Publication	Grade	Quality	Comments
Randomized Controlled Trials (RCT)			
Venkatesh et al, Adjunctive glucocorticoid therapy in patients with septic shock, NEJM 2018 2018	A	Outstanding	ADRENAL Trial: This was a multicenter (69 sites in five countries) of 3800 patients, study intervention was 200 mg/d of Hydrocortisone (HC) by continuous infusion for 7 days without taper in patients with septic shock undergoing mechanical ventilation. There was no difference in 90-day mortality (27.9 vs 28.8%) but there was faster resolution of shock (3 vs 4 days) and shorter time on mechanical ventilation (6 vs 7 days) in the HC group.
Annane et al Hydrocortisone plus fludrocortisone for adults with septic shock NEJM 2018	A	Outstanding	APROCCHSS Trial: This is a multicenter study (34 sites) in France including 1241 patients, study intervention of 200 mg/d of HC given as 50mg every 6 hours IV plus 50 mcg of Fludrocortisone orally daily for 7 days without taper in patients with septic shock requiring at least 0.25 ug/kg/minute of vasopressor (Norepinephrine, Epinephrine, or Dopamine) for at least 6 hours to achieve a MAP of >65 or SBP of >90 mm Hg. 90-day mortality was significantly lower (43.0 vs 49.1%) in the study group; there also was an improvement in shock (as measured by Vasopressor-free days) and organ failure (as measured by SOFA scores) in the study group.
Povoa et al, Impact of stress dose steroids in the patients with septic shock: insights from the PROWESS-Shock trial, Critical Care Clinical 2015	B	Adequate	PROWESS Trial: Included 1695 patients to study droctrecogin-alfa (Xigris) in patients with septic shock but the data was reviewed to look at the comparison of patients who received steroids versus no steroids. There was no specific data on the type, amount, or method of steroid administration. There was no difference in mortality (23.5 vs 23.3%) or resolution of shock in the steroid group.
Lu et al, Early initiation of low-dose hydrocortisone treatment for septic shock: a randomized clinical trial, American J Em Med 2017	A	Good	Early HC Trial: 118 patients, study intervention of 200 mg/d of HC given as continuous infusion for 6 days with tapering over another 6 days (3 days at half then quarter dose) for patients with septic shock. The HC was to be started immediately after IV fluids (20-30 ml/kg over 30-60 minutes) and concurrently with vasopressors to attain a MAP >65 mm Hg. There was no

			difference in mortality (39.7 vs 31.7%) or shock reversal.
Registry – Prospective Observation			
Casserly et al, Low-dose steroids in adult septic shock: results of the Surviving Sepsis Campaign, Intensive Care Med 2012	D	Adequate	This is a registry study that included 17,847 patients with septic shock who received HC at 200-300 mg/d as part of their treatment course. There was an association of higher mortality (41 vs 35%) in the group who received HC.
Retrospective Observation			
Buckley et al, Concomitant vasopressin and hydrocortisone therapy on short-term hemodynamic effects and vasopressor requirements in refractory septic shock, J of Critical Care 2017	D	Good	Vasopressin plus HC: 300 patients with septic shock requiring Norepinephrine infusion after fluid resuscitation to maintain MAP>70 mm Hg. The combination of Vasopressin infusion and HC (at 200-300 mg/d) had a significantly higher rate of hemodynamic response (defined as >50% reduction in Norepinephrine dose while maintaining MAP than either HC or Vasopressin alone.
RCT (In patients without Shock)			
Keh et al, Effect of hydrocortisone on the development of shock among patients with severe sepsis. The HYPRESS Randomized Clinical Trial., JAMA 2016 .	B	Good	HYPRESS Trial: 380 patients with presumed infection causing >2 SIRS (systemic inflammatory response syndrome) criteria and evidence of organ dysfunction but NOT shock. Multicenter study (34 sites) in Germany. Study intervention was 200 mg/d of HC by continuous infusion for 5 days followed by tapering over the following 6 days. There was no significant difference between the groups in the development of septic shock (21.2 vs 22.9%) or hospital mortality (13.5 vs 12.8%). There were more hyperglycemia occurrences in the HC group (90.9 vs 81.5%) but not other adverse effects.
Meta-Analysis			
Lu et al, Effect of low-dose hydrocortisone therapy in adult patients with septic shock: a meta-analysis with trial sequential analysis of	A	Outstanding	Included 13 RCTs and reported no difference in 28-day mortality with HC in patients with septic shock but there was significant improvement in reversal of shock. Subgroup analysis did find lower mortality (28-day, ICU, and hospital) with patients given both HC and Fludrocortisone.

randomized controlled trial, J Intensive Care Med 2018 13 RCTs included in Meta-analysis			
Wang et al, Low-Dose hydrocortisone therapy attenuates septic shock in adult patients but does not reduce 28-day mortality: a meta-analysis of randomized controlled trial, Anesthesia Analgesia 2014	A	Outstanding	Included 8 RCTs which found no difference in 28-day mortality with HC in patients with septic shock but did improve shock reversal (defined as a period of >24 hours with Systolic BP >90 mm Hg without vasopressor support).
Annane et al Cochrane Review 2019	B	Outstanding	Cochrane Review which included 27 RCTs. There was a reduction in 28-day mortality, as well as ICU and hospital mortality in patients with septic shock treated with HC. There was also an increase in shock reversal and reduction in organ failure by SOFA scores by day 7.
Studies evaluating Bolus vs Continuous Infusion of HC			
Ibarra-Estrada et al World J Crit Care Med 2017 Prospective cohort of small size N=59	C	Good	Prospective Cohort of 59 patients with septic shock treated with 200 mg/d of HC either by bolus (50 mg Q 6 hours) or continuous infusion for 7 days. Significantly more patients treated with continuous infusion had reversal of shock by day 7 (83 vs 63%).
Tilouche et al Shock 2019	A	Good	RCT of 58 patients with septic shock treated with 200 mg/d of HC either by bolus (50 mg Q 6 hours) or continuous infusion for 7 days. Shock reversal occurred significantly more in the bolus group (75 vs 44%) and earlier (6 vs 9 days). There was no difference in mortality or ICU length of stay between groups.