ssociation of Children's Diabetes Clinicians

Clinical Guideline

A Practical Approach to the Management of Steroid, Chemotherapy or Transplant Induced Hyperglycaemia or Diabetes in Children and Young People Under 18 years in the Acute or Inpatient Setting

FOR STAFF Healthcare Professionals involved in care of children and young people with Steroid, chemotherapy or transplant induced hyperglycaemia.

PATIENTS Children and young people with steroid, chemotherapy or transplant induced hyperglycaemia.

This guideline is intended for use in managing hyperglycaemia of diabetes induced by steroid therapy, chemotherapy or transplant in children and young people up to the age of 18 years.

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Tables

Abbreviations

ALL- Acute Lymphocytic Anaemia
BG blood glucose
BMI- Body mass index
CBG- Capillary blood glucose
CF- Cystic fibrosis
CNI- Calcineurin inhibitors
DKA – Diabets ketoacidosis
FH- family history
GC glucocorticoid
HDU- high dependancy unit
HSCT- human stem cell transplant
HSS- hyperosmolar hypergycaemic syndrome
IL- Interleukin
NODAT – new onset diabetes after transplant
OGTT oral glucose tolerance test
PICU- Paediatric Intensive care
PTDM – post transplant diabetes mellitus
RCT- Randomised controlled trial
SGA- small for gestational age
SNPs- single nucleotide polymorphisms
TBI- total body irradiation

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Introduction

Hyperglycaemia and or diabetes can be induced by steroid therapy, chemotherapy or post-transplant (solid organ, bone marrow or stem cell) as a result of immunosuppressive therapies.

This guideline is intended to support clinicians, including diabetes specialists, oncologists, haematologists, hepatologists and nephrologists amongst others, in the care of children, who in the absence of pre-existing diabetes, develop hyperglycaemia whilst receiving acute medical or surgical care as an inpatient. The long-term management of treatment induced diabetes is beyond the scope of this guideline.

This guideline is **not intended** to replace established guidelines already in use in Paediatric intensive care units managing hyperglycaemia in the critically unwell child, or for the management children with established type 1 or type 2 diabetes undergoing therapy which exacerbates hyperglycaemia.

Background

Glucocorticoid induced hyperglycaemia/ diabetes

Uncontrolled hyperglycaemia can complicate therapy in children on glucocorticoids, chemotherapy or post-transplant, leading to osmotic symptoms. Diabetic ketoacidosis and Hyperglycaemic hyperosmolar syndrome have been described and hyperglycaemia may also increase the risk of secondary complications (1,2).

Corticosteroid therapy is an established cause of hyperglycaemia, likely developing through several mechanisms including

- inducing or worsening pre-existing insulin resistance,
- beta cell dysfunction
- increasing hepatic gluconeogenesis,
- by stimulating appetite and weight gain (long-term).

The effect of glucocorticoids on glucose metabolism is likely the result of impairment of multiple pathways including beta cell dysfunction (sensitivity to glucose and ability to release insulin) and insulin resistance in other tissues. The impact is dose-dependent (3) and the role of beta cell function (4) and other tissues' sensitivity to insulin (5) may be different depending on whether the glucocorticoid effect is acute or chronic.

Chemotherapy Induced Hyperglycaemia/ Diabetes

This is most commonly seen in children with Acute Lymphoblastic Leukaemia (ALL) receiving asparaginase, with or without glucocorticoids, or in those receiving calcineurin inhibitors (CNI) for immune suppression. CNIs have been shown to impair insulin secretion in clinical studies. Animal studies confirm that treatment with tacrolimus worsened glucose tolerance both in vivo and in vitro and in normal as well as insulin-resistant models, predominantly through decreasing insulin secretion (6, 7)

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Post-Transplant hyperglycaemia

This often seen in the acute phase post-transplant of both solid organs, bone marrow or stem cell. In these early stages a combination of glucocorticoid and immunosuppressive agents, in addition to the hyperglycaemia seen in children with critical illness, complicate the clinical picture.

Post-Transplant Diabetes Mellitus (PTDM)

This is more likely to occur in individuals with pre-existing type 2 diabetes risk factors, including age, obesity and a family history (FH) of type 2 diabetes, and in those with race or ethnicity considered at higher risk than Caucasians for type 2 diabetes—particularly African Americans and Hispanics (8). Multiple mechanisms have been implicated for CNI-associated PTDM including dose dependent effect (9). There is a genetic predisposition and multiple studies have found an association between type 1 and type 2 diabetes candidate gene single nucleotide polymorphisms (SNPs) with risk for PTDM. PTDM has also been associated with SNPs in multiple IL genes (10) Some genes associated with genes for risk of end-organ failure leading to solid organ transplant are also associated with risk of PTDM. Pre-transplant factors including greater age, impaired glucose tolerance parameters, and rapid gain in dry weight on haemodialysis, along with higher prednisolone doses early post-transplant were the important factors associated with the development of PTDM (11).

Hyperglycaemia versus Diabetes

Hyperglycaemia or diabetes is most commonly transient in these scenarios. There is no consensus, once the criteria for diagnosis are met, as to what point diabetes is determined to be permanent. The terms treatment induced "hyperglycaemia" and "Diabetes" are often used interchangeably in the literature.

