

Is the Intensive Care Unit Traumatic? What We Know and Don't Know About the Intensive Care Unit and Posttraumatic Stress Responses

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The intensive care unit (ICU) has been portrayed as psychologically stressful, with a growing body of research substantiating elevated rates of depression, posttraumatic stress disorder (PTSD), and other psychological disruptions in populations of critical care survivors. To explain these psychopathology elevations, some have proposed a direct effect of ICU admission upon the later development of psychopathology, whereas others highlight the complex interaction between the trauma of a life-threatening illness or injury and the stressful life-saving interventions often administered in the ICU. However, the conclusion that the ICU is an independent causal factor in trauma-related psychological outcomes may be premature. Current ICU research suffers from important methodological problems including lack of true prospective data, failure to employ appropriate comparison groups, sampling bias, measurement issues, and problems with statistical methodology. In addition, the ICU literature has yet to investigate important risk and resilience factors that have been empirically validated in the broader stress-response literature. The authors propose the application of these important constructs to the unique setting of the ICU. This review focuses on multiple aspects of the important but complex research question of whether the ICU confers risk for psychological distress above and beyond the traumatic impact of the serious health events that necessitate ICU treatment.

Impact and Implications

Does the ICU contribute to psychopathology above and beyond the traumatic nature of the serious health events that necessitate ICU treatment? The current review raises important methodological concerns about the extant scientific literature linking ICU exposure with psychopathology in populations of critical illness survivors. We suggest empirically validated risk and resilience factors for future application to research in the ICU setting. Addressing fundamental research questions such as who is at risk for ICU-related psychopathology and why will have important clinical and policy implications.

Keywords: intensive care unit, trauma, posttraumatic stress disorder, critical care

Introduction

Recent media coverage has drawn attention to elevated rates of posttraumatic stress disorder (PTSD) following treatment in the intensive care unit (ICU; e.g., Hoffman, 2013; Johns Hopkins Medicine, 2013; Lamas, 2013). In addition to these popular char-

acterizations, a growing body of empirical evidence associates ICU treatment with increased risk for later development of psychopathology in critical illness survivors (Boer et al., 2008; Griffiths, Fortune, Barber, & Young, 2007; Schelling et al., 1998). Yet it is difficult to adjudicate whether observed elevations in psychopathology among ICU-treated individuals reflects the effects of specific ICU treatments, the impact of the life-threatening event that brought the individual to the ICU, or an interaction between the two. To complicate matters further, there are many different types of ICUs (e.g., cardiac, vs. neurological, vs. medical) and a diversity of medical events serious enough to precipitate ICU admission (e.g., cardiac events vs. traumatic injuries vs. bacterial infections). These complexities notwithstanding, some investigators have concluded that ICU admission is an independent risk factor for the development of PTSD, even when controlling for other important disease-related factors (e.g., O'Donnell et al., 2010). In this review, we examine the existing evidence related to

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post-ICU stress and symptom responses, highlight methodological gaps in the literature, and recommend avenues for future research to better determine if aspects of ICU treatment provide additive risk for psychopathology over and above other trauma-related factors.

Isolating the ICU Experience as a Stressor

In spite of evidence associating ICU exposure with increased risk for psychopathology, significant methodological issues have impeded the field's ability to parse the effects of distinct ICU risk factors on psychological outcomes. For instance, it is extremely difficult to disentangle the potentially traumatic impact of the ICU patient's presenting problem—a life-threatening injury or infirmity—from the unique impact of ICU treatment conditions. Given that a stay in the ICU often involves debilitating physical states (e.g., organ failure or coma) as well as intense sedation and other acute medical procedures, such circumstances may minimize, obscure, or distort how patients experience or recall their ICU stay. Moreover, a significant proportion of ICU-treated individuals report little or no recollection of the actual time spent in the ICU (Granja et al., 2005), provoking fundamental questions as to how the purported traumatic impact of the ICU environment might be transmitted in the first place.

Interest in the ICU as a research site has grown rapidly in recent years, with a search for scholarly journal articles using keywords *ICU* and *PTSD* yielding a more than fivefold increase in references when comparing the past decade to the previous decade (i.e., 2005–2015 with 1995–2005). However, the current ICU literature remains unsystematic and derives from a diversity of disciplines including emergency medicine, medical psychiatry, psychology, critical care nursing, anesthesiology, and other areas of medical specialization (e.g., cardiology). Further, across these disciplines, ICU studies commonly use different measurement techniques, examine different causal and predictive factors, and use different methodological conventions, that vary widely according to study design, timing of inquiry, and outcomes of interest. For example, the literature has referred to post-ICU psychological distress as divergent syndromes including ICU psychosis (Misak, 2005), postintensive care syndrome (PICS; Davidson, Harvey, Schuller, & Black, 2013), traditional PTSD (Davydow, Gifford, Desai, Needham, & Bienvenu, 2008), and post-psychosis PTSD (Wade et al., 2014).

To facilitate the organization of this literature,¹ we put forth a conceptual overview (see Figure 1), parsing areas of empirical inquiry into three main domains: (a) ICU-specific factors (predictors), which have been suggested as potentially harmful influences on post-ICU psychological health, (b) psychological outcomes, explored in the literature as putative downstream consequences of ICU treatment and critical illness, and (c) risk and resilience factors, including many constructs yet to be explored in the context of the ICU, but which present promising avenues to future research.

Evidence for Predictors of Post-ICU Psychopathology

Estimates of the prevalence of PTSD following ICU treatment vary greatly, with a recent systematic review citing rates ranging from 5–64% (Griffiths et al., 2007). Other post-ICU psychological

outcomes explored in the literature include depression and anxiety (Davydow, Gifford, Desai, Bienvenu, & Needham, 2009; Rattray, Johnston, & Wildsmith, 2005), delirium (Pandharipande et al., 2006), PTSD (Davydow, Gifford, et al., 2008), sleep abnormalities (Fanfulla et al., 2011), cognitive impairments (Jackson et al., 2007; Carr, 2007), family and social network distress (Jones et al., 2004; Myhren et al., 2009), quality of life (QOL; Dowdy et al., 2005; Granja et al., 2005), and trans-diagnostic general distress (Myhren et al., 2009). Although there is variability across studies, this research has generally focused on a set of medical predictor variables and their relationship with a single type of psychopathology (or cluster of related psychopathologies).

ICU-Specific Factors

The largest body of existing research focuses on ICU medical factors (e.g., medical therapies or interventions), and the relationship such variables play in predicting poor psychological outcomes. A sampling of ICU-specific factors commonly researched for their potential association with psychopathological outcomes include the following: ICU length of stay (LOS), sedation practices (e.g., benzodiazepines or propofol), analgesic practices (generally opioids in the case of pain management), delusional and/or hallucinatory experiences (either related to in-ICU sedative or analgesic therapies and/or consistent with primary medical condition), intubation and reintubation, tracheostomy, MV, pulmonary artery catheter insertion (PAC), and use of physical restraints during ICU treatment (Davydow, Gifford et al., 2008; Davydow, Desai, Needham, & Bienvenu, 2008; Griffiths et al., 2007; Wade, Hardy, Howell, & Mythen, 2013). Across a wide range of studies, including several systematic reviews (Davydow, Gifford, et al., 2008; Griffiths et al., 2007; Wade et al., 2013), a handful of medical factors have emerged as specific features of the ICU environment consistently associated with an array of negative outcomes: sedation regimens, MV (and related intubation practices), and in ICU hallucinations or delusional memories.

Sedation Practices

Sedation practices are a hallmark of ICU medicine and are closely related to the core principals of patient comfort and distress mitigation (Sessler & Varney, 2008). Historically, following the ethos and methodology of the field of general anesthesia, common practice favored deep sedation for ICU patients (Shehabi, Belomo, Mehta, Riker, & Takala, 2013). Generally speaking, it was thought that the medical induction of amnesic states while in the ICU was more humane for patients than allowing them to be lucid enough to permit cogent memories of their time in the ICU (Kress et al., 2003). Of course the primary reason for heavy sedation in the ICU has always been a pragmatic one; medically complex patients necessitate adequate sedation in order to prevent the

¹ For the preparation of this article, we reviewed a large number of empirical studies, the vast majority of which have been discussed elsewhere in either systematic reviews or meta-analyses.

