Recent Consensus Statements in Pediatric Endocrinology: A Selective Review

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Jo Rycroft-Malone,1 PhD, a leading expert in the field of evidence-based medicine, said, “to achieve clinically effective care we must access three strands of evidence: knowledge from research findings, knowledge from clinical experience, and patient-specific information (including preferences and acceptability of an intervention to individuals.”

Clinical guidelines and consensus statements serve to summarize and organize current knowledge on diverse subjects, and provide practical guidelines for proper clinical management. Recommendations should be based on research and evidence derived from appropriate sources. Randomized controlled trials and systematic reviews of randomized controlled trials are usually the preferred sources.2 When a certain aspect of treatment or care has not been covered adequately in the literature, expert opinion is considered in developing guidelines.

In 2008, more than 20 consensus statements were published in the pediatric literature alone. To acquaint the reader in pediatric endocrinology with some of the major findings, the authors summarize the salient points of the latest consensus statements jointly developed by multiple endocrine societies including the Lawson Wilkins Society for Pediatric Endocrinology (LWPES) and the European Society for Pediatric Endocrinology (ESPS). Common to all of the reviewed consensus statements is the bringing

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together of experts in the field to review the literature, evaluate the evidence, and formulate statements representing the views of many. As much as possible, the original intent and language of the statements was respected and paraphrased. For more information and for review of sources used for the consensus statements, the reader is referred to the original published articles.

CONSENSUS STATEMENT ON THE MANAGEMENT OF DIABETIC KETOACIDOSIS IN CHILDREN AND ADOLESCENTS

The purpose was to explore management and complications of diabetic ketoacidosis (DKA) in children and adolescents to formulate a consensus on prevention and reduction of DKA. The statement was endorsed by LWPES, ESPS, International Society for Pediatric and Adolescent Diabetics (ISPAD), Juvenile Diabetes Research Foundation International (JDRF), World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS), European Society for Pediatric Critical Care (ESPCC), European Society for Pediatric and Neonatal Intensive Care (ESPNIC), and Australian Pediatric Endocrine Group (APEG).

Later guidelines published by the American Diabetes Association (ADA) included recommendations of this consensus statement.

Definition of DKA

DKA occurs when there is a disruption in the homeostatic balance between insulin and counter-regulatory hormones secondary to a deficiency in circulating insulin and an increase in levels of catecholamines, glucagon, growth hormone, and cortisol. The result is a state of hyperglycemia, hyperosmolarity, increased lipolysis, ketonemia, and metabolic acidosis secondary to increased ketone body production. Osmotic diuresis, dehydration, and loss of electrolytes are further consequences of the hyperglycemia and acidosis.

The major biochemical diagnostic criteria for DKA include hyperglycemia (blood glucose: >11 mmol/L [approximately 200 mg/dL]) with a venous pH less than 7.3 or bicarbonate less than 15 mmol/L. There are associated minor criteria including glycosuria, ketonuria, and ketonemia. DKA is classified further by the degree of the acidosis:

- Mild (venous pH: <7.30; HCO3: <15 mmol/L)
- Moderate (pH: <7.2; HCO3: <10 mmol/L)
- Severe (pH: <7.1; HCO3: <5 mmol/L)

Clinical features of DKA include dehydration, Kussmaul breathing, severe abdominal pain, nausea, and vomiting; additionally, patients may have fever if infection is also present.

Frequency of DKA

The more prevalent type I diabetes mellitus (TIDM) is in a given region, the less likely it is for DKA to be present at diagnosis. It is more common to see DKA at the onset of diabetes in children less than 4 years of age, children who do not have a first-degree relative with TIDM, and children from families of lower socioeconomic status or without ready access to medical care. Certain medications including glucocorticoids, atypical antipsychotics, and Diazoxide have been indicted as causative agents of DKA in patients not previously diagnosed with TIDM.
Factors such as poor metabolic control, a history of DKA, poor family structure, a psychiatric history, or being a peripubertal or adolescent female increase the risk of DKA in patients with TIDM. The most common reason for the occurrence of DKA (75% of cases) in these patients is either incorrect insulin dosing or absence of insulin. Other causes include insufficient amounts of insulin during stress or illness to balance counter-regulatory hormones and inappropriate cessation of insulin pump therapy.

**Cerebral Edema**

The first signs of cerebral edema (CE) can be subtle and nonspecific and include headache, mental status changes, bradycardia, and hypertension. Studies have shown that CE usually occurs 4 to 12 hours after management of DKA has begun, but it can occur any time before or during treatment. The incidence of CE is up to 1% in all cases of DKA.

