Diabetes Related Emergencies

Dr Ketan Dhatariya MBBS MSc MD MS FRCP PhD

Consultant in Diabetes and Endocrinology

Norfolk and Norwich University Hospitals

Disclosures

- I am the lead author of the updated 2013 edition of the JBDS guidelines for the management of diabetic ketoacidosis

- I am the lead author of the JBDS guidelines on the management of the adult patient with diabetes undergoing surgery or procedures

- I am a co-author on almost all of the other JBDS national guidelines

- I am on the clinical endpoint adjudication committee for the sotagliflozin trials implemented by Lexicon Pharmaceuticals

- In the last 24 months, I have also received consulting fees and honoraria from Genentech, Sanofi Diabetes, and Novo Nordisk

JBDS, Joint British Diabetes Societies.

Topics to Cover

- DKA

- HHS

- Hypoglycaemia

DKA

How Do You Diagnose DKA?

- You need the 'D'
  - A glucose concentration of >11.1mmol/l or
  - A previous diagnosis of diabetes

Table 1—*Diagnostic criteria for DKA and HHS*

	DKA			HHS
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)	Plasma glucose >600 mg/dl
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10	>18
Urine ketone*	Positive	Positive	Positive	Small
Serum ketone*	Positive	Positive	Positive	Small
Effective serum osmolality†	Variable	Variable	Variable	>320 mOsm/kg
Anion gap‡	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method. †Effective serum osmolality: $2[\text{measured Na}^+ \ (mEq/l)] + \text{glucose (mg/dl)}/18$. ‡Anion gap: $(Na^+) - [(Cl^- + HCO_3^- \ (mEq/l)]$. (Data adapted from ref. 13.)

Dhatariya K Lancet Diab Endocrinol 2017;5(5):312-323
Dhatariya K Rev Diab Stud 2016;13(4):217-225
Kitabchi AE et al Diabetes Care 2009;32(7):1335-1343

How Do You Diagnose DKA?

- You need the 'D'
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- You need the 'K'
  - Plasma ketones of ≥3.0mmol/l
  - Urine ketones can be misleading and unhelpful

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- You need the 'A'
  - A pH of <7.3
  - An anion gap of >12
  - A bicarbonate of <15mmol/l

Dhatariya K Lancet Diab Endocrinol 2017;5(5):312-323
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Why is This Important?

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.

How about Dapagliflozin?

Occurrence of diabetic ketoacidosis among type 2 diabetes patients in Humedica/Optum observational data and from the dapagliflozin clinical trial development program

- 5936 patients on dapagliflozin out of the ~1.5 million people on the database between 2011 and 2013

- Mean age 56.9 years

- M=F

- 77% Caucasian, 13% black/African, 2% Asian

Andersson Sundell K, *et al.* CODHy 2015; poster 28. http://www.codhy.com/2015/Uploads/Editor/PDF/POSTER1/28.pdf.

How about Dapagliflozin?

	2011 (N=257)	2012 (N=263)	2013 (N=398)
Venous pH measure	108 (42.0)	89 (33.8)	127 (31.9)
Arterial blood gases.HCO_3	62 (24.1)	64 (24.3)	116 (29.1)
Arterial blood gases.O_2 content	4 (1.6)	5 (1.9)	8 (2.0)
Arterial blood gases.O_2 saturation	100 (38.9)	86 (32.7)	127 (31.9)
Arterial blood gases.PaO_2	100 (38.9)	83 (31.6)	103 (25.9)
Arterial blood gases.total CO_2	43 (16.7)	40 (15.2)	79 (19.8)
Serum bicarbonate	67 (26.1)	62 (23.6)	55 (13.8)
Base excess in blood	71 (27.6)	61 (23.2)	50 (12.6)
Lactic acid	60 (23.3)	55 (20.9)	140 (35.2)
Blood glucose	54 (21.0)	42 (16.0)	43 (10.8)
Urine ketones	88 (34.2)	49 (18.6)	81 (20.4)

All data are presented as n (%).

