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October 26-29
Valencia - Spain

Friday 28th October
12.45-13.45
Hall Auditorio 2

Parallel Satellite Symposium

DKA: a continuing problem in pediatric diabetes. New challenges and opportunities for management and prevention.

Chairperson:
Lori Laffel (USA)

A.MENARINI diagnostics

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Lori Laffel

Chief, Pediatric, Adolescent and Young Adult Section
Senior Investigator, Co-Head, Section on Clinical, Behavioral and Outcomes Research, Joslin Diabetes Center
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Established and emerging risk factors for DKA: recognition and mitigation

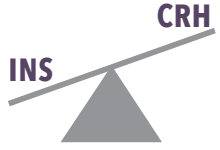
Risk for metabolic decompensation and diabetes ketoacidosis (DKA) increases under a number of circumstances, including new onset diabetes, failure to follow sick day management in the setting of established diabetes, and in association with a number of other conditions. Other contexts in which DKA may develop include surgery, pregnancy, accidents/trauma, non-adherence to diabetes management/insulin administration, disordered eating behaviors with intentional insulin restriction/omission, and with concurrent use of certain medications such as steroids and, more recently, SGLT2 inhibitors.

While new onset diabetes remains an important cause of metabolic decompensation and DKA, it represents the minority of cases of DKA, with rates varying substantially across the globe, from as low as 12% in developed countries to as high as 80% in developing countries[i]. Prevention and early intervention of DKA in persons with new onset diabetes remains challenges, with need for widespread community education.

Triggers of Ketosis and DKA

- **New onset diabetes**
- **Pump failure**
- **Insulin omission**
  - Intentional
  - medication error
- **Pregnancy**
- **Eating disorders**
- **Emotional turmoil**
- **Educational deficiency**
- **Drugs**
  - steroids
  - alchol
  - Cocaine
  - **SGLT2 inhibitors**
- **Infection**
- **Infarction**
- **Surgery**
- **Trauma**
- **Comorbidity**

Mismatch between insulin levels and counter regulatory hormones



Non-adherence and failed sick day management are the leading causes for metabolic decompensation and DKA. As the majority of DKA cases occur in patients with established diabetes, there are opportunities for prevention through careful monitoring and early intervention. In addition to failed sick day management, eating disorders along with disordered eating behaviors (DEB) and use of SGLT2 inhibitors are two interesting and unique contexts in which metabolic decompensation and DKA develop. DEB can take many forms, including extreme dieting for weight loss, binge eating, and purging of calories. Calorie purging can involve laxative or diuretic abuse, excessive exercise, self-induced vomiting, or insulin restriction in persons taking exogenous insulin. Women with diabetes are twice as likely as women without diabetes to display disordered eating behaviors. A particularly dangerous form of calorie purging for persons with insulin-treated diabetes is intentional insulin restriction or omission leading to hyperglycemia and weight loss through uncontrolled glycosuria[ii, iii].

Insulin restriction places one at risk for metabolic decompensation at any time but especially during any intercurrent illness, surgery, or stress due

to the rise in counter-regulatory hormones along with inadequate insulin delivery. Treatment with SGLT2 inhibitors also places insulin-treated persons at risk for metabolic decompensation and DKA for a number of reasons. Often, insulin dose is reduced at the start of SGLT2 treatment, placing persons who are dependent on insulin at risk during any illness or intercurrent stress.

Additionally, glycemic excursions, especially post-prandially, are blunted with SGLT2 inhibition, masking the need to assess hyperketonemia/ketonuria during illness or intercurrent stress, increasing risk for euglycemic or atypical DKA[iv, v].

Frequent monitoring of blood glucose and ketone levels is important for early identification of metabolic decompensation so that additional insulin can be given and appropriate medical help can be sought. In order to avoid DKA, additional insulin and support are needed when blood glucose (BG) and ketone levels are consistently elevated (BG >250-300 mg/dL [13.9-16.7 mmol/L]) (blood ketones (β-hydroxybutyrate, β-OHB) [NOTE: β-OHB 0-0.5 mmol/L normal; 0.6-1.5 mmol/L need for extra insulin; β-OHB >1.6 mmol/L need for extra insulin and DKA risk; and β-OHB >3.0 mmol/L DKA or high risk for DKA].