Increased risk for CE is seen in patients who present with DKA at diagnosis, are younger, and have symptoms of DKA for a longer amount of time. Other risk factors include degree of acidosis at presentation, greater hypocapnia at presentation after adjusting for the severity of acidosis, bicarbonate treatment during DKA, elevated serum urea nitrogen at presentation, and a slower rise in measured serum sodium concentrations during treatment of DKA. Neither the severity of hyperglycemia at presentation of DKA nor the concentration of sodium in intravenous fluids has been shown to increase the risk of cerebral edema.

**Management of DKA**

Mild cases of DKA, in which patients have hyperglycemia and ketosis, but can tolerate oral (PO) and are not dehydrated, do not require inpatient or emergency room management. Patients who are vomiting, cannot tolerate fluids by mouth, or are dehydrated should be evaluated in an emergency room or inpatient setting. Admission to an ICU should be advised in children with severe DKA (prolonged duration of symptoms, mental status changes, or vascular compromise) or patients who are at increased risk of cerebral edema.

The initial assessment of DKA requires a detailed history and physical examination. Degree of dehydration should be assessed using weight, pulse, blood pressure and respiratory effort, capillary refill, and skin turgor. Samples for measurement of glucose, electrolytes, osmolality, venous or arterial pH and pCO2, hemoglobin and hematocrit, and HbA1c should be obtained, as well as a urinalysis for ketones.

Management of DKA in the ICU should include hourly measurement of the vital signs including strict fluid input and output, capillary blood glucose, and neurologic examinations (looking for Cushing’s triad and other signs of cerebral edema). Every 2 to 4 hours, blood gases and chemistries should be done to evaluate electrolytes, serum urea nitrogen (BUN), hematocrit, and blood glucose. More frequent testing is warranted if the patient is critically ill. An electrocardiogram should be considered if potassium measurement is delayed.

**Hydration Status and Fluid Replacement**

Hemodynamic instability and shock are rare in pediatric DKA. Chemical measurements, as a means of assessing fluid deficit, can be unreliable at diagnosis. The extracellular fluid has higher osmolality and fluid shifts from the intracellular to extracellular compartments. Therefore, sodium measured on a blood chemistry is usually lower than the total body sodium. The effective osmolality at the time of presentation is usually in the range of 300 to 350 mOsm/L. Hemoconcentration leads to an increased BUN and hematocrit and may help to differentiate severe extracellular fluid (ECF) contraction from true hyponatremia.
Goals of therapy in DKA include replacement of diminished circulatory volume, repletion of electrolytes, recovery of the glomerular filtration rate (GFR) to further eliminate glucose and ketones from the circulation, and avoidance of complications including cerebral edema. Slower correction of overall fluid deficit with isotonic or near-isotonic fluids can lead to quicker resolution of acidosis. The risk of using large amounts of normal saline is hyperchloremic metabolic acidosis. There is no evidence supporting the use of colloids over crystalloids for DKA therapy.

Fluids given to the child before assessment should be factored into calculation of deficit. Initial intravenous fluid administration should begin immediately with an isotonic solution, which can be given if needed in a 10 to 20 cc/kg bolus over 1 to 2 hours. The remainder replacement intravenous fluid should be given evenly over at least 48 hours. Subsequent fluid management should be with a solution with a tonicity greater than or equal to 0.45% saline. In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy. Because the severity of dehydration may be difficult to determine and can be overestimated, fluid infusion should not exceed a rate of 1.5 to 2 times the usual daily requirement based on age, weight, or body surface area. Urinary losses should not be added to the calculation of replacement fluids.

**Insulin**

After the fluid deficit and electrolyte losses are calculated, low-dose intravenous insulin administration is standard of care. The goal of insulin therapy is to inhibit lipolysis and ketogenesis and decrease the blood glucose levels. A bolus of insulin is not necessary, and its use is controversial. The dose of insulin should be maintained at 0.1 U/kg/h until resolution of ketoacidosis (pH: >7.30; HCO3: >15 mmol/L) or until the anion gap is closed. If the patient has hypoglycemia on maximum amounts of intravenous dextrose, then the insulin drip should be lowered, but not less than 0.05 U/kg/h.

To prevent hypoglycemia, glucose should be added to the intravenous fluid when the plasma glucose falls to approximately 14 to 17 mmol/L (250 to 300 mg/dL), because the resolution of acidemia usually takes longer than the normalization of blood glucose. Five percent glucose can be used initially and then slowly increased to maintain euglycemia on the insulin drip. Reassessment of the patient, review of insulin therapy, and consideration of other possible causes of impaired response to insulin should be considered (eg, infection, errors in insulin preparation, or adhesion of insulin to tubing with very dilute solutions) if biochemical parameters of ketoacidosis do not improve. In the rare event that intravenous insulin cannot be given, insulin may be administered subcutaneously or intramuscularly every hour at the same dose.

