


**INSULIN ALLERGY**

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**OBJECTIVES**

- The learner will be able to define and identify the difference between an immediate or delayed hypersensitivity reaction
- The learner will be able to diagnose an immediate hypersensitivity reaction to insulin
- The learner will be able to treat and manage a patient with an insulin allergy



## CONFLICT OF INTEREST DISCLOSURE

- I have no conflicts of interest
- I have nothing to disclose



## CASE OF DL

- In March 2017, DL was 16 2/12 and was having symptoms of polyuria, polydipsia, weight loss and BG 494 on dad's glucometer (father with T2DM)
- **DL is lean with a BMI of 15.9 (0%ile, Z -2.82)**
- The following morning, DL presented to his PCP and BG was 258 fasting and UA showed glucose and trace ketones



## CASE OF DL

- He was admitted to CHAM from March 17, 2017 through March 18, 2017 where the BG's were never above 200mg/dL and patient was discharged home with a diagnosis of early onset Type 1 DM vs Type 2 DM.
- He was treated with Metformin 500mg BID
- asked to check BG BID



## CASE OF DL-BLOOD RESULTS

• TPO Antibody (0.0 - 5.0) IU/mL	0.7	• GAD(<5) IU/mL	39
• <b>C-Peptide(1.3 - 4.2) ng/mL</b>	<b>2.6</b>	• ICA Screen(NEGATIVE)	NEGATIVE
• Albumin(3.9 - 5.1) g/dL	5.0	• <b>Hemoglobin A1C(4.7 - 6.4) %</b>	<b>9.4</b>
• Bilirubin Total(0.2 - 1.2) mg/dL	0.5	• <b>Est Avg Glc (88 - 137) mg/dL</b>	<b>223</b>
• Bilirubin, Conj(0.1 - 0.3) mg/dL	0.1	• <b>He was not in DKA</b>	
• Alkaline Phos (60 - 270) U/L	253	• Ph, Venous(7.350 - 7.450) pH	7.381
• ALT (0 - 30) U/L	27	• pCO <sub>2</sub> , Venous (35.0 - 45.0) mm Hg	49.4 (H)
• AST(13 - 50) U/L	31	• pO <sub>2</sub> , Venous (80.0 - 100.0) mm Hg	29.1 (L)
• Protein, Total(5.7 - 8.0) g/dL	7.5	• Base Ex, Ven (-3.00 - 3.00) mmol/L	3.80 (H)
• <b>Glucose(70 - 115) mg/dL</b>	<b>187</b>	• HCO <sub>3</sub> , Venous (22.0 - 28.0) mmol/L	28.6 (H)
• IA-2 ANTIBODY <0.8 U/mL	<0.8		



## CASE OF DL

- DL made many dietary changes and HbA1C improved from 9.4% in March 2017 to 6.2% in May 2017, only on Metformin BID lifestyle changes.

Component Latest Ref Rng & Units	3/17/2017	3/17/2017	4/3/2017	5/15/2017
	2:19 PM	2:20 PM		
Hemoglobin A1C 4.7 - 6.4 %	9.4 (H)	9.9 (H)	7.8 (A)	6.2
Estimated Average Glucose (88 - 137) mg/dL	223 (H)	237 (H)		

- Metformin was discontinued in May 2017
- Pt was instructed to continue BID BG checks



## CASE OF DL CONT'D

- DL's mother called the office in September 2017 reporting elevated Blood sugars to the 200's and patient was admitted to CHAM from 9/12/17 through 9/19/17 for insulin initiation.
- He was not in DKA
- HgbA1c 10.9%



## CASE OF DL CONT'D

- Family history
  - T2DM
    - Father
    - Paternal uncle
  - Hypothyroidism
    - mother
- Past medical history
  - Eczema
- Allergies
  - Azithromycin-hives at 6 months of age
  - Fruit-(apples, banana, cherry, mango, grapes, peaches)-lip swelling, throat itching
  - cats
  - Tree pollen
  - Dust
  - birch



