Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

**Supplement 4. eResults**

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1. Flow diagram

Records identified through database searching
MEDLINE n = 287
Embase n = 5,435
CENTRAL n = 394
Clinicaltrials.gov n = 95
WHO ICTRP n = 1,467

Update
MEDLINE n = 629
Embase n = 5,725
CENTRAL n = 882

Additional records identified through other sources (n = 2)

Records after duplicates removed (n = 13,416)

Records screened (n = 13,416)

Records excluded (n = 13,233)

Full-text articles assessed for eligibility (n = 183)

Full-text articles excluded with reasons (n = 140)

Eligible trials (n = 43)
2. Characteristics of included studies

Where age or severity score was reported for each group, the reported values were combined. Where a mean value with standard deviation was unavailable, but a median with interquartile range was available, the mean and SD were calculated using formulae\(^1,2\). If neither of the measures mentioned above was available, the mean value of known SDs was calculated from included studies\(^3\). GC denotes glucocorticoid; vitC, vitamin C; VHD-vitC, very high dose vitamin C; HD-vitC, high dose vitamin C; vitB1, vitamin B1; N/A, not available; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology And Chronic Health Evaluation.

| Study Author year | Age, mean (SD) | Shock | Severity score, mean | Industry-funded | Country | Comparison |
|-------------------|----------------|-------|----------------------|-----------------|---------|------------|
| Bennett Jr 1963\(^4\) | N/A | Yes | N/A | Unclear | US | GC vs placebo or usual care |
| Bollaert 1998\(^5\) | 58 (14.6) | Yes | SAPS 2, 14 | No | France | GC vs placebo or usual care |
| Annane 2002\(^6\) | 61 (16) | Yes | SAPS 2, 58.5 | No | France | GC vs placebo or usual care |
| Yildiz 2002\(^7\) | 57.1 (16.9) | No | APACHE II, 16.6 | Unclear | Turkey | GC vs placebo or usual care |
| Oppert 2005\(^8\) | N/A | Yes | N/A | Unclear | Germany | GC vs placebo or usual care |
| Rinaldi 2006\(^9\) | N/A | No | N/A | Unclear | Italy | GC vs placebo or usual care |
| Kaufmann 2008\(^10\) | 62.3 (17.9) | Yes | APACHE III, 55.2 | Unclear | Germany | GC vs placebo or usual care |
| Sprung 2008\(^11\) (CORTICUS) | 63 (14.5) | Yes | SAPS 2, 49.1 | Yes | France, Germany, et al. | GC vs placebo or usual care |
| Ferron-Celma 2009\(^12\) | 66.5 (4.2) | No | N/A | No | Spain | vitC vs placebo or usual care |
| Hu 2009\(^13\) | 55.3 (36.6) | Yes | APACHE II, 19.1 | Unclear | China | GC vs placebo or usual care |
| Meduri 2009\(^14\) | N/A | No | APACHE III, 71.4 | Unclear | US | GC vs placebo or usual care |
| Arabi 2010\(^15\) | 60 (12.3) | Yes | APACHE II, 29.7 | No | Saudi Arabia | GC vs placebo or usual care |
| Deng 2011\(^16\) | N/A | No | N/A | Unclear | China | GC vs placebo or usual care |
| Yildiz 2011\(^17\) | 62.8 (15.6) | No | APACHE II, 20.7 | Unclear | Turkey | GC vs placebo or usual care |
| Rahardjo 2013\(^18\) | N/A | No | N/A | Unclear | Indonesia | vitC vs placebo or usual care |
| Fowler 2014\(^19\) | N/A | No | N/A | No | US | VHD-vitC vs vitC vs placebo or usual care |
| Gordon 2014\(^20\) | 61.2 (17) | Yes | N/A | No | UK | GC vs placebo or usual care |
| Mirea 2014\(^21\) | N/A | No | N/A | Unclear | Romania | GC (intermittent vs continuous) vs placebo or usual care |
| Donnino 2016\(^22\) | 67.4 (15.7) | Yes | APACHE II, 26.1 | No | US | vitB1 vs placebo or usual care |
| Gordon 2016\(^23\) (VANISH) | 65.6 (17.1) | Yes | APACHE II, 24.4 | No | UK | GC vs placebo or usual care |
| Keh 2016\(^24\) (HYPRESS) | 65 (14.4) | No | APACHE II, 19 | No | Germany | GC vs placebo or usual care |
| Li 2016\(^25\) | 66.1 (10.1) | No | N/A | No | China | GC vs placebo or usual care |
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| Study              | Mortality Rate (SD) | Randomization | APACHE | Study Country | Intervention | Comparator |
|--------------------|---------------------|---------------|---------|---------------|--------------|------------|
| Tongyoo 2016       | 64.4 (16.6)         | No            | II, 21.8| Thailand      | GC vs placebo or usual care |
| Zabet 2016         | 63.9 (14.7)         | Yes           | II, 21  | Iran          | GC vs placebo or usual care |
| Lv 2017            | 66.8 (14.9)         | No            | II, 23.4| China         | GC vs placebo or usual care |
| Annane 2018        | 66 (14)             | Yes           | SAPS 2, 56| France       | GC vs placebo or usual care |
| Balakrishnan 2018   | 54.4 (12.3)         | Yes           | III, 56.4| India        | HD-vitC + GC + vitB1 vs placebo or usual care |
| Rosini 2018         | N/A                 | No            | N/A     | US           | VHD-vitC vs placebo or usual care |
| Venkatesh 2018     | 62.5 (15)           | Yes           | N/A     | Australia, UK, et al. | GC vs placebo or usual care |
| Fowler 2019        | 55.1 (20.4)         | No            | N/A     | USA          | VHD-vitC vs placebo or usual care |
| Jiang 2019         | 59.2 (10.3)         | Yes           | II, 30.5| China        | GC (early vs late) vs placebo or usual care |
| Harun 2019         | 63.7 (17.7)         | Yes           | N/A     | Malaysia     | vitB1 vs placebo or usual care |
| Chang 2020         | 61.6 (14)           | No            | II, 23  | China        | HD-vitC + GC + vitB1 vs placebo or usual care |
| Fuji & Luethi 2020 | 61.7 (15)           | Yes           | III, 80.3| Australia, New Zealand, et al. | HD-vitC + GC + vitB1 vs GC |
| Hwang 2020         | 48.4 (9.9)          | Yes           | N/A     | South Korea  | HD-vitC + vitB1 vs placebo or usual care |
| Iglesias 2020      | 69 (13)             | No            | II, 24.5| US           | HD-vitC + GC + vitB1 vs placebo or usual care |
| Lv 2020            | 59.4 (14.2)         | No            | N/A     | Unlcer China | HD-vitC vs placebo or usual care |
| Mohamed 2020       | 59 (14.9)           | Yes           | N/A     | India        | HD-vitC + GC + vitB1 vs placebo or usual care |
| Moskowitz 2020     | 68.3 (14.4)         | Yes           | N/A     | US           | HD-vitC + GC + vitB1 vs placebo or usual care |
| Petsakul 2020      | 65 (17.8)           | Yes           | II, 27.5| Thailand     | vitB1 vs placebo or usual care |
| Wani 2020          | 54.1 (35.7)         | No            | N/A     | India        | HD-vitC + GC + vitB1 vs placebo or usual care |
| Sevransky 2021     | 60.8 (15)           | No            | II, 26.9| US           | HD-vitC + GC + vitB1 vs placebo or usual care |
| Hussain 2021       | 63.9 (16.3)         | Yes           | II, 20.6| Egypt        | HD-vitC + GC + vitB1 vs GC |
2.1 Comments in assessing Risk of Bias

| Study               | Comments                                                                 |
|---------------------|--------------------------------------------------------------------------|
| Bennett Jr 1963⁴    | year 1963 study, No protocol, About 15 patients < 18 years old          |
|                     | (Selective reporting: Unclear, General comment)                          |
| Rinaldi 2006⁹       | Too many dropouts. (Incomplete outcome data on the all-cause mortality within 1 year but later than 90 days: Unclear, Fraud or concern that might be a source of risk of bias, other bias) |
| Sprung 2008¹¹ (CORTICUS) | Based on the number of missingness and outcomes, incomplete outcome or 21 open label HC infusion are considered to be at low risk of bias. (Incomplete outcome data on the all-cause mortality within 1 year but later than 90 days: Low) Early termination, but without positive results. (Fraud or concern that might be a source of risk of bias, other bias) |
| Arabi 2010¹⁵        | Study interrupted for futility after enrolment of 50% sample size        |
|                     | (Fraud or concern that might be a source of risk of bias, reported in free text, other bias) |
| Balakrishnan 2018³⁰ | Very poor information on baseline characteristics and poor outcome reporting (Selective reporting: High, Baseline imbalance: Unclear) |
| Harun 2019³⁵        | Protocol or trial registry is not available. (Selective reporting: Unclear) Baseline APAHCE2 was higher in the Thiamine group (Baseline imbalance: High) Lack of ITT analysis. 7 patients died after randomization and were excluded. (General comment) |
| Chang 2020³⁶ (HYVCTTSSS) | Placebo was not administered in 70% patients in the control group (Inappropriate study deviation: High) |
| Iglesias 2020³⁹ (ORANGES) | https://clinicaltrials.gov/ct2/show/NCT03422159 See history. (Selective reporting: High) Baseline: patients requiring vasopressors were unbalanced (Baseline imbalance: High) |
| Wani 2020⁴⁴        | requirement for renal replacement therapy, which was planned to measure in the protocol, was not reported in the publication. (Selective reporting: High) |
| Sevransky 2021⁴⁵ (VICTAS) | Sponsor: Nova and some companies seem to be involved? (providing drugs) (Industrial sponsorship) Deviation: the number of patients who did not receive assigned treatment was not balanced in the 2 groups. But I could not tell whether it was by chance or not and its consequence. If it was perfectly blinded, I would say it was may be due to chance and may not be cause big bias. Thirty-three percent of patients in the intervention group and 32% of control patients received clinician-prescribed corticosteroids at a dose of at least 200 mg of hydrocortisone daily equivalent. If corticosteroids have a beneficial effect on VVFD, this would bias the trial results toward the null, although a post hoc sensitivity analysis demonstrated similar findings in patients not receiving open-label corticosteroids. (Inappropriate study deviation: Unclear) |
| Hussain 2021⁴⁶      | significant drop-out (Incomplete outcome data: Unclear) Lack ITT analysis (General comment) |
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### 3. Assessment of transitivity: distribution of effect modifiers

We assessed whether the eligible trials were similar in terms of characteristics that might modify the treatment effect on average so that the transitivity assumption was plausible. The following characteristics were assessed as possible effect modifiers: industrial sponsorship, blinding of the personnel, and vasopressor dependency of the study population. The plausibility of the transitivity assumption was evaluated by comparing the distribution of the effect modifiers across studies grouped by intervention arms through visual inspection. GC denotes glucocorticoid; vitC, vitamin C; VHD-vitC, very high dose vitamin C; HD-vitC, high dose vitamin C; vitB1, vitamin B1.

