



Clinical Guideline

Practical Management of Hyperglycaemic Hyperosmolar State (HHS) in children

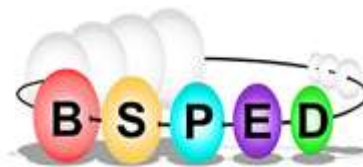
SETTING

FOR STAFF Medical and nursing staff

PATIENTS Children and young people with diabetes mellitus

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Patient group

This guideline is intended for use in managing Hyperglycaemic Hyperosmolar State (HHS) for all children and young people up to the age of 18 years with diabetes mellitus.

1. Introduction

Hyperglycaemic Hyperosmolar State (HHS), previously known as Hyperosmolar Hyperglycaemic Non-Ketotic Coma (HONK), is a triad of severe hyperglycaemia, significant increase in serum osmolality and severe dehydration without marked ketoacidosis. It is a life threatening complication of some forms of uncontrolled diabetes mellitus with significant mortality and morbidity. It is important that HHS is distinguished from Diabetic Ketoacidosis (DKA), which presents with hyperglycaemia, ketosis and acidosis, as the management is significantly different. Both disorders present with dehydration, hyperglycaemia and may show altered levels of mental status or coma. The prevalence of HHS in children and young people is increasing owing to the rise in obesity and Type 2 Diabetes.

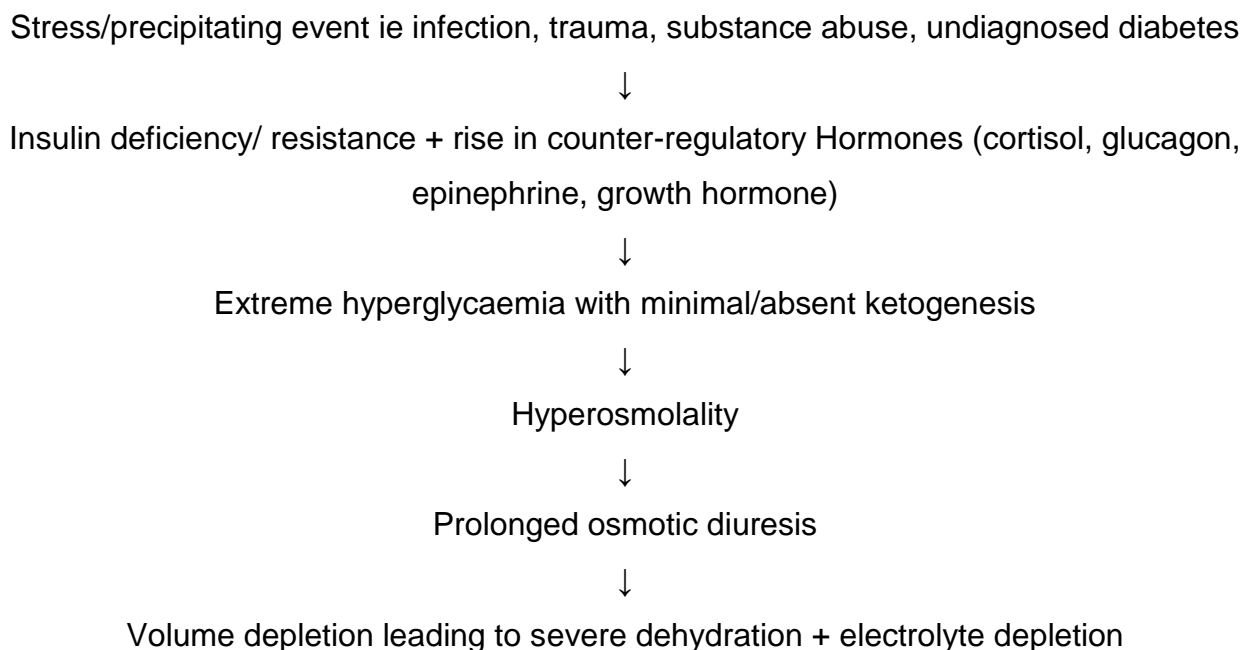
The evidence base for managing HHS in children and young people is scant. There are no prospective studies to guide treatment and current recommendations are extrapolated from adult studies and an understanding of the pathophysiology of HHS. Current studies of HHS in children mainly describe children with Type 2 diabetes and are limited to case series or single-centre reviews. The International Society for Pediatric and Adolescent Diabetes (ISPAD) has written a guideline for the recognition and management of HHS, which underpins this guidance.