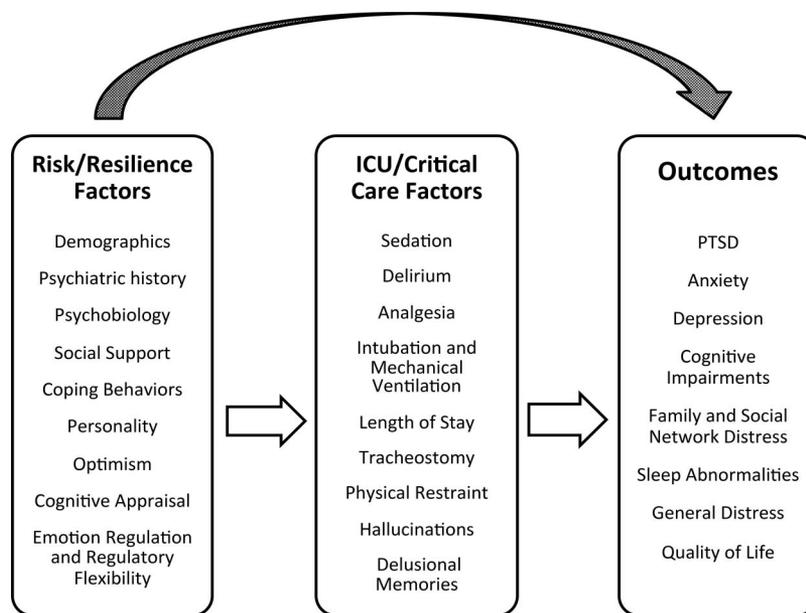


Figure 1. Risk and resilience factors, intensive care unit (ICU)/critical care factors and post-ICU psychological outcomes.

rejection of life-saving medical therapies such as the placement of endotracheal tubes, which facilitate MV.²

In the early to mid-nineties, however, empirical findings began linking excessive sedation with adverse clinical outcomes (e.g., deeper sedation was shown to prolong the length of time patients spent on MV), prompting the publication of the first systematic analgesia and sedation guidelines in 1995 by a joint venture of the American College of Critical Care Medicine (ACCM) and the Society of Critical Care Medicine (SCCM; Shapiro et al., 1995). These guidelines sought to emphasize adequate sedation rather than deep, and advocated for balancing the in-ICU benefits of sedation and analgesia (i.e., management of agitation and pain) with potential downstream risks for adverse outcomes. Subsequent publications of practice parameters (Jacobi et al., 2002; Barr et al., 2013) bolstered previous guidelines with empirical data and began to heavily emphasize not only the medical risks associated with overadministration of in-ICU sedatives (and analgesia), but also adverse psychiatric outcomes, most notably delirium. Despite the changing landscape of sedation theory and practice, the various medical and psychological risks associated with sedation and analgesia administration in the ICU continue to be problematic.

For instance, in a multisite study of ICU patients, Jones et al. (2007) found a direct relationship linking sedation (and analgesic) administration with the development of PTSD at 3-month follow-up. In a study of 43 patients on MV, total dosage of the benzodiazepine lorazepam, was associated with increased risk for elevated PTSD symptom levels at 6-month follow-up (Girard et al., 2007). In another ICU sample of MV patients, individuals who met stringent criteria for high PTSD symptomatology at 2 months were more likely to have been administered midazolam, a benzodiazepine (Samuelson, Lundberg, & Fridlund, 2007). Interestingly, this study found no such association between PTSD symptoms and an alternative sedative, propofol. This finding underscores a broader

debate within the literature pitting benzodiazepines as a class against newer sedatives like propofol, which have different neural mechanisms of action and arguably fewer side effects (Lonardo et al., 2014). In one of the few randomized controlled trials comparing deep sedation with light sedation, Treggiari et al. (2009) found that individuals with deep-sedation group were marginally more likely to have PTSD at 4-weeks. In a sample of ICU survivors of acute lung injury (ALI), depression was found to be associated with a greater mean dosage of benzodiazepines (Dowdy et al., 2009).

Not all studies have found evidence for the putative relationship between sedation and psychopathology. For instance, Weinert and Sprenkle (2008) examined MV patients and failed to find a significant relationship between sedation intensity score and PTSD symptomatology. Given that sedation and analgesia scores in this study were weighted aggregates across drug class (e.g., benzodiazepines vs. opioids) and drug type (e.g., lorazepam, propofol, midazolam), it is possible that the researcher's aggregation methods may have obscured such a relationship.

Recently, strategies for mitigating sedation-related psychopathological risk have emerged, including daily sedation-interruption techniques. These interruption strategies essentially consist of halting a patient's sedation or analgesia for a short period each day, until the patient regains wakefulness or crosses an intolerable pain threshold. Several studies have demonstrated that interruption techniques have positive outcomes, including earlier

² Interestingly, some European ICUs forgo sedation entirely, using padded restraints to achieve toleration of endotracheal intubation and mechanical ventilation (Jones et al., 2007). The risks or benefits of this practice are currently unknown, given the lack of studies comparing United States versus European cohorts matched on similar characteristics.

liberation from MV and decreased risk for PTSD and other psychopathologies (Kress et al., 2003; Parker et al., 2015).

Intubation and MV

(MV, the facilitation of human breathing by a mechanical apparatus, is often achieved via endotracheal tube and sometimes by tracheostomy, and has been identified as a separate risk factor for the development of post-ICU psychopathology. Although the therapies being discussed here are often used in conjunction with one another (e.g., MV generally necessitates sedation in order to be tolerated by patients), MV has been isolated as a unique psychopathology risk factor. In a sample of general ICU survivors, Cuthbertson, Hull, Strachan, and Scott (2004) found a direct correlation between PTSD symptomatology and number of days patients spent on MV. However, the researchers did not find support for a significant relationship between MV and those meeting the clinical cutoff for PTSD diagnosis. In a mixed sample of general, medical, and coronary ICU patients, MV was found to be a predictor of psychological distress, yet MV only predicted short-term distress in this sample, and not long-term PTSD symptomatology at 12-month follow-up (Myhren et al., 2009). In a sample of ICU patients all of whom were intubated and MV, Girard et al. (2007) found that number of days of MV did not significantly predict greater incidence of PTSD symptomatology.

Hallucinations, Delusions, and Memory Problems

At the heart of recent sensationalized coverage of the ICU as psychologically stressful (e.g., Hoffman, 2013), has been the observation that a significant proportion of ICU patients report hallucinatory episodes, consisting of frightening, psychotic, or nightmarish experiences while in the ICU (Jones, Griffiths, Humphris, & Skirrow, 2001). The nature of the relationship between hallucinations or delusions and the eventual development of psychological trauma symptoms is not well understood, although a direct etiologic link to psychological morbidity has been proposed (for a review, see Kiekkas, Theodorakopoulou, Spyrtos, & Baltopoulos, 2010). Prevalence rates of hallucinations and delusions vary widely, ranging between 26% and 73% (Kiekkas et al., 2010), with one recent study focusing on ICU hallucinatory and delusional experiences reporting the presence of delusional or distorted in-ICU memories in 88% of their sample (Wade et al., 2014).

In one of the first studies to substantiate delusional memories as a psychological risk factor, patients with delusional memories related to their ICU stay (as measured by the ICU memory tool), but without factual memories of their time in the ICU were significantly more likely to evidence symptoms of anxiety and depression at 2-weeks postdischarge (Jones et al., 2001). The authors proposed that since those with factual memories were less likely to present with psychological symptoms, perhaps the presence of in-ICU factual memories might buffer patients from later psychological risk. However, future studies have failed to substantiate this claim (e.g., Granja et al., 2008; Weinert & Sprenkle, 2008), and factual memories are no longer presumed to be protective. In another prospective study, the presence of delusional memories in a sample of ICU survivors was significantly correlated with increases in both anxiety and trauma symptoms at 6-month follow-up (Jones et al., 2003).

Both the ICU environment (noises, bells, emergency signals, etc.) and the heavy administration of sedatives (especially benzodiazepines) have been proposed as causal factors for hallucinations and delusions. Weinert and Sprenkle (2008) found a positive linear association between sedation and analgesia administered to a sample of MV patients, and the frequency of delusional memories while in the ICU. These authors also found that patients with the presence of delusional memories were at greater risk for PTSD-like symptoms.

What is perhaps most perplexing for researchers attempting to substantiate the ICU as psychologically stressful is the revelation that many individuals admitted to the ICU report virtually *no* memory that they were ever in the ICU (Wade et al., 2014). Two recent studies evidenced total amnesic states for approximately 18% of patients (Samuelson, Lundberg, & Fridlund, 2006; Weinert & Sprenkle, 2008), whereas another study cited rates of total in-ICU amnesia at a striking 38% (Granja et al., 2005). A study investigating in-ICU amnesia as a possible etiologic factor in ICU-related PTSD found that amnesic states during the ICU predicted posttraumatic stress symptomatology (Granja et al., 2008). However, given that in-ICU amnesia was also associated with longer ICU length of stay, greater illness severity, and greater previous hospital admissions, the authors cautioned that the relationship between ICU-amnesia and PTSD might be a statistical artifact, proposing instead that ICU-amnesia might be a proxy for trauma severity. The absence of in-ICU memories reported by a significant number of study participants presents an interesting problem in the identification of a unique stress profile for the ICU. The question remains as to how the traumatic impact of medical therapies might be transmitted if not at the level of the ICU patient's conscious experience.

