Update in Critical Care

An Old Dog presents New Tricks

Internal Medicine Grand Rounds
University of Texas Southwestern Medical School

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W. C. Yarbrough, MD

Disclaimer:

Old dogs teach young pups. The drug companies know this. Since drug companies fund 90% of all continuing medical education, Old Dogs get put on the speaker bureaus of drug companies. This is the first Grand Rounds where I have discussed specific drugs. I could not find all the drug companies to list, but please assume that I am on the speaker's bureau of every drug company known to man and that I have been paid to give a talk for that drug company. If I am not on the speaker's bureau, then I have received a pen or a meal, or a gift from every drug company known to man. I am also going to start out discussing an off-label, non-FDA approved use of a drug.

Biographical Information

W. C. (Claibe) Yarbrough, M.D.
Associate Professor, Internal Medicine
Pulmonary and Critical Care Medicine
U. T. Soutwestern Medical School
Staff Physician, V.A. North Texas Health Care System

Areas of interest:

Clinical Pulmonary and Critical Care Medicine
Medical Informatics
Severity of Illness Scoring
Immunology

wc.yarbrough@med.va.gov

Introduction

A recent study out of Harvard by Dr. Niteesh K. Choudhry and published in the Annals of Internal Medicine showed that physicians get worse at patient care the longer they are out of training. This study was an analysis of studies in the literature looking at patient care as a function of the years out from training of the physician. A conclusion was that when older physicians are compared with younger physicians, that older physicians have less factual knowledge, are less likely to adhere to appropriate standards of care, and also have worse patient outcomes.

Twelve of the studies assessed the knowledge of physicians. All twelve of these studies showed a negative association between knowledge and experience. The cut-off for this difference seemed to be 40 years of age.

Twenty-four studies assessed the adherence to standards of practice for diagnosis, screening, and prevention. Overall, 15 of these studies (63%) showed a negative correlation with years in practice and adherence to these standards. In one of the studies there was a J-shaped curve. Physicians in practice between 6 and 15 years provided the most appropriate care, whereas physicians in practice less or more than these numbers were worse.

There were 19 studies that assessed physician adherence to therapeutic standards of care. Three quarters of these studies showed a negative correlation between years of practice and appropriate therapy of patients.

Patient outcomes were also affected by how long the physician had been practicing. One study showed that patients treated for acute myocardial infarction had 0.5% increased mortality for every year the physician had been out of school. This was not confined to Medicine patients. More experienced surgeons had higher mortality rates as well.

> **"I am not interested in any drug or technology that was developed after my residency."**
>
> **Tongue-in-cheek remark, speaker at resident's conference, 2005.**

These studies and the conclusions that can be drawn from them are disturbing. The paper was hopeful that this finding would disappear once the current "young pups" matured. The current practice is that the specialty boards for the ABIM expire every ten years. Prior to 1990 that was not the case. Unfortunately, there is evidence that reading may not be sufficient to change practice styles.

Physicians have been associated with the pharmaceutical industry as long as there have been drug companies. Recent articles in the New England Journal of Medicine review and analyze the good and bad aspects of this association. In

the same issue of the NEJM there were two articles on medical errors in residents trained in our older system of education.

The plethora of information in any ICU can exceed human decision-making capabilities. This excess information can lead to unnecessary variations in the clinical care of patients and to a greater likelihood for errors. At the same time, the demand for high-quality care is increasing. Despite excellent evidence for a new therapy, it may take ten to twenty years (average17) for it to become widely used and standard. There is little research being done on how to deliver these therapies effectively and efficiently.

These all point to the suggestion that we have to protect our patients from ourselves.

An electronic medical record with reminders, guidelines, and protocols may be an answer to this progressive bias. Clinical information systems have been discussed in this forum before and clinical reminders in particular were discussed recently.

This protocol will discuss several subjects that require a paradigm shift from our previous way of thinking about these subjects. A fluidity of thought and a lessening of value rigidity seem necessary for us to protect our patients. This is extremely difficult to develop and maintain. Instead, protocols may be needed rather than guidelines. The ICU with a clinical information system lends itself nicely to the use of protocols.

The difference between a guideline and a protocol can be defined as:

•**Guidelines** are general statements or overviews of concepts. They are like textbooks in that they provide little instruction about specific clinical decisions.
•**Protocols** (also called algorithms) are detailed and provide specific instructions for individual clinical decisions.

Choudhry NK. Fletcher RH. Soumerai SB. Systematic review: the relationship between clinical experience and quality of health care **Ann Intern Med**. 2005 Feb 142(4):I54

Weinberger SE. Duffy FD. Cassel CK. "Practice makes perfect"...or does it? **Annals of Internal Medicine**. 2005 Feb 142(4):302-3,.

Lockley SW et al., for the Harvard work hours, health and safety group. Effect of Reducing Interns' Weekly Work Hours on Sleep and Attentional Failures. **N Engl J Med** 2004 Oct 351:1829-1837.

Christopher P. Landrigan CP et al., Effect of Reducing Interns' Work Hours on Serious Medical Errors in Intensive Care Units. **N Engl J Med** 2004 Oct 351:1838-1848.

Drazen JM. Awake and informed. **N Engl J Med** 2004 Oct 351:1884.

Blumenthal D. Doctors and drug companies. **N Engl J Med** 2004 Oct 351:1885-1890.

Studdert DM et al., Financial conflicts of interest in physicians' relationships with the pharmaceutical industry – self regulation in the shadow of federal prosecution. **N Engl J Med** 2004 Oct 351:1891-1900.

Comparison of interventions in the ICU
Use of Drotrecogin alpha as a benchmark

Intervention	Mortality of controls	Mortality of Experimental	Number needed to treat
Xygris (activated protein C)	30.8%	24.7%	17
Low Dose Steroids	63%	53%	10
Early Goal directed Therapy	46.5%	30.5%	7
Lung protective Ventilation	39.8	31%	12
Intensive Glycemic Control	8%	4.6%	28
Restricted transfusions	28%	22%	
Adequate Antibiotic Therapy	52.1%	12.2%	
ICU Staffing (open vs closed)	51%	31%	

Nutrition in the ICU

Nutrition in the ICU was the topic of my first Grand Rounds when I was a young pup. Data obtained since that time suggests a different course of action than what I suggested then. It was a paradigm that patients should be fed early and by the enteral route. Both the timing and the amount may have to change. Parenteral nutrition still has many poor qualities associated with it:

- Intravascular infections
- Complications of line insertion
- Higher costs
- Loss of intestinal villous architecture (leading to translocation of bacteria?)

However, the enteral route also has poor qualities associated with it. It is thought to be associated with increased incidences of hospital acquired and ventilator associated pneumonia.

There is a recognized association between a poor nutritional status and a poor clinical outcome including mortality, morbidity, cost of hospitalization and length of hospitalization. Since the 1960's, we have been able to provide systemic parenteral or enteral nutrition to patients that could not otherwise eat. There were many reasons that we assumed this would improve outcome:

1. The association mentioned above.
2. Nutritional support improves markers of malnutrition.
3. Any organism will die if deprived of nutrients long enough.
4. Retrospective and prospective results of efficacy.

5. Doing something is better than doing nothing.

These reasons are appealing, however there are defects in each.

1. Association does not mean causation.
2. Improving tests does not mean improving outcome.
3. Starvation death only occurs in severe cases (>40% loss)
4. Uncontrolled trials do not assess what would have happened without the intervention.
5. Doing something harmful is not better than doing nothing.

There are few prospective, randomized, controlled trials of nutrition in critically ill patients. Often during the first few days of severe illness the gut does not work. Whether this is secondary to the illness itself or our therapy is not known. Often during this time the patient is on pressors and it is thought that a recumbent position will be of benefit. However, the recumbent position is associated with an increase in nosocomial pneumonia. Also, patients develop a loss of acid formation, even without stress ulcer prophylaxis. This loss of acid formation is thought to be associated with overgrowth of bacteria in the gut. For these reasons we have not fed patients until they have stabilized and can be placed into a semi-recumbent position. If their illness does not allow this within a week, then total parenteral nutrition is considered.