2. Pathophysiology

HHS can be triggered by acute stress, illness, trauma or substance misuse. A relative insulin deficiency or insulin resistance then leads to increased gluconeogenesis and glycogenolysis causing significant hyperglycaemia. However, in contrast to DKA, there is enough endogenous insulin release to prevent ketosis.. The often extreme hyperglycaemia causes the plasma osmolality to rise, which in turn causes a shift in intracellular water into the extracellular space. This leads to hypovolaemia from body water loss and hypertonic dehydration due to excess

sodium. The triad of marked hyperglycaemia, hyperosmolality and significant dehydration causes increased production of counter regulatory hormones including cortisol, catecholamines and glucagon, which then drives further hyperglycaemia (Figure 1)

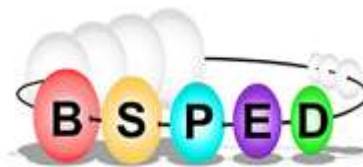
Figure 1. Pathophysiology of HHS



Children and young people who present with altered consciousness and severe dehydration are at increased risk of developing rhabdomyolysis or malignant hyperthermia.

Epidemiology

HHS may occur in children with Type 2 diabetes, Type 1 diabetes, and in infants, especially those with 6q24-related transient neonatal diabetes mellitus. HHS is more classically seen in elderly patients with Type 2 diabetes, although it can rarely occur as a complication in those without diabetes following severe burns, peritoneal dialysis, or haemodialysis. There is increased risk of developing HHS in patients taking certain drugs such as corticosteroids, diuretics, beta-blockers, phenytoin, diazoxide and methadone. HHS is rising in adolescents with Type 2 diabetes, and extreme obesity (body mass index > 30).



Children with undiagnosed diabetes at the time of presentation with HHS usually have Type 2 Diabetes, but not in all cases. A recent survey of hospital admissions with HHS in the US reported that as many as 70% had Type 1 diabetes. Children and young people developing diabetes who are unable to ask for drinks, such as those with learning difficulties, are particularly susceptible to HHS resulting from dehydration.

3. Diagnosis

There are differences in the clinical presentation of DKA and HHS. DKA usually occurs in lean, younger patients with type 1 diabetes and develops within hours to days, while in contrast, HHS is more likely to occur in older, obese patients with type 2 diabetes and can take days or weeks to fully develop. Both conditions present with polydipsia and polyuria leading to dehydration and may have abdominal pain with nausea and vomiting due to the acidosis. Dehydration is often more pronounced in HHS, and Kussmaul respiration (rapid and deep respiration) with acetone breath commonly seen in DKA, is generally absent in HHS.

A definitive diagnosis of HHS should be confirmed through laboratory investigation.

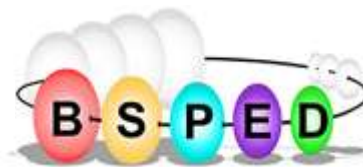
The ISPAD clinical practice consensus guideline criteria for diagnostic features of HHS include:

- Plasma glucose concentration >33.3 mmol/L
- Venous pH > 7.25 ; arterial pH > 7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonaemia
- *Effective serum osmolality > 320 mOsm/kg
- Altered consciousness (e.g., obtundation, combativeness, seizures)
- Anion Gap may be variable[#]

*Serum osmolality = $2 \times$ serum sodium + serum glucose + serum urea (all in mmol/L)

[#] Anion gap = (+) – (Cl⁻ + HCO₃⁻)

There may be overlap between HHS and DKA, making management challenging. Mild acidosis can be present in HHS due to lactic acidosis resulting from severe dehydration. There may also



be extreme hyperglycaemia in DKA resulting in hyperosmolality, particularly if high glucose drinks were used by patients to quench thirst.

