Special Communication | LESS IS MORE

# "Less Is More" in Critically Ill Patients
## Not Too Intensive

Matthijs Kox, PhD; Peter Pickkers, MD, PhD

Text

The current view in intensive care medicine is that very sick patients need very intensive treatment. However, in this group of highly vulnerable patients, more intensive treatment may promote the chances of unwanted adverse effects and hence, iatrogenic damage. Therefore, we state that critically ill patients probably benefit from a more cautious approach. Using data from large clinical trials of previous years, we exemplify that less intensive treatment is associated with a better outcome in intensive care patients and suggest that we reappraise patient management as well as trial design in intensive care medicine while bearing in mind the "less is more" paradigm. We illustrate our case by describing the intensity of the most relevant treatment options for patients with septic shock, including mechanical ventilation, fluid management, blood pressure–targeted therapy, corticosteroids, patient monitoring, sedation, and nutrition. We conclude that treatment of critically ill patients while keeping in mind the "less is more" paradigm might not only benefit the patient but could also have a notable impact on the ever-increasing intensive care–related health care costs.

*JAMA Intern Med*. 2013;173(14):1369-1372. doi:10.1001/jamainternmed.2013.6702
Published online June 10, 2013.

**Author Affiliations:** Department of Intensive Care Medicine, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands (Kox, Pickkers); Department of Anesthesiology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands (Kox); Nijmegen Institute for Infection, Inflammation, and Immunity (N4i), Nijmegen, the Netherlands (Kox, Pickkers).

**Corresponding Author:** Matthijs Kox, PhD, Department of Intensive Care Medicine, Internal Mail 710, Radboud University Nijmegen Medical Center, Geert Grooteplein 10, 6500 HB Nijmegen, the Netherlands (m.kox@ic.umcn.nl).

The phrase "less is more" was first popularized by the German architect Ludwig Mies van der Rohe, one of the pioneers of modern architecture. Because of financial shortages after World War II, the modernist style originally conceived for aesthetic reasons was quickly adopted as a practical program of inexpensive construction. Although not directly related to the current financial crisis, we propose that "less is more" also applies to the treatment of critically ill patients. The current view is that these very sick patients need very intensive treatment. Indeed, the addition of several treatments such as mechanical ventilation and improved hemodynamic monitoring has revolutionized the care of medical and surgical patients who are critically ill. However, because more intensive treatment may promote the chances of unwanted adverse effects, iatrogenic damage is more likely to occur, resulting in unfavorable sequelae and worse outcome in this highly vulnerable group of patients. Therefore, in keeping with the Hippocratic oath (primum non nocere), we state that critically ill patients probably benefit from a more "cautious" approach. In this Special Article, based on data from large clinical trials conducted in the previous years, we show that less intensive treatment is indeed associated with a better outcome in critically ill patients (**Table**). To improve outcome, we should therefore reappraise patient management as well as trial design in intensive care medicine, bearing in mind with the principles of "less is more."

## Respiratory Therapy, Fluids, and Transfusion

To illustrate our case, we describe the intensity of the most relevant treatment options for septic shock, the number 1 cause of death in noncardiac intensive care units (ICUs).[1,24] In most patients with septic shock, mechanical ventilation is required. The first Acute Respiratory Distress Syndrome (ARDS) Network trial has clearly shown that ventilation with lower tidal volumes (6 vs 12 mL/kg) reduces lung injury and improves outcome.[1] Furthermore, higher levels of positive end-expiratory pressure (13 cm of water) did not improve clinical outcome compared with lower levels (8 cm of water),[2] indicating that "more" is not "better."[2] Of interest, recently high-frequency ventilation was found to increase mortality in ARDS patients, illustrating that complicated tertiary approaches to ventilation do not seem to help.[3] Related to respiratory therapy, too-liberal supplementation of oxygen resulting in high $P_{O_2}$ values is associated with, albeit slightly, increased mortality in observational cohorts.[4] Randomized trials to investigate the effects of higher and lower oxygen levels are currently not available. In addition, following the initial fluid resuscitation phase, it has been demonstrated that a more conservative fluid management results in improved lung function and shorter stay in the ICU compared with a more liberal regime.[5] Recently, an extreme example of the benefits of less fluid administration emerged in a study performed in African children presenting with febrile illness and impaired perfusion.[6] Strikingly, a survival benefit was found in children who were withheld from fluid administration compared with those receiving, by US and European standards, conservative fluid boluses.[6] Also, a restrictive strategy of red blood cell transfusion is superior to a liberal one.[7] It is clear that for respiratory and hemodynamic management, less *is* more in the critically ill patient. Remarkably, the same holds true for many adjunctive treatments applied in the ICU.