DKA and SGLT2 Inhibitors

- **Decreased insulin dose**
- **Increased glucagon**
  - SGLT2 affect on α cells
- **Decreased urinary excretion of ketones**
  - SGLT1/2 affect on tubule cells
- **Increased hepatic glucose production**
- **Increased ketogenesis**
- **Exogenous effects: increased exercise, EtOH, dehydration, carb restriction, other stresses (inducing insulin resistance)**

[i] *Usher-Smith et al. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. Diabetologia. 2012;55:2878-2894.*
[ii] *Colton et al. Eating Disorders in Girls and Women with Type 1 Diabetes: A Longitudinal Study of Prevalence, Onset, Remission, and Recurrence. Diabetes Care. 2015;38:1212-7.*
[iii] *Goebel-Fabbri et al. Improvement and emergence of insulin restriction in women with type 1 diabetes. Diabetes Care. 2011;34:545-50.*
[iv] *Modi et al. Euglycemic Diabetic Ketoacidosis. Curr Diabetes Rev. 2016 Apr 21. [Epub ahead of print]*
[v] *Ogawa et al. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig. 2016;7:135-8.*

Thomas Danne

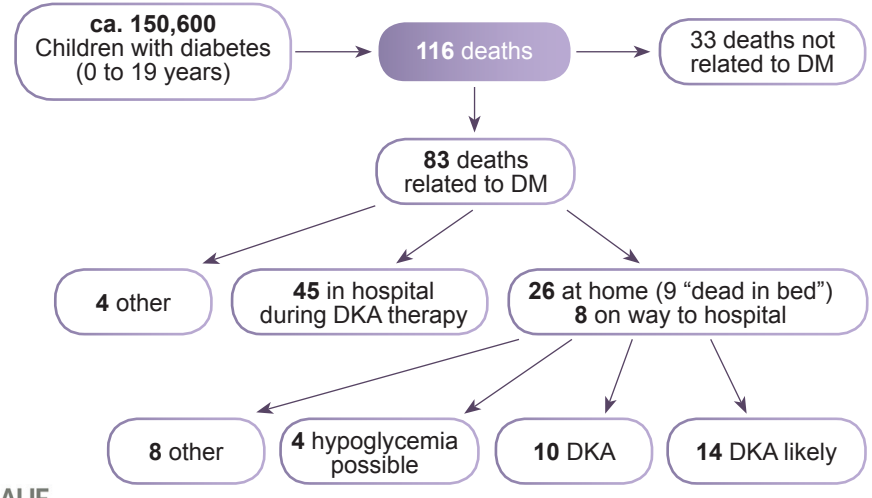
Chief Physician, Department of General Pediatrics, Diabetes, Endocrinology & Clinical Research, Diabetes center for Children and Adolescents, Children´s Hospital „Auf der Bult", Hannover Medical School, Germany.

Prevention and outpatient management of DKA

Diabetic ketoacidosis (DKA) is the most common cause of mortality in children and adolescents with diabetes at onset of diabetes or in children with established diabetes.

A recent analysis of 49,859 individuals <18 years with type 1 diabetes of three multinational registries/audits with similarly advanced, yet differing, health care systems identified females, ethnic minorities, and HbA1c above target being associated with an increased risk of DKA. DKA results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counter-regulatory hormones: catecholamines, glucagon, cortisol and growth hormone. Absolute insulin deficiency occurs in previously undiagnosed diabetes mellitus and when patients on treatment deliberately or inadvertently do not take insulin injections. Even when best practices for insulin pump therapy are followed, infusion-set failure occurs in some patients, potentially leading to DKA. Evidence of unexplained hyperglycemia warrants particular vigilance in the presence of sudden glucose elevation (>250 mg/dL) that is unrelated to a meal and accompanied by nausea or vomiting.

