

Standards in Diabetes Care: The Diabetes Clinic Experience

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Tasks for Today

- New guidelines from American Diabetes Association
- Experience with new onset Diabetes at WCHOB
- Autoimmune comorbidities at diagnosis
- Point of service care
- New research in Type 1 diabetes

American Diabetes Association Standards of Diabetes Care: 2010

- Published annually
- Recommendations based on new research and consensus statements
- Reinforcement of previous practices
- New standards in diagnosis and management
- Recommendations for adults and children

What's new in 2010 – Pertinent to Pediatric Care

- **Diagnosis of Diabetes**
 - FBS ≥ 126 (confirm)
 - 2 hr OGTT ≥ 200
 - Random blood > 200 with symptoms
 - **HbA1c $\geq 6.5\%$** (confirm)***
- HbA1c 5.7 – 6.4%, increased risk of diabetes

HbA1c in Diagnosis of Diabetes

- Use of HbA1c in the diagnosis of diabetes is new
 - Advantages – easy to perform, not dependent on time of day and fasting, more stable, not as affected by stress, well-established assay
 - Disadvantages – does not correlate with average blood sugar in all individuals, when in doubt confirm with another test
- NHANES data
 - Using cut-off of HbA1c $\geq 6.5\%$ will identify 1/3 fewer cases of undiagnosed diabetes than FBS ≥ 126 mg/dL
 - Low sensitivity will be offset by ease of use

Testing for Type 2 Diabetes: Asymptomatic Children

- BMI $> 85^{\text{th}}$ percentile for age/sex
- Two of the following risk factors
 - Family history of T2DM in 1st or 2nd degree relative
 - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
 - Signs of insulin resistance (acanthosis nigricans, dyslipidemia, PCOS, SGA)
 - Maternal history of diabetes or gestational diabetes during the pregnancy
- Age of initiation
 - 10 years
 - Onset of puberty if < 10 years
- Frequency – every 3 years

Prevention of Type 2 diabetes: High risk individuals

- Who is considered high risk?
 - Impaired glucose tolerance (2h glucose OGTT 140-199 mg/dL)
 - Impaired fasting glucose (FPG 100-125 mg/dL)
 - HbA1c 5.7-6.4%
- Refer to support program to achieve
 - 5-10% weight loss
 - Physical activity 150 min/week (walking or more)
- Follow-up counseling important for success
- Very high risk patients
 - Consider metformin (not approved in children)
- Screen annually

New onset Diabetes at WCHOB

- 2008 (71)
 - 60 Type 1 (85%)
 - 11 Type 2 (15%)
- 2009 (119)
 - 98 Type 1 (82%)
 - 21 Type 2 (18%)
- 2010 (15 - through 2/2010)
 - 10 Type 1 (67%)
 - 5 Type 2 (33%)

Features at Onset of Diabetes: Hospital Admissions

Year	Diabetes Diagnosis	% Patients at each HbA1c range			% DKA
		6-7.5%	7.6-10%	>10%	
2008	Type 1 (n=60)	0%	18%	82%	29%
	Type 2 (n= 11)	22%	11%	67%	0%
2009	Type 1 (n=97)	5%	35%	69%	33%
	Type 2 (n=12)*	50%	17%	25%	8%

Does not include individuals diagnosed with IGT or IFG in Endocrine clinic who transitioned to Diabetes clinic as outpatients

* Those with HbA1c drawn at admission

Other diabetes diagnoses

- Cystic Fibrosis Related Diabetes – 1 patient
- s/p pancreatectomy patient for congenital hyperinsulinism – 1 patient
- Autoimmune polyglandular syndrome, type 2 – 1 patient
- MCAD – 1 patient

Autoimmunity & Type 1 Diabetes

Autoimmune comorbidities and Type 1 diabetes

- Autoimmune thyroid disease (most common)
 - 17-30% of individuals with T1DM
- Celiac disease
 - 1-16% of the T1DM population
 - 0.3-1% in the general population
- Primary adrenal failure
 - 0.5% of the T1DM population

