Care Step Pathway - Hyperglycemia, With or Without Development of Type I Diabetes Mellitus (immune destruction of beta cells in the pancreas)

Nursing Assessment

Look:
- Does the patient appear fatigued?
- Does the patient appear dehydrated?
- Does the breath have a sweet/fruity smell?
- Is the patient tachycardic?
- Is the patient vomiting?
- Does the patient appear ill?

Listen:
- Frequent urination?
- Increased thirst?
- Dry mouth?
- Increased hunger?
- Increased fatigue?
- Weight loss?
- Confusion, altered level of consciousness with advanced cases

Recognize:
- Symptoms of diabetes
- Serum glucose levels
- Other immune-related toxicity (and any corticosteroids given)
- Infections

Grading Toxicity

Mild Hyperglycemia
New-onset hyperglycemia glucose >ULN –200 mg OR history of type 2 DM with low suspicion of DKA

Moderate or Worse Hyperglycemia (Likely New-onset Type 1 Diabetes); No DKA
New onset fasting glucose >200 mg/dL or random blood glucose >250 mg/dL OR history of type 2 DM with fasting/random glucose >250 mg/dL; DKA workup negative

Moderate or Worse Hyperglycemia (Likely New Onset Type 1 Diabetes); DKA
New onset fasting glucose >200 mg/dL or random blood glucose >250 mg/dL OR history of type 2 DM with fasting/random glucose >250 mg/dL; DKA workup positive

Management

Overall Strategy
- Monitor glucose at baseline and with each treatment while on therapy and at follow-up visits for at least 6 months
- Any patient who develops new-onset hyperglycemia without risk factors for DM2 should be evaluated for DM1
- Care needs to be taken in managing concurrent immune-related AEs that require corticosteroids because of the impact on blood glucose levels*
- Any patient who develops DM1 from checkpoint inhibitor therapy should be referred to and followed by endocrinology
- Evaluate for symptoms of DKA in patients with new onset fasting glucose >200 mg/dL or random blood glucose >250 mg/dL OR history of type 2 DM with fasting/random glucose >250 mg/dL: excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath
- If DKA is suspected, evaluate per institutional guidelines, including blood pH, metabolic panel, amylase, lipase, urine and/or serum ketones, anion gap, C-peptide level, anti islet cell antibodies, or anti-GAD to (differentiate DM1 and DM2)
- Treatment involves insulin. Corticosteroids are not effective due to almost complete destruction of the pancreatic beta cells from immunotherapy
- Patients who require high-dose corticosteroids for other (or concomitant) immune-related adverse events require close monitoring, as corticosteroids can exacerbate hyperglycemia. If insulin is used, doses often require adjustments as corticosteroids are tapered

Mild Hyperglycemia
- Continue ICI therapy
- Monitor serial blood glucose at each dose
- Institute diet/lifestyle modification
- If necessary, provide antidiabetes medication per institutional protocol
- Consider endocrine consultation if patient is symptomatic/hyperglycemia cannot be controlled

Moderate or Worse Hyperglycemia (Likely New-Onset Type 1 Diabetes); No DKA
- Continue ICI therapy
- Consider endocrinology management for Type 1 DM
- Monitor serial blood glucose at each dose
- Institute diet/lifestyle modification
- Provide antidiabetes medication per institutional protocol

Moderate or Worse Hyperglycemia (Likely New Onset Type 1 Diabetes); DKA
- Hold ICI therapy
- Obtain endocrinology consultation
- Provide inpatient care
- Insulin to be provided as directed by inpatient team and/or endocrinologist
- DKA to be managed per institutional guidelines (e.g., intravenous fluids, potassium supplementation, intravenous insulin, hourly glucose, serum ketones, blood pH, and anion gap)
- Consider resuming ICI therapy once DKA has been corrected and glucose level has been stabilized

Implementation:
- For patients with new-onset Type 1 diabetes, obtain endocrinology referral
- Endocrinology may comanage. The following are key aspects of management:
  - Discuss that DM1 will most likely be permanent
  - Review signs and symptoms of hyper/hypoglycemia
  - Follow patients closely with checks on blood glucose levels, signs of DKA (fruity breath, confusion, nausea, etc), and other symptoms (e.g., increased infections)
  - Provide insulin education (or refer)
  - Discuss possibility of other immune-related AEs, including others of endocrine origin
- Discuss dietary modification

Administering Corticosteroids for a Concomitant irAE:

Corticosteroid taper instructions/calendar as a guide but not an absolute
- Taper should consider patient's current symptom profile
- Close follow-up in person or by phone, based on individual need and symptomatology
- Corticosteroids may cause indigestion; provide antacid therapy daily as gastric ulcer prevention while on corticosteroids (e.g., proton pump inhibitor or H2 blocker if prednisone dosage is >20 mg/day)
- Review corticosteroid medication side effects: mood changes (angry, reactive, hyperaware, euphoric, manic), increased appetite, interrupted sleep, oral thrush, fluid retention
- Be alert to recurring symptoms as steroids taper down and report them (taper may need to be adjusted)

Long-term high-dose corticosteroids:
- Consider antimicrobial prophylaxis (sulfamethoxazole/trimethoprim double dose M/W/F; single dose if used daily) or alternative if sulfa-allergic (e.g., atovaquone [Mepron®] 1500 mg po daily)
- Consider additional antiviral and antifungal coverage
- If extended corticosteroid use, risk for osteoporosis; initiate calcium and vitamin D supplements
- Patients with asthma or who smoke may have decreased sensitivity to corticosteroids

DKA = diabetic ketoacidosis; DM = diabetes mellitus; GAD = glutamic acid decarboxylase; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; po = by mouth; ULN = upper limit of normal