ISPAD Hypoglycaemia responses to comments

1) Dr Gun Forsander (Gothenburg)
   1) Please use mmol/mol as a HbA1c value as well.
   2) The spelling of "analogs" or "analogues" should be consequent in the paper.
   3) Reference 15 lacks authors.
   4) To me it locks strange to write 2.15 hours (p17) - we usually do not think we divide an hour into centesimals?
   All the above corrected

2) Dr Dick Mul (Rotterdam)
   **p4**  Treatment of hypoglycemia should increase the blood glucose by nearly 3 to 4 mmol/L (54 to 70 mg/dL). This can be accomplished by giving glucose tablets or sweetened fluids. Approximately 9 grams of glucose is needed for a 30 kg child and 15 grams for a 50 kg child (approximately 0.3 g/kg).(C) --> comment:
   1) any need to distinguish hypo-treatment in CSII vs MDI?
   Added in the revised section on page 25

2) should a maximal glucose intake be advised in order to prevent reactive hyperglycemia?
   No particular number in literature but most studies used max 20gms CHO or 0.3g/kg without rebound hyperglycemia.

3) Blood glucose monitoring should be performed prior to exercise, and extra carbohydrates should be consumed based on the blood glucose level and the expected intensity and duration of exercise.
   --> comment: please also mention insulin dose reduction prior to sports
   This will be dealt with in the ISPAD exercise chapter

4) Suggestion to add a paragraph (or refer to the specific ISPAD chapter) on technical issues in the measurement of hypo by glucose meters, sensors, FSL etc: what are common pitfalls, how about reliability and precision of the different systems in the hypo-region.
   This would be in technology chapter (can this be confirmed?)

3) Dr Majida Noori (Saudi)
   Hypothyroidism as co morbidity in hypoglycemia
   My comments to add hypothyroidism as co morbidity in hypoglycemia in these children
   I saw few cases of severe hypoglycemia in diabetic children & adolescents, associated with hypothyroidism.
   This has been added in the table (was already in the body)

4) Dr. Dipak Muktan (Nepal)
   1) As Dr. Mul mentioned, the maximum dose of anhydrous glucose (0.3 gm/kg) is better to be mentioned.
   This is already addressed in the para below
   In adults, 20 grams of carbohydrate in the form of glucose tablets raised glucose levels by approximately 2.5 to 3.6 mmol/L (45 - 65 mg/dL) (151-153). This has been extrapolated to 0.3 g/kg in children which would be approximately 9 grams of glucose for a 30 kg child and 15 grams for a 50 kg child.

2) I have seen my colleagues using NG tube in severe hypoglycemia to administer glucose when IV access is difficult, especially in remote places. And i have heard that some of the health personnel are using IV dextrose(5%/10%) via NG tube when IV access is not
Glucagon is not readily available in countries with limited resources. In countries where neither glucagon nor glucose gel may be available; a powder form (glucose D 25 or anhydrous glucose) is used. Sugar or any other powdery substance or thin liquids like a glucose solution or honey should not be given forcibly to the semi/unconscious child. The child should be put in a lateral position to prevent aspiration and a thick paste of glucose (glucose powder with a few drops of water or table sugar crushed into powdered sugar with consistency of thick cake icing) smeared onto the dependent cheek pad; the efficacy of this practice is anecdotal. Although an earlier study in healthy adult volunteers demonstrated poor buccal absorption of glucose (161), sublingual glucose was found to be a child-friendly and effective method of raising blood glucose in severely ill children with malaria (162). In situations where there is a danger of aspiration with no intravenous access available, parenteral glucose solutions may be administered via nasogastric tubes (163).

4) Evidence regarding repeat dose of glucagon in persistent hypoglycemia and its use in malnourished child with diabetes.

No evidence available

5) Dr Julia (Canada)

1) To adapt to more politically correct language, I suggest replacing "developed countries" (page 10) with "high-income countries" and "developing countries" (p. 26) with "low- and middle income countries", or probably even better, with "resource-limited settings".

This has been corrected

2) Following up on Dr. Muktan’s comment, I think it would be great to include alternatives for hypoglycemia treatment including glucagon alternatives for settings where this is not available.

1. Alternatives for hypoglycemia treatment where child is conscious include locally available hard candies, table sugar (1 tsp = 4g), sugar cane (1/3 stick = ~15g), sugar cane juice (4oz = ~15g), any other locally produced juice, ripe mango (1/2 small mango = ~15g).

We haven’t added this as there could be variability and inconsistencies.

