Ketone Management with AID Systems

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Disclosures

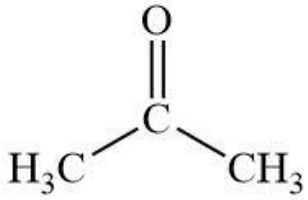
- Research: Medtronic, Dexcom, Abbott, Tandem, Insulet, Beta Bionics, Luna Health, and Lilly

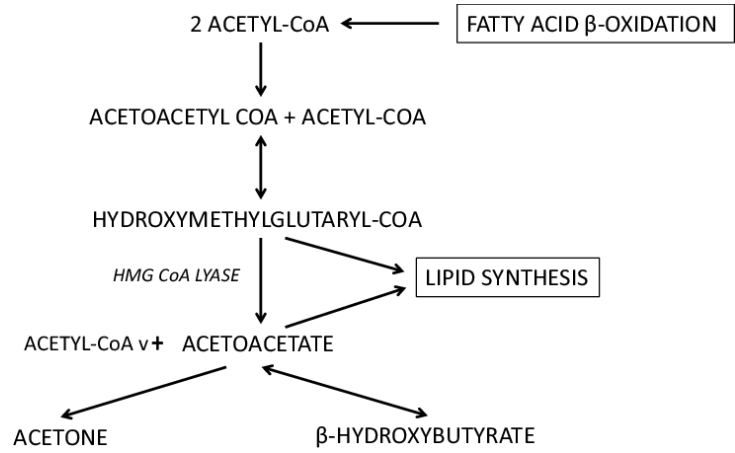
- Speaking, Ad Board: Dexcom, Insulet

Learning Objectives

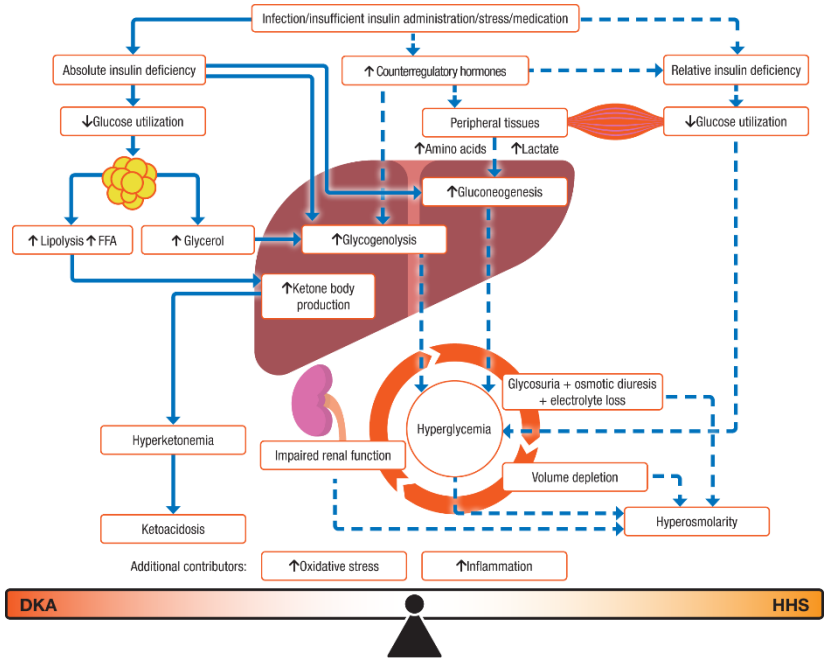
- Understand what ketones are and why they might occur in people using AID systems
- Understand how to test for ketones
- Review ketone management in insulin pumps and AID systems
- Introduce the future of ketone monitoring

Ketones





- Ketones are a breakdown product of fat
- Occur in higher quantities during periods of fasting
- In diabetes, ketones are also produced at higher rates
  - During relative lack of insulin (missed insulin doses, stressors that produce insulin resistance, etc), illnesses (especially vomiting), prolonged fasting and low carbohydrate diets



Umpierrez G, et al. Diabetes Care 2024

Glaser N, et al. Pediatr Diabetes. 2022
Umpierrez G, et al. Diabetes Care 2024

Diabetic Ketoacidosis Criteria

Joint Consensus Statement

DKA	A. DKA Diagnostic Criteria	
	Diabetes/hyperglycemia	Glucose ≥200 mg/dL (11.1 mmol/L) OR prior history of diabetes
	Ketosis	β-Hydroxybutyrate concentration ≥3.0 mmol/L OR urine ketone strip 2+ or greater
	Metabolic Acidosis	pH <7.3 and/or bicarbonate concentration <18 mmol/L