These are the patients they presented as having DKA

Most had:
No pH
No HCO_3
No glucose
No ketones

Andersson Sundell K, *et al.* CODHy 2015; poster 28. http://www.codhy.com/2015/Uploads/Editor/PDF/POSTER1/28.pdf.

Definitions

- Either
  - There is very little DKA with the use of these drugs
- OR
  - The true incidence of DKA (as defined by the company) is vastly underestimated

Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter...

Anne L. Peters,[1] Elizabeth O. Buschur,[2] John B. Buse,[3] Pejman Cohan,[4] Jamie C. Diner,[3] and Irl B. Hirsch[5]

Diabetes...

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF SGLT-2 INHIBITORS AND DIABETIC KETOACIDOSIS

Association of British Clinical Diabetologists (ABCD) position statement on the risk of diabetic ketoacidosis associated with the use of sodium-glucose cotransporter-2 inhibitors

UMESH DASHORA,[1] ALISON GALLAGHER,[2] KETAN DHATARIYA,[3] PETER WINOCOUR[4] AND ROB GREGORY[2] ON BEHALF OF THE ABCD COMMITTEE

Br J Diabetes 2016;16:206-209

Norfolk and Norwich University Hospitals
NHS Foundation Trust

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 1st 24 h after admission

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

The first UK national guideline for managing DKA published

Updated in 2013

Survey of current management

1922

1945

1949

2010

2014

1925

1948

1973

2017

Type 1 diabetes universally fatal

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

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

3 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

Call for the ADA criteria to be updated

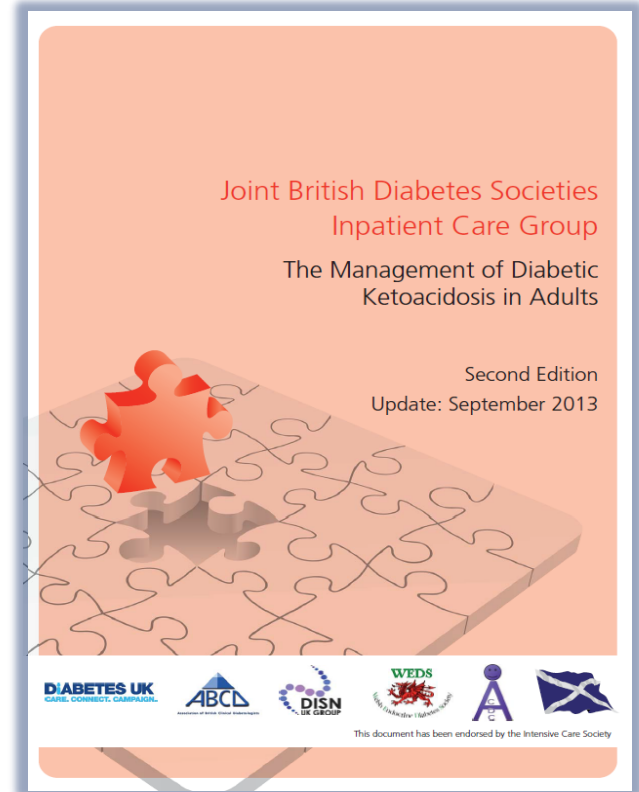RD Lawrence advocates very aggressive fluid management

?
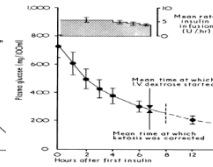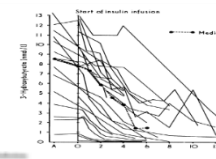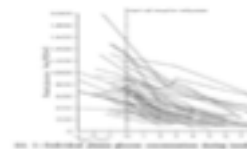
So…

- DKA was treated with
  - Fluid
  - Intravenous insulin
  - Potassium

  - ± bicarbonate & phosphate

But how much and how fast?

How Did We Standardise Treatment?

