=0.002$) as well as MODS (8.2 versus 6.8; $p=0.002$) on days when subjects were noted to

84

exhibit agitated behavior. Jaber et al.[2] described a similar severity of illness association but only in the univariate analysis using the Simplified Acute Physiology Score II.[20]

Clinical Risk Factors

Use of restraints was associated with agitation both on admission and within 24 hours prior to the first agitation event. On admission, by definition, we looked at presence of restraints during one point in time; however, we were able to evaluate percent of restraint use within 24 hours prior to agitation to enhance statistical evaluation. The odds ratio (OR) reported reflected a 1%-of-the-time use of restraints. Calculating for hourly use, using restraints for only 4 hours almost doubled the risk of having agitation; using them for 6 hours increased the risk of agitation over 2.5 times. The use of physical restraints coincides with stress, further aggravating the already existing neuropathology, which may increase stress and agitation even more.[21] However, patient safety is an important consideration when limiting restraint use. All factors should be weighed carefully before making restraint decisions.

Indicators of oxygenation were risk factors for the onset of agitation on admission and within 24 hours prior to agitation and included the SOFA respiratory subscore (categorized P/F) on admission and P/F<200 within 24 hours prior to agitation. A P/F<200 increased the risk of agitation over 4.5 times. This suggests that severe hypoxemia may contribute to the onset of agitation.

The amount of time of mechanical ventilation (MV) also predicted agitation. Calculating for hourly use, using MV for 6 hours almost doubled the OR for agitation; using them for 12 hours increased the risk over 3.5 times, 18 hours over 16 times, and 24 hours over 41 times. Although guidelines suggest weaning as soon as feasible, MV duration (to support respiration/oxygenation) is not usually a few hours. Presence of MV in a critically ill patient should be considered seriously with respect to agitation.

As discussed earlier with the on-admission model, use of MV may be another marker of oxygenation and neurologic dysfunction, although it is not clear why one of these variables is a

85

prediction in the first model and not in the second. Use of MV was not identified in other studies as a predictor of agitation but is related to other types of respiratory measures that have been shown to be predictive.[1;4] Similar to others,[1] acidemia was a risk factor for agitation, which may also reflect respiratory dysfunction and/or a greater level of illness. Not all investigators have evaluated pH with respect to the onset of agitation.[2;4]

The increasing number and types of catheters in the critically ill may certainly lead to discomfort as well as agitation. Specifically, the presence of a GU catheter increased the likelihood of having agitation over 3.5 times; GU catheters have also been associated with agitation in other studies. Yu et al.[22] studied postoperative agitation in 2,000 subjects to identify risk factors. Logistic regression analysis identified presence of a GU catheter to be a predictor of agitation (p=0.022). GU catheters can be painful;[23] it is possible that pain or discomfort may have been the source for these findings.

Lower pain ratings were associated with agitation – no other study has similar results. The explanation for this relationship is unclear as the reverse relationship would be expected. Pain has been shown to be correlated with agitation;[24;25] however, measurement of pain, especially in the critically ill, a population that is often nonverbal, is difficult and valid evaluation is often elusive.

Clinical Outcomes

There was no difference between the number of hospital days prior to ICU admission, ICU length of stay, number of hospital days after ICU, and total hospital length of stay in agitated versus non-agitated patients. Non-agitated patients were more likely to be discharged home rather than to a long-term care facility. Patients with delirium, including those with both hyperactive (agitation) and hypoactive delirium, have been shown to have poorer outcomes including cognitive deficits.[26;27] Our overall mean ICU stay (3.9 days) was much shorter than the ICU length of stay reported by others' 6 days[1;4] and longer.[2;3] Other studies have reported agitation associated with a prolonged ICU stay.[1;2] Different findings can be attributed to

86

differences in populations, agitation measurement, or differences in clinical trends. Of agitated ICU patients, we did not find increased in-hospital mortality. Our mortality rate (19%) was generally similar to others.[1-3]

Adverse events and rates were similar to other studies. Our unplanned or self-extubation rate (15%) was similar to Jaber[2] (17%); however, Woods[1] (26%) was higher. Differences in the sample population and agitation determination could account for the varying rates.

Overall the majority of predictors of agitation on admission as well as 24 hours prior to agitation are clinical in nature. This allows considerable opportunity for intervention to ameliorate or prevent agitation. Current efforts to evaluate need for GU catheters daily and to remove GU catheters as soon as feasible are recommended to reduce catheter-associated urinary tract infection risk. There may be an added benefit of reducing agitation. Current guidelines to reduce ventilator-associated pneumonia encourage backrest elevations greater than 30°. Backrest elevation may result in decreased patient severity of illness and improved oxygenation, with the advantage of diminishing agitation. Limiting restraint use for patients, considered a nurse-sensitive quality indicator by the National Quality Forum,[28] improves patient safety outcomes and may minimize agitation. Using lighter levels of sedation results in improved clinical outcomes (shorter MV, shorter ICU stay, less PTSD, less depression, more accurate assessment of patient issues) and may minimize agitation. Current practice initiatives to gauge readiness for extubation, to facilitate early weaning and shorten ventilator time, may also result in mitigating agitation.

