ABSTRACT. Ethics for the Pediatrician: A Brave New Pediatrics! Managing the Desire for Better Children through Biotechnologic Enhancement. Ryan M. Antiel, Robert M. Jacobson, Philip R. Fischer. This commentary presents a number of relatively common situations in which pediatricians might be asked to facilitate the requests of parents that certain procedures be done to improve the child's life in some aspect. The authors present their views about such actions, which fall under the general category of enhancement. They start by describing a scene from Aldous Huxley's Brave New World, and pose the question, "Perhaps what we now view as well meaning attempts to increase the odds of success for our children will prove a prelude to a fearsome brave new world?"

The authors start with the concept of height augmentation, pointing out that approval for the use of growth hormone to increase ultimate height has gone beyond the treatment of Turner syndrome and chronic renal insufficiency to its use in cases of non-growth hormone-deficient short stature. Another area of concern is the enhancement of athletic performance, which can involve the use of anabolic steroids, creatine, and dietary supplements. Even the improvement of academic performance can become an issue. Should stimulant medication be prescribed to improve a student's ability to study?

Cosmetic improvement is another area that might require the pediatrician to make a difficult decision. The performance of procedures such as otoplasty, shino-plasty, breast augmentation, and liposuction in adolescence is becoming more common. As part of this discussion, the authors point out the widespread acceptance of orthodontic braces, even when there are no concerns about chewing mechanics or dental health. The concept of parents wanting their children to have the "best possible life" is discussed. The authors point out that encouragement and the enhancement of healthy eating, proper sleep, and wearing a bicycle helmet can be considered forms of enhancement. Competitive enhancement is another area that is addressed.

The authors present a lengthy examination of the concept of procreative beneficence, or the duty to bring about the best possible life for a child. This idea is challenged on the basis that such a pursuit of the best possible life for a child is undermining, paradoxical, self-defeating, and overly individualistic.

The reader who considers the views and arguments presented in this commentary will find a great deal of food for thought, as well as the realization that the pediatrician will have to grapple with everyday ethical decisions far different from the classic clinical dilemmas that involve serious disease and matters of life and death. Pediatrics in Review. 2012;33(13):e13-17. URL: pediatricsinreview.appublications.org/cgi/content/full/33/2/e13.
Pediatric Systemic Lupus Erythematosus: More Than a Positive Antinuclear Antibody

Jennifer E. Weiss, MD*

Educational Gap

For the first time in nearly 50 years, a new medication has been approved by the Food and Drug Administration for treating lupus, and other new medicines are becoming available.

Objectives After completing this article, readers should be able to:
1. Describe the common clinical manifestations of systemic lupus erythematosus (SLE).
2. Understand the meaning of a positive antinuclear antibody.
3. Understand the serologic markers associated with SLE.
4. Discuss the treatment and adverse effects of medications used to treat SLE.
5. Understand the special needs of a pediatric patient who has SLE.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease characterized by periods of increased disease activity caused by inflammation of blood vessels and connective tissue. The condition is much more than a positive antinuclear antibody (ANA); it is a disease that causes a great deal of morbidity, and patients can be ill at presentation and throughout their disease course.

Pediatric patients with SLE have a more severe clinical course in comparison with their adult counterparts. Patients typically present with rash, fever, and arthritis, although the presentation may be unpredictable. At the time of diagnosis, most patients will fulfill 4 of the 11 American College of Rheumatology criteria for the classification of SLE (Table 1), revised in 1982. (1) These criteria include both clinical and laboratory features of the disease.

The criteria were revised again in 1997 with changes to the immunologic disorder criterion that involve deleting a positive lupus erythematosus preparation and adding a positive finding of antiphospholipid antibodies based on (1) abnormal immunoglobulin G or immunoglobulin M anticardiolipin antibodies, (2) a positive test for lupus anticoagulant (LA), or (3) a false-positive serologic test for syphilis as described.

Epidemiology

Twenty percent of SLE cases are diagnosed during the first 2 decades of life. Pediatric SLE (pSLE) usually presents in post-pubescent females, with an average age of onset of ~12 years. Before puberty, the male:female ratio is 1:3, but after puberty it increases to 1:9. Ethnicity plays an important role in the incidence of SLE. The incidence of SLE before age 19 years is between 6.0 and 18.9 cases per 100,000 in white girls but is higher in African American (20–30/100,000) and Puerto Rican girls (16.0–36.7/100,000). (2) In addition, the incidence of SLE is higher in Hispanic, Native American, Pacific Islander, and Asian individuals than in white individuals. With more

Abbreviations

ACLA: anticardiolipin antibody
ANA: antinuclear antibody
APLS: antiphospholipid antibody syndrome
ARF: acute rheumatic fever
DIL: drug-induced lupus
dsDNA: double stranded DNA
FDA: Food and Drug Administration
LA: systemic lupus erythematosus anticoagulant
LAC: lupus anticoagulant
MMF: mycophenolate mofetil
NLE: neonatal lupus erythematosus
NSAID: nonsteroidal antiinflammatory drug
pSLE: pediatric systemic lupus erythematosus
SLE: systemic lupus erythematosus

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aggressive treatment, the 5-year survival rate for pSLE approaches 100% and the 10-year survival rate is 86%.

Pathophysiology

Lupus is thought to result from a combination of hormonal and environmental factors in a genetically predisposed individual. Ten percent of patients with SLE have a first-degree relative who has SLE, and affected patients are more likely to have a family member who has an autoimmune disease. HLA class II alleles DR2 and DR3 contribute to disease susceptibility in some patients, as do inherited complement deficiencies, most commonly homozygous C2 or C4 deficiency. Environmental triggers can be as varied as infection (parvovirus, Epstein-Barr virus), medication (antihypertensives, anticonvulsants), hormonal changes (especially sex hormones), and UV light. Disturbances in B and T cells and abnormalities in apoptosis contribute to the pathogenesis of the disease. Recent studies implicate type I interferon, especially dysregulation of interferon-α, as a prime contributor to loss of tolerance, resulting in autoimmunity.

Clinical Characteristics

Each patient afflicted with SLE presents a different clinical scenario. Common signs and symptoms at disease onset include fatigue, fever, weight loss, lymphadenopathy, and hepatosplenomegaly. Other, more specific, findings aid in diagnosis because most patients express classic SLE findings of malar rash and arthritis at presentation. Because SLE is a periodic illness, depending on the constellation and severity of signs and symptoms, often there is a delay in diagnosis with the time from symptom onset to diagnosis ranging from 1 month to 3.3 years (median, 4 months). (3)

Flares of the illness can involve almost any organ system and common findings are described later in this paper.

Table 1. 1982 Revised Criteria for Classification of SLE*

| 1. Malar rash | Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds |
| 2. Discoid rash | Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions |
| 3. Photosensitivity | Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation |
| 4. Oral ulcers | Oral or nasopharyngeal ulceration, usually painless, observed by a physician |
| 5. Arthritis | Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion |
| 6. Serositis | Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR Pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion |
| 7. Renal disorder | Persistent proteinuria >0.5 g/d or >3+ if quantitation not performed OR Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed |
| 8. Neurologic disorder | Seizures: in the absence of offending drugs or known metabolic derangements; eg, uremia, ketoacidosis, or electrolyte imbalance OR Psychosis, in the absence of offending drugs or known metabolic derangements; eg, uremia, ketoacidosis, electrolyte imbalance |
| 9. Hematologic disorder | Hemolytic anemia with reticulocytosis OR Leukopenia: <4000/mm³ total on two or more occasions OR Lymphopenia: <1500/mm³ on two or more occasions OR Thrombocytopenia: <100,000/mm³ in the absence of offending drugs |
| 10. Immunologic disorder | Positive LE cell preparation OR Anti-DNA: antibody to native DNA in abnormal titer OR anti-Smith antibody; presence of antibody to Sm nuclear antigen OR False-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test |
| 11. Antinuclear antibody | An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome |

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation. (Reprinted with permission from Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271–1277.)
article (Table 2). It is important to differentiate SLE from acute rheumatic fever (ARF). Patients with ARF often present with fever and arthritis; however, the rash of ARF, erythema marginatum, can be differentiated from an SLE rash based on its appearance and location. Patients with ARF must have a history of group A Streptococcus infection and fulfill the Jones criteria.

