# Evaluation and Initial Management of Hypopituitarism

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# **Education Gap**

Signs and symptoms of hypopituitarism, in particular diabetes insipidus and decreased linear growth velocity, are frequently overlooked in patients with craniopharyngioma. (1)

# **Objectives** After completing this article, readers should be able to:

- Describe the various pathophysiologic causes associated with hypopituitarism, including craniopharyngioma.
- 2. Recognize the clinical features of pituitary hormone deficiencies.
- Describe the principles of hormone replacement therapy for hypopituitarism.

#### INTRODUCTION

Hypopituitarism affects between I in 4,000 and I in 10,000 live births, with increasing incidence with age. (2) The pituitary, sometimes referred to as the master gland, is positioned in the anterior midline of the brain in the sella turcica. The pituitary controls endocrine function through the release of multiple hormones that can have a direct growth effect on target tissue (trophic effects) or stimulate that tissue to release a hormone that has its effects on other tissues (tropic effects). The anterior pituitary forms as an outpouching of the embryonic oral cavity (Rathke pouch). It is responsible for the release of growth hormone (GH), corticotropin, thyrotropin, prolactin, and the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The posterior pituitary is composed of neuronal projections from the hypothalamus and is responsible for the storage and secretion of oxytocin and antidiuretic hormone (ADH). This article examines the pathologic causes of pituitary dysfunction, their diagnosis, and treatment.

#### CAUSES OF HYPOPITUITARISM

#### Congenital

Congenital hypopituitarism most often results from genetic or embryologic pathologies. Septo-optic dysplasia (SOD) is the most common congenital cause of hypopituitarism, with an incidence as high as I in 10,000. SOD results in

AUTHOR DISCLOSURE Drs Pierce and Madison disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/ investigative use of a commercial product/ device. variable hormonal deficiencies, absence of the septum pellucidum (Figure), and hypoplasia of the optic nerves, often resulting in blindness. (3) Although SOD can be associated with genetic mutations (in *HESX1*, *OTX2*, and *SOX2*), it is most often multifactorial and is associated with abnormal midline brain development. (4) Other defects in midline formation (such as midline cleft lip and/or palate, vascular malformations, absence of the corpus callosum) can also be associated with an embryologic malformation of the pituitary gland.

In cases of SOD or facial midline defects, further screening should be undertaken that includes testing for pituitary hormone deficiencies (see the section on "Evaluation"), ophthalmologic evaluation, and imaging of the central nervous system (CNS) (eg, magnetic resonance imaging [MRI]). Such screening should occur in the neonatal period to prevent complications from untreated hormone deficiency and to assess possible vision deficits that may require accommodation. Rare genetic causes of hypopituitarism include deletions of the "POU domain class I transcription factor," *PIT-1* or *POU1F1*, and the "homeobox protein prophet of PIT-I," encoded by the *PROP1* gene. (5)(6) GH, prolactin, and TSH deficiencies characterize *PIT-1/POU1F1* deletion, whereas *PROP1* deletions can manifest as any combination of deficiencies of the anterior pituitary hormones.

#### Acquired

Later in life, anterior pituitary hormone deficiency can arise from any cause that damages the pituitary, including mass effect (from tumor), infection, autoimmune disease, infiltrative disease, chemotherapy and radiation exposure, and trauma. Any trauma or damage to the sella, pituitary, pituitary blood supply, or hypothalamus can result in hypopituitarism. This includes



Figure. Magnetic resonance imaging of an infant at 4 days of age showing absence of the septum pellucidum.

surgical manipulation as well as motor vehicle collisions, child abuse, and sports-related injuries. There are cases of idiopathic pituitary hormone deficiencies, most commonly isolated idiopathic GH deficiency, but this is always a diagnosis of exclusion.

