

Protocols and Hospital Mortality in Critically Ill Patients: The United States Critical Illness and Injury Trials Group Critical Illness and Injury Trials Group Critical Illness Outcomes Study

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Objective: Clinical protocols may decrease unnecessary variation in care and improve compliance with desirable therapies. We evaluated whether highly protocolized ICUs have superior patient outcomes compared with less highly protocolized ICUs.

Design: Observational study in which participating ICUs completed a general assessment and enrolled new patients 1 day each week.

Patients: A total of 6,179 critically ill patients.

Setting: Fifty-nine ICUs in the United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study.

Interventions: None.

Measurements and Main Results: The primary exposure was the number of ICU protocols; the primary outcome was hospital mortality. A total of 5,809 participants were followed prospectively, and 5,454 patients in 57 ICUs had complete outcome data. The median number of protocols per ICU was 19 (interquartile range, 15–21.5). In single-variable analyses, there were no differences in ICU and hospital mortality, length of stay, use of mechanical ventilation, vasopressors, or continuous sedation among individuals in ICUs with a high versus low number of protocols. The lack of association was confirmed in adjusted multivariable analysis ($p = 0.70$). Protocol compliance with two ventilator management protocols was moderate and did not differ between ICUs with high versus low numbers of protocols for lung protective ventilation in

acute respiratory distress syndrome (47% vs 52%; $p = 0.28$) and for spontaneous breathing trials (55% vs 51%; $p = 0.27$).

Conclusions: Clinical protocols are highly prevalent in U.S. ICUs. The presence of a greater number of protocols was not associated with protocol compliance or patient mortality. (*Crit Care Med* 2015; XX:00–00)

Key Words: intensive care unit; mortality; protocol

Patients with life-threatening illness are managed in critical care units with specialized monitoring and staffing requirements. The care of critically ill patients remains challenging because of patient acuity, competing time demands of other seriously ill patients, in addition to large amounts of clinical, mechanical ventilation, and laboratory information. In such an environment, it can be difficult to consistently provide desired care to each patient. Studies of patients with specific conditions, such as sepsis and the acute respiratory distress syndrome (ARDS), suggest that many patients do not receive desired care (1–3).

The use of clinical protocols that target specific clinical syndromes is one method to decrease unnecessary variation in care and improve compliance with desired therapies (4–6). Clinical protocols are prevalent in academic hospitals in the United States (7) and have been shown to be associated with desired treatments in patients with acute lung injury, ventilator weaning, and sedation management (2, 8–10). The use of clinical protocols in the ICU also appears to not adversely affect trainee knowledge (11). However, the link between the number of protocols available in an ICU and patient outcomes is poorly understood.

The United States Critical Illness and Injury Trials Group-Critical Illness Outcomes Study (USCIITG-CIOS) is a multicenter observational cohort study trial designed to understand the association between ICU organization and structural characteristics on hospital mortality (12). The primary hypothesis being tested was whether highly protocolized ICUs would have improved patient outcomes compared with less highly protocolized ICUs.

MATERIALS AND METHODS

Study Setting

The USCIITG-CIOS is a multicenter, prospective observational study of patients with critical illness treated in ICUs in the United States. The intent and content of the study has been previously described in detail (13). All participating sites received institutional review board approval for data collection using a waiver of informed consent (14).

Study Design

In brief, participating investigators in 69 ICUs first completed a standardized questionnaire regarding patient and organizational characteristics of their ICU, including use of clinical protocols (13). Once this standardized questionnaire was completed and reviewed, participating sites were asked to enroll all newly admitted patients on alternating days of the week 1 day

a week with 5–10 days between enrollments to allow for patient turnover. Thus, patients in the ICU who were present during previous study dates or who left prior to the next study dates were not enrolled.