- In 2010 the JBDS produced a guideline on the management of DKA

- With >120,000 hard copies given out or downloaded

- An updated guideline was published in late 2013

- A national survey was conducted in Autumn 2014

Joint British Diabetes Societies Inpatient Care Group

The Management of Diabetic Ketoacidosis in Adults

Second Edition
Update: September 2013

DIABETES UK   ABCD   DISN UK GROUP   WEDS   A

This document has been endorsed by the Intensive Care Society

https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group

How Commonly Are They Used?

Initiative type	Initiative name	Percentage of sites
JBDS[1] guidelines	DKA and hypoglycaemia guidance (2013)	99.0
	Hypoglycaemia management in hospital (2013)	98.0
	Management of adults with diabetes undergoing surgery (2011)	85.4
	Self-management of diabetes in hospital (2012)	47.3
	Hyperosmolar Hyperglycaemia State (2012)	82.0
	Glycaemic management of enteral-fed stroke patients (2012)	60.0
	Admission Avoidance (front door/AMU protocols) (2013)	30.7
	Steroid use for inpatients with diabetes (2014)	51.2
	Discharge planning (2014)	30.2
	Variable rate insulin infusion (VRIII) for medical inpatients (2014)	85.9

1. Joint British Diabetes Societies (JBDS) for Inpatient Care.

NaDIA 2017 – Data published 9th January 2018

What Does This All Mean?

- The diagnosis of DKA should be very straightforward

- Most SGLT-2 clinical trials have left the diagnosis to local investigators with no prespecified criteria used

- Thus the true incidence is unknown – read all the papers with a degree of scepticism!

- The UK DKA guidelines are very widely used and they work

Other controversies (not covered today)

- How fast to replace potassium?
- Should the insulin be given at a fixed rate?
  - Weight based
  - Other?
- Should the insulin infusion rate be changed as glucose concentrations normalise?
- Why is the ketone threshold 3.0 mmol/L ?
- Should children with DKA be treated differently to adults? (A national survey currently ongoing!)
- Etc., etc., etc.…

HHS

First Mention in English?

- On the 18th August 1886 by Dreschfeld in the Bradshawe Lecture at the Royal College of Physicians of London

  – Diabetic coma "though of small compass, is yet full of interest both to the physician and to the pathologist"

- He described 3 types of coma

  – Drowsiness, passing onto coma

  – An excited nervous system (resembling alcohol intoxication), then drowsiness and coma
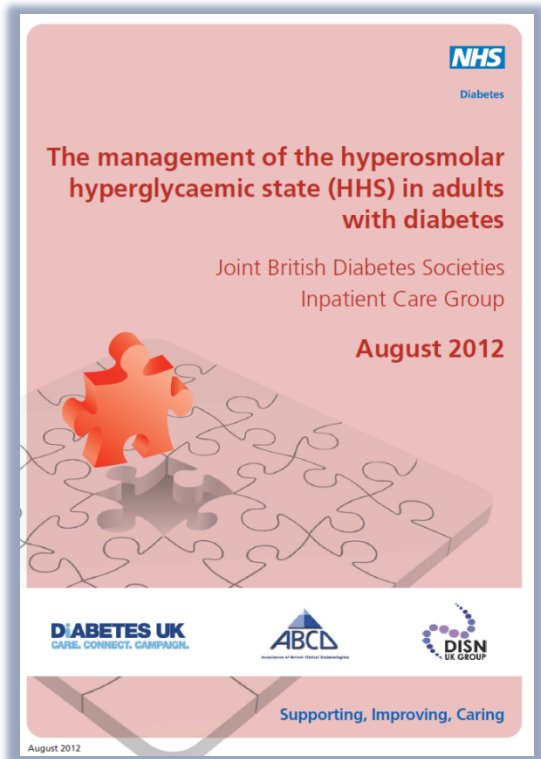
  – Dyspnoea with acetone (the most frequent sort)

Dreschfeld J Br Med J 1886;ii(1338):358-363

Early Mentions of Non Ketotic Diabetes

- RD Lawrence in 1951
    - Described 'lipo-plethoric' or 'fat diabetics'
    - And the rarer 'lipo-atrophic' or 'thin diabetics'
        - This was associated with 'intense lipidaemia'