**Electrolyte Replacement**

In DKA, potassium is lost from the intracellular compartment as a result of insulin deficiency, hypertonicity, and the exchange of hydrogen ions within the cell. Potassium also is lost secondary to vomiting and osmotic diuresis. Therefore, serum levels of potassium are not reliable in the initial work-up of DKA. Once insulin is given, potassium will move from the extracellular to intracellular space, and serum levels will decrease. Repletion of potassium is necessary and should be started once the serum levels are no longer elevated and the patient has urinated.

In DKA, phosphate deficit also occurs as a result of osmotic diuresis and movement across the cell. Treatment with insulin results in movement of phosphate back into the intracellular space and a subsequent drop in serum phosphate. Although studies have not shown significant clinical benefit from phosphate repletion in DKA and its use...
remains controversial, potassium phosphate may be used safely together with potas-
sium chloride to avoid hyperchloremia. Calcium levels should be monitored closely.

**Acidosis**

Fluid replacement and insulin are the first-line agents for treating acidosis. Insulin prevents ketoacid production and breaks it down into bicarbonate. Fluid replacement improves tissue perfusion and increases GFR to aid in acid excretion.

The use of bicarbonate in treating DKA remains controversial. Some studies have shown that bicarbonate may worsen electrolyte abnormalities in DKA by contributing to hypokalemia and hypernatremia via increased sodium load. Bicarbonate also can increase the synthesis of ketones in the liver and thereby slow down the time to recovery from ketoacidosis. Still, a subset of patients with severe DKA (arterial pH: <6.9) who have impaired cardiac contractility, peripheral vasodilatation, poor tissue perfusion, and life-threatening hyperkalemia may benefit from judicious use of bicarbonate.

**Treatment of Cerebral Edema**

The clinician should have high suspicion for CE in patients with DKA, and therapy should commence immediately once diagnosed. The head of the bed should be elevated. Intravenous fluids should be reduced, and intravenous mannitol should be given. If Mannitol is not available, 3% hypertonic saline may be used instead. Mechanical ventilation may be required if the patient’s respiratory status is compromised. Studies have shown poor outcomes in patients with CE associated with DKA who were aggressively ventilated (pCO2 <22 mm Hg). The role of glucocorticoids in treatment of CE in DKA has not been supported.

**Prevention of DKA**

Education and early detection remain the ultimate tools in prevention. Genetic and immunologic diagnostic testing in patients at higher risk for T1DM has been shown to decrease the occurrence of DKA at onset of diabetes. In patients with T1DM, studies have shown that comprehensive health care and education including plans for sick day management and continuous subcutaneous insulin pump malfunction can help to decrease the incidence of DKA.

**CONSENSUS STATEMENT ON IDIOPATHIC SHORT STATURE**

The purpose was to summarize the advances in the management of children with idiopathic short stature (ISS).7

The statement was endorsed by: Growth Hormone Research Society (GHRS), LWPES, European Society for Pediatric Endocrinology (ESPE), Latin American Society of Pediatric Endocrinology (SLEP), Japanese Society of Pediatric Endocrinology (JSPE), Canadian Pediatric Endocrine Group (CPEG), Asia Pacific Pediatric Endocrine Society (APPES), and APEG.

**Definition**

ISS was defined as

\[ \text{“a height more than two standard deviation scores (SDS) below the corresponding mean for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities”} \]

This includes constitutional delay of growth and puberty (CDGP) and familial short stature. Children born small for gestational age, children with syndromes involving
short stature, and children with chronic medical conditions that interfere with growth should be excluded from this definition.

ISS can be subdivided into two groups based on the midparental height (calculated by average of parents' heights + 6.5 cm for boys/- 6.5 cm for girls). One group is children whose adult height is about the same as the midparental height, and the other is children whose adult height is below the midparental height.

Assessment of the Short Child

Each evaluation of a short child should begin with a comprehensive history:

- Birth history (including in utero events, anthropomorphic data at birth, amniocentesis, gestational age, and complications)
- Medical history including hospitalizations, surgeries, medications, chronic diseases, dietary history, developmental history including dentition, which can parallel bone maturation
- Family history focusing on stature, onset of puberty, and chronic diseases of first- and second-degree family members; consanguinity should be documented
- Pubertal history of the patient
- Prior growth point or curves

The physical examination should include the general appearance, any dysmorphic features, and body disproportions. A length should be obtained in all children under 3 years of age with a recumbent stadiometer. A standing stadiometer can be used in cooperative children over 3 years of age. Arm span, sitting height or upper-to-lower segment ratios, body mass index (BMI), and for children younger than 4 years measurement of the head circumference should be included. Pubertal status using Tanner staging should be documented.