The primary outcome measure was hospital mortality. Secondary outcome measures were ICU mortality and ICU and hospital length of stay. The primary exposure variable was the number of protocols present within a single ICU. Protocols were defined prospectively prior to initiation of the study according to the MeSH term definition, as a precise and detailed plan for a regimen of therapy (13). Protocols could be started by a separate physician order or included within standing admission orders (13). We included 26 potential conditions that might be managed using protocols based on discussions by study investigators of common order sets and protocols within their own institutions (e.g., lung protective ventilation and ventilator liberation protocols). We analyzed protocols as both a categorical variable and our primary comparison of highly protocolized (≥ 19 protocols) versus less highly protocolized (< 19 protocols) ICUs based on the median number of protocols of participating centers as previously reported (13). USCITG-CIOS was approved by the ethics review boards of all participating institutions.

Biostatistical Methods

The primary aim was to determine if critically ill patients in highly protocolized ICUs had lower odds of hospital mortality than did those in less highly protocolized ICUs after adjusting for potential confounders. To test this hypothesis, we constructed a multivariable logistic regression model of hospital mortality as a function of a high versus low number of protocols (≥ 19 vs < 19) and adjusted for a priori selected individual- and ICU-level variables. Individual-level variables included age, being male (vs female), categories of admission source (vs being in the emergency department) and admission diagnosis (indicator variables for circulatory, gastrointestinal, nervous system, respiratory, infection, endocrine, and trauma), Acute Physiology and Chronic Health Evaluation (APACHE) II score, race (nonwhite vs white), on mechanical ventilation, having sepsis, and having ARDS. ICU-level variables included type of ICU (surgical vs other), having a daily plan of care review (vs not), bed-to-nurse ratio more than 1.5:1 (vs not), 1 and hospital volume (categorized as 25,000–39,999 and $> 40,000$ vs $< 25,000$ admissions). Participants with missing data in either the outcome or any of the explanatory variables were excluded from multivariable analysis. Given that we enrolled more than one critically ill patient per ICU and that the unit of analysis was an individual within ICU, we used generalized estimating equations with a compound symmetry matrix and a robust variance to account for ICU-level clustering (15). We also conducted a similar analysis in which we treated the number of protocols as a continuous variable modeled using a natural cubic spline with one internal knot at 19.

A secondary aim was to determine compliance with two protocols: low tidal volume ventilation in patients with acute lung injury (i.e., tidal volume per kg of predicted body weight < 6.5 mL/kg) (16) and spontaneous breathing trials in patients

with FiO_2 less than 40% and positive end-expiratory pressure (PEEP) less than 5 cm H_2O (9, 17). We also compared differences in compliance prevalence between highly protocolized and less highly protocolized ICUs. We conducted all analyses in R (<http://www.r-project.org>; R Foundation For Statistical Computing, Vienna, Austria).

RESULTS

Participant Characteristics

We enrolled 6,179 critically ill patients across 59 ICUs (86% of all ICUs who completed the structure and process questionnaire), of which 3% ($n = 202$) were missing information on race and 3% ($n = 168$) were missing information on specific patient-centered outcomes (Fig. 1). A total of 5,809 participants (94%) were followed prospectively. Of these, 5,454 in 57 ICUs (94%) had complete information for inclusion in multivariable analyses. In Table 1, we compared demographics and admission characteristics between the group of participants in ICUs with a high (≥ 19) versus low (< 19) number of protocols. In unadjusted analyses, we found that individuals in less protocolized ICUs were younger and more likely to be white. In contrast, gender, admission source, admission type, type of ICU, hospital teaching status, severity scores (APACHE II and Sequential Organ Failure Assessment), and hospital case volume were similar in individuals in ICUs with a high versus low number of protocols.

Number of Protocols and Hospital Mortality

Participating ICUs had a high number of protocols (Fig. 2). Specifically, no ICU had zero protocols and the median number of protocols in the 59 ICUs included in this analysis was 19 (IQR, 15–21.5). In Table 2, we compared hospital mortality and other selected treatment and outcome variables between individuals in ICUs with a high versus low number

