

Additional file 2: Summary of Mechanistic Studies

Analysis	Rationale	Timing of Test	Amount of Blood Required
Free cortisol versus total cortisol	The ideal method for measurement of adrenal function in critical illness is highly controversial. Adrenocorticotrophic hormone stimulation testing is expensive, cumbersome and difficult to interpret [1, 2] random total cortisol levels may be affected by serum protein levels in critical illness [3-5] and have not consistently correlated with clinically important outcomes [1, 6]. Some recent studies have suggested that free cortisol levels may better reflect adrenal function in critical illness but these studies have not been linked to outcomes in an RCT [7, 8].	Prior to administration of study drug	0.6 ml
Stratification biomarkers	It is currently difficult to predict the outcome of patients with septic shock. Previous studies have shown that younger age[9] was a risk factor for illness severity in these patients. However, more recent gene-expression based work [10, 11] has supported the existence of septic shock sub-classes that predict mortality based on a 100-gene expression signature. Further validation of this finding as a stratification tool for clinical trials is still needed.	Within 24 hours of admission	0.1 ml
25 hydroxyvitamin D and 1,25 hydroxyvitamin D	The hemodynamic status of a patient in shock is a complex interplay between a variety of autonomic, endocrine and physiologic parameters. Although cortisol is felt to play an important role in this hemodynamic status, a recent study by our group suggested that Vitamin D deficiency may have an additive effect on hemodynamic instability [12].	Within 24 hours of admission	0.5 ml

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