Diabetes insipidus (DI) can occur from any injury to the pituitary stalk that damages neuronal projections responsible for the delivery of ADH to the storage vesicles in the posterior pituitary. In cases of isolated DI, an identified cause is found at the time of diagnosis in 50% to 90% of cases, with the most common causes being anatomic abnormalities, central brain tumors, and infiltrative diseases. (7)(8)

Any mass that comes in contact with the hypothalamus or pituitary can place pressure on the sensitive endocrine cells, leading to dysfunction. GH-producing cells are the most sensitive to damage from any cause. Common pediatric tumors include craniopharyngioma, primary brain tumors such as germinomas and optic gliomas, functional and nonfunctional pituitary macroadenomas, and cerebral metastases of other primary cancers such as lymphoma. Prolactinomas deserve special mention because they are often not of a size to cause problems from mass effect. However, hyperprolactinemia can cause negative feedback and inhibition of the hypothalamic-pituitary-gonadal axis, resulting in hypogonadotropic hypogonadism with delayed or arrested puberty. Hyperprolactinemia is also associated with galactorrhea.

Craniopharyngioma is the most common tumor associated with multiple pituitary deficiencies in children. A craniopharyngioma arises from the same oral ectoderm as the anterior pituitary. In a case series of 42 children with craniopharyngioma, only 10% sought medical treatment for symptoms, although more than 50% had evidence of growth failure before identification. (9) GH deficiency is the most common pituitary deficiency seen in craniopharyngioma, affecting up to 75% of patients. Other pituitary hormone deficiencies include gonadotropin deficiency, thyrotropin deficiency, corticotropin deficiency, and DI, with the incidence of each increasing from baseline after surgical intervention. (9) Because surgical excision of the mass can disturb the pituitary and the stalk, the patient should be completely evaluated for deficiencies both before and after surgery to identify any new deficiencies. This is particularly true of GH and ADH.

Even when a brain tumor does not itself damage the pituitary, tumor treatment may result in hypopituitarism. Any radiation exposure to the pituitary can cause permanent pituitary damage, with GH-producing cells again being most sensitive. Although 100% of children who are exposed to more than 30 Gy eventually develop GH deficiency, any brain exposure greater than 22 Gy should prompt evaluation for hormonal deficits. (10) Common chemotherapeutic drugs are not currently believed to result in central

deficiency, but multiple chemotherapy modalities can damage the target organs. High-dose corticosteroids for induction chemotherapy in acute lymphoblastic leukemia can suppress the hypothalamic-pituitary-adrenal axis, but this treatment is not associated with other pituitary hormone deficiencies.

Certain infiltrative diseases also have a predilection for the pituitary, particularly Langerhans cell histiocytosis (LCH), which results from overproliferation of Langerhans cells. The classic triad of LCH symptoms is also referred to as multifocal unisystem disease and includes DI, exophthalmos, and lytic bone lesions. GH deficiency is also common in LCH. In cases that were evaluated retrospectively after an initial diagnosis of idiopathic DI, approximately one-third of patients were subsequently found to have a pathologic etiology, with approximately 50% of those found to have histiocytosis. (8)

CNS infection, such as meningitis, is classically associated with the development of DI, but there is a risk of damage to other hormone-producing cell types as well. Infiltrative infections such as tuberculosis can lead to pituitary destruction.

Hypophysitis is a rare cause of autoimmune damage to the pituitary, similar to other autoimmune lymphocytic processes such as Hashimoto thyroiditis or Addison disease. In most cases, hypophysitis is a diagnosis of exclusion when symptoms of hypopituitarism are present with CNS symptoms such as headache, nausea, or vision problems. No reliable antibody assays are available to test for hypophysitis in peripheral blood and fewer than 400 cases have been reported in the literature. (II)

## SYMPTOMS OF HYPOPITUITARISM

Symptoms of hypopituitarism are related to both hormonal deficits and the timing of the insult to the pituitary. In older children, when not associated with a known disorder, hypopituitarism is often identified after evaluation for poor linear growth. The symptoms most commonly seen in each individual hormone deficiency are listed in Table I. Other symptoms include those from the underlying pathologic cause of the hypopituitarism, such as visual deficits or head-aches from a midline mass, fever or sepsis associated with meningitis, or bony lesions from LCH.

Surgical manipulation of the posterior pituitary creates a classic triphasic ADH response. The first phase, manifested as DI, occurs within 24 hours of surgery. Patients have excessive urine output, often more than 5 to 10 mL/kg per hour. The urine is dilute (specific gravity <1.010 and urine osmolality <100 mOsm/kg), with hypernatremia and increased serum osmolality (often >300 mOsm/kg). The second phase is associated with release of preformed ADH from the dying neurons, resulting in a transient syndrome of

inappropriate ADH secretion (SIADH). Urine output may be normal or decreased in volume but is concentrated (urine osmolality greater than serum) and often accompanied by hyponatremia. After the death of the ADH neurons, the third phase is characterized by permanent DI.