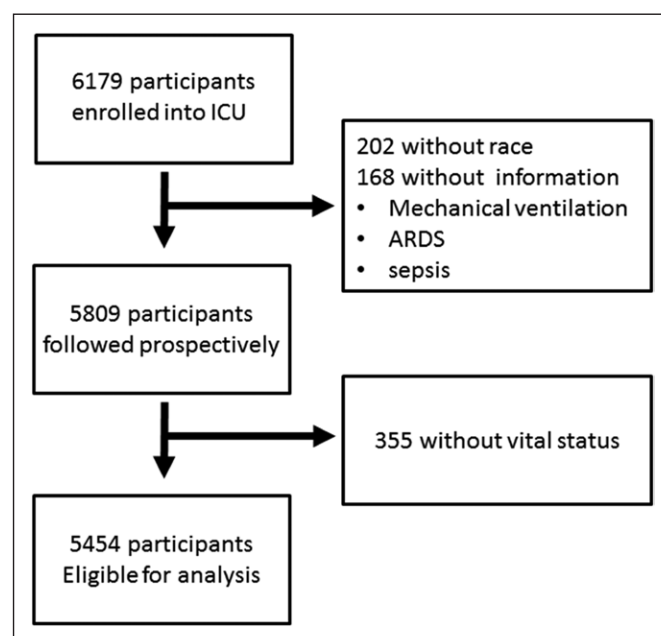


Figure 1. Study enrollment flowchart. ARDS = acute respiratory distress syndrome.

TABLE 1. Characteristics in 6,179 Critically Ill Patients Enrolled Into the United States Critical Illness and Injury Trials Group Clinical Illness Outcomes Study

Variable	High No. of Protocols (≥ 19)	Low No. of Protocols (< 19)	<i>p</i>
No. of patients	3,116	3,063	
Median no. of patients per ICU	101	101	
Age, yr (sd)	61.3 (17.4)	57.8 (16.7)	0.03
Sex, %	57	55	0.50
Race, %			
White (reference)	79	61	
Black	16	29	0.02
Other	5	10	0.02
Admission diagnosis, %			
Cardiovascular only	9	12	0.33
Neurologic only	8	10	0.69
Gastrointestinal only	8	8	0.48
Respiratory only	12	15	0.14
Infection only	5	4	0.29
Endocrine only	1	2	0.34
Trauma only	3	3	0.56
2+ diagnoses (reference)	41	39	
Source of admission, %			
Emergency department (reference)	46	43	
Hospital floor	19	19	0.39
Operating room	23	17	0.73
Other hospital	12	14	0.57
Other	4	4	0.25
Severity index (sd)			
Acute Physiology and Chronic Health Evaluation II, mean	16.7 (7.0)	16.6 (7.5)	0.72
Sequential Organ Failure Assessment, mean	4.8 (3.6)	4.9 (3.8)	0.55
Type of ICU, %			
Surgical (reference)	33	37	
Medical	49	37	0.45
Mixed	18	26	0.87
Teaching status, %			
Academic	93	97	0.58
Nonacademic	7	3	
Annual No. of hospital admissions, %			
< 25,000 (reference)	19	30	
25,000–39,999	34	46	0.94
> 40,000	24	48	0.53

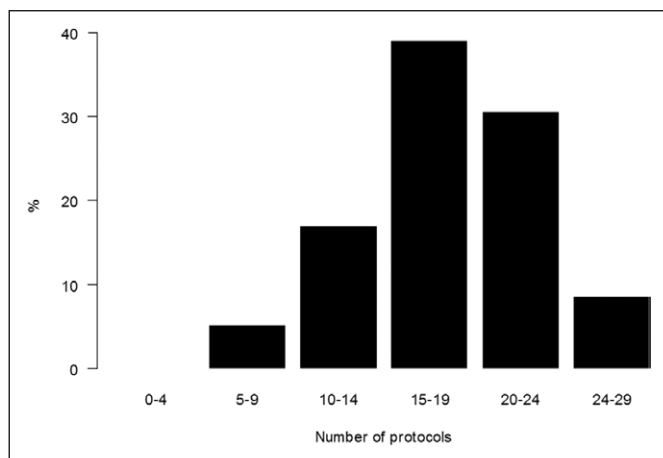


Figure 2. Number of protocols within study ICUs.

of protocols. We did not find differences in hospital or ICU mortality, hospital or ICU length of stay, in use of mechanical ventilation, vasopressors or continuous sedation, or in withdrawal support among individuals in ICUs with a high versus low number of protocols.

