DIABETIC EMERGENCIES

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AIM OF SESSION

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- Understand the differences between Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic State (HHS)

- Explore pathophysiology of DKA and HHS

- Explore the clinical presentation and management of both

- Test your knowledge round

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DIABETES MELLITUS

Diabetes mellitus is the term used to denote a complex group of endocrine disorders, which result in a disturbance of normal glucose metabolism

FACTS AND FIGURES

- About 8.5% of world's population has diabetes
- There are 3.8 million approx. people with diabetes in the UK, that's 1:20 people
- Diabetes is the leading cause of blindness in people of working age
- 24,000 people with diabetes die early, 75,000 deaths in total per year.
- www.diabetes.org.uk

HOSPITAL SPECIFIC FACTS

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- 1 in 25 inpatients with type 1 diabetes develops DKA during their hospital stay
- In 2010, 14,375 acute hospital admissions with DKA as primary diagnosis
- 1,800 annual admissions to ICU with a diagnosis of DKA
- 169 amputations are carried out each week nationally
- Diabetes accounts for 10% of the NHS budget

Rudd et al. (2013) Diabetes UK, National Diabetes Audit (2017)

BACK TO BASICS: INSULIN

- Insulin is a polypeptide or protein hormone essential in enabling the uptake of glucose into cells. Insulin homeostasis is essential for the normal metabolism of proteins, carbohydrates & fats
- Synthesized and stored in beta cells in The Islets of Langerhans
- In a healthy, normal weight person the average daily secretion of insulin is equlivant to 30-40 units
- Many synthetic types with varying speed of action and duration.

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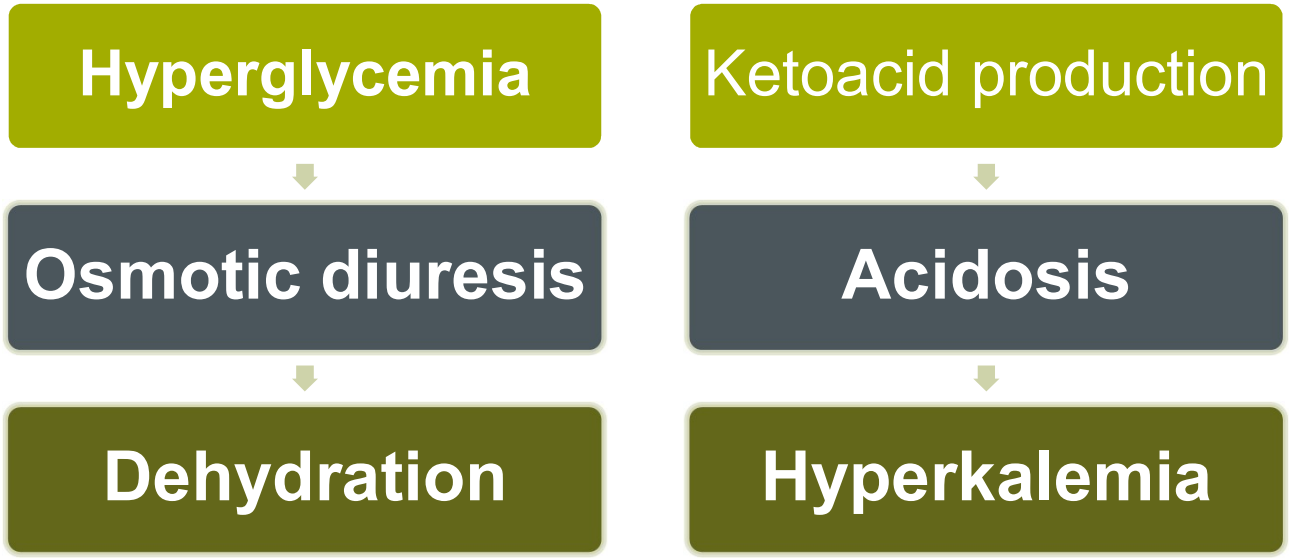
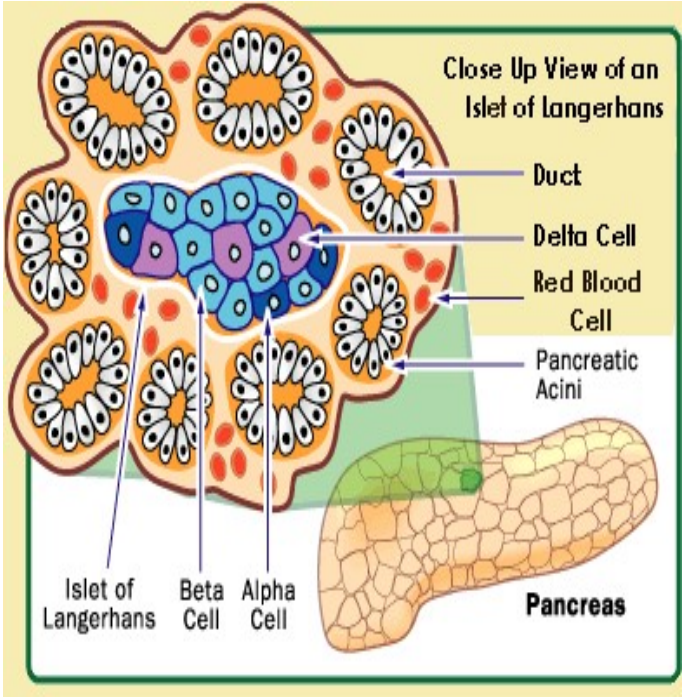
Insulin deficiency