Results from an observational study suggest that providing close to 100% of goal calories is associated with worse clinical outcomes. Patients in this study, on average, received about 50% of their goal calories. The investigators divided this cohort of 187 patients into three groups: those who received 0-32% of recommended calories, those who received 33-65% of goal calories, and those who received >66% of goal calories. The mortality was greatest in the group that received the most calories. Mortality in this group was greater than in the group that received the fewest calories. It was best to receive between a third and two thirds of goal calories than to receive lower or higher intake. The reasons why this should be true are not clear, but may relate to higher incidences of hospital acquired and ventilator associated pneumonia or higher glucose levels (see below).

There is some interest in using nasojejunal tubes rather than nasogastric. The nasojejunal tubes are usually placed endoscopically. A couple of studies suggest that there is no real difference between these two options. One study showed that the patients with nasojejunal tubes tolerated feeding significantly more than the patients with nasogastric tubes. Even when 8 patients were converted from nasogastric to nasojejunal 7 were then able to tolerate feeding. However, there was no difference in total volume of feeding in the first 48 hours and no difference in total time of feeding (8 days). About 30% of both types of tubes were dislodged at some point during the study.

The other study addressed the question of microaspiration between these two types of feeding tubes. On 3 consecutive days, each patient received radiolabeled tube feeds. The radioisotope was then measured in the oropharynx and in the endotracheal tube. At least 1 episode of regurgitation occurred in 81 percent of the nasogastric group and 100 percent of the postpyloric group. The difference was non-significant. At least 1 episode of pulmonary aspiration occurred in 52 percent of gastric patients and 33 percent of postpyloric patients. This was again a non-significant difference. The numbers of episodes per day did not differ significantly between the 2 groups.

Use of Narcan P.O.

The use of evidence-based medicine is our current paradigm. However, there are other valid ways to further our care. A recent treatment circulating especially among surgeons is the use of oral nalaxone (Narcan) to reverse the effects of narcotics on the gut. Narcan is metabolized in the liver and has a significant first pass phenomenon. This allows the drug to act within the intestine without effect on circulating narcotics. Therefore the systemic narcotic does not cause the common paralysis of the gut with constipation, high residual volumes, etc. The dose is 2 to 4 mg. P.O. q4 to q8 hours. This is a non-FDA approved, non-label use of this drug. It comes in 1mg/ml vials and the route of administration has to be clearly understood. Reversal of systemic narcotics in a severely ill patient can be devastating.

Koretz, RL: Nutritional Supplementation in the ICU. **Am J Respir Crit Care Med** 1995; 151:570-573.

Krishnan JA, Parce PB, Martinez A, et al: Caloric intake in medical ICU patients: Consistency of care with guidelines and relationship to clinical outcomes. **Chest** 2003; 124:297-305.

Davies AR et al. Randomized comparison of nasojejunal and nasogastric feeding in critically ill patients. **Crit Care Med** 2002 Mar; 30:586-90.

Heyland DK et al. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: Results of a randomized controlled trial. **Crit Care Med** 2001 Aug; 29:1495-1501

Early Goal-directed therapy

The standard of care for critically ill patients remains largely supportive. However, there is some evidence that early identification and rapid intervention of these patients may decrease mortality. Rapid intervention, at least with defibrillation, has led to an improvement in survival in patients suffering out of hospital arrests. Resuscitation of patients in shock is essential and has been pushed further out before ICU admission. There is little evidence that the type of resuscitation fluid, colloid versus crystalloid, is important. However, there is evidence that early optimization of hemodynamic status can have a significant mortality benefit. This was shown in a randomized, prospective trial of patients with septic shock. Rivers et al. demonstrated that early, goal-directed resuscitation guided by central venous oxygen saturation, using a special

catheter, decreased in-hospital mortality from 46.5% in the standard treatment group to 30.5% in the early goal-directed therapy group. They used the following goals in their study:

- ✓ Central venous pressure: 8-12 mm Hg (12 to 15 mm Hg if ventilated)
- ✓ Mean arterial pressure >=65 mm Hg
- ✓ Urine output >=0.5 mL/kg/hr
- ✓ Central venous or mixed venous oxygen saturation >=70%

They achieved these goals in the emergency department in the initial 6 hours of resuscitation, prior to admission to the ICU. This early 6 hours of resuscitation resulted in an improvement in 28 day mortality. The goals were met if the central venous oxygen saturation or mixed venous oxygen saturation reached 70%. If the saturation was not achieved with fluid resuscitation to the central venous pressure target, then transfusion of packed red blood cells to achieve a hematocrit of >=30% and/or administration of dobutamine (up to a maximum of 20 micrograms/kg/min) was used. The patients receiving the rapid resuscitation received more fluid early, although the amount at 72 hours was the same. They also received more blood products and more dobutamine than the control patients.

It is hard to argue with the success of this study in decreasing mortality with rapid resuscitation. Rapid, goal-directed therapy has been used with success in surgical patients for some time (see refs.). The use of a special catheter to continuously measure oxygen saturation might imply that this method is similar to goal-directed oxygen delivery, which has not been beneficial in medicine patients. This study also seems at odds with the data concerning blood transfusions (see Transfusions). Whatever interpretation is placed on this study, the place to accomplish this rests primarily in the emergency department rather than the ICU. If the patient is admitted quickly, then rapid resuscitation makes sense and the methods used are certainly common practices in an ICU.

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. **N Engl J Med** 2001;345:1368-77.

Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. **JAMA** 1993;270:2699-707. Ovid Full Text Bibliographic Links

Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. **BMJ** 1999;318:1099-103.

Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. **N Engl J Med** 1994;330:1717-22.

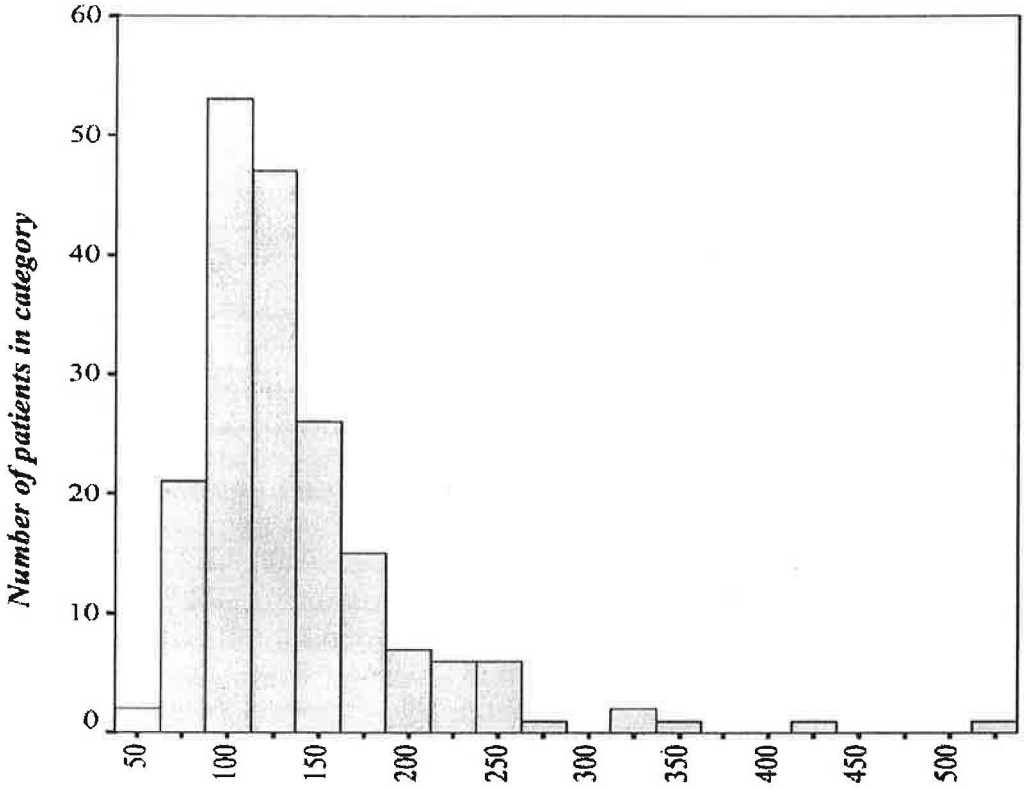
Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients: SvO2 Collaborative Group. **N Engl J Med** 1995;333:1025-32.

Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized,

controlled clinical trial of transfusion requirements in critical care: Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. **N Engl J Med** 1999;340:409-17.

Glucose Control in the ICU

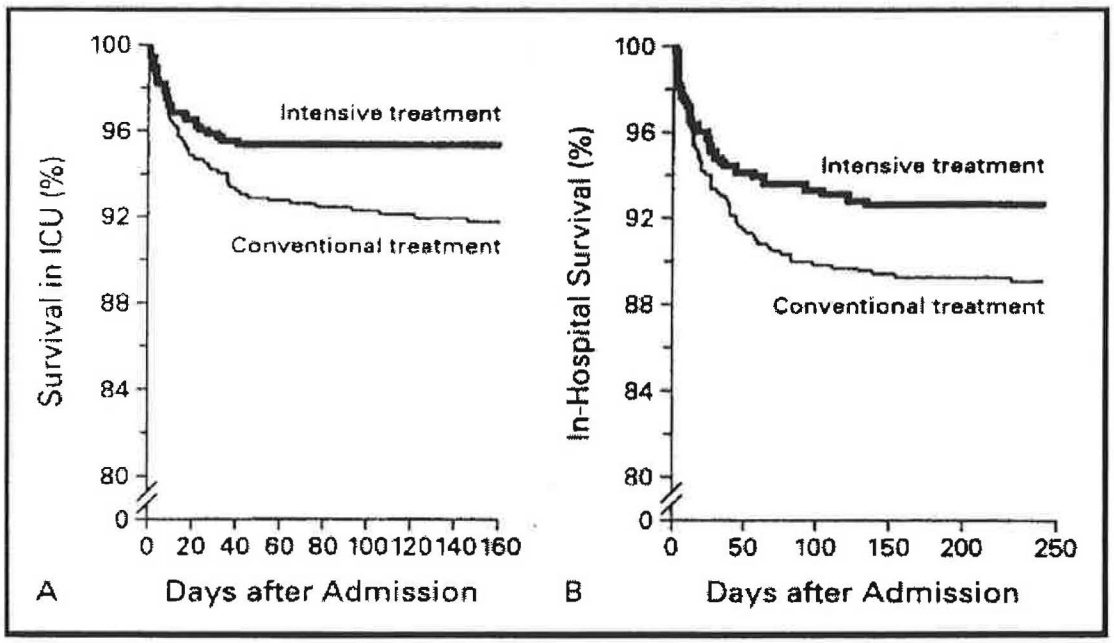
Endocrine abnormalities are common in critically ill patients (see Vasopressin). A recent study has shown that tight glucose control significantly reduces mortality in a group of ICU patients. The figure below shows the glucose levels of patients on admission to the intensive care unit of one university hospital.



This prospective observational study showed that the mortality of patients with normoglycemia was significantly better than that of patients with hyperglycemia on admission. This difference was significant even after correcting for severity of illness (SAPS II) and exclusion of diabetics. The mortality of patients with hyperglycemia was 29.3%, while the mortality of patients with normoglycemia was 13.7%.

The study that showed significant mortality benefit to treatment of hyperglycemia was a prospective, randomized, controlled clinical trial. The population consisted of 1548 patients admitted to a surgical intensive care unit. These patients were randomized to either strict glucose control of (80 to 110 mg/dL) or conventional control (180 to 200 mg/dL). Continuous-infusion insulin was often required to achieve the tight glucose control, although insulin was also used in the

conventional group. Mortality was significantly reduced in patients managed with strict glucose control as compared with the more liberal conventional management strategy (4.6%*vs* 8.0%, $P < 0.04$) as shown below.

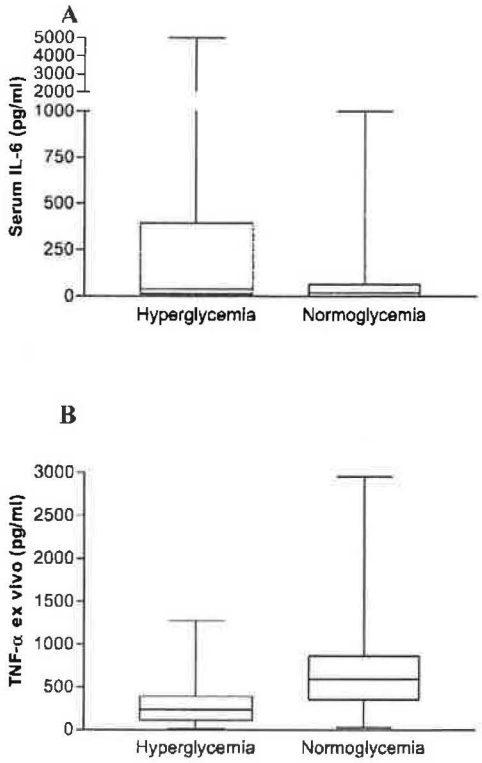


There were four times as many deaths from multiple organ dysfunction with a proven septic focus in the conventional management group compared with the patients managed with intensive insulin. To evaluate whether the insulin or the tight glucose control was responsible for the improved outcome, the same group of investigators used multivariate logistic regression analysis and demonstrated that it was the lower glucose level, not the use of insulin, that was responsible for the observed decrease in mortality. In addition, critical illness polyneuropathy, bacteremia, and inflammation were all statistically and clinically improved by tight glycemic control independent of the dose of insulin given. Some clinicians have extrapolated these results to all critical care patients in general. However, two thirds of the patients in the study were status-post cardiac surgery and the baseline mortality rates were low.

Another researcher has examined this issue in a 14-bed general medical-surgical intensive care unit in a Connecticut community hospital. They used a nurse-driven, insulin-based ICU protocol to maintain serum glucose at lower than 140 mg/dL in all patients. This was implemented on February 1, 2003. Outcomes for the 800 patients who were admitted just before this date were compared with outcomes for 800 patients who were admitted immediately after this date. Demographic and clinical variables were similar in both groups. The intensive-glucose-control patients exhibited fewer cases of new renal failure (3 vs. 12); fewer percentage transfused (21% vs. 25%)(excluding GI bleeders), lower mortality rate (15% vs. 21%); and shorter median length of ICU stay (1.6 vs. 1.9 days). No significant difference was noted in the incidence of ICU-acquired

infections. This time-dependent, before-after design and lack of statistical examination of confounding factors limits the use of this study to generalize this approach to all ICUs.

The prospective observational study (Wasmuth) also observed a positive correlation with serum IL-6 levels and glucose and a negative correlation between TNF-α ex vivo and glucose as shown below. This association with pro- and anti- inflammatory cytokines gives some basis for the pathophysiology behind this phenomenon.



The choice of whether to tightly control glucose centers around the make-up of the ICU. Our surgical collegues at the VA have already adopted this strategy. A reasonable protocol might be in the form of an alert if the glucose is above 140mg/dl, especially if the patient is on any form of glucose infusion. This problem of glucose control might be another reason to withhold feeding until later in the course of recovery (see Nutrition).

Wasmuth, HE, et al. Hyperglycemia at admission to the intensive care unit is associated with elevated serum concentrations of interleukin-6 and reduced ex vivo secretion of tumor necrosis factor-α. **Crit Care Med** 2004 32(5):1109-1114.

Van den Berghe G et al. Intensive insulin therapy in critically ill patients. **N Engl J Med** 2001 Nov 8; 345:1359-1367.

Evans TW. Hemodynamic and metabolic therapy in critically ill patients. **N Engl J Med** 2001 Nov 8; 345:1417-1418.

Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? **J Clin Invest** 114(9):1187-1195.