Limitations of the study are due to the retrospective nature - findings are dependent on data completeness and quality, and the data were not originally recorded for research purposes. However, retrospective reviews are also reflective of usual care and allow investigators to examine processes and outcomes as they occur – they monitor in real time integrating multiple data sources. In an effort to mitigate some of the disadvantages, we used a more stringent

definition of agitation – documentation of the word "agitation" or the RASS tool – and used a larger sample size with good general population representation. Factors associated with agitation on admission as well as within 24 hours included use of restraints. We are as of yet unsure what role they play in agitation.

CONCLUSIONS

Agitation is recognized as a serious problem in ICUs. The main findings of this study were that primarily clinical factors were implicated in the onset of agitation. Agitation was not associated with a longer ICU stay or hospital stay but was associated with multiple significant adverse events.

This study contributes new knowledge to the identification of agitation in the medical and surgical ICU patient populations allowing a better understanding of risk factors of agitation. Identification of patients at particularly high risk for developing agitation provides an opportunity to implement preventative strategies to protect patients from self- and iatrogenic-induced injury. Additional research is needed to identify the cause(s) of agitation, interventional therapies for prevention, and treatment once agitation has occurred.

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Vita

Ruth S. Burk, RN, PhD, MS
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PERSONAL INFORMATION

RUTH S. BURK, RN, PhD, MS

Place of birth: Ft. Campbell, Kentucky; US Citizen

Home Address:
7920 Chowning Road
Henrico, Virginia 23294
804-270-5603

LICENSURE AND CERTIFICATIONS

Virginia R.N.: 0001190644 Multi-State Privilege
ANP: expected to sit for board exam July, 2013

Certifications
2010 – 2011   Preparing Future Faculty Program, Certificate of Completion; Virginia
                        Commonwealth University, Richmond, VA.

2013   ACLS for Healthcare Providers
2010   BLS for Healthcare Providers
2002   EMT-B
2000   Virginia Association of Volunteer Rescue Squads Emergency Vehicle Operator Class 3
2000   BTLS Basic

EDUCATION

Virginia Commonwealth University School of Nursing, Richmond, VA; degree BSN; Date 2004;
                        Major: Nursing
Virginia Commonwealth University School of Nursing, Richmond, VA; degree MS; Date 2011;
          Major: Nursing – Adult Nurse Practitioner
Virginia Commonwealth University School of Nursing, Richmond, VA; degree PhD; Date 2013;
          Major: Biobehavioral Clinical Research; Successfully defended dissertation – expected
          date of graduation: May 2013

ACADEMIC EXPERIENCE

2012   Course Instructor: NURS 511 Laboratory Adult Health, VCU School of
               Nursing, Richmond, VA

2011   Course Instructor: NURS 511 Laboratory Adult Health, VCU School of
                  Nursing, Richmond, VA

2004 – 2009   Teaching Assistant to several instructors, Adult Health, VCU School of Nursing,
                  Richmond, VA

MEMBERSHIP - SCIENTIFIC, HONORARY AND PROFESSIONAL SOCIETIES

2006 – present Member, Southern Nursing Research Society
2006 – present Member, American Nurses Association
2003 – present Member, Association of Acute Care Nurses
2001 – present Legislative Coalition of Virginia Nurses

SPECIAL AWARDS, OTHER HONORS

2003 – present Inductee/member, Phi Kappa Phi Honor Society
2004 – present Inductee/member, Sigma Theta Tau International Honor Society of Nursing
2003   Anne Hamilton Moore Scholarship
2003   Phi Kappa Phi Scholarship
2003   Distinguished Service and valuable assistance, VCU Student Nurses'
               Association and the
                  Greater- Richmond community
2001 – 2004   Dean's List (Undergraduate Studies)

<u>External Grants: Funded</u>

Grap, M.J., **Burk, R.S**. Predictors of Agitation in the Critically Ill; National Institute of Nursing
                  Research, F31NR010436, 2 year award, 08/2009 – 08-2011

<u>Research Experience</u>

2009 – 2013   Grap, M.J., Munro, C.L., Schubert, C., Wetzel, P.A. Effect of backrest elevation
                  on skin integrity in the critically ill. National Institute of Nursing Research, R01
                  NR010381.
               VCU School of Nursing, Richmond, VA
               Graduate Research Assistant