In multivariable analyses, there was no significant association between a high versus low number of protocols and hospital mortality (**Table 3**). We also did not find a dose-response relationship between the number of protocols and hospital mortality (**Fig. 3**). In multivariable logistic regression in which individual patients were the unit of analysis, statistically significant risk factors for death included older age, higher illness severity (APACHE II score), receipt of mechanical ventilation, having sepsis, or having ARDS.

Protocol Compliance

To examine whether the total number of protocols in an ICU was associated with better compliance, we selected two common protocols based on patient and ICU characteristics.

Overall compliance with two ventilator management protocols was found to be low. Of the 453 patients with ARDS under mechanical ventilation, 50% ($n = 227$) of those with full ventilator variables were deemed compliant by having ventilator tidal volumes up to 6.5 mL/kg predicted body weight. We found no difference in the prevalence of compliance with low tidal volume ventilation between individuals in ICUs with a high versus low number of protocols (47% vs 52%; $p = 0.28$). Of the 1,058 critically ill patients under mechanical ventilation who met criteria for weaning ($FiO_2 < 40\%$ and $PEEP < 5$ cm H_2O), only 53% ($n = 559$) received a spontaneous breathing trial. There was no difference in the prevalence of compliance with a spontaneous breathing trial between individuals in ICUs with a high versus low number of protocols (55% vs 51%; $p = 0.27$).

DISCUSSION

We conducted a multicentered observational study of critically ill patients from diverse hospitals in the United States to examine the relationship between hospital protocols and clinical outcomes and found that neither a highly protocolized ICU nor the absolute number of protocols was associated with superior risk-adjusted clinical outcomes. In addition, there was no dose-response relationship between protocols and mortality and compliance was modest for evaluated protocols. These findings were robust to sensitivity analyses testing the associations between specific protocol compliance and outcomes.

The results from this study suggest that the number of protocols may not favorably influence hospital mortality or hospital length of stay in critically ill patients. Other studies have shown that protocols can influence process of care in critically ill patients, such as increasing the use of lung protective mechanical ventilation (8). In addition, implementation of ARDS ventilation protocols has been shown to decrease mortality compared with historical controls (18). In contrast, a multifaceted knowledge translation project was able

TABLE 2. Selected Treatment Variables and Clinical Outcomes

Variable	High No. of Protocols (≥ 19)	Low No. of Protocols (< 19)	<i>p</i>
Treatment, %			
Mechanical ventilation	43	38	0.23
On vasopressors	20	16	0.21
On renal replacement therapy	8	7	0.38
Continuous sedation	35	29	0.14
Outcomes			
ICU mortality, %	12	13	0.64
In-hospital mortality, %	17	17	0.96
ICU length of stay, d (SD)	9.5 (14.9)	9.7 (12.6)	0.65
Hospital length of stay, d (SD)	18.0 (21.7)	18.4 (21.2)	0.59
Withdrawal of support, %	22	20	0.94

