Steroids or Other Cancer-Related Therapies and Glucose Management

Diabetes Update 2022

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Disclosures

- Consultant: Horizon Therapeutics USA, Inc.
- Chair-elect: Midwest section of American Federation for Medical Research (AFMR)
- Committee member: Endocrine Society, American Thyroid Association, American Association for Clinical Endocrinology

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Learning Objectives

- Understand the complex relationship between cancer, cancer therapies and hyperglycemia/diabetes
- Evaluate cancer patients presenting with hyperglycemia/diabetes
- Manage hyperglycemia/diabetes from specific cancer therapies:
  - Glucocorticoids (steroids)
  - Immune checkpoint inhibitors (CPI)
  - Phosphoinositide 3-kinase inhibitors (PI3KI)

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HEALTH CARE DELIVERY SYSTEMS AND IMPLEMENTATION IN DIABETES (ME MCDONNELL AND AR SADHU, SECTION EDITOR)

Check for updates

Patient-Centered Diabetes Care of Cancer Patients

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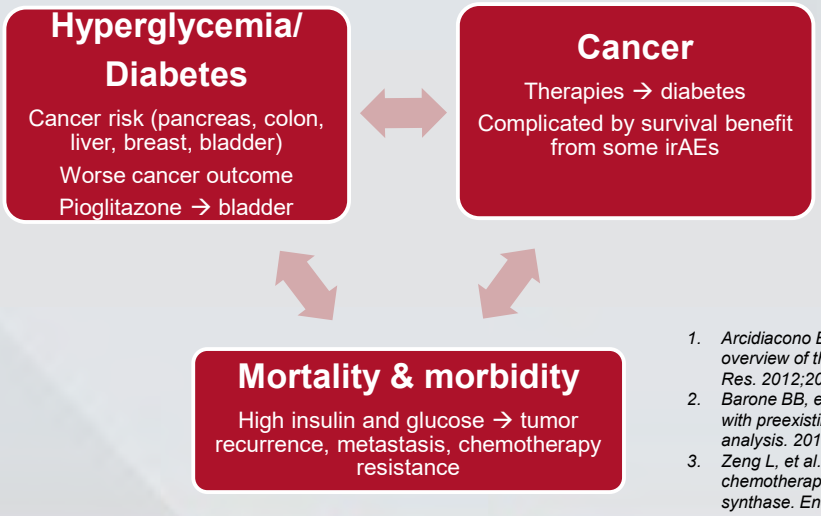
Exploring the Relationship Between Cancer and Hyperglycemia/Diabetes



1. *Arcidiacono B, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res. 2012;2012:789174*
2. *Barone BB, et al. Postoperative mortality in cancer patients with preexisting diabetes. Systematic review and meta-analysis. 2010;33(4):931–9*
3. *Zeng L, et al. Hyperglycaemia confers resistance to chemotherapy on breast cancer cells: the role of fatty acid synthase. Endocr Relat Cancer. 2010;17(2):539–51*

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General Pre-therapy Patient Assessment

- Family and personal history of diabetes and autoimmunity
- *Plasma glucose (PG)* (fasting if possible) and hemoglobin A1c (HbA1c)
- Counseling about symptoms
- Treat newly diagnosed diabetes before starting CPI/steroid/PI3Ki
- For established diabetes → self-monitoring of blood glucose (SMBG)
- Continuous glucose monitor (CGM) in patients at risk of glycemic variability and hypoglycemia, but inpatient use is investigational
- Issues regarding ***HbA1c accuracy***; fructosamine may help
  - rapid onset of hyperglycemia
  - hematologic abnormalities: anemia or transfusions

Davis GM, et al. Diabetes technology in the inpatient setting for management of hyperglycemia. Endocrinol Metab Clin N Am. 2020;49(1):79–93

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General Principles of Management of Diabetes in Cancer Patients

- Initial focus: prevent hypoglycemia, severe hyperglycemia, ketosis
- ADA goals for older adults: pre-meal 90–130; post-meal ≤180 mg/dL
- Patients with reduced life expectancy: lenient glycemic targets
- Stable patients: best possible glycemic status without hypoglycemia
- Common Terminology Criteria for Adverse Events (CTCAE) is preferred by oncologists to grade the severity of hyperglycemia and other adverse events from cancer therapy
  - *any degree of hyperglycemia in CPI-treated patients warrants urgent evaluation for immune-mediated insulin deficiency*