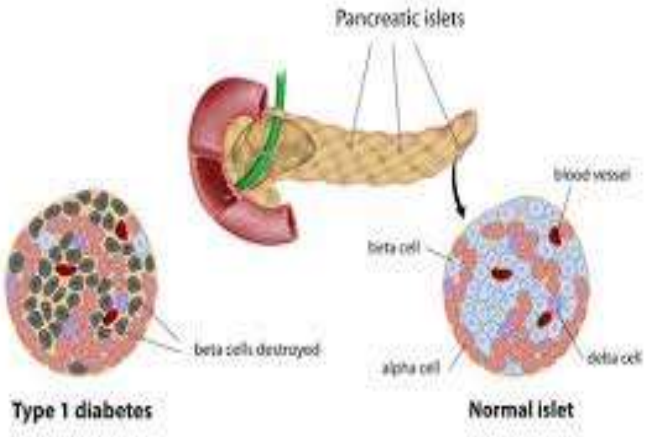


T1DM

T1DM results from destruction of the beta cells in the Islet of Langerhans in the pancreas, resulting in the more or less absolute deficiency of insulin

Most cases caused by autoimmune or idiopathic destruction of the Islets.





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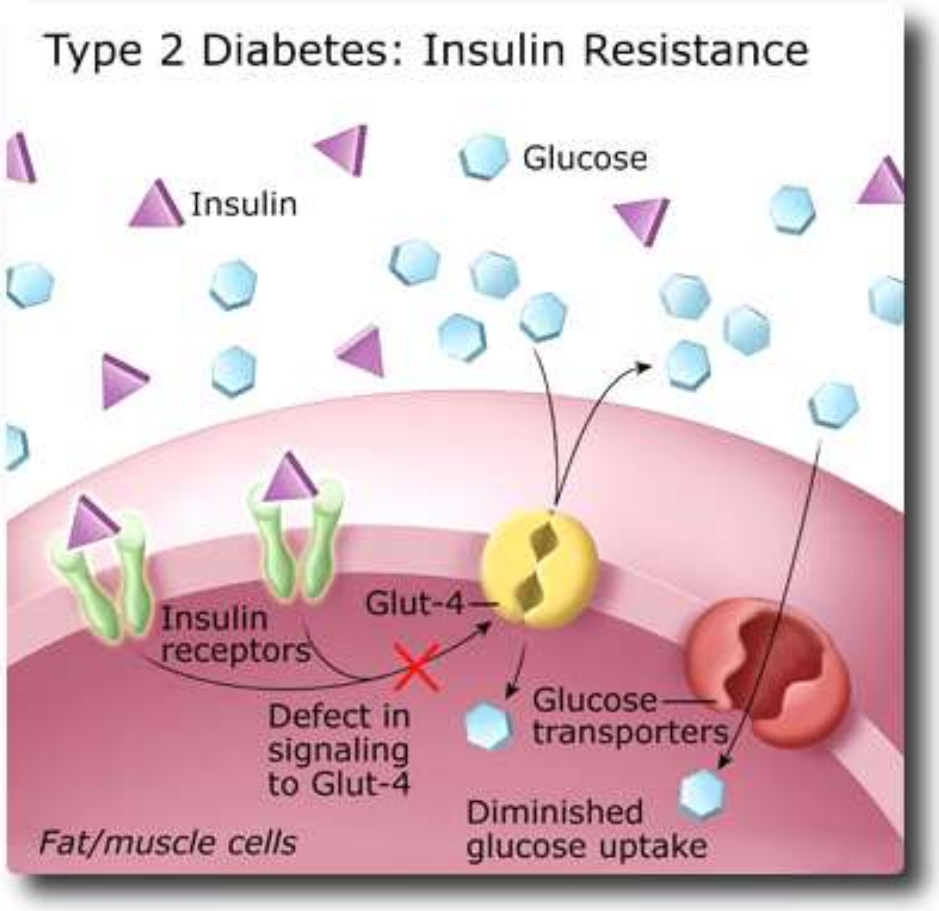
T2DM

Caused by impaired insulin secretion and resistance to its action, often secondary to obesity (80% approximately are obese).

May have normal or abnormally high levels of insulin: insulin resistance occurs

The GLUT-4 receptor mechanism on the cell may be the site of impaired insulin transport

Normally develops later in life >40 years



OTHER SPECIFIC TYPES OF DIABETES

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- Genetic defects of beta cell function
- Disease of the exocrine pancreas (pancreatitis/ carcinomas)
- Endocrinopathies
- Drug induced
- Infections
- Other genetic syndromes
- Gestational Diabetes

DIABETIC EMERGENCIES

DKA
HHS
Hypos
ICU Nurse!!