TABLE 3. Unadjusted and Adjusted Odds Ratios for Hospital Mortality

Variable	Single-Variable Analysis, OR (95% CI)	<i>p</i>	Multivariable Analysis, OR (95% CI)	<i>p</i>
Age (for every 10 yr)	1.17 (1.12–1.23)	< 0.001	1.07 (1.01–1.14)	0.03
Sex (being male)	1.03 (0.90–1.18)	0.66	0.98 (0.84–1.14)	0.77
Race (not white)	1.05 (0.87–1.27)	0.59	1.08 (0.87–1.33)	0.48
ICU type (vs surgical)				
Medical	2.42 (1.74–3.38)	< 0.001	1.22 (0.87–1.69)	0.25
Mixed	1.63 (1.06–2.51)	0.03	1.16 (0.76–1.76)	0.50
Daily plan of care review	0.88 (0.56–1.40)	0.59	1.24 (0.86–1.78)	0.25
Bed:nurse ratio > 1.5:1	1.42 (1.03–1.96)	0.03	0.88 (0.67–1.17)	0.40
On mechanical ventilation	3.21 (2.67–3.87)	< 0.001	1.55 (1.24–1.93)	< 0.001
Sepsis today	2.91 (2.47–3.41)	< 0.001	1.51 (1.28–1.79)	< 0.001
Acute respiratory distress syndrome today	3.04 (2.48–3.71)	< 0.001	1.52 (1.19–1.95)	0.001
Hospital volume (vs < 25,000)				
25,000–39,999	1.07 (0.72–1.64)	0.72	1.02 (0.75–1.39)	0.89
> 40,000	0.98 (0.63–1.51)	0.92	0.72 (0.50–1.04)	0.08
Admission source (vs emergency department)				
Hospital floor	2.14 (1.71–2.69)	< 0.001	1.89 (1.47–2.43)	< 0.001
Operating room	0.50 (0.37–0.69)	< 0.001	0.65 (0.44–0.96)	0.03
Other hospital	1.27 (0.98–1.64)	0.07	1.03 (0.76–1.40)	0.86
Other setting	1.49 (1.02–2.15)	0.03	1.52 (0.89–2.60)	0.13
Admission diagnosis				
Circulatory system (vs other)	1.44 (1.21–1.71)	< 0.001	1.22 (1.01–1.46)	0.03
Gastrointestinal system (vs other)	1.48 (1.22–1.80)	< 0.001	1.34 (1.06–1.69)	0.01
Nervous system (vs other)	1.42 (1.15–1.76)	0.001	1.50 (1.21–1.85)	< 0.001
Respiratory system (vs other)	2.05 (1.76–2.39)	< 0.001	1.30 (1.10–1.54)	0.002
Infection (vs other)	1.61 (1.36–1.92)	< 0.001	0.89 (0.71–1.10)	0.28
Endocrine (vs other)	0.92 (0.64–1.31)	0.63	0.72 (0.52–0.98)	0.04
Trauma (vs other)	0.76 (0.57–1.01)	0.06	0.73 (0.49–1.10)	0.14
Acute Physiology and Chronic Health Evaluation II (10-point increments)	3.58 (3.09–4.16)	< 0.001	2.81 (2.39–3.30)	< 0.001
No. of protocols > 19	0.99 (0.71–1.39)	0.97	0.94 (0.68–1.30)	0.70

OR = odds ratio.

to improve compliance with desired ICU therapies, although patient outcomes were not assessed (19). It may be that any beneficial effects of protocol use are dependent on better compliance, clinician education (1, 3), ICU culture change (20), communication (13), or other essential components of effective delivery of critical care, all of which may influence implementation of protocols. We found that the reported presence of a protocol was not necessarily an indicator that protocols were successfully implemented. In addition, our study evaluated protocols as a whole, and it may be that the effects of

higher impact protocols outweigh the effects of lower impact protocols. Protocols in two specific areas of critical care, for example, have been shown in multiple randomized trials to improve outcomes. These include ventilator weaning protocols with spontaneous breathing trials as the centerpiece of the protocol, and sedation protocols that emphasize reductions in sedative exposure via daily interruption or targeted light sedation (9, 10). In addition, educational efforts that have been included use of protocols and order sets have improved processes of care and patient outcomes in patients with severe

