What is the current concept in early goal directed therapy (EGDT)?

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Survival Sepsis Campaign recommends initial resuscitation in sepsis induced hypo-perfusion (i.e. hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L) should aim to achieve the following goals in first 6 hours of treatment-

1. CVP 8–12 mm Hg
2. MAP ≥ 65 mm Hg
3. Urine output ≥ 0.5 m/kg/hour
4. Superior vena cava oxygenation saturation (Scvo2) or mixed venous oxygen saturation (SvO2) 70% or 65% respectively.

What is the basis of recommendation for EGDT?

Rivers et al, in 2001, in a landmark single center RCT demonstrated that, management aiming to achieve the physiological targets (as stated above) in initial 6 hours resulted in 15.9% absolute reduction of mortality in 28 days. This strategy of management is termed as "Early goal directed therapy (EGDT). [1]

This strategy was tested in a subsequent multicenter RCT in China with a population group of 314 patients with severe sepsis. The authors demonstrated an absolute 17.7% reduction in mortality in the study group.[2]

A meta-analysis following these two studies done by Jones AE et al evaluated the outcome of a ***quantitative resuscitation strategy*** in patients with sepsis. They evaluated the effect of resuscitation commencement timing to the outcome. The meta-analysis concluded that early commencement of quantitative resuscitation strategy (in other words strategy aiming for particular end point/end points) lead to better outcome in terms of mortality. The effect of this goal directed therapy was negated if resuscitation was delayed. The authors did acknowledge that there was significant heterogeneity in the included studies and emphasized on early resuscitation. They said that though resuscitation end point/endpoints were different for different studies but it was the timing of commencement of resuscitation that determined the outcome.[3]

What is the argument against early goal directed therapy (EGDT)?

Three recent studies compared EGT with standard care (ProCESS, ARISE and ProMISe). The summary of the three trails are as following-

	ARISE[6]	PRoMISe[4]	ProCESS[5]
Geographical area	Australia & New Zealand, Finland, Hong Kong and the Republic of Ireland	England	USA
Clinical Question	EGDT Vs Standard Therapy	EGDT Vs Standard Therapy	EGDT Vs protocol based therapy Vs Usual care group***
Population	1600	1260	1352
Base line character diff	1st dose of Abx before randomization	1st dose of Abx before randomization	Not in inclusion criteria (76% patients received Abx before randomization)
APACHE	15.4 +/- 6.5 vs. 15.8 +/- 6.5	18.7 +/-7.1 Vs 18.0+/-7.1	20.8+/-8.1 Vs 20.6+/-7.4 Vs 20.7+/-7.5
Method			
Study group			
Fluid bolus	500mls bolus of crystalloid or colloid	Same	Same

	at least every 30 minutes until CVP > 8mmHg		
Vasopressors	to achieve MAP of > 65 and/or SBP > 90mmHg	Same	Same
Dobutamine	SCVO2 < 70% and Hb > 100g/	Same	Same
Reds cell transfusion	SCVO2 < 70% and Hb < 100g/dl	Same	Same
Oxygen/NIV/ Mechanical ventilation	If ScVO2 is still <70%	Same	Same
Control group			
CVC/ScVO2/Art line	If clinically applicable	If clinically applicable	If clinically applicable
ScVO2	None till 6 hrs	None till 6 hrs	None till 6 hrs
Result/Outcome			
Primary Outcome			
90 days mortality	Nonsignificant (18.6% Vs 18.8%	Nonsignificant (29.5 Vs 29.2%)	60 days mortality Nonsignificant (21 Vs 18.2 Vs 18.9%)
Secondary Outcome			
SOFA at 6 hrs	Not estimated	Significantly higher (EGDT Vs Control)	Not estimated
LOS ICU	Nonsignificant difference	Significantly more (EGDT Vs Control)	Nonsignificant difference
Mortality	28 days- No difference	28 days- No difference	90 days & 1 year- No difference
Vasopressors	Significantly higher requirement (EGDT 76.3% vs. usual care group 65.8%, P<0.001)	No difference	Significantly higher in EGDT (54.9%) Vs protocol based therapy (52.2%) Vs usual care (44.1) (P=0.003)
Fluid administered in 1st 6hrs (EGDT Vs Control)	1964+/-1415 ml Vs 1713+/-1401ml (P<0.001)	2000mls vs. 1784mls	2800 ml Vs 3300 ml Vs 2300 ml
Conclusion			
	EGDT did not lead to any improvement in outcome	EGDT did not lead to any improvement in outcome	No significant benefit in mortality or morbidity, in protocol-based resuscitation Vs bedside

			care in accordance with treating physician's judgement.
Strength			
Method	stringent	stringent	stringent
Cost analysis	nil	included	nil
QUALY (Quality adjusted life year)	nil	Included	nil
Statistical plan published earlier to completion of study	Yes	Yes	Yes
Weakness			
Blinding	No blinding	No blinding	No blinding

*** Usual care group - Bedside providers directed all care, with the study coordinator collecting data but not prompting any actions.

The above mentioned three studies enrolled patients who are less sick (low APACHE II) than the patients in the Rivers trial. This can be thought as a confounding factor for the results. But, in the subgroup analysis in ProCESS study, the sub group of patients who are sickest (even higher APACHE score than in River's trial) did not show improved out come with EGDT.

A recent meta-analysis that included three of the recent trials [4,5,6] and the previous two trials favoring EGDT[1,2] concluded that EGDT decreases 28, 60 and 90 days mortality but with no statistical difference.[7]

The survival sepsis campaign still recommends EGDT with the rational that EGDT has not been proven to be inferior to standard care and the ongoing management bundle has proven the remarkable benefit in mortality over last two decades.[8]

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