HYPOS

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- Results from a mismatch between nutrient intake, activity & insulin timing
- Can be mild(<3.9mmol/l), moderate, or severe (<2.2mmol/l)
- Mild hypo – usually adrenergic with symptoms of tremor, palpitation, sweating, hunger
- Severe hypo characterised by rapid deterioration in responsiveness, loss of consciousness & seizures, cardiac arrest. Requires immediate intervention to correct glucose level

NEUROGLYCOPENIA

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- A reduction in blood glucose in the brain caused by hypoglycemia

- We know the brain cannot make or store glucose and is dependent on blood supply

- Untreated results in seizures, unconsciousness, irreversible brain damage, death.

UNDERSTANDING DKA AND HHS

Both DKA and HHS result as relative or absolute insulin deficiency, this in turn is associated with hyperglycemia.

T2DM with DKA: syndrome known as ketosis prone diabetes
HHS more common complication of T2DM Venkatesh et al (2015).

HHS has replaced the terms hyperglycemia hyperosmolar nonketotic state (HONK)- this was revised as HHS may consists of variable degrees of clinical ketones

They differ clinically by severity of dehydration, ketosis and metabolic acidosis

EUGLYCEMIC DIABETIC KETOACIDOSIS

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Defined as euDKA, DKA without marked hyperglycaemia

Linked to SGLT-2 inhibitors (gliflozins)

Have a tendency to cause DKA in some patients

The biochemical reason for this is unclear, possible linked to noninsulin dependence glucose clearance, hyperglucagonaemia and volume depletion

Delayed recognition and diagnosis is a problem Peters et al (2015) Rendell (2019)