Other Evidence: Demographic Risk Factors and Individual History Variables

Consistent with other areas of stress research, demographic and prior biographical characteristics have been examined for their association with psychopathology after ICU exposure.

Demographic variables: Age and gender. Consistent with the broader stress psychopathology literature, both younger age and female gender have been associated with increased risk for PTSD after ICU discharge in many but not all studies (Scragg, Jones, & Fauvell, 2001; Girard et al., 2007). For example, one prospective cohort study of MV patients found that women had significantly higher scores on a measure of posttraumatic stress symptomatology (PTSS) compared with men (Girard et al., 2007, p. 3). In addition, the same study revealed a significant curvilinear relationship with age and PTSS, such that PTSS increased on average between the ages of 30 to 50 years, after which PTSS scores tended to fall off sharply between the ages of 50–80 (Girard et al., 2007, p. 6). The authors speculated that since older individuals are typically less likely to receive aggressive medical care, PTSD might be less likely in older individuals because they receive less “traumatizing” medical care. This hypothesis remains untested in the literature, although it has been substantiated that older individuals are more likely to withhold from surgery, ventilation, and dialysis while in the hospital (e.g., Hamel et al., 1999).

Female gender was a consistent predictor of stress psychopathology in another sample of MV patients 2-months postdischarge

(Samuelson, Lundberg, & Fridlund, 2007). In another sample, 15% of ICU survivors suffered from clinical levels of PTSD, and among those who met criteria for the disorder there were twice as many symptomatic women as men (subsample ratio 2:1; Scragg et al., 2001, p. 12). Scragg et al. (2001) also found evidence for a negative relationship between age and PTSD confirming the association of younger age with greater risk for post-ICU PTSD. Such data is consistent with larger, population-based epidemiological data suggesting women suffer PTSD more than men (Brewin et al., 2000).

There are, however, some data suggesting no relationship between gender and PTSD post-ICU. In a sample of nearly 1,500 traumatically injured ICU survivors, Davydow, Zatzick, et al. (2009) found no evidence that female gender was associated with an increased risk for PTSD.

Psychopathological history: Previous depression, anxiety.

Evidence from the broader literature on aversive life events suggests that previous psychopathology is a consistent predictor of new, stress-related psychopathology (e.g., Ozer et al., 2008), and this relationship has also been observed in samples of ICU-treated individuals (Parker et al., 2015). In a sample of ALI survivors ($N = 186$), Bienvenu et al. (2013) found that previous history of depressive illness was a significant predictor of risk for post-ICU PTSD. Davydow, Zatzick, et al. (2009) also found pre-ICU depressive illness to be a risk factor for PTSD in a sample of nearly 1,500 ICU patients admitted for traumatic injury. Similarly, Cuthbertson et al. (2004) found that treatment-seeking behaviors for psychological distress prior to ICU predicted eventual development of PTSD. It is important to note, however, that each of these studies assessed previous psychiatric history using retrospective accounts, calling into question the extent to which patient reports of previous psychopathology may have been colored by current psychological distress.

Of note, in one study that looked at previous psychological history but did not examine that history's relationship with post-ICU psychopathology, previous psychological problems were a predictor of increased or prolonged sedative administration while in the ICU (Jones et al., 2007). Whereas the authors could only speculate as to why previous history predicted amount of sedative administration, this finding presents an important potential link for future investigation, sparking questions about the variance accounted for by sedation alone (without prior history of psychopathology) in the prediction of PTSD.

Null Findings in the Literature

Amid a number of factors that are *not* predictive of later psychopathology in ICU samples, two variables stand out as particularly relevant to the current review and to the question of whether the ICU carries a unique stress profile: ICU length of stay and illness severity.

ICU length of stay. Across a host of studies examining the variable length of stay (LOS) for its potential relationship with post-ICU psychological distress, only a handful of studies have found evidence for such a link. In one systematic review of post-ICU risk factors for the development of PTSD, Davydow, Gifford, et al. (2008) found that only one of the nine studies assessing LOS reported any association with later development of PTSD. A number of studies have reported an association between

ICU LOS and the development of PTSD or depression, but these findings appear more consistently in populations of patients with Acute Respiratory Distress Syndrome (ARDS; e.g., Davydow, Desai, et al., 2008; Hauer et al., 2009). The isolation of these findings may be related to the specific pathophysiology of ARDS, but this hypothesis has yet to be empirically substantiated. More broadly, however, the variable LOS represents one of the clearest instances of null findings in the general ICU literature.

This finding suggests interesting implications. If the ICU environment were itself a traumatic stressor, it might be expected that incremental increases in exposure would approximate a dose-response relationship, corroborating a link between additive ICU exposure and further adverse outcomes. However, in the general ICU literature, there is little empirical support for the notion that spending more time in an ICU predicts worse outcomes.

Illness severity. Another curious example of null findings is found in studies of severity of illness. In United States ICUs, illness severity is most commonly indexed using a revised version of the Acute Physiology and Chronic Health Evaluation system (APACHE II; Knaus, Draper, Wagner, & Zimmerman, 1985), a disease classification system designed to help more accurately predict hospital mortality rates. To achieve a numerical rating, the disease classification system uses 12 physiologic markers (including temperature, blood pressure, heart rate, white blood-cell count, and the Glasgow Coma Score) as well as chronic health status and age. Three recent systematic reviews examining ICU-related PTSD found little support for a direct relationship between illness severity as indexed by APACHE II scores, and the eventual development of PTSD (Davydow, Gifford, et al., 2008; Griffiths et al., 2007; Wade et al., 2013).

At first glance, this aggregate evidence seems definitive and an argument might be made for dispensing with the examination of illness severity and its impact on post-ICU psychological outcomes. However, this conclusion seems both premature and lacking in sound theoretical basis when considering evidence from the broader PTSD literature, in which trauma severity has been associated with the development of PTSD (e.g., Brewin et al., 2000). The answer as to why illness severity has not been more effective in predicting downstream psychological morbidity may very well rest with problems attendant to the measurement of the construct. When the APACHE II scoring system is scrutinized more closely—especially as it pertains to the type of sensitivity and precision required for research—some major flaws become apparent.

The APACHE II system was designed to facilitate the comparison of different medical therapies for groups of similarly ill individuals, and to better predict mortality rates in the hospital (Knaus et al., 1985). However, despite its widespread use, little is known about the reliability and validity of the APACHE II (Polderman, Girbes, Thijs, & Strack van Schijndel, 2001). The APACHE II has come under criticism for excessive false positive rates when used to predict individual mortality (with overprediction rates as high as 25%), and critics suggest that it should not be used to predict outcomes at the individual level (Wong, Barrow, Gomez, & McGuire, 1996). Even more disconcerting, one rigorous study of APACHE II implementation in the ICU found APACHE II scores were overestimated in a striking 51% of ICU cases ($N = 186$; Polderman et al., 2001). In addition, it was found that another 26% of the sample's APACHE II scores were underestimated, leading the authors to conclude that as implemented in everyday

ICU clinical practice, wide variability exists in the accuracy of APACHE II estimates. These findings fundamentally call into question the instrument's reliability, the justification of its use for the prediction of downstream psychological outcomes, and the trustworthiness of the conclusion that in-ICU illness severity does not meaningfully predict variance in later psychological outcomes.

Although empirical evidence supports the view that certain ICU-specific medical factors, demographic variables, and previous psychopathology confer greater risk for post-ICU psychopathology, there has been virtually no investigation into underlying psychological variables which may be protective in the face of the acute stress of ICU. In the last decade, significant progress has been made in the study of resilience to acute stressors, and a growing body of important risk and resilience factors have been identified. The next section will discuss variables identified in the resilience literature, suggested as important avenues to future research in the ICU.