1. *Perez A, et al. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014;6(1):9–20. 30.*
2. *American Diabetes Association. Older adults: standards of medical care in diabetes—2021Diabetes Care. 2021;44(Supplement 1):S168-S79.*

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Case 1

- 76 y/o M hospitalized for weakness and confusion 3 weeks after pembrolizumab for multiple myeloma
- Diagnosed with DKA
  - RPG 972 mg/dL
  - HbA1c 7.8 %
  - AG metabolic acidosis, Beta-hydroxybutyrate 5 mmol/L, ketonuria
  - Managed and discharged on basal-bolus insulin
- On follow-up
  - C-peptide <0.1 ng/mL with PG 278 mg/dL
  - 3 autoimmune diabetes Ab +

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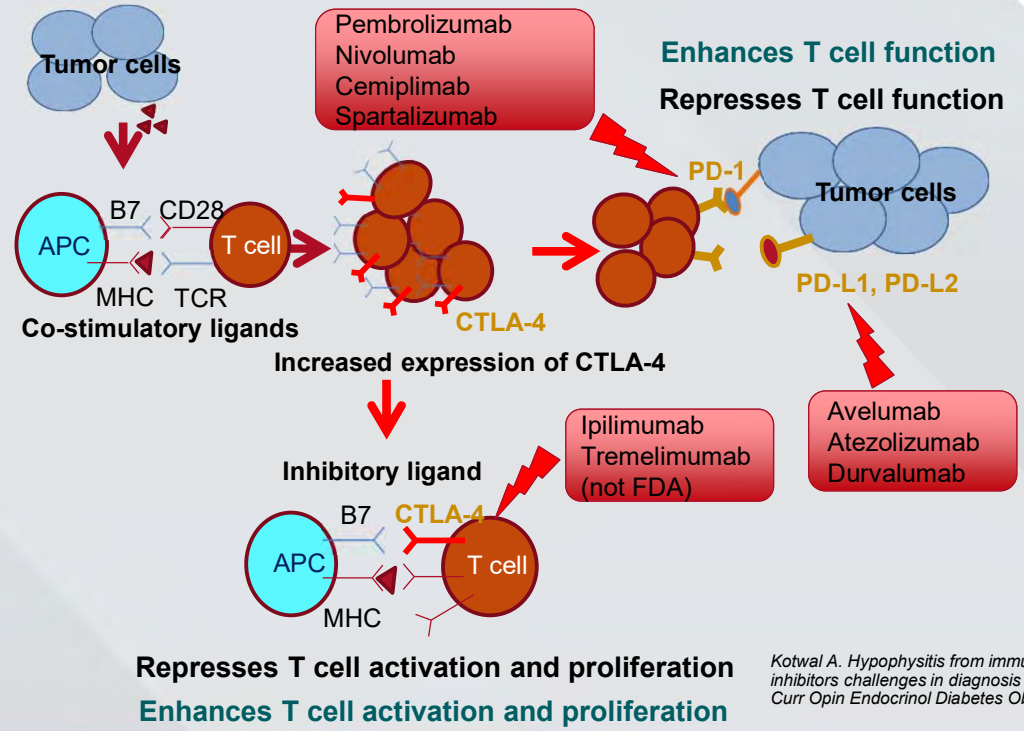

Kotwal A. Hypophysitis from immune checkpoint inhibitors challenges in diagnosis and management. Curr Opin Endocrinol Diabetes Obes 2021

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CPI-induced Diabetes: Pathogenesis

- T cell–mediated destruction of pancreatic β cells like classic type 1 diabetes
- But appears to be distinct from classic type 1 diabetes:
  - HLA class II association: 51.3% HLA-DR4 (associated with classic type 1 diabetes), 14.1% HLA-DR9 (associated with fulminant type 1 diabetes in Asians), 10.3% protective phenotypes for type 1 diabetes
  - 50–80% Type 1 diabetes Ab+
- ***Similarities to classic type 1 diabetes but more rapid onset and progression***

1. *Ma et al., Chinese Medical J 2002*
2. *Nilesen et al. Tissue Antigens 2003*
3. *Perri V et al., Int J Mol Sci 2015*
4. *Fujisawa R et al., Clin Exp Immunol 2015*
5. *Kotwal et al. BMJ Open Diabetes Res Care 2019*

