Newly Diagnosed Type1 Diabetes

DERIC MORRISON

ASSOCIATE PROFESSOR OF ENDOCRINOLOGY

WESTERN UNIVERSITY

Resources

2018 Diabetes Canada Clinical Practice Guidelines

Evidence-based; largely outpatient focused

http://www.diabetes.ca (look under “For Professionals”)

Disclaimer

Classification of Diabetes

Type	Definition
Type 1 diabetes (including LADA form)	Pancreatic beta cell destruction, usually leading to absolute insulin deficiency (A)Immune mediated (B)Idiopathic
Type 2 diabetes	May range from predominantly insulin resistance insulin deficiency to a predominantly secretory defect with insulin resistance
Gestational Diabetes	Glucose intolerance with onset or first recognition in pregnancy
Other types	Variety of uncommon diseases, genetic forms, or diabetes associated with drug use

Clinical features	Type 1 diabetes	Type 2 diabetes	Monogenic diabetes
Age of onset (yrs)	Most <25 by can occur at any age (but not before the age of 6 months)	Usually >24 but incidence increasing in adolescents, paralleling increasing rate of obesity in children & adolescents	Usually <25 Neonatal diabetes <6 months*
Weight	Usually thin, but with obesity epidemic, can have overweight or obesity	>90% at least overweight	Similar to general population
Islet auto-antibodies	Usually present	Absent	Absent
C-peptide	Undetectable/low	Normal/high	Normal
Insulin production	Absent	Present	Usually present
First line treatment	Insulin	Non-insulin antihyperglycemic agents, gradual dependence on insulin may occur	Depends on subtype of MODY
Family history of diabetes	Infrequent (5-10%)	Frequent (75-90%)	Multigenerational, autosomal pattern of inheritance
DKA	Common	Rare	Rare (except for neonatal diabetes*)

*Neonatal diabetes is a form of diabetes with onset <6 months of age, requires genetic testing, and may be amenable to therapy with oral sulfonylurea in place of insulin therapy

Diagnosis of Diabetes

FPG ≥7.0 mmol/L

Fasting = no caloric intake for at least 8 hours

or

A1C ≥6.5% (in adults)

Using a standardized, validated assay in the absence of factors that affect the accuracy of the A1C and not for suspected type 1 diabetes

or

2hPG in a 75 g OGTT ≥11.1 mmol/L

or

Random PG ≥11.1 mmol/L

Random = any time of the day, without regard to the interval since the last meal

A1C, glycated hemoglobin; FPG, fasting plasma glucose; PG, plasma glucose

Confirmatory test required

- In the **absence of symptomatic hyperglycemia**, if a single lab test result is in the diabetes range, a **repeat confirmatory lab test** (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day
- **Repeat the same test** (in a timely fashion) to confirm
- But a **random PG** in the diabetes range in an **asymptomatic** individual should be **confirmed with an alternate test**
- If **results of two different tests** are available and **both are above** the diagnostic thresholds, the diagnosis of diabetes is **confirmed**

2hPG, 2-hour plasma glucose; *AIC,* glycated hemoglobin; *FPG,* fasting plasma glucose; OGTT, oral glucose tolerance test; *PG,* plasma glucose.

Confirmatory test NOT required

- In the case of **symptomatic hyperglycemia**, the diagnosis has been made and a confirmatory test is not required before treatment is initiated.

- To avoid rapid metabolic deterioration in individuals in whom **type 1 diabetes is likely** (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), the initiation of treatment should not be delayed in order to complete confirmatory testing

2hPG, 2-hour plasma glucose; *AIC,* glycated hemoglobin; *FPG,* fasting plasma glucose; OGTT, oral glucose tolerance test; *PG,* plasma glucose.

Considerations when using A1C for Diagnosis

- Need validated standardized assay
- Repeat confirmatory test on another day
- Recognize conditions leading to misleading A1C
- A1C is not used for diagnosis in children, adolescents (as the sole diagnostic test), pregnant women as part of routine screening for gestational diabetes, those with cystic fibrosis or those with suspected type 1 diabetes
- Ethnicity and age can affect A1C results

Key Messages

Type 1 diabetes = Insulin Deficiency

Type 2 diabetes = Insulin Resistance

Gestational diabetes is a type of diabetes that is first recognized or begins during pregnancy

Monogenic diabetes is a rare disorder caused by genetic defects of beta cell function

Obesity and physical signs of insulin resistance (e.g. acanthosis nigricans) are more common in children and adolescents with type 2 diabetes than type 1 diabetes. In adults, a systematic review of clinical indicators identified age at diagnosis of diabetes <30 to 40 years, and time to needing insulin <1 to 2 years as more predictive of type 1 diabetes than body mass index (BMI) (4).

