Newborn Critical Care Center (NCCC) Clinical Guidelines

Hyperglycemia Management and the Use of Insulin

BACKGROUND

Multiple studies in neonates have indicated that persistently elevated serum glucose concentrations (>150 mg/dL) are correlated with adverse clinical outcomes and/or increased mortality.[1] Hyperglycemia in the first 3 days of life is associated with an increased incidence of severe ROP in preterm infants.[2] Studies demonstrate the prevalence of hyperglycemia (glucose >180 mg/dL) to be 30-40% during the first 2 postnatal weeks in ELBW infants and demonstrate an inversely higher risk of hyperglycemia with decreasing gestational age.[3, 4, 5] In one cohort, insulin treatment during the first 28 postnatal days was associated with lower 28- and 70-day mortality (even after adjusting for clinical illness).[3] In another trial of early insulin replacement in very low birth weight infants (<1500 grams), the use of insulin within the first week of life did not decrease mortality and increased the risk of hypoglycemia.[6] Compounding this risk, premature infants have some degree of insulin resistance and delayed insulin response and often require higher insulin doses for response.[7] In addition, studies have demonstrated that the use insulin for tight glycemic control (glucose 72-108 mg/dL) compared to standard practice (glucose 144-180 mg/dL) doubles the risk of hypoglycemia, and increases weight gain and head growth at the expense of linear growth, likely representing increases in fat mass rather than lean mass.[8, 9]

Although the evidence was considered to be very low certainty, a recent, large review (16 studies with data from 5,482 infants) suggests insulin therapy may not improve outcomes of very preterm infants with hyperglycemia.[10] Similarly, studies regarding long-term neurodevelopmental outcomes while somewhat conflicting, support the deleterious effects of hyperglycemia but do not suggest improvement in outcomes with the use of insulin. In a relatively large study (533 infants born <27 gestational weeks with 436 survivors assessed at 6.5 years), neonatal hyperglycemia (glucose >144mg/dL) was associated with lower intelligence scores and worse motor outcomes at 6.5 years of age. Insulin treatment was not associated with either worsened or improved neurodevelopmental outcomes in this cohort.[11] In another study of 151 extremely preterm infants, neonatal hyperglycemia during the first postnatal month was associated with greater immaturity, but did not show an independent association with adverse neurodevelopmental outcomes at 3 years of age.[12] In a smaller study of 102 surviving extremely preterm infants, multiple logistic regression models demonstrated that hyperglycemia (glucose >270mg/dL) was significantly associated with lower normal developmental quotient rates at 18 months corrected age.[13]

In extremely premature infants (< 24 weeks gestation) a “persistent hyperglycemia” (PH) with distinct clinical features has been observed. One study reported extreme prematurity to be the isolated independent risk factor, as nutritional approach and medical treatments, including glucocorticoid therapy, did not emerge as independent risk factors.[14] PH tends to be more severe (glucoses >400 mg/dL) and prolonged (lasting >2 weeks) and often persists even after transitioning off parenteral nutrition to enteral feeding. These infants tend to require more aggressive interventions including prolonged treatment with insulin.

CRITERIA

For glucose 250 - 350 mg/dL and not receiving insulin:

- Consider exogenous glucose sources
- Consider NS for flush solution and as a base solution for medications
- Reduce GIR step wise by 2-3 mg/kg/min to a minimum GIR:
    - 4 mg/kg/min for infants >/=28 weeks PMA
    - 3-4 mg/kg/min for infants < 28 weeks PMA
- Check triglyceride level and adjust fat emulsion as indicated
  (see to ELBW Nutrition guidelines; chart can be used for any infant regardless of PMA)

For persistent glucose >250 - 350 mg/dL despite management per above:

- Consider the use of intermittent insulin. **MUST** be approved by attending or fellow.
- Dose: 0.1 units/kg IV once

If glucose >250 - 350 mg/dL for >6 hours despite insulin boluses (up to 3):

- Consider the use of an insulin infusion. **MUST** be approved by attending or fellow
- Starting dose for ALL patients = 0.05 units/kg/hr
- Titrate insulin infusion per below:

Serum Glucose (mg/dL)	**Insulin Dosing Adjustment**
<50	STOP infusion and administer 5 mL/kg D10W
50-79	STOP infusion and re-check glucose in 30 minutes
80-149	Decrease infusion by 50%
150-249	No change. Continue current dose
250-350	Increase infusion by 0.01 unit/kg/hr
>350	Increase infusion by 0.02 units/kg/hr

If glucose measurement decreases by >100 mg/dL while on insulin decrease insulin infusion by 50%.

GLUCOSE MONITORING

- Check POC glucose 1 hour after flush is completed for an insulin bolus, 1 hour after starting an insulin infusion, 1 hour after changing the insulin infusion rate, 1 hour after changing the GIR.
- Blood glucose must be checked immediately prior to starting the insulin drip (in case the serum glucose has fallen while awaiting arrival/initiation of insulin).
- POC glucoses should be checked <u>every 1-hour</u> during the titration period.
- If glucose remains elevated at 1 hour post titration consider repeating POC glucose at 90 minutes - 2 hours before increasing insulin infusion due to insulin resistance and delayed response.
- Once POC glucose remains <250 mg/dL for two consecutive checks without change in insulin rate or GIR, glucose checks may be spaced to every 2-3 hours.

ADMINISTRATION

- The charge nurse must be notified before starting an insulin infusion.
- The charge nurse is to assist the bedside nurse and both are to independently check the dose with initiation of the insulin infusion
- For a continuous infusion: prime IV tubing with medication and wait 20 minutes before starting infusion to saturate binding sites.
- Insulin drips are run above total fluids unless otherwise specified
- Insulin boluses should be pushed into an access site ***as close to the patient as possible*** (no need to let insulin sit in tubing prior to administration).

ADDITIONAL MONITORING

POTASSIUM and LACTATE

- Insulin infusions are associated with lactic acidosis in neonates, with one review noting a three-fold increase in lactate levels. Intracellular potassium shifts may also occur. [8]
- Obtain arterial or capillary blood gas sample with lactate and potassium level one hour after initiation of insulin infusion.
- Repeat blood gas with lactate and potassium 4 hours after the start of the infusion.
- Consider repeating lactate level every 12 hours if elevated or continuing to rise.
- Monitor potassium levels every 12-24 hours while receiving the insulin infusion.

OTHER

- In the case of persistent hyperglycemia, consider obtaining an echocardiogram to evaluate for cardiac hypertrophy for infants requiring an insulin infusion for >72 hours. [15]

ADJUVANT THERAPIES

- Early enteral feedings have been shown to increase pancreatic function leading to increased endogenous insulin secretion. Whenever possible, enteral feedings should be provided to infants with hyperglycemia, particularly those requiring insulin therapy. [16]
- Optimizing parenteral protein intake has been shown to decrease the need for insulin to treat hyperglycemia in preterm infants.[3, 17]
- Limiting fat emulsion may help to lower serum glucose levels.[18] However, maintaining appropriate ratios of macronutrient sources is also beneficial and providing some source of calories from fat may help to stabilize glucose levels by providing an alternative energy source. *In the absence of hypertriglyceridemia*, avoid decreasing the fat emulsion below 0.5-1 gram/kg/day for an infant with hyperglycemia who is dependent on total parenteral nutrition.
- Hypophosphatemia is associated with hyperglycemia and often precedes hyperglycemia in ELBW infants in the first 2 weeks of life. Although speculative, study findings support the hypothesis that hypophosphatemia may contribute to glucose intolerance, and that correction of this electrolyte disturbance may confer some benefit in glycemic control.[19]

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