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CPI-induced Diabetes: Presentation

- Average age of presentation 64 years
- Frequency: ***PD-1***/PD-L1/combination (up to 2%) >>> CTLA-4
- Median time to onset 5 months (1 week to 2 years)
  - Several months even after CPI is stopped
- Present as new-onset insulin-dependent or worsening pre- or type 2 diabetes
- ***Different from classic type 1 diabetes***: older age of onset, faster progression of insulin deficiency – like fulminant diabetes, lower rate of type 1 diabetes Ab+ (50–80% compared vs. >90), DKA in 2/3rd of cases

1. *Stamatouli AM et al. Diabetes. 2018*
2. *Kotwal A et al. BMJ Open Diabetes Res Care, 2019*
3. *Lo Preiato V et al. Rev Endocr Metab Disord. 2021*
4. *Quandt Z et al. Annu Rev Med. 2021*

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CPI-induced Diabetes: Diagnosis

Screening

Measure FPG (preferably) or RPG and HbA1c before initiation of CPI
- If normal, measure FPG (preferably) or RPG before each infusion (especially for PD-1/PD-L1 inhibitor); HbA1c every 3 months
- Assess autoimmune history, consider type 1 DM Ab measurement[a]
- Patient counselling for symptoms of hyperglycemia and DKA
- If diabetes or prediabetes, optimize blood glucose prior to CPI initiation

Normal baseline evaluation

Prior history of type 2 or prediabetes on oral anti-hyperglycemic ± basal insulin

CPI (especially PD-1/PD-L1 inhibitor alone or in combination with CTLA-4 inhibitor) initiated

Work up

- FPG ≥126 mg/dL or RPG ≥ 200 mg/dL, or
- FPG 100-125 mg/dL or RPG 140-199 mg/dL) with other features[b], or
- Difficult to control glucocorticoid-induced hyperglycemia

→ Repeat FPG, HbA1c, c-peptide[c], type 1 DM Ab[d]

- RPG ≥200 mg/dL and concern for DKA, or
- RPG ≥250 mg/dL and symptoms of hyperglycemia

→ **Evaluate for DKA and HHS** Blood pH, BMP, serum or urine ketones, beta-hydroxybutyrate, serum osmolality

Requiring addition or intensification of insulin without other explanation

→
- Encourage more frequent SMBG
- Repeat FPG, HbA1c, c-peptide[c], type 1 DM Ab[d]

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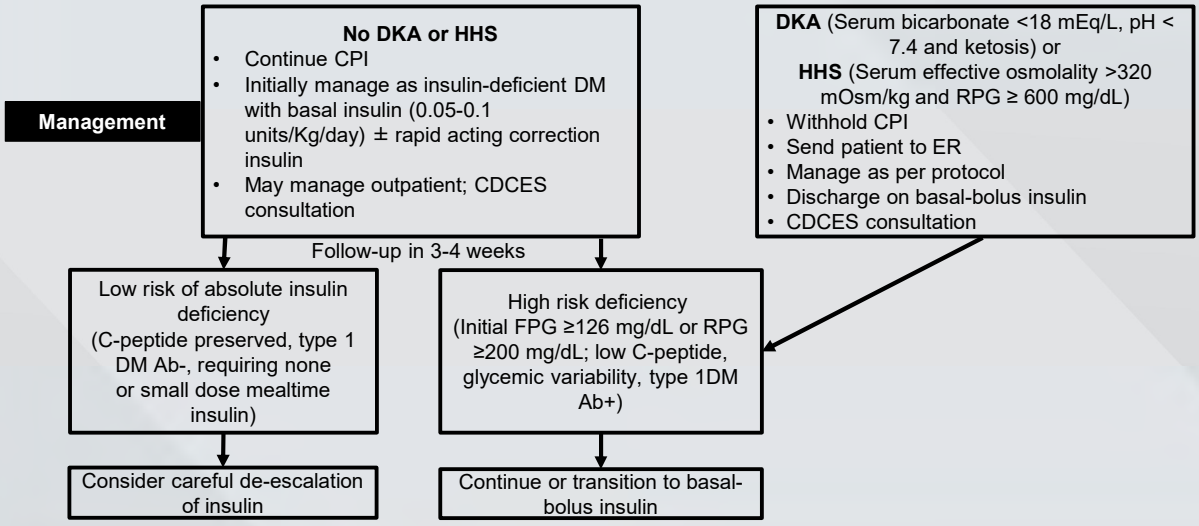
CPI-induced Diabetes: Management