ADA recommendations: Autoimmunity

- Autoimmune Thyroid Disease
 - Antibodies – at diagnosis
 - TSH annually
 - free T4 if TSH is abnormal
 - Treat hypo/hyperthyroidism
- Celiac Disease – Gluten enteropathy
 - Serum IgA and tissue transglutaminase IgA shortly after diagnosis
 - Repeat for symptoms
 - Consider repeating in asymptomatic individuals
 - Referral to gastroenterology for positive screen

Celiac Screening: WCHOB experience

- Prior to August, 2008 – routine screening for celiac disease was rarely performed
- Patients were screened if they were symptomatic
 - Poor growth
 - Unexplained hypoglycemia
 - Diarrhea/abdominal complaints
 - Positive family history

Celiac Screening: WCHOB Experience

- January 2008- July 2008
 - 3/45 screened
 - No positive screens
- August, 2008
 - Addition of serum IgA and ttG to new-onset labs for all new diagnosis of diabetes
- August, 2008 – July 2009
 - 78/92 (85%) screened
 - Of those not tested (14 patients)
 - 40% Type 1 DM
 - 50% Type 2 DM
 - 10% other

Celiac Screening: WCHOB experience

- Positive screens
 - 5/78 = 6.4% of new-onset diabetes (all)
 - Screens are also performed on new onset T2DM
 - 5/69 = 7.2% of new onset T1DM
- Of those
 - 3/5 have biopsy positive disease (60%)
 - 1 was not biopsied
- Positive screens for autoimmune thyroiditis
 - positive antibodies → 12/92 (13%)
 - 3/12 have elevated TSH (25%)

Celiac Disease and Type 1 Diabetes

- Screening with annual labs – cholesterol, T4, TSH, thyroid antibodies, serum IgA, ttG Ab (~ July, 2008)
- 746 patients with T1DM followed by our clinic
- Celiac Disease in our population – Estimate
 - 25/746 (3.4%)

*** Small percent of patients with biopsy positive celiac disease had clinical symptoms that would indicate they should be tested ***

Glycemic Control At Point of Service: HbA1c in Clinic

Hemoglobin A1c as outcome measure in diabetes management

- Hemoglobin A1c (HbA1c) is a measure of average blood sugar over previous 2-3 months
- Measures percent glycation (irreversible process) of hemoglobin
- Used as a clinical tool to assess diabetes control
- Used as a research tool
 - Clinical outcomes related to morbidity, diabetes complications, and mortality
 - Outcome measure in pharmaceutical trials

HbA1c ~ average blood sugars

HbA1c (%)	Average plasma glucose
6	126
7	154
8	183
9	212
10	240
11	269
12	298

Point of Service Glycemic Control Testing

- American Diabetes Association recommends that HbA1c be performed for all diabetic patients
 - 2x per year for patients with stable glycemic control meeting glycemic goals
 - Q3 months for patients not meeting glycemic goals or with changes in diabetes management
- Goal HbA1c in pediatrics
 - Age 0-6 years – 7.5 – 8.5%
 - Age 6-12 years - <8%
 - 12-19 years -- <7.5%
 - Adults <7%
- Can be used to make changes in therapy
- Test performed
 - Central Lab
 - Point of Service

Point of Service HbA1c Testing

- Benefits
 - Quick turn-around (five minutes)
 - Can discuss results in clinic
 - Helpful if patient does not bring blood sugar readings to clinic
 - Follow-up time
- Cons
 - User error
 - Not accurate in certain patients (also with lab A1c)
 - Can not be used for diabetes screening

Point of Service HbA1c: WCHOB experience

- **Bayer A1C-Now+ System**
 - Results in 5 minutes
 - Small (5µL) blood sample
 - Portable – use in multiple exam rooms
 - Easy to use – minimal training required
 - No maintenance
- **Key features**
 - 99% lab accuracy
 - National Glycohemoglobin Standardization Program certified
 - NGSP – standardizes HbA1c results (comparable to those reported in DCCT)
 - CLIA waived
 - Reimbursable (except Community Blue)

Point of Service HbA1c: A1cNow+ WCHOB experience

- **NGSP Certification**
 - Central Lab verification
 - For a given HbA1c result
 - ± 0.85% (95% CI)
- **Accuracy with venous sampling**
 - 99.7%
 - Range -0.8% - +0.7% of the "true" result