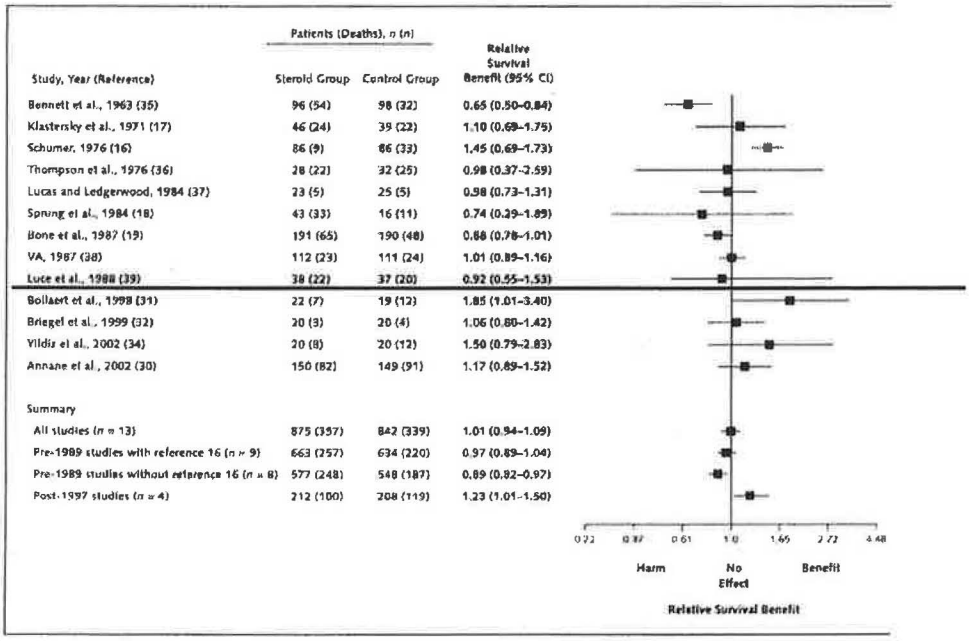
Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. **Mayo Clin Proc** 2004 Aug; 79:992-1000.

Van den Berghe G. Tight blood glucose control with insulin in "real-life" intensive care. **Mayo Clin Proc** 2004 Aug; 79:977-8.

Steroids in Septic Shock

Past studies of the use of high-dose steroids in the treatment of severe sepsis and septic shock have produced disappointing results; many of the clinical studies were poorly designed. Two of the best studies found no significant differences between the treated and control patients with regard to the prevention of shock, the reversal of shock, or overall mortality. This was true in subgroup analysis as well. One study found that mortality secondary to infection was higher in the steroid-treated group. For this reason, high-dose steroids were abandoned.

Effects of steroids on survival in previous and recent sepsis trials



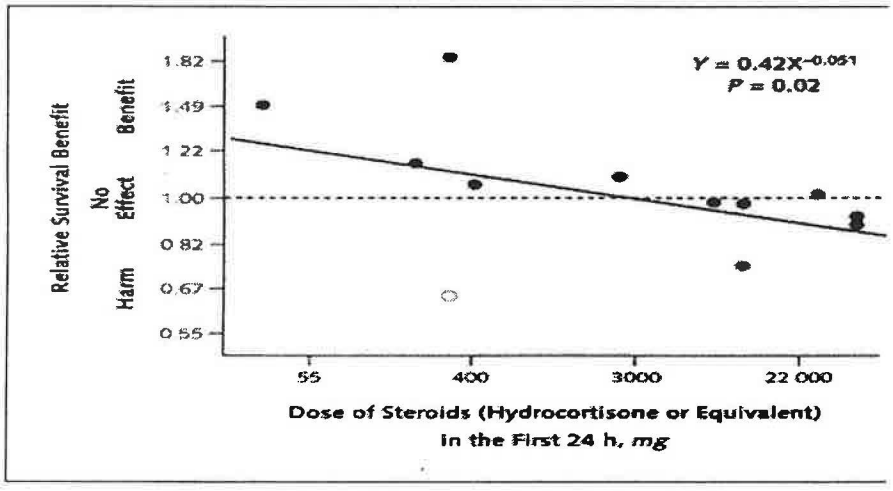
Minneci, P. C. et. al. Ann Intern Med 2004;141:47-56

The picture above shows that there is a difference in those studies done after 1997 using lower doses of steroids. Two small randomized trials provided evidence that longer moderate-dose courses might be beneficial. In a study of 41

patients with septic shock, five days of intravenous hydrocortisone reduced mortality from 63 percent to 32 percent. In a trial with 24 ARDS patients, a month of methylprednisolone reduced in-hospital mortality from 63 percent to 13 percent.
A French trial confirmed these observations. From 1995 to 1999, 300 patients with presumed septic shock from 19 ICUs were enrolled in a randomized, placebo-controlled trial testing the efficacy of 100 mg of intravenous hydrocortisone every 6 hours plus 50 µg of oral fludrocortisone daily for 7 days. All patients underwent a corticotropin stimulation study to detect adrenal insufficiency. The primary study endpoint was 28-day survival in those patients who did not respond to corticotropin stimulation.
There were 229 corticotropin nonresponders. Sixty subjects (53%) receiving corticosteroids died, compared with 73 (63%) receiving placebo. In corticotropin nonresponders, the time to discontinuation of vasopressor therapy was significantly shorter in patients receiving corticosteroids than in those receiving placebo. In corticotropin responders, corticosteroid therapy provided no apparent benefit. Corticosteroids significantly shortened the duration of vasopressor therapy in all patients, although this did not affect the overall mortality rate.

Unfortunately, most serum cortisol is bound to corticosteroid-binding globulin and albumin. It is the **free** cortisol that is the physiologically active component of total cortisol, and this is typically is not measured. Hamrahian, et.al., examined the relationship between total and free cortisol. One group with albumin levels above 2.5g/dl all had normal responses to cosyntropin stimulation, while nearly half of the group with lower albumin levels showed an inadequate response. When the free cortisol was measured at baseline and after stimulation the two groups were identical and higher than healthy controls.

Effects of steroid dose on survival



Minneci, P. C. et. al. Ann Intern Med 2004;141:47-56

There is a large muticenter randomized controlled trial (CORTICUS) that should provide more definitive answers. However, it is recommended that intravenous corticosteroids be given to patients with septic shock who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure. The doses are 200-300 mg of hydrocortisone per day, for 7 days. The dose can be given in three or four divided doses or by continuous infusion.

Since the French study found no benefit in responders, an ACTH stimulation test is given to identify and discontinue therapy in these patients. The positive test should show >9 micrograms/dL increase in cortisol 30-60 minutes after administration of 250-micrograms of ACTH. There is no reason to wait for ACTH stimulation results to administer corticosteroids. Dexamethazone can be used until ACTH can be obtained for stimulation.

Veterans Administration Systemic Sepsis Cooperative Study Group Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis **N Engl J Med** 1987 Sep 10; 317:659-665.

Bone R C; Fisher C J, Jr; Clemmer T P et al A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock **N Engl J Med** 1987 Sep 10; 317:653-658.

Briegel J et al Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study **Crit Care Med** 1999 Apr; 27:723-732.

Annane D et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. **JAMA** 2002 Aug 21; 288:862-71.

Hamrahian AH et al. Measurements of serum free cortisol in critically ill patients. **N Engl J Med** 2004 Apr 15; 350:1629-38.

Minneci PC et al. Meta-analysis: The effect of steroids on survival and shock during sepsis depends on the dose. **Ann Intern Med** 2004 Jul 6; 141:47-56.

Luce JM. Physicians should administer low-dose corticosteroids selectively to septic patients until an ongoing trial is completed. **Ann Intern Med** 2004 Jul 6; 141:70-2.

Ventilation

Mechanical ventilation is associated with significant morbidity and mortality. This was the topic of one of my previous Grand Rounds, so I will not go over much here.

