**Supplemental Digital Content 3**

**Q1 – ACTH vs random**

| **Quality assessment** | | | | | | | **Impact** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| Predicting Hemodynamic Instability | | | | | | | | | |
| 1 | randomised trials | serious 1 | not serious | not serious | serious 2 | none | This is based on a single RCT which randomized 60 patients with septic shock to a low dose ACTH (1ug ACTH) test versus a random cortisol to diagnose adrenal insufficiency. Despite the small numbers, the low dose ACTH test was better able to predict those that required a longer duration of vasopressors and those that were steroid responsive as opposed to the random cortisol. This finding is supported by observational studies as well. | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval

1. Unblinded study.
2. Very small number of patients.

**Q2 – High vs low dose ACTH**

| **Quality assessment** | | | | | | | **Impact** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| Sensitivity/Specificity (assessed with: area under the curve from receiver-operating characteristics) | | | | | | | | | |
| 11 | observational studies 1 | not serious | not serious | not serious | not serious 2 | none | Data is from the Kazlauskaite meta-analysis. In the standard dose (250ug), 30-min cortisol values less than 440nmol/L were highly predictive of CIRCI, and values greater than 833nmol/L ruled out CIRCI. AUC for these categorized test results was 0.82 (95% CI 0.78-0.86). In the low dose (1ug), AUC for these same categorized test results was 0.94 (95% CI 0.90-0.94). | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval

1. Data adjusted for type of cortisol assay.
2. No overlap in AUC confidence intervals from each test.

**Q3 – Salivary cortisol**

| **Quality assessment** | | | | | | | **Impact** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| Correlation between salivary and serum cortisol | | | | | | | | | |
| 2 | observational studies | not serious | not serious | not serious | serious 1 | none | Two studies examined the correlation between salivary and serum free cortisol. One was done in the setting of severe sepsis (Estrada-Y-Martin) and the other in liver cirrhosis (Galbois). The correlation coefficient in 38 patients with sepsis was 0.86 (95% CI 0.78-0.92) and in 88 patients with cirrhosis was 0.91. | ⨁◯◯◯ VERY LOW | CRITICAL |
| Correlation between salivary free & clinical CIRCI - not reported | | | | | | | | | |
| - | - | - | - | - | - | - |  | - | CRITICAL |

**CI:** Confidence interval

1. Small number of patients in only 2 studies.

**Q4 – Plasma free vs plasma total**

| **Quality assessment** | | | | | | | **Impact** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| Ability to predict Illness Severity [multiple] | | | | | | | | | |
|  | observational studies | not serious | not serious | serious a | not serious | none | Ho 2006 - free cortisol better able to predict illness severity in patients with sepsis and free cortisol incrementally varied with illness category (sepsis vs septic shock) whereas total did not. Voseger 2003 - free cortisol varied more with CV surgery whereas total did not. Hamrahian 2004 - free cortisol different between critically ill and healthy controls whereas total was not. Even more pronounced in those with hypoproteinemia. Molenaar 2011 - total cortisol closely correlates to free cortisol in critically ill, septic and non-septic patients with suspected CIRCI, even though the biologically active free cortisol fraction depends on binding proteins and free cortisol better parallels severity of disease than total cortisol. | ⨁◯◯◯ VERY LOW | CRITICAL |

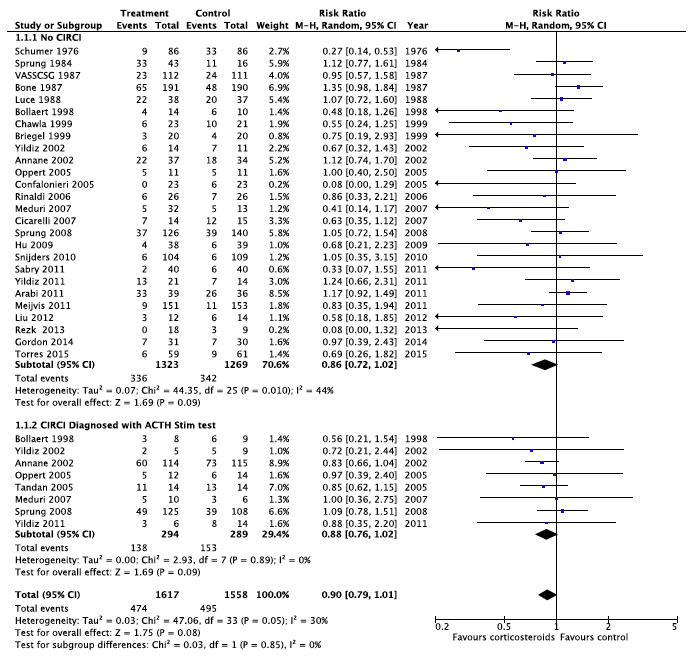
**CI:** Confidence interval

a. Varying patient populations.

References

**Q5 – Hemodynamic response vs 250mcg ACTH**

**Forest Plot**



**Q6 – Corticotropin vs 250mcg ACTH**

No relevant data identified.