The presence of autoimmune markers, such as anti-glutamic acid decarboxylase (GAD) or anti-islet cell (ICA) autoantibodies, may be helpful in identifying type 1 diabetes and rapid progression to insulin requirement (5), but levels wane over time and they do not have sufficient diagnostic accuracy to be used routinely (6). In cases where it is difficult to distinguish between type 1, type 2 and monogenic diabetes, presence of 1 or more autoantibodies (GAD and ICA) indicates type 1 diabetes with a need for insulin replacement therapy; however, the absence of autoantibodies does not rule out type 1 diabetes. If the person has clinical features suggestive of monogenic diabetes (familial diabetes with autosomal dominant pattern of inheritance >2 generations, onset <25 years, not having obesity), genetic testing for monogenic diabetes may be performed (7).

While very low C-peptide levels measured after months of clinical stabilization may favour type 1 diabetes (8), they are not helpful in acute hyperglycemia (9,10). Combined use of autoantibody testing and C-peptide measurement at diagnosis may have diagnostic and prognostic utility in pediatric diabetes, but requires further study (11) (see Type 2 Diabetes in Children and Adolescents chapter, p. S247). One study found that, among individuals presenting in diabetic ketoacidosis (DKA), those with 3 negative antibodies and fasting C-peptide levels >0.33 nmol/L (1 to 3 weeks after resolution of the DKA and 10 hours after the last dose of rapid- or intermediate-acting insulin or metformin, and 24 hours after the last dose of sulfonylurea or long-acting insulin) were often able to discontinue insulin, and be treated with noninsulin antihyperglycemic agents when blood glucose (BG) rose (12). Genetic risk scoring for type 1 diabetes may provide marginal additional information over clinical features and autoantibodies, but it is too early to know its utility in clinical practice (13). Clinical judgement with safe management and ongoing follow up is a prudent approach for all people diagnosed with diabetes, regardless of the type.

Case One

- 25 yr old woman previously well
- 7 days of polyuria and thirst
- 5 kg wt loss
- Visual fluctuations
- Nausea x 2 days then vomiting

→ Emerg Dept

Physical Exam

- Oriented but looks unwell
- Breath smells of fruit
- BP 100/50 lying, 70/- sitting
- HR 120 regular, RR 22 unlaboured
- Temp 38.0°C, O2 sat 98% on R/A
- Neck veins (lying flat) not seen
- Mild abdominal tenderness

Tests

- Random plasma glucose – 25.2 mM
- Serum creatinine/BUN – 116 µM/9.8 mM
- Serum Na and Cl – 130 and 98 mM
- Serum K and $HC0_3$ - 3.8 and 6.0 mM
- Serum osmolality – 295 mOsm/kg
- Arterial blood gases – 90/7.01/25/9
- WBC – 10.0^9 x 10/L
- HB - 150 g/L
- Urine ketones – 3+
- Serum ketones - positive

Serum Anion Gap

$Na - Cl - HCO_3$ Normal ~ 3 to 13 mM

Your patient: 130 – 98 – 6.0 = 26 mM

[(Na + K) – (Cl + HCO_3) Normal ~ 7 to 15 mM]

Diagnosis

- What is the diagnosis?

- What things precipitate this condition?
  - Things that start with “I”

Diagnosis

DKA

New-onset type 1 diabetes

Treatment?

Treatment

- Volume
  - IV Fluids: NS: rate?
- Electrolytes
  - Potassium!!
- Acidosis
  - Insulin
  - When to add Glucose to IV
  - HCO_3

Treatment

YOU

- IV fluids
- IV potassium
- IV insulin
- Precipitating cause (infection, adherence, ischemia, drugs, pregnant)
- Monitoring

MEDICINE

- Transition to SC insulin and PO diet
- Discharge planning

IV Fluids

1. Start an IV (18 gauge at least, 16 gauge if possible).

---

2. Give 0.9% NaCl 1 to 2 L/hr to correct shock (low BP).

3. Reduce IV NS to 500 ml/hr x 4 hrs then 250 ml/hr x 4 hrs

   depending on volume status.