What is the risk of developing treatment induced hyperglycaemia or diabetes.

On Glucocorticoids

There is minimal literature on incidence of glucocorticoid induced hyperglycaemia in children for those treated with steroids alone. Most of the literature looks at children who receive glucocorticoids together with other therapy. In 63% of children (n=46) receiving dexamethasone post stem cell transplant to prevent nausea and vomiting, hyperglycaemia was seen within 5 days (12). Extrapolating from neonatal studies the risk of hyperglycaemia may also be increased in those born SGA, though this has not been studied specifically in older children (13). The development of hyperglycaemia does not appear to be related to cumulative steroid dose in adults (4) or children (14). In much older adults (mean age 60 years) with cancer and glucocorticoid treatment up to 1 in 5 developed hyperglycaemia.

On Chemotherapy

Studies demonstrate varying rates of 16-26% hyperglycaemia in children receiving chemotherapy (14-18). Studies indicate that the risk of hyperglycaemia is increased in older children (over 10 years) (19,20) and obese patients (17) with a family history of diabetes. Hyperglycaemia is also increased in those receiving L asparaginase (compared with PEG) (21). In the paediatric studies on Chemotherapy and hyperglycaemia, most studies are small, with one large cohort of 162 2-18 year olds (17) of whom 1 in 5 developed transient

hyperglycaemia, the risk being increased with BMI>85% and 95th centile, age > 10 years and the use of native L Asparaginase.

Post-Transplant.

Reported rates of transplant induced hyperglycaemia in children range between 5-15% (22-25) with a 9-fold higher risk in multi-organ transplantation (26). The risk of PTMD in children with renal transplantation is increased with hypomagnesemia, high trough tacrolimus levels (27), age > 10 years, BMI <5th and >85th percentile, and steroid use at discharge (28). Post liver transplant incidence of PTDM was 7% affecting 1 in 10 in 5 years, associated with older age, high risk ethnic group and underlying chronic disease CF/ primary sclerosing cholangitis (22). CNIs (eg, tacrolimus and cyclosporine) and inhibitors of the mammalian target of rapamycin (mTOR; eg, sirolimus or rapamycin and everolimus), may contribute to PTDM (29) in children receiving renal transplant (28) and adults receiving renal or liver transplant (3, 30, 31). No paediatric data on hyperglycaemia incidence could be identified in the literature for bone marrow or stem cells transplants. Mycophenolate, mofetil and azathioprine, unlike tacrolimus, have not been shown to have a large impact on insulin action or glucose metabolism and so are not thought to have a major role in post-transplant diabetes mellitus.

Type and timing of glucose abnormalities seen in treatment induced hyperglycaemia

On Glucocorticoids

Different glucocorticoids have varying half-life and potency. There is no paediatric literature on the timing of glucose abnormalities in children with prednisolone or methyl prednisolone**.** Adult data show a peak in glucose 8 hours post prednisolone dose (32) which has implications for the timing of screening as well as management. Alternate day prednisolone in adults leads to alternate day hyperglycaemia in adults (33). One study in children with ALL reported dexamethasone as being associated with fasting hyperglycaemia (34), though the study was not primarily designed for assessment of this outcome. Studies of methylprednisolone in adults demonstrate increased hyperglycaemia risk with increasing number of pulses (35). In adults on dexamethasone treatment with multiple myeloma the optimal time for detection of hyperglycaemia was on afternoon–evening blood glucose measurements (36).

On Chemotherapy.

There is wide variation in the timing of glucose abnormalities in children undergoing chemotherapy between several studies reporting the first 1 – 3 weeks, (37, 38) days (37) or after the 3rd dose of asparaginase and another reporting that 3-17% developed diabetes after 6 months of high dose chemotherapy (39,40).

Post-Transplant.

There were no specific studies looking at or outlining the timing of glucose abnormalities post -transplant in children.

Outcomes of treatment induced hyperglycaemia

When defining screening criteria, it is necessary to consider the risk benefits of screening, and the evidence of the effect of intervention on patient outcome. There is a paucity of data on the outcomes of hyperglycaemia in these patient groups. In hospitalised adults there is evidence that acute hyperglycaemia is associated with increased hospital stay, increased risk of admission to intensive care, higher rates of infection, poor wound healing and overall higher hospital mortality rates (41-45) However it should be noted that acute stress/severe illness can in itself provoke hyperglycaemia in patients who are not prescribed steroids (46).

In glucocorticoid induced hyperglycaemia no paediatric outcome data is available (41,47). In chemotherapy induced hyperglycaemia one study reported in children receiving chemo for ALL, that 6 of 797 had developed DKA, though none required long term insulin therapy (48) and case reports of ketosis and Hyperosmolar coma exist (49,50). In transplant induced hyperglycaemia one study of mortality post liver transplant in children identified 69% of children who died had hyperglycaemia vs 24% of survivors (51). It is difficult to know if the hyperglycaemia is causal or an effect.

