Can Less be More in Intensive Care?

Seven recent randomized clinical trials (RCTs)[1-7] add momentum to a question the intensive care community is increasingly exploring; can "Less be More" in the management of the critically ill? Practices are evolving in this direction with a preference for less invasive monitoring or intervention, less routine changing of invasive devices, and a decrease in the frequency of routine investigations. At the basic human level, it is easier to do something than to do nothing, and the pressure on clinicians to do something is much more in the context of a critically ill patient. Many clinicians have a strong intervention bias to use unproven therapies. But increasingly, clinicians are questioning if this liberal approach is effective or even harmful.[8-11]

There are nonclinical and clinical arguments to support a minimalistic approach. In the context of "less is more," even with equivalent clinical outcomes, lesser therapies can be "more" in terms of more efficient resource utilization. This is equally relevant in the rich and poor economies, and one sees the richer countries fighting an increasingly difficult battle against runaway expenditure. Unfortunately, in the real world, there are financial incentives for clinicians, administrators, and industry to do more rather than less, regardless of the evolving scientific data. Upton Sinclair pithily observed that it is difficult to get a human to understand something, when his/her salary depends on his/her not understanding it.

The main clinical argument against doing too much is that there are adverse outcomes noted with many therapies. We have explored this[11] and cited the literature that demonstrates that less can actually be equivalent or more for multiple Intensive Care Unit (ICU) therapies including O_2 supplementation, drugs in cardiopulmonary resuscitation, and other standard ICU practices including monitoring and life support.

There is reasonable plausibility too in supporting such an approach. During the stress of an illness, many parameters may fall outside the normal range, as part of a protective response. Reversing these protective responses by targeting normal values may be detrimental. Two billion years of eukaryotic evolution and 600 millions of years of large animal evolutionary selection have resulted in complex but poorly understood physiologic adaptations that are ruthlessly efficient in ensuring healing and survival. Our add-on therapies, based on 2–3 centuries of modern medicine, are often too simplistic and superficial to impact outcomes.

Ultimately, however, the concept of "Less is More" needs to be empirically proven. Critical care trials may study surrogate end points or clinical outcomes. While numerous trials have demonstrated physiological benefit, there has been much less success when studying clinical end points. There are a large number of trials where there has been clinical harm despite success in achieving the physiological target.[11] In critical care, the main clinical outcomes are decreased mortality, decreased severity, and a faster and more complete recovery. A lesser severity can be gauged by the duration of the illness and therapy, the degree of invasive interventions needed, and the associated discomfort caused to a patient. Mortality is by far most important and we focus on this in attempting to use empiric data and prove that less is truly more in emergency and ICU patients.

If the "less is more" concept were correct, we hypothesized that, in randomized controlled trials (RCTs), the mortality in the patients in the "less" or control group (receiving placebo, restrictive, or standard therapy) would be significantly lower than in the "more" or intervention group (receiving study intervention or liberal therapy). We reviewed all RCTs related to emergency, acute, or critical care medicine with mortality as an end point published in the New England Journal of Medicine (NEJM) from 2008 onward.[11] In this list [Table 1], updated to October 2016,[1] we found 63 trials. This is not a cherry-picked list. These trials passed the NEJM review and selection process, and we included all which we felt were representative, before doing any analysis. There were a few therapies in conditions with a low (<10%) mortality, but we included them as we felt they represented intensive care practices (PRBC transfusions, thrombolysis in pulmonary embolism, and antibiotic duration). Some studies had more than two arms, and we combined the groups together in a way that a "less" approach was compared to a "more" approach. Trials variously report ICU mortality, hospital mortality, or mortality at specified time points. We used the value reported at the longest follow-up period based on the protocol of each individual study.

In this cohort from 63 RCTs, the total reported mortality in intervention group was 23,601/58,727 (40.19%), and in the

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Table 1: Randomized controlled trials published in the New England Journal of Medicine 2008-Oct 2016. *n* = 63