4. When euvolemic, determine corrected serum [Na]*:
   - If corrected [Na] ≥ 135 mM, switch to 0.45% NaCl
   - If corrected [Na] < 135 mM, continue 0.9% NaCl

5. Add D5W to NaCl when blood glucose ≤ 14 mM

* Corrected [Na] = Lab [Na] + (0.3 x [glucose – 5])

Your patient: Lab Na = 130 mM and glucose = 25.2 mM

Corrected [Na] = 130 + (0.3 x [25.2 – 5]) = 136 mM

(for every 3 mmol/L BG over 8, add 10 meq Na)

IV Potassium

1. Don’t start IV insulin if serum $K^+ < 3.3$ mM.
2. Don’t start IV potassium if serum $K^+ > 5.0 – 5.5$ mM and/or the patient is anuric/AKI (catheterize patient if not sure).
3. Otherwise, start KCl 20 to 40 mmol/L IV per hour.
4. Follow serum lytes closely (see Monitoring slide).

Insulin (I)

1. Don’t start IV insulin if serum K^+ < 3.3 mM.
2. Never use “u” instead of “units”.
3. Give Regular insulin 0.1 units/kg by IV bolus, then 0.1 units/kg/hr by continuous IV infusion.

Your patient (~ 50 kg): Regular insulin 5 units IV bolus, then 5 units/hr by continuous IV infusion.

4. Check capillary blood (fingerstick) glucose levels q1h and notify MD with the result.
5. Adjust IV insulin rate to obtain a fall in blood glucose level of at least 3 mM/hr and ***to close the AG***.

Your patient (pre-insulin bolus/infusion glucose 25.2 mM) and the next glucose was 27.3 mM - increase Regular insulin IV infusion to 10 units/hr.

Insulin (II)

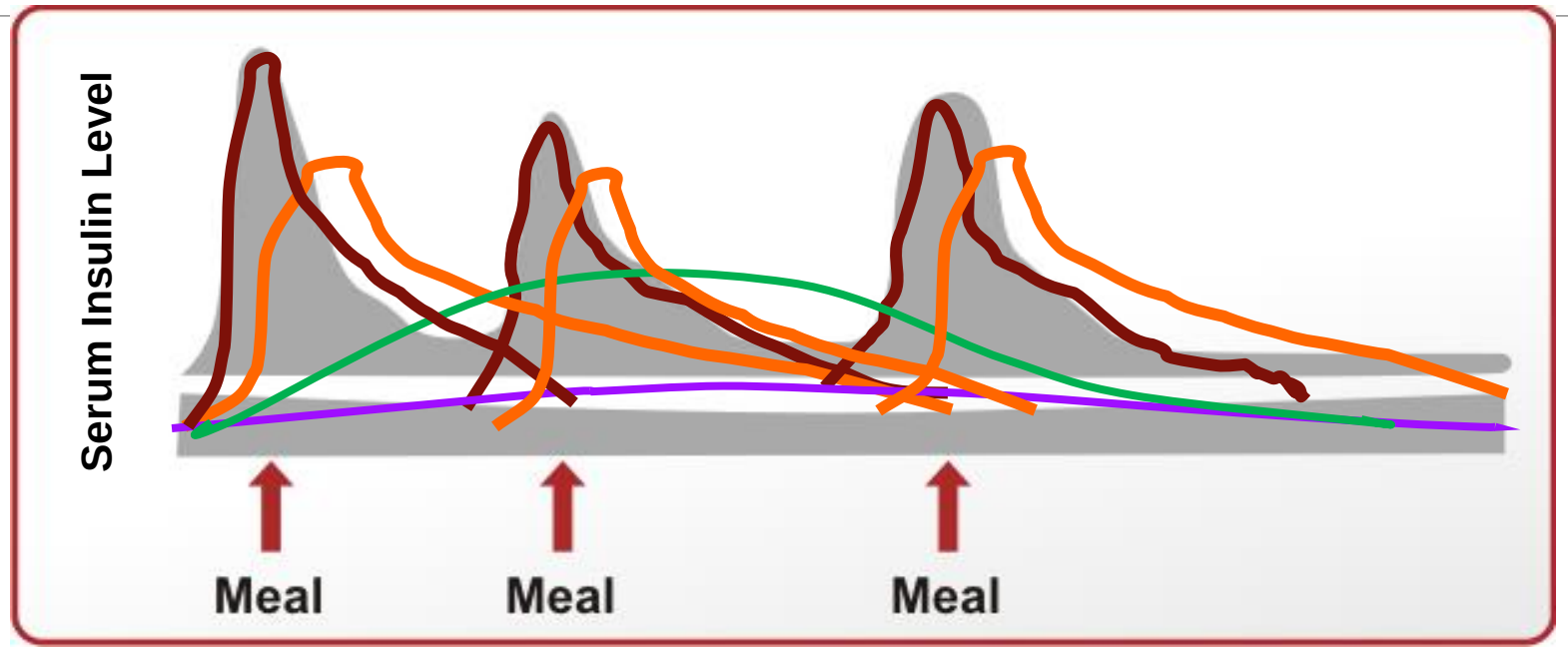
1. Change IV to D5W/0.45% NaCl when blood glucose level ≤ 14.0 mM.
2. Maintain glucose level ~ 11 mM on IV insulin.
3. Continue IV insulin infusion until the **anion gap is normal** and the patient can eat.
4. Start SC insulin:
    1. 0.5 to 0.8 units/kg/wt per day by MDI (basal-bolus)
    2. stop IV insulin infusion 2 hrs ***after*** SC insulin started (rapid acting at a meal)
    3. Transition over with short acting at meal not with Lantus/basal