Mucocutaneous Involvement

Mucocutaneous features of disease are noted in up to 90% of patients with pSLE. Including photosensitivity, there are three rashes described in the SLE classification criteria. The malar or “butterfly” rash is the most common cutaneous manifestation and is the hallmark of the disease. It develops on the malar eminences and crosses the nasal bridge while sparing the nasolabial folds (Fig 1). The forehead and chin also may be affected. The rash can appear as a blush or a maculopapular eruption with an associated scale and usually is not pruritic. A similar rash may be seen in dermatomyositis; however, Gottron papules on the metacarpophalangeal and interphalangeal joints, elbows, and knees are not seen in SLE, and this feature helps distinguish the two.

Discoid lupus, named after its coin shape, is an erythematous rash that primarily affects the face, ears, and scalp, although the upper extremities and upper chest and back may be affected (Fig 2). The rash may scale or crust. The central area may be hypopigmented, whereas the active border may appear hyperpigmented. The lesions may heal with a scar or atrophy, and discoid patches on the scalp may result in a scarring alopecia if the hair follicle is damaged. Discoid lupus may manifest as a feature of systemic disease or it may be an isolated finding. Fewer than 5% of patients who have isolated discoid SLE will progress to SLE.

It is essential that all patients with pSLE practice sun protection year round with a sun protection factor >30 directed against both UV A and B light to try to prevent development of rash and systemic disease flares. Even if they do not have active rash, it is essential that patients with SLE protect themselves from UV light. Patients should be warned about the risk of rash and disease flares from use of tanning beds. For mild-moderate rash, topical corticosteroids or immunomodulators, such as tacrolimus, also may be used, especially in treating discoid SLE.

Hydroxychloroquine, one of four drugs approved for SLE by the Food and Drug Administration (FDA), is one of the mainstays of treatment for any patient with SLE. Not only does the drug help with control of the rash, but it helps to prevent disease flares. In addition, this medication is well tolerated, although some patients suffer abdominal discomfort.

The major complication of hydroxychloroquine treatment is retinal toxicity; therefore, patients need to be screened by an ophthalmologist at baseline and then every 6 to 12 months. The risk of retinal changes is rare, especially if patients are on a dosage lower than 6.5 mg/kg per day. If retinal changes are seen early they are reversible, but the drug must be discontinued. Between ophthalmology visits patients can monitor themselves with an Amsler grid (a grid of vertical and horizontal lines used to determine a person’s central visual field).

For more severe rashes, systemic corticosteroids (also FDA approved for treating SLE) may be needed, usually with the addition of a steroid-sparing agent, such as methotrexate, azathioprine, or mycophenolate mofetil.

For the first time in nearly 50 years, a new medication has been FDA approved for treating SLE. Belimumab, a B-lymphocyte stimulator-specific inhibitor, was approved for the treatment of adult patients with active, autoantibody-positive SLE. Adult patients with SLE with active mucocutaneous symptoms have had the best response in clinical trials. No trials have been performed in patients with pSLE, but trials will likely be under way in the future.

Vasculitic rashes can be part of active SLE. These rashes take on many forms, including palmar erythema and tender skin nodules (Fig 3), purpura, or ulcerations on fingers or toes, pinnae, or nares. Palatal ulceration (Fig 4), as described in the classification criteria, usually is painless and can be detected easily on examination of the oral mucosa. Because the vasculitis is a more systemic process, systemic corticosteroids may be required to treat these lesions.

Raynaud phenomenon can be caused by an underlying connective tissue disease and differs from primary Raynaud disease, in which there is no underlying vasculopathy. Classically, there is a triphasic color change (blue, white, and, on rewarming, red) of the hands or feet, sometimes the ears or nose. Because of vasospasm, the affected area becomes pale and painful, then cyanotic, and on rewarming, erythematous. There may be an associated tingling or burning sensation, especially during the rewarming, erythematous phase. Triggers include exposure to cold, cigarettes, caffeine, and extreme emotion. Patients should avoid triggers and dress warmly, paying attention to keeping the body core, as well as the extremities, warm.

Nail fold capillary changes reflect the vasculopathy that may occur in SLE. Periungual erythema is caused by dilatation of these capillaries. Livedo reticularis occurs in <10% of patients with pSLE. This eruption presents as a reddish-purplish lacy rash, usually on the extremities or torso and often is associated with the presence of antiphospholipid antibodies.
<table>
<thead>
<tr>
<th>Organ System Involvement</th>
<th>At Diagnosis (%)</th>
<th>Within 1 Year After Diagnosis (%)</th>
<th>Ever (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arthritis</strong></td>
<td>157 (61)</td>
<td>159 (62)</td>
<td>171 (67)</td>
</tr>
<tr>
<td><strong>Mucocutaneous involvement</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Malar rash</td>
<td>155 (61)</td>
<td>161 (63)</td>
<td>169 (66)</td>
</tr>
<tr>
<td>Other rash</td>
<td>96 (38)</td>
<td>106 (41)</td>
<td>111 (43)</td>
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<tr>
<td>Oral ulcers</td>
<td>55 (21)</td>
<td>59 (23)</td>
<td>76 (30)</td>
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<td>Alopecia</td>
<td>56 (22)</td>
<td>62 (24)</td>
<td>73 (29)</td>
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<td>Photosensitivity</td>
<td>44 (17)</td>
<td>45 (18)</td>
<td>52 (20)</td>
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<tr>
<td>Nasal ulcers</td>
<td>21 (8)</td>
<td>25 (10)</td>
<td>26 (10)</td>
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<tr>
<td>Digital ulcers</td>
<td>9 (4)</td>
<td>10 (4)</td>
<td>13 (5)</td>
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<td><strong>Nephritis</strong></td>
<td>95 (37)</td>
<td>117 (46)</td>
<td>141 (55)</td>
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<tr>
<td>Mesangial (class II)</td>
<td>14 (5)</td>
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<td>Focal proliferative (class III)</td>
<td>27 (10)</td>
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<td>41 (16)</td>
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<td>Diffuse proliferative (class IV)</td>
<td>45 (18)</td>
<td>50 (20)</td>
<td>65 (26)</td>
</tr>
<tr>
<td>Membranous (class V)</td>
<td>15 (6)</td>
<td>20 (8)</td>
<td>29 (11)</td>
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<tr>
<td>Nephrotic syndrome</td>
<td>20 (8)</td>
<td>22 (8)</td>
<td>25 (10)</td>
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<tr>
<td>Central nervous system</td>
<td>40 (16)</td>
<td>53 (21)</td>
<td>68 (27)</td>
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<tr>
<td>Lupus headache</td>
<td>23 (8)</td>
<td>31 (12)</td>
<td>42 (16)</td>
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<td>Psychosis</td>
<td>14 (5)</td>
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<td>25 (10)</td>
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<td>Cerebrovascular disease</td>
<td>13 (5)</td>
<td>14 (5)</td>
<td>20 (10)</td>
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<td>Cognitive dysfunction</td>
<td>9 (3)</td>
<td>13 (5)</td>
<td>15 (6)</td>
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<tr>
<td><strong>Cardiac</strong></td>
<td></td>
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<tr>
<td>Pericarditis</td>
<td>30 (12)</td>
<td>33 (13)</td>
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<tr>
<td>Myocarditis</td>
<td>3 (1)</td>
<td>5 (2)</td>
<td>6 (2)</td>
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<tr>
<td>Endocarditis</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleuritis</td>
<td>30 (12)</td>
<td>32 (13)</td>
<td>37 (14)</td>
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<tr>
<td>Pneumonitis</td>
<td>1 (0.4)</td>
<td>1 (0.8)</td>
<td>2 (0.8)</td>
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<tr>
<td>Myositis</td>
<td>8 (3)</td>
<td>8 (3)</td>
<td>9 (4)</td>
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<tr>
<td>Diffuse lymphadenopathy</td>
<td>48 (19)</td>
<td>50 (20)</td>
<td>51 (20)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>35 (14)</td>
<td>45 (18)</td>
<td>49 (19)</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
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<tr>
<td><strong>Constitutional symptoms</strong></td>
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<tr>
<td>Fatigue</td>
<td>129 (50)</td>
<td>136 (53)</td>
<td>142 (55)</td>
</tr>
<tr>
<td>Fever</td>
<td>101 (39)</td>
<td>104 (41)</td>
<td>106 (41)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>74 (29)</td>
<td>79 (31)</td>
<td>82 (32)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>51 (20)</td>
<td>72 (28)</td>
<td>72 (28)</td>
</tr>
<tr>
<td>Headache</td>
<td>34 (13)</td>
<td>39 (15)</td>
<td>46 (18)</td>
</tr>
<tr>
<td><strong>Autoantibody (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Anti–dsDNA</td>
<td>184 (72)</td>
<td>214 (84)</td>
<td></td>
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<tr>
<td>Anti–Smith antibody</td>
<td>88 (34)</td>
<td>124 (48)</td>
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<td>Anti–ribonucleoprotein antibody</td>
<td>68 (27)</td>
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<td>Anti–Ro</td>
<td>69 (27)</td>
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<tr>
<td>Anti–La</td>
<td>34 (13)</td>
<td>37 (15)</td>
<td></td>
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<tr>
<td>Antiphospholipid (any)</td>
<td>82 (32)</td>
<td>115 (45)</td>
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<tr>
<td>ACLA</td>
<td>67 (26)</td>
<td>102 (40)</td>
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</tr>
<tr>
<td>LAC</td>
<td>22 (9)</td>
<td>32 (13)</td>
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<tr>
<td>Rheumatoid factor</td>
<td>28 (11)</td>
<td>35 (14)</td>
<td></td>
</tr>
<tr>
<td>Hematologic (any)</td>
<td>141 (55)</td>
<td>161 (63)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75 (29)</td>
<td>80 (31)</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>73 (29)</td>
<td>93 (36)</td>
<td></td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia</td>
<td>58 (23)</td>
<td>63 (25)</td>
<td></td>
</tr>
</tbody>
</table>