Diagnostic Studies

If the history and physical examination do not reveal a specific diagnosis, the following screening tests are indicated:

- A complete blood count
- Sedimentation rate
- A complete metabolic panel
- Screening for celiac disease
- Thyroid function tests
- Insulin-like growth factor (IGF)-1 level
- A radiograph for bone age (BA).

In a female with unexplained short stature or in any male with genital abnormalities, a karyotype should be done. Skeletal survey should be reserved for patients with suspicion of a skeletal dysplasia.

It is strongly recommended that IGF-1 levels be obtained as part of the evaluation. Insulin-like growth factor binding protein (IGFBP-3) measurements add little to the evaluation of short stature except in children younger than 3 years. Measures of spontaneous growth hormone (GH) secretion are not indicated. GH stimulation testing should be performed in any patient with a history and physical examination suggestive of GH deficiency, a low growth velocity or low IGF-1 levels. A peak stimulated GH value less than 10 ng/dL is considered GH deficiency (and thus excludes ISS). If a diagnosis of ISS is made, a head magnetic resonance imaging (MRI) scan is not indicated.
Genetic testing including short stature homeobox (SHOX) gene analysis should be considered in appropriate clinical settings.

**TREATMENT**

The primary goal of treatment is to reach a normal adult height. A secondary goal is to reach a more socially acceptable height during childhood. In the United States, GH treatment has been approved for children shorter than -2.25 SDS (1.2 percentile). Children whose heights are -2 SDS and who are more than 2 SDS below their midparental target height (TH) or their predicted adult height (PAH) also should be considered for treatment. There are no laboratory criteria for starting GH therapy. Optimal age for initiating treatment is 5 years to early puberty (most studies examined children older than 3 to 4 years). The role of PAH in the decision to treat with GH is unclear. The PAH may be inaccurate, but it can be a helpful tool together with other factors (BA, family height and pubertal history, and midparental target height) in deciding to treat.

**Dosing and Duration of GH Treatment**

Current US Food and Drug Administration (FDA)-approved dosing for GH in children with ISS is up to 0.3 to 0.37 mg/kg/wk (42 to 52 μg/k/d). There are no data on long-term safety of doses higher than 0.35 mg/k/wk (50 μg/k/d) in children with ISS. The dose of GH is adjusted based on weight gain and interval growth velocity. IGF-1 measurements are also useful in assessing efficacy, safety, and compliance. Increased short-term growth is achieved with higher IGF-1 values, but there are no long-term studies to assess the safety or ultimate effect of these elevated levels. The current recommendation is if IGF-1 levels are consistently above 2.5 SDS, the dose of GH should be reduced.

There are two groups with differing ideas about when to stop treatment with GH. One group recommends stopping GH when near-adult height is reached (height velocity <2 cm/y or BA >16 years in boys or >14 years in girls). The other group recommends stopping GH when the height is in the normal adult range (above -2 SDS) or has reached another cut-off for the reference adult population. The individual patient’s desire to terminate treatment should be considered at each visit.

**Response to GH**

Change in height SDS of more than 0.3 to 0.5, height velocity increase of more than 3 cm/y, and height velocity SDS increase of more than 1 suggest a successful first-year response to GH. The dose of GH can be increased if the growth velocity is decreased, and compliance is assured. If the rate of growth is still suboptimal after 1 to 2 years of higher doses of GH, then GH treatment should be stopped and other treatment options considered.

Children with ISS on GH therapy (average duration 4 to 7 years) have a mean increase in adult height of 3.5 to 7.5 cm. Responses are highly variable and are dose-dependent. Children who are younger, heavier, who receive higher doses per kilogram, and who are shortest relative to target height have the best growth response. Adult height outcome is influenced negatively by older age at the start of treatment and is influenced positively by a taller midparental height, a taller height at the start of treatment, a greater BA delay, and a greater first-year response to GH therapy.

**Monitoring**

Adverse effects noted in children receiving GH for ISS are generally the same as those previously reported in children receiving GH for other indications, although they occur
less frequently. Height, weight, pubertal development, and adverse effects to GH should be monitored every 3 to 6 months in children treated with GH. Regular evaluations for scoliosis, tonsillar hypertrophy, papilledema, and slipped capital femoral epiphysis should be performed. After 1 year of treatment, the response to GH should be assessed by calculating height velocity SDS and the change in height SDS. A BA may be obtained periodically. No instances of elevated blood glucose in GH-treated patients with ISS have been reported.

