# Intensive Insulin Therapy

## Should we do IIT?

***Nepean WTET summary 8/12/20***

**Background and Rationale**

- Hyperglycaemia associated with insulin resistance is common in the critically ill. In non-diabetic patients, high levels of insulin-like growth factor binding protein-1, reflect impaired hepatocyte response to insulin and is associated with an increased risk of death. The severity and duration of hyperglycaemia correlates with mortality risk (association, not necessarily causation)
- Studies have shown an improvement in mortality with intensive insulin therapy (IIT) and tight glycaemic control in diabetic patients with acute myocardial infarction. This may be extrapolated to the hyperglycaemic critically ill?
- Whilst hyperglycaemia is known to impair immune function and wound healing, this comes from observations in patients with chronic hyperglycaemia (e.g. in poorly controlled diabetics) and may not be applicable in the acute setting. Niekerk et al (crit care 2017) found an elevation of aerobic glycolysis forms necessary intermediates for augmenting immune function and similarly promotes tissue repair (in fact insulin's anti-inflammatory properties may be undesirable)
- Hypoglycaemia is also associated with morbidity and mortality and is at risk with IIT

**Advantages and Disadvantages**

- Advantages of IIT
    - Theorhetically relatively simple (nil additional training or resource required) +/- cheap
    - Benefit seen in acute myocardial infarction - ?extrapolatable to critically ill
    - Seems physiological plausible (or is it?)
- Disadvantages of IIT
    - Intensive monitoring and response – heavy resource use (time and consumables); patient requirements may fluctuate dependent on phase of stress response, steroid use, uptitration/intolerance/disconnection of feeds (enteral vs parenteral) etc
    - Subtle differences between arterial, capillary and venous BSLs – used interchangeably
    - Patients exhibit differential sensitivities and response to insulin (similarly accumulates in renal failure), algorithms only provide a general overview of how to personalise a regimen, which may not be sophisticated enough to titrate to narrow targets
    - Higher risk of hypoglycaemia which is proven to be harmful

**Key studies**

- Berghe (Leuven 1 - surg) NEJM 2001
    - SS RCT; Mechanically ventilated patients (in a primarily, but not exclusively, surgical ICU) randomised to actrapid infusion for either intensive (4.4-6.1mmol/L) vs conventional (10.0-11.1mmol/L) insulin therapy. Stratified by admission type (cardiac >60%; vs non-cardiac to include neuro, thoracic, abdominal, vascular, trauma, burns transplanatation). On admission all patients given IV glucose (200-300g/24h) and day 2 changed to feeding (TPN or PN+EN or EN). N=1548 (over 12m)

    - Primary outcome; death from any cause during ICU stay; 4.6% vs 8.0%, P<0.04 (predominantly those in ICU >5d)
    - Mean BSL 5.7 +/-1.1 vs 8.5+/-1.8 mmol/L. IIT reduced in-hospital mortality by 34%, blood stream infections by 46% and there was less multiorgan failure. 2.9% hypoglycaemia (<2.2)
- Berghe (Leuven 2 - med) NEJM 2006
    - SS RCT; Medical ICU patients, randomised to intensive (start when >6.1mmol/L targeting 4.4-6.1mmol/L) vs conventional insulin (start when >12mmol/L targeting 10-11mmol/L) therapy using actrapid infusion. N=100
    - Primary outcome; death from any cause in hospital, not significantly different. However when looked at subgroup of those requiring ICU for =/>3d, significantly less hospital (43% vs 52.5%, P=0.009) and trend towards reduced ICU (31.3% vs 38.1%, P=0.05) deaths with IIT
    - Less newly acquired AKI (5.9% vs 8.9%, P=0.04) and more rapid weaning from mechanical ventilation in those with IIT
- VISEP NEJM 2008
    - MC 2x2 factorial RCT; Severe sepsis patients randomised to intensive (started when >6.1mmol/L targeting 4.4-6.1mmol/L) vs conventional (started when >11.1mmol/L targeting 10-11mmol/L) insulin therapy and hydroxyethyl starch (HES) vs Ringer's lactate for fluid resuscitation. N=537 (stopped early for safety concerns)
    - Primary outcome; 28d mortality and morbidity measured by mean score for organ failure (co-primary end point); no significant difference in IIT compared to conventional insulin
    - Hypoglycaemia in 12.1% vs 2.1% (P<0.001). Higher renal failure and trend towards higher mortality with HES (see other starch trials)
- NICE-SUGAR NEJM 2009
    - MC RCT; Medical and surgical ICU patients expected to require ICU treatment =/>3d. Randomised to intensive (4.5-6.0mmol/L) vs conventional (=/<10mmol/L) glucose control via intravenous actrapid and protocol algorithms. Discontinued when patient eating and drinking or discharged from ICU (resumed if readmitted <90d) -whichever happened first. N=6030 data analysed
    - Primary outcome; death from any cause by d90; 27.5% vs 24.9% (OR 1.13, 95% CI 1.02-1.28, P=0.02). Upheld even after adjustment for baseline risk factors (adjusted OR 1.14, 95% CI 1.01-1.29, P=0.04) with a higher proportion of CVS related deaths. (Mortality at d28 not significantly different)
    - Possible trend towards benefit with IIT in patients receiving corticosteroids or with trauma
    - Serious adverse events due to hypoglycaemia (=/<2.2mmol/L); 6.8% vs 0.5%

**Summary (my practice)**

- My usual practice in non-diabetic ICU patients is to wait for two consecutive (=/>1h apart) BSLs =/>11.0mmol/L prior to commencement of insulin. If critically ill (e.g. need for vasopressors or invasive mechanical ventilation) I commence intravenous insulin (unclear subcutaneous absorption) with titration (as per local protocol), targeting a BSL 6-10mmol/L. I am mindful of drivers that may cause fluctuations, the patient's nutritional status and their underlying renal function
- If diabetic (outside of hyperglycaemic emergencies) I target a bespoke a glycaemic range relative to their usual level of control
- It is possible with the advent of emerging technology (continuous noninvasive BSL monitoring) that tight glycaemic control may be able to be instituted in a safe manner (avoiding hypoglycaemia) and as such further studies into specific subgroups that may benefit from IIT may be revisited. On the other hand, similar to fever in infection, acute hyperglycaemia may be an appropriate physiological response and a degree of tolerance of this may actually be beneficial. I await further studies in this field.