| Comparison | Study | Industry-funded | Shock | Study personnel blinded |
|------------|-------|-----------------|-------|------------------------|
| HD-vitC + GC + vitB1 vs GC | Fujii & Luethi 2020 | No or Unclear | Yes | No or Unclear |
| HD-vitC + GC + vitB1 vs GC | Hussein 2021 | No or Unclear | Yes | No or Unclear |
| HD-vitC + GC + vitB1 vs placebo or usual care | Balakrishnan 2018 | No or Unclear | Yes | Yes |
| HD-vitC + GC + vitB1 vs placebo or usual care | Chang 2020 | No or Unclear | No | No or Unclear |
| HD-vitC + GC + vitB1 vs placebo or usual care | Iglesias 2020 | No or Unclear | No | Yes |
| HD-vitC + GC + vitB1 vs placebo or usual care | Mohamed 2020 | No or Unclear | Yes | No or Unclear |
| HD-vitC + GC + vitB1 vs placebo or usual care | Moskowitz 2020 | No or Unclear | Yes | Yes |
| HD-vitC + GC + vitB1 vs placebo or usual care | Wani 2020 | No or Unclear | No | No or Unclear |
| HD-vitC + GC + vitB1 vs placebo or usual care | Sevransky 2021 | No or Unclear | No | Yes |
| VHD-vitC vs vitC vs placebo or usual care | Fowler 2014 | No or Unclear | No | Yes |
| HD-vitC + vitB1 vs placebo or usual care | Hwang 2020 | No or Unclear | Yes | Yes |
| VHD-vitC vs placebo or usual care | Rosini 2018 | No or Unclear | No | Yes |
| VHD-vitC vs placebo or usual care | Fowler 2019 | Yes | No | Yes |
| HD-vitC vs placebo or usual care | Zabet 2016 | No or Unclear | Yes | Yes |
| HD-vitC vs placebo or usual care | Lv 2020 | No or Unclear | No | No or Unclear |
| vitC vs placebo or usual care | Ferron-Celma 2009 | No or Unclear | No | Yes |
| vitC vs placebo or usual care | Rahardjo 2013 | No or Unclear | No | Yes |
| GC vs placebo or usual care | Bennett Jr 1963 | No or Unclear | Yes | Yes |
| GC vs placebo or usual care | Bollaert 1998 | No or Unclear | Yes | Yes |
| GC vs placebo or usual care | Annane 2002 | No or Unclear | Yes | Yes |
| GC vs placebo or usual care | Yildiz 2002 | No or Unclear | No | Yes |
| GC vs placebo or usual care | Oppert 2005 | No or Unclear | Yes | Yes |
| GC vs placebo or usual care | Rinaldi 2006 | No or Unclear | No | No or Unclear |
| GC vs placebo or usual care | Kaufmann 2008 | No or Unclear | Yes | Yes |
| GC vs placebo or usual care | Sprung 2008 | Yes | Yes | Yes |
| GC vs placebo or usual care | Hu 2009 | No or Unclear | Yes | No or Unclear |
| GC vs placebo or usual care | Meduri 2009 | No or Unclear | No | Yes |
| GC vs placebo or usual care | Arabi 2010 | No or Unclear | Yes | Yes |
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| Intervention                  | Study Year | Risk of Bias | Mort. Rate | Direct Evidence |
|-------------------------------|------------|--------------|------------|-----------------|
| GC vs placebo or usual care   | Deng 2011  | No or Unclear| No         | No              |
| GC vs placebo or usual care   | Yildiz 2011| No or Unclear| No         | Yes             |
| GC vs placebo or usual care   | Gordon 2014| No or Unclear| Yes        | No              |
| GC vs placebo or usual care   | Mirea 2014 | No or Unclear| No         | No              |
| GC vs placebo or usual care   | Gordon 2016| No or Unclear| Yes        | Yes             |
| GC vs placebo or usual care   | Keh 2016   | No or Unclear| No         | Yes             |
| GC vs placebo or usual care   | Li 2016    | No or Unclear| No         | No              |
| GC vs placebo or usual care   | Gordon 2016| No or Unclear| Yes        | Yes             |
| GC vs placebo or usual care   | Tongyoo 2016| No or Unclear| No         | Yes             |
| GC vs placebo or usual care   | Lv 2017    | No or Unclear| No         | Yes             |
| GC vs placebo or usual care   | Annane 2018| No or Unclear| Yes        | Yes             |
| GC vs placebo or usual care   | Venkatesh 2018| Yes        | Yes        | Yes             |
| GC vs placebo or usual care   | Jiang 2019 | No or Unclear| Yes        | No              |
| vitB1 vs placebo or usual care| Donnino 2016| No or Unclear| Yes        | Yes             |
| vitB1 vs placebo or usual care| Petsakul 2020| No or Unclear| Yes        | Yes             |
| vitB1 vs placebo or usual care| Harun 2019 | No or Unclear| Yes        | No              |
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4. All-cause mortality from 90 days to 1 year

4.1. Heterogeneity: Between-study variance within a comparison and the network

OR denotes odds ratio; GC, glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; N/A, not available.

| Comparisons                              | Number of studies | Expected variance for ORs from empirical distribution [95% range] | Estimated variance | Forest plot |
|-------------------------------------------|-------------------|------------------------------------------------------------------|------------------|-------------|
| HD-vitC+GC+vitB1 vs GC                    | 1                 | 0.014 [0.0008 to 0.25]                                           | N/A              | 0.0018 N/A |
| HD-vitC+GC+vitB1 vs placebo or usual care| 1                 | 0.017 [0.001 to 0.30]                                           | N/A              | 0.0018 N/A |
| HD-vitC+vitB1 vs placebo or usual care    | 1                 | 0.017 [0.001 to 0.30]                                           | N/A              | 0.0018 N/A |
| GC vs placebo or usual care               | 7                 | 0.017 [0.001 to 0.30]                                           | 0.0065           | 0.0018 No heterogeneity |

**Forest plot of pairwise comparison**

**GC vs placebo or usual care**

| Study | Experimental Events | Control Events | Odds Ratio | OR | 95%-CI | Weight |
|-------|---------------------|----------------|------------|----|--------|--------|
| Vennis 2010 | 571 1512 | 547 1803 | 1.23 | 1.18 | 1.04 | 0.9138 |
| Annan 2019 | 285 311 | 328 629 | 1.23 | 1.18 | 1.04 | 0.9138 |
| Spang 2010 | 137 21 | 200 323 | 1.13 | 1.17 | 0.96 | 0.9138 |
| Wang 2015 | 65 187 | 87 267 | 1.09 | 1.09 | 0.96 | 0.9138 |
| Annan 2002 | 100 150 | 112 200 | 1.01 | 1.01 | 0.96 | 0.9138 |
| Tongyl 2016 | 35 9 | 38 90 | 0.95 | 0.95 | 0.91 | 1.04 0.9138 |

4.2. Inconsistency

4.2.1. side-split

Number of loops = 1. OR denotes odds ratio; RoR, Ratio of Ratios (direct versus indirect); GC, glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1.

| comparison                     | Number of studies | OR from NMA | OR from direct comparison | OR from indirect comparison | RoR | p-value |
|--------------------------------|-------------------|-------------|---------------------------|-----------------------------|-----|--------|
| HD-vitC+GC+vitB1:GC            | 1                 | 1.2         | 1.23                      | 1.18                        | 1.04| 0.9138 |
| HD-vitC+GC+vitB1:placebo or usual care | 1       | 1.13        | 1.12                      | 1.17                        | 0.96| 0.9138 |
| HD-vitC+vitB1:GC               | 0                 | 1.31        |                           | 1.31                        | .   | .      |
| HD-vitC+vitB1:HD-vitC+GC+vitB1 | 0                 | 1.09        |                           | 1.09                        | .   | .      |
| HD-vitC+vitB1:placebo or usual care | 1       | 1.24        |                           | .                           | .   | .      |
| GC:placebo or usual care       | 7                 | 0.95        | 0.95                      | 0.91                        | 1.04| 0.9138 |
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### 4.2.2. global
Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model = 0.01 (df=1, p=0.9159)

### 4.3. Risk of bias within studies of each comparison
green bar = low, yellow bar = moderate, red bar = high. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1.

![Risk of bias within studies of each comparison](image)

### 4.4. Funnel plot
The treatments were in order of combination therapies first, monotherapies, and placebo or usual care, as the combination therapies have recently been investigated in small trials. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; PBO, placebo or usual care.

![Funnel plot](image)
4.5. P-scores of treatment

P-scores are calculated from the point estimates and standard errors of the network estimates. The P-score of treatment can be interpreted as the mean extent of certainty that the treatment is better than any other treatment. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1.

| Treatment                  | P-score |
|----------------------------|---------|
| 1. GC                      | 0.8072  |
| 2. placebo or usual care   | 0.5497  |
| 3. HD-vitC+vB1             | 0.3286  |
| 4. HD-vitC+GC+vB1          | 0.3146  |
5. Severity of organ dysfunction over 72 hours

5.1. Network graph

Network graph of all available pairwise comparisons between the eligible interventions. The size of the nodes shows the total number of patients accumulated for each treatment. The breadth of the edges was weighted according to the inverse of the variance of the direct summary effect. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C.

5.2. Heterogeneity: Between-study variance within a comparison and the network

GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C; SMD, standardised mean difference; N/A, not available.

| Comparisons                          | Number of studies | Expected variance of SMD from empirical distribution [95% range] | Estimated variance of SMD in comparison | Estimated variance of SMD in network | Forest plot          |
|--------------------------------------|-------------------|-----------------------------------------------------------------|----------------------------------------|------------------------------------|----------------------|
| HD-vitC + GC + vitB1 vs GC           | 2                 | 0.027 [0.00001 to 4.95]                                         | 0                                      | 0.0759                            | No evidence          |
| HD-vitC + GC + vitB1 vs placebo or usual care | 6                 | 0.033 [0.0001 to 10.2]                                         | 0                                      | 0.0759                            | No heterogeneity     |
| HD-vitC + vitB1 vs placebo or usual care | 1                 | 0.033 [0.0001 to 10.2]                                         | N/A                                    | 0.0759                            | N/A                  |
| VHD-vitC vs placebo or usual care    | 1                 | 0.033 [0.0001 to 10.2]                                         | N/A                                    | 0.0759                            | N/A                  |
| HD-vitC vs placebo or usual care     | 1                 | 0.033 [0.0001 to 10.2]                                         | N/A                                    | 0.0759                            | N/A                  |
| vitC vs placebo or usual care        | 1                 | 0.033 [0.0001 to 10.2]                                         | N/A                                    | 0.0759                            | N/A                  |
| GC vs placebo or usual care          | 5                 | 0.033 [0.0001 to 10.2]                                         | 0.1740                                 | 0.0759                            | Suspected Heterogeneity |
| vitB1 vs placebo or usual care       | 1                 | 0.033 [0.0001 to 10.2]                                         | N/A                                    | 0.0759                            | N/A                  |
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**Forest plots**

**HD-vitC + GC + vitB1 vs GC**

| Study                          | Experimental Total Mean | SD | Control Total Mean | SD | Standardised Mean Difference | SMD | 95% CI | Weight |
|--------------------------------|-------------------------|----|--------------------|----|-------------------------------|-----|-------|--------|
| Fujii & Lucetti 2020 (VITAMINS) | 2.10                    | 0.80 | 2.9000              | 0.90 | -0.82                         | -0.32 | [-0.64; 0.00] | 65.3%  |
| Husson 2021                     | 4.72                    | 2.4950 | 3.72              | 2.7250 | 0.27                         | 0.27 | [0.07; 0.47] | 26.7%  |