**Alternative to GH Treatment**

Anabolic steroids, such as oxandrolone (given orally) and testosterone (patch or gel) are alternative treatment options. Both have been shown useful in boys with CDGP and short stature greater than -2.5 SDS. If the adult height prediction is close to the target height, then testosterone has been shown to be the most appropriate treatment. Oxandrolone has not been shown to significantly increase predicted or measured adult height.

IGF-1 is FDA-approved for short stature associated with severe IGF deficiency and normal GH secretion. Children first should be given a trial of GH, and if they do not respond, IGF-1 should be considered. Data are lacking regarding efficacy and safety.

GnRH analogs (GnRHa) are not recommended to be used alone in children with ISS, but in combination with GH it has potential value if it is used for at least 3 years. Its use might be considered if the PAH is below 2 SDS at the time of onset of puberty. When using GnRHa, one must consider the psychological effects of delaying puberty.

Studies using aromatase inhibitors (AIs) for at least 2 years have shown that males with ISS on GH have an increase in PAH. The long-term efficacy and safety of AI in males have not been demonstrated. No data support the use of AI in females.

**CONSENSUS STATEMENT ON THE MANAGEMENT OF THE CHILD BORN SMALL FOR GESTATIONAL AGE THROUGH TO ADULTHOOD**

The purpose was to identify key health issues facing children born small for gestational age (SGA) and to propose management strategies.

The statement was endorsed by: ESPE, LWPES, GHRS, SLEP, APPES, APEG, JSPE.

**Definition**

To diagnose a child as SGA the following information must be obtained:

- Gestational age (preferably calculated from the first trimester ultrasound examination)
- Birth weight, length, and head circumference
- Reference cut-off defined by a comparable population of patients, below which the definition lies.

The definition of SGA is birth weight or birth length less than -2 SD below the mean specific for the population. Children born SGA must be monitored for many health issues including heart disease, perinatal morbidity, associated neurodevelopmental disorders, poor growth/short stature, and metabolic irregularities.

**Early Growth and Development**

Longitudinal studies of growth in children born SGA have shown weight catch-up usually occurs in the first 6 months, while height catch-up can take up to 2 years. Ninety percent of children born SGA do catch-up. Factors that decrease the chance
of catch-up growth include severe prematurity, growth retardation, and very low birth weight, while having tall parents increases the likelihood of catch-up. Children born SGA should be monitored with measurements of length, weight, and head circumference every 3 months for the first year of life and every 6 months thereafter. Pediatricians should be aware of children who do not catch-up in the first 6 months of life or remain short by 2 years of age. These children should be referred to a pediatric endocrinologist.

Children born SGA have increased central adiposity and decreased lean mass. Studies have shown rapid weight gain in infancy is associated with obesity as an adult; therefore earlier dense feedings for SGA infants may not be appropriate.

**Endocrinopathies and Metabolic Disorders**

Overall, there are no true endocrinopathies associated with SGA. Classic growth GH deficiency usually is not seen. IGF1 and IGFBP3 levels are decreased 1 SDS in SGA children; however, they are not predictive of growth velocity or adult height. Routine evaluation of the hypothalamic-pituitary-adrenal and the thyroid axes are not recommended.

Being born SGA is not associated with late or early puberty. The small population of children who do have early puberty also have rapid puberty, leading to faster bone maturation and ultimately decreased adult height. Bone age is unreliable in children born SGA, and height prediction based on it is not routinely recommended. Hypospadias and cryptorchidism are observed in children born SGA.

Type 2 diabetes mellitus, adolescent hypertension, impaired glucose tolerance, and dyslipidemia have not been shown to occur more frequently in children born SGA. Insulin resistance, however, has been shown to occur as early as 1 year of age. Although the overall prevalence of risk factors is low, young adults born SGA have a higher incidence of metabolic risk factors (2.3%), especially if they are obese, of a certain ethnicity, and have strong family history.

**Management of Growth and Puberty**

Early evaluation of short children born SGA is recommended. There are over 40 years of research on the use of GH in children with SGA, and its use has been approved by the FDA and the European Agency for the Evaluation of Medicinal Products. The general consensus is that children between the ages of 2 to 4 years born SGA who have not caught up with a height less than 2.5 SD should be treated with GH. If the child is over the age of 4 years and does not show catch-up growth, then a height of 2 SD should be used as the cut-off. The starting dose of GH is 0.24 to 0.49 mg/kg/wk (35 to 70 µg/kg/d), with the higher doses used in those with the most marked growth retardation.

