Interventions to Reduce Mortality among Patients Treated in Intensive Care Units

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Purpose: Using sensitivity analysis to estimate the impact, in terms of patient lives, of the failure to use proven therapies known to reduce mortality in critically ill intensive care unit patients.

Materials and Methods: We identified high-impact interventions published in the last 5 years in the *Journal of the American Medical Association* or New England Journal of Medicine, extracted the absolute risk reduction associated with each intervention and gleaned the national incidence of each condition and the percent of the population not receiving the cited therapy from the literature. From this information, we calculated national estimates of the excess deaths from failure to use these therapies.

Results: With consistent and appropriate implementation of the 5 cited evidence-based interventions, we found a total of 167,819 lives could be saved per year, with a range of 137,670 to 197,965 lives saved per year.

Conclusions: Mistakes of omission are common in the critical care setting and lead to significant preventable mortality. There is a significant gap between the discovery of effective interventions and their use in clinical practice. By viewing the delivery of healthcare as a science and increasing funding for health services research, we may be able to increase the use of effective therapies and, as a result, reduce patient mortality.

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Mounting evidence suggests that effectively constructed and implemented therapies can improve care and increase survival of patients in health care settings.1,2 Despite a large volume of rigorously tested and verified interventions that improve patient outcomes, patients can only count on receiving these interventions half of the time.3,4 The impact of these errors of omission on patient outcomes is poorly understood and not well documented.

Intensive care units (ICUs), caring in the United States for 4.4 million people a year while costing approximately 1% of the gross domestic product, are not exempt from this trend, varying widely with regard to practice, organizational structure and morbidity rates.5-10 There are several interventions, identified from well-conducted randomized trials or systematic reviews that can reduce mortality in critically ill patients.11-15 Although the extent to which these therapies are routinely used is unknown, ICU mortality rates have not decreased to the extent predicted by recent clinical studies.16,17 Systematic implementation of ICU interventions, either independently or concurrently if appropriate, could result in a significant reduction of the current 12% mortality rate among ICU patients.18 The specific aim of this paper is to estimate the number of preventable deaths in the United States from the failure to use interventions known to reduce mortality in critically ill patients.

**MATERIALS AND METHODS**

**Study Design**

To achieve our aims, we conducted a literature review. We identified interventions published in the *Journal of the American Medical Association* or the *New England Journal of Medicine* estimated how often people in the United States received these therapies, and calculated national estimates of the excess deaths from failure to use these therapies. Our goal was not to identify every intervention known to improve mortality in critically ill patients but rather to identify significant interventions published in major journals for which there is consensus that the interventions ought to be used.16,19

**Data Sources**

We required four data sources to estimate the number of preventable deaths. First, we identified effective interventions. Second, we estimated the
number of patients at risk for that disease in the US population. Third, using the results of the study, we estimated the absolute risk reduction associated with the use of the intervention. Fourth, we approximated the percent of the exposed population not receiving the identified therapy and then calculated the number of preventable deaths.

Identification of Interventions

To identify interventions known to reduce mortality in critically ill patients published in high impact journals, we searched 2 major journals: *New England Journal of Medicine* and *Journal of the American Medical Association*. Two independent observers performed a web-based, systematic literature review of these journals. We included randomized trials or systematic reviews, published in the last 5 years, of interventions that reduce mortality in critically ill patients that were implemented in an ICU (search terms: ICU, mortality, critically ill and January 1998 through August 2003, JAMA limited to Caring for the Critically Ill Patient, N ENGL J MED limited to Original Articles). Two ICU physicians (P. J. P and S. M. B.) selected articles that met inclusion criteria and for which there was general agreement about their use. For each selected article, we abstracted data regarding study population, intervention, and the absolute effect of the intervention on mortality.

Estimates of the Number of Patients at Risk

For each disease that the above interventions targeted, incidence data were abstracted from published data and a pharmaceutical company’s marketing research. 20-24 When needed, we multiplied incident data by the current US population of 280,000,000 to estimate numbers at risk. 25 The population numbers chosen were well cited in the literature.