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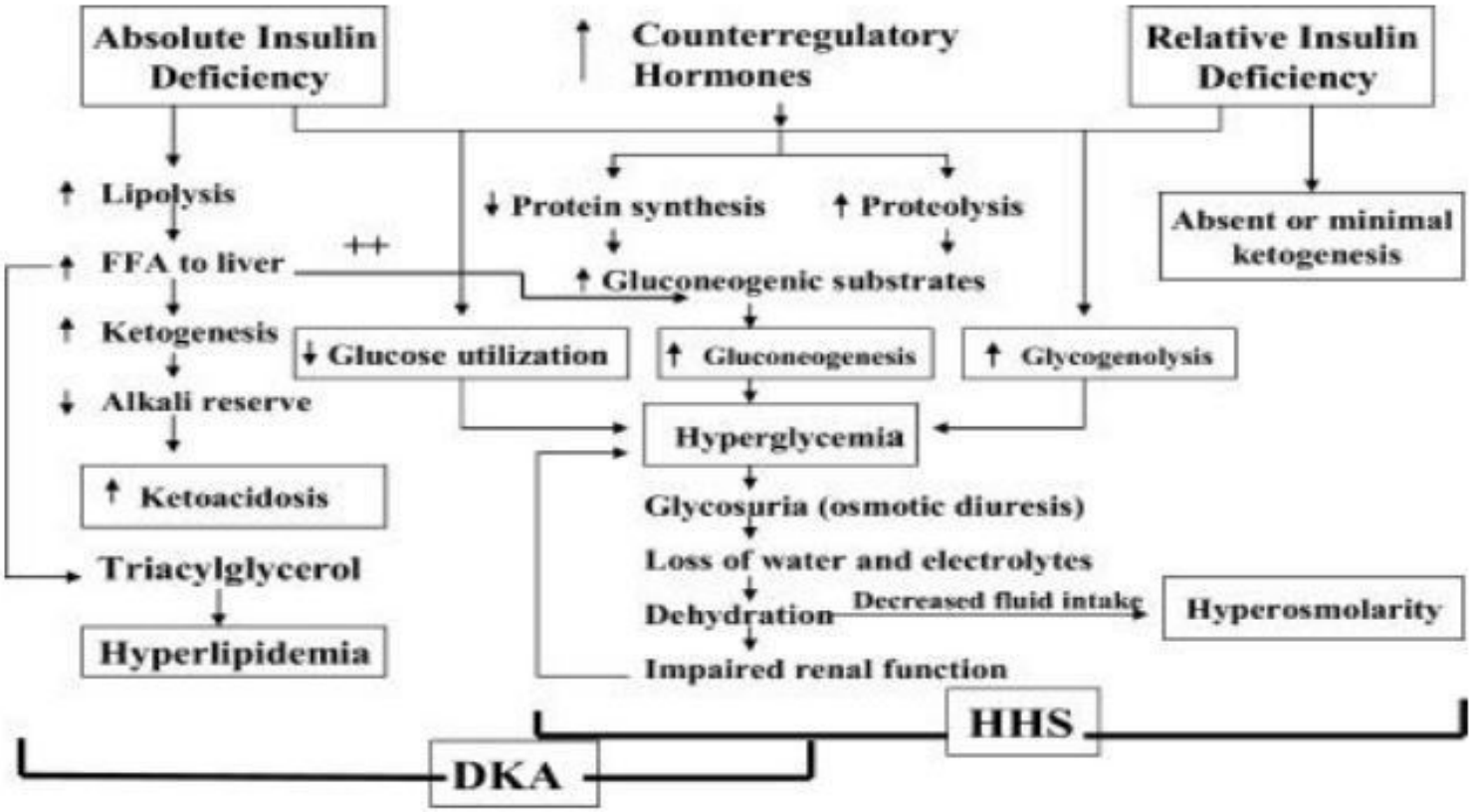
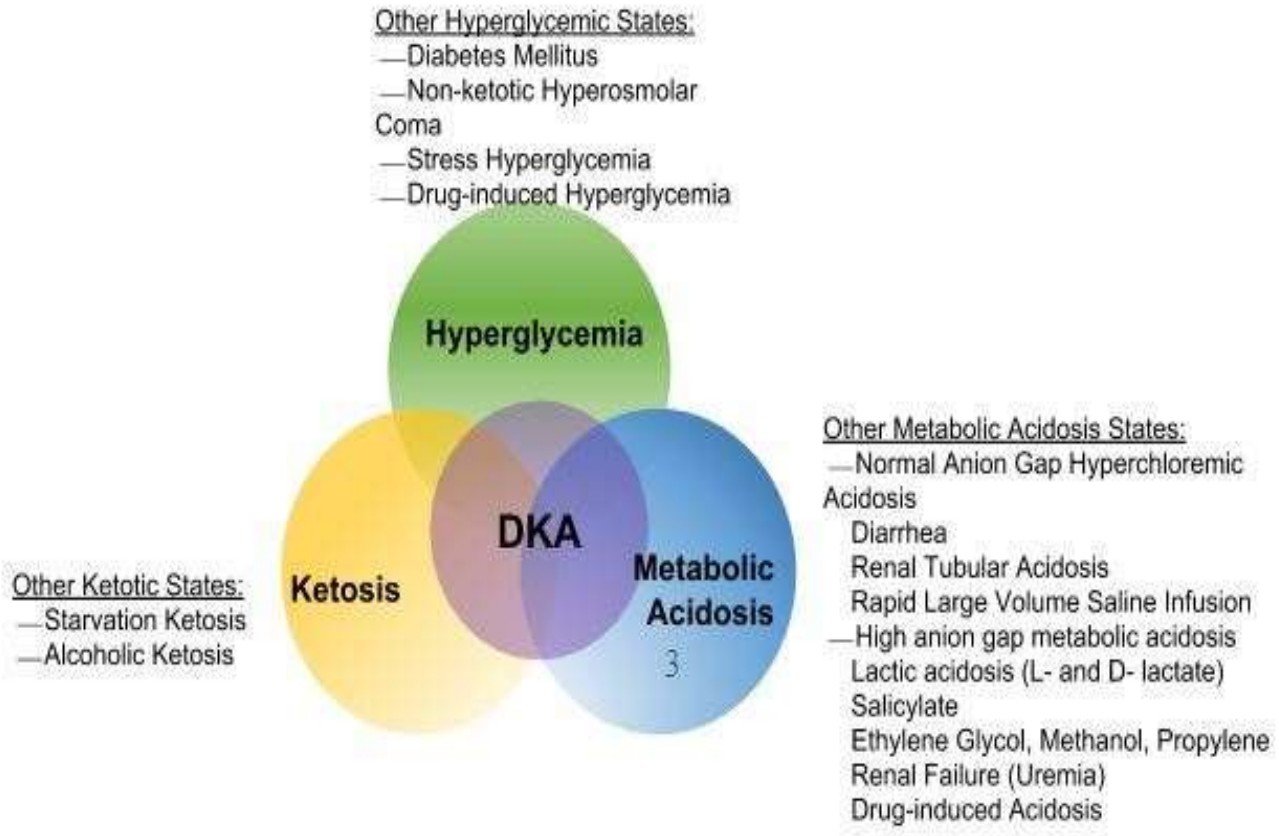
PATHOPHYSIOLOGY OF DKA AND HHS



TRIAD OF DKA


Other Hyperglycemic States:
—Diabetes Mellitus
—Non-ketotic Hyperosmolar Coma
—Stress Hyperglycemia
—Drug-induced Hyperglycemia
Hyperglycemia
DKA
Ketosis
Metabolic Acidosis
Other Ketotic States:
—Starvation Ketosis
—Alcoholic Ketosis
Other Metabolic Acidosis States:
—Normal Anion Gap Hyperchloremic Acidosis
Diarrhea
Renal Tubular Acidosis
Rapid Large Volume Saline Infusion
—High anion gap metabolic acidosis
Lactic acidosis (L- and D- lactate)
Salicylate
Ethylene Glycol, Methanol, Propylene
Renal Failure (Uremia)
Drug-induced Acidosis