Age and height SDS at the start of treatment, midparental height, and dose of GH all influence the response during the first 2 to 3 years. Children with recognized syndromes respond less well to GH than those with nonsyndromic SGA. A growth velocity of more than + 0.5 SDS in the first year of treatment is considered a positive response to GH treatment. If there is a poor response, re-evaluation is indicated, including consideration of compliance, dose of GH, diagnosis, and the decision to discontinue treatment. In those with a positive response, withdrawal of GH therapy after 2 to 3 years leads to catch-down growth and is not recommended. GH should be stopped in adolescence when the growth velocity falls to less than 2 cm/y.

There is no evidence that the addition of a GnRH analog is associated with additional height gain in children born SGA. Pre-treatment IGF-1 levels may have a role in predicting responsiveness to GH, and in those receiving treatment, IGF-1 levels should be monitored regularly.
monitoring may be a useful tool for dose optimization. Some syndromes, such as Bloom’s syndrome or Fanconi syndrome may carry risks that may contraindicate the use of GH therapy. Adverse effects from GH treatment are not seen more commonly in children born SGA compared with other conditions.

Consequences in Adulthood

Studies have shown that children born SGA are at increased risk for metabolic consequences later on in life. Most of the evidence, however, comes from observational studies not limited to children born SGA. A rapid weight gain in infancy has been associated with an increased risk of obesity. Both small and large sizes at birth have been reported to be associated with increased risk of type 2 diabetes and glucose intolerance. Women born SGA are at an increased risk of having an SGA infant, preeclampsia, and gestational diabetes.

CONSENSUS STATEMENT ON MANAGEMENT OF INTERSEX DISORDERS

The purpose was to review the management of intersex disorders and devise a consensus statement on definitions, diagnosis, and management, and formulated proposals for future studies.15

The consensus statement was endorsed by LWPES, ESPE.

Introduction and Definitions

The definitions and nomenclature for intersex disorders are being reviewed and reworked continually as a result of dissatisfaction among health care professionals, families, and patients with the current terminology. The term disorders of sex development (DSD), as defined by congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical was proposed by the consensus committee. This phrase would replace terminology such as intersex, pseudohermaphroditism, hermaphroditism, and sex reversal, as these terms are potentially imprecise and derogatory (Table 1).

Psychosexual development is shaped by both biologic and environmental influences including exposure to androgens, genetics, neuro-anatomy, and family and social history. To understand psychosexual development, one must define its three components:

1. Gender identity—a person’s self-representation as male or female (some individuals may not identify exclusively with either)

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<thead>
<tr>
<th>Previous</th>
<th>Proposed</th>
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<tbody>
<tr>
<td>Intersex</td>
<td>Disorders of sex development (DSD)</td>
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<tr>
<td>Male pseudohermaphrodite, undervirilization of an XY male</td>
<td>46, XY DSD</td>
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<tr>
<td>Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female</td>
<td>46, XX DSD</td>
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<tr>
<td>True hermaphrodite</td>
<td>Ovotesticular DSD</td>
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<tr>
<td>XX male or XX sex reversal</td>
<td>46, XX testicular DSD</td>
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<tr>
<td>XY sex reversal</td>
<td>46, XY complete gonadal dysgenesis</td>
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2. Gender role—the psychological characteristics that are sexually dimorphic within the general population, such as toy preferences and physical aggression.

3. Sexual orientation—the direction(s) of erotic interest (heterosexual, bisexual, homosexual).

Gender dissatisfaction occurs more often in people with DSD than in the general population and signifies discontent with sex assignment. Psychosocial care, like medical and surgical care, is an integral part of DSD management.

Clinical Management of DSD

DSD usually is diagnosed in newborns with atypical genitalia, with congenital adrenal hyperplasia (CAH) remaining the most common cause.\textsuperscript{16} DSD, however, may be diagnosed in the older child or adult who presents with gynecomastia or hematuria in a male, inguinal hernia, virilization, or primary amenorrhea in a female, or delayed/partial puberty or previously unrecognized genital ambiguity.

Specifically, criteria suggestive of DSD include:

- Obvious genital ambiguity
- Female genitalia with an enlarged clitoris, posterior labial fusion, or an inguinal/labial mass
- Male genitalia with bilateral undescended testes, micropenis, isolated perineal hypospadias, or mild hypospadias with undescended testis
- Family history of DSD
- Discordance between genital appearance and a prenatal karyotype.

In newborns with DSD, gender assignment should not occur until an evaluation is performed by an experienced multidisciplinary team including a pediatric endocrinologist, surgeon/urologist, psychologist/psychiatrist, geneticist, gynecologist, and neonatologist. All individuals should receive a gender assignment. The families should be involved in the decision-making process, and in the case of older children, the patient should be involved also.