Table. Interventions for Which "More" Has Been Shown to Be Associated With Worse Outcome

| Intervention | Effect | Type of Study |
|---|---|---|
| Respiratory therapy | | |
| Higher tidal volume (12 vs 6 mL/kg)[1]; higher PEEP (13 vs 8 cm of water)[2]; high-frequency ventilation[3] | Increased mortality[1,3] and days on ventilator[1]; no benefit[2] | RCT[1-3] |
| High $Po_2$[4] | Increased mortality[4] | Observational study[4] |
| Fluids and transfusion | | |
| Liberal fluid management vs strict regime[5]; conservative vs no fluid administration[6] | Worsened lung function,[5] increased days on ventilator, and ICU stay[5]; increased mortality[6] | RCT[5,6] |
| Liberal vs restrictive red blood cell transfusion[7] | Increased mortality[7] | RCT[7] |
| Blood pressure–targeted therapy | | |
| Increasing MAP >65 mm Hg[8]; higher vasopressor use[9]; higher vasopressor infusion rates vs lower rates + vasopressin[10]; higher vs lower dosage of L-NMMA[11] | No benefit[8]; increased mortality[9,11]; increased mortality (only in less severe septic shock)[10] | RCT[8,10]; observational study[9]; post hoc analysis of RCT[11] |
| Corticosteroids | | |
| High-dose corticosteroids[12] | Increased mortality[12] | RCT[12] |
| Cardiac therapy | | |
| Prophylactic lidocaine treatment to reduce VF[13] | Increased mortality[13] | RCT[13] |
| Monitoring | | |
| Swan-Ganz cathether[14] | No benefit[14] | RCT[14] |
| Daily routine x-ray examinations[15] | No benefit[15] | Observational study[15] |
| Antibiotics | | |
| Longer duration of antibiotic treatment[16] | No benefit[16] | RCT[16] |
| Renal therapy | | |
| High vs low volume renal replacement therapy[17] | No benefit[17] | RCT[17] |
| Sedation | | |
| Continuous sedation vs daily interruption of sedatives (lower sedative use)[18]; daily interruption of sedatives vs no sedation[19] | Increased days on ventilator[18,19] and ICU stay[18] | RCT[18,19] |
| Nutrition and glucose control | | |
| High vs moderate caloric intake[20]; target feeding vs permissive underfeeding[21]; full enteral nutrition vs trophic nutrition[22] | Increased mortality[20,21]; no benefit[22] | Observational study[20]; RCT[21,22] |
| Strict vs less strict glucose control in patients that are predominantly fed enterally[23] | Increased mortality[23] | RCT[23] |

Abbreviations: ICU, intensive care unit; L-NMMA, $N_G$-monomethyl-L-arginine; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; RCT, randomized clinical trial; VF, ventricular fibrillation.