Table 2—DKA classification and suggested level of care by severity: mild, moderate, or severe

	Mild DKA	Moderate DKA	Severe DKA
"D": history of diabetes or elevated glucose level	Glucose ≥200 mg/dL (11.1 mmol/L)	Glucose ≥200 mg/dL (11.1 mmol/L)	Glucose ≥200 mg/dL (11.1 mmol/L)
"K": ketonemia	β-Hydroxybutyrate 3.0–6.0 mmol/L	β-Hydroxybutyrate 3.0–6.0 mmol/L	β-Hydroxybutyrate >6.0 mmol/L
"A": acidosis	• pH >7.25 to <7.30 or bicarbonate 15–18 mmol/L	• pH 7.0–7.25 • Bicarbonate 10 to <15 mmol/L	• pH <7.0 • Bicarbonate <10 mmol/L
Mental status	Alert	Alert/drowsy	Stupor/coma
Suggested level of care	Regular or observation nursing unit	Step-down unit or intermediate care unit	Intensive care unit

Not all variables need to be fulfilled to be defined as either mild, moderate, or severe, and the admission site and level of care are ultimately a clinical decision.

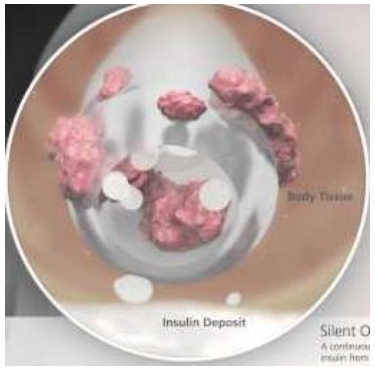
ISPAD Guidelines

- Hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dl])
- Venous pH <7.3 or serum bicarbonate <18 mmol/L(C)
- Ketonemia (blood ß-hydroxybuyrate ≥3 mmol/L) (C) or moderate or large ketonuria.

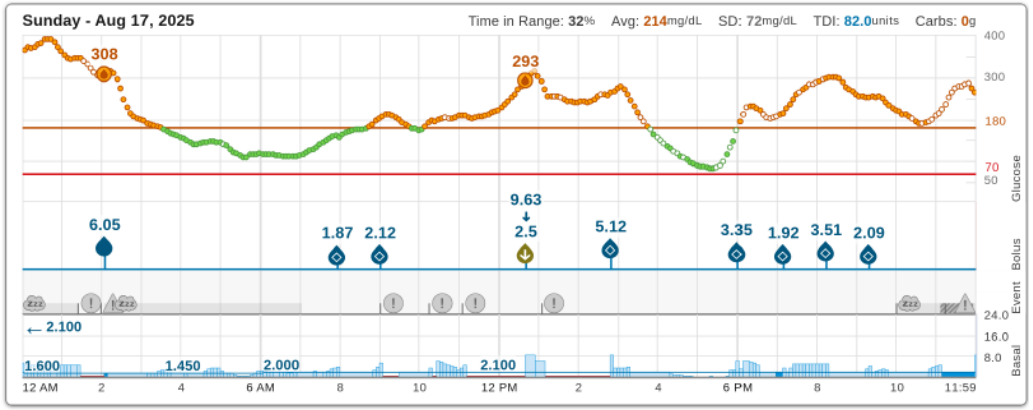
- Mild: venous pH < 7.3 or serum bicarbonate <18 mmol/L[24]
- Moderate: pH < 7.2 or serum bicarbonate <10 mmol/L
- Severe: pH < 7.1 or serum bicarbonate <5 mmol/L