**Random effects model**

| 122 | 118 |
|-----|-----|
| 0.30 | [-0.50; -0.05] | 100.0% |

| Heterogeneity: $I^2 = 0\%$, $\hat{Q} = 0$, $p = 0.85$ |

**HD-vitC + GC + vitB1 vs placebo or usual care**

| Study                          | Experimental Total Mean | SD | Control Total Mean | SD | Standardised Mean Difference | SMD | 95% CI | Weight |
|--------------------------------|-------------------------|----|--------------------|----|-------------------------------|-----|-------|--------|
| Savadi 2021 (VICTAS)           | 2.65                    | 2.9824 | 2.6573              | 3.7283 | -0.10                         | -0.10 | [-0.28; 0.07] | 48.9%  |
| Medkowtitz 2020 (VICTAS)       | 4.10                    | 4.1200 | 8.10              | 4.3000 | 0.17                         | 0.17 | [0.04; 0.31] | 16.6%  |
| Greb et al. 2020 (ORANGE)      | 4.93                    | 3.1410 | 6.93              | 3.3400 | 0.19                         | 0.19 | [0.04; 0.34] | 11.7%  |
| Wani 2020                      | 5.64                    | 3.5500 | 3.62              | 3.9400 | 0.17                         | 0.17 | [0.06; 0.28] | 9.6%   |
| Mohamed 2020 (VICTOR)          | 2.60                    | 2.6000 | 2.60              | 2.6000 | -0.11                         | -0.11 | [-0.23; 0.01] | 8.2%   |
| Chang 2020 (YYCITAS)           | 3.50                    | 3.3000 | 1.50              | 3.0000 | 0.23                         | 0.23 | [0.08; 0.39] | 7.2%   |

**Random effects model**

| 539 | 533 |
|-----|-----|
| -0.17 | [-0.20; 0.05] | 100.0% |

| Heterogeneity: $I^2 = 0\%$, $\hat{Q} = 0$ [0.0000; 0.1028], $p = 0.64$ |

**GC vs placebo or usual care**

| Study                          | Experimental Total Mean | SD | Control Total Mean | SD | Standardised Mean Difference | SMD | 95% CI | Weight |
|--------------------------------|-------------------------|----|--------------------|----|-------------------------------|-----|-------|--------|
| Spring 2008 (CORTICUS)         | 10.12                   | 1.5260 | 10.12              | 1.5260 | -0.09                         | -0.09 | [-0.17; 0.00] | 24.6%  |
| Tongyoo 2016                    | 9.00                    | 2.9000 | 9.00              | 2.9000 | 0.00                         | 0.00 | [-0.02; 0.02] | 22.1%  |
| Arabi 2010                      | 2.7500                  | 1.9500 | 1.9500            | 1.9500 | -0.23                         | -0.23 | [-0.46; -0.01] | 19.8%  |
| Opset 2005                      | 8.08                    | 8.6312 | 23.12            | 7.1738 | 0.53                         | 0.53 | [0.20; 0.85] | 16.2%  |
| Rinaldi 2006                    | 7.00                    | 2.1411 | 6.00              | 1.0700 | 0.22                         | 0.22 | [0.15; 0.35] | 16.2%  |

**Random effects model**

| 414 | 411 |
|-----|-----|
| 0.22 | [-0.64; 0.20] | 100.0% |

| Heterogeneity: $I^2 = 84\%$, $\hat{Q} = 0.1740$ [0.0340; 1.9773], $p < 0.01$ |
5.3. Inconsistency

5.3.1. side-split
Number of loops = 1. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1: VHD-vitC, very high dose vitamin C; vitC, vitamin C; SMD, standardised mean difference.

| comparison | Number of studies | SMD from NMA | SMD from direct comparison | SMD from indirect comparison | Difference | p-value |
|------------|-------------------|--------------|---------------------------|-----------------------------|------------|---------|
| HD-vitC+GC+vitB1 vs HD-vitC+vitB1 | 0 | -0.27 | . | -0.27 | . | . |
| HD-vitC+GC+vitB1 vs placebo/usual care | 6 | -0.27 | -0.21 | -0.54 | 0.33 | 0.2913 |
| HD-vitC+GC+vitB1 vs VHD-vitC | 0 | -0.55 | . | -0.55 | . | . |
| HD-vitC+GC+vitB1 vs vitB1 | 0 | -0.42 | . | -0.42 | . | . |
| HD-vitC+GC+vitB1 vs vitC | 0 | -0.11 | . | -0.11 | . | . |
| HD-vitC+vitB1 vs placebo/usual care | 1 | 0 | 0 | . | . | . |
| HD-vitC+vitB1 vs VHD-vitC | 0 | -0.27 | . | -0.27 | . | . |
| HD-vitC+vitB1 vs vitB1 | 0 | -0.15 | . | -0.15 | . | . |
| HD-vitC+vitB1 vs vitC | 0 | 0.17 | . | 0.17 | . | . |
| VHD-vitC vs placebo/usual care | 1 | 0.27 | 0.27 | . | . | . |
| VHD-vitC vs vitB1 | 0 | 0.12 | . | 0.12 | . | . |
| VHD-vitC vs vitC | 0 | 0.44 | . | 0.44 | . | . |
| HD-vitC vs HD-vitC+GC+vitB1 | 0 | -0.15 | . | -0.15 | . | . |
| HD-vitC vs HD-vitC+vitB1 | 0 | -0.43 | . | -0.43 | . | . |
| HD-vitC vs placebo/usual care | 1 | -0.43 | -0.43 | . | . | . |
| HD-vitC vs VHD-vitC | 0 | -0.70 | . | -0.70 | . | . |
| HD-vitC vs vitB1 | 0 | -0.58 | . | -0.58 | . | . |
| HD-vitC vs vitC | 0 | -0.26 | . | -0.26 | . | . |
| vitC vs placebo/usual care | 1 | -0.17 | -0.17 | . | . | . |
| GC vs HD-vitC+GC+vitB1 | 2 | 0.11 | 0.30 | -0.03 | 0.33 | 0.2913 |
| GC vs HD-vitC+vitB1 | 0 | -0.17 | . | -0.17 | . | . |
| GC vs placebo/usual care | 5 | -0.17 | -0.25 | 0.08 | -0.33 | 0.2913 |
| GC vs VHD-vitC | 0 | -0.44 | . | -0.44 | . | . |
| GC vs HD-vitC | 0 | 0.26 | . | 0.26 | . | . |
| GC vs vitB1 | 0 | -0.31 | . | -0.31 | . | . |
| GC vs vitC | 0 | 0 | . | 0 | . | . |
| vitB1 vs vitC | 0 | 0.31 | . | 0.31 | . | . |
| vitB1 vs placebo/usual care | 1 | 0.15 | 0.15 | . | . | . |

5.3.2. global
Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model = 1.55 (df=1, p=0.2129)
6. League table for comparisons of all-cause mortality at the longest follow-up in studies published in 2010 or after and severity of organ dysfunction over 72 hours.

Odds ratios in orange cells denote comparisons of all-cause mortality from 90 days to one year post randomization in studies published in 2010 or after with a treatment in the column versus a treatment in the row. Standardized mean differences in blue cells denote comparisons of severity of organ dysfunction over 72 hours with a treatment in the row versus a treatment in the column. 95% confidence intervals and 95% prediction intervals are presented below the odds ratios. Bold text denotes comparisons where 95% confidence intervals or 95% prediction intervals do not cross null effect (1 for ORs, 0 for SMDs). OR denotes odds ratio; SMD, standardized mean difference; CI, confidence interval; Prl, prediction interval; VHD-vitC, very high-dose vitamin C (≥ 12g per day); HD-vitC, high-dose vitamin C (≥ 6g per day); vitC, vitamin C (< 6g per day); GC, low-dose glucocorticoid (< 400 mg/day); vitB1, vitamin B1 (any dose).
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

7. Duration of vasopressor therapy

7.1. Network graph

Network graph of all available pairwise comparisons between the eligible interventions. The size of the nodes shows the total number of patients accumulated for each treatment. The breadth of the edges was weighted according to the inverse of the variance of the direct summary effect. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1: VHD-vitC, very high dose vitamin C; vitC, vitamin C.

7.2. Heterogeneity: Between-study variance within a comparison and the network

The expected variance from empirical distribution is not available for differences in means of the duration of vasopressor therapy. Standardised mean difference was calculated to compare the estimated variance with the expected variance from empirical distribution. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1: VHD-vitC, very high dose vitamin C; vitC, vitamin C; SMD, standardised mean difference; N/A, not available.

| Comparisons                        | Number of studies | Expected variance for SMD from empirical distribution\(^{4^*}\) median [95\% range] | Estimated variance for SMD in comparison | Estimated variance for SMD in network |
|------------------------------------|-------------------|---------------------------------------------------------------------------------|------------------------------------------|--------------------------------------|
| HD-vitC + GC + vitB1 vs GC         | 2                 | 0.027 [0.00001 to 4.95]                                                        | N/A                                      | 0.5013                               |
| HD-vitC + GC + vitB1 vs placebo or usual care | 4 | 0.033 [0.0001 to 10.2]                                                        | 0.0299                                  | 0.5013                               |
| VHD-vitC vs vitC                   | 1                 | 0.027 [0.00001 to 4.95]                                                        | N/A                                      | 0.5013                               |
| VHD-vitC vs placebo or usual care  | 1                 | 0.033 [0.0001 to 10.2]                                                        | N/A                                      | 0.5013                               |
| HD-vitC vs placebo or usual care   | 2                 | 0.033 [0.0001 to 10.2]                                                        | 0                                        | 0.5013                               |
| vitC vs placebo or usual care      | 1                 | 0.033 [0.0001 to 10.2]                                                        | N/A                                      | 0.5013                               |
| vitB1 vs placebo/usual care        | 1                 | 0.033 [0.0001 to 10.2]                                                        | N/A                                      | 0.5013                               |
| GC vs placebo or usual care        | 10                | 0.033 [0.0001 to 10.2]                                                        | 0.6336                                   | 0.5013                               |
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

**Forest plots**

**HD-vitC + GC + vitB1 vs GC**

| Study                        | Experimental Total Mean | Experimental SD | Control Total Mean | Control SD | Mean Difference | MD  | 95% CI | Weight |
|------------------------------|-------------------------|-----------------|--------------------|------------|----------------|-----|--------|--------|
| Fujii & Luettel 2020 (VITAMINS) | 90  46.40              | 43.3000         | 90  48.00          | 41.4000    | -1.60          | -1.80| [-3.36; 0.16] | 69.9%  |
| Hussain 2021                 | 47  112.00             | 73.4100         | 47  136.00         | 73.4100    | -24.00         | -25.30| [-26.98; 5.68] | 31.1%  |

Random effects model: 137
Heterogeneity: $I^2 = 45\%$, $t^2 = 116.2518$, $p = 0.17$