2007 – 2009   Grap, M.J., Munro, C.L., Schubert, C., Wetzel, P.A. (Pilot study) Effect of
                  backrest elevation on skin integrity in the critically ill.
               VCU School of Nursing, Richmond, VA
               Graduate Research Assistant

92

2001 – 2009   Grap, M.J., Wetzel, P., Best, A., Munro, C., Sessler, C., Pickler, R. Sedation
               effects in mechanically ventilated patients. National Institute of Nursing
               Research, R01 NR009506
               VCU School of Nursing, Richmond, VA
               Graduate Research Assistant

2003 – 2004   Grap, M.J., Wetzel, P., Best, A., Munro, C., Sessler, C., Pickler, R. (Pilot study)
               Observation of Behavior in Mechanically Ventilated Children
               VCU School of Nursing, Richmond, VA
               Research Assistant

2004 – 2007   Sessler, C.N., Grap, M.J., Munro, C.L., Jefferson, D. Anesthesia Recovery in
               Critical Care (ARC2): Assessing sedation and agitation, Baxter Healthcare
               VCU School of Nursing, Richmond, VA
               Graduate Research Assistant

2005 – 2008   Al-Majid, Pidcoe, P.S. (Pilot study) Effects of Endurance Exercise on
               Biobehavioral Outcomes of Fatigue
               VCU School of Nursing, Richmond, VA
               Research Assistant

2005 – 2007   Affiliation Agreement Research Assistant; Supervisor - Dr. A. DeLellis
               VCU School of Nursing, Richmond, VA

2002 – 2004   Pickler, R. Bottle feeding readiness in preterm infants; National Institute of Nursing Research, 3
               VCU School of Nursing, Richmond, VA;
               Data Personnel
2002   McCain, N. Alternative Stress Management Interventions in HIV Disease, National Center for (
               VCU School of Nursing, Richmond, VA
               Volunteer Research Assistant

MAJOR COMMITTEES

2006 – 2008   Doctoral Program Committee, VCU School of Nursing, Richmond, VA
2001 – 2011   Honor Council; VCU-MCV campus; School of Nursing

OTHER SCHOLARLY, RESEARCH OR ADMINISTRATIVE EXPERIENCE

Review activities
Manuscript Reviewer. Intensive and Critical Care Nursing, 2009 - present
Manuscript Reviewer. Heart & Lung, 2010 - present

BIBLIOGRAPHY

Papers published (refereed journal)
Ruth S. Burk, Grap, M.J. Backrest position in prevention of pressure ulcers and ventilator-
associated pneumonia: Conflicting recommendations. Heart & Lung, 41(6), 536-545.

Publications under review (refereed journal)*:*

Burk, R.S., Grap, M.J., Munro, C.L., Schubert, C., Sessler, C.N.; Agitation in Adult Critically Ill Patients: Significance, Risk Factors, and Evaluation. <u>American Journal of Critical Care</u>.

Burk, R.S., Grap, M.J., Munro, C.L., Schubert, C., Sessler, C.N.; Agitation Onset, Frequency, and Associated Temporal Factors in the Adult Critically Ill. <u>American Journal of Critical Care</u>.

Publications in process:

Burk, R.S., Bataille, A., Pepperl, A., Rooney, M. Grap, M.J., Schubert, C. Effects of subject position and operator on high-frequency ultrasound scan quality.

Lucas, V.S., **Burk, R.S.**, Creehan, S. The use of high frequency ultrasound for dermal tissue investigation.

<u>Poster Presentations</u>

Burk, R., Bataille, A, Rooney, M., Pepperl, A., Grap, M.J., Schubert, C.M. 2013 National Teaching Institute & Critical Care Exposition: Effect of subject position and operator on high-frequency ultrasound scan quality

Burk, R.; Lucas, V; Grap, M.J., 2013 Southern Nursing Research Society Annual Conference: Measuring Skin Integrity Using High Frequency Ultrasound – A Validation Procedure

Burk, R.; Grap, M.J., 2012 State of the Science Congress on Nursing Research: Incidence and Temporal Factors of Agitation in the Critically Ill

Burk, R.S.; Grap, M.J., 2011 Southern Nursing Research Society Annual Conference: Agitation in the Critically Ill

Burk, R.S.; Grap, M.J., 2009 State of the Science Congress on Nursing Research: Predictors of Agitation in the Critically Ill

Burk, R.; Grap, M.J., 2009 Graduate Student Research Symposium: What Do We Really Know About Agitation in the Adult Intensive Care Unit Patient?

Burk, R.; Grap, M.J., 2007 Southern Nursing Research Society Annual Conference: "Backrest Position in Prevention of Ventilator Assisted Pneumonia and Pressure Ulcers: Recommendation Conflict