Estimate of Population Percentage not Receiving Therapy

When available, data were gleaned from published studies. 20,26,27 When not available, we estimated the use of these therapies based on performance in a cohort of 23 ICUs through the Volunteer Hospitals of America (VHA) working to improve ICU care, or on pharmaceutical company information. 21,28 If no data source were available, we estimated, consistent with a broad range of other interventions, that half the patients received the therapy. 3

Estimate of Preventable Deaths

For each intervention identified, we calculated the number needed to treat (NNT), that is the number of patients that must receive the intervention to prevent one death. The NNT is equal to one over the absolute risk. Annual preventable deaths were estimated by the following calculation: Incidence of specific diseases in the United States multiplied by the percentage of patients not receiving therapy divided by the NNT. Although the time period for the studies varied, they were all less than 1 year. Because some of our estimates of the number of patients at risk and the percentage of patients not receiving the therapy are imprecise, we conducted sensitivity analysis for these variables.

RESULTS

Our literature review identified 89 abstracts and we included 5 studies (4 randomized trials and 1 systematic review) in our analysis that met inclusion criteria and are widely accepted. 16,20,29 We summarize these studies in Table 1.

Table 2 lists the number of patients at risk in the United States, the percentage of patients not receiving a given intervention, the number of patients needed to treat in order to prevent 1 death, and the preventable deaths in the United States annually. Our assumptions to estimate the relevant populations and the number of preventable deaths for each intervention are discussed below.

ICU Physician Staffing

Using Medicare data and published literature, we estimated the number of ICU admissions to be 4,400,000 annually. 5 The range of patients not receiving therapy (63%-90%) was based on a national health care reporting database containing 40 million patients and a nationally representative survey of hospitals, as well as from a survey conducted for the Leapfrog Group. 20,26 To estimate the NNT for ICU physician staffing, we applied the 30% relative risk reduction to the average ICU mortality of 12% to provide NNT of 25. 11,18 The total number of annual preventable deaths was calculated to be 134,640 with a range of 110,880 to 158,400.

Activated Protein C

We estimated that 190,000 patients had severe sepsis with an APACHE II score greater than 24,
based on a correspondence with a major pharmaceutical company. The exclusion criteria used in our estimate are stricter than those cited in the article, and instead followed recommendations by the Food and Drug Administration. Therefore, our incidence number may be conservative, espe-

table 1. Interventions to Reduce Mortality

<table>
<thead>
<tr>
<th>Citation</th>
<th>Intervention</th>
<th>Time Period for Mortality</th>
<th>Mortality Rate Without Intervention</th>
<th>Mortality Rate With Intervention</th>
<th>Absolute Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane, et al JAMA 288:862-871, 2002</td>
<td>A 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly decreased risk of death in patients with septic shock and relative adrenal insufficiency who were treated in the ICU without increasing adverse events.</td>
<td>28 day</td>
<td>63</td>
<td>53</td>
<td>10</td>
</tr>
<tr>
<td>Van den Berghe, et al N Engl J Med 345:1359-1367, 2001</td>
<td>Intensive insulin therapy to maintain blood glucose at or below 110 mg/dL reduced morbidity and mortality among critically ill patients in the surgical ICU.</td>
<td>1 year</td>
<td>8</td>
<td>4.6</td>
<td>3.4</td>
</tr>
<tr>
<td>ARDS Network N Engl J Med 342:1301-1308, 2000</td>
<td>In patients with acute lung injury and acute respiratory distress syndrome, lower tidal volume ventilation resulted in decreased mortality and number of ventilator days.</td>
<td>28 day</td>
<td>39.8</td>
<td>31</td>
<td>8.8</td>
</tr>
</tbody>
</table>

*Study provided a relative risk reduction of 30% that was applied to an average ICU mortality of 12%.11,18