**HD-vitC + GC + vitB1 vs placebo or usual care**

| Study                        | Experimental Total Mean | Experimental SD | Control Total Mean | Control SD | Mean Difference | MD  | 95% CI | Weight |
|------------------------------|-------------------------|-----------------|--------------------|------------|----------------|-----|--------|--------|
| Mohamed 2020 (VICTOR)        | 45  24.50              | 22.6000         | 43  35.12          | 24.2000    | -10.60         | -12.40| [-12.74; 0.54] | 37.6%  |
| generalized 2020 (ORANGES)   | 60  27.00              | 22.0000         | 57  35.00          | 18.0000    | -26.00         | -32.80| [-37.32; 14.57] | 32.3%  |
| Wani 2020                    | 50  75.72              | 20.2000         | 59  96.13          | 40.0000    | -20.11         | -24.43| [-24.43; -6.39] | 24.8%  |
| Chang 2020 (HYVCTTSSS)       | 22  56.71              | 62.2688         | 24  63.87          | 59.9024    | -0.86          | -4.097| [-29.84]       | 5.4%   |

Random effects model: 177
Heterogeneity: $I^2 = 34\%$, $t^2 = 24.0567$ [0.000; 100.0000], $p = 0.21$

**HD-vitC vs placebo or usual care**

| Study                        | Experimental Total Mean | Experimental SD | Control Total Mean | Control SD | Mean Difference | MD  | 95% CI | Weight |
|------------------------------|-------------------------|-----------------|--------------------|------------|----------------|-----|--------|--------|
| Lv 2020                      | 61  28.00              | 16.5233         | 56  45.18          | 32.0343    | -17.68         | -26.04| [-26.04; -7.32] | 67.4%  |
| Zabel 2016                   | 14  49.64              | 28.6700         | 14  71.97          | 1.6000     | -18.93         | -26.08| [-10.76]       | 100.0% |

Random effects model: 75
Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.53$

**GC vs placebo or usual care**

| Study                        | Experimental Total Mean | Experimental SD | Control SD | Mean Difference | MD  | 95% CI | Weight |
|------------------------------|-------------------------|-----------------|------------|----------------|-----|--------|--------|
| Sprung 2008 (CORTIVIGUS)     | 251 80.58             | 17.5949         | 246 143.41 | 30.4255        | -62.53| [-65.51; -59.56] | 12.9%  |
| Li 2016                      | 29  13.64              | 6.4700          | 29  20.34   | 12.5600        | -6.70 | [-19.94; 6.56]    | 12.9%  |
| Verkate 2019 (ADRENAL)       | 1983 60.80            | 82.1197         | 1980 121.21 | 121.2623       | -40.91| [-46.97; -34.86] | 12.8%  |
| He 2009                      | 34  68.70              | 10.5200         | 30  128.21  | 17.0000        | -60.99| [-63.57; -58.42] | 12.8%  |
| Gordon 2019 (VANISH)         | 201 52.56             | 41.0698         | 207 56.77   | 54.9378        | -4.21 | [-13.86; 5.44]    | 12.8%  |
| Lv 2017                      | 68  94.00              | 87.0000         | 60  91.20   | 96.0000        | -7.20 | [-25.66; 21.25]   | 9.0%   |
| Tongyao 2016                 | 96  118.20             | 72.0000         | 99  163.20  | 136.8000       | -48.00| [-78.49; -17.10] | 9.1%   |
| Minna 2014                   | 117 130.48             | 101.0400        | 94  163.20  | 146.0000       | -43.72| [-85.85; 0.41]    | 7.0%   |
| Oppel 2005                   | 18  62.02              | 49.0719         | 23  121.79  | 117.7357       | -59.77| [-112.96; -6.58] | 5.6%   |
| Arabi 2010                   | 38  182.40             | 117.8400        | 38  228.00 | 143.0400       | -45.60| [105.19; 13.99]   | 4.9%   |

Random effects model: 2698
Heterogeneity: $I^2 = 56\%$, $t^2 = 255.7718$ [157.1574; 369.1543], $p = 0.01$

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Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

### 7.3. Inconsistency

#### 7.3.1. Side-split

Number of loops = 2. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C; MD, mean difference; N/A, not available.

| comparison                  | Number of studies | MD from NMA | MD from direct comparison | MD from indirect comparison | Difference | p-value |
|-----------------------------|-------------------|-------------|---------------------------|----------------------------|------------|---------|
| GC vs HD-vitC               | 0                 | -11.71      | -11.71                    | N/A                        |            |         |
| GC vs HD-vitC+GC+vitB1      | 2                 | -6.16       | 11.02                     | -17.95                     | 28.97      | 0.1904  |
| GC vs placebo/usual care    | 10                | -30.95      | -34.63                    | -5.66                      | -28.97     | 0.1904  |
| GC vs VHD-vitC              | 0                 | -23.75      | N/A                       | -23.75                     |            |         |
| GC vs vitB1                 | 0                 | -21.55      | N/A                       | -21.55                     |            |         |
| GC vs vitC                  | 0                 | 12.25       | 12.25                     | N/A                        |            |         |
| HD-vitC vs HD-vitC+GC+vitB1 | 0                 | 5.55        | 5.55                      | N/A                        |            |         |
| HD-vitC vs placebo/usual care| 2               | -19.24      | -19.24                    | N/A                        |            |         |
| HD-vitC vs VHD-vitC         | 0                 | -12.04      | N/A                       | -12.04                     |            |         |
| HD-vitC vs vitB1            | 0                 | -9.84       | N/A                       | -9.84                      |            |         |
| HD-vitC vs vitC             | 0                 | 23.96       | 23.96                     | N/A                        |            |         |
| HD-vitC+GC+vitB1 vs placebo/usual care | 4 | -24.79 | -16.68 | -45.65 | 28.97 | 0.1904 |
| HD-vitC+GC+vitB1 vs VHD-vitC| 0                 | -17.59      | N/A                       | -17.59                     |            |         |
| HD-vitC+GC+vitB1 vs vitB1   | 0                 | -15.39      | N/A                       | -15.39                     |            |         |
| HD-vitC+GC+vitB1 vs vitC    | 0                 | 18.41       | 18.41                     | N/A                        |            |         |

#### 7.3.2. global

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model = 1.72 (df=1, p=0.1899)
8. League table for comparisons of time to cessation of vasopressor therapy and ICU length of stay.

| MD | 95%CI | 95%PrI |
|----|-------|--------|
| placebo or usual care | -24.8 (-44.3 to -5.3) | (-2.3 to 1.0) |
| HD-vitC+GC +vitB1 | -7.2 (-74.9 to 60.5) | (-2.5 to 2.3) |
| No data available | No data available | No data available |
| HD-vitC+vitB1 | -19.2 (-50.1 to 11.6) | (-2.8 to 1.0) |
| No data available | No data available | No data available |
| VHD-vitC | -43.2 (-110.9 to 24.5) | (-3.2 to 1.7) |
| No data available | No data available | No data available |
| HD-vitC | -31.0 (-45.4 to -16.5) | (-2.4 to 0.8) |
| No data available | No data available | No data available |
| HD-vitC | -9.4 (-63.8 to 45.0) | (-2.3 to 2.1) |
| No data available | No data available | No data available |

Mean differences in orange cells denote comparisons of time to cessation of vasopressor therapy with a treatment in the column versus a treatment in the row. Mean differences in blue cells denote comparisons of ICU length of stay with a treatment in the row versus a treatment in the column. 95% confidence intervals and 95% prediction intervals are presented below the odds ratios. Bold text denotes comparisons where 95% confidence intervals or 95% prediction intervals do not cross 0. MD denotes mean difference; CI, confidence interval; PrI, predictive interval; VHD-vitC, very high-dose vitamin C (≥ 12g per day); HD-vitC, high-dose vitamin C (≥ 6g per day); vitC, vitamin C (< 6g per day); GC, low-dose glucocorticoid (< 400 mg/day); vitB1, vitamin B1 (any dose).
9. ICU length of stay

9.1. Network graph

Network graph of all available pairwise comparisons between the eligible interventions. The size of the nodes shows the total number of patients accumulated for each treatment. The breadth of the edges was weighted according to the inverse of the variance of the direct summary effect. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C.

![Network graph of ICU length of stay](image)

9.2. Heterogeneity: Between-study variance within a comparison and the network

The expected variance from empirical distribution is not available for differences in means of the length of ICU stay. Standardised mean difference was calculated to compare the estimated variance with the expected variance from empirical distribution. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C; SMD, standardised mean difference; N/A, not available.

| Comparisons                          | Number of studies | Expected variance of SMD from empirical distribution\[\text{median [95% range]}\] | Estimated variance of SMD in comparison | Estimated variance of SMD in network |
|--------------------------------------|-------------------|--------------------------------------------------------------------------------|-----------------------------------------|-------------------------------------|
| HD-vitC + GC + vitB1 vs GC          | 2                 | 0.027 [0.00001 to 4.95]                                                        | 0                                       | 1.2155                              |
| HD-vitC + GC + vitB1 vs placebo or usual care | 5                 | 0.033 [0.0001 to 10.2]                                                          | 0                                       | 1.2155                              |
| VHD-vitC vs placebo or usual care   | 1                 | 0.033 [0.0001 to 10.2]                                                          | N/A                                     | 1.2155                              |
| HD-vitC vs placebo or usual care    | 2                 | 0.033 [0.0001 to 10.2]                                                          | 0                                       | 1.2155                              |
| vitC vs placebo or usual care       | 1                 | 0.033 [0.0001 to 10.2]                                                          | N/A                                     | 1.2155                              |
| GC vs placebo or usual care         | 11                | 0.033 [0.0001 to 10.2]                                                          | 0.0071                                  | 1.2155                              |
| vitB1 vs placebo or usual care      | 2                 | 0.033 [0.0001 to 10.2]                                                          | 0                                       | 1.2155                              |
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

Forest plots

**HD-vitC + GC + vitB1 vs GC**

| Study | Experimental Total | Standard Deviation | Control Total | Standard Deviation | Mean Difference | MD | 95%-CI | Weight |
|-------|--------------------|--------------------|---------------|--------------------|-----------------|-----|--------|--------|
| Hussain 2021 | 47 9.79 4.069 | 47 8.32 4.9710 | 1.47 [-2.1; 4.14] | 63.0% |
| Fuji & Luethi 2020 (VITAMINN) | 107 8.45 18.0000 | 104 8.62 7.5300 | 1.63 [-2.06; 5.32] | 17.0% |

**Random effects model**

| Weight | 154 | 151 |
|--------|-----|-----|
| Heterogeneity: $I^2 = 0$, $t^2 = 0$, $p = 0.94$ |

**HD-vitC + GC + vitB1 vs placebo or usual care**

| Study | Experimental Total | Standard Deviation | Control Total | Standard Deviation | Mean Difference | MD | 95%-CI | Weight |
|-------|--------------------|--------------------|---------------|--------------------|-----------------|-----|--------|--------|
| Savariansky 2021 (VICTAS) | 250 4.70 4.4738 | 245 4.70 4.4744 | -0.00 [-0.79; 0.78] | 66.6% |
| Iglesias 2020 (ORANGE) | 68 4.76 4.5000 | 65 4.68 3.4500 | 0.10 [-1.21; 1.41] | 24.5% |
| Cheng 2020 (HYVOTTSSS) | 40 9.14 6.7666 | 40 7.78 5.9977 | 0.35 [-2.46; 3.16] | 5.3% |
| Mackowiak 2020 (ACTS) | 101 11.63 16.5461 | 95 11.58 15.7956 | 0.06 [-4.45; 4.54] | 2.1% |
| Mohamed 2020 (VICTOR) | 48 12.44 14.2000 | 43 8.44 8.1600 | 4.00 [8.91; 8.81] | 1.6% |