Despite being severely dehydrated, children and young people with HHS may show fewer clinical signs of dehydration due to the hyperosmolality maintaining intravascular volume. In addition, urinary losses continue to be large during treatment and so replacement of fluid quickly is required to prevent shock.

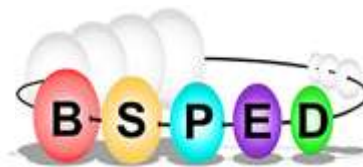
Recommendations –

Confirm the diagnosis of HHS using laboratory investigations and the ISPAD clinical practice consensus guideline criteria:

- Plasma glucose concentration >33.3 mmol/L
- Venous pH > 7.25 ; arterial pH > 7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonaemia
- Effective serum osmolality > 320 mOsm/kg
- Altered consciousness
- Anion Gap may be variable

4. Management

HHS is a medical emergency and patients must be admitted to a hospital with facilities for paediatric resuscitation. Prompt recognition of the condition and timely treatment is extremely important. Management of HHS includes general resuscitation, rapid restoration of the intravascular volume, replacement of fluid and electrolyte deficits, and correction of hyperglycaemia and hyperosmolality. All children and young people with HHS should be admitted to high dependency or intensive care unit for frequent monitoring as complications are common and they require a high level of nursing and medical care.



General Resuscitation:

Airway:

- Ensure that the airway is patent. Consider the use of airway adjuncts.
- If consciousness level is reduced or child has recurrent vomiting, insert a nasogastric tube, aspirate and leave on open drainage.

Breathing:

- Give 100% oxygen by face-mask

Circulation:

- Insert IV cannula and take blood samples (glucose, blood gas, sodium, potassium, chloride, magnesium, calcium, phosphate, urea, creatinine)
- Cardiac monitor for T waves
- Measure blood pressure and heart rate
- Start resuscitation fluid urgently

Fluids

Patients usually present with severe dehydration following a prolonged phase of osmotic diuresis. Losses of water exceed sodium losses resulting in hypertonic dehydration. The principal aim of fluid resuscitation is restoration of the intravascular volume using isotonic fluid (0.9% sodium chloride solution) until haemodynamic stabilisation

- Give 20ml/kg of 0.9% sodium chloride solution as a bolus if signs of shock. Repeat boluses should be given as needed until peripheral perfusion is restored.
- Once vital signs have stabilised, replacement fluids of 0.45-0.9% sodium chloride solution over 24 to 48 hours, assuming fluid deficit of 12-15% body weight. It may be necessary to continue with 0.9% sodium chloride solution if circulating volume remains depleted.
- Aim for a gradual decline in plasma sodium of 0.5mmol/L per hour by adjusting sodium concentrations in fluids
- Plasma glucose should fall by around 4-6 mmol/L per hour with adequate rehydration



- If plasma glucose decreases by more than 5mmol/L per hour after the first 4 hours, it is recommended that consideration is given to adding 5% glucose to the rehydration fluids.
- Failure of expected fall in plasma glucose should prompt reassessment of renal function.
- Urinary loss replacement is recommended with 0.45-0.9% sodium chloride solution because of the high risk of circulatory collapse.

Underlying Precipitating Causes

Once fluid resuscitation has started, underlying or precipitating causes of HHS (such as infection) must be identified and treated at the same time. Precipitating causes of HHS include infection, undiagnosed diabetes and substance abuse.

A full clinical assessment should be carried out, including possible risk factors:

- history from family/patient
- physical examination looking for acanthosis nigricans, obesity, signs of trauma or infection
- mental state
- neurological state
- renal function assessment
- family history etc.