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CPI-induced Diabetes: Management caveats

- **Initially treat as insulin-dependent diabetes**
  - then adjust based on additional data
- Patients older, sicker and may get high dose steroids requiring frequent insulin changes
- **Risk for rapid insulin deficiency, DKA**
- Glucocorticoids not useful (tried in n=4)
- *Insulin deficiency usually persists with higher glycemic variability and more challenging management than classic type 1 diabetes*

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Case 2

- 54-year-old M with prediabetes (HbA1c 6.2%) and non-small cell lung cancer was started on gemcitabine and cisplatin which required dexamethasone on the day of chemotherapy (day 1), and daily for the subsequent 2 days (days 2 and 3)
- Random PG 246 mg/dL and polyuria that interrupted his sleep
- SMBG before breakfast and dinner
  - Pre-breakfast: 162–196 mg/dL on days 2, 3, and 4; 128–156 mg/dL on day 5 and beyond
  - Pre-dinner: 268 to 395 mg/dL on day 1, 2 and 3; 190–220 mg/dL on day 4; <200 mg/dL by day 5

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Steroid-induced Diabetes: Pathogenesis

- Induction of insulin resistance through down-regulation of glucose transporter 4 (GLUT4)
- Increased gluconeogenesis in the liver
- Decreased insulin secretion at the pancreatic islet cell
- Reduced binding of insulin to the insulin receptor

1. *Perez A, et al. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014;6(1):9–20*
2. *Oyer DS, et al. How to manage steroid diabetes in the patient with cancer. J Support Oncol. 2006;4(9):479–83.*

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Steroid-induced Diabetes: Presentation

- Post-meal hyperglycemia is typical on dose equivalents of >10 mg prednisone or equivalent
- New diabetes OR 1.4 to 2.3; 2-50% rate of hyperglycemia
- Risk factors: duration of treatment, increased age, increased weight, prior glucose intolerance, family history diabetes
- Best criterion is a random PG >200 mg/dL, and ideally patients should perform SMBG both pre-meal and 2 h post-meal, especially focusing on lunch and dinner

1. *Perez A, et al. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014;6(1):9–20.*
2. *Tamez-Pérez HE, et al. Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. World J Diabetes. 2015;6(8):1073–81.*
3. *Oyer DS, et al. How to manage steroid diabetes in the patient with cancer. J Support Oncol. 2006;4(9):479–83.*

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Steroid-induced Diabetes: Diagnosis & Management

Prior History of Diabetes, Not on Insulin

Glucose ≥ 140 mg/dL fasting or ≥ 200 mg/dL random[a], adherent to diabetes medications

Daily Glucocorticoids

(Dexamethasone ≥ 2mg/ day or Prednisone ≥ 10mg/day)

NPH Insulin prior to AM meal added to usual DM regimen; CDCES consultation
- Generally, can start with NPH 0.15 units per kg[b]
- Titrate up by 2 units every 1-2 days to achieve pre-dinner glucose < 200 mg/dL
- Add evening dose after 1 week if fasting glucose >180 mg/dL
- Titrate evening dose by 2 units every 1-2 days to achieve fasting glucose < 180 mg/dL

Intermittent Dose Glucocorticoids (daily on and after treatment days)

Prednisone, Methylprednisolone:	Dexamethasone:
Dose insulin on every day glucocorticoid is given	Dose insulin on every day dexamethasone is given plus 2 additional days

Alternative or if NPH ineffective after 4 weeks: Use premixed insulin prior to AM meal
- Generally, can start with premixed 0.2 units per kg (or same dose as previous NPH, whichever is lower)[b]
- Titrate up by 2 units every 1-2 days to achieve pre-dinner glucose <200 mg/dL
- Add evening dose after 1 week if fasting glucose >180 mg/dL
- Titrate evening dose up by 2 units every 1-2 days to achieve fasting glucose < 180 mg/dL
- If steroid is intermittent, use response at last cycle to inform insulin dosing in next cycle