Protective Factors Associated With Resilient Outcomes

Focusing on ICU-specific risk factors is a priority in the context of the critical care environment, given that such factors may be preventable and within the ability of the larger medical community to curb. For example, in the face of evidence linking sedation regimens with psychopathology, ICU sedation guidelines have been changing in recent years (Shehabi et al., 2013). Although the examination of risk factors associated with the ICU has been extensive and continues to evolve, few studies to date have examined whether individual difference variables (either endogenous psychological variables or exogenous environmental factors) may play a role in how people cope with the stress of the ICU. In addition, there has been little to no ICU research investigating protective factors known to be associated with resilient outcomes in other stress-response contexts. We consider below the application of a growing body of evidence from the literatures focusing on coping, emotional flexibility, and resilience, to the ICU setting to better understand and predict resilient outcomes after ICU exposure. The following is a summary of predictors and protective factors associated with resilient outcomes, now well established in the stress-response literature, which we propose for future directions in ICU research.

Emotion Regulation and Regulatory Flexibility

Emotion regulation refers broadly to the varied ways in which individuals experience, influence, and express their emotions across differing contexts (Gross, 1998). Deficits in emotion regulation have been implicated across many psychopathologies and may play an important etiologic role (Aldao, Nolen-Hoeksema, & Schweizer, 2010). *Expressive flexibility* is a related domain pertaining to an individual's ability to either enhance or suppress emotion across differing contexts (Bonanno, Papa, Lalande, Westphal, & Coifman, 2004). Evidence suggests a relationship between expressive flexibility and resilient outcomes in the face of acute life stress (Bonanno et al., 2004; Westphal et al., 2010). Likewise, difficulties with expressive flexibility have been linked to chronic psychopathology (e.g., Gupta & Bonanno, 2011). The importance of flexibility in emotion regulation has been emphasized by Bonanno and Burton (2013), who proposed an integrative framework

known as *regulatory flexibility* for understanding how different emotion regulation strategies play an adaptive or maladaptive role, depending upon contextual demands.

The study of individual differences in emotion regulation makes sense when feasible in the context of the ICU, given that the ICU presents unique, sometimes stressful demands upon individuals, which likely in turn necessitates the employment of varied regulatory strategies for the management of stress and emotional responsiveness. In addition, the study of emotion regulation would likely facilitate the prediction of psychological distress patterns following ICU exposure, as well as the course of those patterns over time. The overall ability to be flexible in emotional expression, for instance, has been shown to predict the resilient outcomes in the face of the stress of spousal loss (Coifman & Bonanno, 2010). The application of the study of emotion regulation to the ICU setting presents an exciting opportunity for advances in the prediction and understanding of who will do well after ICU exposure and why.

Coping Strategies and Cognitive Appraisals

Cognitive appraisal and coping strategies (Lazarus & Folkman, 1984) have a long history of application in the study of stressful life events, and have been shown to predict psychological adjustment. A recent longitudinal study of spinal cord injury (SCI), found that individuals who appraised SCI as a challenge to be overcome (i.e., used challenge appraisals vs. threat appraisals) were more likely to be in the resilient, low-depression symptom trajectory (Bonanno, Kennedy, Galatzer-Levy, Lude, & Elfström, 2012). Similarly, individuals who were less likely to appraise SCI as a threat were more likely to show a trajectory of stable low-anxiety symptoms over time. Bonanno et al. (2012) also found that coping variables predicted outcome trajectories. Specifically, fighting spirit (making the best of life in the face of aversive events) and acceptance were two coping strategies consistently linked with resilient outcomes and a longitudinal trajectory of low anxiety symptoms. Coping and appraisal processes are important variables in the study of adjustment to serious health events like SCI, and application to the ICU seems both relevant and promising.

Coping Flexibility and Coping Self-Efficacy

Coping flexibility has been conceptualized as an individual's ability to choose from a variety of coping strategies and to flexibly use these strategies to meet changing environmental demands (Cheng, Lau, Chan, 2014). Analogously to the regulatory flexibility model of emotion regulation (Bonanno & Burton, 2013), an individual's coping flexibility depends upon access to a diverse repertoire of strategies as well as upon the skillful deployment of coping strategies across contexts. Empirical evidence suggests that coping flexibility has a positive relationship with psychological well-being and predicts decreases in psychological distress (Roussi, Krikeli, Hatzidimitriou, & Koutri, 2007; Cheng et al., 2012; Cheng et al., 2014). In a sample of gastro-intestinal cancer patients, for example, Cheng et al. (2012) found that individuals who varied coping strategies to meet changing contextual demands reported more psychological well-being than individuals who uniformly (i.e., fixedly) applied a passive coping strategy. Similarly,

empirical evidence suggests that breast cancer patients who flexibly use varied coping strategies are less likely to be psychologically distressed (Roussi et al., 2007).

Coping self-efficacy is a related domain and refers broadly to an individual's confidence in their ability to cope with the sequelae (both minor and major) of aversive life events. It has recently been shown that coping self-efficacy is associated with resilience to traumatic stress pathology (deRoon-Cassini, Mancini, Rusch, & Bonanno, 2010). In a study of single-incident traumatic injury survivors followed longitudinally after hospital admission, individuals high on a measure of coping self-efficacy were more likely to be in the resilient trajectory, compared with the chronically distressed trajectory (deRoon-Cassini et al., 2010).

Optimism and Other Personality Variables

Optimism has been proposed as a protective factor in the face of acute life stress, with empirical data substantiating an association between optimism and resilient outcomes. In a longitudinal study of psychological distress after breast cancer diagnosis, Lam et al. (2010) found that decreased optimism was associated with a pattern of chronic distress over time. Likewise, Galatzer-Levy and Bonanno (2014) found that optimism predicted longitudinal trajectories of depression after heart attack incidence, with optimistic individuals being more likely to be resilient (i.e., demonstrate a pattern of stable, low depression symptoms over time) compared with other more depressed symptom profiles. Optimism has been examined in a handful of ICU studies, including one in which trait optimism predicted both anxiety and depression scores at 1-year follow up (Myhren et al., 2009). In general, broader personality traits have also been associated with greater resilience to PTSD, including extraversion and conscientiousness, whereas neuroticism and negative emotionality have been positively associated with PTSD development (Jakšić, Brajković, Ivezic, Topić, & Jakovljević, 2012).

Social Support

Social support has been a variable of considerable focus within the stress response literature, and evidence suggests it may play an important protective role against the development of PTSD (Brewin et al., 2000). Social support has been empirically associated with resilient trajectories across a diversity of traumatic events, including natural disasters (Bonanno, Galea, Bucchiarelli, & Vlahov, 2007; Bonanno, Brewin, Kaniasty, & Greca, 2010), the SARS bio-epidemic (Bonanno et al., 2008), and combat deployment (Pietrzak et al., 2010). A small handful of studies have examined social support as a protective factor within the ICU setting (e.g., Deja et al., 2006; Jones et al., 2003), although this body of research is still developing. One study found that social support was significantly negatively associated with PTSD symptoms in a sample of ICU patients admitted for ARDS (Deja et al., 2006). This association in ICU-treated individuals between social support and decreased psychological distress presents another promising avenue for future research, though further exploration is needed before broader conclusions may be drawn.

Psychobiology

Without exception, individuals admitted to the ICU are in the throes of a physically life-threatening event requiring both signif-

icant medical treatment and the recruitment of the body's innate immune response. In this way, ICU patients may differ from other types of individuals who are exposed to a life-threatening event but are not physically injured or for whom the physical injury is superficial. Interestingly, the immune system and central nervous system responses to environmental stressors instantiated in the Hypothalamic-Pituitary-Adrenal (HPA) Axis response are closely coupled. Specifically, glucocorticoids are distributed throughout the body through blood following release from the HPA-Axis altering expression patterns of genes that drive inflammation, and ultimately leading to broad suppression of proinflammatory gene networks and antiviral programmed gene responses. Further, the brain's detection of proinflammatory and antiviral cytokines in the periphery stimulates the release of glucocorticoids (Sorrells & Sapolsky, 2007). The close relationship between innate immune and innate stress responses may help to explain why classes of drugs such as steroids suppress both inflammation and alter stress reactivity with the likely mechanism of action being the suppression of the glucocorticoid release from the HPA-Axis (Miller, Cohen, & Ritchey, 2002; Raison & Miller, 2003; Singh, Petrides, Gold, Chrousos, & Deuster, 1999; Wirtz et al., 2007; Yehuda, Yang, Buchsbaum, & Golier, 2006). Indeed, some researchers have already begun to experiment with the administration of glucocorticoids to ICU patients, with the goal of dampening stress responsivity and decreasing the incidence of PTSD following critical care treatment (Schelling et al., 2006; Hauer et al., 2014). The complex relationship between the inflammatory, immune, and innate stress responses via the central nervous system represent another exciting avenue for future exploration, and ICU-treated individuals represent a unique population within which to explore these important psychobiological factors.