Consider further investigations including full blood count, CXR, CSF, throat swab, blood culture, urinalysis, culture and sensitivity etc. Administer broad spectrum IV antibiotics if infection is presumed or suspected, due to the high risk of mortality with HHS.

Monitoring

Careful monitoring is crucial to ensure fluid and electrolytes are replaced adequately and thus prevent complications. One-to-one nursing is vital.



The following should be recorded in the nursing and medical notes

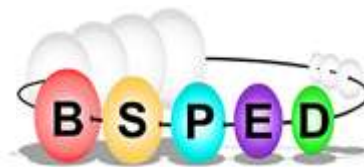
- Volume of fluid administered hourly
- Urine output hourly
- Hourly blood glucose concentration
- Plasma electrolytes (sodium, potassium, chloride, magnesium, calcium, phosphate, urea, creatinine) 2-3 hourly
- Hourly blood pressure and basic observations of vital signs, neuro observations
- Hourly level of consciousness initially, using the modified Glasgow coma score
- ECG monitoring, for potassium changes

Nursing staff should be asked to immediately alert medical staff to any symptoms such as headache, slowing of pulse rate, or any change in either conscious level or behaviour, which may indicate cerebral oedema, or any changes in the ECG trace, especially signs of hypokalaemia, including ST segment depression and prominent U-waves.

Insulin Treatment

Do not start insulin until adequate fluid resuscitation and rehydration has been achieved. High glucose concentration helps the maintenance of intravascular volume therefore overaggressive insulin treatment and a rapid drop in plasma glucose can lead to circulatory collapse and thrombosis if fluid replacement is inadequate. Insulin is given at much lower rates than in DKA because there is minimal ketosis.

- Insulin treatment should be started when plasma glucose is no longer falling at a rate of at least 3 mmol/L per hour.
- Consider starting insulin treatment earlier in patients with more severe ketosis or acidosis (a mixed DKA / HHS picture)
- Start continuous insulin infusion at approximately 0.025-0.05 units/kg/hour, and aim to achieve a fall of plasma glucose of 3-4mmol/L per hour
- Do not give insulin boluses or subcutaneous insulin



Electrolytes

Patients with HHS will have significant depletion of potassium, phosphate and magnesium.

Potassium

- Prior to insulin starting, potassium replacement is probably only needed if plasma potassium concentration is less than 5.5 mmol/l. Give potassium chloride 40mmol in 1000 ml of replacement fluids once renal function has been assessed.
- During insulin treatment and rehydration, serum potassium levels fall rapidly; therefore, it is recommended that potassium replacement should be initiated before insulin is started, with the goal of maintaining a plasma potassium concentration in the range of 4–5 mmol/L. Higher rates of potassium may be required once insulin is initiated
- Monitor potassium levels 2-3 hourly with blood gases
- ECG monitoring is required to recognise early signs of potassium derangement.

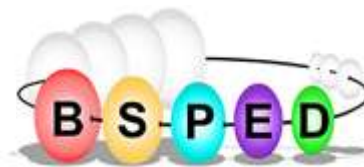
Phosphate

Phosphate should be checked every 2-3 hours as severe hypophosphataemia can contribute to rhabdomyolysis, haemolytic uraemia, muscle weakness and paralysis. There are no studies on the use of phosphate therapy for HHS and the beneficial effect of phosphate therapy is purely theoretical.

- If replacement required, give a 50:50 mix of potassium phosphate and potassium chloride or potassium acetate in the IV fluids
- However be aware that phosphate administration can lead to a risk of hypocalcaemia, tetanus and soft tissue calcification

Magnesium

Magnesium deficiency both exacerbates potassium loss and decreases cellular potassium uptake. Hypomagnesaemia increases distal potassium secretion and impairs sodium-potassium-adenosine triphosphatase (Na-K-ATPase), which consequently decreases cellular



uptake of potassium ions. Magnesium replacement should be considered in patients with low potassium levels and severe hypomagnesaemia and/or hypocalcaemia

- Give Magnesium 25-50 mg/kg per dose for 3-4 doses given every 4 to 6 hours with a maximum infusion rate of 150mg/min and a maximum of 2grams/hour
- There is however no evidence in HHS of whether replacement is beneficial.

