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Psychological Outcomes after Critical Illness
Is It Time to Rethink Our Paradigm?

A growing body of literature has documented the consequences of critical illness, delineating the ways in which an ICU stay may constitute a life-altering event. Survivors of critical illness go on to suffer from functional disability, cognitive impairment, and psychological symptomatology, with resultant decrements in quality of life (1–3). Although this constellation of symptoms has received due attention and recognition as a postintensive care syndrome (4), thus far, interventions to improve these long-term outcomes have not been successful (5–8).

In this issue of the *Journal*, Cox and colleagues (pp. 66–78) present results from a randomized multicenter clinical trial conducted in survivors of critical illness and their family members, aimed at improving psychological symptomatology measured at 3 and 6 months (9). Patients who received mechanical ventilation for at least 48 hours (and their family member) were randomly assigned to either a telephone and web-based coping skills training (CST) intervention or an educational program. The CST intervention consisted of two psychologists who aimed to provide six weekly 30-minute telephone sessions intended to teach participants coping skills (e.g., relaxation, cognitive restructuring), in addition to the availability of web-based content. The educational program consisted of six videos containing information about critical illness (without discussing its psychological effect), as well as two phone calls to address participants' questions. Layperson stakeholders contributed to the trial's design and were influential in the decision to have this "active" control. The primary outcome was the change in the Hospital Anxiety and Depression Scale (HADS) summary score between baseline and 3 months. Secondary outcomes included the HADS score at 6 months and posttraumatic stress disorder symptoms, as well as assessments examining quality of life, overall health, coping, and self-efficacy.

Despite more than 6,000 attempted contacts to participants, adherence (defined as completion of at least one phone call) was only moderate (63% for CST vs. 65% for education), with a mean of 2.7 sessions completed for the CST group and 0.8 for the education group. At 3 months, there was no difference in the HADS score between groups; there also were no significant differences in any secondary outcomes at either point. However, in prespecified subgroup analyses, education was superior to CST at 3 months for patients mechanically ventilated for more than 7 days, whereas CST was superior to education at 6 months for patients with a high baseline HADS summary score (>14). Thus, the main findings of the trial are negative, although there was a hypothesis-generating subgroup finding with some face validity.

In relation to the trial itself, there are several possible explanations for the negative result. First, the "active" control may have blunted the ability to identify a positive effect of the CST intervention. However, observed estimates of the HADS score were similar to those from other nonintervention studies (10, 11), which may indicate that neither intervention was effective. Second, separation between the experimental groups may not have been achieved because of inadequate delivery of the intervention, as there were no measured differences in adaptive coping and self-efficacy. Third, the study population may have been too heterogeneous. As the authors intimate, perhaps the intervention would have demonstrated efficacy in the subgroup of patients with high baseline levels of distress. As with all subgroup analyses, this positive finding may represent a type 1 error, but these patients also demonstrated improvements in measures of self-efficacy and overall global health. Last, the intervention may simply not be effective.

Considering that this study follows several others that failed to improve psychological outcomes after critical illness (or resulted in a signal for harm), we must ask: Is the current model of how we approach this problem correct? At this time, we view the presence of psychological symptomatology after critical illness as pathologic. However, it is not entirely surprising that we see elevated levels of depression and anxiety as people deal with the stress of a potentially traumatic and life-altering event. In particular, the sooner after the event outcomes are measured, the more likely we may be to capture fluctuations in normal grief and adjustment. At this juncture, it may be informative to examine the approach to treating grief (after the death of a loved one) in psychiatry. Interventions to enhance adaptation to grief in this setting have also had mixed results, with studies showing signals for harm and smaller-than-expected treatment effects (12), leading to some concern that intervening on "normal" grief may actually interfere with natural coping processes (13). Also, negative symptoms of grief peak by 6 months, suggesting that the timeframe of diagnosis, intervention, and follow-up for problematic grief should be appropriately shifted (14). These findings have led to a consensus approach that focuses more on secondary or tertiary prevention, offering interventions to patients either who seek them out or who have demonstrated persistent and disruptive symptomatology, as opposed to a primary prevention strategy of administering interventions to all comers (12, 13). However, an important caveat to drawing these parallels is that the loss of a loved one is a singular event, and survivors of critical illness are more likely to have continued stressors, as evidenced by the fact that many

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patients in this trial were unable to complete sessions as a result of ongoing illness, hospitalization, or death.

Despite its limitations, this trial represents an important contribution to the literature. It offers invaluable insight into the challenges of conducting clinical trials in this area, and perhaps most important, highlights the fact that interventions should likely be targeted toward defined subpopulations of survivors. As only 30–40% of survivors have persistent psychological symptoms (10, 11), the next fundamental knowledge gap may be the robust identification of which survivors are actually at risk for serious sequelae. This may be achieved in part by allowing time for cases to "declare themselves" or through use of techniques to delineate phenotypes of psychological distress (15). Although next steps will undoubtedly require further research, the hardest task may lie in reconsidering our current paradigm. Only after such questions have been satisfactorily answered can we ensure that commendable efforts to advance the field, such as those presented by the authors, are not wasted. ■

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Genetic Variants and Altered Expression of Non-*CFTR* Genes May Explain Differences in Cystic Fibrosis Severity

Cystic fibrosis (CF) is an inherited disorder caused by loss-of-function variants in the *CFTR* gene. Considering that a single mutation (F508del) in *CFTR* occurs in 86% of all people with CF and 46% have F508del homozygosity, the unexplained heterogeneity observed in disease severity (1) is likely due to non-*CFTR* genetic variation and environmental factors (2). In this issue of the *Journal*, Polineni and colleagues (pp. 79–93) investigate the genomic mechanisms of CF lung severity by correlating nasal mucosal gene expression with severity using an age-adjusted severity score based on FEV_1 and age-specific survival estimates, the Kulich normal residual mortality-adjusted (KNoRMA) score (range = −2 to 3) (3, 4). Genes that were found within biological pathways upregulated with severity/KNoRMA were then traced back to previously described severity susceptibility loci (5). The authors' overall goal was to identify gene expression and genetic variants that together correlate with and potentially explain the heterogeneity observed in disease severity.

In gene expression studies, differences in expression are traditionally determined by comparing diseased tissue with healthy tissue. In such cases, gene expression differences are amplified

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