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Mortality and Denial of Admission to an Intensive Care Unit

In this issue of the *Journal*, Robert and colleagues (pp. 1081–1087) present data from a prospective, observational study supporting a higher than expected mortality among patients who were initially denied admission to an intensive care unit (ICU) because of lack of beds (1). Specifically, the authors compared 28-day and 60-day mortality of 1,139 critically ill patients admitted immediately to 10 ICUs in France with 193 patients who were initially denied admission because the unit was full. In multivariable conditional logistic regression, the authors found that the odds of death at 60 days for patients who were initially denied ICU admission but admitted after subsequent referral increased by a factor of 1.8 (95% confidence interval 1.03 to 3.26; $P = 0.04$) compared with those who were immediately admitted. The authors used conditional logistic regression to measure the effect of a denied ICU admission on mortality because this model assumes that the baseline odds of death are the same for all patients within each ICU but that these baseline odds may differ between ICUs (2, 3), thus effectively accounting for heterogeneity in mortality across ICUs. Their analysis adjusted for age, previous history of disease, Glasgow Coma Scale score, presence of shock, plasma creatinine $>250 \mu\text{mol/L}$ ($>2.9 \text{ mg/dl}$), prothrombin time <30 seconds, and $>10 \text{ L/minute}$ of supplemental oxygen. The authors conclude that inappropriate regional ICU bed-to-population ratios lead to unnecessary deaths and call for additional ICU beds and more effective admission policies.

IS THE SOLUTION TO PROVIDE MORE BEDS?

The finding by Robert and colleagues of a higher mortality for patients who were initially denied admission to an ICU is not surprising. Other investigators have also documented higher mortalities in patients whose ICU admission was denied or delayed for a variety of reasons (4–8). However, the call for action by Robert and colleagues for more ICU beds is not entirely supported by their findings. First, it is essential to understand that intensive care services are a universally scarce resource but also come at a great cost to the general public. In the United States, each day of intensive care costs on average \$3,000, and it is estimated that ICUs account for 13% of hospital costs, 4% of the national health expenditures, and approximately 1% of the GDP (9, 10). At \$150 billion (based on the 2011 U.S. GDP), this number is staggering given that ICU beds comprise about 10% of all hospital beds. Daily costs of critical care are also very expensive in several

European countries, with estimated values ranging from \$1,300 to \$2,700 (7, 11). Very few cost-effective analyses of intensive care services have been conducted. One recent study evaluated the cost of life saved by an ICU admission as \$100,000 (7); however, this and other analyses have not adjusted for quality of life and fail to address the actual costs of critical care per quality-adjusted life years.

Second, the addition of more ICU beds alone without a re-evaluation of health care use at large would fail very quickly to do anything except add to the size of the current problem. As discussed elsewhere (12, 13), a multifaceted approach is necessary to meet increasing needs for intensive care. Specifically, other important strategies for consideration include an increased number of trained critical care providers (14); increased education and preventive medicine services at the population level; earlier and more targeted discussions of advanced directives and end-of-life issues with patients by general practitioners and specialists (15); greater number of intermediate care beds where higher-level care monitoring can be conducted; increased use of telemedicine for critical care (16); regionalization of ICU use (17, 18) and transfer of high-acuity patients to specialized critical care centers (19); more efficient use of intensive care to reduce length of stay via the use of closed ICUs (20, 21); and reliance on trained intensivists (20) and standardized care protocols (22). Moreover, better guidelines by governments and critical care societies developed using a serious and careful approach are needed to better define limits of critical care costs; otherwise, unregulated and inconsistent rationing at the bedside will continue to occur by providers who may be conflicted on individual cases (23, 24). Ultimately, decisions about how best to balance limited resources between critical care and other non-critical care strategies rests upon all members of a society.

ANALYSES OF OBSERVATIONAL STUDIES INVOLVING MULTIPLE INTENSIVE CARE UNITS

This study also illustrates some challenges in the design, analysis, and reporting of observational studies involving multiple ICUs, in which the ICU and not the individual is the unit of analysis. Both design and analysis of these studies require that investigators account for a clustering effect in outcomes by ICU; for example, expected mortalities of patients within an ICU are likely to be more similar than expected mortalities of patients in other

TABLE 1. MORTALITY AT 60 DAYS IN PATIENTS ADMITTED IMMEDIATELY TO THE ICU AND IN PATIENTS INITIALLY DENIED ADMISSION TO THE ICU, STRATIFIED BY ICU

ICU	Immediately admitted (<i>n</i> = 1131)			Initially denied admission (<i>n</i> = 192)			Difference in 60-d mortality (%)
	Number dead at 60 d	Total	Mortality at 60 d (%)	Number dead at 60 d	Total	Mortality at 60 d (%)	
A	52	228	22.8	2	11	18.2	−4.6
B	26	95	27.4	0	1		
C	43	123	35.0	5	18	27.8	−7.2
D	21	105	20.0	4	12	33.3	13.3
E	5	31	16.1	19	50	38.0	21.9
F	34	160	21.2	11	24	45.8	24.6
G	38	95	40.0	7	12	58.3	18.3
H	38	131	29.0	6	8	75.0	46
I	30	87	34.5	5	23	21.7	−12.7
J	21	76	27.6	5	33	15.2	−12.5
Mean (SD)			27.4 (7.5)			37.0 (19.8)	9.7 (20.2)

ICUs because of variations in practice, structure, and organization across ICUs. Ignoring the effect of clustering by ICU at the time of design may lead to an underpowered study and at the time of analysis to an overstatement of statistical significance. Equally important is the need to report summary statistics by ICU when interpreting findings. As shown in Table 1, mortality was lower in patients who were immediately admitted versus those denied admission in five ICUs, but higher in four ICUs; and one ICU had insufficient information because it only had one subject among those initially denied admission. Data are even sparser among those who were admitted after subsequent referral, in which case only four ICUs had 10 or more patients.