**Random effects model**

| Weight | 504 | 496 |
|--------|-----|-----|
| Heterogeneity: $I^2 = 0$, $t^2 = 0.000000; 12.2699$, $p = 0.62$ |

**HD-vitC vs placebo or usual care**

| Study | Experimental Total | Standard Deviation | Control Total | Standard Deviation | Mean Difference | MD | 95%-CI | Weight |
|-------|--------------------|--------------------|---------------|--------------------|-----------------|-----|--------|--------|
| LV 2020 | 61 5.27 3.8723 | 56 4.89 3.3490 | 0.38 [0.93; 1.68] | 87.8% |
| Zabdi 2016 | 14 21.45 10.2300 | 14 20.97 13.0400 | 0.88 [7.80; 9.86] | 2.2% |

**Random effects model**

| Weight | 75 | 70 |
|--------|----|----|
| Heterogeneity: $I^2 = 0$, $t^2 = 0.000000; 0.91$ |

**GC vs placebo or usual care**

| Study | Experimental Total | Standard Deviation | Control Total | Standard Deviation | Mean Difference | MD | 95%-CI | Weight |
|-------|--------------------|--------------------|---------------|--------------------|-----------------|-----|--------|--------|
| Gordon 2016 (VANISH) | 201 6.70 5.9736 | 207 7.09 6.7189 | -0.28 [-1.58; 0.98] | 14.4% |
| Hu 2009 | 34 4.19 2.8600 | 32 8.36 2.4800 | -1.18 [-2.46; 0.10] | 14.2% |
| Venkatesh 2018 (ADRENAL) | 1893 10.25 18.9471 | 1890 10.00 26.7078 | -5.18 [-6.63; 3.67] | 13.6% |
| Khan 2016 (HYPRESS) | 177 9.40 7.4744 | 176 10.76 8.2222 | -1.28 [-2.99; 0.49] | 13.1% |
| Merz 2014 | 117 11.53 5.6900 | 54 11.87 5.4800 | -0.14 [-1.12; 0.83] | 12.6% |
| Arit 2010 | 39 9.20 6.4000 | 36 9.60 6.0000 | -0.40 [-3.21; 2.41] | 9.5% |
| Rinaldi 2006 | 20 18.25 6.6908 | 20 20.75 6.6908 | -1.50 [-5.65; 2.65] | 6.2% |
| Spang 2008 (CORTICUS) | 250 18.00 31.0000 | 247 18.00 17.0000 | 1.00 [-3.35; 5.35] | 5.9% |
| LV 2017 | 56 10.80 17.5000 | 60 10.20 13.1000 | 0.70 [-1.49; 3.89] | 4.2% |
| Medcalf 2009 | 48 8.00 6.0000 | 52 12.00 18.0000 | -4.60 [-12.48; 0.48] | 3.4% |
| Gordon 2014 | 51 14.50 14.6000 | 50 19.50 14.5000 | -5.50 [-12.11; 2.11] | 2.7% |

**Random effects model**

| Weight | 2028 | 2755 |
|--------|-------|-------|
| Heterogeneity: $I^2 = 71%, t^2 = 2.8307[0.0000; 12.6394], p = 0.01$ |

**vitB1 vs placebo or usual care**

| Study | Experimental Total | Standard Deviation | Control Total | Standard Deviation | Mean Difference | MD | 95%-CI | Weight |
|-------|--------------------|--------------------|---------------|--------------------|-----------------|-----|--------|--------|
| Henripin 2015 | 32 6.67 5.4320 | 33 7.00 6.9746 | -0.33 [-3.37; 2.70] | 62.8% |
| Dzien 2016 | 43 8.35 6.5027 | 45 9.48 11.4870 | -1.13 [-6.07; 3.81] | 37.2% |

**Random effects model**

| Weight | 75 | 78 |
|--------|----|----|
| Heterogeneity: $I^2 = 0$, $t^2 = 0.75$ |
9.3. Inconsistency

9.3.1. side-split

Number of loops = 2. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1: VHD-vitC, very high dose vitamin C; vitC, vitamin C; MD, mean difference.

| comparison                      | Number of studies | MD from NMA | MD from direct comparison | MD from indirect comparison | Difference | p-value   |
|---------------------------------|-------------------|-------------|---------------------------|-----------------------------|------------|-----------|
| GC vs HD-vitC                   | 0                 | -1.88       | -1.88                     |                             |            |           |
| GC vs HD-vitC+GC+vB1            | 2                 | -1.75       | -1.51                     | -1.89                       | 0.37       | 0.8003    |
| GC vs HD-vitC+vB1               | 0                 | -0.43       | -0.43                     |                             |            |           |
| GC vs placebo/usual care        | 11                | -1.46       | -1.51                     | -1.14                       | -0.37      | 0.8003    |
| GC vs VHD-vitC                  | 0                 | 0.44        | 0.44                      |                             |            |           |
| GC vs vitB1                     | 0                 | -0.81       | -0.81                     |                             |            |           |
| GC vs vitC                      | 0                 | 1.44        | 1.44                      |                             |            |           |
| HD-vitC vs HD-vitC+GC+vB1       | 0                 | 0.12        |                           | 0.12                        |            |           |
| HD-vitC vs HD-vitC+vB1          | 0                 | 1.44        |                           | 1.44                        |            |           |
| HD-vitC vs placebo/usual care   | 2                 | 0.41        | 0.41                      |                             |            |           |
| HD-vitC vs VHD-vitC             | 0                 | 2.31        |                           | 2.31                        |            |           |
| HD-vitC vs vitB1                | 0                 | 1.07        |                           | 1.07                        |            |           |
| HD-vitC vs vitC                 | 0                 | 3.31        |                           | 3.31                        |            |           |
| HD-vitC+GC+vB1 vs HD-vitC+vB1   | 0                 | 1.32        |                           | 1.32                        |            |           |
| HD-vitC+GC+vB1 vs placebo/usual care | 5         | 0.29        | 0.38                      | 0.01                        | 0.37       | 0.8003    |
| HD-vitC+GC+vB1 vs VHD-vitC      | 0                 | 2.19        |                           | 2.19                        |            |           |
| HD-vitC+GC+vB1 vs vitB1         | 0                 | 0.95        |                           | 0.95                        |            |           |
| HD-vitC+GC+vB1 vs vitC          | 0                 | 3.19        |                           | 3.19                        |            |           |
| HD-vitC+vB1 vs placebo/usual care | 1         | -1.03       | -1.03                     |                             |            |           |
| HD-vitC+vB1 vs VHD-vitC         | 0                 | 0.87        |                           | 0.87                        |            |           |
| HD-vitC+vB1 vs vitB1            | 0                 | -0.37       | -0.37                     |                             |            |           |
| HD-vitC+vB1 vs vitC             | 0                 | 1.87        |                           | 1.87                        |            |           |
| VHD-vitC vs placebo/usual care  | 1                 | -1.9        | -1.9                      |                             |            |           |
| vitB1 vs placebo/usual care     | 2                 | -0.66       | -0.66                     |                             |            |           |
| vitC vs placebo/usual care      | 1                 | -2.9        | -2.9                      |                             |            |           |
| VHD-vitC vs vitB1               | 0                 | -1.24       | -1.24                     |                             |            |           |
| VHD-vitC vs vitC                | 1                 | 1           | 1                         |                             |            |           |
| vitB1 vs vitC                   | 0                 | 2.24        | 2.24                      |                             |            |           |

9.3.2. global

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model = 0.06 (df=1, p=0.7989)
10. All-cause mortality at the longest follow-up

10.1. Heterogeneity: Between-study variance within a comparison and the network

GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C; OR, odds ratio; N/A, not available.

| Comparisons | Number of studies | Expected variance for ORs from empirical distribution | Estimated variance in comparison | Estimated variance in network | Forest plot |
|-------------|------------------|-----------------------------------------------|---------------------------------|-------------------------------|-------------|
| HD-vitC + GC + vitB1 vs GC | 2 | 0.014 [0.0008 to 0.25] | 0.0196 | 0.0018 | No evidence |
| HD-vitC + GC + vitB1 vs placebo or usual care | 6 | 0.017 [0.001 to 0.30] | 0 | 0.0018 | No heterogeneity |
| HD-vitC + vitB1 vs placebo or usual care | 1 | 0.017 [0.001 to 0.30] | N/A | 0.0018 | N/A |
| VHD-vitC vs vitC | 1 | 0.014 [0.0008 to 0.25] | N/A | 0.0018 | N/A |
| VHD-vitC vs placebo or usual care | 2 | 0.017 [0.001 to 0.30] | 0 | 0.0018 | No evidence |
| HD-vitC vs placebo or usual care | 2 | 0.017 [0.001 to 0.30] | 0.6702 | 0.0018 | No evidence |
| vitC vs placebo or usual care | 2 | 0.017 [0.001 to 0.30] | 0.7293 | 0.0018 | No evidence |
| GC vs placebo or usual care | 17 | 0.017 [0.001 to 0.30] | 0.0239 | 0.0018 | No heterogeneity |
| vitB1 vs placebo or usual care | 3 | 0.017 [0.001 to 0.30] | 0 | 0.0018 | No evidence |

**Forest plot**

**HD-vitC + GC + vitB1 vs GC**

**HD-vitC + GC + vitB1 vs placebo or usual care**

Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

VHD-vitC vs placebo or usual care

| Study                  | Experimental Events | Control Events | Odds Ratio | OR     | 95% CI Weight |
|------------------------|---------------------|----------------|------------|--------|---------------|
| Fowler 2019 (CITRIS-AL8) | 25                  | 38             | 0.49       | 0.20   | 0.94          |
| Fowler 2014            | 4                   | 8              | 0.60       | 0.00   | 0.40          |
| **Random effects model** | **92**              | **90**         |            |        |               |

HD-vitC vs placebo or usual care

| Study                  | Experimental Events | Control Events | Odds Ratio | OR     | 95% CI Weight |
|------------------------|---------------------|----------------|------------|--------|---------------|
| LV 2020                | 15                  | 24             | 0.43       | 0.20   | 0.56          |
| Zitter 2016            | 2                   | 9              | 0.09       | 0.01   | 0.89          |
| **Random effects model** | **75**              | **70**         |            |        |               |

vitC vs placebo or usual care

| Study                  | Experimental Events | Control Events | Odds Ratio | OR     | 95% CI Weight |
|------------------------|---------------------|----------------|------------|--------|---------------|
| Fontaine-Calza 2009    | 5                   | 4              | 2.26       | 0.38   | 13.17         |
| Fowler 2014            | 3                   | 6              | 0.36       | 0.05   | 2.12          |
| **Random effects model** | **18**              | **18**         |            |        |               |