## CASE OF DL-HYPERSENSITIVITY

- DL received his first dose of Humalog insulin 5units on 9/12/17 at 2:50pm.
- Shortly thereafter, DL developed erythematous induration at the injection site on the left arm
- He subsequently developed diffuse urticaria on the left arm with pruritus.
- The reaction was responsive to Benadryl 25mg and resolved 1.5 hours. No anaphylaxis and VSS.
- He continued to develop urticarial lesions at the IV site, left cheek, left upper arm and upper chest.
- He never developed lip/tongue swelling, itchy throat, SOB, eye symptoms or GI symptoms



## 15 MINUTES AFTER HUMALOG INJECTION...



Site of Humalog Injection



## HYPERSENSITIVITY TO INSULIN

- Hypersensitivity reactions to human insulin and insulin analogues are rare
- Since the introduction of recombinant human insulin, the prevalence of insulin allergy is about <1% to 2.4%
- Patients maybe allergic to the insulin molecule or to excipients (additives)
- IgE mediated reactions are most common



## HYPERSENSITIVITY REACTIONS 101

### HYPERSENSITIVITY REACTIONS

Innocuous materials can cause hypersensitivity in certain individuals



leading to unwanted inflammation → damaged cells and tissues

Non-proper reaction of the immune system to foreign substances

Mainly harmless substances – after second or multiple exposure

Type I. „immediate“	Type II.	Type III.	Type IV. „late“
Antibody mediated			T cell mediated



## HYPERSENSITIVITY REACTIONS 101

### Immediate

- Develop within 1 hour of injection and can be local or systemic
- Local reactions
  - Rapidly developing pruritic erythema or wheal at injection site
- Systemic reactions
  - Generalized urticaria, pruritus and angioedema

### Delayed

- Develop typically between 6-24 hours after injection
- Usually transient and resolve spontaneously within a few weeks after continuation of therapy
- Commonly eczematous skin changes or induration or nodules at site of injection

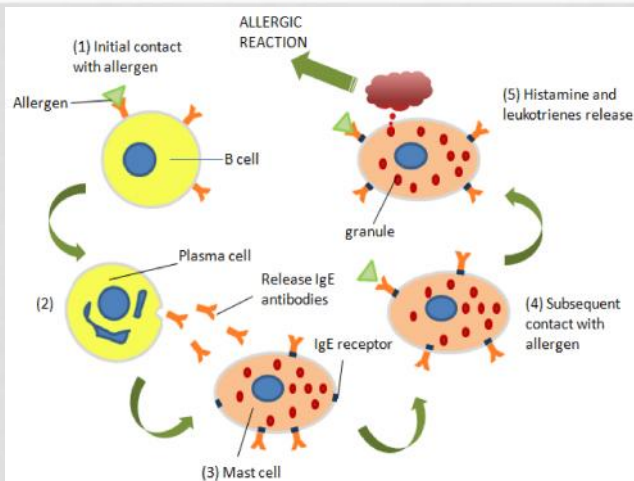


## HYPERSENSITIVITY REACTIONS 101

- Immediate reactions
  - Usually IgE mediated, type 1 immunologic reactions to insulin or an additive
  - Type 1 drug allergies-sensitization to the drug (antigen) develops in susceptible individuals prior to the initial allergic reaction, this means that there is formation of IgE molecules and binding of these molecules to high affinity IgE receptors on mast cell and basophils
  - Sensitization occurs when a person develops IgE antibodies to a substance that is inhaled, ingested or injected
  - Newly formed IgE antibodies stick to mast cells and basophils
  - Once sensitization has occurred, re-exposure to the drug/antigen can lead to cross-linking of IgE on the surface of mast cell and basophils causing release of histamine and other inflammatory mediators.



## HYPERSENSITIVITY REACTIONS 101





## HYPERSENSITIVITY TO INSULIN

- Both human insulin and insulin analogues can cause allergic reactions, as well as the additives to the insulin preparations
  - Human Insulin
    - NPH (neutral protamine hagedorn)
    - Regular
  - Insulin Analogues
    - Lispro
    - Aspart
    - Glargine
    - Glulisine
    - Detemir
    - Degludec
  - Additives to insulin
    - Protamine sulfate
    - Metacresol
    - zinc
    - Latex




