**Supplemental Digital Content 1. TREATMENT PICO QUESTIONS**

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| **Questions** | **Population** | **Intervention (experimental exposure)** | **Comparator****(reference exposure)** | **Outcomes** | **Keywords** | **MESH terms** |
| Q1 Should patients with CIRCI be treated with corticosteroids? | Adults and children (not neonates) and critical illness with CIRCI Community acquired pneumonia, including severe influenza CAP Community acquired pneumoniaMeningitisNon-septic SIRS with Shock - Burns\*- Cardiac arrest- Cardiopulmonary bypass grafting | Intravenous or oral corticosteroids (not topical) | No treatment orplacebo  | *Primary outcome* 1. Resolution (or improvement) of *acute manifestations* of CIRCI [shock; respiratory failure; MODS; etc.] OR clinical cure as defined by primary author of studies2. Mortality: hospital or 28 or 90 days]*Secondary outcomes:* Effective anti-inflammatory response [cytokines, CRP, etc.]Duration of: life-supportive treatment, ICU stay, hospital stayMedium-long-term outcome: - Mortality, QoL, functional capacity, PTSS, etc.  Others: Tissue hypoperfusion (measures with lactate level or scoring systems)*Harms:*Any treatments harms | ICU, intensive care, adults, children, pediatrics, critical illness, CIRCI, critical illness-related corticosteroid insufficiency, sepsis, infection, septic shock, SIRS, systemic inflammatory response syndrome, CAP, HCAP, pneumonia, meningitis, ARDS, ALI, acute lung injury, trauma, cardiac arrest, shock, hypotension, cardiogenic shock, steroids, corticosteroids, dexamethasone, hydrocortisone, Solu-Cortef, Solu-Medrol, methylprednisoneprednisone, prednisolone, betamethasone, fludrocortisone, cortivasol, fluorinef, mineralocorticoid, glucocorticoidadrenal hormones | Critical Care, Adrenocorticotropic Hormone, Adrenal Insufficiency, Pediatrics, Adult, sepsis, systemic inflammatory response syndrome, pneumonia, meningitis, respiratory distress syndrome (adult), wounds and injuries, heart arrest, shock, hydrocortisone |
| Q2 Are synthetic corticosteroids superior to hydrocortisone for the treatment of CIRCI? | Adults and children (not neonates) and critical illness with CIRCI (as defined by original studies’ authors)Community acquired pneumonia, including severe influenza CAP Community acquired pneumoniaMeningitisNon-septic SIRS with Shock - Burns\*- Cardiac arrest- Cardiopulmonary bypass grafting | PrednisonePrednisoloneMethylpredniso-loneBetamethasoneDexamethasoneFludrocortisoneHydrocortisone + fludrocortisoneCortivasol | Hydrocortisone | *Primary outcome* 1. Resolution (or improvement) of *acute manifestations* of CIRCI [shock; respiratory failure; MODS; etc.] OR clinical cure as defined by primary author of studies2. Mortality hospital or 28 or 90 days]*Secondary outcomes:* Effective anti-inflammatory response [cytokines, CRP, etc.]Duration of: life-supportive treatment, ICU stay, hospital stayMedium-long-term outcome: - Mortality, QoL, functional capacity, PTSS, etc.  Others: Tissue hypoperfusion (measures with lactate level or scoring systems)*Harms:*Any treatments harms |  |  |
| Q3 Is response to treatment dependent on: (a) time, (b) dose, (c) duration, (d) tapering. Q3b. Does secondary prevention improve overall response to treatment? | Adults and children (not neonates) and critical illness with CIRCI (as defined by original studies’ authors)Community acquired pneumonia, including severe influenza CAP Community acquired pneumoniaMeningitisNon-septic SIRS with Shock - Burns\*- Cardiac arrest- Cardiopulmonary bypass grafting | Timing: early (< 24h) Daily dose: ≤ 300 mg HC (equivalent) Duration: versus long ( ≥ 72 hours: ≥7 days; ≥ 14 days; ≥ 21 days) Tapering: fast (≤ 4 days) OR slow (>4 days)Implementation of secondary prevention  | late (< 72h, < 7 days, < 14 days)>300 HC (equivalent) short (<72 hours) No tapering No Implementation of secondary prevention  | *Primary outcome* 1. Resolution (or improvement) of *acute manifestations* of CIRCI [shock; respiratory failure; MODS; etc.] OR clinical cure as defined by primary author of studies2. Mortality hospital or 28 or 90 days]*Secondary outcomes:* Effective anti-inflammatory response [cytokines, CRP, etc.]Duration of: life-supportive treatment, ICU stay, hospital stayMedium-long-term outcome: - Mortality, QoL, functional capacity, PTSS, etc.  Others: Tissue hypoperfusion (measures with lactate level or scoring systems)*Harms:*Any treatments harms |  |  |

**\***For “burns” we made the initial recommendation: “We suggest using corticosteroids in burns” (conditional recommendation, low quality of evidence). Following external peer review, we changed the statement “to suggest against the use of corticosteroids in patients with burns and without shock” (conditional recommendation very low quality of evidence), and a suggestion for the use of corticosteroids in burned patients with vasopressor-dependent shock (conditional recommendation, very low quality of evidence). However, these alterations were insufficient to solve the disagreement between the Task Force and external peer reviewers. Subsequently, compromise through the editorial process ended up with this question being left off and being reconsidered in the next update of these guidelines.