3) For severe hypoglycemia if glucagon or a nearby health care facility are not available, regular table sugar can be "crushed" to make powdered sugar which, if mixed with a bit of water can be made into a paste (similar to thick cake icing) that can be applied to the child's gums (similar to glucose gel). 1 unsifted tbsp of powdered sugar corresponds to 8g of glucose

This has been updated on pages 27/28 as above

4) NG tube can be inserted and D10-50% given per NG
The comment on NG tube has been included but not the concentration as no literature around on 50% glucose through NG.

6) Dr Fergus Cameron (Melbourne)

1) In the text it says that “Acute hypoglycaemia has been attributed in 4-10% of deaths in a population-based cohorts and international registries”. The supporting reference is that of Seaquist et al. The Seaquist et al paper is simply a report of a consensus statement and does not supply primary data. Instead the Seaquist et al paper cites the following primary sources:

141 deaths in 219,061 person-years of follow-up from 1989 to 2005. 73 deaths occurred prior to 2003. Of the 141 deaths there was data on 134. Of the 134 deaths, 47 were attributable to diabetes. Of the 47 deaths attributable to diabetes, 27 were said to be caused by DKA and 5 due to hypoglycaemia. No clarity as to how the ‘death due to hypoglycaemia’ statement was arrived at (the investigators did not review the case notes as far as I can tell). Putting this aside the 5/147 gives 3% incidence rate in a cohort that is arguably not at all representative of today’s clinical context of paediatric care.

The focus of this paper is upon cognitive function and hypoglycaemia. In passing it mentions 53 deaths in the DCCT/EDIC study period of which 3 were attributable to hypoglycaemia (all 3 deaths occurred in the EDIC phase). There is no mention whether these 3 are adults or adolescents at the time of death but given it was during the EDIC phase it would appear likely they were adults. There is also no mention as to how the cause of death was ascertained. This was not a population based cohort.

Feltbower RG, Bodansky HJ, Patterson CC, et al. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of Diabetes in Children and Young Adults. Diabetes Care 2008;31:922–926
This paper analysed all-cause mortality in all ages in West Yorkshire 1978-2004. Thirty two deaths (25 = male) were said to occur from acute diabetes complications and of these 8 deaths were said to be due to hypoglycaemia (no mention as to how this diagnosis was ascertained). It is not stated what ages these patients were but given the preponderance of males (25/32) and the lack of association between acute complications and gender during childhood, one could assume they were mostly adults.

This paper follows up patients from 1973 until the end of 2002. Causes of death were reviewed by a Clinic Review Committee. There was 1 cause of death attributable to hypoglycaemia in people aged < 19 years over the study period (out of a total number of 26 deaths in this age group).
In summary the data cited is inexact and inappropriate in terms of ages germaine to childhood/adolescence and the current therapeutic era.

Sorry to bang on about this but figures such as the ‘4-10% of deaths due to hypoglycaemia’ can have an enormous impact upon patients, parents and policy makers. For a start I was taught never to cite percentages when the ‘n’ is less than 100- it implies a greater gravitas to the data than it deserves. Inaccurate statements about risk of hypo-related death feed into the angst of parents who resist tightening up metabolic control.

I would think a more accurate statement would be “In the pre- and immediate post-DCCT period, acute hypoglycaemia was been associated with a handful of deaths in several population-based paediatric cohorts. Data from contemporary cohorts are lacking”. I wouldn’t cite the Jacobsen or the Seaquist paper but would cite the other 3 primary references.

It has been known for some time that hypoglycemia can kill experimental animals and there have been many reports of deaths associated with hypoglycemia in both type 1 and type 2 diabetes. There has been debate as to whether these associations reflect causality (37) and there is only one case report which directly links hypoglycemia to death in an adult (38). Primary brain death may occur with profound and prolonged hypoglycemia but a more likely mechanism of death is through the induction of arrhythmias since hypoglycemia is known to be pro-arrhythmogenic (39-41).

Hypoglycemic mortality rates have been reported in cohorts of patients with diabetes. In the pre and immediate post-DCCT period up to more than a decade ago, acute hypoglycaemia was assigned as the cause of death in 4% (42), 7% (43) and 10% (44) of deaths in population-based cohorts and international registries of childhood-onset diabetes, with most deaths in adults. In a recent report from Wales with a follow-up for 42, 801 patient-years (11.8 years) of diabetes, hypoglycemia was difficult to ascertain with certainty as the cause of death, although 6 out of the 30 deaths were thought to be the result of hypoglycemia based on the clinical judgement and death certification (45). In a long-term Norwegian study with 241 deaths reported during a mean follow-up of 16.8 years, hypoglycemia was certain in 8 and considered probable in 12 of the total 20 hypoglycemia-related deaths (46).

2) Under the “dead in bed” section.