- Sament and Schwartz in 1957 describe a case where 270 units of insulin reduced glucose from 87mmol/L to 39mmol/L
    - Describing much greater insulin sensitivity compared to DKA

Lawrence RD BMJ 1951;1:373
Sament S S Afr Med J 1957;31(36):893-894
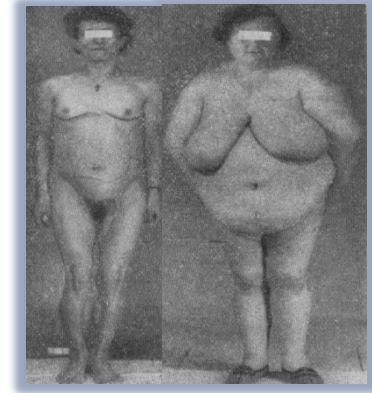
Joint British Diabetes Societies for Inpatient Care

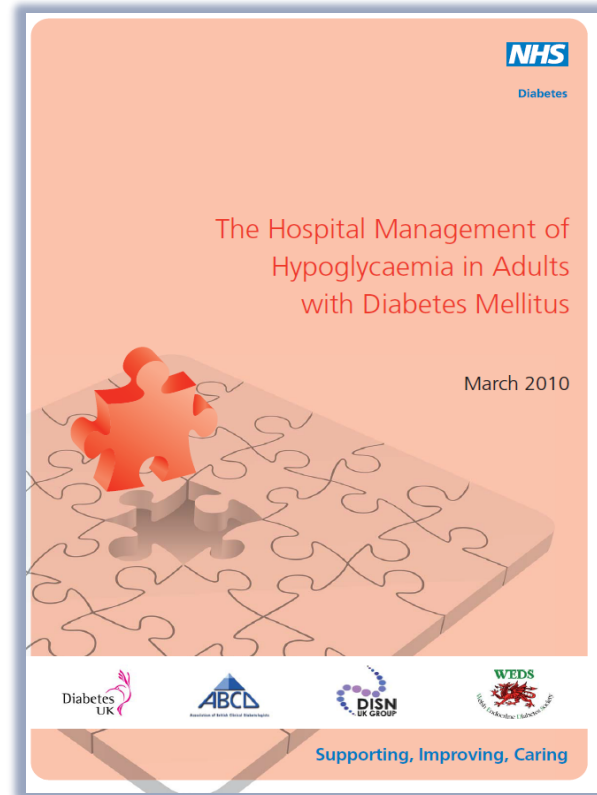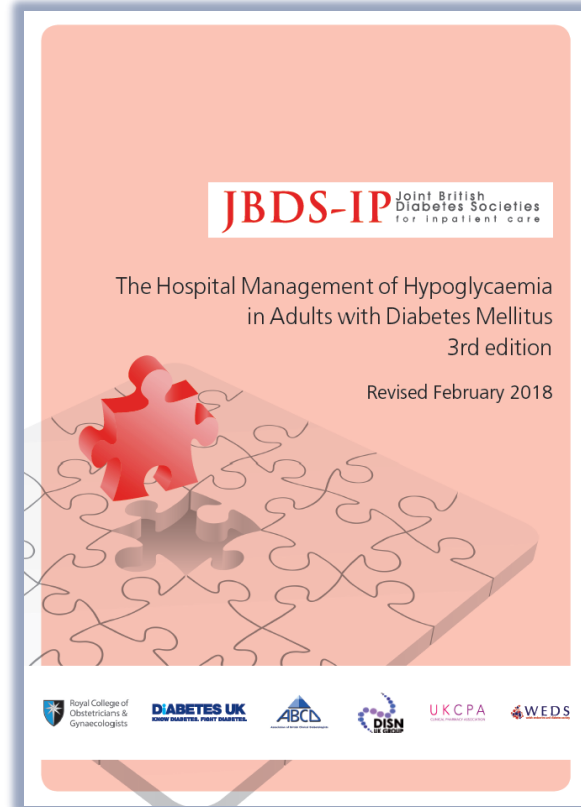- In August 2012 JBDS published a national guideline on the management of HHS