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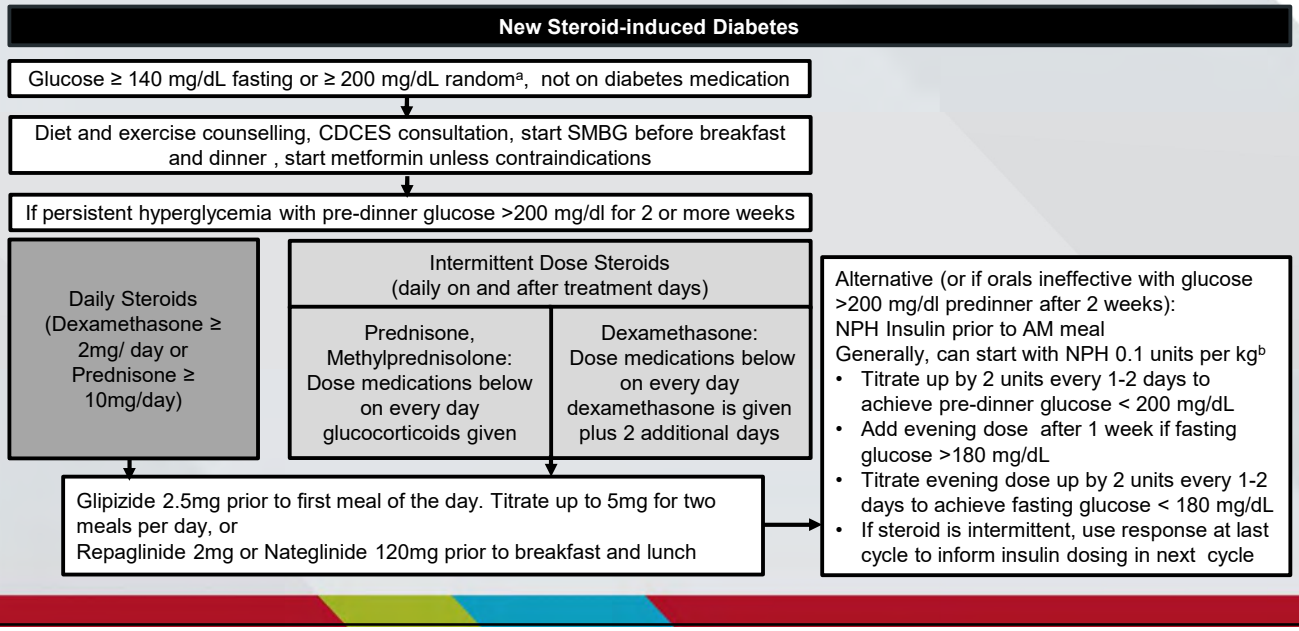
Steroid-induced Diabetes: Diagnosis & Management



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Steroid-induced Diabetes: Management caveats

- Consider steroid pharmacokinetics, steroid dose, frailty, weight, food intake, and renal function
- NPH usually with daily prednisone to cover post-prandial hyperglycemia and return of relative insulin sensitivity overnight
  - RCTs of NPH vs. MDI in hospital setting do not show superiority
- For patients already on insulin
  - Focus on increasing prandial coverage: basal 25%, mealtime 30–50%
- Steroids may unmask underlying insulin resistance
- Consider half-life steroid: insulin required up to 2 days after dexamethasone

Aberer F, et al. A practical guide for the management of steroid induced hyperglycaemia in the hospital. J Clin Med. 2021;10(10):2154.

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Case 3

A 53-year-old woman with metastatic breast cancer and no history of DM developed hyperglycemia with a PG of 208 mg/dL a week after initiation of alpelisib, a PI3K inhibitor, 1000 mg twice daily. Her SMBG continued to rise ranging from 200 to 260 mg/dL; hence, empagliflozin 10 mg daily was initiated. Hyperglycemia improved after alpelisib dose reduction but worsened again to 200–300 mg/dL after dose increase leading to initiation of insulin detemir 0.2 units/kg every evening and increased empagliflozin. On this regimen, she achieved an average SMBG below 200 mg/dL. Unfortunately, she had disease progression and alpelisib was discontinued as were the DM medications; 1 week later, her fasting PG was again less than 100 mg/dL.