Taken together, the above variables represent a sampling of risk and resilience factors from the broader stress-response literature that seem particularly applicable to the ICU environment. Many of the above constructs, which may play a role in buffering or moderating stress responsivity in the context of the ICU, have been designed to be measured both with experimental paradigms as well as self-report instruments (e.g., expressive flexibility has been examined both with a computer-based experimental paradigm, as well as with a validated and reliable questionnaire; Burton & Bonanno, 2015). As such, they present cost-effective and time-efficient constructs for examination in future ICU research protocols. The application and study of these novel constructs in the context of the ICU will also increase the relevance of ICU research to developing theory and methods elsewhere in the literature.

Methodological Issues

Despite evidence associating ICU-specific factors with psychopathology, the question remains of how to adjudicate whether the ICU confers risk for broad ranging psychopathologies above and beyond the risk associated with the traumatic life event that compelled ICU treatment. We propose a number of methodological advances consistent with approaches used to answer similarly complex questions about the etiology of heterogeneous responses to extreme stressors.

True Prospective Data

Access to informative pre-ICU data would represent a significant methodological advance. Exposure to a traumatic life event often temporally precedes the ICU stay itself, in some cases by a significant margin. Patients are often admitted to the ICU following downstream health deterioration arising from complications with a primary medical intervention or health condition (e.g., bacterial infection at a surgical site). True prospective data would help to adjudicate whether such individuals were experiencing psychological distress before the traumatic event, directly in relation to the impact of the traumatic life event, or whether the distress appeared to intensify after exposure to the intensive care setting. These methods might in turn facilitate the arbitration of what portion of variance in psychological outcomes is accounted for primarily by the original stressful life event, additively after ICU exposure, or by previous psychological morbidity.

The necessity of pretraumatic (i.e., true prospective) data on psychological functioning has been emphasized in the broader stress-response and PTSD literatures (Bonanno, 2004; Bonanno, Westphal, & Mancini, 2011). However, although large epidemiological research projects have become more common (e.g., Health and Retirement Study; University of Michigan), these United States data sets have typically not included the necessary variables to address ICU-related questions (i.e., ICU admission, length of stay, and trauma symptom measures). However, at least one European study has used the use of large population-based samples to assess the impact of previous psychological morbidity upon post-ICU psychopathology. Using data from Danish national medical databases, Wunsch et al. (2014) found that MV patients without a prior psychiatric history were at increased risk for psychopathology following ICU treatment.

Equivalent Comparison Groups

Another significant methodological advance would be the employment of an equivalent comparison group. This solution necessitates two groups: one exposed to the ICU and the other a comparison group, consisting of individuals with comparable injuries or health events, yet importantly without ICU admission.³ At least one study has attempted this scientifically rigorous experimental design to good effect by comparing two samples of non-fatal injury patients, one with ICU admission and one without (O'Donnell et al., 2010). This study showed that admission to the ICU was associated with a threefold increase in PTSD risk. An unavoidable limitation of such a design is that statistical control is not the same as experimental control. Among other differences, the two groups differed on illness severity scores and hospital LOS, which while statistically controlled for, may indicate that the samples were different in other important and unmeasured ways. Nevertheless, the authors' rigorous study design allowed them to conclude that ICU admission itself is a risk factor for PTSD (O'Donnell et al., 2010).

A substantial problem in applying this study design more broadly is that most health events necessitating ICU treatment are very serious and are rarely treated elsewhere. Again we consider such cases as a major cardiac event or stroke, or a serious bacterial infection that has entered into the bloodstream (sepsis). These conditions are life-threatening and require specialized and advanced medicine in order to stabilize patients who are suffering

from them. A group of patients with these qualifying conditions leaves very little possibility for an adequate comparison group with both the presence of a comparably stressful health event, but without ICU exposure.

One possible solution to this dilemma is to compare two separate samples, both treated in ICUs, but from parts of the country (or the world) where medical interventions differ substantially. Reportedly in parts of Europe, for instance, MV is not achieved by heavy sedation. Rather, these ICUs use physical restraints to ensure that ventilation tubes are not removed by agitated or especially uncomfortable patients (Jones et al., 2007). The comparison of United States and European samples (ideally matched on important subject variables) with these distinct between-subjects differences might significantly improve the ability to answer questions about the relative contribution of sedation and/or physical restraints to patients' psychological distress. However, this scenario also invokes the possibility of problematic cultural confounds (Scandinavian countries, for instance, have a much higher relative standard of living). However, a rigorously designed study with proper matching for important subject variables (e.g., socioeconomic status, ethnicity, etc.) might begin to address such confounds effectively.

In general, very little current ICU research uses comparison groups of any kind, though there are likely creative ways to counteract this deficit. For instance, it should be possible to select individuals exposed to a particular form of medical intervention and to compare these individuals with similar ICU patients who did not receive such treatments. Within a single ICU site, it should be theoretically possible to compare individuals who received MV therapy with a group of individuals who were not MV. Instead, most studies examining MV in the literature use it as an inclusion criterion (e.g., Samuelson et al., 2007), rather than seeking to find a methodologically sound, meaningful comparison group. The systematic comparison of patients with and without certain ICU medical therapies would substantially contribute to the field's ability to parse the unique contributions of specific ICU medical therapies to downstream psychiatric risk.

Sampling Bias

In terms of ICU sampling procedures, two main problems exist. First, as aforementioned, many published ICU studies have highly specific samples, selected for a specific medical condition (e.g., ARDS or patients requiring MV). Although this makes sense from the perspective of researching the unique profile of specific medical conditions, it does little to advance the field's understanding of the overall prevalence rates of PTSD or other psychological problems after intensive care treatment. Further, without sound population estimates of the risk for the development of these disorders after ICU treatment, it becomes difficult to meaningfully assess which specific medical conditions carry the highest psychological burden.

A second problem with ICU samples rests in the significant mortality rates attendant to this population. In general, ICU studies

³ According to classical experimental theory, this is known as a *non-equivalent comparison group design* (Campbell, Stanley, & Gage, 1963). The lack of random assignment classifies this design as quasi-experimental.

lose approximately 40% of the initial sample due to death. Although no comprehensive solution for addressing mortality rates in this population has been proposed (since this is naturally a very sick population), questions arise as to substantial statistical differences between study completers and individuals who died over the course of the study. At the very least, all research conducted in this context should report differences in the sample of survivors compared with those who die during the course of the study. Instead, very few studies conduct adequate sample comparisons to control for threats to internal validity due to attrition.

Measurement Problems

Problems with the APACHE II system have already been proposed, and the usage of APACHE II as an appropriate measure of subjective illness severity has been called into question earlier in this review. It seems evident that although the APACHE II system may be useful in algorithms predicting hospital mortality rates, it may lack the reliability and sensitivity necessary to be used in the prediction of more distal outcomes such as trauma-related psychopathology. Further, it is also possible that the APACHE system may not be an appropriate metric when assessing the psychological impact of a particular individual's health condition (even were it possible to reduce the sources of systematic error in the implementation). APACHE II scores may instantiate a valid and reliable index of medical severity, but not of how severe these health conditions are on a human scale, either subjectively or as seen by other people. To address this hypothesis, it would be important to contrast ICU-treated individual's self-rated health with a doctor or nurse's rating of illness severity, which might in turn be compared to APACHE II scores to see if the three measurement techniques converge.

Conclusions

The ICU experience has been characterized as psychologically stressful by the popular media while the extant empirical literature has highlighted elevations in PTSD symptoms following ICU exposure. However, little research to date has tried to meaningfully parse the variance in psychopathology associated with the impact of the health event precipitating ICU admission from the variance in outcomes associated with ICU-specific medical therapies. It remains possible that the range of ICU therapies currently associated with increased psychological morbidity in the literature are acting largely as proxies for stressor severity. Although the literature to date does not support the conclusion that illness severity is a predictor of psychopathology, problems with measurement may account for some of this failure. Further, the conclusion that increased exposure to the ICU environment predicts worse outcomes fundamentally lacks empirical basis, given null findings for a dose-response relationship in the general ICU literature.

Although the development of new tools for saving lives is clearly an important priority, individuals are now living longer lives after ICU treatment and thus understanding the psychological impact of the ICU experience becomes an important and worthy research goal. As the area of inquiry surrounding the ICU increases in breadth, the application of new constructs to the ICU environment will facilitate better understanding of how individual differences interact with the ICU treatment factors. These factors should

include important risk and resilience factors explored elsewhere in the stress-response literature. Finally, sound methodological improvements such as those reviewed here can substantively contribute to the field's ability to parse such fundamental questions as who will do poorly after a trip to the ICU and why.