GC vs placebo or usual care

| Study                  | Experimental Events | Control Events | Odds Ratio | OR     | 95% CI Weight |
|------------------------|---------------------|----------------|------------|--------|---------------|
| Venkatesh 2018 (ADRENAL) | 571                | 574            | 0.99       | 0.86   | 1.13          |
| Annane 2018 (APROCHSS) | 285                | 326            | 0.79       | 0.63   | 0.99          |
| Springer 2006 (CORTICUS) | 137               | 127            | 1.11       | 0.77   | 1.59          |
| Gordon 2016 (VANSM)    | 62                  | 57             | 1.17       | 0.77   | 1.80          |
| Keh 2016 (HIFRESS)     | 45                  | 37             | 1.29       | 0.76   | 2.12          |
| Annane 2002            | 102                 | 112            | 0.70       | 0.42   | 1.16          |
| Tangaroa 2016          | 37                  | 40             | 0.89       | 0.50   | 1.59          |
| Mira 2014              | 44                  | 40             | 0.88       | 0.45   | 1.69          |
| LV 2017                | 23                  | 19             | 1.42       | 0.67   | 3.02          |
| Modell 2009            | 23                  | 48             | 3.99       | 1.39   | 11.43         |
| Vidal 2011             | 16                  | 27             | 2.16       | 0.43   | 3.67          |
| Arabi 2010             | 33                  | 12             | 2.12       | 0.68   | 6.08          |
| Gordon 2014            | 7                   | 31             | 0.96       | 0.09   | 3.16          |
| Opavc 2005             | 7                   | 11             | 0.89       | 0.20   | 2.43          |
| Vidal 2002             | 8                   | 20             | 0.44       | 0.13   | 1.57          |
| Ballard 1998           | 7                   | 22             | 0.27       | 0.07   | 0.99          |
| LV 2016                | 3                   | 29             | 1.00       | 0.18   | 5.42          |
| **Random effects model** | **3691**            | **3816**       |            |        |               |

vitB1 vs placebo or usual care

| Study                  | Experimental Events | Control Events | Odds Ratio | OR     | 95% CI Weight |
|------------------------|---------------------|----------------|------------|--------|---------------|
| Domino 2016            | 19                  | 18             | 1.19       | 0.51   | 2.77          |
| Hanun 2016             | 14                  | 12             | 1.36       | 0.50   | 3.68          |
| Piette and 2002        | 5                   | 7              | 0.64       | 0.17   | 2.39          |
| **Random effects model** | **100**             | **103**        |            |        |               |
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

10.2. Inconsistency

10.2.1. side-split

Number of loops = 2. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C; OR, odds ratio; RoR, Ratio of Ratios (direct versus indirect).

| comparison                                      | Number of studies | OR from NMA | OR from direct comparison | OR from indirect comparison | Ratio of ratios | p-value |
|------------------------------------------------|-------------------|-------------|---------------------------|-----------------------------|-----------------|---------|
| HD-vitC+GC+vitB1 vs HD-vitC+vitB1               | 0                 | 0.84        |                           | 0.84                        |                 |         |
| HD-vitC+GC+vitB1 vs placebo or usual care      | 6                 | 1.04        | 1.06                      | 0.98                        | 1.09            | 0.7772  |
| HD-vitC+GC+vitB1 vs VHD-vitC                   | 0                 | 1.96        |                           | 1.96                        |                 |         |
| HD-vitC+GC+vitB1 vs vitB1                      | 0                 | 0.95        |                           | 0.95                        |                 |         |
| HD-vitC+GC+vitB1 vs vitC                       | 0                 | 1.23        |                           | 1.23                        |                 |         |
| HD-vitC vs HD-vitC+GC+vitB1                    | 0                 | 0.33        |                           | 0.33                        |                 |         |
| HD-vitC vs HD-vitC+vitB1                       | 0                 | 0.27        |                           | 0.27                        |                 |         |
| HD-vitC vs VHD-vitC                            | 0                 | 0.64        |                           | 0.64                        |                 |         |
| HD-vitC vs vitB1                               | 0                 | 0.31        |                           | 0.31                        |                 |         |
| HD-vitC vs vitC                                | 0                 | 0.40        |                           | 0.40                        |                 |         |
| HD-vitC+vitB1 vs placebo or usual care         | 1                 | 1.24        | 1.24                      |                             |                 |         |
| HD-vitC+vitB1 vs VHD-vitC                      | 0                 | 2.33        |                           | 2.33                        |                 |         |
| HD-vitC+vitB1 vs vitB1                         | 0                 | 1.13        |                           | 1.13                        |                 |         |
| HD-vitC+vitB1 vs vitC                          | 0                 | 1.46        |                           | 1.46                        |                 |         |
| VHD-vitC vs vitB1                              | 0                 | 0.48        |                           | 0.48                        |                 |         |
| VHD-vitC vs vitC                               | 1                 | 0.63        | 1.67                      | 0.28                        | 5.86            | 0.1973  |
| VHD-vitC vs placebo or usual care              | 2                 | 0.53        | 0.50                      | 20.92                       | 0.02            | 0.1358  |
| HD-vitC vs placebo or usual care               | 2                 | 0.34        | 0.34                      |                             |                 |         |
| vitC vs placebo or usual care                  | 2                 | 0.85        | 1.01                      | 0.24                        | 4.18            | 0.4759  |
| GC vs HD-vitC+GC+vitB1                         | 2                 | 0.94        | 1.00                      | 0.92                        | 1.09            | 0.7772  |
| GC vs HD-vitC+vitB1                            | 0                 | 0.79        |                           | 0.79                        |                 |         |
| GC vs VHD-vitC                                 | 0                 | 1.84        |                           | 1.84                        |                 |         |
| GC vs HD-vitC                                  | 0                 | 2.87        |                           | 2.87                        |                 |         |
| GC vs placebo or usual care                    | 17                | 0.98        | 0.97                      | 1.06                        | 0.92            | 0.7772  |
| GC vs vitB1                                    | 0                 | 0.89        |                           | 0.89                        |                 |         |
| GC vs vitC                                     | 0                 | 1.15        |                           | 1.15                        |                 |         |
| vitB1 vs vitC                                  | 0                 | 1.29        |                           | 1.29                        |                 |         |
| vitB1 vs placebo or usual care                 | 3                 | 1.1         | 1.1                       |                             |                 |         |

10.2.2. global

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model = 2.37 (df=3, p=0.5000)
10.3. Risk of bias within studies of each comparison
vitC denotes vitamin C; vitB1, vitamin B1.
10.4. Funnel plot

The treatments were in order of combination therapies first, monotherapies, and placebo or usual care, as the combination therapies have recently been investigated in small trials. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C.
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

### 10.5. Summary of confidence in network estimates

Clinically important threshold for odds ratio was defined at 1.2 to judge imprecision of the effect estimates. Incoherence in the summary table refers to inconsistency assessment in 5.2. vitC denotes vitamin C; vitB1, vitamin B1.

| Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|------------|-------------------|-------------------|----------------|--------------|-------------|---------------|-------------|------------------|
| **MIXED EVIDENCE** | | | | | | | | |
| glucocorticoid vs placebo/usual care | 17 | Some concerns | Low risk | No concerns | No concerns | No concerns | No concerns | Moderate |
| placebo/usual care vs vitC (high dose) + glucocorticoid + vitB1 | 6 | Some concerns | Low risk | No concerns | Major concerns | No concerns | No concerns | Very low |
| placebo/usual care vs vitB1 | 3 | Major concerns | Low risk | No concerns | Major concerns | No concerns | No concerns | Very low |
| placebo/usual care vs vitC (high dose) | 2 | Major concerns | Low risk | No concerns | No concerns | No concerns | No concerns | Low |
| placebo/usual care vs vitC (very high dose) | 2 | Some concerns | Low risk | No concerns | No concerns | No concerns | Some concerns | Low |
| glucocorticoid vs vitC (high dose) + glucocorticoid + vitB1 | 2 | Some concerns | Low risk | No concerns | Major concerns | No concerns | No concerns | Very low |
| placebo/usual care vs vitC | 2 | Some concerns | Low risk | No concerns | Major concerns | No concerns | Some concerns | Very low |
| placebo/usual care vs vitC (high dose) + vitB1 | 1 | No concerns | Low risk | No concerns | Major concerns | No concerns | No concerns | Low |
| vitC vs vitC (very high dose) | 1 | Some concerns | Low risk | No concerns | Major concerns | No concerns | Some concerns | Very low |
| **INDIRECT EVIDENCE** | | | | | | | | |
| glucocorticoid vs vitC (high dose) + vitB1 | 0 | No concerns | Low risk | No concerns | Major concerns | No concerns | No concerns | Low |
| vitC (high dose) + vitB1 vs vitC (very high dose) | 0 | No concerns | Low risk | No concerns | Major concerns | No concerns | No concerns | Low |
| vitB1 vs vitC (high dose) | 0 | Major concerns | Low risk | No concerns | No concerns | No concerns | No concerns | Low |
| vitC (high dose) vs vitC (high dose) + glucocorticoid + vitB1 | 0 | Major concerns | Low risk | No concerns | No concerns | No concerns | No concerns | Low |
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

| Comparison                                                                 | Some concerns | Low risk | No concerns | Some concerns | No concerns | No concerns | Risk   |
|----------------------------------------------------------------------------|---------------|----------|-------------|---------------|-------------|-------------|--------|
| glucocorticoid vs vitC (very high dose)                                    | 0             |          |             |               |             |             | Low    |
| vitB1 vs vitC (very high dose)                                            | 0             |          |             |               |             |             | Low    |
| glucocorticoid vs vitC (high dose)                                        | 0             |          |             |               |             |             | Moderate|
| vitC (high dose) vs vitC (high dose)+vitB1                                 | 0             |          |             |               |             |             | Moderate|
| vitC (high dose)+glucocorticoid+vitB1 vs vitC (very high dose)             | 0             |          |             |               |             |             | Moderate|
| glucocorticoid vs vitB1                                                   | 0             |          |             |               |             |             | Very low|
| glucocorticoid vs vitC                                                    | 0             |          |             |               |             |             | Very low|
| vitB1 vs vitC                                                             | 0             |          |             |               |             |             | Very low|
| vitB1 vs vitC (high dose)+glucocorticoid+vitB1                            | 0             |          |             |               |             |             | Very low|
| vitB1 vs vitC (high dose)+vitB1                                            | 0             |          |             |               |             |             | Very low|
| vitC vs vitC (high dose)                                                  | 0             |          |             |               |             |             | Very low|
| vitC vs vitC (high dose)+glucocorticoid+vitB1                             | 0             |          |             |               |             |             | Very low|
| vitC vs vitC (high dose)+vitB1                                             | 0             |          |             |               |             |             | Very low|
| vitC (high dose) vs vitC (very high dose)                                 | 0             |          |             |               |             |             | Very low|
| vitC (high dose)+glucocorticoid+vitB1 vs vitC (high dose)+vitB1            | 0             |          |             |               |             |             | Very low|

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10.6. P-scores of treatment

P-scores are calculated from the point estimates and standard errors of the network estimates. The P-score of treatment can be interpreted as the mean extent of certainty that the treatment is better than any other treatment. HD-vitC denotes high dose vitamin C; VHD-vitC, very high dose vitamin C; vitC, vitamin C; GC, glucocorticoid; vitB1, vitamin B1.

| Treatment                      | P-score |
|--------------------------------|---------|
| 1. HD-vitC                     | 0.9543  |
| 2. VHD-vitC                    | 0.8219  |
| 3. vitC                        | 0.4987  |
| 4. GC                          | 0.4482  |
| 5. placebo or usual care       | 0.3927  |
| 6. HD-vitC+GC+vitB1            | 0.3266  |
| 7. vitB1                       | 0.3089  |
| 8. HD-vitC+vitB1               | 0.2485  |
11. All-cause mortality from 90 days to 1 year: only studies with low risk of bias

11.1. Network graph

Network graph of all available pairwise comparisons between the eligible interventions. The size of the nodes shows the total number of patients accumulated for each treatment. The breadth of the edges was weighted according to the inverse of the variance of the direct summary effect. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C.