Ketone Development in AID Users

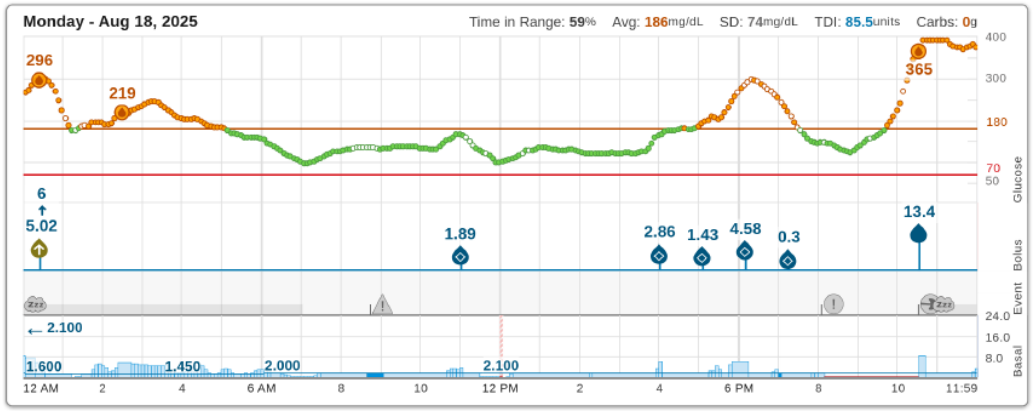
- Insulin deficiency (missing insulin)
  - In pump users specifically:
    - Infusion site failure
    - Pump battery failure
    - Run out of insulin
    - Prolonged insulin suspension (algorithmic or manual)



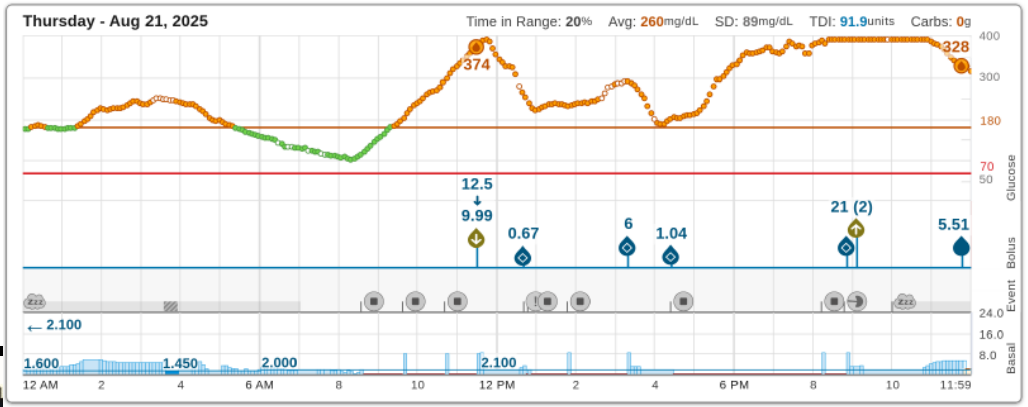
Wadwa RP, et al Pediatr Diabetes 2017



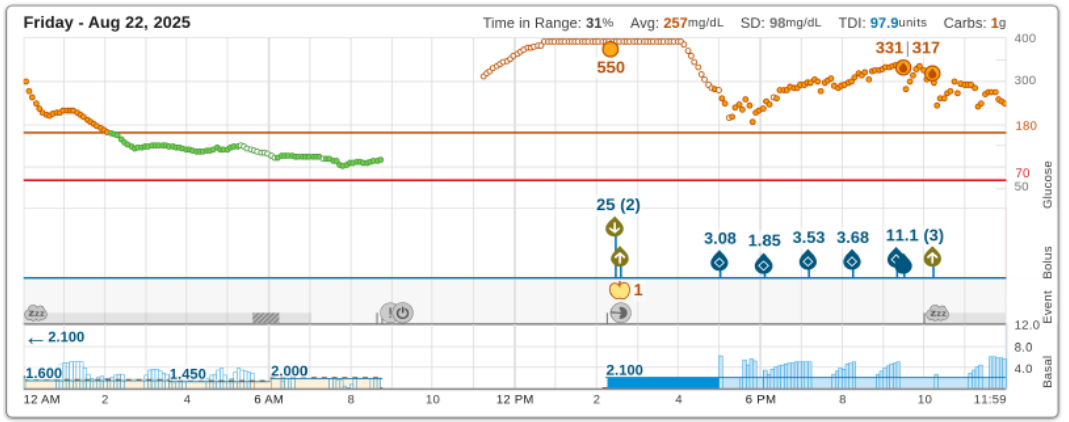
Pump Alarms: 1:25 AM - Low Power; 9:01 AM - Occlusion; 10:15 AM - Occlusion; 11:05 AM - Occlusion; 1:04 PM - Occlusion. **CGM Alerts:** 1:59 AM - CGM Out of Range; 11:14 PM - CGM Out of Range.