#### **EVALUATION**

#### Hormones

Each individual hormone should be assessed during laboratory testing. Although idiopathic isolated GH deficiency is seen rather commonly, other isolated pituitary hormone deficiencies are relatively rare. Accordingly, clinicians should test for all anterior hormone deficiencies once any single deficiency, including GH, is identified. It is also critical that testing for corticotropin, LH, FSH, thyrotropin, and GH include evaluation of both the pituitary hormone itself and the target organ hormones. Frankly low concentrations of pituitary hormones are not necessary to diagnose deficiency; they may be inappropriately normal in the setting of target hormone deficiency.

GH has a typically pulsatile release that makes evaluation of a random value difficult to interpret. Instead, screening for GH deficiency relies on evaluation of the secondary growth factors insulin-like growth factor-I (IGF-I) and insulin-like growth factor-binding protein-3 (IGFBP-3). Both are produced by the liver in response to the presence of GH. These growth factors have longer half-lives than GH and are maintained at a steady level in response to normal pulsatile GH secretion. If growth factor values are low, formal testing for GH can be performed through stimulation of GH secretion. This is typically achieved by a combination of medications that either directly promote GH secretion or create stress in the body (such as hypoglycemia) that results in GH secretion.

Cortisol has circadian release that increases the difficulty of assessment with a random value, similar to GH. However, the tropic hormone corticotropin is required by the adrenal glands to maintain secretory function. If corticotropin is missing, adrenals atrophy and cortisol release is impaired. Corticotropin deficiency can result in adrenal crisis if profound or prolonged. Adrenal crisis is characterized by hypotension and cardiac instability. Laboratory testing is via provocative testing of the adrenal glands through administration of exogenous corticotropin. If central deficiency (corticotropin deficiency) is suspected, a small dose of corticotropin is used  $(I \mu g)$ , based on the concept that a normally functioning gland is sensitive but an atrophic gland is not. (12) This is in contrast to the  $250 - \mu g$  corticotropin stimulation test that is performed if there is suspicion of primary adrenal insufficiency. With either dose, the cortisol is measured at 30 minutes, with a

HORMONE MISSING	SIGNS AND SYMPTOMS
Growth hormone	Linear growth failure, increased adiposity, decreased muscle mass, fatigue If congenital: neonatal hypoglycemia, micropenis
Corticotropin	Nausea, vomiting, weight loss, prolonged duration of common illnesses, hypotension, fatigue
Thyrotropin	Fatigue, dry hair, dry skin, linear growth failure, constipation, weight gain despite decreased intake, bradycardia If congenital and untreated: development delays, intellectual disability
Prolactin	Inability to lactate after pregnancy
Luteinizing hormone/Follicle-stimulating hormone	Delayed or absent pubertal development with lack of pubertal growth spurt, secondary amenorrhea, decreased libido, osteoporosis If congenital: micropenis, undescended testicles
Antidiuretic hormone	Polyuria, polydipsia, nocturia, dehydration, hypernatremia

## TABLE 1. Common Signs and Symptoms Associated with Hormone Deficiencies

passing value of 18  $\mu$ g/dL (496.6 nmol/L). (13) In addition, measurement of both baseline corticotropin and cortisol concentrations can aid in distinguishing between primary and secondary adrenal insufficiency because corticotropin will be elevated in the setting of primary disease. Random corticotropin values, especially if measured without a concomitant cortisol value, are rarely helpful diagnostically.

Thyrotropin deficiency is manifested by low circulating thyroid hormone (free thyroxine [T4]) concentrations in the setting of a low or normal thyrotropin values. A normal thyrotropin with a low free T4 is considered inappropriately normal because intact feedback would result in elevation of the thyrotropin above the normal range. In general, when evaluating suspected hypothyroidism, clinicians should assess both thyrotropin and free T4 to avoid missing central causes of hypothyroidism.