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PI3KI-induced Diabetes: Pathogenesis

- 4 FDA-approved: alpelisib, copanlisib, idelalisib, and duvelisib
- PI3Kα isoform mediates uptake of glucose into skeletal and adipose tissues and regulates hepatic glycogenolysis and gluconeogenesis
- alpelisib and copanlisib that target α isoform are commonly associated with insulin resistance and hyperglycemia,
  - whereas idelalisib and duvelisib are not.

Goncalves MD, et al. Phosphatidylinositol 3-kinase, growth disorders, and cancer. N Engl J Med. 2018;379(21):2052–62

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PI3KI-induced Diabetes: Presentation

- The most commonly reported severe or life-threatening adverse effect of PI3Kα inhibitors is hyperglycemia, with an incidence of 50–64%
- Some risk factors: age less than 65 years, pre-existing type 2 DM and maximum fasting PG >153 mg/dL at baseline, BMI over 25 kg/m2, and Asian race
- Alpelisib-treated patients, the fasting glucose levels generally peak within the first 2 weeks of treatment, while

copanlisib tends to result in a transient hyperglycemia where glucose levels peak 5 to 8 h post-infusion and return to baseline levels prior to the next infusion

1. *Shields M, et al. A systematic review and meta-analysis of selected toxicity endpoints of alpelisib. Oncotarget. 2020;11(42).*
2. *Goldman JW, et al. Hyperglycemia associated with targeted oncologic treatment: mechanisms and management. Oncologist. 2016;21(11):1326–36.*
3. *Rugo HS, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with Hrpositive advanced breast cancer. Ann Oncol. 2020;31(8):1001–10.*

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PI3KI-induced Diabetes: Management caveats

- Only approved for advanced disease (alpelisib for advanced and metastatic breast cancer and copanlisib for relapsed follicular lymphoma) → usually poor prognosis so glycemic target is higher than diabetes or hyperglycemia from CPIs and glucocorticoids
- Prioritize insulin sensitizers: metformin remains the most utilized in clinical trials and mechanistically should improve insulin sensitivity
- Minimize use of agents that activate insulin-signaling pathways: endogenous insulin and hyperinsulinemia states with tumor growth and development so we avoid sulfonylureas
- Use insulin if necessary

1. *Busaidy NL, et al. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. J Clin Oncol. 2012;30(23):2919–28.*
2. *Lawrence RD. Renal threshold for glucose: normal and in diabetics. Br Med J. 1940;1(4140):766–8.*
3. *Novosyadlyy R, et al. Insulin-mediated acceleration of breast cancer development and progression in a nonobese model of type 2 diabetes. Cancer Res. 2010;70(2):741–51.*