Point of Service HbA1c: WCHOB experience

● Potential Sources of Error

○ User Error

- Inadequate sample
- Inadequate mixing
- Failure to apply sample



○ Assignment of result to wrong patient (portability and transcription of data)

○ Patient features

- Hemoglobin variant
- Glycation defect

Point of Service HbA1c: A1cNow+ WCHOB experience

Initiated use in Children's Diabetes Center Clinic in August, 2009
Pilot study in clinic to assess the degree of reproducibility of HbA1c by device vs. Lab HbA1c

- 10 consecutive patients
- Type 1 DM
- A1cNow+ in clinic
- A1c sent to central lab (9/10 to Kaleida laboratory)

Bayer Device A1cNow+	Lab HbA1c	Delta Device - Lab
9.50%	10.50%	-1% <input checked="" type="checkbox"/>
7.20%	7.10%	0.10%
9.70%	9.60%	0.10%
7.50%	8.0%*	-0.50%
8.00%	7.90%	0.10%
8.20%	8.70%	-0.50%
7.50%	7.90%	-0.40%
9.00%	9.50%	-0.50%
12.70%	14.40%	-1.70% <input checked="" type="checkbox"/>
13%	14.40%	-1.40% <input checked="" type="checkbox"/>

- 7/10 met standard for $\pm 0.85\%$
- Those that did not
 - HbA1c >> 10% (poor control)
 - Upper testing limit of device is HbA1c of 13%

Point of Service HbA1c: A1cNow+ WCHOB experience

● When should device HbA1c be repeated at centralized lab

- Result discrepant from previous
- Result discrepant from meter readings
- Failure to obtain reading
- Reading $\geq 13\%$

● When not to use device

- Individuals with Hb variants
- Individuals with glycation defects

● Consider fructosamine level

- Measures glycosylation of albumin
- Glycemic control over last 2-3 weeks

Research Frontiers: Type 1 Diabetes

New Research in Type 1 Diabetes

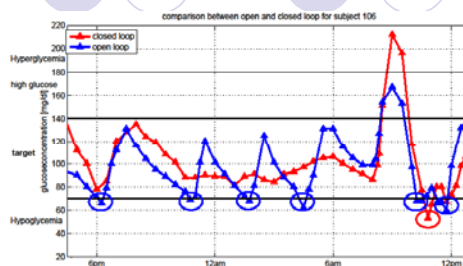
- Artificial Pancreas Project
- Non-exclusive partnership between Juvenile Diabetes Research Foundation and Johnson & Johnson (Animas pump)

● Components

- Insulin Pump
- Continuous Glucose Sensor – Interstitial Glucose
- Algorithms allowing sensor readings to be translated to changes in insulin deliver by the insulin pump



Artificial Pancreas Running the Show



- ❖ Closed loop – blood sugar 80-100 overnight
- ❖ Lows: 1 vs. 6
- ❖ Highs: 1 vs. 1
- ❖ Time out of goal range 1 hour vs. 4 hour

Artificial Pancreas Project

- Goal is to have first generation device to FDA within 5 years
- Hypoglycemia is a significant limiting factor for achieving optimal diabetes control
- Hypoglycemia shut-off option
 - Medtronic
 - Insulin pump + CGMS
 - When interstitial blood sugar drops below a threshold, insulin pump will suspend for up to 2 hours
 - Currently available in Europe and Latin America
 - FDA approval in progress

New Research in Type 1 Diabetes

- Immunomodulatory therapies in recently diagnosed patients
 - At diagnosis, a percent of pancreatic islets β -cells are still present and capable of releasing insulin
 - Number is insufficient to fully restore glycemia
 - Partial remission/honeymoon
 - Goal is to preserve those β -cells
 - Improved diabetes control
 - Lower insulin requirement
 - Potential for future studies to expand remaining β -cell population

New Research in Type 1 Diabetes

- Immunomodulatory Therapy Targets
 - T-cells
 - Immunomodulatory polypeptides
 - Cytokines