Parents and patients are afraid of hypoglycemia not DKA as potential cause of death



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KINDER- UND JUGEND-KRANKENHAUS

Causes of death in children with T1DM 1990-96 DKA = diabetic ketoacidosis

Edge, et al. Arch Dis Child 1999; 81:318-23

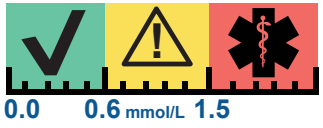
Management of an episode of DKA is not complete until its cause has been identified and an attempt made to treat it. Home measurement of blood β-hydroxybutyrate when compared to urine ketone testing decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) by the early identification and treatment of ketosis. Parents and patients should learn how to recognize and treat impending DKA with additional rapid- or short-acting insulin and oral fluids.
If glucose levels do not normalize within 2 hours of administering a correction bolus, the patient should check his or her blood ketones. Urine ketone

determination should be abandoned since ketones show up late in urine compared with blood and also decrease later after supplemental insulin is administered. Since ketones in the blood or urine signal an advanced failure in insulin delivery, the patient should also administer rapid- or fast-acting insulin by pen or syringe, based on his or her correction dose algorithm. The current infusion set and infusion reservoir/cartridge should be replaced during this time as well. A blood ketone level of >0.7–1.5 mmol/L (urine ketones, negative to small) may require a larger dose of insulin (e.g., twice the correction dose). If blood ketones are above 1.3 mmol/L (urine ketones, moderate to large), the patient should call the diabetes team for advice about additional insulin replacement, since this level of ketones indicates initial risk for acidosis. Blood ketones >3 mmol/L (urine ketones, large) require emergency care

A recent development concerns adjunct therapy with SGLT-2 inhibitors. These oral drugs seem to be associated with euglycemic DKA and ketosis. Patients with type 1 or type 2 diabetes who experience nausea, vomiting, or malaise, or develop a metabolic acidosis in the setting of SGLT-2 inhibitor therapy, should be promptly evaluated for the presence of urine and/or serum ketones.

Conclusions

- Prevention of DKA appears to be an elusive goal
- Early detection and proper mangement saves lives
- β-ketone-measurement allows „realtime“ DKA diagnosis and mangement
- This may become even more important when off-label adjunct therapy with SGLT-inhibition becomes more widespread practice.



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In conclusion, prevention of DKA appears to be an elusive goal. However, early detection and proper management saves lives. β-ketone-measurement has an important role in this respect as it allows „realtime“ DKA diagnosis and management.

Ivana Rabbone

Centre of Pediatric Diabetes, Regina Margherita Children's Hospital, Turin, Italy

DKA management in children and adolescents: ISPED (Italian Society of Pediatric Endocrinology and Diabetology) Recommendations

Diabetic ketoacidosis (DKA) is an acute emergency that occurs both in newly diagnosed patients and in those with known diabetes. It should be noted that all used guidelines are based on limited high-quality scientific evidence and much of the content is based on expert consensus. Nevertheless, it is important to have written recommendations to improve DKA management and increase the effectiveness and safety of clinical practice.

In Italy, pediatric diabetologists belonging the Diabetes Study Group of Italian Society of Endocrinology and Diabetology (ISPED) sought to write and implement recommendations for DKA management from an evidence-based pathway taking into account the last 2014 ISPAD consensus guidelines and subsequent critical review articles in an attempt to reduce the considerable variability in management among pediatric centers and improve overall treatment of pediatric DKA.