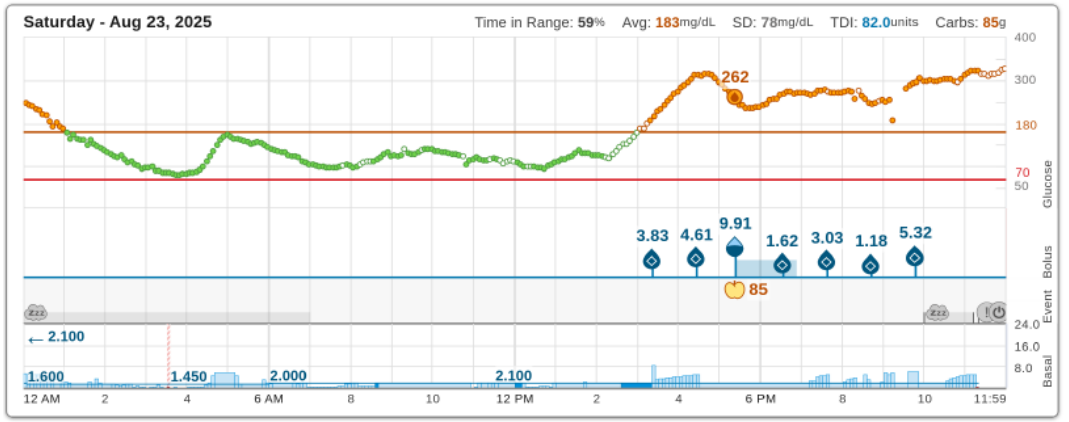
Pump Alarms: 8:05 PM - Empty Cartridge. **CGM Alerts:** 8:44 AM - CGM Out of Range.



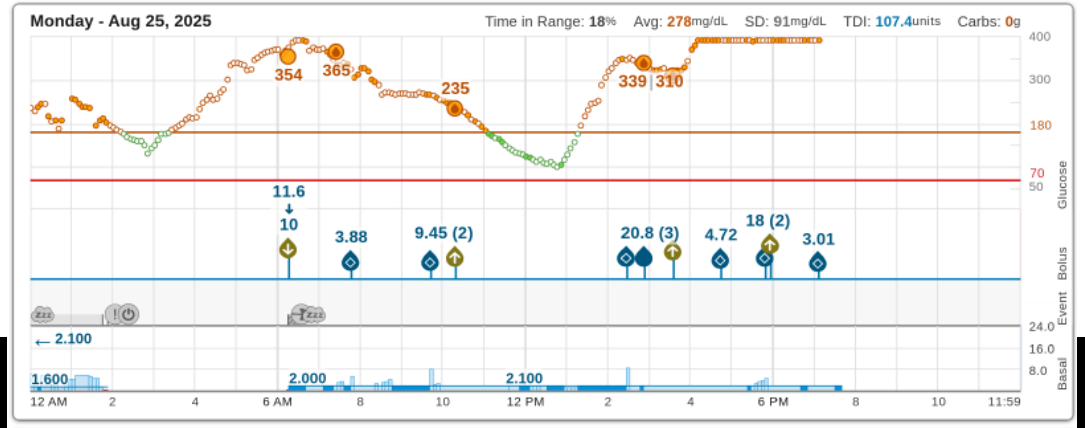
Pump Alarms: 12:40 PM - Occlusion.



Pump Alarms: 8:38 AM - Low Power.



Pump Alarms: 11:12 PM - Low Power.



Pump Alarms: 1:45 AM - Low Power.

Ketone Development in AID Users

- Illnesses
  - Relative insulin deficiency
- Stress and trauma
  - Relative insulin deficiency
- Prolonged fasting
  - Breakdown of alternative fuels

DKA in AID Users

- Mixed reports on risk for DKA in people utilizing insulin pumps

- Report from Sweden (N=99 children <18 yo):
  - Of DKA admissions, 74.7% CSII, 25.3% MDI
  - 85.2% of mild DKA ($p<0.001$) and 57.9% of moderate/severe DKA ($p=0.82$) was in pump users
  - HbA1c was higher in MDI users at DKA admission ($p<0.05$)
  - 98.1% of pump users and 68.2% of MDI users reported having access to ketone meters at home
  - CGM use was 55.7% of pump users and 28.0% of MDI users (overall population use is around 90+% for both)

- Report from the DPV (Germany, Austria, Switzerland, Luxembourg) (N=13,922, aged 2-20 yo)
  - Higher rate of DKA in closed-loop vs open-loop ($p<0.0001$), but lower HbA1c in closed-loop vs open-loop ($p<0.001$)

- A US based report of 15,104 admissions (7547 pump and 7557 matched controls)
  - 20.9% vs 20.4% of admissions were for DKA (pump vs control)

