**Supplemental Table 1**

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| **Study (Year)** | **Design** | **Patient population** | **Intervention** | **Comparator group** | **Primary Outcome(s)** | **Comments** |
| **RCT (completed)** |  |  |  |  |  |  |
| CITRIS-ALI (2019)(4) | Randomized, double-blind,  placebo-controlled, multicenter (7 sites) trial | Adults (N = 167) with sepsis and ARDS | IV Vitamin C (50mg/kg in dextrose 5%in water, every 6 hours for 96 hours.  (n = 84) | Placebo (dextrose 5%in water only) every 6 hours for 96 hours  (n = 83) | 1) Change in modified SOFA score at 96 hours; 2) C-reactive protein levels; 3) thrombomodulin levels  No differences between groups | Mortality was lower in intervention group.  No adverse events. |
| VITAMINS (2020)(5) | Open-label, randomized clinical trial  Multicenter  (10 ICUs in Australia, New Zealand, and Brazil) | Adults (N = 216) with septic shock  Enrolled  within 24 hours of diagnosis with septic shock | HAT therapy  IV Vitamin C (1.5 g every 6 hours), Hydrocortisone (50mg every 6 hours), and Thiamine (200mg every 12 hours), until shock resolution or up to 10 d.  (n = 109) | Hydrocortisone (50mg every 6 hours) alone until shock resolution or up to 10 days.  (n = 107) | Duration of time alive and  free of vasopressor up to day 7.  No significant difference between groups | No serious adverse events |
| ORANGES (2020)(7) | Randomized, double-blind, placebo-controlled trial, in 2 sites (community hospitals) | Adults with sepsis or septic shock; therapy initiated in the ED  Average time to study drug was 10 h | HAT therapy  Hydrocortisone 50 mg q6h, Vitamin C 1.5g q6h, and Thiamine 200 mg q 12 hours,  for a maximum of 4 days.  (n=68) | Matching saline placebo for a maximum of 4 days.  (n=69) | 1)Resolution of shock (vasopressor discontinuation) - significantly quicker in HAT therapy (27 vs 53 h, P < .001)  2)Change in SOFA score on Day 4.  No difference between groups | No significant diff in rates of RRT or oxaluria between the groups. |
| ACTS (2020)(8) | Randomized, blinded trial, multicenter (N=14) | Adults (N = 205) with septic shock  Average time from vasopressor initiation to study drug - 13.5 h | HAT therapy  hydrocortisone (50 mg), Vitamin C (1500 mg), , and Thiamine (100 mg) every 6 hours for 4 days  (n = 103) | Placebo  Volume matched  (n = 102) | Change in SOFA scores at 72 hours.  No significant difference | No difference in major adverse events  Open-label corticosteroids by the clinicians was allowed |
| ATESS (2020)(6) | Randomized, controlled trial, double-blind, multicenter (4 sites, ED) | Adults (N = 111) with septic shock  Median time to study drug was 9 h. | IV Vitamin C (50 mg/kg) and Thiamine (200 mg) q 12 h for 48 h  (n = 53) | Placebo (identical volume of 0.9% saline)  q 12 h for 48 h  (n = 58) | Change in SOFA score at 72 hrs.  No significant difference | Open-label Hydrocortisone in more than 50% of the patients (balanced between the 2 groups). |
| VICTAS (2021)(9) | Randomized, double-blind, adaptive, placebo-controlled, Multicenter (N=43 sites), trial  Planned enrollment - 2000 patients. | Adults with sepsis-induced acute respiratory and/or cardiovascular dysfunction.  Median time to study drugs was 14.7 hours | Hydrocortisone (50 mg), IV Vitamin C (1.5 g), and Thiamine (100 mg), within 4 h of randomization and then every 6 h up to 96 h.  Open-label corticosteroids by the clinicians was allowed. | Placebo (matched volume) every 6 hours up to 96 hours. | Ventilator- and vasopressor-free days (VVFDs) in the first 30 days following randomization.  Underpowered to detect difference due to early termination. | After 501 participants were enrolled, additional funding for the trial was withheld due to a change in the funder’s priorities. |
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| **RCT (ongoing)** |  |  |  |  |  |  |
| RESPOND(10) | Open label, randomized controlled, multicenter (ANZICS – PSG, Brazil, Korea), 3-arm trial | Children (8 days – 17 yrs.) admitted to PICU with septic shock treated with inotropes for at least two hours | Standard therapy, plus  1)Hydrocortisone + Vitamin C  2)Hydrocortisone alone  1:1:1 allocation to the 2 interventions and standard therapy arms. | Standard therapy | Time alive and free of vasopressors, censored at 7 days | Long-term outcomes: quality of life, developmental scale and functional score. |
| VITaCCA | Randomized placebo-controlled, double-blind, 3-arm with 1:1:1 allocation, multi-center (7 sites Netherlands) trial | Adults with cardiac arrest admitted to the ED, and with ROSC (N = 270) | IV Vitamin C at 1) supplemental dose (3g/day) and 2) pharmacologic dose (10d/day). | Placebo | Change in R-SOFA score at 96 h |  |
| VICToRY | Pilot study, randomized, blinded, multicenter (20 Burn Units worldwide) | Adults (N=180) with severe burn injury | IV Vitamin C high dose (200mg/kg/day x 96 hours)  + Standard burn care | Placebo + Standard burn care | 28-day composite outcome of Persistent Organ Dysfunction (POD) and all-cause mortality | Pilot feasibility trial prior to larger RCT |
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| **Other studies** |  |  |  |  |  |  |
| Marik (2017)(2) | Pre-post retrospective, propensity-matched study, single center | Adults with sepsis or septic shock (N = 94) | Pre-cohort (n=47) – HAT Hydrocortisone (50 mg q6h), Vitamin C (1.5 g q6h) and Thiamine (200 mg q 12h)  Post cohort:Historical (n=47) | NA | Hospital mortality - significantly lower in the treatment group (8.5% vs.40.4%), P < .001. The propensity adjusted odds of mortality in vitamin C group was 0.13 (95% CI, 0.04-0.48; P = 0.002). | SOFA score decreased vasopressors weaned faster in Vitamin C group. |
| Coloretti (2020)(3) | Pre-post retrospective, propensity-matched study, single center | Adults with Sepsis (N=112)  Matched 1:1 using a propensity score model | Pre-cohort: Hydrocortisone alone (N=56)  Post-cohort: HAT therapy (N=56) | NA | Length of mechanical ventilation  Significantly lower in Post-cohort.  Hospital mortality  No significant difference |  |
| Wald (2021)(11) | Retrospective, propensity-matched study, single center | Children with septic shock requiring  Vasopressors (N = 557) | 1)HAT therapy group 2)Hydrocortisone alone group  3)Standard care | NA | Mortality  HAT therapy vs. untreated  30-d (9 vs. 28%, p = 0.03)  90-d (14 vs. 35%, p = 0.02).  HAT therapy vs. hydrocortisone  30-d (9% vs. 28%, p = 0.03)  90-d (14% vs. 33%, p= 0.04) |  |