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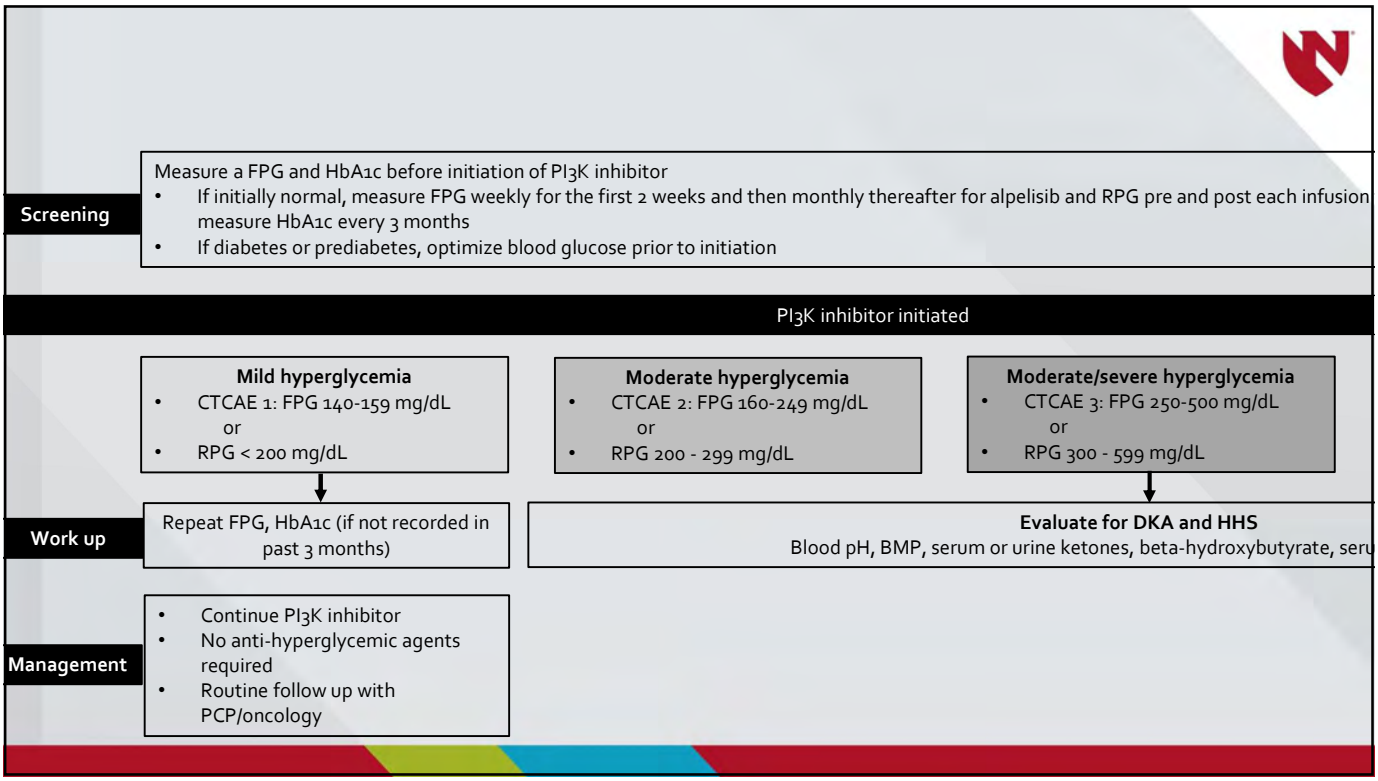
Screening
Measure a FPG and HbA1c before initiation of PI3K inhibitor
If initially normal, measure FPG weekly for the first 2 weeks and then monthly thereafter for alpelisib and RPG pre and post each infusion measure HbA1c every 3 months
If diabetes or prediabetes, optimize blood glucose prior to initiation
PI3K inhibitor initiated
Mild hyperglycemia
CTCAE 1: FPG 140-159 mg/dL
or
RPG < 200 mg/dL
Moderate hyperglycemia
CTCAE 2: FPG 160-249 mg/dL
or
RPG 200 - 299 mg/dL
Moderate/severe hyperglycemia
CTCAE 3: FPG 250-500 mg/dL
or
RPG 300 - 599 mg/dL
Work up
Repeat FPG, HbA1c (if not recorded in past 3 months)
Evaluate for DKA and HHS
Blood pH, BMP, serum or urine ketones, beta-hydroxybutyrate, seru
Management
Continue PI3K inhibitor
No anti-hyperglycemic agents required
Routine follow up with PCP/oncology