Wersall J, et al Pediatr Diabetes, 2022
Karges B, et al The Lancet, 2025
Alshami A, et al J Clin Med, 2021

Testing for Ketones

- Urine ketones
  - Measures acetoacetate
  - Compare color after 30-60 seconds with the color chart
  - 2-4 hours behind blood levels
  - Cheaper
  - More burdensome (have to find bathroom, etc)

- Blood ketones
  - Whole blood sample
  - Measures β-hydroxybutyrate
  - Provides real-time ketone levels
  - More expensive
  - Easier to use than urine

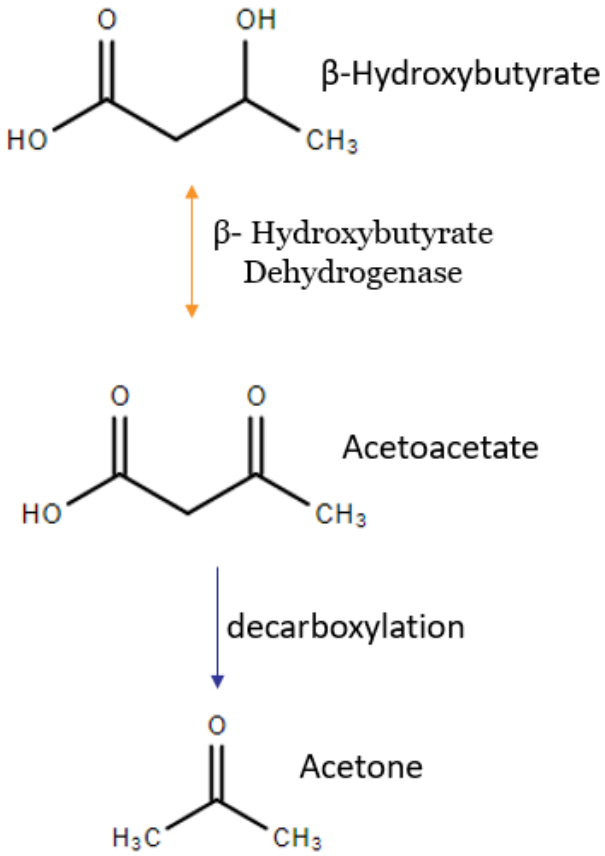
- Breath ketone analyzer
  - Measures exhaled acetone
  - Can be impacted by alcohol consumption
  - May be dependent on technique (more difficult in younger children)
  - Not as accurate for T1D (especially for kids)
  - Primarily marketed for those on keto-diets (without diabetes)

Akturk, Cobry J Diabetes Complications 2021

Urine Testing

Blood ketone testing

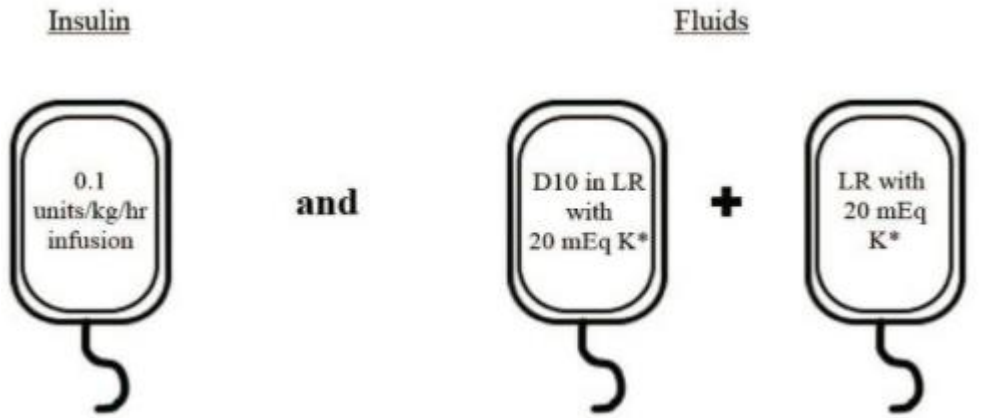
Breath ketone analyzer



Misra & Oliver, Diabetes Medicine, 2015

Treatment for Ketones

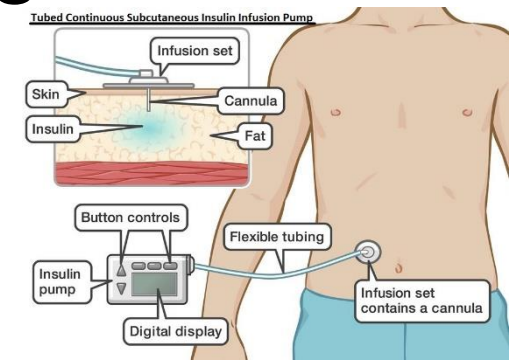
- Fluids – flush out ketones
- Insulin
- Carbohydrates (under certain circumstances)
- If significant (ie DKA), often require hospital management
  - If mild, often can be treated at home