## HYPERSENSITIVITY TO INSULIN-DIAGNOSIS

- Skin testing
  - Insulins are applied undiluted for prick testing
  - If negative then intradermal testing is performed with diluted insulin
  - Prick tests and intradermal tests are read after 15 minutes
  - Wheal >3mm is positive for prick testing and intradermal testing
  - The size of the wheal determines the likelihood of a reaction, but not the severity of a reaction
- Allergy testing-absence of measureable levels of specific IgE antibodies makes an immediate type 1 allergy unlikely
  - Insulin specific IgE
  - Latex specific IgE
  - Protamine specific IgE
  - Total serum IgE



### SKIN PRICK TESTING DL

Basaglar 1+	Apidra 3+	Histamine 2+
Levemir 1+	NPH 2+	Saline with Phenol 2+
Tresiba 1+	Regular 1+	Humalog 3+
	Lantus 4+	Novolog 4+



### ADDITIONAL SPT

Saline with phenol 1+
Metacresol with phenol 1+
Saline without additives 1+



## ADDITIVES IN INSULIN PRODUCTS

**Additives and excipients in commonly available insulin products\***

Insulin	Trade name in United States	Protamine (yes/no)	Other	Availability outside of United States
<b>Rapid-acting (duration two to four hours)</b>				
Aspart	Novolog	No	Metacresol, glycerin, phenol, zinc	Yes (Novolog®)
Lispro	Humalog	No	Metacresol, glycerin, zinc	Yes (Humalog, Lantus®)
Glibenclamide	Apidra	No	Metacresol, m-cresol, polyoxylated 20	Yes (Apidra)
<b>Short-acting (duration five to eight hours)</b>				
Regular	Humulin N, Novolin R, Novolin R-Ralston	No	Metacresol, glycerin, zinc	Yes (Actrapid Human, Humulin, others)
U-100 concentrated	Humulin N-Ralston U-500	No	Metacresol, glycerin, zinc	Yes
<b>Intermediate-acting (duration 14 to 24 hours)</b>				
NPH (human insulin isophane suspension)	Humulin N, Novolin N, Novolin N-Ralston	Yes	Metacresol, glycerin, phenol, zinc	Yes
<b>Intermediate-acting mixtures (duration 14 to 24 hours with a more rapid peak)</b>				
75 percent isophane protamine and 25 percent isophane	Humalog Mix 75/25	Yes	Metacresol, glycerin, phenol, zinc	Yes (Humalog Mix, Humalog Mix 25, Humalog Mix)
70 percent isophane protamine and 30 percent isophane	Novolog Mix 70/30	Yes	Metacresol, glycerin, phenol, zinc	Yes (Novolog 30)
<b>Intermediate to long-acting (duration 8 to 24 hours, dose dependent)</b>				
Dezemir	Levemir	No	Metacresol, glycerin, phenol, zinc	Yes (Levemir)
<b>Long acting (duration 20 to &gt;24 hours)</b>				
Glargine	Lantus	No	Metacresol, glycerin, zinc, polyoxylated 20 in 10 mg vials, not in 3 ml cartridge	Yes (Basaglar, Lantus, Optimum)

Insulin products listed are produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) or a non-pathogenic strain of *Escherichia coli*.



## HYPERSENSITIVITY TO INSULIN – CASE OF DL

- DL's IgE levels-LOW
  - Bovine insulin <0.1
  - Porcine insulin <0.1
  - Human insulin <0.35
  - **Latex (<0.10) 1.58**



## TREATING HYPERSENSITIVITIES

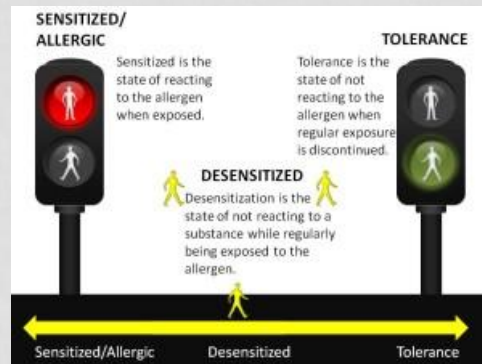


## HYPERSENSITIVITY TO INSULIN-MANAGEMENT

- Desensitization
  - Aim is to restore tolerance to the allergen by reducing its tendency to induce IgE production
  - Patients are desensitized by injection with escalating doses of allergen, starting with tiny amounts, a schedule that gradually decreases the IgE dominated response
  - Mechanism of action of desensitization is complex but ultimately the induction of regulatory T cells secreting IL-10 and/or TGF-beta, skew the response away from IgE production.
  - Associated with a decrease in insulin specific IgE
  - Many different protocols
    - Series of gradually increasing subcutaneous doses
    - CSII through an insulin pump