*aType of nephritis was determined by using the World Health Organization classification system. (5) Two patients did not undergo renal biopsy and are not included in this table.

*bNot requiring narcotic analgesia.

Alopecia may be one of the presenting manifestations of the disease. It occurs classically in the frontal area but can be diffuse. As the disease activity lessens, patients usually grow new hair.

Musculoskeletal Involvement
Arthralgia and arthritis are very common in pSLE. Unlike the arthritis characteristic of juvenile idiopathic arthritis, SLE arthritis usually is nonerosive. Often there is symmetric involvement of both the large and small joints, primarily the knees, wrists, ankles, and fingers. Patients who have SLE can develop an unusual type of arthritis called Jacouard arthropathy (ulnar deviation of the second to fifth fingers and subluxation of the metacarpophalangeal joints). Myalgia and myositis are less common, but may occur in patients with SLE. Muscle involvement also is common in the so-called “overlap syndrome,” in which there are findings common to SLE as well as other rheumatic illnesses.

Nonsteroidal antiinflammatory drugs (NSAIDs) are the usual first-line medications, along with hydroxychloroquine. When there is severe arthritis, particularly when it occurs in parallel with other organ system involvement, corticosteroids may be needed.

Methotrexate also can be used to treat arthritis. It is a disease-modifying agent commonly prescribed for juvenile idiopathic arthritis and works well as a steroid-sparing agent in patients with pSLE who have arthritis.
severe cases of arthritis, tumor necrosis factor-α inhibitors have been used. Adult patients with SLE with musculoskeletal disease have demonstrated a good response in the belimumab trials.

Renal Involvement
Renal disease is the greatest contributor to morbidity and mortality in the pSLE population. Up to 65% of patients with pSLE are affected, usually within the first year of diagnosis. Renal disease may manifest as proteinuria, microscopic hematuria, hypertension, or elevated blood urea nitrogen and creatinine levels. Eighteen percent of patients may develop nephrotic syndrome. (4) Immune complexes involving DNA and anti-double stranded DNA (dsDNA) deposit in the mesangium and subendothelial space, leading to activation of complement and an influx of inflammatory cells.

These changes manifest histologically as mesangial, focal, or diffuse proliferative glomerulonephritis, and clinically with an active urine sediment (red blood cells, white blood cells, and cellular and granular casts), low complement levels (C3, C4), elevated anti-dsDNA levels, and proteinuria. A spot first-morning urine protein-to-creatinine ratio often is used as an indicator of proteinuria and active renal disease.

A renal biopsy with histologic, immunofluorescent, and electron micrographic analysis is necessary to classify the histologic type of renal disease. Because the class and severity of the renal disease guides treatment, biopsy results play a major role in determining therapy. The International Society of Nephrology and the Renal Pathology Society (5) have revised the original World Health Organization classification of renal biopsy findings in SLE into six different classes (Table 3). Patients may change from one class to another either before or during treatment.

Minimal mesangial lupus nephritis (class I) is the mildest form of nephritis and patients may have a normal urinalysis and creatinine level. This class does not require specific treatment and generally has a good prognosis. Approximately 25% of patients with pSLE will have mesangial proliferative lupus nephritis (class II). These patients may have microscopic hematuria or proteinuria. Treatment consists primarily of a low to moderate dose of corticosteroids over several months. This class of renal disease is considered very mild, but there is always risk of progression.

Focal lupus nephritis (class III) affects 41% of patients with pSLE and often presents with hematuria and proteinuria. Nephrotic syndrome, hypertension, and abnormal blood urea nitrogen and creatinine levels also may be found. Diffuse lupus nephritis (class IV) is the most common and most severe type of lupus nephritis, affecting ~65% of patients. Patients present with hematuria, proteinuria, hypertension, low C3 and C4 levels, and elevated anti-dsDNA levels. This class is similar to class III with the major difference being that more than 50% of glomeruli have evidence of active proliferation.

Most pediatric rheumatologists and nephrologists would treat pSLE patients with class III and IV disease aggressively. This treatment includes high-dose oral corticosteroids (2 mg/kg) or intravenous pulse methylprednisolone (30 mg/kg, max of 1 g) plus potent immunosuppressive agents.

In the adult population with SLE, induction of remission therapy with either cyclophosphamide or mycophenolate mofetil (MMF) routinely is used (6) and the same medications are being used to treat pSLE. Most pediatric rheumatologists probably would start induction therapy with 3 to 6 months of cyclophosphamide and, if the patient has a good response, transition to MMF.

Although cyclophosphamide is effective, risks associated with this medication include bone marrow suppression, alopecia, infection, malignancy, and infertility. The risk of gonadal failure is dose dependent. Some physicians treat post-pubertal girls with luprolide acetate to suppress oogenesis, thus preventing damage caused by cyclophosphamide to dividing cells and lessening the risk of infertility. Because cyclophosphamide also is toxic to spermatogonia and spermatocytes, the best solution for post-pubertal boys to maintain their reproductive capacity would appear to be sperm banking.

MMF inhibits guanosine nucleotides and B- and T-cell proliferation and has antiinflammatory properties. This medication is being used more widely in treating pSLE, especially because the issue regarding fertility is not a concern. Unlike cyclophosphamide, which is given intravenously at monthly intervals, MMF is an oral medication, taken twice daily. Its major adverse effects are abdominal pain and diarrhea; as a result, compliance is of greater concern with MMF. In addition, studies comparing it with traditional treatments, such as cyclophosphamide or azathioprine, have not been done in the pediatric population.

Treatment of major organ system involvement in SLE has taken a page out of the oncologists’ book with the aim of achieving remission through intensive therapy at the time of diagnosis, followed by less-intensive medications for the maintenance phase (a step-down rather than a step-up approach).

Newer medicines are becoming available, such as rituximab, a chimeric monoclonal anti-B-cell antibody directed at the CD20 antigen that can lead to the depletion of
B cells. Its use in nephritis is controversial. Many case reports have demonstrated efficacy, but in a controlled trial of lupus nephritis, the drug did not offer any additional benefit when given as an adjunct to standard therapy. Rituximab can be used alone or with any of the agents mentioned previously. Despite optimal therapy, proteinuria may not resolve completely and an angiotensin-converting enzyme inhibitor can be used to protect the kidney.