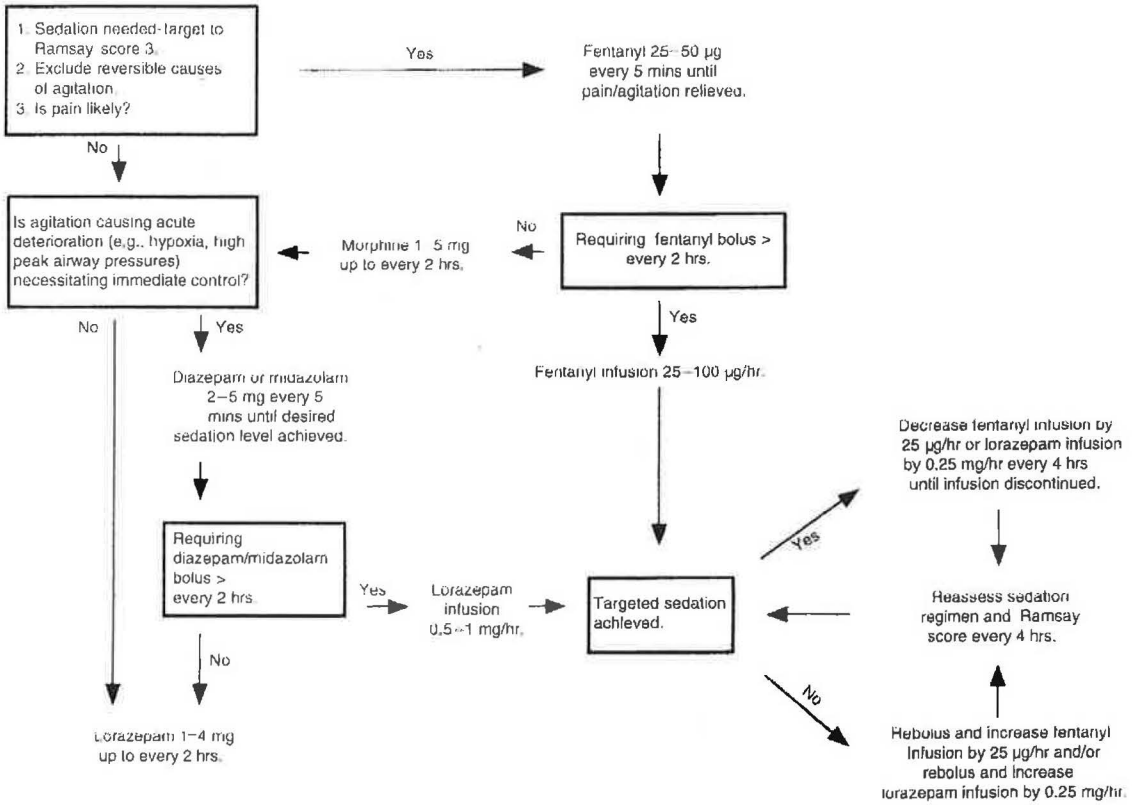
The ARDS-Network trial showed that ventilating patients with acute respiratory distress syndrome with tidal volumes of 6 ml/kg resulted in better outcomes than when a more conventional volume of 12 ml/kg was used. This resulted in a decrease in mortality from 39.8% in the conventional group to 31.0% in the low tidal volume group. Clinicians should use as a starting point a reduction in tidal volumes over 1 to 2 hrs to a "low" tidal volume (6 mL/kg lean body weight) as a goal in conjunction with the goal of maintaining end-inspiratory plateau pressures of <30 cm H_2O. While there is no optimum level of PEEP that has been shown to

be of benefit, a minimum amount should be used to prevent lung collapse at end-expiration, but not so much as to exceed the plateau pressure limits. The use of between 8 and 15 cm H2O based on oxygenation and FiO2 is common.

The use of noninvasive ventilation to avoid intubation has been shown to be of benefit in multiple studies. These studies have shown reduced length of ICU stay, decreased mortality, and other clinical benefits in selected patients with acute respiratory failure treated initially with noninvasive positive pressure ventilation.

Several studies demonstrate that daily spontaneous breathing trials reduce the duration of mechanical ventilation. Successful completion of spontaneous breathing trials leads to a high likelihood of successful discontinuation of mechanical ventilation. Spontaneous breathing trials have been shown to be superior to weaning by IMV or pressure.

The use of sedation "holidays" and a nurse-driven sedation protocol have been shown to decrease both time on mechanical ventilation and length of hospitalization. One is shown below:



Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. **N Engl J Med** 2000;342:1301-8

Brochard L, Mancebo J, Wysocki M, *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. **N Engl J Med** 1995;333:817–22.

Martin TJ, Hovis JD, Costantino JP, *et al.* A Randomised, prospective evaluation of noninvasive ventilation for acute respiratory failure. **Am J Respir Crit Care Med** 2000;161:807–13.

Çelikel T, Sungur M, Ceyhan B, *et al.* Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. **Chest** 1998;114:1636–42.

Esteban A, Alia I, Tobin MJ, et al: Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. **Am J Respir Crit Care Med** 1999; 159: 512–518

Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. **N Engl J Med** 1996; 335: 1864–1869

Esteban A, Alia I, Gordo F, et al: Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. **Am J Respir Crit Care Med** 1997; 156: 459–465

Kress JP, O'Connor MF, Hall JB: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. **N Engl J Med** 2000; 342:1471–1477

Kollef MH, Levy NT, Ahrens TS, et al: The use of continuous IV sedation is associated with prolongation of mechanical ventilation. **Chest** 1998;114:541–548

Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. **N Engl J Med** 2000; 342: 1471–1477

Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. **Crit Care Med** 1999; 27: 2609–2615

Ely EW et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. **N Engl J Med** 1996; 335: 1864-1869

Kollef MH et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. **Crit Care Med** 1997; 25: 567-574

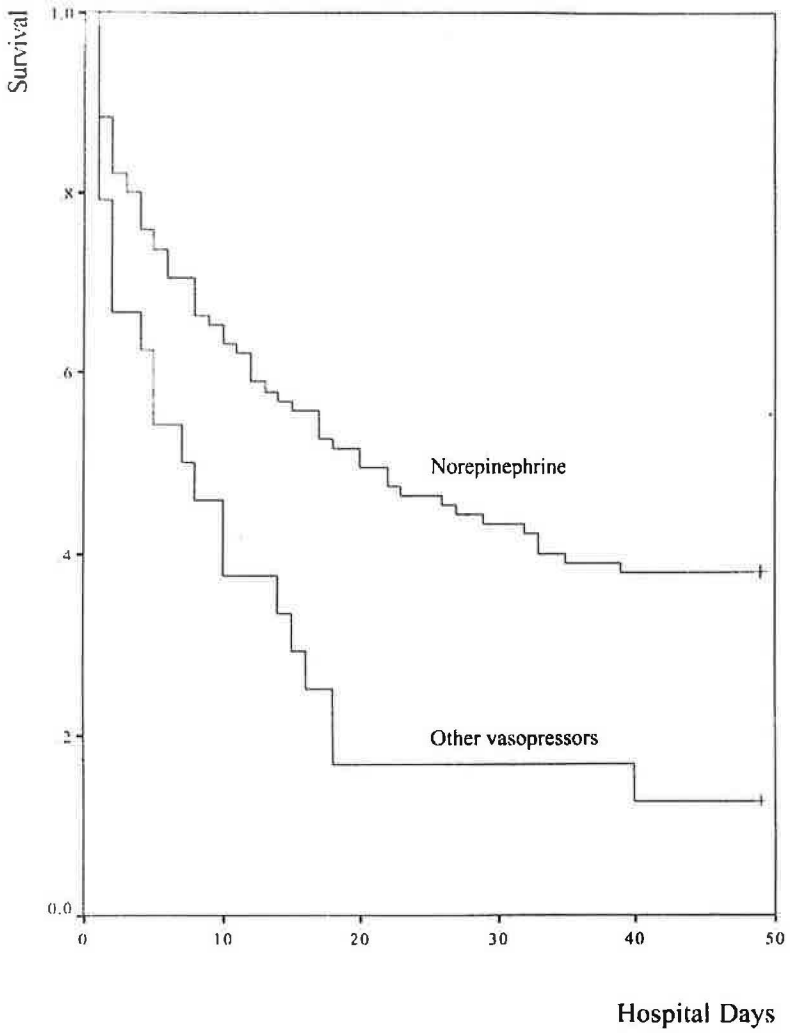
Marelich GP et al. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. **Chest** 2000 Aug;118(2):459-67

Vitacca M et al. Comparison of two methods for weaning patients with chronic obstructive pulmonary disease requiring mechanical ventilation for more than 15 days. **Am J Respir Crit Care Med** 2001 Jul 15;164(2):225-30

Vasopressor Therapy

Vasopressor agents are used when an appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion. These agents are often required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension. They are often used even when a fluid challenge is in progress and hypovolemia has yet to be corrected. One rationale for their use is that below a certain mean arterial pressure, autoregulation in various vascular beds can be

lost, and perfusion can become linearly dependent on pressure. Therapy with vasopressors help achieve a minimal perfusion pressure and maintain adequate flow. There is sparse evidence for one pressor agent over another. One study found that the use of norepinephrine was the only variable out of 19 that correlated with increased survival (shown below).