## HYPERSENSITIVITY TO INSULIN-MANAGEMENT

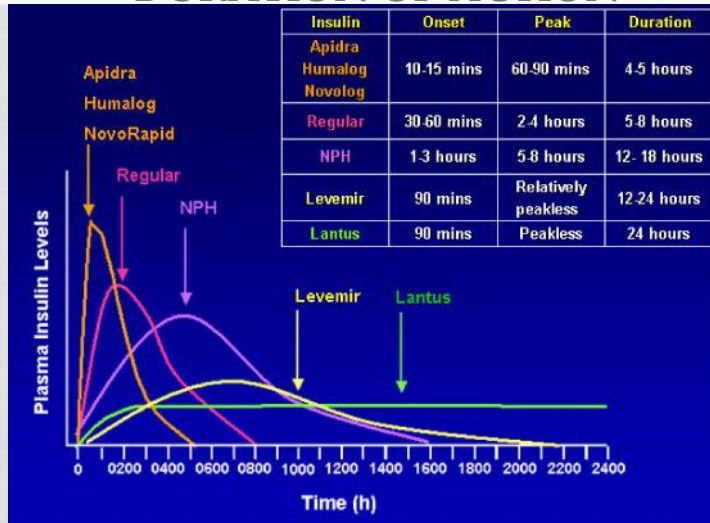


## HYPERSENSITIVITY TO INSULIN-DL

- DL was transferred to PICU with the Allergy and Immunology team for planned desensitization with regular insulin given that in the event of DKA, regular insulin is typically used. Desensitization was performed on HD#4 with no adverse reactions and patient remained stable throughout PICU stay



## HYPERSENSITIVITY TO INSULIN- REVIEW OF INSULIN ONSET AND DURATION OF ACTION



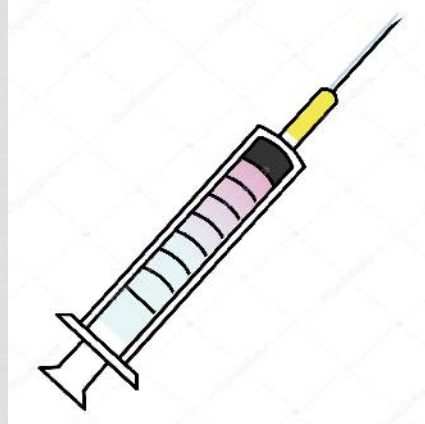
## HYPERSENSITIVITY TO INSULIN-OUR TREATMENT

- DL was desensitized to Regular Insulin
- He was managed with Zyrtec daily
- He was managed on injections of Regular Insulin every 6-7 hours
- He had hives after missing Regular insulin for about 11 hours
- Instructed to inject regular insulin 30 mins pre-prandial



## HYPERSENSITIVITY TO INSULIN-OUR TREATMENT

- Then desensitized to Tresiba and Novolog with skin testing and both results were "equivocal". Pt was challenged with Tresiba with the allergist and was switched to Tresiba daily with Regular insulin for meals and correction doses
- \*remember, prior to desensitization, all antihistamines should be stopped



## HYPERSENSITIVITY TO INSULIN-OUR TREATMENT

- Insulin pump concerns: without consistent exposure to insulin secondary to a pump/site failure, DL could develop a reaction when he was re-introduced to insulin
- October 2017 Insulin pump started with Regular Insulin and continued Tresiba 1 unit daily. IOB/duration of insulin action for regular insulin in the pump was set to 5 hours and patient was still instructed to bolus 30 minutes before meals.
- November 2017 Novolog challenge was successful and DL was transitioned to using Novolog insulin in his pump with continued Tresiba daily
- Current A1c 5.7%
- Considering MODY testing ...topic for next year...



## THANK YOU

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  - My CPNP friend and dance mom Audrey Bregante

## QUESTIONS





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