Table 2. Calculations of Preventable Deaths

<table>
<thead>
<tr>
<th>Citation</th>
<th>Incidence</th>
<th>Percent Not Receiving Therapy</th>
<th>Number Needed to Treat to Prevent one Death</th>
<th>Range of Preventable Deaths in the United States Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pronovost, et al JAMA 288:2151-2162, 2002</td>
<td>4,400,000 (5)</td>
<td>76.5</td>
<td>25</td>
<td>134,640</td>
</tr>
<tr>
<td>Annane, et al JAMA 288:862-871, 2002</td>
<td>101,112 (22)†</td>
<td>50</td>
<td>10</td>
<td>5,056</td>
</tr>
<tr>
<td>ARDS Network, N Engl J Med 342:1301-1308, 2000</td>
<td>89,000† (24)</td>
<td>75</td>
<td>29.4</td>
<td>11,523-13,170</td>
</tr>
</tbody>
</table>

Total: 167,819
Range: 137,670-197,965

*Population presented as 76.6% of septic shock patients, who are 3% of the total ICU admissions per year (22,32)
†Population presented as 11% of the total ICU admissions per year (5,32)

Data presented in incidence per 100,000 person-years was multiplied by the current United States population of 280,000,000.25
cially when ongoing studies looking at broader applications of protein C therapy are concluded.\textsuperscript{16} The range of the population not receiving therapy, 85\%-93\%, was obtained from 2002 and projected 2003 prescriptions of activated protein C (APC).\textsuperscript{21} The NNT, 16.4, was obtained from the randomized APC trial.\textsuperscript{12} The total number of annual preventable deaths was calculated to be 10,311 with a range of 9,847 to 10,774.

**Steroids in Sepsis**

We estimated 132,000 cases of septic shock are cared for in the ICU annually based on the application of a 3\% septic shock incidence in an multicenter Italian ICU study to the total number of American ICU patients.\textsuperscript{5,22} To estimate the population at risk, we conservatively multiplied this number by the percentage of corticotrophin non-responders in the study, 76.6\%, creating a population of 101,112 septic shock nonresponders. This is a cautious estimate when the projected 1.5\% per year increase in sepsis cases due to the growing elderly population is considered.\textsuperscript{23} Because there is no national database for the percentage of patients not receiving this therapy, we estimated that 50\% of patients were receiving this therapy, based on recent *New England Journal of Medicine* findings.\textsuperscript{3} In addition, our experience with 24 hospitals working with the VHA, Inc to improve the care of patients with septic shock demonstrated that only 30\% of septic shock patients received steroids. Given these imprecise estimates, a large range was used for these numbers in the sensitivity analysis. The NNT, 10, was obtained from the randomized trial.\textsuperscript{13} The total number of annual preventable deaths was calculated to be 5,056 with a range of 1,517 to 8,595.

**Glucose Control**

We estimated that 484,000 patients were in the ICU with a length of stay (LOS) greater than 7 days. This data were obtained from the total ICU admission data as stated above, and a large, year-long LOS study, which found that 11\% of patients had a LOS greater than 7 days.\textsuperscript{5,31} The entire ICU admission population was used, based on a recent review article and a recent critical care and infectious disease consensus conference suggesting the application of tight glucose control to all ICU patients, even though the original article’s study population was only surgical ICU patients.\textsuperscript{16,19} Despite this, we feel our estimate to be conservative, since the study found a decrease in mortality in patients with a LOS of greater than 5 days, and we used patients with a LOS of greater than 7 days.\textsuperscript{16,32} The percentage of the population not receiving tight glucose control therapy, 70\%-80\%, was estimated from an unpublished, nationwide study of ICUs conducted by the VHA in 23 ICUs.\textsuperscript{28}

The NNT, 29.4, was obtained from the randomized trial.\textsuperscript{14} The total number of annual preventable deaths was calculated to be 12,347 with a range of 11,523 to 13,170.

**Acute Respiratory Distress Syndrome**

We estimated 89,000 cases of acute respiratory distress syndrome (ARDS) annually based on a National Institutes of Health ARDS network database.\textsuperscript{24} The percent of the population not receiving therapy, 50\%-90\%, was taken from an abstract on the use of low-tidal volume therapy and the ICU data of one urban, academic medical center.\textsuperscript{29} A wide range was also used for this number in the sensitivity analysis given the imprecise estimation. The NNT, 11.4, was obtained from the randomized trial.\textsuperscript{15} The total number of annual preventable deaths was calculated to be 5,465 with a range of 3,903 to 7,026.