Bicarbonate

Bicarbonate therapy is contraindicated in HHS because of the risk of severe hypokalaemia and bicarbonate therapy may also adversely affect oxygen delivery.

Recommendations Summary –

- Correct shock with 20ml/kg boluses of 0.9% Sodium Chloride
- Once vital signs have stabilised, replace fluids over 24-48 hours assuming a fluid deficit of 12-15% using 0.45%-0.9% Sodium Chloride aiming for a reduction in plasma sodium of 0.5 mmol/l per hour. (ISPAD recommendations)
- Replace urinary losses using 0.45%-0.9% Sodium Chloride
- Replace potassium (40mmol/1 litre of rehydration fluid) once renal function is known
- Identify and treat any precipitating factors. In particular have a low threshold for the use of broad spectrum antibiotics if infection is suspected.
- Patients should be nursed with 1 to 1 care in an HDU or PICU setting
- ECG monitoring is required to detect signs of potassium derangement
- Monitor electrolytes every 2-3 hours
- Start insulin only after adequate fluid replacement and when plasma glucose is no longer decreasing by 3 mmol/l per hour. Start continuous insulin infusion at approximately 0.025-0.05 units/kg/hour, and aim to achieve a fall of glucose of 3-4mmol/L per hour
- Consider phosphate and magnesium replacement
- Patients must be reviewed by a senior paediatrician and discussed with consultants with expertise in paediatric diabetes and paediatric intensive care.



5. Outcomes and Complications

Delay in diagnosis of HHS in children is common. Several complications have been reported in children and young people with HHS, and morbidity and mortality from these complications are significant. Venous thrombosis can occur, especially when central venous catheters are inserted. In adults, low molecular weight heparin has been recommended, but it is not advised routinely in children. It should be considered if the individual risk of thrombosis is very high. A number of cases of rhabdomyolysis in children with HHS have been reported. A pattern of malignant hyperthermia, compartment syndrome and ventricular arrhythmias with a high mortality rate has also been reported in several children. Rapid correction of hyperglycaemia and hyperosmolality can lead to cerebral oedema because of an osmotic gradient between brain and plasma. Other fatal complications of HHS include acute renal failure, arrhythmias, and cerebral and systemic vascular accidents.

Due to the high mortality and morbidity associated with HHS, patients should be reviewed by a senior paediatrician and discussed with Consultants with expertise in diabetes and paediatric intensive care. The mortality rate associated with HHS is reported to be considerably higher in adult patients, ranging from 10% to 20%, compared with 1% to 5% in DKA.