There is also a lack of data or papers looking at whether clinical outcomes improved following treatment for hyperglycaemia compared to not treating hyperglycaemia in children. It is therefore not possible to state which children may or may not benefit from intervention. There was a presumption that hyperglycaemia was likely to worsen outcomes therefore treatment was likely to be beneficial especially if symptomatic (with symptomatic often very poorly defined).

A number of studies in adults indicate hyperglycaemia or evolution of steroid induced diabetes adversely affects graft/transplant organ health and overall survival post renal or liver transplantation (52,53) Clinical outcomes related to the treatment of hyperglycaemia and PTDM remain under evaluation. To date one study of the use of an intensive insulin regime post cardiac transplant in adults identified no short-term safety issues in which the blood glucose targets were very tight (4.5-6.1mmol/L) (54) but long-term effects were not included. A prospective randomised control trial of insulin therapy post-renal transplant in those with established diabetes (55) demonstrated those randomised to target blood glucose of 3.1-6.1mmol/L in the first 72 hours as opposed to <10mmol/L had the same outcomes in terms of graft function but those in the group with tighter targets were at greater risk of rejection. Early basal insulin used to treat posttransplant hyperglycemia in adults (<3 weeks) has been reported to significantly decrease the odds of developing PTDM within the first year by 73% (56). A larger randomized controlled clinical trial in adults (ITP-NODAT, clinicaltrials.org: NCT01683331) is nearing completion and has been undertaken to evaluate whether these findings are reproducible in a large, multicentre trial.
There are no studies looking at whether intervention compared to non-intervention affected these outcomes, so it is not possible to say whether treatment mitigated the adverse outcome associated with hyperglycaemia or steroid induced diabetes.

RECOMMENDATONS:

Screening for Treatment induced diabetes

Recommendation 1 (Grade D)

In view of the limitations of evidence of benefits of screening for hyperglycaemia, or intervention if hyperglycaemia is detected screening should be limited to high risk groups, in whom it is more likely that intervention will reduce the risk of acute complications of hyperglycaema. Consideration should be given to screening for diabetes in the groups described in table 1.

Table 1. Groups eligible for inpatient screening for hyperglycaemia and diabetes

Treatment	Category 1 Routine glucose screening	Category 2 Or any of the below with any treatment
High dose glucocorticoid therapy	High glucocorticoid doses **and high dose treatment duration will exceed 7 days** *see table 2 and 3 for high glucocorticoid doses and equivalents	Systemically unwell with fever and/or cardiovascular/ haemodynamic compromise. Or Osmolar symptoms develop (excessive thirst, passing more urine than usual, dehydration, weight loss, unexplained tiredness) Or If > 10 years old with other significant risk factors for diabetes (BMI >85th centile, acanthosis, strong FH type 2 Diabetes)
Chemotherapy	If on Asparaginase	
Post-transplant	If on concomitant glucocorticoids and /or calcineurin inhibitors	

Table 2: Glucocorticoid dose equivalents (adapted from 56, 57)

Glucocorticoid	Milligram equivalents	Half-life hours
Hydrocortisone	20mg	8
Prednisolone	5mg	16-36
Methylprednisolone	4mg	18-40
Dexamethasone	0.75 mg	36-54

Table 3: High dose Glucocorticoids*; screening recommended if daily steroid dose equals or exceeds the following at each given age **

Age	Prednisolone dose/day	Dexamethasone dose/day	Methyl Prednisolone dose/ day
1-5 years	7.5mg	1.5mg	6mg
5-10 years	12mg	2.5mg	10mg
10-12 years	15mg	3mg	12mg
12+ years	20mg	3mg	15mg

*calculated doses above have been extrapolated from adult doses in studies which were used to study glucocorticoid effects of CHI and insulin metabolism converted to mg/ m^2 (rather than to determine thresholds at which hyperglycaemia occurs), and guideline group experience with high dose prednisolone use in children.

**please refer to appendix B for steroid dose equivalents in mg/m^2/ day

Recommendation 2 Grade D

Children with suspected diabetes should be referred to and discussed with your local diabetes team. This should be a same day referral if any of the following symptoms are present: polyuria, polydipsia, weight loss and/ or lethargy.

Recommendation 3 Grade D

In children who are not acutely unwell, screening with a daily urine testing for glycosuria will identify most significant hyperglycaemia. This urine should be collected late afternoon/ early evening in view of the action profiles of the some long acting steroids (32). The presence of glycosuria should prompt blood glucose testing as per recommendation 4. Blood glucose testing may also be performed if blood testing is being performed regularly for other reasons.

Recommendation 4 (Good Practice Point)

In very sick or symptomatic patients, or those with glucosuria should include 4 CBG per day, including 1 fasting glucose, then further CBG 2 hours post lunch, pre-evening meal and mid to late evening. Blood glucose should be re-checked if the child has eaten within the last 2 hours.

Recommendation 5 (Good Practice Point)

If blood glucose has not exceeded 11.1 mmol in 48 hours and clinical condition improving, consider discontinuing CBG screening unless symptoms appear (Table1) and consider continuing urine screening for glycosuria for 5-7 days.