Despite this study, dopamine is an acceptable alternative. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine.

There is mounting evidence in favor of the use of vasopressin in the use of septic shock. Patients in septic shock are depleted of vasopressin. Vasopressin has many actions that should be advantageous in septic shock. It binds to V1 receptors on vascular smooth muscle to cause vasoconstriction. It binds to V2

receptors in the kidney collecting ducts to increase water permeability and resorption. It binds to V3 pituitary receptors to increase ACTH and cortisol production. The use of vasopressin is to replenish a deficiency, not deliver a therapeutic dose. It should be given in physiologic amounts of 0.01 to 0.04 Units per minute. Care should be used in writing this order, as it is **not** in micrograms/kg/min or some other weight-based formula. Also, its main utility is in decreasing the need for exogenous catacholamine administration.

Vasopressin is **not** to be titrated to the blood pressure and **not** to be used at doses over 0.04 Units per minute. Higher doses have been associated with cardiac ischemia, decreased cardiac output and arrest. As an Old Dog, I can remember when we used vasopressin in patients bleeding from esophageal varices. It acted to decrease perfusion to the gut, thereby decreasing portal vein pressures. For this reason, it should **ONLY** be used in hyperdynamic states. At the VA we use non-invasive Impedence Cardiography to confirm this hyperdynamic state and monitor stroke volume. Otherwise, this might be one good reason to place a right heart catheter.

	Beta-1	Beta-2	Alpha-1	DA^+	Dosing	½ life
Epinephrine	++++	+++	++++	0	2-10 mcg/min	<2min
Isoproterenol	++++	+++	0	0	2-20 mcg/min	2.5-5 min
Dopamine	++++	+	+++	++++	0.5-20 mcg/kg/min	2min
Norepinephrine	++	0	++++	0	2-50 mcg/min	<2min
Phenylephrine	0	0	++++	0	0.5-5 mcg/kg/min	2.5 hrs.
Vasopressin	0	0	0	0	0.01-0.04 U/min	10-35min

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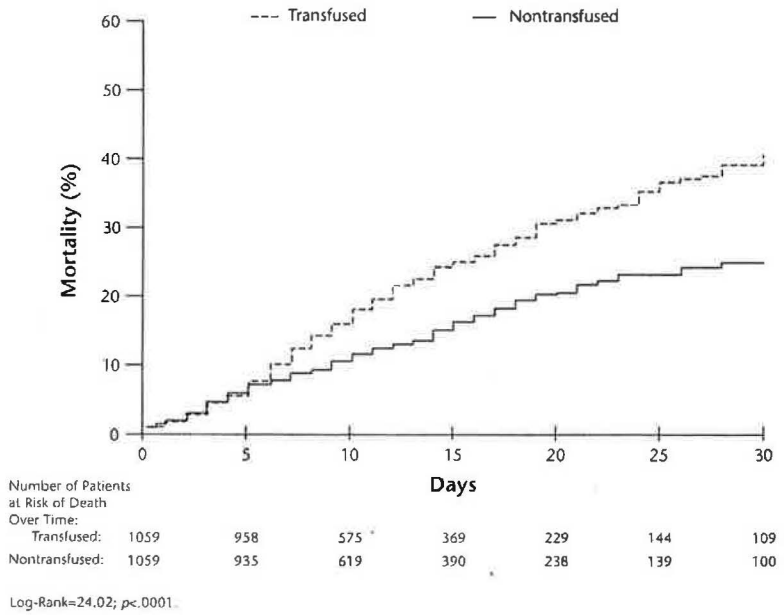
Transfusions

Anemia is common in critically ill patients. Fully 95% of ICU patients are anemic by day 2 and, as a consequence of this anemia, they receive an extraordinarily large number of RBC transfusions. Between 40% and 50% of all patients admitted to ICUs receive at least one unit of blood and the average receive almost 5 units during their ICU admission. The practice patterns for transfusions have changed very little over the past decade. Historically the most common threshold for transfusion has been a hemoglobin of 10 gm/dl or a hematocrit of 30%. This threshold was based on very little data, but has been propagated for decades. In the ICU almost half of all transfusions are performed for either no identifiable reason or for low hematocrit alone.

Blood transfusion is thought to be fairly benign and the optimum hemoglobin for patients with critical illness has not been specifically investigated. However, a major trial suggested that a hemoglobin of 7–9 g/dL is adequate for most critically ill patients. A transfusion threshold of 7.0 g/dL was not associated with an increased mortality rate and a lack of transfusion was associated with less mortality at 28 days (see below), as well as less congestive heart failure.

This transfusion threshold contrasts with the target of a hematocrit of 30% in patients with low central venous oxygen saturation during the first 6 hrs of resuscitation of septic shock (see Early Goal-directed therapy).



In a multicenter, randomized, double-blind trial, researchers enrolled 1302 adults in medical or surgical ICUs with hematocrits lower than 38%. Patients received either recombinant erythropoetin (40,000 U once weekly, max. of 4 injections) or placebo. The need for transfusions in these patients was determined by each patient's physician. During 4 weeks of follow-up, a significantly lower proportion of the patients on erythropoetin received transfusions (50.5% vs. 60.4%). The total number of transfused units also was significantly lower in the erythropoetin group. There were no significant differences between groups in 28-day mortality or hospital length of stay. The 10-percentage-point difference between groups suggests that for every 10 ICU patients who receive erythropoetin, 1 could avoid transfusion.

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Antibiotic Therapy and Resistance in the ICU

Antibiotics are used extensively in the ICU setting. Infection on admission as well as development of infection after admission is common. When patients in the intensive care unit develop infiltrates on chest x-rays, it is often difficult to distinguish between pneumonia, atelectasis, and pulmonary edema. Most of these patients receive empirical antibiotic therapy until the etiology can be sorted out. This leads to overuse of antibiotics in the ICU.

Resistance to Antibiotics

Resistant organisms are increasingly common on admission to the ICU and often develop in the ICU while the patient is being treated. The cost of nosocomial infections in terms of both lives and money is staggering. Nosocomial infections are thought to cause an estimated 44,000 to 98,000 deaths yearly at a cost of $17-29 billion. We have made significant progress in decreasing the incidence of these infections. In the past decade, the incidence of ICU, nosocomial respiratory infections, urinary tract infections, and catheter-associated bloodstream infections declined. This data from the CDC from hundreds of hospitals across the nation showed that bloodstream infections were down 31 to 44 percent in all intensive care settings.

Unfortunately there is other evidence that resistance to antibiotics is increasing in the general population. The problem of antibiotic resistance is thought to be from unnecessary and overuse of broad-spectrum antibiotics by physicians. Resistance has been a problem in our intensive care units for some time. It is thought that this in turn has made resistance within the rest of the hospital a problem. This increase in resistance has now become a problem outside of the hospital. These assumptions are supported by many articles including a recent article linking antibiotic use with resistance in Europe using an extensive database (see references). The increasing problem with Methicillin resistant Staphlococcus aureus (MRSA) was made acutely personal for me when my youngest son developed MRSA skin abscesses of his legs after scraping his knee on artificial turf during football practice.