Key points of Italian DKA Management (1)

- Begin with an isotonic solution (0.9% saline) at **5-10 ml/kg/h** over 90-120 min (not exceeding 300 ml/h); do not use colloids
- At the beginning of hydration if hypokalemic, but at the latest from the start of insulin therapy, add potassium (20 mmol/L before or 40 mmol/L from the start of insulin infusion) **as 50% potassium chloride and 50% potassium phosphate**
- Start IV insulin infusion as human regular insulin not before 90-120 min and never give an insulin bolus. It is recommended to utilize an automated syringe for insulin delivery
- The recommended insulin dosage is 0.05-0.1 U/kg/hour according to patient's age, but less insulin **(0.025-0.05/kg/hour)** is better and safer

Key points of Italian DKA Management (2)

- Continue from the third hour with **0.9% saline**
- The rate of IV fluid should be calculated to rehydrate evenly over at least 48 hours; be careful not to exceed **1.5 times the daily maintenance**
- When the blood glucose level drops to 250-300 mg/dl (14-17 mmol/l), or decreases faster than 100 mg/dl (6 mmol/l))/hr, **add glucose 5-10%**, but the fluid replacement should continue to have a **tonicity equal to or greater than 0.45% saline**
- The use of bicarbonate is not recommended

A tool for calculating fluids, potassium and insulin requirements could be helpful to better manage a patient in DKA. To help physicians managing DKA according to scientific recommendations, Menarini has developed GlucoLog DKA Expert, a CE Marked software able to: 1) recording clinical observations; 2) calculating fluid requirement and osmolality; 3) balancing insulin and potassium iv infusion; 4) monitoring hourly BG, UG, Ketones, Laboratory tests, fluid input and output, ECG, BP, heart and respiratory rate, neurological assessment using GCS; 5) corrected sodium concentration for hyperglycemia.

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Curricula vitae

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Dr. Lori Laffel is Chief of the Pediatric, Adolescent and Young Adult Section and a Senior Investigator/Co-Head of the Section on Clinical, Behavioral and Outcomes Research at the Joslin Diabetes Center, as well as a Professor of Pediatrics at Harvard Medical School. Under Dr. Laffel's leadership, the pediatric program at Joslin has quadrupled in size and is recognised worldwide as a major pediatric diabetes centre for clinical care and research.

Dr. Laffel has been the Principal Investigator on multiple NIH and foundation funded grants. Her research focuses on understanding and overcoming challenges to adherence in patients with diabetes in order to improve glycemic control, biomedical, and psychosocial outcomes; and optimizing use of diabetes technologies, including automated insulin delivery systems. She has been the Principal Investigator and Program Director of NIH-funded postdoctoral fellowship and early career development training grants for paediatric endocrinologists entering the field of diabetes research. She is actively involved with the American Diabetes Association (ADA), as a member of the Boston Leadership Board, a recent past member of the National Board of Directors of the American Diabetes Association, the National Committee for Professional Practice Guidelines, chair on the ADA's Working Group on Transitions in Care for Young Adults with Diabetes, and past chair of ADA's Youth Strategies Committee. She is also a member of the Research Advisory Committee of the JDRF. She also has been a member of the Advisory Board of the International Society of Pediatric and Adolescent Diabetes and a member of the Clinical Advisory Committee for the JDRF. She was Co-Chair of the JDRF CGM Study. She was also the co-editor on the recently released *ADA-JDRF Sourcebook on Type 1 Diabetes through the Life*. She is recipient of the American Diabetes Association's 2015 Outstanding Physician-Clinician Award, the Greater Boston Chamber of Commerce 2016 Pinnacle Award, and the 2016 University of Miami School of Medicine Hall of Fame Award.

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Prof. Dr. Thomas Danne is the Director of the Department of General Pediatrics Endocrinology/Diabetology & Clinical Research at the “Auf der Bult” Hospital for Children and Adolescents, Hannover Medical School, Germany, which is the largest pediatric diabetes center in Germany. Presently he is appointed as Chairman of the SWEET-project (www.sweet-project.eu) and work-package leader of the INNODIA-project (www.innodia.eu).

He is the Past-President of the International Society for Pediatric and Adolescent Diabetes (ISPAD), the German Diabetes Association (DDG) and the German Diabetes Aid (diabetesDE). He is a former Research Fellow of the Joslin Diabetes Center of Harvard Medical School in Boston. His research interests include basic and clinical research in pediatric diabetology with special emphasis on new insulins, insulin pumps, glucose sensors and the artificial pancreas. Dr. Danne has published over 150 peer reviewed papers is on the Editorial board of several journals and has contributed to several books.