Diagnosis of treatment induced diabetes

Recommendation 6 (Grade D)

Glucocorticoid induced diabetes is diagnosed in the majority of children with findings of symptoms of hyperglycemia, with a random plasma glucose of ≥ 11.1 mmol/L or more than 2 random plasma glucose values of ≥ 11.1 mmol/L whilst on high dose glucocorticoids (60).

Recommendation 7 (Grade D)

Chemotherapy (ie. Drug) induced diabetes is diagnosed in the majority of children with findings of symptoms of hyperglycemia, with a random plasma glucose of ≥ 11.1 mmol/L or more than 2 random plasma glucose of ≥ 11.1 mmol/L whilst on chemotherapy (60). Note in patients on concomitant glucocorticoids and chemotherapy both agents may be contributory.

Recommendation 8 (Grade D)

A diagnosis can also be made in the above scenarios with an 8 h fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL), 2 h post 75 g oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L (200 mg/dL), HbA_{1c} ≥ 48mmol/mol in the presence of an elevated random plasma glucose of ≥ 11.1 mmol/L but these are less commonly used for diagnosis of treatment induced diabetes for practical reasons (60).

Recommendation 9 (Grade D)

Post-transplant hyperglycaemia is diagnosed in the majority of children with findings of symptoms of hyperglycemia, with a random plasma glucose of ≥ 11.1 mmol/L or more than 2 random plasma glucose of ≥ 11.1 mmol/L post organ transplant (61).

The diagnosis of Post-Transplant Diabetes Mellitus (PTDM) was defined and updated in 2013 using ANY of the American Diabetes Association/World Health Organization criteria (60) for the diagnosis of diabetes once the transplant recipient has been discharged from the hospital and tapered to their maintenance immunosuppression (61). However, HbA1c should **not** be used alone to screen for diagnosis of PTDM within the first year after transplant.
There is overlap in that those on chemotherapy or post-transplant may also be on glucocorticoids

Initial assessment and investigations

Recommendation 10 (Good Practice Point)

Children with confirmed hyperglycaemia must be reviewed and evaluated for

- osmotic symptoms
- current treatment
- potential precipitants and exacerbating factors,
- presence of infections/ sepsis,

- glucose and nutritional intake,
- nutritional status,
- family history,

The following examinations/ evaluations should take place.

- hydration status
- fluid balance
- features of DKA or HHS. (1,2)

Initial investigations should include:

- capillary blood ketones
- capillary gas
- Plasma glucose (avoid sampling from lines delivering glucose infusions)
- U+Es, Cr, and
- plasma osmolality
- HbA1c,

Recommendation 11 (Good Practice Point)

Type 1 diabetes is the most common form of diabetes and can present incidentally in children on therapy or with other chronic diseases. If a diagnosis of diabetes is made ketones and acid/base status must be checked to guide acute management, and blood taken for Insulin antibodies to help determine aetiology. Monogenic diabetes should also be considered.

Management of treatment induced Diabetes

The management will depend on the individual clinical scenario. The aims of treatment would be to

- reduce osmotic symptoms
- avoid dehydration
- improve nutrition
- prevent DKA or non-ketotic hyperosmolar coma

There is no evidence in children to recommend specific oral treatments or insulin therapy of hyperglycaemia related to glucocorticoids, chemotherapy or transplantation.

There are no studies looking at treatment of glucocorticoid, chemotherapy or transplant induced hyperglycaemia in children with diet or lifestyle advice, though diet and lifestyle has been used to reduce calorie intake in children treated for leukaemia with the aim of reducing comorbidities (62). In chemotherapy and post-transplant there are no RCT studies to determine efficacy of lifestyle modification in the management of treatment induced diabetes in adults or children, however there is some emerging interest in lifestyle modification effects on the risk of PTDM in adults (63, 64).

Considering oral agents one very small retrospective report of 17 children suggested metformin, with or without insulin, was safe in children with t-ALL on steroids and asparaginase with relatively modest hyperglycaemia (65), though there are continuing concerns regarding the risk of lactic acidosis (66) and renal dysfunction, as well as drug induced haemolytic anaemia (67). In addition, the slow onset of action limits efficacy in many scenarios. There is some limited evidence to support thiazolidiones in adults with glucocorticoid induced hyperglycaemia (68). There are no published studies to support specific oral therapy or insulins in chemotherapy induced hyperglycaemia in adults. Other oral therapies for steroid induced, chemotherapy or PTDM have not been evaluated in children, and are without consensus opinion in adult care (69, 70, 71).

In adult studies IV insulin is effective acutely in transplant induced hyperglycaemia (53,54,72) and NPH has been demonstrated to be effective in high dose prednisolone induced hyperglycaemia in pregnant women with type 1 diabetes for hyperemesis (73). In children treatment of PTDM, in practice, is limited primarily to insulin (74)

There is no published evidence to recommend specific glucose targets in children with treatment induced hyperglycaemia. The Joint British Diabetes Societies (JBDS) recommend target levels in adult inpatients for blood glucose of 6-10 mmol/ L on treatment, with an acceptable range of 4-12 acutely, but there are no longer term outcome studies to support this (76). These targets reflect recommendations for the management of sick adults in hospital rather than the management of hyperglycaemia per se.