Finally, the interpretation of findings can be affected by the underlying assumptions of the statistical models chosen. As previously stated, conditional logistic regression assumes that the baseline odds of death for patients within each ICU are similar but may vary by ICU. If we assume that the baseline risk is similar, nonadjusted analyses of 60-day mortality between immediately admitted versus initially denied admission in nine ICUs with sufficient data was not statistically significant ($P = 0.19$, paired t test; $P = 0.16$, paired Wilcoxon rank-sum test; $P = 0.09$, exact conditional logistic regression). However, one could equally argue that such an assumption may be inadequate for these data and that instead patients who were initially denied admission may have a different baseline risk than those immediately admitted. Under this scenario, nonadjusted analysis of 60-day mortality between immediately admitted (27%) versus initially denied admission (37%) was also not statistically significant ($P = 0.20$, t test; $P = 0.28$, weighted t test; $P = 0.40$, Wilcoxon rank-sum test). Differences between nonadjusted and adjusted analyses ($P = 0.06$ for adjusted odds ratio of death at 60 days between patients immediately admitted versus those initially denied admission) for this study could be due to adequate adjustment of confounders as they could be due to a sparse-data bias (25), and sensitivity analyses may help shed light regarding the robustness of findings.

CONCLUSIONS

The finding of a higher mortality for patients who were initially denied admission to an ICU is not surprising. Better policies by government and critical care societies are needed to help guide resource allocation for ICU services. Critical care costs can be expected only to rise; thus, a multifaceted approach including more efficient use of available critical care services in combination with non-critical care services centering on prevention at the population level and early discussions about end-of-life care are needed. Finally, heterogeneity in clinical outcomes across ICUs is an important factor in both the design and analysis of multicenter observational studies, and ignoring it may lead to overly liberal conclusions. Journal editors and consensus statements such as

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) regarding observational studies involving multiple clusters (26) should consider requesting that cluster-level data be presented for evaluation of results by readers.

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WILLIAM CHECKLEY, M.D., Ph.D.
School of Medicine
Johns Hopkins University
Baltimore, Maryland

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Control of Fever in Septic Shock: Should We Care or Intervene?

One of the primary criteria for definition of septic shock is fever (and other signs of systemic inflammatory response). Many view fever as the body's natural beneficial response to infection, whereas others contend that fever is harmful and should be controlled.

In this issue of the *Journal* (pp. 1088–1095), this latter question is addressed in a proof-of-principle multicenter randomized controlled trial (RCT) evaluating the safety and efficacy of cooling febrile patients who had septic shock (1). The intervention group ($n = 101$) had external cooling to normothermia for 48 hours, whereas controls ($n = 99$) had usual care without cooling. Cooling was safe (no difference in adverse events), decreased need for vasopressors, induced shock reversal more frequently (86% vs. 73%), and decreased 14-day mortality rates (19% vs. 34%).

Strengths of this study were that it was a randomized controlled trial, that there were few exclusion criteria, that fever was controlled quickly, and that there were well-aligned primary and secondary outcomes. However, the sample size was relatively small, the primary outcome variable was decrease of vasopressor use (not mortality), and some other issues raise questions that I now address.

Fever is caused by increased levels of cytokines and centrally induced prostaglandin E_2 and $PGF_{2\alpha}$, resetting the hypothalamic temperature control center. Some of the potential benefits of controlling fever in septic shock are decreased global oxygen demand (when oxygen supply is limited), thus decreasing needs for oxygen and vasopressors; decreased risk of oxygen supply/demand mismatch (e.g., in heart, kidney, brain, liver, and gut); decreased metabolic rate (lessening the early catabolic stage of septic shock); and decreased risk of septic encephalopathy (e.g., agitation), thereby decreasing the need for sedatives and antipsychotic drugs. Many drugs (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [e.g., ibuprofen (2, 3)], and corticosteroids

[4]) and devices (e.g., cooling blankets, sophisticated cooling machines, and hemofiltration [5]) decrease temperature. However, few interventions that control fever have been evaluated in RCTs.

On the other hand, fever may be beneficial because fever increases clearance of microorganisms, immune response, and the heat shock response (6–8). Furthermore, control of fever can worsen outcomes (9, 10), whereas increasing temperature after endotoxemia can improve outcomes in animal models (11). In a retrospective cohort study, use of corticosteroids for fever control in H1N1-infected patients was associated with increased mortality (12). Finally, patients with septic shock who have hypothermia have a higher mortality than patients with fever (13).

The mechanism of cooling is likely very important in the effects of cooling on clinical efficacy. For example, the positive results of Schortgen and colleagues (1) contrast sharply with an RCT of intravenous ibuprofen, which rapidly decreased temperature and prostaglandins but had no effects on mortality in severe sepsis (2). Differences between these two trials include the populations studied (septic shock [1] vs. severe sepsis [2]), mortality endpoints (14 d [1] vs. 30 d [2]) and the intervention for cooling (cooling blankets [1] vs. ibuprofen [2]). Not only was control of fever not associated with benefit in the ibuprofen trial, ibuprofen was more efficacious (i.e., decreased mortality) in patients who were hypothermic at inclusion (13).

Cooling can cause shivering and so increase need for sedation and even neuromuscular paralyzing medications. In the study by Schortgen and coworkers (1), the use of sedation and neuromuscular paralysis was similar between groups (baseline and during the 48-h intervention period), and temperature, vasopressor use, and mortality were similar in patients with and without neuromuscular blockers. It is not clear whether there was a protocol or whether clinicians managed sedation and neuromuscular blockers.