References

- Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical Psychology Review, 30*, 217–237. <http://dx.doi.org/10.1016/j.cpr.2009.11.004>
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gélinas, C., Dasta, J. F., . . . the American College of Critical Care Medicine. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical Care Medicine, 41*, 278–306. <http://dx.doi.org/10.1097/CCM.0b013e3182783b72>
- Bienvenu, O. J., Gellar, J., Althouse, B. M., Colantuoni, E., Sricharoenchai, T., Mendez-Tellez, P. A., . . . Needham, D. M. (2013). Post-traumatic stress disorder symptoms after acute lung injury: A 2-year prospective longitudinal study. *Psychological Medicine, 43*, 2657–2671.
- Boer, K. R., van Ruler, O., van Emmerik, A. A., Sprangers, M. A., de Rooij, S. E., Vroom, M. B., . . . the Dutch Peritonitis Study Group. (2008). Factors associated with posttraumatic stress symptoms in a prospective cohort of patients after abdominal sepsis: A nomogram. *Intensive Care Medicine, 34*, 664–674. <http://dx.doi.org/10.1007/s00134-007-0941-3>
- Bonanno, G. A. (2004). Loss, trauma, and human resilience: Have we underestimated the human capacity to thrive after extremely aversive events? *American Psychologist, 59*, 20–28. <http://dx.doi.org/10.1037/0003-066X.59.1.20>
- Bonanno, G. A., Brewin, C. R., Kaniasty, K., & Greca, A. M. (2010). Weighing the costs of disaster: Consequences, risks, and resilience in individuals, families, and communities. *Psychological Science in the Public Interest, 11*, 1–49. <http://dx.doi.org/10.1177/1529100610387086>
- Bonanno, G. A., & Burton, C. L. (2013). Regulatory flexibility: An individual differences perspective on coping and emotion regulation. *Perspectives on Psychological Science, 8*, 591–612. <http://dx.doi.org/10.1177/1745691613504116>
- Bonanno, G. A., Galea, S., Bucciarelli, A., & Vlahov, D. (2007). What predicts psychological resilience after disaster? The role of demographics, resources, and life stress. *Journal of Consulting and Clinical Psychology, 75*, 671–682. <http://dx.doi.org/10.1037/0022-006X.75.5.671>
- Bonanno, G. A., Ho, S. M., Chan, J. C., Kwong, R. S., Cheung, C. K., Wong, C. P., & Wong, V. C. (2008). Psychological resilience and dysfunction among hospitalized survivors of the SARS epidemic in Hong Kong: A latent class approach. *Health Psychology, 27*, 659.
- Bonanno, G. A., Kennedy, P., Galatzer-Levy, I. R., Lude, P., & Elfström, M. L. (2012). Trajectories of resilience, depression, and anxiety following spinal cord injury. *Rehabilitation Psychology, 57*, 236–247. <http://dx.doi.org/10.1037/a0029256>
- Bonanno, G. A., Papa, A., Lalande, K., Westphal, M., & Coifman, K. (2004). The importance of being flexible: The ability to both enhance and suppress emotional expression predicts long-term adjustment. *Psychological Science, 15*, 482–487. <http://dx.doi.org/10.1111/j.0956-7976.2004.00705.x>
- Bonanno, G. A., Westphal, M., & Mancini, A. D. (2011). Resilience to loss and potential trauma. *Annual Review of Clinical Psychology, 7*, 511–535.
- Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults.

- Journal of Consulting and Clinical Psychology*, 68, 748–766. <http://dx.doi.org/10.1037/0022-006X.68.5.748>
- Burton, C. L., & Bonanno, G. A. (2015). Measuring ability to enhance and suppress emotional expression: The flexible regulation of emotional expression (FREE) scale. *Psychological Assessment*. <http://dx.doi.org/10.1037/pas0000231>
- Campbell, D. T., Stanley, J. C., & Gage, N. L. (1963). *Experimental and quasi-experimental designs for research*. Boston, MA: Houghton Mifflin.
- Carr, J. (2007). Psychological consequences associated with intensive care treatment. *Trauma*, 9, 95–102. <http://dx.doi.org/10.1177/1460408607083963>
- Cheng, C., Chan, N. Y., Chio, J. H. M., Chan, P., Chan, A. O. O., & Hui, W. M. (2012). Being active or flexible? Role of control coping on quality of life among patients with gastrointestinal cancer. *Psycho-Oncology*, 21, 211–218. <http://dx.doi.org/10.1002/pon.1892>
- Cheng, C., Lau, H. P. B., & Chan, M. P. S. (2014). Coping flexibility and psychological adjustment to stressful life changes: A meta-analytic review. *Psychological Bulletin*, 140, 1582–1607. <http://dx.doi.org/10.1037/a0037913>
- Coifman, K. G., & Bonanno, G. A. (2010). When distress does not become depression: Emotion context sensitivity and adjustment to bereavement. *Journal of Abnormal Psychology*, 119, 479–490. <http://dx.doi.org/10.1037/a0020113>
- Cuthbertson, B. H., Hull, A., Strachan, M., & Scott, J. (2004). Post-traumatic stress disorder after critical illness requiring general intensive care. *Intensive Care Medicine*, 30, 450–455. <http://dx.doi.org/10.1007/s00134-003-2004-8>
- Davidson, J. E., Harvey, M. A., Schuller, J., & Black, G. (2013). Post-intensive care syndrome: What it is and how to help prevent it. *American Nurse Today*, 8(5). Retrieved from <http://www.americannursetoday.com/>
- Davydow, D. S., Desai, S. V., Needham, D. M., & Bienvenu, O. J. (2008). Psychiatric morbidity in survivors of the acute respiratory distress syndrome: A systematic review. *Psychosomatic Medicine*, 70, 512–519. <http://dx.doi.org/10.1097/PSY.0b013e31816aa0dd>
- Davydow, D. S., Gifford, J. M., Desai, S. V., Bienvenu, O. J., & Needham, D. M. (2009). Depression in general intensive care unit survivors: A systematic review. *Intensive Care Medicine*, 35, 796–809. <http://dx.doi.org/10.1007/s00134-009-1396-5>
- Davydow, D. S., Gifford, J. M., Desai, S. V., Needham, D. M., & Bienvenu, O. J. (2008). Posttraumatic stress disorder in general intensive care unit survivors: A systematic review. *General Hospital Psychiatry*, 30, 421–434. Retrieved from <http://www.sciencedirect.com/science/article/pii/S0163834308000807>
- Davydow, D. S., Zatzick, D. F., Rivara, F. P., Jurkovich, G. J., Wang, J., Roy-Byrne, P. P., . . . MacKenzie, E. J. (2009). Predictors of posttraumatic stress disorder and return to usual major activity in traumatically injured intensive care unit survivors. *General Hospital Psychiatry*, 31, 428–435. <http://dx.doi.org/10.1016/j.genhosppsych.2009.05.007>
- Deja, M., Denke, C., Weber-Carstens, S., Schröder, J., Pille, C. E., Hokema, F., . . . Kaisers, U. (2006). Social support during intensive care unit stay might improve mental impairment and consequently health-related quality of life in survivors of severe acute respiratory distress syndrome. *Critical Care (London, England)*, 10(5), R147. <http://dx.doi.org/10.1186/cc5070>
- DeRoon-Cassini, T. A., Mancini, A. D., Rusch, M. D., & Bonanno, G. A. (2010). Psychopathology and resilience following traumatic injury: A latent growth mixture model analysis. *Rehabilitation Psychology*, 55, 1–11. <http://dx.doi.org/10.1037/a0018601>
- Dowdy, D. W., Bienvenu, O. J., Dinglas, V. D., Mendez-Tellez, P. A., Sevransky, J., Shanholtz, C., & Needham, D. M. (2009). Are intensive care factors associated with depressive symptoms 6 months after acute lung injury? *Critical Care Medicine*, 37, 1702–1707. <http://dx.doi.org/10.1097/CCM.0b013e31819fea55>
- Dowdy, D. W., Eid, M. P., Sedrakyan, A., Mendez-Tellez, P. A., Pronovost, P. J., Herridge, M. S., & Needham, D. M. (2005). Quality of life in adult survivors of critical illness: A systematic review of the literature. *Intensive Care Medicine*, 31, 611–620. <http://dx.doi.org/10.1007/s00134-005-2592-6>
- Ehring, T., & Quack, D. (2010). Emotion regulation difficulties in trauma survivors: The role of trauma type and PTSD symptom severity. *Behavior Therapy*, 41, 587–598. <http://dx.doi.org/10.1016/j.beth.2010.04.004>
- Fanfulla, F., Ceriana, P., D'Artavilla Lupo, N., Trentin, R., Frigerio, F., & Nava, S. (2011). Sleep disturbances in patients admitted to a step-down unit after ICU discharge: The role of mechanical ventilation. *Sleep: Journal of Sleep and Sleep Disorders Research*, 34, 355–362.
- Galatzer-Levy, I. R., & Bonanno, G. A. (2014). Optimism and death: Predicting the course and consequences of depression trajectories in response to heart attack. *Psychological Science*, 25, 2177–2188.
- Galatzer-Levy, I., Burton, C. L., & Bonanno, G. A. (2012). Coping flexibility, potentially traumatic life events, and resilience: A prospective study of college student adjustment. *Journal of Social and Clinical Psychology*, 31, 542–567. <http://dx.doi.org/10.1521/jscp.2012.31.6.542>
- Girard, T. D., Shintani, A. K., Jackson, J. C., Gordon, S. M., Pun, B. T., Henderson, M. S., . . . Ely, E. W. (2007). Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: A prospective cohort study. *Critical Care (London, England)*, 11(1), R28. <http://dx.doi.org/10.1186/cc5708>
- Granja, C., Gomes, E., Amaro, A., Ribeiro, O., Jones, C., Carneiro, A., . . . the JMIP Study Group. (2008). Understanding posttraumatic stress disorder-related symptoms after critical care: The early illness amnesia hypothesis. *Critical Care Medicine*, 36, 2801–2809. <http://dx.doi.org/10.1097/CCM.0b013e318186a3e7>
- Granja, C., Lopes, A., Moreira, S., Dias, C., Costa-Pereira, A., Carneiro, A., & the JMIP Study Group. (2005). Patients' recollections of experiences in the intensive care unit may affect their quality of life. *Critical Care (London, England)*, 9(2), R96–R109. <http://dx.doi.org/10.1186/cc3026>
- Griffiths, J., Fortune, G., Barber, V., & Young, J. D. (2007). The prevalence of post traumatic stress disorder in survivors of ICU treatment: A systematic review. *Intensive Care Medicine*, 33, 1506–1518.
- Gross, J. J. (1998). The emerging field of emotion regulation: An integrative review. *Review of General Psychology*, 2, 271–299. <http://dx.doi.org/10.1037/1089-2680.2.3.271>
- Gupta, S., & Bonanno, G. A. (2011). Complicated grief and deficits in emotional expressive flexibility. *Journal of Abnormal Psychology*, 120, 635–643. <http://dx.doi.org/10.1037/a0023541>
- Hamel, M. B., Teno, J. M., Goldman, L., Lynn, J., Davis, R. B., Galanos, A. N., . . . the SUPPORT Investigators. (1999). Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. Patient age and decisions to withhold life-sustaining treatments from seriously ill, hospitalized adults. *Annals of Internal Medicine*, 130, 116–125. <http://dx.doi.org/10.7326/0003-4819-130-2-199901190-00005>
- Hauer, D., Kaufmann, I., Stewe, C., Briegel, I., Campolongo, P., & Schelling, G. (2014). The role of glucocorticoids, catecholamines and endocannabinoids in the development of traumatic memories and post-traumatic stress symptoms in survivors of critical illness. *Neurobiology of Learning and Memory*, 112, 68–74.
- Hauer, D., Weis, F., Krauseneck, T., Vogeser, M., Schelling, G., & Roozendaal, B. (2009). Traumatic memories, post-traumatic stress disorder and serum cortisol levels in long-term survivors of the acute respiratory distress syndrome. *Brain Research*, 1293, 114–120. <http://dx.doi.org/10.1016/j.brainres.2009.04.014>
- Hoffman, J. (2013, July 23). Nightmares after the I. C. U. *The New York Times*, p. D1. Retrieved from <http://nytimes.com>