Finally, hypertension, if present, must be treated aggressively and maintenance of a normal blood pressure should be the goal. The use of corticosteroids may

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial lupus nephritis</td>
</tr>
<tr>
<td>II</td>
<td>Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence</td>
</tr>
<tr>
<td></td>
<td>Mesangial proliferative lupus nephritis</td>
</tr>
<tr>
<td>III</td>
<td>Focal lupus nephritis</td>
</tr>
<tr>
<td>III (A)</td>
<td>Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving &lt;50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations</td>
</tr>
<tr>
<td>III (A/C)</td>
<td>Active and chronic lesions: focal proliferative and sclerosing lupus nephritis</td>
</tr>
<tr>
<td>III (C)</td>
<td>Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse lupus nephritis</td>
</tr>
<tr>
<td>IV-S (A)</td>
<td>Active lesions: diffuse segmental proliferative lupus nephritis</td>
</tr>
<tr>
<td>IV-G (A)</td>
<td>Active lesions: diffuse global proliferative lupus nephritis</td>
</tr>
<tr>
<td>IV-S (A/C)</td>
<td>Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis</td>
</tr>
<tr>
<td>IV-S (C)</td>
<td>Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis</td>
</tr>
<tr>
<td>IV-G (C)</td>
<td>Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis</td>
</tr>
<tr>
<td>V</td>
<td>Membranous lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations</td>
</tr>
<tr>
<td>V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Advanced sclerosis lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>≥90% of glomeruli globally sclerosed without residual activity</td>
</tr>
</tbody>
</table>

*Indicate the proportion of glomeruli with active and with sclerotic lesions.

†Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents. Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

exacerbate the hypertension. Overall, if patients are treated early and aggressively, they should go into remission and experience normalization of laboratory parameters.

Patients with membranous lupus nephritis (class V) (29%) commonly present with nephrotic syndrome, which may occur alone or in combination with other types of nephritis. Patients generally are treated with oral corticosteroids for a few months and may require a steroid-sparing agent, such as MMF. Class V nephritis tends to have a better prognosis than class III and IV, but can be refractory to treatment and the proteinuria can be significant, at times >5 g per day. Patients can suffer from severe secondary effects to up and including anasarca.

Advanced sclerosing lupus nephritis (class VI) is characterized by global sclerosis of more than 90% of glomeruli, the result of healing of prior inflammatory injury. Unfortunately, these changes represent end-stage kidney disease and immunosuppression is not helpful for these patients.

**Neuropsychiatric Involvement**

Neuropsychiatric disease occurs in up to two-thirds of patients with pSLE and often presents within the first year of diagnosis. (3) It is the second leading cause of morbidity and mortality. The highest percentage of neuropsychiatric involvement is manifested as headache. Most other neuropsychiatric manifestations affect fewer than 60% of patients and may present as decreased concentration and cognitive dysfunction, psychosis, seizures, transverse myelitis, central nervous system vasculitis, or stroke. Indeed, SLE can cause almost any neurologic disorder. Headaches are very common in the adolescent population and it may be difficult to determine if the headache should be attributed to SLE. One rule of thumb has been that SLE headaches are not responsive to non-narcotic analgesia.

Treatment of neuropsychiatric disease needs to be directed toward the specific problem, but most patients will require high-dose corticosteroids and immunosuppression with cyclophosphamide, MMF, or azathioprine. Therapy is given in much the same way as for nephritis, by using an induction and maintenance approach.

**Hematologic Involvement**

More than 60% of patients with pSLE will have cytopenia. Leukopenia, usually secondary to lymphopenia, is found in two-thirds of patients and may provide a clue to the diagnosis. Anemia is seen frequently and although it can be the classic Coombs-positive hemolytic anemia, patients also may have a normocytic normochromic anemia of chronic disease. This latter anemia, however, would not be considered as fulfilling a criterion for diagnosis of SLE. Thrombocytopenia may be found in up to 30% of patients. Patients presenting with idiopathic thrombocytopenia and Evans syndrome (idiopathic thrombocytopenia and hemolytic anemia), especially adolescent girls, should be evaluated for SLE. Cytopenias usually respond to moderate- to high-dose corticosteroids. Intravenous γ-globulin (2 g/kg) often is effective in treating thrombocytopenia, with refractory cases often responding to rituximab. Very rarely is splenectomy required to control the thrombocytopenia.

A more recently described hematologic entity is the antiphospholipid antibody syndrome (APLS). APLS may be primary or secondary to an underlying connective tissue disease, such as SLE. Manifestations can include thrombocytopenia, arterial or venous thrombosis, stroke, transient ischemic attack, chorea, recurrent fetal loss, or avascular necrosis. Laboratory abnormalities include a positive LA, elevated anticardiolipin and antiphospholipid antibodies, or a prolonged partial thromboplastin time. The term LA is a misnomer because patients actually are in hypercoagulable state. Patients with a positive LA are especially at risk for thrombosis, in particular deep vein thrombosis, thromboemboli, and stroke. Patients with lupus who have anticardiolipin antibodies have twice the risk of venous thrombosis, and patients with a positive LA have six times the risk of venous thrombosis compared with patients with SLE without these antibodies. (7)

Patients presenting with any of these complications need to be screened for other disorders of coagulation, such as antithrombin III deficiency or protein S or C deficiency. It is still not entirely clear how best to treat patients who have a positive LA but do not have a history of previous thrombosis or signs and symptoms of APLS because low-level titers can be an incidental finding. Guidelines have been developed to help guide decision-making. Some physicians would treat patients with APLS with low-dose aspirin, although there is no documented evidence of efficacy for preventing a vascular event.

**Pulmonary Involvement**

Pulmonary involvement may manifest as pleuritis, pleural effusion, pneumonitis, pulmonary hemorrhage, and pulmonary hypertension. Pleuritis is the most common manifestation and patients may complain of dyspnea and sharp, stabbing chest pain during inspiration. Other causes of dyspnea include restrictive lung disease. Pulmonary function tests will be abnormal, demonstrating a restrictive defect and possibly a decreased diffusion capacity. Radiographs may demonstrate interstitial infiltrates, pleural thickening, and elevated hemi-diaphragms. Shrinking lung syndrome results from an impairment of the diaphragm secondary to pleural thickening and fibrosis. A small
effusion can be managed with NSAIDs, although most likely these patients will need corticosteroid therapy.

Pulmonary hemorrhage, although rare, is life-threatening. This complication must be considered in any patient with pSLE who experiences acute shortness of breath and a sudden drop in hemoglobin concentration. Pulse methylprednisolone in combination with cyclophosphamide therapy usually is required to treat pulmonary hemorrhage.

Cardiac Involvement
Patients with lupus are at risk for pericarditis, pericardial effusion, myocarditis, Libman-Sacks endocarditis, bacterial endocarditis, and premature atherosclerosis. The risk of myocardial infarction is low in pSLE, although an infarct must always be considered in the differential diagnosis of chest pain. Pericarditis with pericardial effusion is the most common cardiac complication in pSLE and often is a cause of recurrent chest pain. Pericarditis presents as anterior chest pain and dyspnea that is exacerbated by lying flat. Lupus pericarditis can be treated with NSAIDs alone for mild cases and with the addition of corticosteroids for large effusions or severe pain.

Patients who have both adult and pSLE are at risk for premature atherosclerosis. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus trial, a prospective multicenter study of 221 racially and ethnically diverse patients with pSLE, identified both traditional and non-traditional risk factors for carotid intima-media thickness as a marker for subclinical atherosclerosis. Increased BMI, male gender, increased creatinine clearance, elevated lipoprotein(a) levels, increasing age, weight-adjusted prednisone dose, and azathioprine use all were associated with increased carotid intima-media thickness. (8) Hydroxyclooroquine, which most patients are given because of its mild immunosuppressive effect, also has lipid-lowering properties, another reason for using it for treating SLE. All patients should be counseled on proper nutrition and exercise. Limiting the amount and duration of corticosteroid use is extremely important to help minimize atherosclerosis and weight gain, but almost all patients with pSLE will need corticosteroids at times to achieve disease control.

Finally, lupus valvulitis (Libman-Sacks endocarditis) may predispose patients undergoing dental procedures to bacterial endocarditis. Although there is no consensus as to the best medical practice, some physicians, out of concern for an undetected Libman-Sacks endocarditis, will prescribe antibiotic prophylaxis to all patients with SLE before dental procedures.