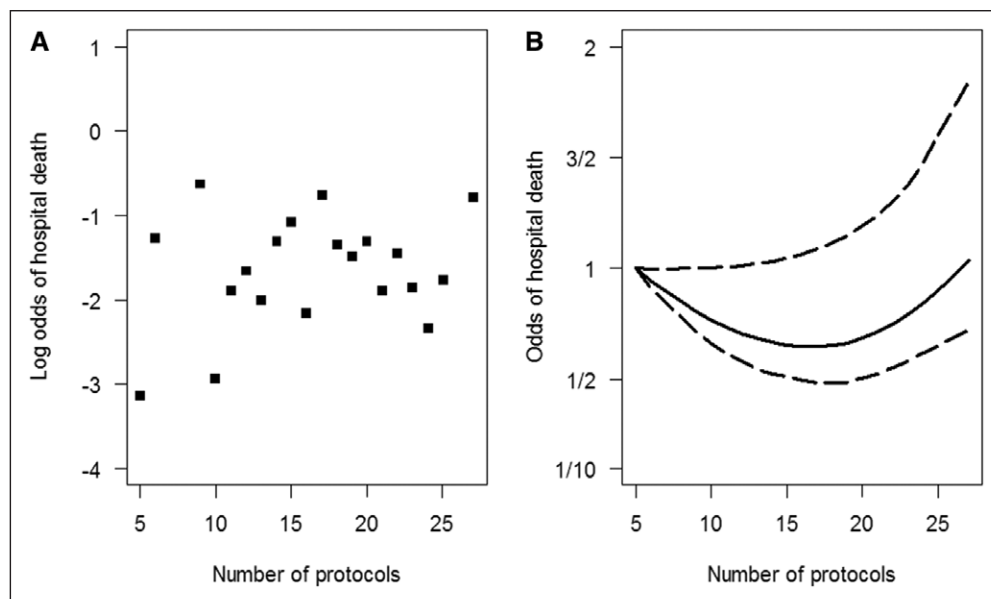


Figure 3. Unadjusted log odds of hospital mortality and protocols (A) and adjusted relationship between hospital mortality and protocols (B).

sepsis (1, 3). Finally, it may be possible that this study included patients who could potentially be harmed by the use of standardized protocols.

Our study has several important limitations. First, we collected ICU structural and organizational information from U.S. hospitals and primarily academic institutions. Our findings may therefore not be generalizable to ICUs in other locations or to community-based ICUs. A recent survey of 1,265 ICUs in 75 countries found an association between nurse staffing ratio and hospital death but did not provide data on protocols (21). In addition, our study was observational with missing data for some covariates, and thus, we cannot draw absolute conclusions about causality. In addition, we cannot rule out the possibility that our results can be explained by unmeasured confounders. Most ICUs participating in the study had a high number of protocols, and it is not known whether our findings would translate to ICUs with fewer protocols. The presence of protocols was self-reported, and we do not have data on how robust the protocol was or what was included in the protocol. We only tested ventilator protocols for compliance, so it is possible that the other protocols would have had a different relationship between number of protocols and compliance. We chose ventilator protocols for study since they are highly prevalent in ICUs, and the treatment effect for mechanical ventilation appears to be similar across different types of patients (13, 22). In addition, we cannot rule out the possibility that our results could be caused by unmeasured confounders. To minimize this possibility, we adjusted for factors individual and ICU-level factors that could be associated with our primary outcome measure. Furthermore, our data do not allow for conclusions about whether protocols may have benefit in certain situations, such as baseline levels of care or staffing. The use of APACHE II has not been validated other than on the first day of hospital admission or in trauma patients, despite

its frequent use in these situations. Finally, we collected data once a week, which might have led to some misclassification. It is possible that daily collection would have provided different findings. We conducted analyses that address several possible limitations, including modeling protocols as both a continuous and a dichotomous variable. Despite these limitations, our study has significant strengths, including large sample size, geographically disperse multicenter design, and observational study with prospectively collected data.

Although disease and syndrome mortality caused by critical illness have decreased in the past 20 years (3, 23, 24),

several resource intensive efforts to decrease ICU mortality have not been successful (25–28). Protocols may be an effective means to minimize variances in care, but the current data and that of others indicate that the presence of a protocol does not ensure its appropriate use (29). In parallel to our findings, recent studies have shown that wide implementation of a surgical safety checklist did not decrease surgical complications (29) and the inclusion of protocolized usual care for patients with severe sepsis and septic shock abrogates the effect of previously demonstrated targeted interventions (30).

CONCLUSIONS

Clinical protocols are widely present in U.S. ICUs. A greater number of protocols in the ICU were not associated with greater protocol compliance or with improved outcomes such as length of stay or mortality. Methods to ensure appropriate protocol implementation and protocol compliance should be further examined, and other factors that promote culture and behavioral change may be necessary to improve patient outcomes with the use of clinical protocols in critically ill patients.

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