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Education/Training/Career

- 1991 M.D., University of Turin, School of Medicine, Turin, Italy.
- 1995 Postgraduate Course on Paediatrics, University of Turin, Italy.
- 2000-2003 PhD in Experimental Paediatrics, University of Turin, Italy.
- 2008 Master in Management of Diabetes and Metabolic Diseases, University of Parma, Italy.

- 1997-today Assistant of Paediatrics at the Department of Paediatrics – Paediatric Diabetes Centre- Children's Hospital "Regina Margherita" of Turin, Italy.
- 2011-2013 Professor in Pediatrics at the University of Turin (Italy) "Faculty of Movement Science".
- 2013-2015 Coordinator Diabetes Study Group of ISPED (Italian Society Pediatric Endocrinology and Diabetology).

Her main interests are: 1) Type 1 and Type 2 diabetes; 2) Lipid metabolism; 3) Obesity.
Ivana Rabbone is an active member of Italian Society of Paediatrics (S.I.P.), Italian Society of Paediatric Endocrinology and Diabetes (ISPED), Italian Society of Diabetes (S.I.D.).

She is author or co-author of more than 150 publications on national and international journals, among them 75 are peer-reviewed.
In the activity of new drug development, Dr. Rabbone has conducted several trials in agreement with Good Clinical Practice.

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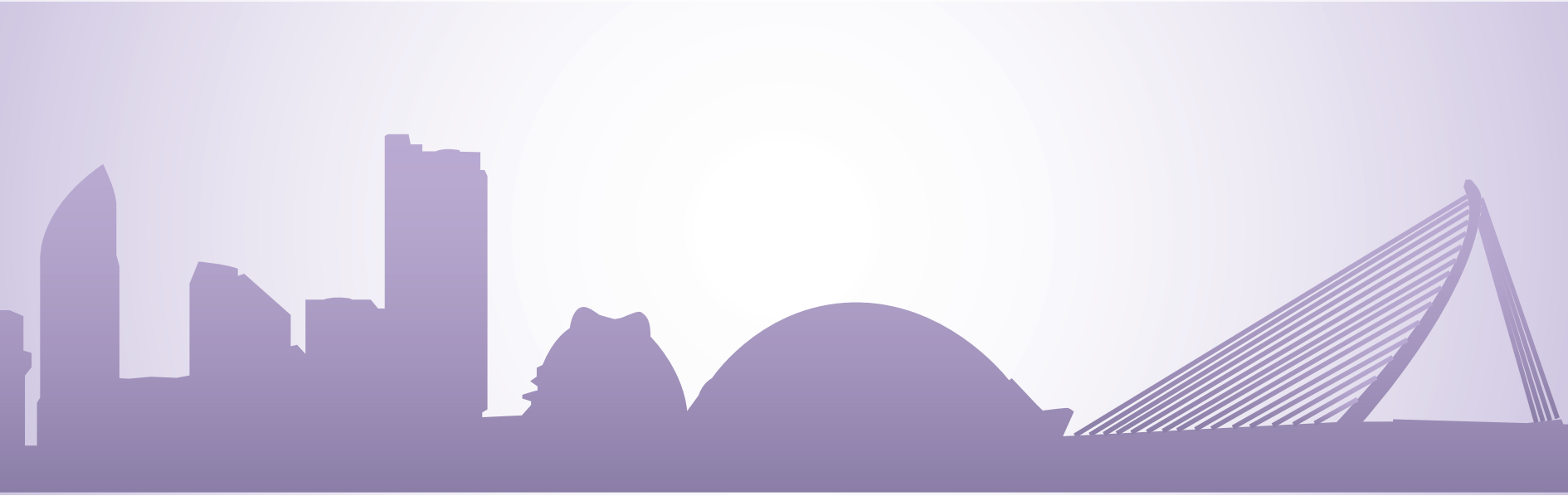

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