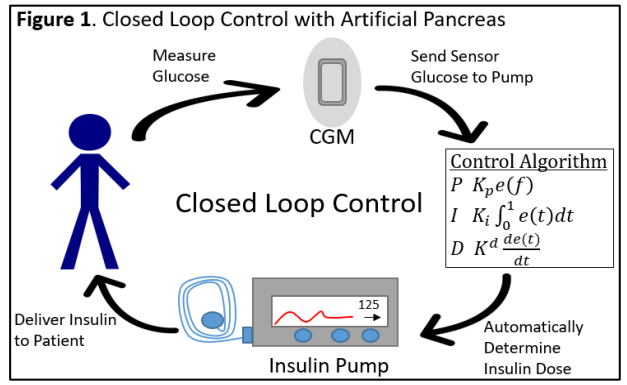


Automated Insulin Delivery (AID) Systems

- Hybrid Closed-Loop
  - For best results, requires user-initiated boluses for carbohydrate intake

- Fully Closed-Loop
  - Minimal user engagement, no carbohydrate or correction boluses required
  - Reduces burden
    - But potentially reducing awareness





Existing Commercial Automated Insulin Delivery Systems

- **Medtronic MiniMed 780G AHCL**:
  - Approved in 2023
- **Tandem t:slim X2 with Control IQ**:
  - Approved in 2019
    - **Tandem Mobi**: Approved in 2023
- **Insulet Omnipod 5**:
  - Approved in 2022
- **Beta Bionics iLet**:
  - Approved in 2023
- **Sequel twiist:**
  - Approved in 2024

MiniMed™ 780G

Tandem® t:slim X2™ and Mobi

Omnipod 5™

iLet Bionic Pancreas™

Sequel twiist™

Ketone Management with AID Systems

- Ketones develop due to the same reasons as other pump users
  - Infusion site failure
  - Pump battery failure
  - Running out of insulin
  - Prolonged insulin suspension (manual)
  - Illnesses/stress
- Unique to AID systems
  - Prolonged insulin suspension (automated)
- There is not consistency in guidelines for ketone management
- Not all institutions have defined protocols for ketone management
  - Fewer in relation to AID systems specifically

Marks B, et al Horm Res Paediatr, 2024

Special Considerations with AID Systems

- Lack of insulin (infusion set failure, pump battery failure, empty cartridge)
  - Change infusion site (if not otherwise explainable)!!
  - Ensure routine pump battery charging
  - Adjust alarms to avoid low cartridge
  - Remind to check for insulin and battery regularly (ie at bedtime)

- Illness (and steroid use) may require higher insulin doses due to stress response and insulin resistance
  - Some pumps have temporary basal rate features to temporarily increase insulin delivery
    - Depends on the pump what a temporary rate does (impacts automation or not)
  - Some pumps take days to “learn” insulin needs and won’t respond quickly enough
    - May need to temporarily exit automation (can use a static temp basal rate or new profile)
    - And/or do injection doses

Special Considerations with AID Systems

- AID systems in general don't have a mechanism for "ketone" dosing of insulin
  - Giving more insulin than recommended may result in an insulin on board (IOB) amount that reduces other insulin delivery (basal and/or autocorrections)
  - Either discontinue the AID temporarily or monitor closely with frequent ketone testing and manual insulin dosing
- iLet does not have "correction" doses or manual boluses
  - Unable to provide a "ketone" bolus through the pump
  - Recommend disconnecting and giving injection insulin until resolved
- Medtronic does not allow manual boluses in Smart Guard
  - Must go into manual mode to manually dose insulin

Special Considerations with AID Systems

- Do we need separate protocols for AID vs pump?
  - How complicated do we want to make it for patients?
  - Major issue with ketone management is the lack of giving an injection and changing the site?
    - We should be reinforcing this with all pump and AID users
  - Due to the glucose-responsive nature, if glucose is dropping due to the injected insulin, the AID algorithm will decrease insulin delivery, potentially suspending further insulin administration.
    - Insulin needs are very high during ketosis, so risk of hypoglycemia may be low
  - What is of more concern, treating the ketones and getting insulin to avoid DKA and hospitalization or potentially managing a post treatment hypoglycemic event?
    - Potential for delayed insulin restart and worsening or return of ketosis (if exiting automation or suspending pump)
  - No evidence on frequency of post-ketone injection hypoglycemia to know if it is a true issue or if this is theoretical.
  - What are AID users really doing?
    - Do they suspend AID after the injection, or do they just do their injection, change the site, and then run the pump as normal?
    - Most likely they are running the pump as normal.