Gastrointestinal Involvement
Gastrointestinal involvement occurs in approximately one-third of patients and may manifest as serositis, vasculitis, pancreatitis, or enteritis. Abdominal pain is a primary complaint. Vasculitis puts patients at risk for bowel perforation. Pancreatitis may be caused by several factors, including active SLE, infection, or corticosteroid use. Most patients have functional asplenia and are at risk for sepsis from Streptococcus pneumoniae and other encapsulated bacteria. These patients should be immunized against pneumococcus, meningococcus, and Haemophilus influenzae type B.

Endocrine Involvement
Hypothyroidism is very common in SLE. Hyperthyroidism, on the other hand, has been described rarely. Diabetes mellitus may develop as a result of corticosteroid use and obesity. Delayed puberty is common and studies are under way looking at pubertal development and the role of puberty in affecting pSLE. Irregular menses are common during periods of active disease. The use of estrogen-containing oral contraceptive agents in pSLE is controversial, and other methods of birth control are recommended.

Laboratory Evaluation
Laboratory testing serves two important roles: to aid in diagnosis and to monitor disease activity. A complete blood count is needed to evaluate potential cytopenias. A comprehensive metabolic panel may reveal transaminisits, hypoalbuminemia, or an elevated creatinine level. Because most patients present with constitutional symptoms and inflammation, an elevated erythrocyte sedimentation rate is very common. Despite active inflammation, C-reactive protein levels can remain normal in pSLE; however, these levels are elevated during active infection. A urinalysis should be performed to screen for proteinuria, hematuria, and other components of active urinary sediment.

In SLE, there is production of myriad autoantibodies that recognize nuclear antigens, as well as many other cellular and tissue components. The ANA is found in 99% of patients with SLE, but also may be positive in other rheumatic diseases, such as mixed connective tissue disease and dermatomyositis. The ANA also may be positive in up to one-third of the healthy population and in family members of patients with SLE. It is helpful that a negative ANA makes the diagnosis of SLE extremely unlikely. ANA is not useful to monitor disease activity. A positive ANA therefore should be interpreted along with the clinical symptoms and having a definite diagnosis in...
mind. There is no level of ANA that is diagnostic for SLE, but higher levels, such as a titer of 1:1280 would be suspicious for SLE.

The anti-dsDNA on the other hand is very specific for SLE and may be found in >75% of patients with pSLE. The anti-dsDNA level usually is checked at the time of diagnosis and throughout the disease course to monitor disease activity. A high value in conjunction with other disease activity measures is suggestive of active SLE.

The anti-Smith antibody and anti-ribonucleoprotein antibody often are ordered together as an anti-extractable nuclear antigen panel. The anti-Smith antibody is highly specific for SLE and may be found in up to 50% of patients. This antibody may remain elevated regardless of disease activity and therefore is not useful in monitoring disease activity. The anti-ribonucleoprotein antibody may be found in patients who have classic SLE, but often indicates the patient’s diagnosis is a mixed connective tissue disease (SLE with features of systemic sclerosis or dermatomyositis).

Other antibodies can also be seen in SLE, such as SS-A (anti-Ro) and SS-B (anti-La). Complement levels, specifically C3 and C4, are monitored in SLE, and low or undetectable levels are expected in SLE during periods of active disease. The anti-dsDNA and complement levels are important disease markers and help guide medication dosing.

**Neonatal Lupus Erythematosus**

Neonatal lupus erythematosus (NLE) occurs in 1% of infants who experience transplacental passage of maternal SSA or SSB antibodies. The most common manifestations are rash, cytopenias, and hepatitis with hepatomegaly. Congenital heart block from antibody-mediated damage to the conducting system is the most feared complication, and may be seen in up to 30% of infants born with NLE. As a consequence, all pregnancies in mothers with SLE or known positivity for SSA and SSB antibodies are considered high risk and require close monitoring.

Fetal bradycardia is the first sign of NLE and must be evaluated at 16 weeks’ gestation and at continuing intervals throughout pregnancy. Mothers are started on dexamethasone as soon as a fetus is identified as having heart block to decrease maternal antibodies and inflammation of the conducting system and to delay the onset of fibrosis. The rash of NLE is similar to that seen in subacute SLE and is erythematous with a raised border, particularly prominent on sun-exposed areas and around the eyes (Fig 5). The skin may have a fine scale. UV light will worsen the rash and should be avoided as much as possible.

Except for the heart block, all other manifestations will resolve without intervention, usually within 6 months—the time it takes for maternal antibodies to disappear. Approximately 30% to 50% of infants who develop congenital heart block will require pacemaker implantation, usually within the first 24 months. These children need close follow-up; however, it is unlikely that they will go on to develop SLE.

**Drug-Induced Lupus**

The classic medications that induce drug-induced lupus (DIL) include minocycline, procainamide, hydralazine, penicillamine, isoniazid, quinidine, phenytoin, and carbamazepine. Anti–tumor necrosis factor agents, such as infliximab, adalimumab, and etanercept have also been implicated in DIL. The prevalence of DIL is equal in males and females, although minocycline-induced lupus is usually seen in adolescent girls using the medication.
for treatment of acne. Chronic use of the medication is required to develop DIL.

Patients often present with constitutional symptoms, photosensitive rash, arthralgia, myalgia, and serositis. Subacute cutaneous lupus also may be present. Positive antihistone antibodies are present in 95% of patients with DIL and help to distinguish these patients from patients with systemic disease, although patients with classic SLE also may test positive for antihistone antibodies. Antineutrophilic cytoplasmic antibodies may be positive. Treatment of DIL requires discontinuing the offending agent. A trial of NSAIDs, hydroxychloroquine, and possibly corticosteroids may be needed. Symptoms usually abate within weeks to months of stopping the medication; however, in some patients DIL will evolve into true SLE.

Complications of Corticosteroids
As stated, corticosteroids are a mainstay of treatment for SLE. Unfortunately, a number of adverse effects can affect the patient not only medically but from a psychosocial standpoint as well. Once corticosteroids are started, patients can gain weight easily, become hirsute, and develop acne, striae, and a cushingoid facies. These effects tempt all patients, but particularly the adolescent girl, to abandon adherence to their medical regimen. Infection, thinning of the skin, short stature, personality changes, sleep disturbance, irregular menses, and mood swings may also occur. Hypertension, glaucoma, and cataracts can develop and should be screened for regularly. Patients may develop avascular necrosis of any bone but this complication is particularly common in the femoral head. Any patient with SLE on corticosteroids suffering from hip pain, with or without limited hip motion, should have imaging studies done to rule out avascular necrosis.

Role of the Pediatrician
Rheumatologists are involved in the care of patients who have SLE; however, the pediatrician’s involvement does not need to be peripheral. At each office visit, the patient should be screened for hypertension. It is important that patients are up to date on their vaccinations. Those on immunosuppressive medications cannot receive live virus vaccines, but should be given the 23-valent pneumococcal vaccine and the annual influenza vaccine. If patients have a fever they should be seen in the pediatric office for a thorough evaluation and antibiotics should be used judiciously. Care should be given to try to avoid sulfonamides because their use can result in a disease flare.

In the United States, Section 504 of the Rehabilitation Act and the Americans with Disabilities Act mandate that children with chronic disease have a right to have accommodations made to their educational plans that will allow them to succeed academically. A 504 plan or an individual education plan (IEP) should be put in place if needed. School teachers and guidance counselors should know that patients with pSLE may need assistance with note taking or getting from class to class if they have active arthritis. Patients should not be penalized if they cannot keep up with their peers in physical education class. Patients also may be absent from school because of disease flares or doctors’ appointments.

Patients with pSLE do best when care is provided by a team approach that involves the rheumatologist, primary care physician, ophthalmologist, nephrologist, and social worker or child life therapist. These patients need close monitoring, and the patient and family often need extra support. It is important to counsel patients on medication compliance and on healthy diet and exercise, and to ensure proper follow-up with the various subspecialists whom the patient sees.

