Pathogenesis of disease – diabetic ketoacidosis

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Disclosures

- None

Diagnostic Criteria – ADA and JBDS

	DKA		
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10
Urine ketone	Positive	Positive	Positive
Serum ketone	Positive	Positive	Positive
Effective serum osmolality	Variable	Variable	Variable
Anion gap	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

DIAGNOSIS:

Ketonaemia $\geq$ 3.0mmol/L **or** significant ketonuria (more than 2+ on standard urine sticks)

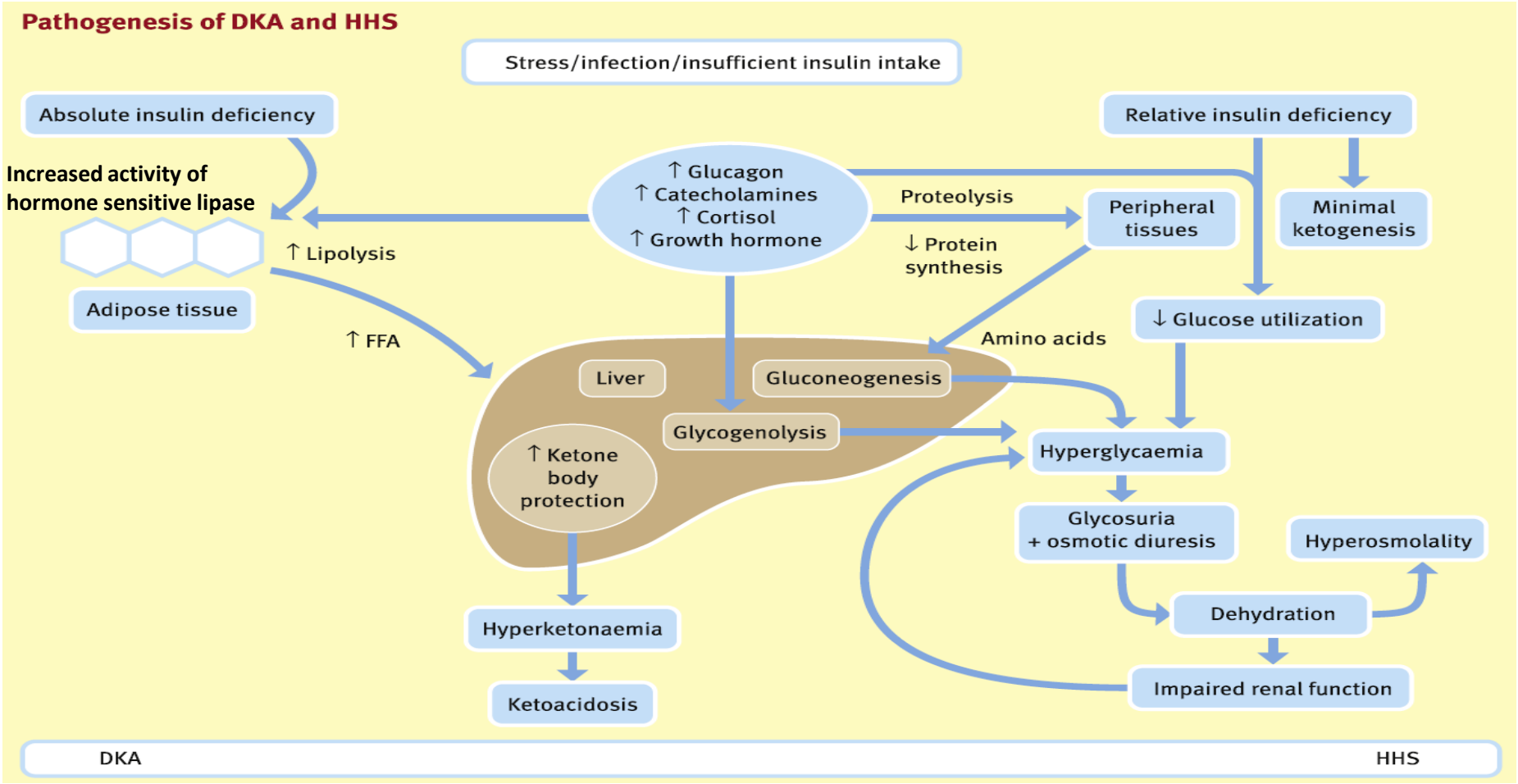
Blood glucose > 11.0mmol/L or known diabetes mellitus (200 mg/dL)

Bicarbonate ($HCO3^-$) < 15.0mmol/L **and/or** venous pH < 7.3

ADA, American Diabetes Association; DKA, diabetic ketoacidosis; JBDS, Joint British Diabetes Societies.