Testing for gonadotropin deficiency should always be performed using a highly sensitive assay that can measure results less than I mIU/mL. It should include testing for both LH and FSH as well as the patient-appropriate sex steroid (estrogen or testosterone). Similar to thyrotropin deficiency, normal gonadotropin values in the setting of low sex steroid values at the normal age of puberty should raise concern for pituitary insufficiency.

Central DI from ADH deficiency is primarily manifested by the clinical symptoms of polyuria and polydipsia. Normal serum sodium concentrations can be maintained unless the patient is unable to sustain adequate free water intake, whether due to developmental stage, absent thirst mechanism, profound illness, or iatrogenic causes such as nil per os status for surgery. In this setting, the excessive loss of free water causes hypernatremia with resultant increase in plasma osmolality. Urine is inappropriately dilute for the serum sodium concentration. The water deprivation test involves monitoring of a patient during restricted access to free water. Urine output, serum sodium, and serum and urine osmolality are frequently assessed to determine if the patient develops hypernatremia with elevated serum osmolality in the setting of inappropriately high urine output with low urine osmolality. Because of the risk of developing significant hypernatremia, this test should only be performed in the hospital where frequent monitoring is available.

#### Identification of Acquired Cause

Because most acquired cases of hypopituitarism are associated with a treatable disease, identifying and treating the cause is as important as hormone replacement. Often the first step is imaging of the brain via MRI with and without contrast. This can identify the solid and cystic sellar mass characteristic of craniopharyngioma (Figure) as well as smaller areas of hypoenhancement associated with pituitary adenomas. Hypophysitis is extremely rare but can appear as an enlarged or diffusely hyperenhanced pituitary gland. Skull fractures and other signs of trauma are often readily evident on imaging, although they can be missed when small. Tumor markers for common brain tumors include human chorionic gonadotropin and  $\alpha$ -fetoprotein.

#### TREATMENT

Treatment for hypopituitarism is, in principle, very simple: replace the target hormones that are deficient. In practice, such replacement can be relatively complicated and requires close patient monitoring and appropriate dose adjustments.

#### Adrenal Insufficiency

Once the cause has been identified, treatment should be directed toward that pathology. However, before undertaking any surgical interventions, it is critical to treat any adrenal insufficiency and administer the appropriate stress-dose level of cortisol replacement both during and immediately following surgery. If neurosurgical intervention is undertaken, postsurgical use of high-dose dexamethasone is appropriate for replacement stress dosing, although hydrocortisone should be initiated at the end of the corticosteroid weaning period. Hydrocortisone has a half-life in serum of 6 to 8 hours and, therefore, ideally should be administered 3 times a day (morning, mid-afternoon, and evening). The maintenance replacement hydrocortisone dose is 7 to 9 mg/m<sup>2</sup> per day. If doses cannot be administered in even allotments, the larger dose frequently is provided in the morning to better mimic the normal surge in cortisol upon waking. Stress dosing also is necessary in times of illness. Typically, doses are doubled for fevers and tripled for any vomiting or diarrhea. Patients (and parents in particular) must be trained in the use of emergency hydrocortisone injection (approximately 10 times maintenance) that can be administered intramuscularly if the patient has suspected adrenal crisis or is unable to take oral medications.

#### Hypothyroidism

Thyroid hormone is replaced with levothyroxine, the righthanded isomer of T<sub>4</sub>. Levothyroxine is well absorbed and can be converted to the active hormone, triiodothyronine, in target tissues to allow for tissue-specific control of thyroid signaling. Weight-based higher doses of thyroid hormone are required in younger children, and appropriate replacement is critical for normal neurodevelopment in the first 3 years after birth. The schedule in Table 2 is modified from the protocol used in cases of congenital hypothyroidism; doses may be less for patients with some pituitary function, although the monitoring frequency is similar. Patients are monitored through measurement of free T<sub>4</sub> alone, with the goal of maintaining the values in the upper half of the normal range.