## Blood Pressure–Targeted and Cardiac Therapy

Patients with septic shock require vasopressor therapy by definition. Although the use of different vasopressor agents appears to result in similar outcome, increasing mean arterial pressure above 65 mm Hg showed no benefit.[8] Furthermore, vasopressor load was shown to be associated with mortality in an observational study.[9] While there is no direct evidence for adverse effects of high vasopressor use (there are no randomized clinical trials comparing different dosages), most pharmacological adverse effects are dose dependent. Hence, combinations of (lower dosages) of vasopressors might be beneficial compared with the use of higher dosages of a single vasopressor, and indeed there is some evidence for this. For instance, vasopressin therapy in combination with norepinephrine resulted in a significant survival benefit in patients with mild septic shock compared with patients treated with norepinephrine alone, although this was not the case in patients with severe shock.[10] Also, while the nitric oxide synthase inhibitor $N^G$-monomethyl-L-arginine (L-NMMA) was associated with worse outcome in the complete group of patients with septic shock, those who received a lower infusion rate (<5 mg/kg/h) had an improved survival rate relative to placebo-treated patients, suggesting that lower dosages are beneficial.[11]

## Corticosteroids, Monitoring, and Antibiotics

Patients with refractory shock who require high dosages of vasopressor therapy might benefit from corticosteroids. However, in the early trials, high dosages of corticosteroids resulted in adverse outcome.[12] In later trials it was demonstrated that lower corticosteroid dosages may improve outcome, especially when administrated early in those with refractory shock.[25,26] In case of impending myocardial infarction, prophylactic treatment with lidocaine, while reducing the incidence of ventricular fibrillation, actually increases mortality.[13] Another argument in support of "less is more" in critically ill patients is the fact that studies have failed to demonstrate that more invasive hemodynamic monitoring using Swan-Ganz catheters is beneficial for the ICU patient.[14] Furthermore, daily routine x-ray examinations, another form of monitoring, were not shown to be useful,[15] and even a shorter duration of antibiotic treatment (guided by procalcitonin levels) was not associated with worse outcome,[16] while liberal use of antibiotics has many disadvantages, among which increased risk of the development of resistance is the most important one.

## Renal Therapy, Sedation, Nutrition, and Glucose Control

Patients with septic shock often develop acute kidney injury, for which renal replacement therapy can be initiated, but increasing ultrafiltrate volume has not showed any benefit.[17] Most patients with septic shock will be sedated. The old paradigm was to deeply sedate to facilitate adequate patient management. It is now becoming increasingly clear that less[18] or even no[19] sedation is superior. Finally, patients need nutrition, and it has emerged that high caloric

intake is associated with increased mortality,[20] whereas low caloric intake via the enteral route (permissive underfeeding) reduces hospital mortality in critically ill patients.[21] In line, it was recently demonstrated in ARDS patients that full enteral feeding is not superior compared with trophic feeding in terms of time on ventilator or mortality.[22] Furthermore, early initiation of parenteral nutrition worsens outcome,[27] suggesting it is better to limit caloric intake via the parenteral route until enteral feeding is possible. Related to this issue, beneficial effects of intensive glucose control therapy were found in ICU patients who receive larger amounts of parenteral calories,[28] while it was found to increase mortality in patients who are predominantly fed via the enteral route.[23] From these studies, it might be concluded that very strict glucose regulation is not beneficial by itself and only nullifies the deleterious effects of early parenteral administration of calories.

## Exceptions to the Rule

Naturally, there are some notable exceptions to the rule; sometimes "more is more." For instance, early mobilization of critically ill patients,[29] infection prevention by means of decontamination of the digestive tract and oropharynx,[30] and high-intensity ICU physician[31] and nurse[32] staffing is associated with better outcome. Furthermore, hemodynamic optimization and/or early goal-directed therapy is associated with better outcome following major surgery[33] and in the early phase of sepsis.[34] Nevertheless, equipoise still remains, and 3 trials (United States, United Kingdom, and Australia) are under way to evaluate the true effectiveness of early goal-directed therapy. Furthermore, a highly intensive and invasive treatment such as extracorporeal circulation membrane oxygenation has proved its value during the 2009 H1N1 influenza pandemic.[35] However, a recent observational study indicates that the effectiveness of extracorporeal circulation membrane oxygenation in ARDS patients is highly dependent on chest wall mechanics and that inappropriate use of extracorporeal circulation membrane oxygenation can be avoided in many patients by partitioning respiratory system mechanics between lung and chest wall.[36]