Kitabchi AE, *et al. Diabetes Care* 2009;32:1335–1343;

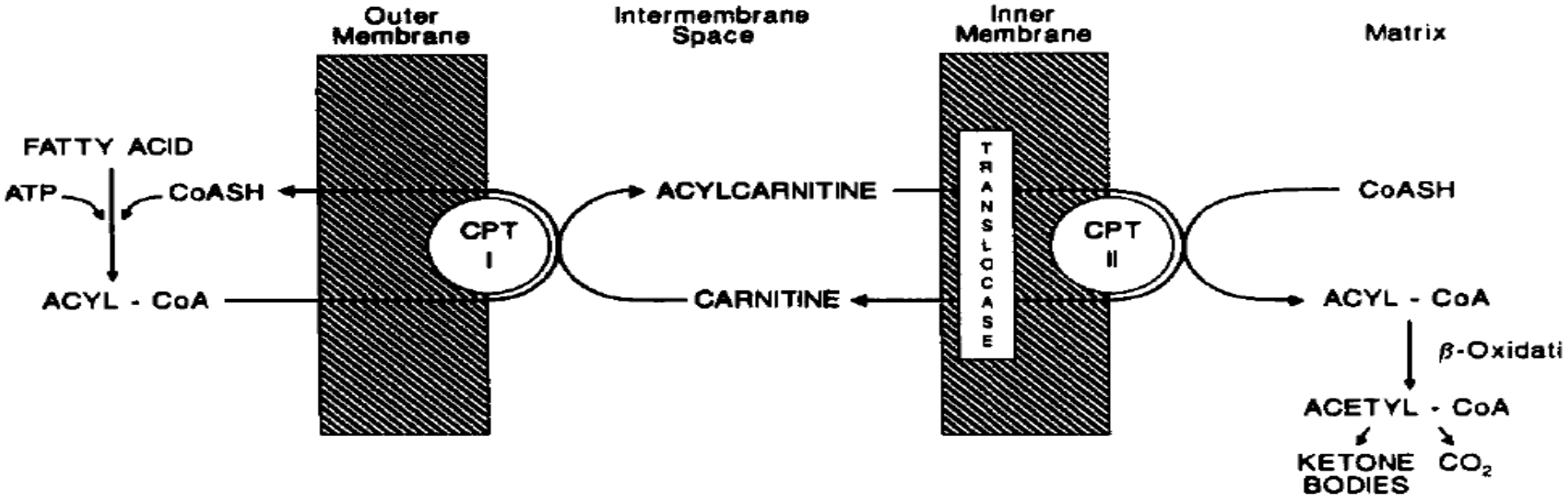
Association of British Clinical Diabetologists. Joint British Diabetes Societies (JBDS) for Inpatient Care Group. http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm. Accessed 30 March 2016.



FFA, free fatty acids; HHS, hyperosmolar hyperglycaemic state.

English P, *et al. Postgrad Med J* 2004;80:253–261.

Ketogenesis



McGarry JD, *et al. Diabetes Metab Rev* 1989;5:271–284.

Controversies in the Management of DKA

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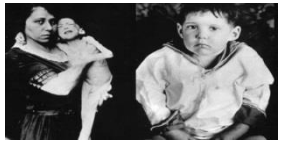
Timeline



1922

Type 1 diabetes universally fatal

In 1925, Joslin reports that 31 out of 33 patients with DKA survive – with gentle fluid replacement

1945

Howard Root in Boston reports reduction in mortality from 12% to 1.6% between 1940 and 1944 – using up to 1770 units of insulin in the first 24 h after admission

1948

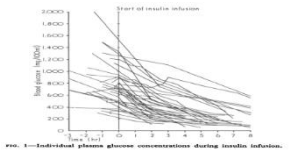
Micks in Dublin used 100 units for those in 'pre-coma' and 100 units every 15 minutes – between 500 and 2000 units, depending on severity of coma

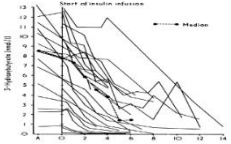
RD Lawrence advocates very aggressive fluid management

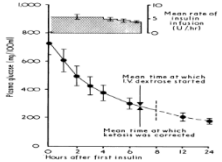
1949

1973

Malins and Black in Birmingham used between 140 and 1400 units of insulin in the first 24 h depending on severity in 170 consecutive cases







Three consecutive papers in the *BMJ* showed that low-dose insulin infusions (5–6 units/h) work just as well as high-dose in lowering glucose and ketones

2010

The first UK national guideline for managing DKA published

Updated in 2013

2014

Survey of current management

?