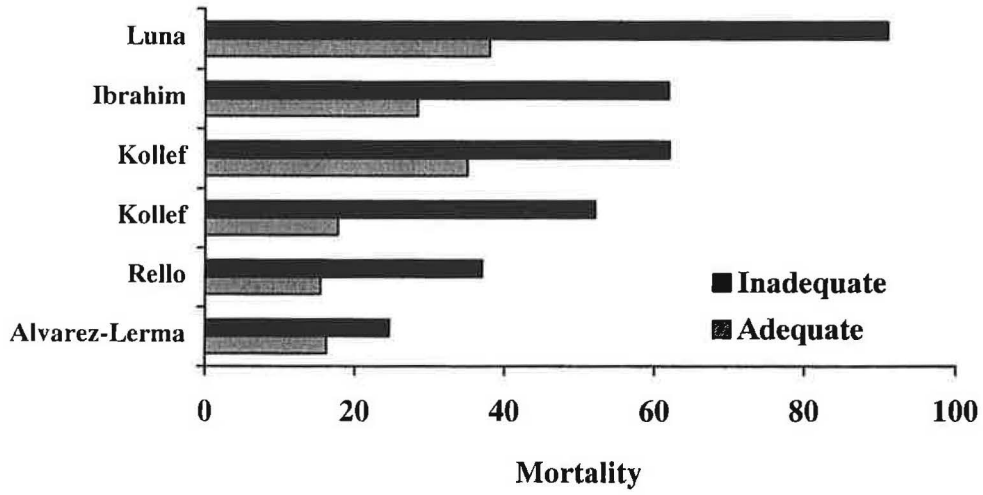
However, the cause of antibiotic resistance is not completely clear as evidenced by a small study by Bartoloni et al. These investigators studied antibiotic resistance in a small village located at 1700 meters in the Bolivian highlands. It is a steep 3-hour climb from the nearest clinic. The population lives in huts with no plumbing and rain is the only source of water. None of the animals are brought into the village or given antibiotic laden feed. On a single day in 1999, they performed stool swab cultures on 108 villagers, which represented 80% of the entire village population. The investigators looked at resistance to four antibiotics and found the following resistance levels in E. coli:

- None 29%
- Tetracycline – 64%

- Ampicillin – 58%
- Bactim – 50%
- Chloramphenicol – 41%
- All four drugs – 34%

Only 8 subjects had ever had any antibiotic in their lives, only 6 had ever visited the nearest clinic, and only 4 had ever been hospitalized. It is hard to believe that the resistance levels seen in these villagers are from antibiotic pressures.

The right antibiotic is important for good outcomes.
There are numerous studies that have shown an increased mortality with inadequate antimicrobial therapy compared to adequate antimicrobial therapy as shown in the graph below:



Early antibiotics are important for good outcomes.
The timing of treatment is also important. Houck, et al., in a retrospective study of thousands of Medicare patients over 65 year of age showed that administration of antibiotics within four hours of diagnosis of pneumonia resulted in decreased mortality. This has become a Joint Commission of Accreditation of Hospital Organizations (JCAHO) standard for hospital performance.

Timing is usually not a problem in the ICU. So much data is collected and disseminated so quickly, that antibiotics are frequently started with every spike of fever or bump in WBC.

The etiologic organism and therefore the correct antibiotic is unknown
It is impossible to determine the etiologic organism from the clinical data on presentation. There are numerous studies showing that the appearance on chest x-ray does not help to differentiate the causative organism. The gram stain of the sputum does not correlate with the lower respiratory infection. For similar

reasons, the sputum culture does not correlate well with the lower respiratory tract infection. There are numerous studies showing that when these are combined with blood cultures and acute and convalescent titers that the etiologic organism can be found in, at most, only 50% of the cases of pneumonia. One study looked at 90 different clinical variables using linear regression techniques to find 5 things, such as WBC, lobar infiltrate, etc. that helped distinguish a cause of pneumonia. However, discriminate function analysis only allowed 41% accuracy in placing the patient in an etiologic group. If our choice of antibiotic is dependent on our guess of the etiologic organism, then we are doomed to fail.

Short courses of antibiotics are as good as long courses.
This statement is less intuitive. In a randomized study by Chastre, et al., Ventilator-associated pneumonia (VAP) was treated for eight days and compared with a more traditional course of 15 days of antibiotic. There was no difference in ICU mortality, recurrent infections, mechanical-ventilation-free days, organ failure-free days, length of ICU stay, or 60-day mortality. As might be expected, there were fewer days on antibiotics.

Less overall antibiotic use is important for good outcome.
This is another less intuitive statement. In a randomized trial, Singh, et al., used the clinical pulmonary infection score (CPIS) as an operational criterion in decision-making for antibiotic treatment of ventilated patients with fever and pulmonary infiltrates. This score is calculated as below:

Table 1. Clinical pulmonary infection score as used by Singh et al. (1) in their study on controlled antibiotic therapy in intensive care units

Temperature, °C
0 points: ≥36.5 and ≤38.4
1 point: ≥38.5 and ≤38.9
2 points: ≥39.0 or ≤36.0
White blood cell count, mm^3
0 points: ≥4000 and ≤11,000
1 point: <4000 or >11,000 (add 1 point for band forms ≥50%)
Tracheal secretions
0 points: absence of tracheal secretions
1 point: presence of nonpurulent tracheal secretions
2 points: presence of purulent tracheal secretions
Oxygenation: Pao_2/Fio_2, mm Hg
0 points: >240 or ARDS[a]
2 points: ≤240 and no ARDS
Pulmonary radiography[b]
0 points: no infiltrate
1 point: diffuse (or patchy) infiltrate
2 points: localized infiltrate
Patients with a score of >6 were assumed to have ventilator-associated pneumonia (VAP) and were treated as such. Patients with a score of ≤6 (implying a low likelihood of VAP) were randomized to receive either standard therapy (choice and duration of antibiotics at the discretion of physicians) or ciprofloxacin monotherapy, with reevaluation in 3 days. Reevaluation was on the basis of recalculating the CPIS score, with the addition of two new variables:
Progression of pulmonary infiltrate
0 points: no radiographic progression
2 points: radiographic progression (after CHF and ARDS are excluded)
Culture of tracheal aspirate[b]
0 points: no growth of pathogenic bacteria or rare or light quantity only
1 point: pathogenic bacteria in moderate or heavy quantity

ARDS, acute respiratory distress syndrome; PAOP, pulmonary artery occlusion pressure; CPIS, clinical pulmonary infection score; CHF, congestive heart failure.

[a]ARDS is defined as a $Pao_2/Fio_2 \leq 200$, PAOP ≤ 18 mm Hg, and acute bilateral infiltrates; [b]add one extra point if the same pathogenic bacteria were seen on Gram stain.

Patients with a score of greater than 6 were assumed to have VAP and treated with antibiotics chosen by their physician. If the score was less than, or equal to 6, then the patients were randomized to standard therapy or a single antibiotic with reassessment at 3 days. In the patients being reassessed, if the CPIS remained below 6, then the antibiotic was stopped. The other group was left to the discretion of their physician. The end-points for this study were:

1. mean length of ICU stay decreased from 14.7 days to 9.4 days p=0.04
2. superinfection with resistant org. decreased from 38% to 14% p=0.17
3. All cause mortality decreased from 30% to 13%, but p=0.06 did not quite reach statistical significance.

This study has been widely misinterpreted as proving that an abbreviated course of antibiotics is sufficient for ventilator associated pneumonia. However, the real impact of this study was that a protocol to review antibiotic need resulted in less antibiotic used and improved patient outcomes.

Other studies have used more invasive techniques to systematically review the need for antibiotics and stop unnecessary use of antibiotics. The clear message is that strategies that lead physicians to stop unnecessary antibiotic use will result in improved patient outcome and lower multiple drug-resistant organisms than if the physicians are left without control.

The Parkland Memorial Hospital Medicine Intensive Care Unit uses a protocol similar to Singh, et al., to treat ventilator associated pneumonia. The VA ICUs hope to adopt it soon.