![Network graph image]

11.2. Heterogeneity: Between-study variance within a comparison and the network

| Comparisons                    | Number of studies | Expected variance for ORs from empirical distribution \[95% range\] | Estimated variance | Forest plot                  |
|-------------------------------|-------------------|---------------------------------------------------------------|-------------------|-----------------------------|
| HD-vitC+vitB1 vs placebo or usual care | 1                 | 0.017 \[0.001 to 0.30\]                                      | N/A               | 0.0320                      | N/A                      |
| GC vs placebo or usual care   | 3                 | 0.017 \[0.001 to 0.30\]                                      | 0.0320            | 0.0320                      | Suspected heterogeneity  |

*Forest plot*

GC vs placebo or usual care

| Study          | Experimental Events | Control Total | Odds Ratio | OR    | 95%-CI | Weight |
|----------------|---------------------|---------------|------------|-------|--------|--------|
| Annane 2018    | 265                 | 611           | 0.79       | [0.63; 0.99] | 52.1%  |
| Khan 2016      | 45                  | 168           | 1.29       | [0.78; 2.12] | 24.1%  |
| Annane 2002    | 102                 | 100           | 0.70       | [0.42; 1.16] | 23.6%  |

*Random effects model*

Heterogeneity: $I^2 = 43\%$, $t^2 = 0.0320$, $p = 0.17$
11.3. League table of NMA results
Odds ratios denote comparisons of all-cause mortality from 90 days to one year in low risk of bias studies with a treatment in the row versus a treatment in the column. 95% confidence intervals and 95% prediction intervals are presented below the odds ratios. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1.

| OR (95% CI) (95% PrI) | placebo or usual care | HD-vitC + vitB1 |
|------------------------|-------------------|-----------------|
| HD-vitC + vitB1        | 1.24 (0.51 to 3.01) (0.003 to 601.3) | 0.70 (0.27 to 1.78) (0.001 to 456.22) |
| GC                     | 0.86 (0.64 to 1.17) (0.04 to 17.22) | 0.70 (0.27 to 1.78) (0.001 to 456.22) |

11.4. Component network meta-analysis
Component network meta-analysis was not performed due to the scarcity of available data.
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

12. All-cause mortality at the longest follow-up: Only studies published in 2010 or after

12.1. Network graph

Network graph of all available pairwise comparisons between the eligible interventions. The size of the nodes shows the total number of patients accumulated for each treatment. The breadth of the edges was weighted according to the inverse of the variance of the direct summary effect. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1: VHD-vitC, very high dose vitamin C; vitC, vitamin C.

12.2. Heterogeneity: Between-study variance within a comparison and the network

| Comparisons                        | Number of studies | Expected variance for ORs from empirical distribution on median [95% range] | Estimated variance in comparison | Forest plot |
|------------------------------------|-------------------|---------------------------------------------------------------------------|---------------------------------|-------------|
| HD-vitC + GC + vitB1 vs GC         | 2                 | 0.014 [0.0008 to 0.25]                                                   | 0.0196                          | No evidence |
| HD-vitC + GC + vitB1 vs placebo or usual care | 6                 | 0.017 [0.001 to 0.30]                                                   | 0                               | No heterogeneity |
| HD-vitC + vitB1 vs placebo or usual care | 1                 | 0.017 [0.001 to 0.30]                                                   | N/A                             | N/A          |
| VHD-vitC vs vitC                   | 1                 | 0.014 [0.0008 to 0.25]                                                   | N/A                             | N/A          |
| VHD-vitC vs placebo or usual care  | 2                 | 0.017 [0.001 to 0.30]                                                   | 0                               | No evidence |
| HD-vitC vs placebo or usual care   | 2                 | 0.017 [0.001 to 0.30]                                                   | 0.6702                          | No evidence |
| vitC vs placebo or usual care      | 1                 | 0.017 [0.001 to 0.30]                                                   | N/A                             | N/A          |
| GC vs placebo or usual care        | 11                | 0.017 [0.001 to 0.30]                                                   | 0                               | No heterogeneity |
| vitB1 vs placebo or usual care     | 3                 | 0.017 [0.001 to 0.30]                                                   | 0                               | No evidence |
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

**Forest plots**

**HD-vitC + GC + vitB1 vs GC**

| Study | Experimental Events | Control Events | Odds Ratio | OR | 95% CI | Weight |
|-------|---------------------|---------------|------------|----|--------|--------|
| Fuji & Lucent 2020 (VITAMINS) | 30 | 105 | 25 | 102 | 1.23 | [0.66; 2.30] | 62.4% |
| Hesdari 2021 | 17 | 47 | 21 | 47 | 0.70 | [0.31; 1.60] | 37.6% |

**Random effects model**

Heterogeneity: $I^2 = 12\%$, $Q = 0.0196$, $p = 0.29$

```
OR  95% CI  Weight
1.00 [0.58; 1.70] 100.0%
```

**HD-vitC + GC + vitB1 vs placebo or usual care**

| Study | Experimental Events | Control Events | Odds Ratio | OR | 95% CI | Weight |
|-------|---------------------|---------------|------------|----|--------|--------|
| Sarratt et al 2021 (VICTAIS) | 102 | 252 | 94 | 249 | 1.12 | [0.78; 1.61] | 49.7% |
| Modarresi 2020 (ACTS) | 38 | 101 | 39 | 99 | 1.20 | [0.74; 2.01] | 17.7% |
| Wani 2020 | 20 | 51 | 21 | 50 | 0.90 | [0.41; 2.04] | 9.5% |
| Mohammadi 2020 (VICTOR) | 26 | 45 | 23 | 43 | 1.11 | [0.51; 2.39] | 8.8% |
| Ngouamba 2010 (ORANGE) | 11 | 63 | 13 | 69 | 0.83 | [0.34; 2.10] | 8.0% |
| Chang 2020 (PROCTSSS) | 11 | 40 | 14 | 40 | 0.70 | [0.27; 1.82] | 6.9% |

**Random effects model**

Heterogeneity: $I^2 = 0\%$, $Q = 0$, $p = 0.99$

```
OR  95% CI  Weight
1.07 [0.83; 1.37] 100.0%
```

**VHD-vitC vs placebo or usual care**

| Study | Experimental Events | Control Events | Odds Ratio | OR | 95% CI | Weight |
|-------|---------------------|---------------|------------|----|--------|--------|
| Fouhe 2019 (OCTIS-AL) | 25 | 94 | 39 | 62 | 0.49 | [0.26; 0.93] | 90.7% |
| Fouhe 2014 | 4 | 8 | 5 | 8 | 0.60 | [0.08; 4.40] | 5.3% |

**Random effects model**

Heterogeneity: $I^2 = 0\%$, $Q = 0$, $p = 0.99$

```
OR  95% CI  Weight
0.50 [0.27; 0.92] 100.0%
```

**HD-vitC vs placebo or usual care**

| Study | Experimental Events | Control Events | Odds Ratio | OR | 95% CI | Weight |
|-------|---------------------|---------------|------------|----|--------|--------|
| Lima 2020 | 15 | 61 | 24 | 56 | 0.43 | [0.20; 0.94] | 65.3% |
| Zabet 2016 | 2 | 14 | 9 | 14 | 0.09 | [0.01; 0.99] | 24.7% |

**Random effects model**

Heterogeneity: $I^2 = 50\%$, $Q = 0.6702$, $p = 0.13$

```
OR  95% CI  Weight
0.25 [0.06; 1.08] 100.0%
```

**GC vs placebo or usual care**

| Study | Experimental Events | Control Events | Odds Ratio | OR | 95% CI | Weight |
|-------|---------------------|---------------|------------|----|--------|--------|
| Vankadawala 2018 (ADRENAL) | 571 | 1812 | 574 | 1803 | 0.99 | [0.86; 1.13] | 21.9% |
| Armoire 2018 (APROCCOR) | 286 | 611 | 328 | 625 | 0.79 | [0.63; 0.99] | 17.5% |
| Sprung 2008 (CORTICUS) | 137 | 242 | 127 | 235 | 1.11 | [0.77; 1.59] | 11.0% |
| Gordon 2016 (VANGAL) | 62 | 291 | 57 | 267 | 1.17 | [0.77; 1.70] | 6.9% |
| Kuh 2016 (vPRESS) | 48 | 168 | 37 | 167 | 1.25 | [0.78; 2.02] | 7.2% |
| Armoire 2002 | 102 | 150 | 112 | 149 | 0.70 | [0.42; 1.16] | 7.0% |
| Tongue 2016 | 37 | 98 | 40 | 99 | 0.89 | [0.50; 1.56] | 5.8% |
| Mohe 2014 | 44 | 117 | 22 | 54 | 0.68 | [0.46; 1.00] | 4.0% |
| Lu 2017 | 23 | 58 | 19 | 60 | 1.42 | [0.67; 3.02] | 3.7% |
| Makkai 2005 | 20 | 48 | 6 | 32 | 3.55 | [1.15; 11.43] | 2.0% |
| Yildiz 2011 | 16 | 27 | 12 | 28 | 1.26 | [0.43; 3.67] | 2.0% |
| Arab 2010 | 23 | 35 | 26 | 36 | 2.12 | [0.68; 6.69] | 1.8% |
| Gordon 2014 | 7 | 31 | 7 | 30 | 0.96 | [0.39; 2.56] | 1.6% |
| Opper 2005 | 7 | 18 | 11 | 23 | 0.69 | [0.20; 2.43] | 1.5% |
| Yildiz 2002 | 9 | 20 | 12 | 20 | 0.44 | [0.20; 1.63] | 1.4% |
| Boffa 1988 | 7 | 22 | 12 | 19 | 0.37 | [0.07; 0.98] | 1.4% |
| Li 2016 | 3 | 29 | 3 | 29 | 1.00 | [0.18; 6.42] | 0.6% |

**Random effects model**

Heterogeneity: $I^2 = 30\%$, $Q = 0.0239$, $p = 0.12$

```
OR  95% CI  Weight
0.99 [0.84; 1.15] 100.0%
```
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

12.3. Inconsistency

12.3.1. side-split

Number of loops = 2. GC denotes glucocorticoid; HD-vitC, high dose vitamin C; vitB1, vitamin B1; VHD-vitC, very high dose vitamin C; vitC, vitamin C; OR, odds ratio.

