**Supplemental Digital Content 1**

**DIAGNOSIS PICO QUESTIONS**

**CIRCI - Diagnosis**

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| --- | --- | --- | --- | --- | --- | --- |
| **Questions** | **Population** | **Diagnostic test** | **Comparator****(reference exposure)** | **Outcomes** | **Keywords** | **MESH Headings** |
| Q1 Is total cortisol response to ACTH superior to random plasma total cortisol for the diagnosis of CIRCI? | Adults and children (not neonates) and critical illness | Plasma Peak cortisol level post ACTHPlasma Delta cortisol | Plasma Basal cortisol level  | *Primary outcome:* Clinical cure as defined by primary author of studies OR Resolved CIRCI symptomsMortality*Secondary outcomes:* Tissue hypoperfusion (measures with lactate level or scoring systems)Multiorgan system failureAssessmentLength of stay | ICU, intensive care, adults, children, pediatrics, critical illness, cortisol level, plasma cortisol, ACTH, corticotrophin, adrenocorticotrophic, adrenal hormones, delta cortisol, basal cortisol, cosyntropin, CIRCI, critical illness-related corticosteroid insufficiency | Critical Care, Adrenocorticotropic Hormone, Adrenal Insufficiency, Pediatrics, Adult |
| Q2 Is plasma free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI? | Adults and children (not neonates) and critical illness | Plasma unstimulated free cortisol level Plasma peak free cortisol levelPlasma delta free cortisol | Plasma unstimulated, peak and delta total cortisol level | *Primary outcome:* Clinical cure as defined by primary author of studies OR Resolved CIRCI symptomsMortality*Secondary outcomes:* Tissue hypoperfusion (measures with lactate level or scoring systems)Multiorgan system failureAssessmentLength of stay | Free cortisol, peak cortisol, delta free cortisol |  |
| Q3 Is salivary free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI? | Adults and children (not neonates) and critical illness | Salivary free cortisol | Plasma unstimulated, peak and delta total cortisol level | *Primary outcome:* Clinical cure as defined by primary author of studies OR Resolved CIRCI symptomsMortality*Secondary outcomes:* Tissue hypoperfusion (measures with lactate level or scoring systems)Multiorgan system failureAssessmentLength of stay | Salivary free cortisol |  |
| Q4 Is 1 µg ACTH test superior to 250µg ACTH test for the diagnosis of CIRCI? | Adults and children (not neonates) and critical illness | Plasma peak and delta cortisol post 1 µg ACTH | Plasma peak and delta cortisol post 250 µg ACTH | *Primary outcome:* Clinical cure as defined by primary author of studies OR Resolved CIRCI symptomsMortality*Secondary outcomes:* Tissue hypoperfusion (measures with lactate level or scoring systems)Multiorgan system failureAssessmentLength of stay | ACTH Stimulation test, ACTH Stim test, cosyntropin stimulation test, corticotrophin test; tetracosactide test, Synacthen testStandard stimulation test; low dose stimulation test |  |
| Q5 Is hemodynamic response to hydrocortisone (50 to 300 mg) superior to 250µg ACTH test for the diagnosis of CIRCI? | Adults and children (not neonates) and critical illness | Reduction in vasopressor therapy requirement (or equivalent measure) | Plasma peak and delta cortisol post 250 µg ACTH | *Primary outcome:* Clinical cure as defined by primary author of studies OR Resolved CIRCI symptomsMortality*Secondary outcomes:* Tissue hypoperfusion (measures with lactate level or scoring systems)Multiorgan system failureAssessmentLength of stay | Solucortef, vasopressors, pressors, inotropes, vasoactive medications | Hydrocortisone, vasoconstrictor agents |
| Q6 Is corticotropin level superior to 250µg ACTH test for the diagnosis of CIRCI? | Adults and children (not neonates) and critical illness | Plasma level corticotropin | Plasma peak and delta cortisol post 250 µg ACTH | *Primary outcome:* Clinical cure as defined by primary author of studies OR Resolved CIRCI symptomsMortality*Secondary outcomes:* Tissue hypoperfusion (measures with lactate level or scoring systems)Multiorgan system failureAssessmentLength of stay |  |  |

**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.

**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.

**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 sepsis ‘heterogeneous’ sepsis CAP/HCAP CAP Community acquired pneumonia MeningitisSeptic shock ARDSTrauma Multiple trauma Head trauma | 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, solucortef, solumedrol, methylprednisone, prednisone, prednisolone, betamethasone, fludrocortisone, cortivasol, fluorinef, mineralocorticoid, glucocorticoidadrenal hormones | Critical Care, Adrenocorticotropic Hormone, Adrenal Insufficiency, Pediatrics, Adult, sepsis, systemic inflammatory response syndrome, respiratory distress syndrome (adult), wounds and injuries, 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)sepsis ‘heterogeneous’ Septic shock ARDSTrauma Multiple trauma Head trauma | PrednisonePrednisoloneMethylprednisoloneBetamethasoneDexamethasoneFludrocortisoneHydrocortisone + 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)Septic shock ARDSTrauma Multiple trauma Head trauma | 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 |  |  |

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