#### **Growth Hormone Deficiency**

Recombinant GH is available to treat patients with GH deficiency. As a peptide hormone, it is currently only available as a subcutaneous injection that must be administered daily. Typically, initial replacement doses range from 0.025 to 0.05 mg/kg per day, with monitoring of IGF-I values and growth velocity. Goal IGF-I values should be in the upper half of the normal range. Growth velocity should be age-appropriate, although it may be higher than normal in the first 6 to I2 months of

replacement. GH should not be administered in the setting of active malignancy because of theoretical concerns for increasing cancer proliferation. Patients are typically advised to wait I year after surgical resection of a craniopharyngioma and at least 2 years after successful treatment of other malignancies before beginning GH replacement therapy. Some of the most significant adverse effects of GH treatment are increased risk for glucose intolerance and hyperinsulinism, slipped capital femoral epiphysis, pseudotumor cerebri, and pancreatitis. Overall, GH replacement in a deficient child is generally considered to be safe.

#### **Gonadotropin Deficiency**

Gonadotropin deficiency results in low concentrations of sex-specific sex steroids: testosterone in males and estrogen in females. This results in absent puberty manifested by failure to develop breast tissue and menstruation in girls and failure to increase testicular size in boys. Deficiencies in testosterone/estrogen increase the risk for osteoporosis as well as metabolic abnormalities. Replacement is started around the time of mean entrance into puberty for the patient's sex (ie, age 10 years for girls, age 11–12 years for boys).

Estrogen is available as either a transcutaneous patch or pill. Many experts prefer the transcutaneous method because it bypasses the "first-pass hepatic metabolism" seen with oral medication and may result in better replacement with lower risk. Doses start small and are increased approximately every 6 months in an effort to mimic the natural progression of secondary sexual characteristics. Once the uterine lining has received sufficient estrogen stimulation, there may be breakthrough vaginal bleeding. At this time, progesterone is typically added to stabilize the uterine lining and is periodically stopped to allow a regular withdrawal bleeding or menses.

Testosterone replacement is available for boys in either an intramuscular or topical preparation. Initial doses are small (approximately I/8th–I/4th the normal adult dose of 200 mg testosterone) and if given intramuscularly, are spaced out approximately monthly. Doses are increased every 6 months in an effort to mimic the natural progression of secondary sexual characteristics and to allow for continued linear growth before the closure of the growth plates.

#### **Diabetes Insipidus**

Central DI is treated with synthetic ADH, most commonly in the form of oral desmopressin (DDAVP). For patients with an intact thirst mechanism, the goal of therapy is to provide sufficient relief from polyuria and polydipsia to allow the individual to sleep through the night without nocturia and to participate in normal daily activities without

AGE	DAILY WEIGHT- BASED DOSE	Frequency of Monitoring
0-12 months	10-15 <b>µ</b> g/kg	Every 1-3 months
1-5 years	4-6 $\mu$ g/kg	Every 3-6 months
6-12 years	3-5 $\mu$ g/kg	Every 6-12 months
>12 years	2-3 $\mu$ g/kg	Every 6-12 months

## TABLE 2. Levothyroxine Dose Recommendations

excessive disruption. Breakthrough polyuria and polydipsia must be allowed at least once during a 24-hour period because it is during this time that the patient self-regulates to maintain a normal serum sodium concentration. The starting dose of DDAVP is 0.05 to 0.2 mg once daily, and doses are titrated to effect, often requiring twice-daily and sometimes three times-daily dosing to achieve adequate control of urine output.

For patients with impaired thirst due to hypothalamic injury or patients unable to regulate their own intake (eg, those who have developmental disability or are dependent on gastrostomy tubes), the usual strategy for DDAVP dosing is to provide maximal antidiuresis in concert with a fluid prescription. Maximal antidiuresis allows for approximately 0.5 mL/kg per hour of urine output, and the corresponding fluid prescription provides replacement of urine output plus insensible losses. Initial titration of such a regimen almost always requires an inpatient stay with careful monitoring of intake and output as well as frequent serum sodium measurement.

#### CONCLUSION

Hypopituitarism is a rare but complex diagnosis in the pediatric patient that requires thorough evaluation and treatment. It can result from a multitude of causes, including mass effect, trauma (mechanical, chemical, or radiological), autoimmune/autoinflammatory or infiltrative disease, and/ or infection. Among pediatric patients with hypopituitarism, some of the most common causes are craniopharyngioma, SOD, and brain tumors (including treatment). Treatment involves the physiologic replacement of the end-organ hormones that are deficient, with close monitoring for adequacy of replacement.