Monitoring

1. Vital signs q1h x 4 then re-assess.
2. Measure ins/outs q1h x 8 hours then re-assess.
3. Capillary blood (fingerstick) glucoses q1h. Call results to MD.
4. Serum lytes, AG (the lab or you do this), random glucose, BUN, creatinine q2h x 4 then re-assess.
5. Use a flowsheet (EMR if **ALL** info available)
6. Sips to diabetic diet as tolerated unless there's a good reason for the patient to remain NPO.

Pharmacotherapy in Type 1 Diabetes Checklist

- ✓ USE basal-bolus injection therapy or continuous subcutaneous insulin infusion
- ✓ TAILOR insulin regimens to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status, and ability for self-management
- ✓ COUNSEL about the risk, prevention and treatment of insulin-induced hypoglycemia


Serum Insulin Level
Meal
Meal
Meal
Time
Human Basal
Analogue Basal
Human Bolus
Analogue Bolus

Types of insulin			
Insulin type (trade name)	**Onset**	**Peak**	**Duration**
BOLUS (prandial or mealtime) insulins			
Rapid-acting insulin analogues (clear) • Insulin aspart (NovoRapid®) • Insulin glulisine (Apidra®) • Insulin lispro (Humalog®) U-100 U-200 • Faster-acting insulin aspart (Fiasp®)	 9–20min 10–15min 10–15min 4min	 1–1.5h 1–1.5h 1–2h 0.5-1.5h	 3–5h 3.5–5h 3–4.75h 3-5h
Short-acting insulins (clear) • Insulin regular (Humulin®-R, Novolin® ge Toronto) • Insulin regular U-500 (Entuzity® (U-500)	 30min 15min	 2–3h 4-8h	 6.5h 17-24h
BASAL insulins			
Intermediate-acting (cloudy) • Insulin neutral protamine Hagedorn (Humulin® N, Novolin® ge NPH)	1–3h	5–8h	Up to 18h
Long-acting insulin (clear) • Insulin detemir (Levemir®) • Insulin glargine U-100 (Lantus®) • Insulin glargine U-300 (Toujeo®) • Insulin glargine biosimilar (Basaglar®) • Insulin degludec U-100, U-200 (Tresiba®)	90min	Not applicable	U-100 glargine 24h, detemir 16–24h U-300 glargine >30h degludec 42h
PREMIXED insulins			
Premixed regular insulin –NPH (cloudy) • Humulin® 30/70 • Novolin® ge 30/70, 40/60, 50/50	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Premixed insulin analogues (cloudy) • Biphasic insulin aspart (NovoMix® 30) • Insulin lispro/lispro protamine (Humalog® Mix25 and Mix50)			

Insulin Therapy in Type 1 Diabetes

BASAL – BOLUS INJECTION THERAPY

Bolus insulin at meal times + basal insulin once or twice a day

OR

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

"insulin pump therapy" with continuous subcutaneous infusion of insulin via a catheter

Must Counsel About Hypoglycemia

Must counsel all patients with type 1 diabetes about hypoglycemia: recognition, treatment, prevention

Assess risk factors for severe hypoglycemia

Assess for hypoglycemia unawareness and treat accordingly

Benefits of Continuous Subcutaneous Insulin Infusion (CSII)

For individuals using basal bolus injections (BBI), changing to CSII provides

- Small improvement in A1C
- Improved treatment satisfaction and diabetes specific related QOL
- Reduction in severe hypoglycemia if there is a high baseline rate of severe hypoglycemia (non-severe and nocturnal hypoglycemia unchanged)

BBI, basal-bolus insulin; *CSII*, continuous subcutaneous insulin infusion; *QOL*, quality of life

Yeh HC et al. Ann Intern Med 2012;157:336-47. Pickup JC et al. Diabet Med 2008;25:765-74.