Diagnostic Criteria – ADA and JBDS

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Kitabchi AE, *et al. Diabetes Care* 2009;32:1335–1343;
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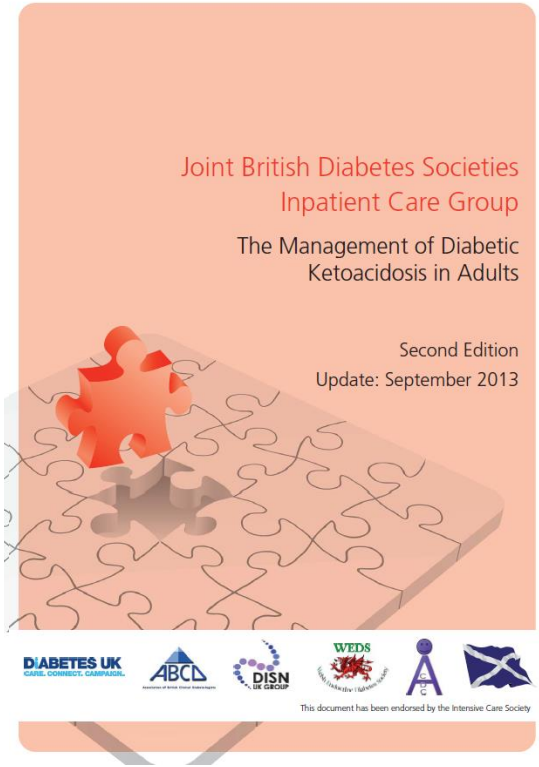
Some (Recent) History

- In 2010, the JBDS produced a guideline on the management of DKA
- With >20,000 hard copies given out or downloaded
- An updated guideline was published in late 2013
- A national survey was conducted in autumn 2014



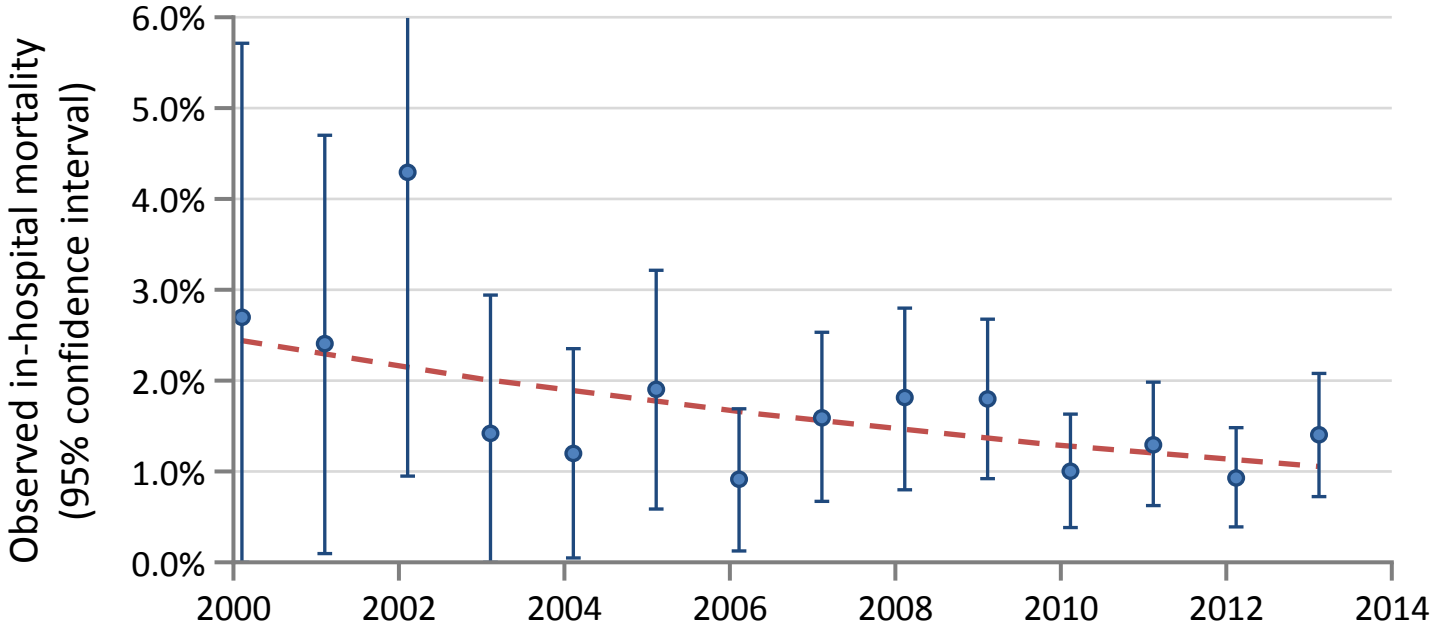
Association of British Clinical Diabetologists. Joint British Diabetes Societies (JBDS) for Inpatient Care Group. http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm. Accessed 30 March 2016.

A Question I Ask Myself

- How do we know that what we are doing is correct?

Intriguing Evidence

Mortality of 8533 people with DKA admitted to all ICUs across Australia and New Zealand



ICU, intensive care unit.

Venkatesh B, et al. *Critical Care* 2015;19:451.

What Did We Do to Answer That Question?

Joint British Diabetes Societies Inpatient Care Group

Data collection tool for the Management of Diabetic Ketoacidosis (DKA) in Adults

(Admission to Discharge)

Name of Hospital: Your grade ☐Consultant ☐SpR ☐CMT ☐DISN ☐Other.....