Similarly, in paediatric PICU protocols insulin is commenced in critically ill children with the aim of maintaining blood glucose below 12 mmol/L (77). The endocrine society (78) recommend pre-meal BG 5.6- 7.8 and random BG <10 in hospitalised adults in a non-critical care setting based on a review of available evidence. These are in line with ADA recommendations (79) but did not discuss diabetes aetiology.

Recommendation 12 (Grade D)

DKA and HHS require management using the relevant DKA and HSS guidelines irrespective of the diabetes aetiology (1,2).

Recommendation 13 (Good Practice Point)

In the absence of DKA or HHS, if the child is acutely unwell and/or unstable or significantly dehydrated or has a significant infection then IV insulin sliding scale (**Appendix 1**) should be commenced, until clinical condition improves, and blood glucose reaches targets.

Recommendation 14 (Good Practice Point)

In an otherwise clinically stable child with hyperglycaemia a decision to treat should be based on their clinical condition, the presence of osmolar symptoms, the expected duration and pattern of precipitating treatment. Not all children with treatment induced hyperglycaemia will require treatment.

Recommendation 15 (Good Practice Point)

There is no evidence to support dietary and lifestyle measures for the management of treatment induced diabetes, however hyperglycaemia can be exacerbated by the use of TPN, high glucose oral load (high energy drinks/ mango juice etc) and where a child is stable and safe it is reasonable to switch to low glucose fluids, and exclusion of highly refined glucose drinks whilst monitoring blood glucose for a 12-24 hour period prior to reconsidering insulin therapy. In circumstances where nutritional status is expected to be adversely compromised by reducing glucose intake insulin therapy is the most appropriate treatment.

Recommendation 16 (Good Practice Point)

Consider with the child's primary consultant whether there is scope, or a plan, to adjust therapy, in particular the fluid regime, feeds, TPN, glucocorticoid dose, and doses of tacrolimus other immunosuppressants (75). There is no evidence to adjust glucocorticoid type.

Recommendation 17 (Good Practice Point)

Subcutaneous long acting insulin treatment should be commenced initially if IV insulin is not needed to control severe acute hyperglycaemia in the PICU or HDU setting. Long acting insulin doses starting at 0.2 units kg/ day are safe in practice and similar to adult doses recommended for steroid induced diabetes. Some children may need insulin doses increased rapidly and correction doses of rapid insulin, guided by blood glucose monitoring, particularly when insulin resistance is significant, and compounded by glucocorticoid induced hyperphagia.

Please note:

1. The timing of the insulin dose should also take account of the timing of steroid doses and nutritional therapies such as overnight NG feeds etc. In children on prednisolone, Insulatard is preferred by some units as the peak in action corresponds to the peak rise in blood glucose when prednisone is given in the morning. However, if prednisolone is dosed twice daily a second dose of Insulatard may be required prior to evening meal
2. Some units prefer to use Levemir in preference to Lantus in patients with malignancy or post-transplant. Please refer to appendix C.

Recommendation 18 (Good Practice Point)

Continue blood glucose monitoring 4 hourly, increasing insulin by 10-30% every 1-2 days to maintain fasting glucose < 10. Consider adjusting long acting insulin or changing insulin regimens if high doses are needed (more likely with dexamethasone). Check for ketones if BG>14 mmol/L in view of risk of DKA

Recommendation 19 (Good Practice Point)

Consider adding in rapid insulin if there is evidence of marked post prandial hyperglycaemia. There is no evidence as to doses or methodology for rapid acting insulin. Consensus would support either fixed rapid insulin doses or 0.1-0.2 unit/kg/ dose corrections with dose adjustment according to blood glucose response. Escalate treatment with insulin correction doses in the presence of ketosis and hyperglycaemia, or DKA therapy in the presence of ketosis and acidosis

Recommendation 20 (Grade D)

Treatment induced diabetes can be transient therefore insulin may require weaning or discontinuing if blood glucose levels are falling, or in the case of glucocorticoid induced diabetes glucocorticoids are weaned or discontinued.

Recommendation 21 (Good Practice Point)

There is no evidence to support the use of metformin in the acute setting, due to its slow onset of action. Additionally, there is a potential risk of lactic acidosis and metformin should be avoided or discontinued during acute illnesses or infections. There is experience, however, suggesting metformin can be of use as an adjunct to insulin therapy in reducing very high insulin doses in those who are not acutely unwell. It can be particularly useful to restart metformin several days prior to future chemo cycles when these have induced diabetes previously.

Recommendation 22 (Grade D)

Blood glucose levels of 5.6 mmol to 12 mmol, avoiding hypoglycaemia are safe targets for children with treatment induced hyperglycaemia

Risk of long-term Diabetes

Whilst this guideline is not intended to address the management of permanent diabetes it is expected that acute hyperglycaemia will raise questions from families and young people regarding the risk of permanent diabetes.

Glucocorticoid and chemotherapy induced diabetes are more likely to resolve and relate to the duration of therapy (21,47,79-82). Hyperglycaemia may re-emerge with future courses of similar treatment, when blood glucose monitoring should be re-instituted.