Small-sized observational studies of burned patients with septic shock reported reduction in vasopressor requirement with the administration of hydrocortisone [1, 2]. There was only one randomized trial of 32 patients with burn and vasopressor dependent shock, of whom 78% had suspicion of CIRCI [3]. In this trial, as compared to placebo, a 7-day treatment with 200 mg of i.v. hydrocortisone reduced the duration of vasopressors (57 vs. 120 hours, P=0.035), and increased the proportion of vasopressor-free patients at 72 hours (67% vs. 13%, P=0.007). This trial was terminated early due to slow recruitment, and the primary outcome was modified *a posteriori*. In addition, the authors stated that “early deaths have been excluded from analysis of the primary outcome to avoid overestimation of treatment effects”. Then, the per-protocol analysis excluded 4 patients in the hydrocortisone group and 1 patient in the placebo group. In the intent-to-treat analysis there were 10/16 and 3/16 deaths (RR= 3.33; 95%CI [1.12, 9.90]) in the hydrocortisone and placebo arms, respectively. Contact with the primary author of this trial provided the information that owing to significant imbalanced between groups in terms of severity of illness, the trial’s data safety and monitoring board, and trial’s sponsor, decided not to discontinue the trial although knowing the exact death rates in both groups (communication with Drs F. Venet and S. Tissot, dated September 9, 2017). Following this, the Task force members agreed that there was sufficient imprecision surrounding mortality outcome, and sufficient value of corticosteroid-sparing effects of vasopressor to suggest using corticosteroids in burned patients with vasopressor-dependency. In contrast, external peer-reviewers thought that the balance between desirable and undesirable effects should support against the use of corticosteroids.

1. Winter W, Kamolz L, Donner A, Hoerauf K, Blaicher A, Andel H. Hydrocortisone improved haemodynamics and fluid requirement in surviving but not non-surviving of severely burned patients. Burns J Int Soc Burn Inj. 2003;29:717–20.
2. Fuchs PC, Bozkurt A, Johnen D, Smeets R, Groger A, Pallua N. Beneficial effect of corticosteroids in catecholamine-dependent septic burn patients. Burns J Int Soc Burn Inj. 2007;33:306–11.
3. [Venet F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Venet%20F%5BAuthor%5D&cauthor=true&cauthor_uid=25619170), [Plassais J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Plassais%20J%5BAuthor%5D&cauthor=true&cauthor_uid=25619170), [Textoris J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Textoris%20J%5BAuthor%5D&cauthor=true&cauthor_uid=25619170), et al. Low-dose hydrocortisone reduces norepinephrine duration in severe burn patients: a randomized clinical trial. [Crit Care.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Venet+Crit+Care+2015) 2015 Jan 26;19:21.

**Criteria for considering studies:**

**Inclusion criteria:**

*Language restriction*: NO

 *Years of the publication* 2008-2014

 *Inclusion of the guidelines* Yes

 *Inclusion of quality indicators* Yes

 *Inclusion for systematic reviews (quality, quantitative analyses):* Systematic reviews, meta-analyses of randomized studies

 *Inclusion of randomized trials* Yes

*Inclusion of observational studies for harms (quality, design, applicability, sample size, statistical methods) observational studies of harms that used multivariate adjustment to reduce the bias; cost-effectiveness analyses.*

**Exclusion criteria:**

*Population exclusion criteria:* chronic adrenal insufficiency, neonates

*Outcomes exclusion criteria:* intermediate outcomes such as instrumental or laboratory measures

*Settings exclusion criteria:* none

*Timing exclusion criteria: none*

**Recommended Search strategy:**

*Relevant databases such as* [*Medline*](http://www.ncbi.nlm.nih.gov/pubmed/)*,* [*Cochrane*](http://www.cochrane.org/cochrane-reviews)*,* [*EMBASE*](http://www.elsevier.com/online-tools/embase)

[*ClinicalTrials.gov*](http://clinicaltrials.gov/)

**Data collection and analysis***:*

Will conduct the overview of the reviews following the framework from the Cochrane collaboration.

Will use dual data extraction and quality control.

Will abstract exact definitions and coding of CIRCI as used in the original studies

**Quality assessment of the primary studies**

We will evaluate risk of bias in randomized trials using Cochrane risk of bias tool as high, low or unclear. We will evaluate the risk of bias in non -randomized studies with the AHRQ tool.

**Quality assessment of the body of evidence according to the GRADE framework synthesis of evidence**

We will categorize the evidence according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias. We will use the GRADE methodology and categorize the quality of evidence as high, moderate, low, or very low. We will downgrade the quality of evidence from randomized studies from high to moderate if at least one from four domains did not meet criteria, e.g. the body of evidence is biased or indirect, or treatment effect is imprecise or inconsistent.

We will downgrade the risk of bias from all randomized trials from low to high if at least one RCT had high risk of bias. We will judge consistency based on statistical heterogeneity test.

We will judge precision according to the number of the events (e.g. >300 would provide informative size for the relative differences of >25%) and width of 95%CI.

For observational studies, we will upgrade the quality of evidence from low for large treatment effects (e.g.>50% absolute risk differences or >100% relative increase in odds or rates of the outcomes), dose response association, or adjustment for known confounding factors.

**Strength of recommendations**

The authors will assign strength of the recommendations based on overall quality of evidence, balances between benefits and harms using the GRADE methodology. A proportion of >80% of Task Force members voting similarly was considered as consensus.

**Search results**

Based on the PICO, we developed a search strategy using relevant databases such as Pubmed, EMBASE, and Cochrane library as well as clinicaltrials.gov registry. We searched theses databases up to December 2014 and updated the searchers quarterly till delivery of the guidelines.