Benefits of Continuous Glucose Monitoring (CGM)

If using BBI or CSII with SMBG, adding CGM with high sensor adherence provides

- Improvement in A1C with no increase in hypoglycemia
- Improvement in QOL, diabetes distress, fear of hypoglycemia

If using sensor-augmented pump (SAP) therapy with nocturnal hypoglycemia, using SAP with low glucose suspend provides

- Reduction in nocturnal hypoglycemia with no A1C increase

BBI, basal-bolus insulin; *CSII,* continuous subcutaneous insulin infusion; *CGM*, continuous glucose monitoring; *SMBG*, self-monitoring of blood glucose; *SAP,* sensor augmented pump; *QOL*, quality of life

Bergenstal RM et al. N Engl J Med 2010;363:311-20. Bergenstal RM et al. N Engl J Med 2013;368:224-32.

Adjunctive therapy in type 1 diabetes

Metformin, SGLT2 inhibitors (dapagliflozin, empagliflozin, sotagliflozin), GLP-1 receptor agonist (liraglutide) have been studied

Metformin did not provide sustained metabolic or CV benefits

SGLT2 inhibitors demonstrated some metabolic benefits but risk of DKA needs to be better understood

Liraglutide also showed some metabolic benefits but there are no current indications for use in type 1 diabetes

NO recommendation for adjunctive therapy

CV, cardiovascular; *DKA*, diabetic ketoacidosis

Key Messages

Basal-bolus insulin routines (i.e., multiple daily injections or continuous subcutaneous insulin infusion) are the preferred insulin management regimens for adults with type 1 diabetes

Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management

All individuals with type 1 diabetes should be counselled about the risk, prevention and treatment of hypoglycemia. Avoidance of nocturnal hypoglycemia may include changes in insulin therapy and increased monitoring

Key Messages

If glycemic targets are not met with optimized multiple daily injections, CSII may be considered. Successful CSII therapy requires appropriate candidate selection, ongoing support and frequent involvement with the health-care team

CGM may be offered to people not meeting their glycemic targets, who will wear the devices the majority of the time, in order to improve glycemic control

CGM, continuous glucose monitoring; *CSII*, continuous subcutaneous insulin infusion

Case

34 Healthy Female

Presents with urinary frequency and dysuria

Found to have glucosuria and yeast infection

FHx: T2DM 2 grand parents and uncle, mother hypothyroid

BMI: 34.5 kg/m2

A1c 10.7%

Management

Started on metformin, titrated to 1 g BID

Insulin Glargine 10 U qhs

Anti GAD +

Case

38 Healthy Male

~3 months thirst and polyuria, ~ 5 lb weight loss

Presented with glucose 17, anion gap 22, treated with SQ insulin 5 Units x3

Started on metformin500 mg BID, Sugars still 16-23

Family history: 1 grandfather with DM2

BMI 29, A1c 11%

Management?

Insulin

- Glargine 15 U daily and Lisproa 3/5/5 Units

Case

23 Healthy female

Presented with abdominal pain and vomiting

Family History: DM2 Grandmother and aunt, DM1 2 cousins

BMI 15.1 kg/m2

RBG 13, A1c 6.4%

Started on metformin

Diagnosis?

Case

Despite metformin 1g BID

Increasing polydipsia and polyuria

15 lb weight loss

BGs 11-20

Repeat A1c 14.8%

Diagnosis? Management?

Case

Insulin glargine 6 Units Daily

Lispro 3 Units as Meals

Case

6 months later

Glargine 16 Units daily

Lispro 3/5/4

3 kg weight gain

BGs 3.8-8.1

A1c 7.1%

Summary

Suspect DM1

Weight loss, hyperglycemic symptoms, family history, Lower BMI, younger age, ketosis

Treat with insulin if DM1 or ketosis or weight loss

Beware hypoglycemia/insulin sensitivity

Don’t interrupt insulin (basal) even if BG low or fasting

Start screening for complications ~ 5 yr post diagnosis

Questions?