

## 10.4.b. Optimal glucose control: Carbohydrate restricted formula + insulin therapy

March 2013

**NEW SECTION in 2013**

**Recommendation:** There are insufficient data *to recommend low carbohydrate diets in conjunction with insulin therapy for critically ill patients.*

**Discussion:** The committee noted that the use of a low carbohydrate enteral formula with the use of insulin therapy in one study aimed at a higher blood sugar range <180 mmol/L vs intensive insulin therapy aimed at < 150 mmol/L had no effect on clinical outcomes and was associated with a significant reduction in hypoglycemia. Although this is consistent with the data seen with the use of tighter glycemic control (see section 10.4 a Optimal Glucose Control: Insulin therapy), the committee felt there was not enough evidence to put forward a recommendation for the use of a carbohydrate restricted diet in conjunction with insulin therapy.

### Semi Quantitative Scoring

| Value                          | Definition   | 2013 Score (0,1,2,3) |
|--------------------------------|--|----------------------|
| Effect size                    | Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size  | 0                    |
| Confidence interval            | 95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval  | 0                    |
| Validity                       | Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of VAP--a higher score indicates presence of more of these features in the trials appraised | 1                    |
| Homogeneity or Reproducibility | Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials  | n/a                  |
| Adequacy of control group      | Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)  | 2                    |
| Biological plausibility        | Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)   | 2                    |
| Generalizability               | Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings =3.         | 1                    |
| Low cost                       | Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU  | 3                    |
| Feasible                       | Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU   | 2                    |
| Safe                           | Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm   | 3                    |

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**Question:** Does tight blood sugar control result in better outcomes in the critically ill adult patient?

**Summary of evidence:** There was one level 2 study reviewed that compared a carbohydrate restrictive enteral diet with insulin therapy (to maintain blood sugars <180 mmol/L) vs intensive insulin therapy to maintain blood sugars <150 mmol/L.

**Mortality:** Based on the single study, carbohydrate restricted formula plus insulin therapy aimed at higher blood sugar range (<180 mmol/L) had no effect on mortality when compared to intensive insulin therapy aimed at a tighter blood sugar of < 150 mmol/L (RR 1.10, 95% CI 0.75, 1.61, p=0.63)\*.

**Infections and length of stay:** Based on the single study, carbohydrate restricted formula plus insulin therapy aimed at higher blood sugar range (<180 mmol/L) when compared to intensive insulin therapy aimed at a tighter blood sugar of < 150 mmol/L had no effect on incidence of pneumonia (RR 0.95, 95% CI 0.67, 1.35, p=0.78)\* or ICU length of stay (p=0.9)\*.

**Hypoglycemia:** Based on the single study, carbohydrate restricted formula plus insulin therapy aimed at higher blood sugar range (<180 mmol/L) was associated with a significant decrease in hypoglycemic events when compared to intensive insulin therapy aimed at a tighter blood sugar of < 150 mmol/L (RR 0.22, 95% CI 0.09, 0.52, p<0.001)\*.

#### Conclusions:

- 1) Carbohydrate restricted formula plus insulin therapy aimed at blood sugar range (<180 mmol/L) vs intensive insulin therapy to maintain blood sugars < 150 mmol/L, has no effect on mortality, incidence of pneumonia or ICU length of stay in critically ill patients.
- 2) Carbohydrate restricted formula plus insulin therapy aimed at blood sugar range (<180 mmol/L) vs, vs intensive insulin therapy to maintain blood sugars < 150 mmol/L, is associated with a significant decrease in hypoglycemia in critically ill patients.

\*Risk ratio, confidence interval, and p-value calculated using Review Manager 5.1.

**Table 1. Randomized studies evaluating carbohydrate restricted formula + insulin therapy in critically ill patients**

| Study              | Population                                    | Methods (score)                                | Intervention  | Mortality # (%)      |                       | Infections # (%)   |  |
|--------------------|---|--|---|----------------------|-----------------------|--|--|
|                    |   |  |   | Carb Restriction ICU | Intensive Insulin ICU | Carb Restriction   | Intensive Insulin  |
| 1) de Azevedo 2010 | Multidisciplinary ICU and trauma ICU<br>N=351 | C.Random: no<br>ITT: no<br>Blinding: no<br>(6) | Carbohydrate restrictive EN with insulin therapy (to maintain BG <180) vs intensive insulin therapy (BG <150) | 42/169 (25)          | 38/168 (22.6)         | Carb Restriction<br>Pneumonia<br>44/169 (26)<br>UTI<br>16/169 (9)<br>Surgical<br>16/169 (9)<br>Catheter-related<br>8/169 (5) | Intensive Insulin<br>Pneumonia<br>46/168 (27)<br>UTI<br>11/168 (7)<br>Surgical<br>15/168 (9)<br>Catheter-related<br>10/168 (6) |

**Table 1. Randomized studies evaluating carbohydrate restricted formula + insulin therapy in critically ill patients (continued)**

| Study              | LOS days             |                          | Ventilator days  |                   | Other   |   |
|--------------------|----------------------|--------------------------|------------------|-------------------|---|---|
|                    | Carb Restriction ICU | Conventional Insulin ICU | Carb Restriction | Intensive Insulin |   |   |
| 1) de Azevedo 2010 | 8 (4-14)             | 7 (4-15)                 | NR               | NR                | Carb Restriction<br>Hypoglycemia<br>6/169 (4)<br>Nutritional intake (%) requirement at day 3<br>80 (89) | Intensive Insulin<br>Hypoglycemia<br>27/168 (16)<br>97 (92) |