### Summary
- **Based on strong research evidence and consensus, the most common disease manifestations at diagnosis of pSLE are constitutional symptoms, arthritis, malar rash.** (4)(5)
- **Based on some research evidence and consensus, patients with pSLE tend to have major organ system involvement (renal/central nervous system) and a greater disease burden compared with adults. Despite these findings, mortality is low.** (4)(5)
- **Based on some research evidence and consensus, the diagnosis of pSLE is unlikely if the ANA is negative, and most patients with SLE have a positive ANA at a titer ≥1:160.** (9)
- **Based on strong research evidence, both MMF and cyclophosphamide can be used for induction therapy in class III and IV lupus nephritis.** (10)
- **Based on strong research evidence, patients with SLE and antiphospholipid antibodies or LA have a two and six times greater risk of venous thrombosis, respectively, compared with patients with SLE without antiphospholipid antibodies.** (7)
- **Based on strong research evidence, patients with pSLE have a higher risk for subclinical atherosclerosis when there is weight-adjusted prednisone use, azathioprine use, increasing age, male gender, high BMI, abnormal creatinine clearance, and elevated lipoprotein(a) levels.** (8)
ACKNOWLEDGMENTS The author thanks Drs B. Anne Eberhard and Kathleen A. Haines for critically reviewing this manuscript.

References

Suggested Reading
PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Beginning this past January, learners can take Pediatrics in Review quizzes and claim credit online only. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician’s Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for AMA PRA Category 1 Credit™. In order to successfully complete 2012 Pediatrics in Review articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with 2012 Pediatrics in Review, AMA PRA Category 1 Credit™ be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. The most common skin manifestation of systemic lupus erythematosus is:
   A. Alopecia
   B. Discoid lupus
   C. Gottron papules
   D. Malar (butterfly rash)
   E. Psoriasis

2. A patient with discoid lupus is prescribed hydroxychloroquine. Of the following, what intervention should be performed at least annually to monitor for drug toxicity?
   A. A bone density study (DEXA)
   B. Ophthalmologic examination
   C. Plasma creatinine
   D. Prothrombin time
   E. Pulmonary function testing

3. According to the American Rheumatologic Association, which of the following conditions is a diagnostic criterion for systemic lupus erythematosus?
   A. Arthralgia
   B. Hemolytic anemia
   C. Interstitial pneumonitis
   D. Splenomegaly
   E. Vaginal ulcerations

4. The leading cause of morbidity and mortality in systemic lupus erythematosus is:
   A. Arthritis
   B. Nephritis
   C. Neuropsychiatric lupus
   D. Pericarditis
   E. Pneumonitis

5. Approximately what percentage of children with SLE will have anti-double-stranded DNA antibodies at the time of diagnosis?
   A. 1%
   B. 10%
   C. 25%
   D. 50%
   E. 75%
Educational Gap

Although most pediatric thyroid masses are benign, some are malignant; thus, pediatricians must be able to assess for risk of malignancy and order appropriate diagnostic tests in conjunction with consultation with an endocrinologist.

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

1. Develop a differential diagnosis and initial evaluation plan for a child or adolescent presenting with a thyroid mass.
2. List the risk factors associated with malignant thyroid nodules.
3. Understand the limitations of ultrasonography and fine-needle aspiration biopsy in the assessment of a thyroid nodule.
4. Recognize the risk factors inherent in surgical thyroidectomy.
5. Appreciate the current controversies in the management of pediatric thyroid nodules.

Introduction

Whether as part of a well-child examination, or in response to a patient or parent concern, it is important for the pediatrician to feel comfortable examining the thyroid gland. Although most pediatric thyroid masses are benign (Table 1 and Fig 1), in the event that a lesion is discovered, the pediatrician should be able to assess risk factors for malignancy and order appropriate diagnostic tests while awaiting consultation from the pediatric endocrinologist.

Epidemiology

Palpable thyroid nodules in the pediatric and adolescent population are relatively rare, having an estimated prevalence of 0.2% to 1.4%, which is 5 to 10 times less than in adults. (1) Studies estimate 9% to 50% (mean, 26.4%) of thyroid nodules in children and teenagers are cancerous, significantly higher than the estimated 10% to 14% of lesions in adults. (2) In fact, thyroid cancers are the third most common solid tumor in children and adolescents, with an annual incidence of 1.75 per 100,000. (3) The female-to-male ratio of malignant thyroid disease is age specific, with a ratio of 1 to 6 in children 5 to 9 years old, 1 to 1 in 10- to 14-year-olds, and 2 to 1 in 15- to 19-year-olds. (4) Well-differentiated thyroid carcinomas (WDTCs) comprise the vast majority of pediatric thyroid malignancies, with papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma accounting for 80% to 95% and 5% to 15% of these tumors, respectively. (5)(6)

Clinical Aspects

The History: Assess for High-Risk Factors

Most patients who have a malignant thyroid nodule present with an incidentally found, painless thyroid mass.
and are clinically and biochemically euthyroid. A thorough history is essential in assessing the likelihood of malignancy once a thyroid nodule is discovered. A history of ionizing radiation to the head or neck is an independent risk factor for the development of thyroid malignancies. Several decades may pass between the radiation exposure and the development of thyroid cancer. Historically, radiation was used to treat tonsillar hypertrophy, thymic enlargement, facial acne, and hemangiomas of the face and neck. Although these treatment modalities are not used today, irradiation of the head and neck is relatively common in children undergoing treatment for other forms of childhood cancer; thus, screening for thyroid malignancies should be a routine part of their posttreatment follow-up care.

The family history is of particular significance during the evaluation of a thyroid nodule because there are several syndromes (Table 2) associated with thyroid cancer that follow an autosomal dominant mode of inheritance. A family history of thyroidectomies, thyroid malignancies, or other cancers suggests that the child with the thyroid nodule has a genetic predisposition to the development of thyroid carcinoma. Although extremely rare in the United States, iodine deficiency has been linked to thyroid cancers, and determining if the child originates from an area of endemic iodine deficiency is crucial. Thyroid nodules in prepubertal children have a higher risk of malignancy. A thyroid nodule found in a male younger than 15 years old has the greatest chance of being malignant.

The review of systems is invaluable in stratifying the risk of malignancy and guiding the evaluation. If a patient has symptoms consistent with hyperthyroidism, such as tachycardia or tremulousness, the thyroid mass is likely a solitary toxic adenoma or a multinodular goiter, both of which secrete thyroid hormone autonomously. Caution must be exhibited when a patient presents with a discrete thyroid mass and symptoms of hypothyroidism, such as cold intolerance or constipation. Although the nodule in this situation likely represents inflammatory change in the setting of Hashimoto thyroiditis, some literature suggests that the presence of chronic lymphocytic thyroiditis raises the risk for thyroid cancers. (7) Although rare in young patients with thyroid nodules, voice changes, symptoms of airway compression, or rapid growth of the lesion are worrisome for malignancy. However, if the patient complains of pain or tenderness over the nodule, hemorrhage into a cyst, thyroid abscess, or an inflammatory process should be considered before malignancy.

The Physical Examination

The physical examination also provides clues to help differentiate between a benign and malignant process. The size of the nodule does not have any diagnostic value. (1)(2)(3) A nodule that is firm to palpation, irregularly shaped, fixed to the surrounding tissue, or associated with regional lymphadenopathy is concerning for malignancy (Fig 2). However, if the mass is painful to the touch or associated with overlying erythema, a suppurative thyroiditis is higher on the differential and should be treated appropriately.

Occasionally, thyroid carcinoma will present as a peripheral, nontender lymph node enlargement without a detectable thyroid nodule being present. Therefore, it is imperative to consider thyroid malignancy in the differential diagnosis of all painless cervical lymphadenopathy, especially if the patient has any other risk factors.

Table 1. Benign Thyroid Masses

<table>
<thead>
<tr>
<th>Simple colloid cyst</th>
<th>Follicular adenoma</th>
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<tbody>
<tr>
<td>Multinodular goiter</td>
<td>Thyroglossal duct cyst</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Inflammatory changes</td>
</tr>
<tr>
<td>Thyroid abscess</td>
<td>Teratoma</td>
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</table>

Figure 1. A. A patient with an ectopic thyroid gland (upper protuberance) before treatment. B. The same patient a few months after starting levothyroxine. Note how the gland has shrunk in response to treatment.
Evaluation

Laboratory Tests

The function of the thyroid gland should be assessed by measuring thyroid-stimulating hormone (TSH), thyroxine, and, in cases where hyperthyroidism is suspected, triiodothyronine. Any endocrine abnormalities should be corrected before surgical intervention. Although laboratory tests cannot differentiate a benign process from a malignant one, a suppressed TSH level is suggestive of a hyperfunctioning nodule. In this situation, an iodine-123 thyroid uptake and scan is warranted to evaluate for a toxic adenoma or a multinodular goiter. Anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies also should be measured because their presence may signify an increased risk of malignancy.