Year diabetes diagnosed?		Age	Gender: ☐ Male ☐ Female

1. Ethnicity ☐ Not stated

White	Mixed	Asian / British Asian	Black / Black British	Other
☐ a) British ☐ b) Irish ☐ c) Any other white background	☐ d) White /Black Caribbean ☐ e) White / Black African ☐ f) White and Asian ☐ g) Any other mixed background	☐ h) Indian ☐ i) Pakistani ☐ j) Bangladeshi ☐ k) Any other Asian	☐ l) Caribbean ☐ m) African ☐ n) Any other Black background	☐ o) Chinese ☐ p) Any other ethnic group

2. Date / time of Admission: (dd/mm/yy hh:mm) 3. Date / time of Discharge: (dd/mm/yy hh:mm)

4. Did this episode of DKA occur in someone who was already an inpatient? ☐ Yes ☐ No ☐ Not recorded

5. How many previous admissions for DKA have they had in the last 12 months?..... 6. Date of death .....(dd/mm/yy)

7. Cause(s) of death: 1)..... 2)..... 3).....

Diagnosis of DKA (Where appropriate please put a x in the box)

8) Was the diagnosis confirmed according to diagnostic criteria? ☐ Yes ☐ No ☐ N/A

a) Blood ketones ..... mmol/L	**DIAGNOSIS of DKA (JBDS):** Ketonaemia > 3.0mmol/L or significant ketonuria (more than 2+ on standard urine sticks)	**10. Was treatment area?** a) ☐ Level 1? (eg general ward area) b) ☐ Level 2? (eg high dependency area) c) ☐ Level 3? (eg ITU) d) ☐ Acute medical unit? e) ☐ A&E f) ☐ Other? (please state) .....
b) Urine ketones		
c) Blood glucose .....mmol/L	Blood glucose > 11.0mmol/L or known diabetes mellitus Bicarbonate (HCO3-) < 15.0mmol/L and/or venous pH < 7.3	
d) pH	**9. If you use different diagnostic criteria for diagnosing DKA – please list them here** Ketones .....mmol/L Glucose.....mmol/L pH..... Other.....	**11. Do you use the JBDS DKA guidelines?** a) ☐ Yes b) ☐ No
e) Bicarbonate .....mmol/L		

Joint British Diabetes Societies Inpatient Care Group

Institutional Standards for the Management of Diabetic Ketoacidosis (DKA) in Adults
(Complete one per Institution)

Name of Hospital:		Date form completed:	
Form completed by		Grade	

(Put N/A= not applicable or NR = not recorded)

1. Guidelines	Yes	No	Don't know
a) Do you have a DKA **treatment pathway**?			
b) Do you have **local guidelines for managing DKA**?			
c) Do you have an **Integrated Care Plan (ICP)** for DKA?			
d) Are your guidelines **current and valid**?			
e) What are your guidelines based on? ☐ i) Joint British Diabetes Societies guidance? ☐ ii) Other..... *(please state)*			

2. Staffing	Yes	No	Don't know
a) In the clinical areas where patients with DKA are initially cared for, do you have **trained health care professionals** available to measure blood ketone levels 24 hours per day?			
b) Do you have **dedicated inpatient diabetes specialist nurses** at a staffing level of 1WTE per 300 beds? If the answer is **NO** – what is your current DISN staffing level per 300 beds?.....WTE			
c) Do you have a **clinical lead** responsible for the implementation & audit of DKA guidelines?			

3. Monitoring	Yes	No	Don't know
a) In the clinical areas where patients with DKA are initially cared for, do you have the facility to **measure blood ketones** in your Trust?			
b) Do you have **blood glucose testing meters that are centrally connected** in your Trust?			

4. Audit / Education	Yes	No	Don't know
a) Do you have a **quality assurance scheme** in place for both glucose and ketone meters?			
b) Have you **audited the outcomes** of your patients admitted with DKA the last past?			
c) Do you **monitor against performance indicators** eg those listed in the JBDS guideline?			
d) Do you have a **rolling educational programme** for medical staff?			
e) Do you have a **rolling educational programme** for nursing staff?			

5. Patients	Yes	No	Don't know
a) Do your patients have access to the specialist diabetes **team within 24 hours of admission?**			
b) Do your patients have the choice to **self-manage their diabetes**?			