- Irwin, M. R., & Cole, S. W. (2011). Reciprocal regulation of the neural and innate immune systems. *Nature Reviews Immunology*, *11*, 625–632. <http://dx.doi.org/10.1038/nri3042>
- Jacobi, J., Fraser, G. L., Coursin, D. B., Riker, R. R., Fontaine, D., Wittbrodt, E. T., . . . Lumb, P. D. (2002). Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Critical Care Medicine*, *30*, 119–141.
- Jackson, J. C., Obremskey, W., Bauer, R., Greevy, R., Cotton, B. A., Anderson, V., . . . Ely, E. W. (2007). Long-term cognitive, emotional, and functional outcomes in trauma intensive care unit survivors without intracranial hemorrhage. *The Journal of Trauma*, *62*, 80–88. <http://dx.doi.org/10.1097/TA.0b013e31802ce9bd>
- Jakšić, N., Brajković, L., Ivezić, E., Topić, R., & Jakovljević, M. (2012). The role of personality traits in posttraumatic stress disorder (PTSD). *Psychiatria Danubina*, *24*, 256–266.
- Johns Hopkins Medicine. (2013, February 26). PTSD symptoms common among ICU survivors. *ScienceDaily*. Retrieved from www.sciencedaily.com/releases/2013/02/130226081238.htm
- Jones, C., Bäckman, C., Capuzzo, M., Flaatten, H., Rylander, C., & Griffiths, R. (2007). Precipitants of post-traumatic stress disorder following intensive care: A hypothesis generating study of diversity in care. *Intensive Care Medicine*, *33*, 978–985.
- Jones, C., Griffiths, R. D., Humphris, G., & Skirrow, P. M. (2001). Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Critical Care Medicine*, *29*, 573–580. <http://dx.doi.org/10.1097/00003246-200103000-00019>
- Jones, C., Skirrow, P., Griffiths, R. D., Humphris, G. H., Ingleby, S., Eddleston, J., . . . Gager, M. (2003). Rehabilitation after critical illness: A randomized, controlled trial. *Critical Care Medicine*, *31*, 2456–2461. <http://dx.doi.org/10.1097/01.CCM.0000089938.56725.33>
- Jones, C., Skirrow, P., Griffiths, R. D., Humphris, G., Ingleby, S., Eddleston, J., . . . Gager, M. (2004). Post-traumatic stress disorder-related symptoms in relatives of patients following intensive care. *Intensive Care Medicine*, *30*, 456–460. <http://dx.doi.org/10.1007/s00134-003-2149-5>
- Jubran, A., Lawm, G., Duffner, L. A., Collins, E. G., Lanuza, D. M., Hoffman, L. A., & Tobin, M. J. (2010). Post-traumatic stress disorder after weaning from prolonged mechanical ventilation. *Intensive Care Medicine*, *36*, 2030–2037. <http://dx.doi.org/10.1007/s00134-010-1972-8>
- Kiekkas, P., Theodorakopoulou, G., Spyrtatos, F., & Baltopoulos, G. I. (2010). Psychological distress and delusional memories after critical care: A literature review. *International Nursing Review*, *57*, 288–296. <http://dx.doi.org/10.1111/j.1466-7657.2010.00809.x>
- Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). APACHE II: A severity of disease classification system. *Critical Care Medicine*, *13*, 818–829. <http://dx.doi.org/10.1097/00003246-198510000-00009>
- Kress, J. P., Gehlbach, B., Lacy, M., Pliskin, N., Pohlman, A. S., & Hall, J. B. (2003). The long-term psychological effects of daily sedative interruption on critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, *168*, 1457–1461. <http://dx.doi.org/10.1164/rccm.200303-4550C>
- Lam, W. W., Bonanno, G. A., Mancini, A. D., Ho, S., Chan, M., Hung, W. K., . . . Fielding, R. (2010). Trajectories of psychological distress among Chinese women diagnosed with breast cancer. *Psycho-Oncology*, *19*, 1044–1051. <http://dx.doi.org/10.1002/pon.1658>
- Lamas, D. J. (2013). Delirium-induced flashbacks plague many former ICU patients. *The Boston Globe*. Retrieved from <http://bostonglobe.com>
- Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York, NY: Springer.
- Lonardo, N. W., Mone, M. C., Nirula, R., Kimball, E. J., Ludwig, K., Zhou, X., . . . Barton, R. G. (2014). Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. *American Journal of Respiratory and Critical Care Medicine*, *189*, 1383–1394. <http://dx.doi.org/10.1164/rccm.201312-2291OC>
- Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: Glucocorticoid-resistance model. *Health Psychology*, *21*, 531–541.
- Misak, C. (2005). ICU psychosis and patient autonomy: Some thoughts from the inside. *The Journal of Medicine and Philosophy*, *30*, 411–430. <http://dx.doi.org/10.1080/03605310591008603>
- Myhren, H., Tjøien, K., Ekeberg, O., Karlsson, S., Sandvik, L., & Stokland, O. (2009). Patients' memory and psychological distress after ICU stay compared with expectations of the relatives. *Intensive Care Medicine*, *35*, 2078–2086. <http://dx.doi.org/10.1007/s00134-009-1614-1>
- O'Donnell, M. L., Creamer, M., Holmes, A. C., Ellen, S., McFarlane, A. C., Judson, R., . . . Bryant, R. A. (2010). Posttraumatic stress disorder after injury: Does admission to intensive care unit increase risk? *Journal of Trauma and Acute Care Surgery*, *69*, 627–632. <http://dx.doi.org/10.1097/TA.0b013e3181bc0923>
- Ozer, E. J., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2008, August). Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. In *Annual Meeting of the International Society for Traumatic Stress Studies, 14th, Nov, 1998, Washington, DC*. This article is based on a paper presented at the aforementioned meeting (No. 1, p. 3). Educational Publishing Foundation.
- Pandharipande, P., Shintani, A., Peterson, J., Pun, B. T., Wilkinson, G. R., Dittus, R. S., . . . Ely, E. W. (2006). Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*, *104*, 21–26. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16394685>
- Parker, A. M., Sricharoenchai, T., Raparla, S., Schneck, K. W., Bienvenu, O. J., & Needham, D. M. (2015). Posttraumatic stress disorder in critical illness survivors: A metaanalysis. *Critical Care Medicine*, *43*, 1121–1129. <http://dx.doi.org/10.1097/CCM.0000000000000882>
- Pietrzak, R. H., Johnson, D. C., Goldstein, M. B., Malley, J. C., Rivers, A. J., Morgan, C. A., & Southwick, S. M. (2010). Psychosocial buffers of traumatic stress, depressive symptoms, and psychosocial difficulties in veterans of Operations Enduring Freedom and Iraqi Freedom: The role of resilience, unit support, and postdeployment social support. *Journal of Affective Disorders*, *120*, 188–192. <http://dx.doi.org/10.1016/j.jad.2009.04.015>
- Polderman, K. H., Girbes, A. R. J., Thijs, L. G., & Strack van Schijndel, R. J. M. (2001). Accuracy and reliability of APACHE II scoring in two intensive care units Problems and pitfalls in the use of APACHE II and suggestions for improvement. *Anaesthesia*, *56*, 47–50. <http://dx.doi.org/10.1046/j.1365-2044.2001.01763.x>
- Raison, C. L., & Miller, A. H. (2003). When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *The American Journal of Psychiatry*, *160*, 1554–1565. <http://dx.doi.org/10.1176/appi.ajp.160.9.1554>
- Rattray, J. E., Johnston, M., & Wildsmith, J. A. W. (2005). Predictors of emotional outcomes of intensive care. *Anaesthesia*, *60*, 1085–1092. <http://dx.doi.org/10.1111/j.1365-2044.2005.04336.x>
- Roussi, P., Krikeli, V., Hatzidimitriou, C., & Koutri, I. (2007). Patterns of coping, flexibility in coping and psychological distress in women diagnosed with breast cancer. *Cognitive Therapy and Research*, *31*, 97–109. <http://dx.doi.org/10.1007/s10608-006-9110-1>
- Samuelson, K., Lundberg, D., & Fridlund, B. (2006). Memory in relation to depth of sedation in adult mechanically ventilated intensive care patients. *Intensive Care Medicine*, *32*, 660–667.
- Samuelson, K. A. M., Lundberg, D., & Fridlund, B. (2007). Stressful memories and psychological distress in adult mechanically ventilated intensive care patients: A 2-month follow-up study. *Acta Anaesthesiologica Scandinavica*, *51*, 671–678. <http://dx.doi.org/10.1111/j.1399-6576.2007.01292.x>
- Schelling, G., Roozendaal, B., Krauseneck, T., Schmoelz, M. D. E., Quervain, D., & Briegel, J. (2006). Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery.