## Summary

- On the basis of observational studies, (1)(2)(3)(4)(5)(6)(7)(8) hypopituitarism has an increasing prevalence with increasing age.
- On the basis of case reports and observational studies, (3)(4) septo-optic dysplasia is the most common congenital cause of hypopituitarism.
- On the basis of epidemiologic studies, (1)(2)(3)(4)(5)(6)(7)(8)(9) (10)(11) other causes of hypopituitarism include genetic or anatomic abnormalities (including midline facial defects), trauma, mass effect, infection, and autoimmune and infiltrative diseases.
- On the basis of case reports and expert opinion, single detected pituitary hormone deficiencies are rarely isolated and should prompt evaluation of the other pituitary hormones. Pituitary hormone values may be inappropriately normal in the setting of end-organ hormone deficiency.
- On the basis of expert opinion and case reports, (9) clinical features of hypopituitarism can initially be subtle and vary based on the hormones involved, although poor linear growth is a prominent finding in many deficiencies and should prompt consideration of further testing.
- On the basis of expert opinion, diabetes insipidus is characterized by loss of free water from an inability to concentrate the urine that results in hypernatremic dehydration if untreated.

References for this article are at http://pedsinreview.aappublications. org/content/37/9/370.

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- You are preparing a medical student to see a 16-year-old boy with a history of injury to the posterior pituitary as a result of head trauma associated with basilar skull fracture. Of the following, you explain that this region of the pituitary is responsible for the production of:
  - A. Antidiuretic hormone (ADH).
  - B. Corticotropin.
  - C. Gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]).
  - D. Growth hormone (GH).
  - E. Thyrotropin.
- 2. A term newborn presents with hypoglycemia and poor visual fixation. Magnetic resonance imaging (MRI) of the brain shows absence of the septum pellucidum, and laboratory evaluation demonstrates deficiency of multiple pituitary hormones. Which of the following is the most appropriate diagnosis for this newborn's presentation?
  - A. Birth trauma.
  - B. Congenital syphilis.
  - C. Genetic deletion resulting in deficient production of anterior pituitary hormones.
  - D. Kallmann syndrome.
  - E. Septo-optic dysplasia.
- 3. A 12-year-old girl presents with exophthalmos and a lytic lesion in the skull. She is diagnosed with Langerhans cell histiocytosis. Which of the following pituitary disorders is most commonly associated with this condition?
  - A. Central adrenal insufficiency (corticotropin insufficiency).
  - B. Central hypothyroidism (thyrotropin deficiency).
  - C. Delayed puberty due to gonadotropin deficiency.
  - D. Diabetes insipidus (ADH deficiency).
  - E. Hyperprolactinemia (overproduction of prolactin).
- 4. A 7-year-old male with septo-optic dysplasia is scheduled for bilateral indirect hernia repair. Which of the following hormone levels is the most important to assess prior to surgery?
  - A. GH.
  - B. Insulin-like growth factor-1.
  - C. LH.
  - D. Cortisol.
  - E. FSH.
- 5. A 6-year-old boy presented with growth failure, headaches, personality changes, and visual field deficits. MRI of the brain revealed a tumor involving the pituitary gland. The tumor was recently resected. In regards to subsequent GH replacement therapy, the most appropriate statement is that GH therapy:
  - A. Is associated with an unacceptable risk of adverse events in childhood.
  - B. Is monitored by measuring random GH concentrations.
  - C. Should be deferred until 6 months after surgery.
  - D. Should begin in the immediate postoperative period.
  - E. Should not be given in the setting of active malignancy.

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## **Evaluation and Initial Management of Hypopituitarism** Melinda Pierce and Lisa Madison

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#### Diagnosis

The diagnosis of AFRS is based on clinical findings. In 1994, Bent and Kuhn proposed a set of criteria based on characteristic clinical, radiographic, pathologic, and immunologic features. The 5 major criteria are: 1) nasal polyposis, 2) eosinophilic mucus containing fungal hyphae without evidence of fungal invasion into sinus tissue, 3) characteristic CT scan findings, 4) presence of fungi on direct microscopy or culture of a surgically obtained mucus specimen, and 5) skin or serologic testing demonstrating a type 1 hypersensitivity reaction to fungi. Minor criteria include: 1) history of asthma, 2) peripheral eosinophilia, and 3) predominance of unilateral disease.