Results

- 283 forms were received from 72 hospitals between May and November 2014
- There are hundreds of messages in the data!
- A few of the main messages are:

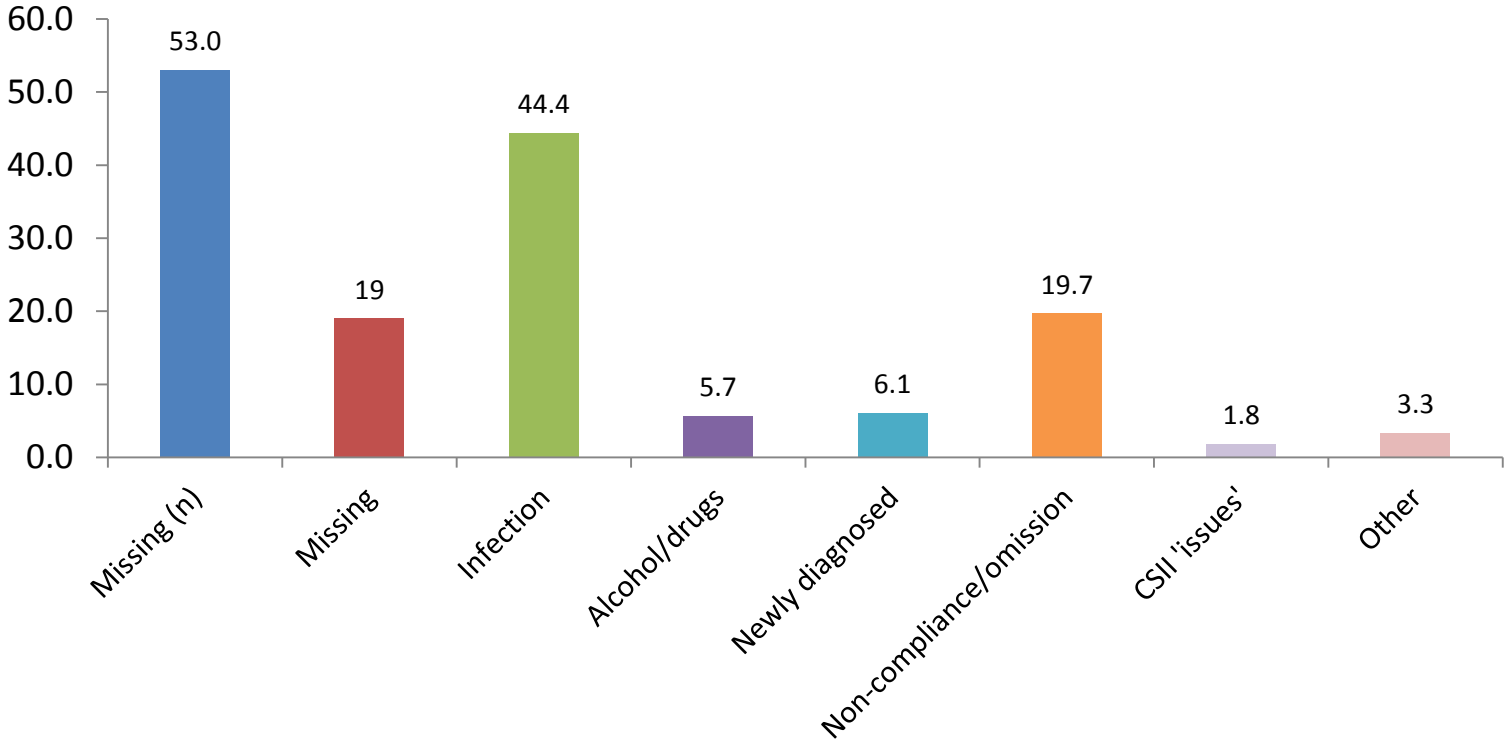
Dhatariya KK, *et al. Diabet Med* 2016;33:252–260.

Times (Median)

- Admission to diagnosis – 35.5 min
- Admission to starting 0.9% NaCl – 41.5 min
- Admission to starting FRIII – 60 min
- Admission to resolution – 18.7 hours
- To hospital discharge – 2.6 days

FRIII, fixed-rate intravenous insulin infusion.
Dhatariya KK, *et al. Diabet Med* 2016;33:252–260.

Precipitants (%)



CSII, continuous subcutaneous insulin infusion.

Dhatariya KK, *et al. Diabet Med* 2016;33:252–260.

Causes of DKA Across the World

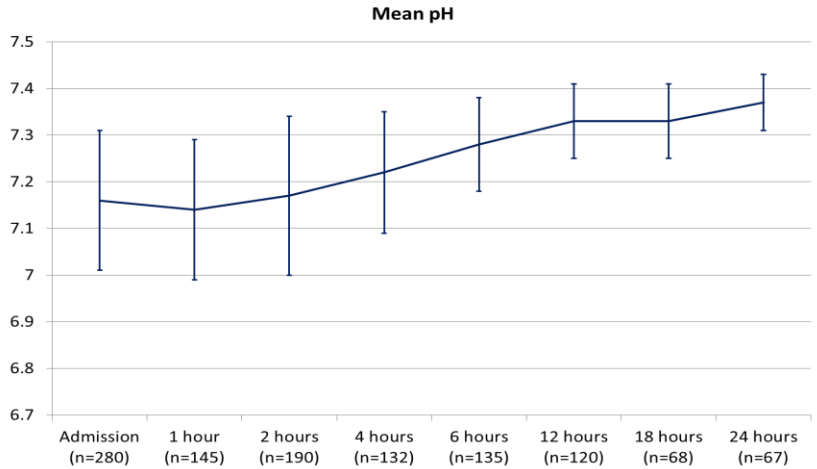
Precipitating cause, %	Australia	Brazil	China	Indonesia	Korea	Nigeria	Spain	Syria	Taiwan	USA	UK
New diagnosis of diabetes mellitus	5.7	12.2	NR	3.3	NR	NR	12.8	NR	18.2	17.2–23.8	6.1
Infection	28.6	25.0	39.2	58.3	25.3	32.5	33.2	47.8	31.7	14.0–16.0	44.4
Poor adherence	40	39	24	13.3	32.7	27.5	30.7	23.5	27.7	41.0–59.6	19.7
Other	25.7	15	10.9	17.1	11.2	4.8	23.3	7.8	6.2	9.7–18	10.8
Unknown	NA	8.8	25.9	8	30.8	34.6	NA	20.9	16.2	3.0–4.2	19.0