**DISCUSSION**

The Institute of Medicine report “To Err is Human” suggested between 44,000 and 98,000 people die each year in the United States because of medical errors.\textsuperscript{33} These estimates are based in general on mistakes of commission, things caregivers do to patients, and did not include mistakes of omission—the failure to use therapies we ought to. Our study suggests that mistakes of omission may pose a much greater threat to patient safety. We found that consistent and appropriate implementation of 5 evidence-based interventions in critically ill patients can prevent 137,670 to 197,965 deaths, a far greater number of patients than “To Err is Human” estimated for all of US healthcare.

While these numbers are clearly a rough estimate and subject to debate, they highlight the staggering number of preventable deaths from failing to implement evidence-based interventions in ICU patient care. While we used conservative estimates of incidence and intervention use, the impact of these interventions may not be additive. In addition, our study included only 5 high profile ICU interventions and neglected the multiple other interventions that may also reduce ICU mortality and
mortality within other high risk specialties such as surgery, cardiovascular disease, and dialysis.

These results suggest there is an enormous gap between therapies that are known to be effective and their use in clinical practice. Although alarming, these results are entirely predictable based on the dispersion of the United States government’s research dollars. Ninety-nine percent of US research dollars, largely through the National Institutes of Health and Industry, are spent understanding disease biology and identifying effective therapies with 1%, largely through the Agency for Healthcare Research and Quality and Foundations, left to learn how that patients receive these therapies safely. With only half of the patients receiving the interventions they ought to, this research paradigm needs to be reconsidered. We need to view the delivery of healthcare as a science as well as an art and rigorously learn how to increase the extent to which effective therapies are used. Focused and funded efforts to improved use of effective therapies have benefitted Medicare and VA patients, patients in the VHA and Institute for Healthcare Improvement, as well as patients in other fields and specialties.

Indeed, our research team, with funding from Agency for Healthcare Research and Quality (AHRQ), is currently implanting the interventions used to reduce blood stream infections and improve ventilator care in the 108 ICUs in Michigan. We can no longer assume that our learning ends with discovering effective therapies; to improve patients’ outcomes, we need a more balanced research portfolio that values the end as well as the beginning of the translation superhighway.

There are several limitations to our study. First, we selected only 5 interventions for our analysis. We sought to be conservative and include interventions that are widely accepted by caregivers. Had we included a larger number of studies, the estimated number of preventable deaths would increase. Second, to estimate preventable deaths, we relied upon various sources of information, with varying degrees of random and systematic error. Nevertheless, we conducted sensitivity analyses of our assumptions.

We recognize that there is some controversy about the intervention in the control group in the ARDS trial potentially causing us to overestimate the treatment benefit. Even with the most conservative assumptions, the results are significant. Indeed, the lower estimate of the number of preventable deaths (137,670) from not using these 5 therapies in ICU care exceeds the total estimate of preventable deaths from mistakes of commission. Third, we assumed that the effect of each intervention was independent and additive. This may not be so and would decrease the potential number of lives saved. Fourth, we estimated the effect of the intervention based on results from one study. Nevertheless, the interventions are supported with a large body of evidence and consensus conference practice guidelines.

Fifth, our literature search was neither complete nor based on highly systematic search methods such as journal impact or citation counts. We sought to identify interventions from the most highly read US journals. We believe more rigorous research methods would only have added to the number of lives that could be saved with broad applications of evidenced based medicine. Finally, the results achieved in the randomized trial (efficacy) may not be replicated when broadly applied (effectiveness) due to such factors as study exclusion criteria and study bias. Nonetheless, the randomized trials provide us with the best available estimate of the efficacy of the interventions.

Mistakes of omission, the failure to use therapies known to be effective, are common and present a significant opportunity to improve care. We estimate the failure to use 5 commonly accepted therapies in critical care results in between 137,670 to 197,965 preventable deaths per year. The current research paradigm that focuses mainly on understanding disease biology and identifying effective therapies needs to be reconsidered. Greater research and effort is needed to help ensure that patients receive the therapies they ought to receive. This will likely come from evaluating how the organization, finance and delivery of health care influence physician behavior.

REFERENCES
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