## Conclusions

It is becoming clear that following decades of increasingly more intensive treatment of critically ill patients, a more cautious approach for the vulnerable ICU patient is in many cases associated with improved outcome. While it may prove to be a difficult task to convince more and more ICU physicians to do less, implementation of evidence-based reduction of therapy intensities is of vital importance. With regard to ICU trial design, instead of investigating the effects of altering a single therapy, it would be of interest to evaluate the efficacy of combinations of lower dosages or intensities of certain therapies to reduce the chances of adverse effects to occur. Last but not least, keeping the "less is more" paradigm in mind in the treatment of critically ill patients might not only benefit the patient but could also have a notable impact on the ever-increasing ICU-related health care costs and thereby benefit the society as a whole, especially in these times of financial hardship.

ARTICLE INFORMATION

**Accepted for Publication:** March 16, 2013.

**Published Online:** June 10, 2013. doi:10.1001/jamainternmed.2013.6702.

**Author Contributions:** *Study concept and design:* Both authors.
*Drafting of the manuscript:* Kox.
*Critical revision of the manuscript for important intellectual content:* Pickkers.
*Study supervision:* Pickkers.

**Conflict of Interest Disclosures:** None reported.

REFERENCES

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.

2. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351(4):327-336.

3. Ferguson ND, Cook DJ, Guyatt GH, et al; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med*. 2013;368(9):795-805.

4. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care*. 2008;12(6):R156.

5. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.

6. Maitland K, Kiguli S, Opoka RO, et al; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364(26):2483-2495.

7. Hébert PC, Wells G, Blajchman MA, et al; Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med*. 1999;340(6):409-417.

8. Bourgoin A, Leone M, Delmas A, Garnier F, Albanèse J, Martin C. Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. *Crit Care Med*. 2005;33(4):780-786.

9. Dünser MW, Ruokonen E, Pettilä V, et al. Association of arterial blood pressure and vasopressor load with septic shock mortality: a post hoc analysis of a multicenter trial. *Crit Care*. 2009;13(6):R181.

10. Russell JA, Walley KR, Singer J, et al; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887.

11. López A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med*. 2004;32(1):21-30.

12. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med*. 1987;317(11):653-658.

13. Sadowski ZP, Alexander JH, Skrabucha B, et al. Multicenter randomized trial and a systematic overview of lidocaine in acute myocardial infarction. *Am Heart J*. 1999;137(5):792-798.

14. Harvey S, Harrison DA, Singer M, et al; PAC-Man study collaboration. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet*. 2005;366(9484):472-477.

15. Graat ME, Choi G, Wolthuis EK, et al. The clinical value of daily routine chest radiographs in a mixed medical-surgical intensive care unit is low. *Crit Care*. 2006;10(1):R11.

16. Bouadma L, Luyt CE, Tubach F, et al; PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375(9713):463-474.

17. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal

function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med*. 2002;30(10):2205-2211.

**18**. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.

**19**. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*. 2010;375(9713):475-480.

**20**. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest*. 2003;124(1):297-305.

**21**. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *Am J Clin Nutr*. 2011;93(3):569-577.

**22**. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307(8):795-803.

**23**. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.

**24**. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.

**25**. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862-871.

**26**. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.

**27**. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365(6):506-517.

**28**. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet*. 2009;373(9663):547-556.

**29**. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-1882.

**30**. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med*. 2009;360(1):20-31.

**31**. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA*. 2002;288(17):2151-2162.

**32**. Cho SH, Hwang JH, Kim J. Nurse staffing and patient mortality in intensive care units. *Nurs Res*. 2008;57(5):322-330.

**33**. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay: a randomised, controlled trial [ISRCTN38797445]. *Crit Care*. 2005;9(6):R687-R693.

**34**. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.

**35**. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306(15):1659-1668.

**36**. Grasso S, Terragni P, Birocco A, et al. ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure. *Intensive Care Med*. 2012;38(3):395-403.