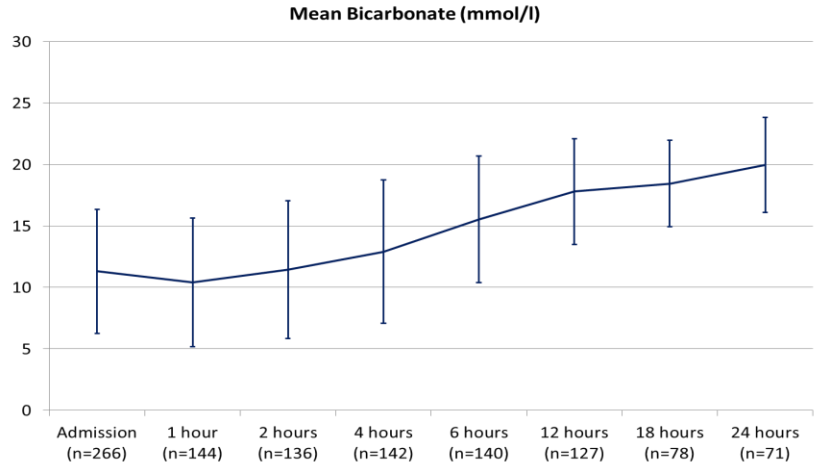
NA, not available; NR, not reported.

Umpierrez G, *et al. Nat Rev Endocrinol* 2016;12:222–232; Dhatariya KK, *et al. Diabet Med* 2016;33:252–260.

Fixed-Rate Intravenous Insulin

- The use of 0.1 units/kg/h led to excellent rises in pH and bicarbonate – so DKA resolved by 18.77 hours

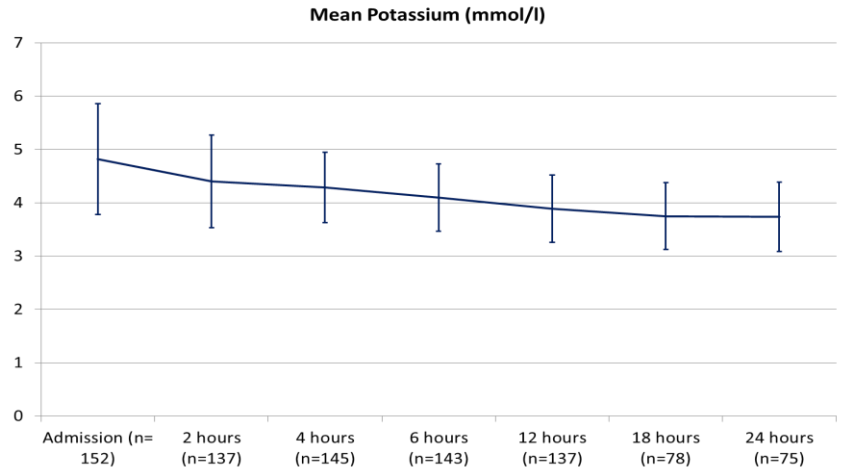




Dhatariya KK, *et al. Diabet Med* 2016;33:252–260.

Potassium

- However, despite an aggressive potassium replacement regimen – more than 50% of patients became hypokalaemic



Dhatariya KK, *et al. Diabet Med* 2016;33:252–260.