Category	*n*	Trial name	Intervention and disease	Intervention mortality	Control mortality	Primary outcome	Mortality outcome	Reference
Cardiovascular Shock Sepsis	1	VASST[a]	Vasopressin versus noradrenaline in septic shock	172/392	188/379	Similar	Similar	N Engl J Med 2008;358:877-87
	2	CORTICUS	Steroids in septic shock	86/251	78/248	Similar	Similar	N Engl J Med 2008;358:111-24
	3	SOAP II[a]	Dopamine versus noradrenaline in septic shock	517/821	565/858	Similar	Similar	N Engl J Med 2010;362:779-89
	4	PROWESS SHOCK	APC in severe sepsis	287/842	269/822	Similar	Similar	N Engl J Med 2012;366:2055-64
	5	IABP-SHOCK-II	IABP in cardiogenic shock	119/300	123/298	Similar	Similar	N Engl J Med 2012;367:1287-96
	6	SEPSISPAM	MBP target in septic shock	142/388	132/388	Similar	Similar	N Engl J Med 2014; 370:1583-93
	7	ProMISE	EDGT	184/623	181/620	Similar	Similar	N Engl J Med 2015; 372:1301-11
	8	ProCESS[b]		129/439	267/902	Similar	Similar	N Engl J Med 2014; 370:1683-93
	9	ARISE		147/792	150/796	Similar	Similar	N Engl J Med 2014; 371:1496-1506
	10	ALBIOS	Albumin in sepsis	365/888	389/893	Similar	Similar	N Engl J Med 2014; 370:1412-21
	11	FEAST[c] Normotensive group	Saline or albumin in severe pediatric sepsis	254/2126	91/1044	Adverse	Increased	N Engl J Med 2011;364:2483-95
		FEAST Hypotensive group		9/13	9/16	Adverse	Similar	
	12	6S	HES in shock	202/398	173/400	Adverse	Increased	N Engl J Med 2012;367:124-34
	13	CHEST		597/3315	566/3336	Similar	Similar	N Engl J Med 2012;367:1901-11
	14	CARRESS-HF	Ultrafiltration in CCF	16/94	13/94	Adverse	Similar	N Engl J Med 2012;367:2296-304
	15	LEOpards	Levosimendan for the prevention of acute organ dysfunction in sepsis	97/258	84/256	Similar	Similar	N Engl J Med 2016;375:1638-48
Respiratory ARDS Mechanical ventilation	16	ACURASYS	Neuromuscular blockers in ARDS	56/177	66/162	Beneficial	Decreased	N Engl J Med 2010;363:1107-16
	17	PROSEVA	Prone position in ARDS	56/237	94/229	Beneficial	Decreased	N Engl J Med 2013;368:2159-68
	18	OSCAR	HFOV in ARDS	166/398	163/397	Similar	Similar	N Engl J Med 2013;368:806-13
	19	OSCILLATE		129/275	96/273	Adverse	Increased	N Engl J Med 2013;368:795-805
	20	FLORALI[d]	NIV versus CPAP versus O_2 in respiratory failure	31/110	35/200	Beneficial (CPAP group)	Decreased (CPAP group)	N Engl J Med 2015;372:2185-96
	21	HARP-2	Simvastatin in ARDS	67/258	90/279	Similar	Similar	N Engl J Med 2014;371:1695-703
	22		Rosuvastatin in ARDS	108/379	91/366	Similar	Similar	N Engl J Med 2014;370:2191-200
Renal	23	ATN	Intensity of RRT	302/563	289/561	Similar	Similar	N Engl J Med 2008;359:7-20
	24	RENAL		322/721	352/743	Similar	Similar	N Engl J Med 2009;361:1627-38