- Panther Program
  - Hyperglycemia with Insulin Pump
  - Pantherprogram.org
  - In conjunction with our general sick day guidelines
- Hard to create a single AID-specific protocol due to unique features of each AID system
- Is there utility in creating device specific guidelines?

If your glucose has been over 300 mg/dL for 2 hours or more, check ketone levels and follow the steps in the chart below...

Ketone levels:

0.1-0.9 mmol/L
= **normal** to **small** ketones

1. **Give correction bolus via insulin pump**
2. **Recheck glucose and ketone levels in 2 hours**
   a. If your glucose is still ***over*** **250 mg/dL** **AND** ketone levels are ***below*** **1.0 mmol/L**, change infusion set and give correction bolus with new infusion set every 2 hours until glucose is below 180 mg/dL
   b. If your glucose is still ***over*** **250 mg/dL** **AND** ketone levels are **1.0 mmol/L** ***or more***, follow the instructions below based on the ketone level
   c. If glucose is ***below*** **250 mg/dL**, you may continue using your current infusion set. Give correction bolus every 2 hours until glucose is below 180 mg/dL

1.0-2.5 mmol/L
= **moderate to large** ketones

1. **Give injection of insulin by syringe or pen NOW (not through pump)**
   You will need more insulin than your usual correction dose because of the ketones. Talk to your diabetes care team about how to calculate your dose.
2. **Change infusion set**
3. **Drink water**
4. **Recheck glucose and ketone levels every 2 hours** and give correction bolus with new infusion set every 2 hours after syringe/pen injection until ketones are below 1.0 mmol/L and glucose is below 180 mg/dL

>2.5 mmol/L
= **extra large** ketones

1. **Give injection of insulin by syringe or pen NOW (not through pump)**
   You will need more insulin than your usual correction dose because of the ketones. Talk to your diabetes care team about how to calculate your dose.
2. **Change infusion set**
3. **Follow ALL steps for "ketones 1.0-2.5 mmol/L" and CALL your diabetes care team** if ketone levels are not decreasing 2 hours after you gave insulin dose by syringe/pen

Go to the ER or CALL 911 if experiencing confusion, frequent vomiting, or rapid breathing

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Rady Children's (courtesy of Christy Byer-Mendoza)

Ketone Action Plan when using an Insulin Pump

Urine Ketones: Negative, Trace or Small or **Blood ketones:** 0.0 to 0.6 mmol/L	✓ Give normal correction bolus through the insulin pump. ✓ Recheck glucose levels and ketone levels in 2 hours. ☐ After 2 hours, if glucose levels are **below 250 mg/dl**, you may continue to use your current infusion set. Give correction bolus every 2 hours until glucose is below 180 mg/dl. ☐ After 2 hours, if glucose level is **greater than 250 mg/dl** and ketone levels are small or less: o Change infusion set (including cartridge/reservoir and insulin) o Give correction bolus every 2 hours through pump until glucose is below 180 mg/dl ✓ If ketones are moderate-large (above 0.6 mmol/L), follow plan below ✓ Ok to exercise.
Urine Ketones: Moderate or **Blood ketones:** 0.6 to 1.5 mmol/L	**If glucose is below 130 mg/dl, please contact our diabetes team at 858-966-4032, option 2.** **If glucose is greater than 130 mg/dl, follow instructions below:** **Give injection of insulin by syringe or pen NOW (not through pump)** ☐ If correction factor is **50 or less**, add 2 units of insulin to your usual correction. ☐ If correction factor is **51-100**, add 1 unit of insulin to your usual correction. ☐ If correction factor is **100-200**, add 0.5 units of insulin to your usual correction. ☐ If correction factor is **greater than 200**, please call the Diabetes team. ✓ Change infusion set. ✓ Recheck glucose and ketone levels every 2 hours; give correction (usual dose PLUS additional as directed above) through new infusion set every 2 hours until ketones are negative, trace, or small (blood ketones below 0.6 mmol/L) and glucose is below 180 mg/dl. ✓ Drink water. No exercise until ketones are small, trace, or negative (blood ketones less than 0.6 mmol/L).
Urine Ketones: Large or **Blood ketones:** above 1.5 mmol/L	**If glucose is below 130 mg/dl, please contact our diabetes team at 858-966-4032, option 2.** **If glucose is greater than 130 mg/dl, follow instructions below:** **Give injection of insulin by syringe or pen NOW (not through pump)** ☐ If correction factor is **50 or less**, add 3 units of insulin to your usual correction. ☐ If correction factor is **51-100**, add 2 units of insulin to your usual correction. ☐ If correction factor is **100-200**, add 1 unit of insulin to your usual correction. ☐ If correction factor is **greater than 200**, please call the Diabetes team. ✓ Change infusion set. ✓ Recheck glucose and ketone levels every 2 hours; give correction (usual dose PLUS additional as directed above) through new infusion set every 2 hours until ketones are small, trace, or negative (blood ketones below 0.6 mmol/L) and glucose is below 180 mg/dl. ✓ Drink water. No exercise until ketones are small, trace, or negative (blood ketones less than 0.6 mmol/L). **If feeling unwell or if ketones are large for 4 hours or more, call the on-call doctor.**