Which Is Similar to Other Data

- In 40 consecutive cases in a single centre in Canada
  - 38% developed significant hypokalaemia (<3.3 mmol/L) during the first 48 hours
  - Most were preventable
    - Not stopping insulin during hypokalaemia
    - Inadequate potassium replacement

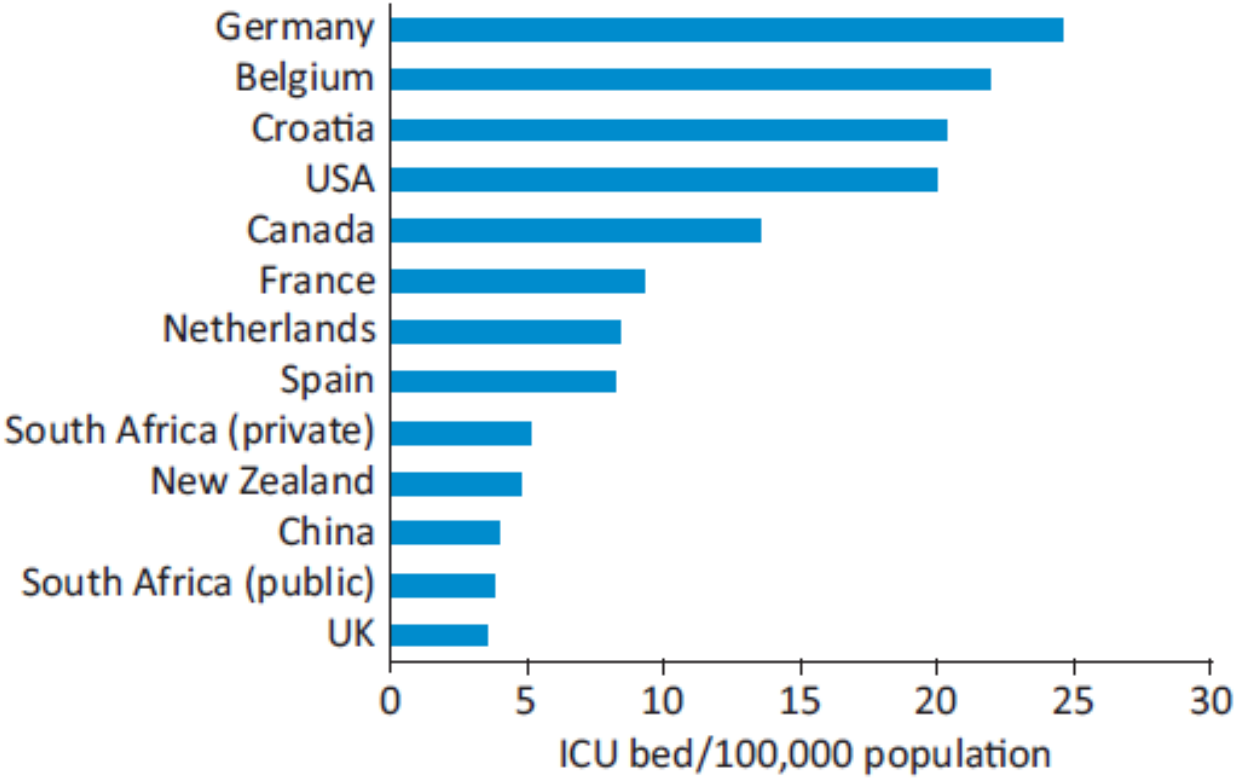
Wong B, *et al. Can J Diabetes* 2016; in press; DOI: http://dx.doi.org/10.1016/j.jcjd.2015.10.002.

Questions for Discussion – in No Particular Order

- The ‘processes’ at the front door were done well – but later were done less well
  - What can be done to ensure consistent good practice?
- In 67% of patients, potassium dropped to less than 4.0 mmol/L at 24 hours. No harm came to them, but was this luck or judgement?
  - Should the rate of potassium infusion be increased, even if this incurs more resources – e.g. central lines, transfer to HDU, more intensive monitoring?

HDU, high dependency unit.

But the Beds Aren't Available



ICU, intensive care unit.

Fletcher S. *Future Hosp J* 2016;3:55–57.

Hypoglycaemia

- 27.6% of patients had glucose levels <4.0 mmol/L during their treatment
  - Should anything be done about that?
- In the patients in whom long-acting insulin was not continued, 30% of patients became hypoglycaemic; in those in whom it was continued, 36.6% developed hypoglycaemia
  - Does this matter?
- One suggestion is to change to a VRIII when ketone levels drop to <3.0 mmol/L, regardless of glucose levels

VRIII, variable-rate intravenous insulin infusion.

Other (Potential) Controversies

Table 3. Summary of patients with treatment-emergent serious adverse events of DKA and related events in the canagliflozin development programme for type 2 diabetes