PRECIPITATING CAUSES

Infection
Missed doses of insulin / poor adherence to treatment
New diagnosis of diabetes mellitus
Alcohol or drugs
Pancreatitis
Cardiovascular disease / Stroke
Diarrhoea and vomiting
Psychological illness relating to eating disorders
Severe physiological stress
Pregnancy
Drugs that affect carbohydrate metabolism

THE 5 I'S

Infection	Urinary, respiratory, skin
Infarction	Myocardial infarction, stroke, bowel, bone, skin
Infant on board	Pregnancy
Indiscretion with diet	Non-compliance with diabetic diet (e.g., sugar, carbohydrates or alcohol)
Insulin lack	Pump failure, skipping insulin doses

CLINICAL PRESENATION

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DKA

History (rapid onset)

Hyperventilation ‘Kussmaul’ breathing

Polyuria

Polydipsia

Weight loss

Nausea and vomiting

Confusion, altered consciousness, coma

Dehydration

Lethargic

Ketonic breath

Abdominal pain

HHS

History (gradual onset)

More common in the elderly

Polyuria

Dehydration

Confusion, agitation, drowsy

Focal neurological deficit, seizures, obtunded and coma

DIAGNOSTIC CRITERIA

EMCRIT.ORG

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Table 1—*Diagnostic criteria for DKA and HHS*

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

ICU ADMISSION CRITERIA

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Capillary ketones over 6 mmol/L

Bicarbonate level below 5 mmol/L

Venous/arterial pH below 7.1

Hypokalaemia on admission (under 3.5 mmol/L)

Glasgow coma score less than 12 or abnormal AVPU scale

Oxygen saturation below 92% on air (assuming normal baseline respiratory function)

Systolic blood pressure (BP) below 90 mm Hg

Pulse over 100 or below 60 bpm

Anion gap above 16.2

GOAL OF CLINICAL MANAGEMENT

DKA treat the underlying cause

Fluid Resuscitate

Suppression of ketogenesis

Reduction of blood glucose

Correction of electrolyte disturbance

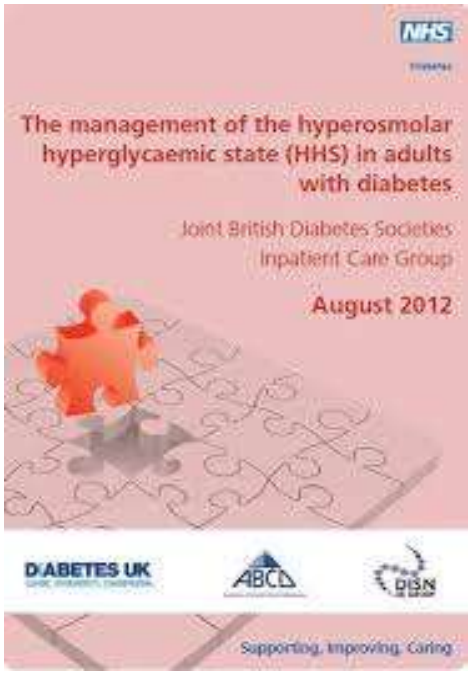
HSS treat the underlying cause

Normalise the osmolality

Replace fluid and electrolyte losses

Normalise blood glucose

TREATMENT LETS DISCUSS YOUR PRACTICE AREAS



The Management of Diabetic Ketoacidosis in Adults

For young people under the age of 18 years use British Society of Paediatric Endocrinology and Diabetes (BSPED) guidelines: http://www.bsped.org.uk/professional/guidelines/docs/DKAGuideline.pdf

Diagnostic criteria: all three of the following must be present

- capillary blood glucose above 11 mmol/L
- capillary ketones above 3 mmol/L or urine ketones ++ or more
- venous pH less than 7.3 and/or bicarbonate less than 15 mmol/L

BOX 1: Immediate management: time 0 to 60 minutes

(T=0 at time intravenous fluids are commenced)

If intravenous access cannot be obtained request critical care support immediately

Action 1: Commence 0.9% sodium chloride solution (use large bore cannula) via infusion pump.
See Box 2 for rate of fluid replacement

Action 2: Commence a fixed rate intravenous insulin infusion (IVII). (0.1unit/kg/hr based on estimate of weight) 50 units human soluble insulin (Actrapid® or Humulin S®) made up to 50ml with 0.9% sodium chloride solution. If patient normally takes long acting insulin analogue (Lantus®, Levemir®) continue at usual dose and time

Action 3: Assess patient
- o Respiratory rate; temperature; blood pressure; pulse; oxygen saturation
- o Glasgow Coma Scale
- o Full clinical examination

Action 4: Further investigations
- Capillary and laboratory glucose
- Venous BG
- U & E
- FBC
- Blood cultures
- ECG
- CXR
- MSU

Action 5: Establish monitoring regimen
- Hourly capillary blood glucose
- Hourly capillary ketone measurement if available
- Venous bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter
- 4 hourly plasma electrolytes
- Continuous cardiac monitoring if required
- Continuous pulse oximetry if required

Action 6: Consider and precipitating causes and treat appropriately

HDU/level 2 facility and/or insertion of central line may be required in following circumstances (request urgent senior review)

- Young people aged 18-25 years
- Elderly
- Pregnant
- Heart or kidney failure
- Other serious co-morbidities
- Severe DKA by following criteria
  - Blood ketones above 6 mmol/L
  - Venous bicarbonate below 5 mmol/L
- Venous pH below 7.1
- Hypokalaemia on admission (below 3.5 mmol/L)
- GCS less than 12
- Oxygen saturation below 92% on air (Arterial blood gases required)
- Systolic BP below 90 mmHg
- Pulse over 100 or below 60 bpm
- Anion gap above16 [Anion Gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$]

BOX 2: Initial fluid replacement

Restoration of circulating volume is priority

Systolic BP (SBP) below 90mmHg

Likely to be due to low circulating volume, but consider other causes such as heart failure, sepsis, etc.