New Research in Type 1 Diabetes

- T-Cell Directed Therapies
 - Anti-CD3 therapies (teplizumab, otelixizumab)
 - monoclonal antibody therapy
 - Blocks function of effector T-cells that play a role in autoimmune destruction of β -cells
 - Induces function of regulatory T-cells that modulate the autoimmune process
 - Preliminary data demonstrates that C-peptide production is preserved compared to placebo 24 months after drug administered

Currently 7 studies ongoing to assess efficacy in patients with new-onset Type 1 diabetes (www.clinicaltrials.gov)

New Research in Type 1 Diabetes

- Immunomodulatory Polypeptides
 - Glutamic Acid Decarboxylase – 65 kD (GAD-65)
 - Autoantibody present in T1DM
 - Immunization with GAD-65
 - Increases production of regulatory cytokines
 - Protection of β -cell function

Phase II and III trials to assess efficacy in new-onset T1DM and in patients at high risk for developing diabetes (prevention)

Currently 5 studies ongoing to assess efficacy in patients with new-onset Type 1 diabetes (www.clinicaltrials.gov)

New Research in Type 1 Diabetes

- Cytokine Blockade
 - Tumor Necrosis Factor alpha ($\text{TNF}\alpha$) plays an active role in the pathogenesis of Type 1 Diabetes
 - Hypothesis:
 - Blockade of $\text{TNF}\alpha$ can prolong partial remission period in new onset patients
 - Agent – Etanercept
 - Recombinant soluble $\text{TNF}\alpha$ receptor fusion protein that binds to $\text{TNF}\alpha$ clearing it from the circulation
 - Approved for treatment of rheumatoid arthritis, psoriasis, JRA

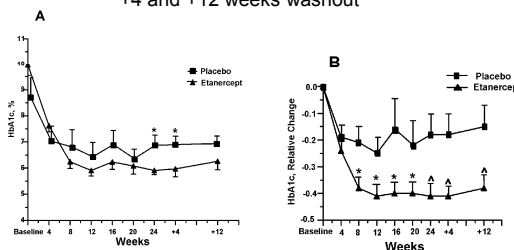
Etanercept Treatment in Children with New Onset Type 1 Diabetes

- Pilot study (WCHOB site)
 - Randomized, placebo-controlled, double-blind
- 18 subjects, new onset type 1 diabetes randomized (24 weeks, 12 week washout)
 - Placebo (10 subjects)
 - Etanercept 2x/week (8 subjects)
- Study endpoints
 - Change in HbA1c
 - C-peptide production following Sustacal meal
 - Safety

Mastrandrea, LD, Yu, J, Behrens, T, Buchlis, J, Albini, CH, Fournier, S, Quattrin, T. (2009) Etanercept treatment in children with new onset type 1 diabetes: pilot randomized placebo controlled double blind study. Diabetes Care, 32(7) 1244-1249

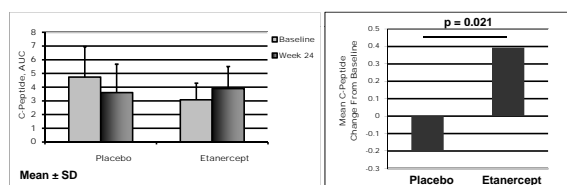
Etanercept Treatment in Children with New Onset Type 1 Diabetes

HbA1c during treatment and +4 and +12 weeks washout



Etanercept Treatment in Children with New Onset Type 1 Diabetes

C-peptide production at Baseline and Week 24



Etanercept Treatment in Children with New Onset Type 1 Diabetes

- Safety Data
 - No severe events
 - Cold Symptoms – 2x greater higher in treatment group
 - Abdominal pain – 1 subject in treatment group
 - ANA titer positive in 7 subjects at baseline
 - No subjects with negative ANA converted during the study

Immunomodulatory Therapies

- Summary
 - Evidence that interventions during partial remission period may halt autoimmune process and preserve β -cell function
 - Cons
 - Intervention post-diagnosis
 - Involves separate injections or infusions
 - Side effects
 - Risk of infectious disease because of immunomodulatory activity (etanercept and TB)
 - May require repeated treatments
 - May need to combine therapies to optimize success

Conclusions

- HbA1c as screening/diagnostic tool
- Screening for autoimmune diseases that alter glycemic control at diagnosis
- Point of Service glycemic control testing
- The future of Type 1 diabetes