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Category	*n*	Trial name	Intervention and disease	Intervention mortality	Control mortality	Primary outcome	Mortality outcome	Reference
	25	AKIKI	Timing of RRT	150/311	153/308	Similar	Similar	N Engl J Med 2016; 375:122-133
Neurology CVA	26	ECASS III	Thrombolysis in CVA	32/418	34/403	Beneficial	Similar	N Engl J Med 2008;359:1317-29
TBI	27	DESTINY II	Hemicraniectomy in CVA	20/49	47/63	Beneficial	Decreased	N Engl J Med 2014;370:1091-100
	28	MR CLEAN	Endovascular treatment for CVA	49/233	59/267	Beneficial	Similar	N Engl J Med 2015;372:11-20
	29	EXTEND IA		3/35	7/35	Beneficial	Similar	N Engl J Med 2015;372:1009-18
	30	ESCAPE		17/164	28/147	Beneficial	Decreased	N Engl J Med 2015;372:1019-30
	31	SWIFT PRIME		9/98	12/97	Beneficial	Similar	N Engl J Med 2015;372:2285-95
	32	REVASCAT		19/103	16/103	Beneficial	Similar	N Engl J Med 2015;372:2296-306
	33	MR RESCUE		12/64	13/54	Similar	Similar	N Engl J Med 2013;368:914-23
	34	SYNTHESIS		14/181	11/181	Similar	Similar	N Engl J Med 2013;368:904-13
	35	IMS III		83/434	48/222	Similar	Similar	N Engl J Med 2013;368:893-903
	36	INTERACT 2	BP control in ICH	166/1399	170/1430	Similar	Similar	N Engl J Med 2013;368:2355-65
	37	ATACH-2		33/481	34/480	Similar	Similar	N Engl J Med 2016; 375:1033-1043
	38	TTM	Hypothermia after CPR	235/473	225/466	Similar	Similar	N Engl J Med 2013;369:2197-206
	39	THAPCA		94/151	97/134	Similar	Similar	N Engl J Med 2015;372:1898-908
	40	TBI PROTECT	Progesterone in TBI	83/442	69/440	Similar	Similar	N Engl J Med 2014;371:2457-66
	41	TBI SYNAPSE[e]		109/591	95/588	Similar	Similar	N Engl J Med 2014;371:2467-76
	42	DECRA	Craniectomy in TBI	14/73	15/82	Adverse	Similar	N Engl J Med 2011;364:1493-502
	43	RESCUEicp[f]		54/201	92/188	Similar	Decreased	N Engl J Med 2016;375:1119-30
	44	BEST-TRIP	ICP monitoring in TBI	56/157	67/167	Similar	Similar	N Engl J Med 2012;367:2471-81
	45	EUROTHERM	Hypothermia in TBI	69/194	51/192	Adverse	Similar	N Engl J Med 2015;373:2403-12
	46	FAST-MAG	Mg in CVA	132/857	131/843	Similar	Similar	N Engl J Med 2015;372:528-36
General ICU Abdominal	47	PANTER	Limited approach in pancreatitis	7/45	8/43	Beneficial	Similar	N Engl J Med 2010;362:1491-502
Antibiotics DVT and PE Blood transfusion	48		Selective gut decontamination[g]	1249/3949	632/1990	Similar (beneficial after data adjustment)	Similar	N Engl J Med 2009;360:20-31
Metabolic Fever CPR	49	STOP-IT[i]	Antibiotic duration in peri-operative septic abdomen	3/257	2/260	Similar	Similar	N Engl J Med 2015;372:1996-2005
	50	PROTECT	LMWH versus UFH for DVT prophylaxis	414/1873	459/1873	Similar	Similar	N Engl J Med 2011;364:1305-14
	51	LIFENOX	LMWH in medical patients	348/4171	355/4136	Similar	Similar	N Engl J Med 2011;365:2463-72

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Category	*n*	Trial name	Intervention and disease	Intervention mortality	Control mortality	Primary outcome	Mortality outcome	Reference
	52	PEITHO[l]	Thrombolysis in PE	12/506	16/499	Similar	Similar	N Engl J Med 2014;370:1402-11
	53	EPANIC[h]	Early TPN	255/2312	257/2328	Beneficial	Similar	N Engl J Med 2011;365:506-17
	54	CALORIES	Early TPN versus EN	442/1184	464/1188	Similar	Similar	N Engl J Med 2014;371:1673-84
	55	REDOXs[i]	Glutamine	259/611	218/607	Adverse	Increased	N Engl J Med 2013;368:1489-97
	56	TRISS	Liberal versus restrictive PRBC	223/496	216/502	Similar	Similar	N Engl J Med 2014;371:1381-91
	57	ABLE[j]	Fresh versus old blood	448/1211	430/1219	Similar	Similar	N Engl J Med 2015;372:1410-8
	58	TITRe-2[l]	Liberal PRBC in cardiac surgery	26/1003	42/1000	Similar	Decreased	N Engl J Med 2015;372:997-1008
	59	FOCUS[l]	Liberal or restrictive transfusion in high-risk patients after hip surgery	52/995	43/1000	Similar	Similar	N Engl J Med 2011;365:2453-62
	60	NICE SUGAR	Tight glucose control	829/3010	751/3012	Adverse	Increased	N Engl J Med 2009;360:1283-97
	61	HEAT	Fever control	55/346	57/344	Similar	Similar	N Engl J Med 2015;373:2215-24
	62	ROC	CPR technique	11,482/12,653	9961/11,058	Similar	Similar	N Engl J Med 2015;373:2203-14
	63		Lignocaine and amiodarone in CPR[k]	1484/1967	833/1059	Similar	Similar	N Engl J Med 2016; 374:1711-1722