- Give 500ml of 0.9% sodium chloride solution over 10-15 minutes. If SBP remains below 90mmHg repeat whilst requesting senior input. Most patients require between 500 to 1000ml given rapidly.
- Consider involving the ITU/critical care team.
- Once SBP above 90mmHg give 1000ml 0.9% sodium chloride over next 60 minutes. Addition of potassium likely to be required in this second litre of fluid

Systolic BP on admission 90 mmHg and over

- Give 1000ml 0.9% sodium chloride over first 60 minutes

Potassium replacement

Potassium level (mmol/L)	Potassium replacement mmol/L of infusion solution
> 5.5	Nil
3.5-5.5	40 mmol/L
< 3.5	senior review – additional potassium required

BOX 3: 60 minutes to 6 hours

Aims of treatment:

- Rate of fall of ketones of at least 0.5 mmol/L/hr OR bicarbonate rise 3 mmol/L/hr and blood glucose fall 3 mmol/L/hr
- Maintain serum potassium in normal range
- Avoid hypoglycaemia

Action 1: Re-assess patient, monitor vital signs

- Hourly blood glucose (lab blood glucose if meter reading 'HI')
- Hourly blood ketones if meter available
- Venous blood gas for pH, bicarbonate and potassium at 60 minutes, 2 hours and 2 hourly thereafter.
- If potassium is outside normal range, re-assess potassium replacement and check hourly. If abnormal after further hour seek immediate senior medical advice

Action 2: Continue fluid replacement via infusion pump as follows:

- 0.9% sodium chloride 1L with potassium chloride over next 2 hours
- 0.9% sodium chloride 1L with potassium chloride over next 2 hours
- 0.9% sodium chloride 1L with potassium chloride over next 4 hours
- Add 10% glucose 125ml/hr if blood glucose falls below 14 mmol/L

More cautious fluid replacement in young people aged 18-25 years, elderly, pregnant, heart or renal failure. (Consider HDU and/or central line)

Action 3: Assess response to treatment

Insulin infusion rate may need review if

- Capillary ketones not falling by at least 0.5 mmol/L/hr
- Venous bicarbonate not rising by at least 3 mmol/L/hr
- Plasma glucose not falling by at least 3 mmol/L/hr
- Continue fixed rate IVII until ketones less than 0.3 mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18 mmol/L

If ketones and glucose are not falling as expected always check the insulin infusion pump is working and connected and that the correct insulin residual volume is present (to check for pump malfunction).

If equipment working but response to treatment inadequate, increase insulin infusion rate by 1 unit/hr increments hourly until targets achieved.

Additional measures

- Regular observations and Early Warning Score (EWS)
- Accurate fluid balance chart, minimum urine output 0.5ml/kg/hr
- Consider urinary catheterisation if incontinent or anuric (not passed urine by 60 minutes)
- Nasogastric tube with airway protection if patient obtunded or persistently vomiting
- Measure arterial blood gases and repeat chest radiograph if oxygen saturation less than 92%
- Thromboprophylaxis with low molecular weight heparin
- Consider ECG monitoring if potassium abnormal or concerns about cardiac status

BOX 4: 6 to 12 hours

Aims:

- Ensure clinical and biochemical parameters improving
- Continue iv fluid replacement
- Avoid hypoglycaemia
- Assess for complications of treatment e.g. fluid overload, cerebral oedema
- Treat precipitating factors as necessary

Action 1: Re-assess patient, monitor vital signs

- If patient not improving by criteria in Box 3 seek senior advice
- Continue iv fluid via infusion pump at reduced rate
  - o 0.9% sodium chloride 1L with potassium chloride over 4 hours
  - o 0.9% sodium chloride 1L with potassium chloride over 6 hours
- Add 10% glucose 125ml/hr if blood glucose falls below 14 mmol/L

Reassess cardiovascular status at 12 hours; further fluid may be required.