A comprehensive history including prenatal and family history should be obtained followed by a complete physical examination. The examination of the genitalia must be thorough and documented well. Anatomy should be compared with published norms.

Initial testing should be tailored to clinical findings depends on availability of testing at the individual center. First-line testing should include:

- Fluorescence in situ hybridization (FISH) with X- and Y-specific probe detection (even when prenatal karyotype is available)
- A full karyotype
- Imaging of the abdomen and pelvis via sonography
- Measurement of 17-hydroxyprogesterone
- Testosterone
- Gonadotropins
- Anti-Müllerian Hormone
- Serum electrolytes
- Urinalysis.

The results obtained from these tests should be sufficient for making a diagnosis within the category of DSD. Should the diagnosis remain elusive, additional testing can include
Human chorionic gonadotropin- and adrenocorticotropic-stimulation tests (to assess testicular and adrenal steroid biosynthesis)

Urinary steroid analysis by gas chromatography mass spectroscopy

Imaging studies

Gonadal biopsies

DNA analysis of the main genes in the pathway of testis differentiation and functionality.

Despite all of the available testing, only 20% of cases of DSD have an identified molecular diagnosis. Only 50% of 46,XY children with DSD will receive a definitive diagnosis.

Assigning Gender in Newborns

After a comprehensive evaluation, deciding on gender assignment is a daunting and stressful task for both the health care team and family. The following evidence from patients with DSD should be used along with individual factors including opinions of the family and their cultural practices, genital appearance and surgical options, a need for lifelong replacement therapy, and potential for fertility. Evidence to assist in sex assignment includes

Markedly virilized 46, XX infants with CAH should be raised as female, because more than 90% of patients with 46XX CAH identify as female.

60% of patients with 5-alpha-reductase-deficiency assigned female as a newborn and who then virilized at puberty lived as males. This along with the potential for fertility as a male should be discussed when deciding on gender assignment. Although fertility is less well documented in 17-beta-hydroxysteroid dehydrogenase deficiency, the same considerations should be made.

25% of patients with partial androgen insensitivity syndrome (PAIS), androgen biosynthetic defects, and incomplete gonadal dysgenesis were dissatisfied with their assigned sex whether male of female.

Available data support male rearing in all patients with micropenis, again taking into consideration fertility.

Potential for fertility on the basis of gonadal differentiation and genital development should be considered in patients with ovotesticular DSD

Prenatal androgen exposure, testicular function at and after puberty, phallic development, and gonadal location should be considered in patients with mixed gonadal dysgenesis (MGD).

65% of individuals with cloacal exostrophy lived as female, but there was still variability in gender identity outcome.

Surgical Management

Surgeons should have both pediatric training and expertise in DSD surgery. Early genitoplasty is acceptable if the cause of DSD has been identified, and severe virilization (Prader 3 to 4) exists. Genitoplasty should be performed in concordance with repair of the common urogenital sinus. The surgical procedure should focus on preservation of erectile function and the innervation of the clitoris. Vaginal dilatation should not be used in childhood. It is expected that revision of surgeries done in infancy will be necessary at the time of puberty or shortly after.

If there is less severe clitoromegaly and no involvement of the urogenital sinus, then surgery should be postponed until adolescence. Once a patient with an absent or inadequate vagina is psychologically motivated and a full partner is involved, then
vaginoplasty should be performed. Unfortunately, self-dilatation, skin substitution, and bowel vaginoplasty all have pros and cons, and none has been universally successful.

If hypospadias is associated with a DSD, then surgical repair and testosterone supplementation are recommended. There is no evidence that removal of asymptomatic discordant structures prophylactically is necessary. Symptoms in the future may suggest the need for surgical removal.

The testes in patients with DSD raised female should be removed to prevent malignancy in adulthood. Because the earliest reported malignancy was at 14 years of age, a parents’ right to refuse removal of the testes until adolescence is supported. The availability of estrogen-replacement therapy allows for the option of early removal at the time of diagnosis. The streak gonad in a patient with MGD raised male should be removed in early childhood. Females with gonadal dysgenesis (bilateral streak gonads) and Y-chromosome material should have bilateral gonadectomy performed in early childhood. Gonadectomy should be performed before puberty in patients with androgen biosynthetic defects raised female.

Testicular biopsy should be performed at puberty in patients with gonadal dysgenesis to monitor for pre-malignant lesion termed carcinoma in situ or undifferentiated intratubular germ cell neoplasia. If the biopsy is positive, the patient should be given the option of sperm banking. Treatment with local low-dose radiation is curative.