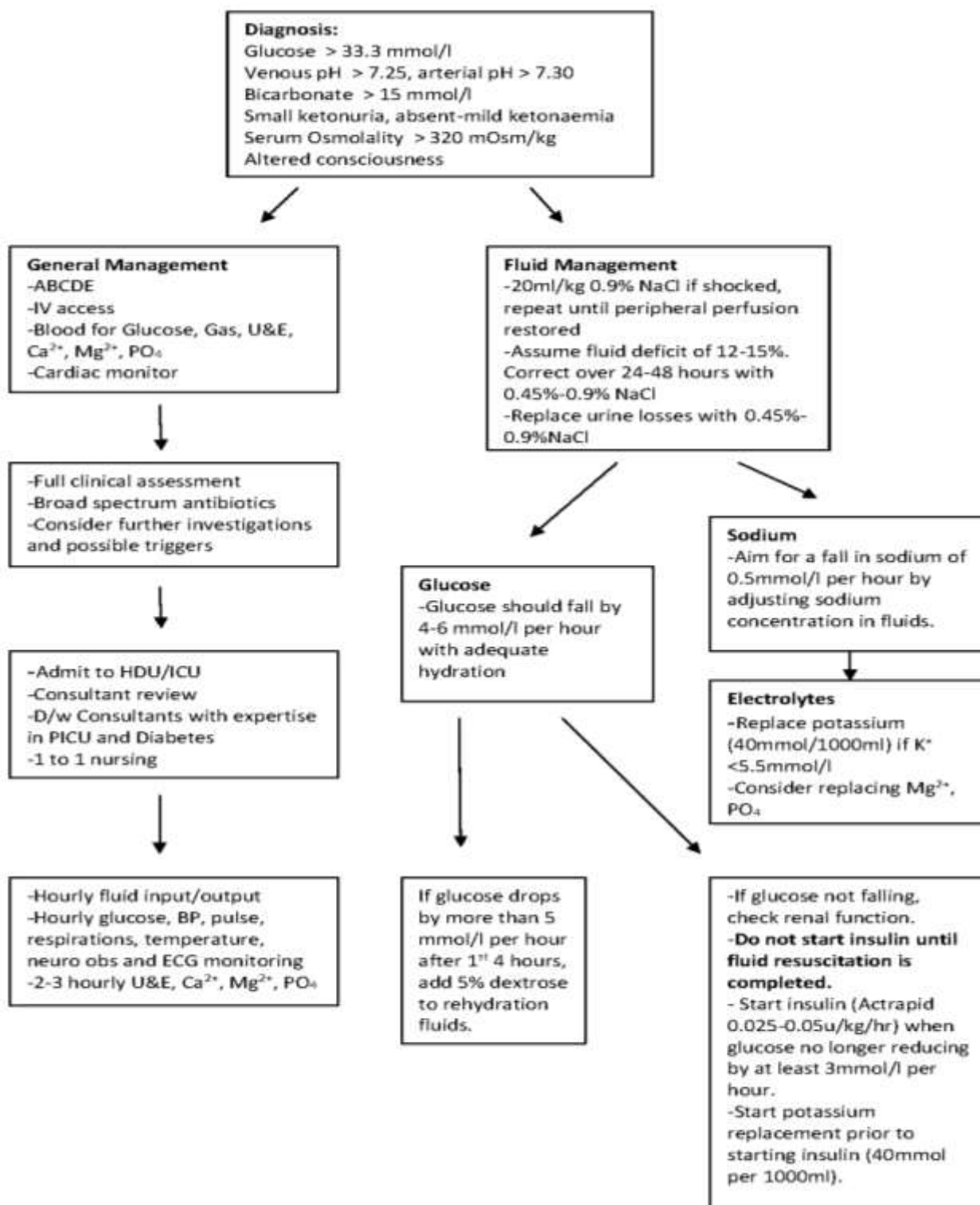
Subsequent Progress

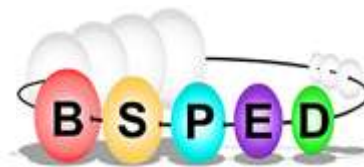
Following recovery many patients presenting will require insulin treatment only for a short while, and many can be managed effectively with diet or oral agents. Patients should be given close follow up after discharge.

Conclusions

The recognition and management of HHS in children and young people with diabetes requires a high degree of awareness and suspicion by healthcare professionals. Meticulous care during fluid resuscitation is vital to prevent complications and to reduce mortality. The successful management of HHS requires careful and adequate correction of dehydration, hyperglycaemia and electrolyte deficits. Any precipitating factors must be identified and treated appropriately. Improving patient and clinician education, regular follow up and easy access to healthcare resources are important in preventing this potentially fatal complication of diabetes.

6. Flow Diagram





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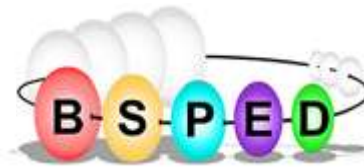
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