The overall prevalence of diabetes in adults surviving childhood cancer has been reported as 2.5% to 15.6% across a number of studies (83-86). Risk factors include total body irradiation (TBI), untreated hypogonadism, and abdominal adiposity (a feature related to cranial radiation therapy). Proposed mechanisms include B cell damage, weight gain, reduced physical activity, metabolic syndrome effects, inflammatory mediators and cytokines, and with respect to TBI the alteration of mitochondrial function in muscle liver and pancreas leading to insulin resistance (85). There is no prevalence data for childhood prevalence of diabetes following cancer.

The limited literature suggests PTMD has a greater likelihood persisting and requiring continuing therapy and monitoring than other forms of treatment induced diabetes, though this varies between organ transplant type. In children post liver transplant one study demonstrated an average duration of 4.6 months insulin therapy in 8% of children which resolved over 4.9 years in 83% (87). The risk of diabetes post-transplant in children is lower for renal transplants (4.6%), compared to liver transplants (11.2%) at 3 years (22,28,88). Risks for PTDM are also lower than in adults post renal and liver transplant (26.4% at 3 years and 36% at 5 years respectively) (31,74, 88) The lowest PTDM risk was seen in cardiac transplant;

3.6% at 7 years (89). The higher risk in adults may be related to the greater risk of type 2 in adults as higher c-peptide increases the risk of permanent diabetes. This information is not available for children.
Following HCST in a study, including 106 adults and 74 children, there was a peak in hyperglycaemia with initial intensive treatment and then a cumulative long-term risk of diabetes (30% at 2 years), which was related to TBI. The rates and pattern of PTDM in children and adults were similar. Approximately 1 in 3 who developed diabetes post HSCT still had diabetes after 2 years (90).

It is well known that hyperglycaemia in the first week following transplant is very common and should not be used to diagnose permanent diabetes (56, 91). It should be treated as this may have some benefit in reducing the risk of post-transplant diabetes at 1 year (56). A formal diagnosis of post-transplant diabetes is best made when patients are stable on their expected maintenance suppression infection free and with stable graft function (61) It should be noted that, currently, the diagnosis of PTDM has no "end date." If an adult or a pediatric solid organ transplant recipient is diagnosed with diabetes 1, 10, or 40 years later, it is still eligible to be called PTDM. The significance or impact of the diagnosis of PTDM made in the first year compared to five years after transplant has yet to be determined.

Recommendation 23 (Good Practice Point)

Parents and young people should be counselled that hyperglycaemia and diabetes may be transient or permanent. If transient there is a risk of recurrence with future similar therapies thus vigilance for symptoms and blood glucose monitoring will be required. Diabetes in association with transplantation has a greater likelihood of being permanent.

Recommendation 24 (Good Practice Point)

Where treatment induced diabetes has occurred in a scenario where treatment courses are recurrent (ie. chemotherapy cycles) blood glucose screening should be commenced at treatment onset, in preference to urine glucose screening. Previous effective treatment must be taken into account to allow prevention, where possible (ie. Metformin), and at minimum prompt management.

Recommendation 25 (Good Practice Point)

If diabetes persists beyond the acute inpatient stay long-term support and follow up with the diabetes team should be offered and consideration can be given to other therapeutic options.

Appendix A: Insulin sliding scale and fluids.

Fluids

Use 5% glucose 0.9% saline with 20mmol/mol potassium chloride (KCL), unless clinical scenario requires alternative glucose supply – eg TPN. Discuss fluid requirements with their primary clinician.

It is important to avoid any significant changes in glucose infusion rate whilst on the scale. If glucose containing fluids are altered (ie. Due to prescribed time off TPN) this must be pre-empted by increasing the frequency of blood glucose monitoring to 15-30 minutes post change and adjusting the insulin infusion rate.

The primary clinician may require the child to receive a fixed amount of fluid. If there are no fixed fluid requirements please refer to maintenance fluid calculation in table 3, and consider, together with their primary clinical team, whether deficit and ongoing losses need to be added.

Table 4 Maintenance fluid calculation

	Body weight in kg	**Fluid requirements in 24 hours**
For each kg between	3-9kg	100ml/kg
For each kg between	10-20kg	Add an additional 50ml/kg
For each kg over	Over 20kg	Add an additional 20ml/kg

Insulin Infusion (93,94)

- Dilute 50 units soluble insulin (Actrapid) in 50 ml normal saline; 1 unit per ml.
- Start infusion at
    - 0.025 ml/kg/h (i.e., 0.025 U/kg/hour) if BG is between 6–8mmol/l,
    - 0.05 ml/kg/h if 8–12 mmol/l,
    - 0.075 ml/kg/h between 12–15 mmol/l
    - 0.1 U/kg/h if > 15 mmol/l.
- Monitor BG hourly. Adjust IV insulin accordingly.
- If BG <5mmol/l, stop the IV insulin infusion but only for 10–15 min. Give bolus of IV 10% glucose 2ml/kg; recheck BG 15 minutes later.