Diagnostic Considerations:

1. Site of infection – likely organisms
2. Previous antibiotic exposure
3. Previous colonization
4. Local antibiotic resistance trends

The first of the diagnostic considerations is usually made at the bedside at the time of admission. However, the others require data obtained from the old chart. Even when the data is electronic, it may not be in a form that is easily accessible. El Amari et al., showed that a significant risk factor for antibiotic resistance was previous treatment with the antibiotic that later showed development of resistance. This is easily understood considering the way that different microorganisms share DNA that encodes for antibiotic resistance. Another consideration concerns the energy expenditure by the microorganism to continue production and/or expression of the proteins or genes developed by selection pressure, which would determine how long it takes for those clones to abate once the selection pressure is gone.

Studies concerning antibiotic use from the LDS hospital in Utah have been presented in this forum before. Evans et al., showed that management of patients using the HELP electronic medical record system there improved patient outcomes in the ICU. Computer-based antibiotic assistance was given in the form of recommendations based on microbiology reports, allergy history, and ICU specific antibiograms. The mean length of hospital stay was significantly less when the recommendations were followed. The patient outcomes were also better when the recommendations were followed than when those recommendations were overridden by the physicians.

Therapeutic ideas that impact this problem.

1. Antibiotic stewardship
2. De-escalation therapy
3. Shorter course therapy

Our previous concept of antibiotic therapy has been to use fairly narrow coverage of infection using antibiotics chosen on the basis of cost. If this did not work, then broader coverage was instituted and continued for at least two weeks. These therapeutic considerations help maximize individual patient outcomes, while at the same time minimize the development and propagation of antibiotic resistance. The shorter course therapy seems obvious and was discussed above.

Antibiotic Stewardship

This concept concerns using antibiotics in individual patients by determining what organisms are common in the particular ICU and site of infection. This maximizes the likelihood that the patient will be covered by the antibiotics chosen. A current antibiogram (or antimicrbiogram) is important in determining what antibiotic coverage to use in any given situation. There are several software programs that use the recent microbiologic data from the hospital computer to form a antibiogram and even make recommendations much like those from LDS hospital discussed above.

Another aspect of this concept concerns choosing antibiotics based on their propensity, or lack of propensity, to have resistance develop during the course of therapy. Not all antibiotics have the same potential to have resistance develop against them. This is shown in the table below:

Antibiotic	Anti-*P. aeruginosa* Activity	*P. aeruginosa* Resistance Potential
Piperacillin-tazobactam	++++	+
Ceftazidime	++++	++++
Cefepime	++++	+
Imipenem	++++	++++
Meropenem	++++	+
Gentamicin	+	++++
Amikacin	++	+
Levofloxacin	++	+
Ciprofloxacin	+++	++++

Cunha BA. *Semin Respir Infect.* 2002;17:231-239.

This table shows the activity of selected antibiotics against Pseudomonas aeruginosa. Another organism could have been chosen, but this organism is a common problem in the ICUs across the country. One study from a Boston hospital showed that 144 patients (30 percent) had resistance, at the time of admission, whereas resistance emerged in 30 (6 percent). The mortality rate was 27 percent for patients in whom resistance emerged, compared with 6 percent for the remaining patients. Also, the median length of stay following identification of the initial isolate was 7 days for patients with baseline resistance, but 24 days for those in whom resistance emerged.

While antibiotics within a class of antibiotics may have similar activity against the organism in question, they may have very different potential for resistance to develop against them. As can be seen in the table, Ciprofloxacin has good activity against P. aeruginosa when compared to Levofloxacin. However, the potential for resistance to develop is much different and less with Levofloxacin. Therefore, when choosing a fluoroquinalone to use in an ICU, one would pick Levofloxacin over Ciprofloxacin to protect patients against the development of resistance if Pseudomonas aeroginosa were a problem or to keep it from becoming a problem. As a caveat, at the VA, we have altered the dose of Levofloxacin to better cover susceptible organisms after considering the half-life

of the drug. Another study looked at the hazard ratio for resistance to develop against certain drugs. Ciprofloxacin had a hazard ratio of 9.2, but this was dwarfed by the hazard ratio of 44 for Imipenem. Meropenem requires two mutations to occur for resistance to develop and does not have the same propensity for seizures found in Imipenem.

De-escalation therapy

This concept insures that the patient is covered with the correct antibiotic early and completely. The importance of using the "right" antibiotic and using it early was discussed above. Also in the discussion above, it is apparent that we are unable to predict what organism is infecting our patient. Therefore, using a broad spectrum coverage protects the patient. Once the organism is found and susceptibilities known, then the antibiotics are "de-escalated" to a minimum of coverage for that organism. The shortest effective course is used to treat the patient. This concept maximizes effectiveness of the antibiotics used and minimizes the formation of resistance by shortening the length of time antibiotics are used unnecessarily.

Protocols

Focusing on acquisition costs for antibiotics is a short-sighted method. This focus only leads to antagonism between clinicians and the pharmacy or therapeutics leaders. Using appropriate antibiotics, whether an expensive carbapenem or an inexpensive aminoglycoside, is far superior and will lead to decreased antibiotic usage, decreased costs, and decreased resistance.

There are interesting mathematical models that predict an incredible decrease in resistance within the hospital if rules are followed. The most incredible part of the model is that the decrease occurs in a matter of weeks rather than months or years.

Protocols are necessary because strategies that leave physicians to use antibiotics without control lead to increases in morbidity, mortality, and resistance. We seem to be unable to reason reliably once we are in the middle of treating a patient.

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ICU Staffing

There are numerous studies that suggest that physician staffing patterns affect clinical outcomes in intensive care units. The high use of critical care specialists and having a "closed" ICU affect clinical outcome. Most of these studies are cohort studies where outcomes are measured before and after new staffing arrangements were implemented. These studies suggest significantly lower mortality both within the ICU and in the hospital as well as lower length of stay in both the ICU and the hospital. The Leapfrog Group, a large coalition of organizations that provide health care benefits for employees, has made ICU staffing by intensivists one of its top priorities.

Another factor in mortality is the workload within the ICU, especially peak occupancy, but also patient acuity, and ratio of occupied beds to appropriately staffed beds. When ICU occupancy exceeded full capacity there was increased mortality of 43% as opposed to 28% at lower occupancy.

Protocols

Protocols have been shown to be of benefit in many situations. However, complicated protocols are difficult to implement. Physicians are not very good at taking orders themselves and poor at following them. Most protocols, in order to work effectively will have to have some "buy-in" from the physicians and most of the work of the protocol will fall on nurses, respiratory therapists and other health care workers.

The aviation industry has done a wonderful job of using safety as a cornerstone to obtain buy-in and adherence to protocols. One of the hardest parts of this team approach is reliance on communication between participants of different rank, such as pilot and co-pilot, or even pilot and flight attendant. In the ICU this is shown by nurses' report of high levels of collaboration or teamwork among their nursing peers, but lower collaboration with physicians. When the physicians were polled, they reported high levels of collaboration with both nurses and other physicians. This discrepancy can represent differences in status, authority, gender, training and responsibility. This is true in the cockpit as well as in the ICU. However, in order for protocols to work effectively, communication among all of the health care team must be developed and maintained.

Systematic rules of conduct and treatment can help our patients. One list of questions to be made at the bedside of every patient covers very simple as well as important concerns for every ICU patient.

1. Can the patient be weaned from mechanical ventilation?
2. Is pain controlled, sedation titrated, and restraints appropriate?
3. Is nutrition adequate?
4. Is the head of the bed elevated?
5. Is prophylaxis for DVT and stress ulcer in place?

As can be seen by this list, most of ICU care is supportive. Our first order of business is to do no harm in our care of the patient. It is unfortunate but real that much of that protection has to be from ourselves.

Errors of Omission versus errors of commission

Adverse drug reactions have been discussed in this forum before, both by myself and more extensively by Dr. Carol Croft. Solutions to these errors have included computerized physician order entry, bar code administration, and electronic medical records. However, these errors are errors of commission. A much more important error is one of omission. Errors of omission are more pervasive and further reaching than errors of commission. One study determined the cost of omission of five recent advances in medical care. The estimated cost of these errors of omission in terms of human life was twice the estimate of all adverse drug reactions put together. The solution for errors of omission might include protocols, clinical reminders, continuing education, and computer surveillance of patient data.

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