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Treatment group	C 300 mg	Placebo	C 100 mg	C 100 mg	C 300 mg	C 300 mg	C 300 mg	C 100 mg	C 100 mg	C 300 mg	S 100 mg	C 300 mg
Adverse event	Acidosis DKA (non-TEAE)	Metabolic acidosis	DKA	DKA	Metabolic acidosis	DKA	Ketoacidosis	DKA	DKA	DKA	DKA	Ketoacidosis
Blood glucose, mg/dL (mmol/L)*	Acidosis: 369 (20.5) DKA: 533 (29.6)	N/A	400 (22.2)	347 (19.3)	>500 (>27.8)	>500 (>27.8)	148–320 (8.2–17.8)†	481 (26.7)	400 (22.2)	470 (26.1)	481 (26.7)‡	571 (31.7)
pH	Acidosis: 7.24 DKA: N/A	N/A	7.14	N/A	6.82	N/A	N/A	7.23	7.022	N/A	7.22‡	N/A
Bicarbonate, mEg/L	Acidosis: 15 DKA: 15	N/A	15	N/A	3.4	N/A	13.6‡	11.7	1.8	N/A	11.4‡	N/A
Anion gap, mmol/L	Acidosis: 6 DKA: 17	N/A	25	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ketones (blood or urine)	Acidosis: +blood DKA: +blood, +urine	N/A	+Blood	N/A	+Blood	N/A	N/A	+Blood	N/A	N/A	N/A	+Urine

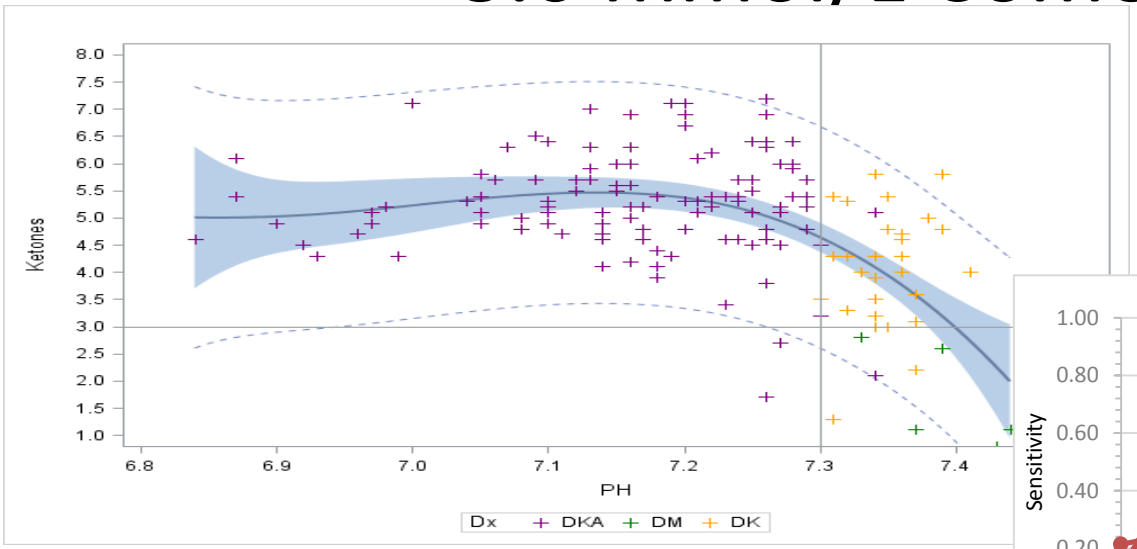
*Blood glucose value at presentation of the adverse event; †Range of all values reported; specific days and times not reported; ‡Specific date not reported.

17,956 randomised to canagliflozin or placebo

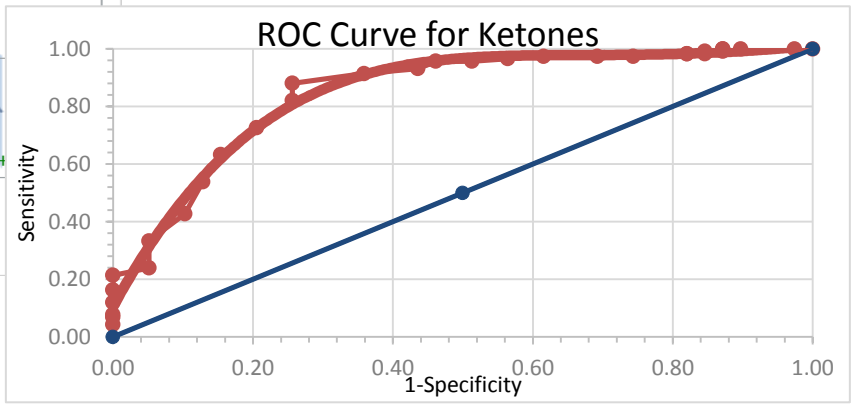
C, canagliflozin; S, sitagliptin; TEAE, treatment-emergent adverse event.

Erondu N, *et al. Diabetes Care* 2015;38:1680–1686.

Where Did a Ketone Concentration of 3.0 mmol/L Come From?



188 children admitted with an hyperglycaemic emergency between 2009 and 2014 with DKA, DK or DM



A cut-off point of 3.0 mmol/L has a sensitivity of 97.4% and a specificity of only 30.8%

A cut-off point of 4.4 mmol/L has a sensitivity of 88% and a specificity of 74.4%

DK, diabetes ketosis; DM, diabetes mellitus; Dx, diagnosis; ROC, receiver operating characteristic.

Clarke, *et al.* Submitted for publication.

Controversies in the Management of DKA

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