If you are uncertain about any of these instructions, please call Rady's diabetes team at:

858-966-4032, option 2 - Monday through Friday from 8:30am to 4:30pm

Non-business hours, weekends, and holidays, call the hospital operator at 858-576-1700, press 0 and ask for the endocrinologist on call to be paged.

Ketone Action Plan when using an iLet Insulin Pump

Urine Ketones: Negative, Trace or Small or **Blood ketones:** 0.0 to 0.6 mmol/L	**Check to make sure:** ☐ iLet is charged, has insulin, and is displaying CGM values. ☐ Your infusion set is in place and not leaking. ☐ Continue to monitor glucose levels. ☐ If glucose remains above 250 mg/dl after 90 minutes, check ketones again. ✓ Ok to exercise.
Urine Ketones: Moderate or **Blood ketones:** 0.6 to 1.5 mmol/L	**Give injection of insulin by syringe or pen NOW (not through pump). Disconnect from iLet at the time of injection.** ☐ Drink water. ☐ Recheck glucose and ketone levels in 90 minutes. ☐ If ketones are small, trace or negative, insert a new infusion set and reconnect to the iLet. ☐ If ketones are moderate or large, call healthcare provider. ✓ No exercise until ketones are small, trace, or negative (blood ketones less than 0.6 mmol/L).
Urine Ketones: Large or **Blood ketones:** above 1.5 mmol/L	**Give injection of insulin by syringe or pen NOW (not through pump). Disconnect from iLet at the time of injection.** ☐ Drink water. ☐ Recheck glucose and ketone levels in 90 minutes. ☐ If ketones are small, trace or negative, insert a new infusion set and reconnect to the iLet. ☐ If ketones are moderate or large, call healthcare provider. ✓ No exercise until ketones are small, trace, or negative (blood ketones less than 0.6 mmol/L). **If feeling unwell or if ketones are large for 4 hours or more, call the on-call doctor.**

If you are uncertain about any of these instructions, please call Rady's diabetes team at:

858-966-4032, choose option for nurse - Monday through Friday from 8:30am to 4:30pm

Non-business hours, weekends, and holidays, call the hospital operator at 858-576-1700, press 0 and ask for the endocrinologist on call to be paged.

Future of Ketone Monitoring

- Current ketone testing methods are cumbersome, expensive, and only show point-in-time levels
- Abbott Diabetes Care has developed a continuous dual glucose ketone (DGK) sensor, currently under FDA review.
- Considerations include when to alert on a ketone level
  - (ie, show no data until ketones are over 1?)

Continuous Ketone Monitoring and AID

- The future of ketone integration into AID systems
  - How will algorithms use the ketone data?
  - If producing ketones, concern for infusion site failure, so AID automation may have limited impact.
  - May provide early notification of infusion site failures.

- Announcements have been made that Sequel twiist and Tandem Control-IQ will integrate with Abbott's continuous dual glucose ketone (DGK) sensor
  - For the time being, likely only as a data element to display, not impacting the algorithm itself?

Thank You!

- **The BDC APRN Research Team**
  - Gregory Forlenza, MD
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  - Emily Fivekiller, RN
  - Angela Karami
  - Lindsey Towers
  - Estella Escobar

- **Our patients and families**