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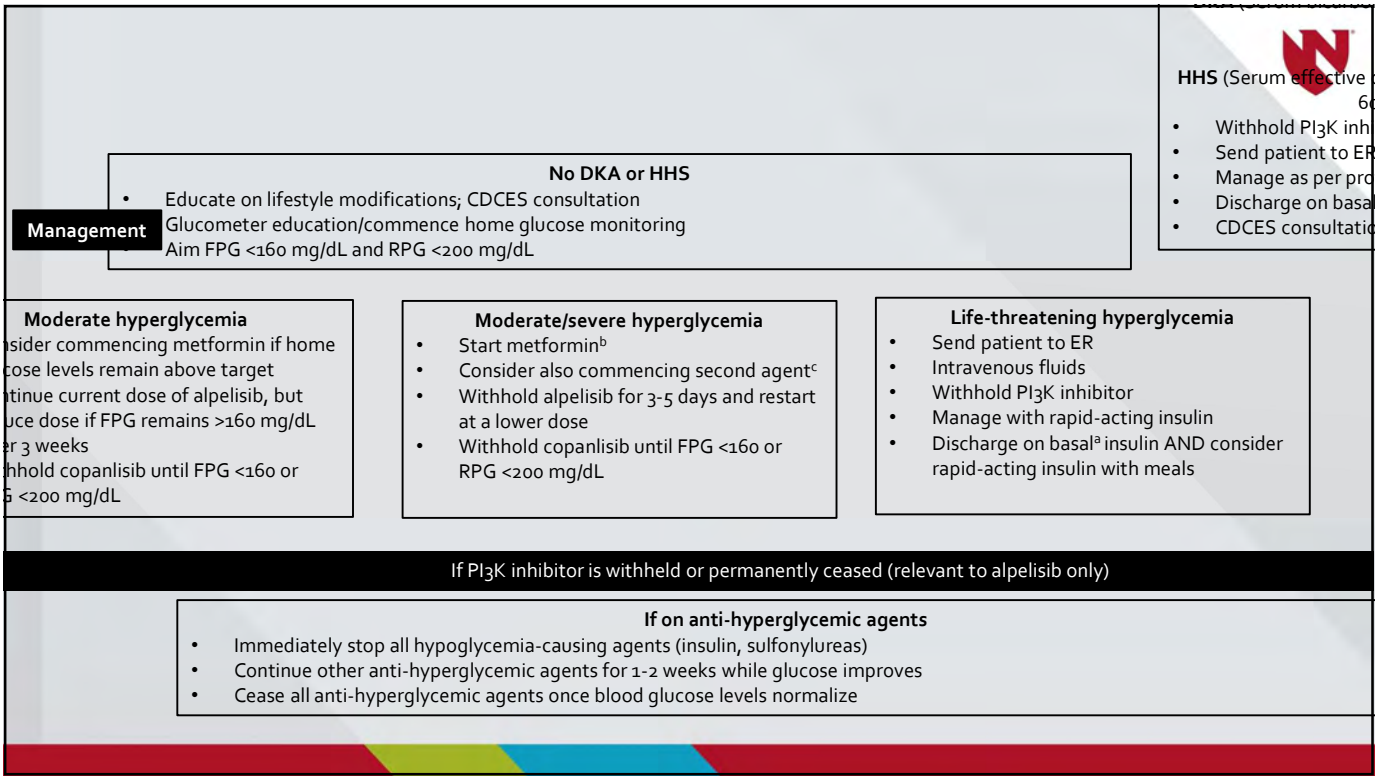
HHS (Serum effective
Withhold PI3K inh
Send patient to ER
Manage as per pro
Discharge on basal
CDCES consultatio
Management
No DKA or HHS
Educate on lifestyle modifications; CDCES consultation
Glucometer education/commence home glucose monitoring
Aim FPG <160 mg/dL and RPG <200 mg/dL
Moderate hyperglycemia
nsider commencing metformin if home
cose levels remain above target
ntinue current dose of alpelisib, but
uce dose if FPG remains >160 mg/dL
er 3 weeks
hhold copanlisib until FPG <160 or
G <200 mg/dL
Moderate/severe hyperglycemia
Start metformin[b]
Consider also commencing second agent[c]
Withhold alpelisib for 3-5 days and restart at a lower dose
Withhold copanlisib until FPG <160 or RPG <200 mg/dL
Life-threatening hyperglycemia
Send patient to ER
Intravenous fluids
Withhold PI3K inhibitor
Manage with rapid-acting insulin
Discharge on basal[a] insulin AND consider rapid-acting insulin with meals
If PI3K inhibitor is withheld or permanently ceased (relevant to alpelisib only)
If on anti-hyperglycemic agents
Immediately stop all hypoglycemia-causing agents (insulin, sulfonylureas)
Continue other anti-hyperglycemic agents for 1-2 weeks while glucose improves
Cease all anti-hyperglycemic agents once blood glucose levels normalize

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Care of the Cancer Patient with Diabetes: Concluding remarks

- Care of the cancer patient with hyperglycemia/diabetes is complex
- CPIs: rapid referral capacity can prevent DKA and hospitalizations
- Steroids: endocrinologists should be involved in dose adjustments
- Liberalize glucose targets based on comorbidities, use of CGM to minimize finger-sticks, enhance in-person or remote access, specific dietary recommendations
- “Meet patients where they are” literally and figuratively to improve their quality of life
- As a cancer patient moves from intensive to maintenance therapy, and hopefully to surveillance and survivorship, management of metabolic disease requires an inter-disciplinary approach.

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