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Appendix B: High dose steroid equivalents per m^2 /day

	Prednisolone dose > mg / m^2 / day	Dexamethasone > mg / m^2 / day	Methyl Prednisolone > mg / m^2 / day
High dose	15	3	12

Appendix C: Long acting insulin options

Insulin glargine is more potent in activating the human IGF-1 receptor than other insulins including insulin determir (Levemir) (96) leading to concerns that Glargine (Lantus) may increase cancer risk. Early analyses of German insurance company data demonstrated excess cancers in type 2 patients but could not evidence causal link (97). A Swedish study and Scottish data demonstrated a potential breast cancer risk however there were some methodological issues in the above studies and a link could neither be refuted or confirmed (98,99) as per statements released by EMA and FDA in July 2009 and Dec 2011 respectively (100, 101).
Subsequent to the release of these statements a large insurance-based study in France (102) looked at adults (40-79 years) starting insulin with type 2 diabetes and concluded no increase in risk of cancer after 4 years follow up. However more recently a Canadian group (103) using UK clinical practice research data link studied women over 40 years with T2DM followed up to 2015 and looked at all insulins, including determir, and determined increased Breast cancer risk (OR 1.44) from 5 years post insulin treatment in women using Glargine.

All of these studies excluded those with a previous history of malignancy. Insulin resistance is also an independent risk factor for Cancer. Some of the children for whom this guideline is intended will

a. have had cancer already, and so at a greater risk of a second malignancy
b. be insulin resistant
c. be immunosuppressed

thus some units elect to use alternative long acting insulin in preference to glargine where suitable alternative exists, for those with a pre-existing Ca diagnosis or pre-existing risk factors for cancers.,

Appendix D: Search strategies – Evidence for steroid induced, chemotherapy or transplant related diabetes

Evidence for screening on steroids, post-transplant or on chemotherapy (CS) *no papers

Steroids AND hyperglycaemia
Steroid-induced diabetes
Glucocorticoids AND hyperglycaemia
Glucocorticoid-induced diabetes
Steroid-induced diabetes AND monitoring
Post-transplant AND hyperglycaemia AND monitoring
Chemotherapy AND hyperglycaemia AND monitoring
Hyperglycaemia AND glucocorticoid AND CGMS *
Hyperglycaemia AND steroid AND CGMS" *
Hyperglycaemia AND glucocorticoid AND continuous glucose monitoring *
Hyperglycaemia AND steroid AND continuous glucose monitoring *
Other sources: existing guidelines -Oxford, Birmingham, Nottingham, Portsmouth, ABCD, West Lothian

Frequency of glucose abnormalities in children on steroids, post-transplant, or on chemotherapy, tacrolimus, cyclosporine, L asparaginase

Search terms	Articles identified
Glycosuria AND (cyclosporine) ti,ab OR cyclosporine*ti.ab OR (tacrolimus,ti,ab OR (tacrolimus*)ti,ab OR (L asparaginase)ti,ab OR (L asparaginase*)ti,ab 19	16
Glycosuria AND (cyclosporine) ti,ab OR cyclosporine*ti.ab OR (tacrolimus,ti,ab OR (tacrolimus*)ti,ab OR (L asparaginase)ti,ab OR (L asparaginase*)ti,ab 19 AND pediatric* or Paediatric*)	1
Glycosuria AND (cyclosporine) ti,ab OR cyclosporine*ti.ab OR (tacrolimus,ti,ab OR (tacrolimus*)ti,ab OR (L asparaginase)ti,ab OR (L asparaginase*)ti,ab 19	4
((hyperglycaemia or hyperglycemia) ti,ab OR HYPERGLYCEMIA/) 21 23 (cyclosporine) ti,ab OR cyclosporine*ti.ab OR (tacrolimus,ti,ab OR (tacrolimus*)ti,ab OR (L asparaginase)ti,ab OR (L asparaginase*) AND (child*OR infant* OR pediatric* or Paediatric*)35	68
Glycosuria AND 35((steroids) ti,ab) AND STEROID/ OR , Chemotherapy) ti,ab OR Transplant * ti,ab 4,5,6,7) 23 25 AND (child*OR infant* OR pediatric* or Paediatric*)35	26
1((hyperglycaemia or hyperglycemia) ti,ab OR HYPERGLYCEMIA/)20 35((steroids) ti,ab) AND STEROID/ OR , Chemotherapy) ti,ab OR Transplant * ti,ab 4,5,6,7) 23 AND (child*OR infant* OR pediatric* or Paediatric*)	133
28 Transplant * ti,ab 43 HYPERGLYCEMIA/ep AND (child*OR infant* OR pediatric* or Paediatric*)	9
(Chemotherapy) ti,ab 6 AND 43 HYPERGLYCEMIA/ep AND (child*OR infant* OR pediatric* or Paediatric*)	3
5 (STEROID/, 43 HYPERGLYCEMIA/ep AND (child*OR infant* OR pediatric* or Paediatric*)	0
4(steroids) ti,ab, 43 HYPERGLYCEMIA/ep AND (child*OR infant* OR pediatric* or Paediatric*)	2
hyperglycaemia or hyperglycemia) ti,ab AND , 5 (STEROID/, 23 AND (child*OR infant* OR pediatric* or Paediatric*)	14
1 (hyperglycaemia or hyperglycemia) ti,ab AND (chemotherapy)ti,ab) 6, AND 23 (child*OR infant* OR pediatric* or Paediatric*)	44