Check for fluid overload

Action 2 – Review biochemical and metabolic parameters

- At 6 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution is defined as ketones less than 0.3 mmol/L, venous pH over 7.3 (do not use bicarbonate as a surrogate at this stage).
- Ensure referral has been made to diabetes team

If DKA not resolved review insulin infusion (see BOX 3 Action 3)
If DKA resolved go to BOX 6

BOX 5: 12 to 24 HOURS

Expectation: By 24 hours the ketonaemia and acidosis should have resolved. Request senior review if not improving

Aim:

- Ensure that clinical and biochemical parameters are continuing to improve or are normal
- Continue iv fluid replacement if not eating and drinking.
- If ketonaemia cleared and patient is not eating and drinking move to a variable rate IVII as per local guidelines
- Re-assess for complications of treatment e.g. fluid overload, cerebral oedema
- Continue to treat precipitating factors
- Transfer to subcutaneous insulin if patient is eating and drinking normally.

Action 1 – Re-assess patient, monitor vital signs
Action 2 – Review biochemical and metabolic parameters

- At 12 hours check venous pH, bicarbonate, potassium, capillary ketones and glucose
- Resolution is defined as ketones <0.3 mmol/L, venous pH>7.3
- If not resolved review fluid **Box 4 Action 1** and insulin infusion **Box 3 Action 3**

If DKA resolved go to Box 6

BOX 6: Resolution of DKA

Expectation: Patient should be eating and drinking and back on normal insulin.
If DKA not resolved identify and treat the reasons for failure to respond.
This situation is unusual and requires senior and specialist input.

Transfer to subcutaneous insulin

Convert to subcutaneous regime when biochemically stable (capillary ketones less than 0.3 mmol/L, pH over 7.3) and the patient is ready and able to eat. **Do not discontinue intravenous insulin infusion until 30 minutes after subcutaneous short acting insulin has been given**
Conversion to subcutaneous insulin should be managed by the Specialist Diabetes Team. If the team is not available use local guidelines. If the patient is newly diagnosed it is essential they are seen by a member of the specialist team prior to discharge.
Arrange follow up with specialist team.

Groups represented: Association of British Clinical Diabetologists; British Society for Endocrinology and Diabetes and Association of Children's Diabetes Clinicians; Diabetes Inpatient Specialist Nurse (DISN) Group; Diabetes UK; NHS Diabetes (England); Northern Irish Diabetologists; Society of Acute Medicine; Welsh Endocrine and Diabetes Society, Scottish Diabetes Group.

HHS MANAGEMENT

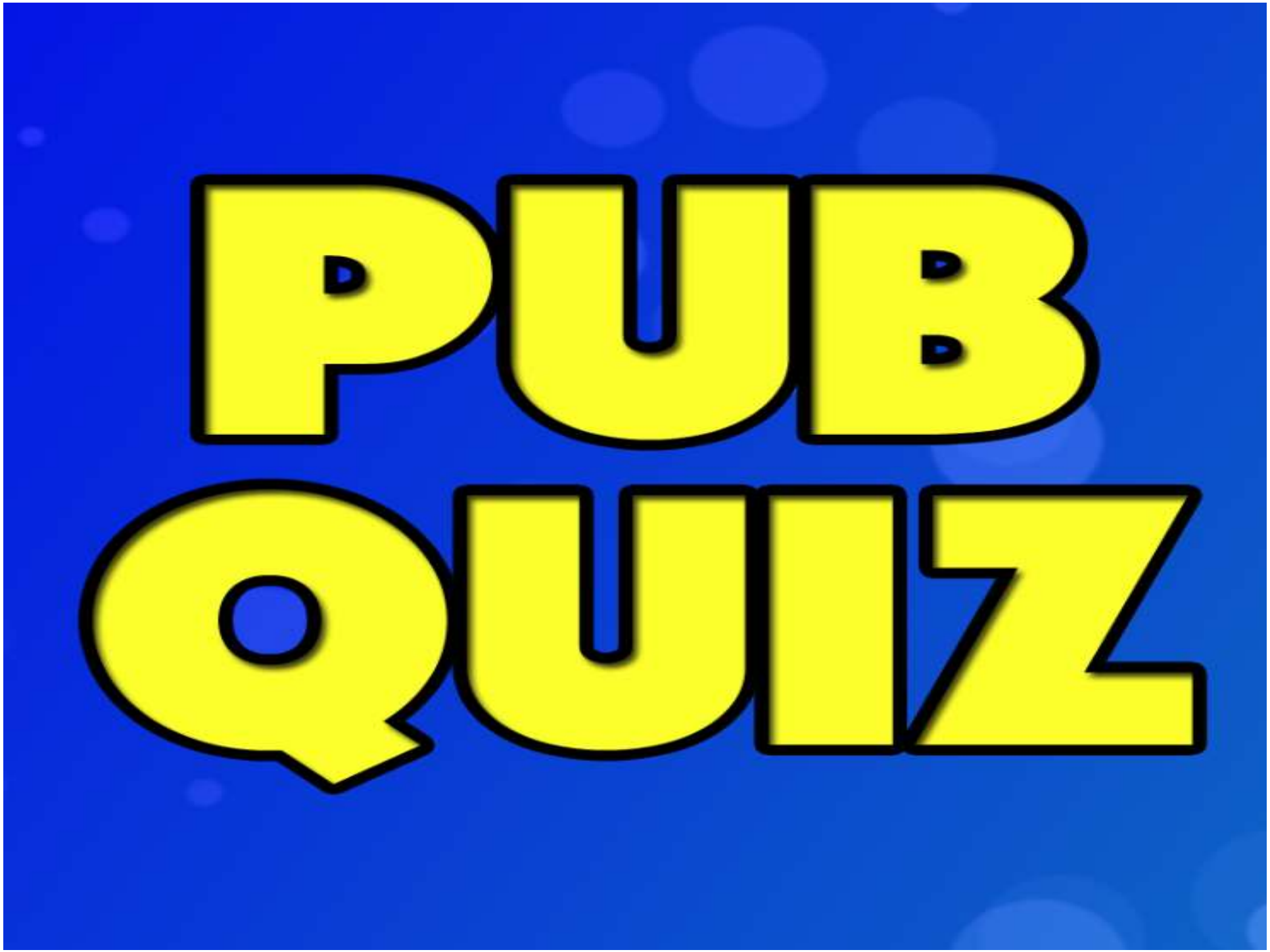
- Goals-
- Fluid resuscitate, replace 50% of fluid losses in first 12 hours
- Replace electrolytes-risks with K+ pending on renal function
- Vigorous fluid resuscitation should clear hyperglycaemia
- If ketones present commence FRII insulin 0.05units/kg/hr
- VTE prophylaxis
- Foot protection / pressure area care