[a]In VASTT, we took vasopressin as the intervention and in SOAP-2 we took noradrenaline as the intervention as they represented the therapy being tested against an older or more conventional standard, [b]In the ProCESS study, we took the usual care and the standard protocolized care as the standard/less group and the EDGT as the intervention/more, [c]In the FEAST study, in the non-hypotensive stratum, we took the placebo to be less/standard and both the saline and albumin groups to be more/intervention. In the hypotensive stratum, saline was taken as standard and albumin was taken as the intervention, dIn FLORALI, we took standard O_2 and CPAP as the less group and NIV as the more group, [e]In TBI SYNAPSE study, the death and severe disability combined was the reported outcome and we obtained the mortality data through a personal communication with the author, [f]In RESCUEicp, the lower mortality was accompanied by an increase in bad neurological outcomes. For the sake of this analysis, we have taken it as a mortality benefit, [g]In the trial (number 48) evaluating SDD, we took selective decontamination of the digestive tract and selective oral decontamination as the intervention and placebo as control, [h]In EPANIC, we took early TPN as the more therapy and late at the less therapy, [i]REDOXs was a two-by-two factorial trial looking at glutamine and antioxidants. For this analysis, we took glutamine as the intervention, [j]In ABLE, we took the fresh blood as the intervention and the old blood as standard, [k]In the trial (number 63) evaluating drugs in CPR, lignocaine or amiodarone was taken as the intervention and placebo as the control, [l]Four of these studies had much lower (<10%) overall mortality than usually seen in ICU. We included them as they represented common ICU issues involving PRBC transfusions, thrombolysis in PE, and antibiotic duration in the septic postoperative abdomen (TITRE-2, FOCUS, PEITHO, STOP-IT). APC: Activated protein C; IABP: Intra-aortic balloon pumping; MBP: Mean blood pressure; ARDS: Acute respiratory distress syndrome; HFOV: High-frequency oscillatory ventilation; NIV: Noninvasive ventilation; RRT: Renal replacement therapy; ICH: Intracerebral hemorrhage; CVA: Cerebrovascular accident; BP: Blood pressure; CPR: Cardiopulmonary resuscitation; PRBC: Packed red blood cell; PE: Pulmonary embolism; DVT: Deep venous thrombosis; TBI: Traumatic brain injury; TPN: Total parenteral nutrition; LMWH: Low-molecular-weight heparins; UFH: Unfractionated heparin; ICP: Intracranial pressure; ICU: Intensive Care Unit; CPAP: Continuous positive airway pressure; SDD: Selective digestive decontamination; CCF: Congestive cardiac failure; EGDT: Early goal directed theraopy; HES: HydroxyEthyl starch; EN: Enteral nutrition

control group, it was 20,752/53,568 (38.74%). The relative risk of death in the intervention group of patients was 1.0374 (95% confidence interval: 1.0224–1.0526; $P < 0.001$). Though the absolute difference appears relatively low at 1.45%, it denotes a statistically significant higher mortality. This translates to an additional death for every 69 patients enrolled in the intervention arms of these trials. This adds empiric evidence to the concept that doing less in ICU may result in significantly lower mortality in a wide spectrum of emergency or critically ill patients.

Medicine is not a black and white field, and a therapy may be beneficial even if it does not decrease mortality. For this reason, many trials report a composite end point which may or may not include mortality. To evaluate the impact of intervention on these other relevant end points, we compared the number of positive, neutral, and adverse outcomes in terms of reported primary end points. We did not include nonmortality secondary end points, *post hoc*-adjusted outcomes, or subgroup benefits in our analysis. Only eight therapies reported improved mortality or other clinically meaningful primary outcomes (continuous positive airway pressure in respiratory failure, thrombolysis in cerebrovascular accident [CVA], neuro-intervention in CVA, surgical control of intracranial pressure [ICP] in CVA, prone position ventilation in ARDS, neuro-muscular-blockers in

acute respiratory distress syndrome [ARDS], liberal transfusion after cardiac surgery, and limited approach in pancreatitis) while seven therapies worsened outcomes (hydroxy ethyl starch solutions for fluid resuscitation, fluid bolus in pediatric nonhypotensive sepsis, high-frequency oscillatory ventilation in ARDS, glutamine supplementation, early total parenteral nutrition, surgical ICP control in traumatic brain injury, and hypothermia in traumatic brain injury). The majority had no impact on the primary outcome. This further strengthens the case for the judicious use of unproven therapies.

It is worth pointing out that "Less is More" is not a lazy approach; rather, it is a well-researched and carefully thought-out strategy aimed at getting rid of the therapies that do not improve clinical outcomes. This analysis of more than 100,000 patients from high-quality NEJM RCTs in the past decade demonstrates that the majority of studies failed to demonstrate clinical benefit. A judiciously restrictive approach, besides being resource efficient, could be associated with an overall mortality benefit. In critical care, simplicity may be the ultimate form of sophistication.

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