CT scan is the preferred radiologic imaging test. On noncontrast scans, the hallmark finding is opacification of affected sinuses with material of heterogenous densities. Serpiginous areas of increased attenuation surrounded by areas of low attenuation represent calcium in the allergic mucin. Total serum IgE concentrations are typically raised to between 1,200 and 9,600  $\mu$ g/L (1.2 and 9.6 mg/L). Due to rare reports of AFRS and concurrent allergic bronchopulmonary aspergillosis, the clinical evaluation must rule out pulmonary involvement. Isolated fungal balls without the presence of allergic mucin in paranasal sinuses represent another form of noninvasive fungal rhinosinusitis and should be considered in the differential diagnosis. Previous sinus surgery, oral-sinus fistulas, previous chemotherapy, and atopy have been discussed as risk factors. In contrast to AFRS, surgical resection alone appears curative for fungal balls. Finally, forms of invasive fungal sinusitis typically encountered in immunosuppressed patients can usually be ruled out by carefully reviewing the patient's clinical history and by histology demonstrating the absence of mucosal invasion with fungal hyphae.

#### Treatment

Effective management of AFRS involves a combination of medical and surgical treatment and requires a team approach between the otolaryngologist and the allergist, with other specialists consulted as needed. Functional endoscopic sinus surgery is performed to remove the fungal allergenic load, restore drainage of the sinuses, and obtain a mucus specimen for microscopy and culture. Surgery is followed by first systemic and then topical intranasal corticosteroids to effectively reduce the inflammatory reaction in the affected tissues and prevent recurrence. Careful clinical follow-up evaluation of patients is required because multiple recurrences over months and years are common. Recurrences are often managed with corticosteroid rescue regimens and/or repeat surgical debridement. In this context, monitoring total serum IgE concentrations can help assess disease activity. Other treatment options, including systemic/topical antifungal therapy, immunotherapy, and leukotriene modulators, have been used in refractory cases. However, very little evidence supports such treatment modalities, and no clear treatment guidelines exist.

#### Lessons for the Clinician

- Clinicians should consider allergic fungal rhinosinusitis (AFRS) in children and especially adolescents who have difficult-to-treat chronic rhinosinusitis with polyps.
- The mainstay of treatment of this inflammatory process is surgical removal of allergic mucin followed by oral corticosteroids.
- For patients with AFRS and sensitization to Aspergillus species antigens, clinicians must exclude a diagnosis of concomitant allergic bronchopulmonary aspergillosis.

Suggested Readings for this article are at http://pedsinreview. aappublications.org/content/37/10/439.

## Corrections

A sharp-eyed reader pointed out a typographical error in the June 2016 article "Preventing Infections in Children with Cancer" (Lighter-Fisher J, Stanley K, Phillips M, Pham V, Klejmont, LM. *Pediatr Rev.* 2016;37(6):247–258, doi: 10.1542/ pir.2015-0059). On page 252, column one, the odds ratio (OR) of "0.11" given for the reduction of invasive fungal infection with use of antifungal prophylaxis is incorrect. The OR should read "0.44." The online version of the article has been corrected. The journal regrets the error.

A Canadian reader noted an error in one of the SI calculations in the September 2016 review "Evaluation and Initial Management of Hypopituitarism" (Pierce M, Madison L. *Pediatr Rev.* 2016;37(9):370, DOI: 10.1542/pir.2015-0081). On page 373, column 1, line 1, the passing value of 18  $\mu$ g/dL should be 496.6 nmol/L. The online version of the article has been corrected. The journal regrets the error.

The April 2016 review "Physical Abuse of Children" (Glick JC, Lorand MA, Bilka KR. *Pediatr Rev.* 2016;37(4):146, DOI: 10.1542/pir.2015-0012) contained a typographical error on page 147, column 2, in the Epidemiology section, where the fourth sentence should read: "Neglect is the most common form of child maltreatment, constituting 75% of indicated reports; 17% are attributable to physical abuse." The online version of the article has been corrected. The journal regrets the error.



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The online version of this article, along with updated information and services, is located on the World Wide Web at: http://pedsinreview.aappublications.org/content/37/9/370

An erratum has been published regarding this article. Please see the attached page for: http://pedsinreview.aappublications.org//content/37/10/441.full.pdf

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