**Replacement of Sex Steroids**

The goal of replacement of sex steroids in patients with DSD is to mimic normal pubertal maturation so that the patient experiences a normal pubertal growth spurt, secondary sexual characteristics, and appropriate bone mineral accumulation. Testosterone is available as an intramuscular depot injection, an oral preparation, and transdermal preparations. The depot injection is the most commonly used. Patients with PAIS may require supraphysiologic doses of testosterone for optimal effect.

Females with hypogonadism require estrogen supplementation to induce a pubertal growth spurt, secondary sexual characteristics such as breasts, and menarche. A progestin usually is added after breakthrough bleeding develops or within 1 to 2 years of continuous estrogen. In women without a uterus, there is no evidence that the addition of cyclic progesterone is beneficial.

**Psychosocial Management and Long-Term Outcomes**

Psychosocial care provided by mental health staff with expertise in DSD is an integral part of management of DSD. The earliest age at which gender identity can be assessed accurately remains unclear, but it is thought to begin before the age of 3 years. Atypical gender role behavior is more common in children with DSD. In affected children and adolescents who report significant gender dysphoria, a specialist in psychosexual development is crucial to help the patient identify feelings about gender. If the patient expresses a desire to change gender, the patient’s wish should be supported. Patients with DSD often complain of sexual aversion and lack of arousability, which often are misinterpreted as decreased libido. A support network including medical and psychological professionals is crucial to identifying and treating these important issues.

There is much needed follow-up for long-term outcomes for patients with DSD including medical, surgical, and psychological. What is known is related mainly to surgical outcomes and sexual function. Early surgery, while successful in many cases, does run the risk of decreased sexual sensitivity, loss of clitoral tissue, and cosmetic
concerns. The success of the surgery depends on the experience, skill, and technique of the surgeon. Scarring may need revision to insure proper sexual function. Surgery to construct a neovagina carries a risk of neoplasia. The degree of hypospadias and the amount of erectile tissue play a large role in the surgical result of undermasculinized males with a phallus. Feminizing genitoplasty requires less surgery to achieve an acceptable outcome compared to masculinizing genitoplasty and results in fewer urologic difficulties.

The highest tumor risk is found in TSPY (testis-specific protein Y-encoded) positive gonadal dysgenesis and PAIS with intra-abdominal gonads, whereas the lowest risk (<5%) is found in ovotestis and complete androgen insensitivity syndrome (CAIS). For a complete list please refer to the consensus statement (Box 1).

Addendum to Consensus Statement

Since publication of the consensus statement on management of intersex disorders, some have recommended the term atypical genitalia replace the previous term ambiguous genitalia.17,18

REFERENCES


Box 1
Abbreviations of organizations

| APEG-Australian Pediatric Endocrine Group |
| APPES-Asia Pacific Pediatric Endocrine Society |
| CPEG-Canadian Pediatric Endocrine Group |
| ESPCC-European Society for Pediatric Critical Care |
| ESPNIC-European Society of Pediatric and Neonatal Intensive Care |
| ESPE-European Society for Pediatric Endocrinology |
| GHRSL-Growth Hormone Research Society |
| ISPAD-International Society |
| JDNF-Juvenile Diabetes Research Foundation International |
| JSPE-Japanese Society of Pediatric Endocrinology |
| LWPES-Lawson Wilkins Pediatric Endocrine Society |
| SLEEP-Latin American Society of Pediatric Endocrinology |
| WFPICCS-World Federation of Pediatric Intensive and Critical Care Societies |
Clinical guidelines and consensus statements serve to summarize and organize current knowledge on diverse subjects, and provide practical guidelines for proper clinical management. Recommendations should be based on research and evidence derived from appropriate sources.

Consensus Statement on 21-Hydroxylase Deficiency from The Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology. Joint lwpes/espe caah working group. A well-organized multidisciplinary team (including specialists in pediatric endocrinology, psychosocial services, pediatric surgery/urology, and genetics) is essential for the diagnosis and management of the infant with ambiguous genitalia. It is important that the coordinator of the team has experience in the long-term care of the patient with CAH and provides a consistent message to the parents. Clinical evaluation in term and premature neonates. Clinical guidelines and consensus statements serve to summarize and organize current knowledge on diverse subjects, and provide practical guidelines for proper clinical management.

In 2008, more than 20 consensus statements were published in the pediatric literature alone. This article summarizes the salient points of the latest consensus statements jointly developed by multiple endocrine societies including the Lawson Wilkins Society for Pediatric Endocrinology and the European Society for Pediatric Endocrinology. As much as possible, the original intent and language of the statements was respected and paraphrased.