- Annals of the New York Academy of Sciences*, 1071, 46–53. <http://dx.doi.org/10.1196/annals.1364.005>
- Schelling, G., Stoll, C., Haller, M., Briegel, J., Manert, W., Hummel, T., . . . Peter, K. (1998). Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Critical Care Medicine*, 26, 651–659. <http://dx.doi.org/10.1097/00003246-199804000-00011>
- Scragg, P., Jones, A., & Fauvel, N. (2001). Psychological problems following ICU treatment*. *Anaesthesia*, 56, 9–14.
- Sessler, C. N., & Varney, K. (2008). Patient-focused sedation and analgesia in the ICU. *Chest Journal*, 133, 552–565. <http://dx.doi.org/10.1378/chest.07-2026>
- Shapiro, B. A., Warren, J., Egol, A. B., Greenbaum, D. M., Jacobi, J., Nasraway, S. A., . . . the Society of Critical Care Medicine. (1995). Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit. *Critical Care Medicine*, 23, 1596–1600. <http://dx.doi.org/10.1097/00003246-199509000-00021>
- Shehabi, Y., Bellomo, R., Mehta, S., Riker, R., & Takala, J. (2013). Intensive care sedation: The past, present and the future. *Critical Care (London, England)*, 17, 322. <http://dx.doi.org/10.1186/cc12679>
- Singh, A., Petrides, J. S., Gold, P. W., Chrousos, G. P., & Deuster, P. A. (1999). Differential hypothalamic-pituitary-adrenal axis reactivity to psychological and physical stress. *The Journal of Clinical Endocrinology and Metabolism*, 84, 1944–1948.
- Sorrells, S. F., & Sapolsky, R. M. (2007). An inflammatory review of glucocorticoid actions in the CNS. *Brain, Behavior, and Immunity*, 21, 259–272. <http://dx.doi.org/10.1016/j.bbi.2006.11.006>
- Treggiari, M. M., Romand, J. A., Yanez, N. D., Deem, S. A., Goldberg, J., Hudson, L., . . . Weiss, N. S. (2009). Randomized trial of light versus deep sedation on mental health after critical illness. *Critical Care Medicine*, 37, 2527–2534. <http://dx.doi.org/10.1097/CCM.0b013e3181a5689f>
- Wade, D. M., Brewin, C. R., Howell, D. C. J., White, E., Mythen, M. G., & Weinman, J. A. (2014). Intrusive memories of hallucinations and delusions in traumatized intensive care patients: An interview study. *British Journal of Health Psychology*, 20, 613–631.
- Wade, D., Hardy, R., Howell, D., & Mythen, M. (2013). Identifying clinical and acute psychological risk factors for PTSD after critical care: A systematic review. *Minerva Anestesiologica*, 79, 944–963.
- Weinert, C. R., & Sprenkle, M. (2008). Post-ICU consequences of patient wakefulness and sedative exposure during mechanical ventilation. *Intensive Care Medicine*, 34, 82–90.
- Westphal, M., Seivert, N. H., & Bonanno, G. A. (2010). Expressive flexibility. *Emotion*, 10, 92–100. <http://dx.doi.org/10.1037/a0018420>
- Wirtz, P. H., von Känel, R., Emini, L., Ruedisueli, K., Groessbauer, S., Maercker, A., & Ehlert, U. (2007). Evidence for altered hypothalamus-pituitary-adrenal axis functioning in systemic hypertension: Blunted cortisol response to awakening and lower negative feedback sensitivity. *Psychoneuroendocrinology*, 32, 430–436. <http://dx.doi.org/10.1016/j.psyneuen.2007.02.006>
- Wong, D. T., Barrow, P. M., Gomez, M., & McGuire, G. P. (1996). A comparison of the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Trauma-Injury Severity Score (TRISS) for outcome assessment in intensive care unit trauma patients. *Critical Care Medicine*, 24, 1642–1648. <http://dx.doi.org/10.1097/00003246-199610000-00007>
- Wunsch, H., Christiansen, C. F., Johansen, M. B., Olsen, M., Ali, N., Angus, D. C., & Sørensen, H. T. (2014). Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. *JAMA: Journal of the American Medical Association*, 311, 1133–1142. <http://dx.doi.org/10.1001/jama.2014.2137>
- Yehuda, R., Yang, R. K., Buchsbaum, M. S., & Golier, J. A. (2006). Alterations in cortisol negative feedback inhibition as examined using the ACTH response to cortisol administration in PTSD. *Psychoneuroendocrinology*, 31, 447–451. <http://dx.doi.org/10.1016/j.psyneuen.2005.10.007>

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