Calcitonin is used to screen for medullary thyroid carcinoma (MTC), a cancer that originates from the parafollicular or C cells of the thyroid gland. Although an elevated level is highly suggestive of MTC, a normal level does not rule out microscopic disease. Although less sensitive than calcitonin, a serum carcinoembryonic antigen is useful for detecting MTC and monitoring for disease recurrence. Sporadic MTC is rare in the pediatric population, and MTC usually clusters in families. The inherited forms of MTC, either as part of multiple endocrine neoplasia or familial MTC, are due to an activating mutation in the RET gene. If such a condition is suspected, genetic analysis should be performed. Additionally, evaluation for a concomitant pheochromocytoma with a 24-hour urinary catecholamine collection is imperative, because this tumor would need to be removed before thyroid surgery to prevent hypertensive crisis.

Ultrasonography

Ultrasonography of the thyroid gland and regional lymph nodes offers a radiation-free method of characterizing thyroid nodules and assessing for local metastasis. Although carcinoma cannot be diagnosed by ultrasonography alone, certain imaging findings are more commonly seen in malignant lesions (see Table 3 and Fig 3). Ultrasonography can detect changes in the cervical lymph nodes, a finding that greatly increases the likelihood of malignancy. Nonpalpable thyroid nodules, which carry the same risk for malignancy as palpable nodules, may be detected. Studies have found that, if there are multiple nodules, the individual risk of malignancy in each nodule decreases, but the overall cancer risk remains the same as for a patient with a solitary nodule.

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) is considered the gold standard for preoperative diagnosis of thyroid nodules in adults. Three recent studies (1)(5)(9) investigated the utility of FNAB in pediatrics, and each concluded that FNAB is a highly sensitive test that should be utilized in all pediatric patients presenting with a thyroid nodule. A meta-analysis of 12 studies of pediatric FNAB found the pooled sensitivity to be 82% and specificity 91%. Assuming that 20% of pediatric thyroid nodules are malignant, the meta-analysis determined the accuracy, positive predictive

Table 2. Autosomal Dominant Syndromes With Predisposition to Thyroid Malignancy

<table>
<thead>
<tr>
<th>Syndrome Description</th>
<th>Predisposition to Thyroid Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary thyroid carcinoma (MTC)</td>
<td>Multiple endocrine neoplasia type 2a: MTC, pheochromocytoma, and parathyroid adenoma</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2b: MTC, pheochromocytoma, mucosal neuromas, marfanoid habitus</td>
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<tr>
<td>Familial MTC: isolated MTC</td>
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<tr>
<td>Gardner syndrome: thyroid, breast, and colon cancers; lipomas; intestinal polyposis; osteomas</td>
<td></td>
</tr>
<tr>
<td>Cowden disease: thyroid and breast cancers, multiple hamartomas</td>
<td></td>
</tr>
<tr>
<td>Familial adenomatoid polyposis</td>
<td></td>
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</tbody>
</table>

Figure 2. A patient with marked cervical lymphadenopathy (all protuberances) before diagnosis of PTC.
value, and negative predictive value of FNAB to be 83.6%, 55.3%, and 98.2%, respectively. FNAB under ultrasonographic guidance allows for nonpalpable nodules to be biopsied and decreases the chance of a nondiagnostic biopsy. Benign FNAB results, such as the finding of a colloid nodule, can prevent unnecessary surgery. Atypical or malignant cytology guides the appropriate surgical intervention.

FNAB is not without limitations. The diagnostic yield depends on the person obtaining the biopsy to collect a sufficient sample and on the skill of the pathologist making the cytology report. It is difficult to obtain a diagnostic sample from nodules <1 cm. Although FNAB can identify PTC, follicular adenomas and carcinomas cannot be distinguished by FNAB alone and require surgical pathologic analysis to determine if the lesion invades the thyroid capsule. Nine to 20% of FNABs are nondiagnostic. (5) In that event, the physician must use other clinical criteria to decide whether to proceed with surgical resection or continued observation. The small neck size of young children and the need for sedation in most pediatric patients pose additional challenges in obtaining an FNAB. Adverse events, such as hemorrhage or abscess formation, are extremely rare after an FNAB.

**Surgical Management**

Although a consensus exists for early, prophylactic total thyroidectomy in children at risk for inheritable MTC, (10) the optimal surgical management of WDTC in the pediatric and adolescent population remains controversial. Proponents of lobectomy cite lower rates of surgical complications in comparison with total or near-total thyroidectomy. The most frequent complications of total thyroidectomy, permanent hypoparathyroidism with resultant hypocalcemia and permanent laryngeal nerve paralysis causing voice changes and dysphagia, occur in ~2% and 1% of patients, respectively. (11) Studies comparing the recurrence rate in children who underwent total thyroidectomy versus lobectomy are conflicting. Some authors refute that intergroup differences exist, whereas others have found recurrence rates up to 50% higher in the lobectomy group.

Although no official recommendations exist, most centers today support total or near-total thyroidectomy for pediatric WDTC. Despite a slightly higher surgical risk, total thyroidectomy allows radioactive iodine scanning and thyroglobulin levels to be used to detect metastases and disease recurrence (see next section). The majority of patients with PTC have microscopic foci of PTC in the contralateral thyroid lobe. Removing the entire gland eliminates these foci as potential sites of disease recurrence. This procedure decreases the need for a “completion thyroidectomy,” a second surgery associated with higher rates of surgical complications. (6)

The extent to which cervical lymph nodes should be surgically explored and dissected remains debated; broad
exploration increases the risk of surgical complications, whereas less extensive investigation may miss disease. (12) After lobectomy, most individuals remain euthyroid without medication, but a total thyroidectomy will necessitate lifelong levothyroxine supplementation.

Postoperative Management

Assessing and Treating Metastases With Radioiodine

Pediatric patients afflicted with thyroid cancer have a higher incidence of lymph node involvement and distant metastases at initial presentation in comparison with adults. Each thyroid cancer metastasizes differently. PTC invades regional lymph nodes and the lungs, follicular thyroid carcinoma seeds hematologically to the lungs and liver, and MTC utilizes the lymphatic system to spread cancerous cells. WDTC cells, unlike those of MTC, are able to concentrate iodine. This property is utilized to identify WDTC metastases and remnant tissue in the thyroid bed by the use of a radioiodine whole-body scan (WBS).

WBS can be done only after a near-total or total thyroidectomy because iodine-avid thyroid tissue concentrates radioiodine more efficiently than cancerous cells, thereby limiting the detection and treatment of metastases. To maximize uptake, radiographic contrast must not have been administered in the previous 2 to 3 months, and high iodine content foods must be avoided for several weeks. Levothyroxine is replaced by triiodothyronine supplementation 4 to 6 weeks before the scan. Two weeks before all thyroid hormone support is withdrawn causing a rise in thyrotropin, ideally >30 mIU/L. Because this action renders the patient hypothyroid, some centers utilize recombinant human thyrotropin (rh-thyrotropin) injections instead, although its use in children does not have Food and Drug Administration approval.

After confirming thyrotropin elevation, the patient drinks radioactive iodine (I-131) and 24 to 72 hours later undergoes WBS by the use of a scintillation camera designed to capture emitted radiation from the ingested isotope (Fig 4). Residual tumor or significant tissue in the thyroid bed warrants surgical reexplanation. If WBS reveals metastases or minimal remnant thyroid tissue, a larger treatment dose of I-131 is given with the goal of destroying the cancerous cells or ablating the remaining tissue.