NHS
Diabetes

The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes

Joint British Diabetes Societies Inpatient Care Group

August 2012

DIABETES UK
CARE. CONNECT. CAMPAIGN.   ABCD   DISN UK GROUP

Supporting, Improving, Caring

August 2012

https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group

ADA and JBDS HHS Definitions

	ADA (2009)	JBDS (2012)
Plasma glucose	>600mg/dl (33.3mmol/l)	>540mg/dl (30mmol/l)
Arterial pH	>7.3	>7.3
Serum bicarbonate	>18mEq/l	>15mmol/l
Urine ketones	Small	Not referenced
Serum ketones	Small	<3.0mmol/l
Effective serum osmolality	>320mOsm/Kg	>320mOsm/Kg
Anion gap	Variable	Not referenced
Mental status	Stupor / coma	Not referenced

Kitabchi AE et al Diabetes Care 2009;32(7):1335-1343
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Hypoglycaemia

There's a Guideline for That

NHS

Diabetes

The Hospital Management of Hypoglycaemia in Adults with Diabetes Mellitus

March 2010

Diabetes UK

ABCD
Association of British Clinical Diabetologists

DISN
UK GROUP

WEDS

Supporting, Improving, Caring

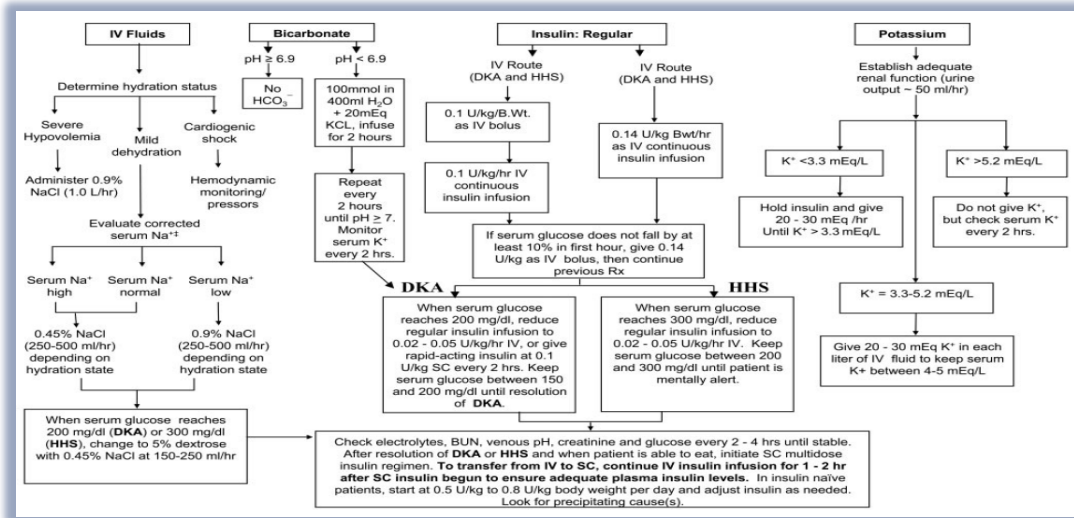https://abcd.care/joint-british-diabetes-societies-jbds-inpatient-care-group

It's Also Been Revised

Do These Regimens Work?

- No idea

- Another national survey is needed!

The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes

Joint British Diabetes Societies Inpatient Care Group

August 2012

Kitabchi AE et al Diabetes Care 2009;32(7):1335-1343

Summary

- The management of DKA and HHS has come a long way over the last 75 years

- The evolution of treatment pathways has been incremental and national guidelines have, to date, been consensus based

- Evidence is needed to see if they do what we want them to do

  Type in 'ABCD' and 'JBDS' into Google to get all the UK guidelines for free

Diabetes Related Emergencies

www.norfolkdiabetes.com

ketan.dhatariya@nnuh.nhs.uk

@ketandhatariya