PREDICTIONS OF MORTALITY

Patients not on insulin at presentation have a worse outcome compared to those with prior insulin therapy. Venkatesh *et al* (2015)

Elevated plasma urea concentration is associated with increased mortality >25mmols/L. Venkatesh *et al* (2015)

Gald et al (2019) recent retrospective study had 5 deaths in a cohort of 84 patients. 3 of these deaths related to DKA directly. The link to these deaths is unclear, however the study did identify that almost half of the patients had hypokalaemia in the first 24hours.


PUB
QUIZ

ROUND 1

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1. What class of drugs have been linked to euglycemic diabetes? Can you give an example?

   Glifozins, dapaglifozin, canaglifozin, canaglifozin/metformin

2. How do steroids cause T2DM?

   Steroids can cause the liver to become resistant to insulin, it carries on releasing glucose

3. What counter regulatory hormones are released during DKA?

   Glucagon, growth hormone, cortisol and catecholamines-resulting in high BM secondary to accelerated gluconeogenesis.

4. What are the three components that result in DKA?

   Hyperglycemia, acidemia, ketonemia

5. How does HHS differ from DKA clinically?

   Severity of dehydration, ketosis and metabolic acidosis

ROUND 2

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1. List 4 common clinical presentation features of DKA and HHS

   Abdo pain, nausea and vomiting, confusion and dehydration

2. List 3 clinical presentation features that may differ from DKA in HHS

   History, gradual onset, high osmolality, focal neurological deficit

3. What is the goal of treatment in DKA?

   Stop ketogenesis, reverse acidosis, normalise BM, fluid resuscitate

4. How does insulin cause hypokalemia?

   Insulin can push K+ from the extracellular to intracellular space

5. What are the risk of rapid fluid resuscitation in the elderly?

   Heart failure, cerebral oedema

CASE STUDY, HARVEY

PMH: Unwell 3 months ago with influenzia, last 36 hours polyuria, nausea, vomiting and increased thirst.

Fit and well, third year student. No known drug / ETOH intake. Weight 90 kg approx.

On arrival to ICU:

Vital signs: RR 35 labored, SpO2 90% NRB, HR 125 reg, BP 90/50mmhg, Temp 37.5. GCS 13/15. Confused and agitated.

Last venous gas pH 7.1, Bicarbonate 10, K+ 3.0mmols Na+ 135mmols/L K+ 6.0mmols/L

BM –Hi

Capillary ketones 6 mmols/L

Treatment to date: 1 L Normal Saline, 2nd liter running over 1 hour, antiemetic, Actrapid Insulin Infusion fixed rate 6 units/hour.

CASE STUDY, DORIS

Cardiac arrest call to ward: found to be unresponsive ? Cause CT head pending, managed with PR lorazepam and loading does phenytoin.

Vitals on arrival to ICU: RR 10, Spo2 96% NRB, HR 90 reg, BP 88/44mmhg. Postictal GCS 11/15. Guidel airway insitui. Incontinent of urine.

PMH: T2DM diet controlled, admitted with falls unsteady gait ? Cause. Weight 75 kg approx.

Hypertension, CKD stage 2

BM 35mmols/L, blood ketones 2 mmols/L, pH 7.35, serum osmolality 376 mosmol/ kg K+ 3.8mmols/L Na 153mmols/L.

FUTURE RESEARCH

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The patient experience

Prevention and education

Insulin regimes and continuing long acting insulin

Point of care testing, the patient

Best clinical area to monitor and care for patients

Standardised protocols

Euglycemic DKA, pharmacokinetics and pharmacodynamics of SGLT-2 inhibitors

Prediction of mortaility

SUPPORT

www.diabetes.org.uk

helpline@diabetes.org.uk

Diabetes UK 0345-123-2399

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