| comparison                                      | Number of studies | OR from NMA | OR from direct comparison | OR from indirect comparison | Ratio of ratios | p-value |
|-------------------------------------------------|-------------------|-------------|---------------------------|----------------------------|-----------------|---------|
| HD-vitC+GC+vitB1 vs HD-vitC+vitB1                | 0                 | 0.85        | 0.85                      | 0.85                       | 0.85            | 0.85    |
| HD-vitC+GC+vitB1 vs placebo or usual care       | 6                 | 1.05        | 1.07                      | 0.98                       | 1.1             | 0.7494  |
| HD-vitC+GC+vitB1 vs VHD-vitC                    | 0                 | 2.1         | 2.1                       | 2.1                        | 2.1             | 2.1     |
| HD-vitC+GC+vitB1 vs vitB1                       | 0                 | 0.95        | 0.95                      | 0.95                       | 0.95            | 0.95    |
| HD-vitC+GC+vitB1 vs vitC                        | 0                 | 3.21        | 3.21                      | 3.21                       | 3.21            | 3.21    |
| HD-vitC+vitB1 vs placebo or usual care          | 1                 | 1.24        | 1.24                      | 1.24                       | 1.24            | 1.24    |
| HD-vitC+vitB1 vs VHD-vitC                       | 0                 | 2.48        | 2.48                      | 2.48                       | 2.48            | 2.48    |
| HD-vitC+vitB1 vs vitB1                          | 0                 | 1.12        | 1.12                      | 1.12                       | 1.12            | 1.12    |
| HD-vitC+vitB1 vs vitC                           | 0                 | 3.78        | 3.78                      | 3.78                       | 3.78            | 3.78    |
| VHD-vitC vs vitB1                               | 0                 | 0.45        | 0.45                      | 0.45                       | 0.45            | 0.45    |
| VHD-vitC vs vitC                                | 1                 | 1.53        | 1.67                      | 1.1                        | 1.52            | 0.8505  |
| VHD-vitC vs placebo/usual                       | 2                 | 0.5         | 0.5                       | 0.5                        | 0.5             | 0.5     |
| HD-vitC vs HD-vitC+GC+vitB1                     | 0                 | 0.33        | 0.33                      | 0.33                       | 0.33            | 0.33    |
| HD-vitC vs HD-vitC+vitB1                        | 0                 | 0.28        | 0.28                      | 0.28                       | 0.28            | 0.28    |
| HD-vitC vs VHD-vitC                             | 0                 | 0.69        | 0.69                      | 0.69                       | 0.69            | 0.69    |
| HD-vitC vs vitB1                                | 0                 | 0.31        | 0.31                      | 0.31                       | 0.31            | 0.31    |
| HD-vitC vs vitC                                 | 0                 | 1.05        | 1.05                      | 1.05                       | 1.05            | 1.05    |
| HD-vitC vs placebo or usual care                | 2                 | 0.34        | 0.34                      | 0.34                       | 0.34            | 0.34    |
| vitC vs placebo or usual care                   | 1                 | 0.33        | 0.36                      | 0.24                       | 1.50            | 0.8505  |
| GC vs HD-vitC                                   | 0                 | 2.83        | 2.83                      | 2.83                       | 2.83            | 2.83    |
| GC vs HD-vitC+GC+vitB1                          | 2                 | 0.93        | 0.99                      | 0.91                       | 1.1             | 0.7494  |
| GC vs HD-vitC+vitB1                             | 0                 | 0.78        | 0.78                      | 0.78                       | 0.78            | 0.78    |
| GC vs placebo or usual care                     | 11                | 0.97        | 0.97                      | 1.06                       | 0.91            | 0.7494  |
| GC vs VHD-vitC                                  | 0                 | 1.94        | 1.94                      | 1.94                       | 1.94            | 1.94    |
| GC vs vitB1                                     | 0                 | 0.88        | 0.88                      | 0.88                       | 0.88            | 0.88    |
| GC vs vitC                                      | 0                 | 2.97        | 2.97                      | 2.97                       | 2.97            | 2.97    |
| vitB1 vs vitC                                   | 0                 | 3.37        | 3.37                      | 3.37                       | 3.37            | 3.37    |
| vitB1 vs placebo or usual care                  | 3                 | 1.1         | 1.1                       | 1.1                        | 1.1             | 1.1     |

12.3.2. global

Q statistic to assess consistency under the assumption of a full design-by-treatment interaction random effects model = 0.14 (df=2, p=0.9338)
13. References
1. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
2. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785-1805.
3. Furukawa TA, Barbuli C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol. 2006;59(1):7-10.
4. Bennett Jr. I, Finland M, Hamburger M, Kass E, Lepper M, Waisbren B. The Effectiveness of Hydrocortisone in the Management of Severe Infections. JAMA. 1963;183(6):462-465.
5. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med. 1998;26(4):645-650.
6. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288(7):862-871.
7. Yildiz O, Doganay M, Aygen B, Guven M, Kelestimur F, Tutuu A. Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. Crit Care. 2002;6(3):251-259.
8. Oppert M, Schindler R, Husung C, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. Crit Care Med. 2005;33(11):2457-2464.
9. Rinaldi S, Adembru C, Grechi S, De Gaudio AR. Low-dose hydrocortisone during severe sepsis: effects on microalbuminuria. Crit Care Med. 2006;34(9):2334-2339.
10. Kaufmann I, Briegel J, Schliephake F, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-neutrophil neutrophil functions. Intensive Care Med. 2008;34(2):344-349.
11. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358(2):111-124.
12. Ferron-Celma I, Mansilla A, Hassan L, et al. Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery. J Surg Res. 2009;153(2):224-230.
13. Hu B, Li JG, Liang H, et al. [The effect of low-dose hydrocortisone on requirement of norepinephrine and lactate clearance in patients with refractory septic shock]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2009;21(9):529-531.
14. Meduri GU, Golden E, Umerberger R. Prospective Double-Blind Randomized Clinical Trial on the Effects of Low-Dose Hydrocortisone Infusion in Patients with Severe Sepsis. Chest. 2009;136(4).
15. Arabi YM, Aljunah A, Dabbagh O, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ. 2010;182(18):1971-1977.
16. 邓秋明, 尚东, 万献尧. 小剂量激素对感染性休克患者凝血功能的影响. 中国危重病急救医学. 2011;23(3):183-184.
17. Yildiz O, Tanriverdi F, Simon S, Aygen B, Kelestimur F. The effects of moderate-dose steroid therapy in sepsis: A placebo-controlled, randomized study. J Res Med Sci. 2011;16(11):1410-1421.
18. Rahardjo TM, Redjeki I, Maskoen I. Effect of vitamin C 1000 mg IV therapy to lactate level, base deficit and Svo2 in septic patient. Crit Care Med. 2013;41.
19. Fowler AA, 3rd, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014;12:32.
20. Gordon AC, Mason AJ, Perkins GD, et al. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Crit Care Med. 2014;42(6):1325-1333.
21. Mirea L, Ungureanu R, Pavelscu D, et al. PP007-MON: Discontinuous Corticosteroids Administration Increase the Risk of Hyperglycaemia in Septic Shock. Clinical Nutrition. 2014;33.
22. Donnino MW, Andersen LW, Chase M, et al. Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study. Crit Care Med. 2016;44(2):360-367.
23. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. JAMA. 2016;316(5):509-518.
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

24. Keh D, Trips E, Marx G, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. *JAMA*. 2016;316(17):1775-1785.
25. Li G, Gu C, Zhang S, Lian R, Zhang G. Value of glucocorticoid steroids in the treatment of patients with severe community-acquired pneumonia complicated with septic shock. *Chin Crit Care Med.* 2016;28(9):780-784.
26. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care*. 2016;20(1):329.
27. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *J Res Pharm Pract*. 2016;5(2):94-100.
28. Lv QQ, Gu XH, Chen QH, Yu JQ, Zheng RQ. Early initiation of low-dose hydrocortisone treatment for septic shock in adults: A randomized clinical trial. *Am J Emerg Med*. 2017;35(12):1810-1814.
29. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med*. 2018;378(9):809-818.
30. Balakrishnan M, Gandhi H, Shah K, et al. Hydrocortisone, Vitamin C and thiamine for the treatment of sepsis and septic shock following cardiac surgery. *Indian J Anaesth*. 2018;62(12):934-939.
31. Rosini JM, Arnold R, Schuchardt BJ, Gissendaner J, Kowalski R, Capan M. High Dose Intravenous Ascorbic Acid in Severe Sepsis. *Acad Emerg Med*. 2018;25 Suppl 1:S108-S109.
32. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med*. 2018;378(9):797-808.
33. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA*. 2019;322(13):1261-1270.
34. Jiang X YD, Zhao H, Yang F, Yuan Z, Lu P, Tian H. Early low-dose glucocorticoid therapy effectively suppresses serum pro-inflammatory factors such as IL-6 and inhibits apoptosis of CD4+ cells in septic shock patients. *Int J Clin Exp Med*. 2019;12(1):718-723.
35. Harun NF, Cheah SK, Yusof AM, et al. Intravenous thiamine as an adjuvant therapy for hyperlactatemia in septic shock patients. *Crit Care Shock*. 2019;22(6):288-298.
36. Chang P, Liao Y, Guan J, et al. Combined Treatment With Hydrocortisone, Vitamin C, and Thiamine for Sepsis and Septic Shock: A Randomized Controlled Trial. *Chest*. 2020;158(1):174-182.
37. Fujii T, Lueithi N, Young PJ, et al. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA*. 2020;323(5):423-431.
38. Hwang SY, Ryoo SM, Park JE, et al. Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Med*. 2020;46(11):2015-2025.
39. Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial. *Chest*. 2020;158(1):164-173.
40. Lv SJ, Zhang GH, Xia JM, Yu H, Zhao F. Early use of high-dose vitamin C is beneficial in treatment of sepsis. *Ir J Med Sci*. 2020.
41. Mohamed ZU, Prasannan P, Moni M, et al. Vitamin C Therapy for Routine Care in Septic Shock (ViCTOR) Trial: Effect of Intravenous Vitamin C, Thiamine, and Hydrocortisone Administration on Inpatient Mortality among Patients with Septic Shock. *Indian J Crit Care Med*. 2020;24(8):653-661.
42. Moskowitz A, Huang DT, Hou PC, et al. Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock: The ACTS Randomized Clinical Trial. *JAMA*. 2020;324(5):423-431.
43. Petsakul S, Morakul S, Tangsujaritvijit V, Kunawut P, Singhathas P, Sanguanwit P. Effects of thiamine on vasopressor requirements in patients with septic shock: a prospective randomized controlled trial. *BMC Anesthesiol*. 2020;20(1):280.
44. Wani SJ, Mufii SA, Jan RA, et al. Combination of vitamin C, thiamine and hydrocortisone added to standard treatment in the management of sepsis: results from an open label randomised controlled clinical trial and a review of the literature. *Infect Dis (Lond)*. 2020;52(4):271-278.
Supplement to: Fujii T, Salanti G, Belletti A, et al. Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis.

45. Sevransky JE, Rothman RE, Hager DN, et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. *JAMA*. 2021;325(8):742-750.

46. Hussein AA, Sabry NA, Abdalla MS, Farid SF. A prospective, randomised clinical study comparing triple therapy regimen to hydrocortisone monotherapy in reducing mortality in septic shock patients. *Int J Clin Pract*. 2021;75(9):e14376.

47. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41(3):818-827.

48. Rhodes KM, Turner RM, Higgins JP. Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *J Clin Epidemiol*. 2015;68(1):52-60.