What patterns of glucose abnormalities are seen during treatment with Prednisone, methylprednisolone, dexamethasone

*Search terms Medline 1946 to present limited to abstracts / humans/ English language Glucose (196487) AND	Articles identified	Title relevant	Abstract Relevant
Prednisolone (18820)	292	58	14
Limit child	6	6	6
Methylprednisolone (3558)	79	10	6
Limit child	1	1	1
Dexamethasone (8512)	256	24	5
Limit child	2	2	2
TOTAL		92	34

What are the risk factors for steroid, transplant or chemotherapy induced diabetes

*Multiple papers identified also relevant to risk factors identified from above search on patterns of glucose abnormalities; supplementary search completed as below

Search terms Medline 1946 to present limited to abstracts / humans/ English language Hyperglycaemia ***or*** hyper glycaemia mp or diabetes mellitus (134959) **AND**	Articles identified	Title relevant	Abstract Relevant
Risk factors (727272) AND Steroid*mp (292103) (limit child)	161 (21)	21	21
Risk factors (727272) AND transplant (4499)	1	1	1
Risk factors (727272) AND Chemotherapy mp (353602)	47 (8)	8	8

Criteria for diagnosis of and Natural history of Steroid induced Diabetes, Transplant related Diabetes or Chemotherapy induced Diabetes

Conducted an electronic database searches of the Cochrane Library, PUBMED, MEDLINE, Embase, PsycINFO and CINAHL using an iterative search strategy. Terms of search "Steroid" OR "TRANSPLANT" OR CHEMOTHERAY" AND "diabetes" OR "hyperglycaemia"

What are the outcomes in children with Steroid induced Diabetes, Transplant related Diabetes or Chemotherapy induced Diabetes

Search terms		Articles identified	Relevant
Steroid and hyperglycaemia	Limited 0-18 years	556	0
Steroid induced diabetes	Limited 0-18 years	130	0
Steroid induced hyperglycaemia	Limited 0-18 years	381	0
Glucocorticoid induced diabetes	Limited 0-18 years	99	0
Glucocorticoid induced hyperglycaemia	Limited 0-18 years	45	0
Steroid induced diabetes and outcome		422	0
Steroid induced diabetes and outcome		53	0
Steroid induced hyperglycaemia and prognosis	Limited 0-18 years	18	0
Steroid induced diabetes prognosis		300	0

Steroid induced diabetes prognosis	Limited 0-18 years	38	0
Steroid induced diabetes and complications		1751	0
Steroid induced diabetes and complications	Limited 0-18 years	138	0
Post transplant diabetes	Limited 0-18 years	320	0
Post transplant hyperglycaemia	Limited 0-18 years	0	0

What treatments are available to treat Steroid induced Diabetes, Transplant related Diabetes or Chemotherapy induced Diabetes

Search Terms: Medline (OVID)

1	*Child OR *adolescent OR *pe?diatric
2	Hyperglyc?emia OR Diabetes
3	Steroids OR corticosteroids
4	Transplant OR transplantation
5	Chemotherapy
6	1 AND 2 AND 3
7	1 AND 2 AND 4
8	1 AND 2 AND 5

Abstracts were reviewed for relevance. References were reviewed for further relevant studies.

Duration of treatment for treatment induced diabetes

Searches limited to English language and last 10 years, 0-18 years

Diabetes Mellitus, Type 2/ or DIABETES MELLITUS/ or diabetes.mp. or Diabetes Mellitus, Type 1/
AND steroid.mp. or STEROIDS/ AND duration AND (treatment.mp. or Therapeutics/)
44 studies-3 relevant papers

Prognosis for treatment induced diabetes

Diabetes Mellitus, Type 2/ or DIABETES MELLITUS/ or diabetes.mp. or Diabetes Mellitus, Type 1/ AND prognosis.mp. or PROGNOSIS/ AND (chemotherapy.mp. or Drug Therapy/ OR transplant.mp. or Transplants/ steroid.mp. or STEROIDS/) AND treatment.mp. or Therapeutics/
4 relevant papers in children

Monitoring of treatment

Planned search Terms:
Diabet* or Hyperglyc* or Blood sugar AND Steroid* or Chemo* or Transplant*
AND Treat* or monitor*
(OPTIONAL AND)
Child* or P?ediatri* or <18years

1524 Titles reviewed
205 Abstracts reviewed
51 Full texts read
33 Included

Appendix E: Criteria Used to Assess Levels of Evidence and Strength of Recommendations

Table 5: Grades of evidence for recommendations

Recommendation	Grade of recommendation
1, 13, 14, 15, 19,	D
2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 17,18, 20, 21, 22, 23, 24	Good Practice point

LEVELS OF EVIDENCE

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATIONS

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

Good practice points

✔ Recommended best practice based on the clinical experience of the guideline development group

Authors: ACDC Guideline Development Group M Kershaw N Wright, SM Ng, CJ Agwu, J Drew, C Moudiotis, F Regan, A Timmis, A Soni, E Williams, C Steele, V Whittle, G Gupte, S. Bailey, F Hussain, J Calvert, S Hawnt, D.Swain, C Buckley

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