“.. there is increasing evidence that a combination of severe nocturnal hypoglycaemia (42) and autonomic neuropathy can cause changes in cardiac repolarisation (43) and result in this devastating complication (43, 44).

Reference #42 is a well-known case report of a single patient. As far as I am aware this is the only published case report of an episode of hypoglycaemia associated with a diabetic death (in a non-suicide context). I’m not sure that n=1 amounts to ‘increasing evidence’

Reference #44 is a two page mini-review article. I’m not sure that it merits being cited in a consensus guidelines. Notwithstanding this caveat, the authors canvass the possibility that the finding that some forms of ‘more complete’ autonomic neuropathy associated with severe hypoglycaemia are less likely to result in QT changes (Lee et al Diabetes 2004; 53:1535-42). The review also goes on to state that the association between a history severe hypoglycaemia and prior to a dead in bed event is an epidemiologic finding. A history of severe hypoglycaemia is simply an epidemiologic risk factor equal to being male, Caucasian, higher HbA1C, overall glycaemic instability and lower BMI.
As I understand it there are currently three main theories about ‘dead in bed’ syndrome:

i) ? Hypoglycaemia causing a fatal heart arrhythmia
   Subtle ECG changes with hypoglycaemia occur equally during the daytime and night-time (Novodvorsky et al epub Feb 17)
   -> My comment: we see plenty of day-time hypoglycaemia so why don’t we see day-time arrhythmia?

   ECG changes appear to be greater if hypoglycaemia is induced in a clamp study compared to real world ambulant conditions (Christensen et al J Diabet Complic 2014; 28:723-8)
   -> My comment: the clamp data (cited in reference #43 and elsewhere) probably over-estimates the actual link between hypoglycaemia and arrhythmia.

   At best I think it only fair to say that the potential mechanistic link between a hypoglycaemic episode and a fatal arrhythmia remains unclear.

ii) ? Autonomic neuropathy leading to arrhythmic death.
   Recent meta-analysis found enormous variability in published incidence rates of autonomic neuropathy in kids (Tang et al Pediatr Diabetes 2013; 14:239-48)
   ->My comment: This does not explain why most dead-in-bed episodes occur in younger (not older) adults, who have greater rates of autonomic neuropathy.

iii) ? Hypoglycaemia leading to a seizure and hypoxia
   Classically no sign of any disturbance in DIB cases

Hypoglycemia is also proposed to play a role in the “dead-in-bed” syndrome, which is more prevalent in patients with type 1 diabetes than in the general population. In a coroner’s case series, dead-in-bed syndrome accounted for ~15% of deaths in young adult males (≤ 40 years) with diabetes (47). Although the aetiology is not well established, it has been postulated that it may be secondary to prolongation of QT interval caused by number of factors; acute hypoglycemia (48) on the background of autonomic neuropathy (49) and possible genetic influences (50). These changes in cardiac repolarisation can lead to fatal ventricular arrhythmias and may contribute to the sudden nocturnal death of young individuals with type 1 diabetes(51). It is likely that the more widespread use of continuous glucose monitoring (CGM) and the increased use of population based databases will shed clearer light on the true incidence of hypoglycemic death in the future.

There is a recent mini-review paper published on International Hypoglycemia study Group website: IHSGonline.com by Phillip Cryer and Simon Heller.

I guess the 7th paragraph of this paper says it all for me- the confusion between ‘association’ vs ‘causation’ and that if one is to attempt to extrapolate from associative data to a potential causative process there has to be a plausible biological mechanistic link. The references I cited above show that the biologic studies linking arrhythmias to hypoglycaemia as a potential biologic link are far from clear cut. It is pretty clear still that the data between hypoglycaemia and death is overwhelmingly just associative and originates mostly from the adult T2D literature. Cryer and Heller cite the review by Goto et al (their ref #23) as the strongest support for a causal link. In the context of T1D in youth the Goto et al review is not helpful as a) the review is of T2D in adults and b) in the review the major cause of cardiovascular death are infarctions, coronary vascular disease and congestive cardiac failure, not arrhythmias. Given that the ISPAD guidelines are around T1D in youth and that nobody has found myocardial infarcts/CCF as a cause of sudden death in youth, I can’t see that Goto et al review is relevant or that the case for a causative link is any stronger.
Apologies for being perhaps overly pedantic, but the guidelines will be an important reference document and read by many. It is important that where the evidence is robust it is acknowledged and where the evidence is speculative/associative at best, this too is acknowledged. For all of the reasons above I feel that the evidence suggesting that severe hypoglycaemia causes dead in bed is debatable and that this should be acknowledged. I do not think that there is ‘increasing evidence’.

This section on hypoglycemia as cause of death and dead in bed syndrome is updated on pages 10 and 11.