Dosing of I-131 is another area of debate in managing pediatric WDTC, because no research-driven guidelines exist regarding its administration. The benefits of I-131, namely decreased disease recurrence, need to be weighed against the risks of treatment. Acute, and generally transient, side effects of I-131 include nausea, sialadenitis, altered taste, leucopenia, thrombocytopenia, and menstrual irregularities. Potential long-term risks of I-131 include decreased fertility, pulmonary fibrosis, and an increased risk of secondary malignancy, such as leukemias and solid tumors. (3) A second WBS is completed 6 months after the initial administration of radioiodine therapy to assess if a second treatment dose of I-131 is warranted.

Thyroglobulin Levels

Thyroglobulin, a protein used in the production of endogenous thyroid hormone, is produced exclusively by the thyroid gland and thyroid cancers. This property allows thyroglobulin to be used in athyreotic patients as an adjuvant to WBS in disease surveillance for WDTC. Thyrotropin stimulation causes thyroglobulin to rise, and levels should be measured after levothyroxine withdrawal or following rh-thyrotropin injection. In general, thyroglobulin levels >8 ng/mL while the patient is hypothyroid
or >2 ng/mL after rh-thyrotropin injection suggest disease recurrence or a residual thyroid remnant. Levels of thyroglobulin should be undetectable when thyrotropin levels are not elevated. Antithyroglobulin antibodies interfere with the thyroglobulin assay, so it is important to screen patients for the presence of these antibodies.

**Thyrotropin Suppression**

Because thyrotropin promotes WDTC growth, it is believed that depriving the cancerous cells of this stimulation will limit their expansion. This deprivation is achieved by administering sufficient levothyroxine to suppress endogenous thyrotropin production. The degree of suppression is also under debate, with most advocating for thyrotropin levels of 0.1 to 0.4 μU/L in patients with low risk of recurrence and <0.02 μU/L in high-risk patients. The benefits of thyrotropin suppression need to be balanced against its potential risks. Long-term complications of excessive levothyroxine include headaches, insomnia, difficulty concentrating, and problems with skeletal maturation and mineralization.

**Long-Term Follow-up**

Specific guidelines for long-term follow-up of pediatric thyroid carcinomas do not exist and recommendations are based on the individual institution’s experiences. Most centers advocate that, for the first 18 to 24 months after thyroidectomy, patients should undergo WBS and thyroglobulin measurement twice a year. I-131 can be administered every 6 months until WBS and thyroglobulin levels suggest that the WDTC has been eliminated. When there has been no evidence of disease for 12 consecutive months, these studies can be performed annually for the next 2 years, and then again 3 years later.

Assuming that there has been no disease recurrence, these surveillance studies should be conducted every 5 years. As the child grows older, it is important to arrange for continuity of care with an adult endocrinologist.

**Prognosis**

Fortunately, even when there is advanced tumor staging and metastases at presentation, pediatric and adolescent patients with WDTC have an excellent prognosis, having higher survival rates than their adult counterparts who have less invasive disease. The overall survival rate is ~99% at 10 years, 95% at 20 years, and 90% at 30 years. Although thyroid carcinoma is rarely fatal in children and teenagers, this population is at an increased risk for disease recurrence. Historically, the progression-free survival rates are markedly lower, being 65% to 70% at 5 years, 61% at 10 years, and 46% at 20 years. (6)(12) Thyroid capsule invasion, soft-tissue invasion, positive surgical margins, presence of distant metastases at diagnosis, and presentation at <15 years old have been cited as risk factors for disease recurrence. (12) The impact of more aggressive surgical treatment, use of radioiodine, and thyrotropin suppression remains to be seen.

**Summary**

- Based on strong research evidence, thyroid nodules in children and teenagers are more likely to be malignant than in adults.
- Based on strong research evidence, a history of ionizing radiation to the head or neck is an independent risk factor for the development of thyroid malignancies.

- There is strong research evidence, including a recent meta-analysis, (9) supporting the use of fine-needle aspiration biopsy in the evaluation of all pediatric and adolescent patients presenting with a thyroid nodule.
- The surgical management and postoperative care of pediatric and adolescent patients who have well-differentiated thyroid carcinomas remains controversial, because the rarity of the disease limits the ability to conduct randomized, prospective research studies.
- Numerous studies have demonstrated that, despite presenting with more advanced disease, pediatric and adolescent patients with thyroid carcinoma have a higher survival rate than adults.
- The American Thyroid Association has issued strong evidence-based recommendations for the management of medullary thyroid carcinoma, including RET mutation testing and early prophylactic total thyroidectomy in children with high-risk mutations. (10)

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PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Beginning this past January, learners can take Pediatrics in Review quizzes and claim credit online only. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician’s Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for AMA PRA Category 1 Credit™. In order to successfully complete 2012 Pediatrics in Review articles for AMA PRA Category 1 Credit™, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with 2012 Pediatrics in Review, AMA PRA Category 1 Credit™ be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. A 17-year-old boy is noted to have a palpable thyroid nodule on a routine examination. Which of the following findings makes it more likely that his nodule is malignant?
   A. Age >15 years
   B. Cervical lymphadenopathy
   C. Male gender
   D. Nodule is tender
   E. Tachycardia

2. The boy’s mother has had thyroid carcinoma, a risk factor for his having a malignancy. He undergoes ultrasonography. Which of the following ultrasonographic findings is most consistent with malignancy?
   A. A lymph node having a sharp margin is noted
   B. Intranodal microcalcifications are present
   C. Lesion is hyperechoic
   D. Lesion is wider than tall
   E. Nodule lacks central vascularization

3. The decision is made to perform a fine-needle aspiration biopsy (FNAB). Which of the following statements about FNAB is true?
   A. Fifty percent of FNABs are nondiagnostic
   B. FNAB is specific but not sensitive
   C. FNAB is straightforward and performed easily
   D. Hemorrhage and abscess formation are common complications
   E. It is difficult to obtain a diagnostic sample from nodules <1.0 cm

4. The boy is found to have a well-differentiated thyroid carcinoma. Most medical centers would recommend the following therapy:
   A. Chemotherapy
   B. Radiation therapy
   C. Radioactive iodine
   D. Thyroid lobectomy
   E. Total thyroidectomy

5. After surgery, the boy and his parents ask about his prognosis. Given his age, lack of metastases, and absence of local invasion, you feel comfortable telling them that the probability of 10-year survival is approximately:
   A. 55%
   B. 67%
   C. 75%
   D. 85%
   E. 99%
Complementary, Holistic, and Integrative Medicine: Crohn Disease

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Author Disclosure
Drs Leiby and Vazirani have disclosed no financial relationships relevant to this article.
This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Introduction
Crohn disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by periods of relapse and remission. In a genetically predisposed individual, environmental factors lead to a dysregulated adaptive immune response resulting in chronic intestinal inflammation and the potential long-term complications of intestinal stricture and perianal disease. (1) In pediatric CD, there is the additional complication of corticosteroid dependence, resulting in growth failure and significant psychosocial impact. (2) The need for surgical intervention in children is considerable also, with 5% requiring surgery at 1 year from diagnosis and 18% at 5 years. (3)

The clinical severity and location of disease often dictate what agents are chosen to treat CD, with the goal being to induce and then maintain long-term remission. Conventionally, 5-aminosalicylate (5-ASA) therapy, such as mesalamine, is used often for mild disease, although the evidence for this approach is not considered robust. (4) For moderate to severe disease, data reveal that earlier use of immunomodulators, such as the thiopurines or methotrexate, may act to decrease corticosteroid exposure and hospitalizations. (5)(6) Recently, infliximab, a monoclonal antibody directed against tumor necrosis factor α, has been shown to be efficacious in the induction and maintenance of remission in moderate to severe pediatric CD. (7) Despite strong evidence for benefit, potential adverse effects, including infection and malignancy, affect the acceptance of immune modulating therapies. (8)

The incidence of complementary and alternative medicine (CAM) use in pediatric patients with IBD ranges from 40% to 70%, (9)(10)(11)(12) with concern over adverse effects and lack of efficacy of conventional therapies being common reasons for such use. Use of CAM is increased particularly in patients who have a worse quality of life (QoL). (10)(13) In this article, we review the evidence for CAM therapy in CD as drawn from adult and pediatric data available in the English language.

Supplements
Glutamine
The amino acid glutamine is the preferred substrate for enterocytes, essential in a catabolic state such as IBD. Animal studies reveal glutamine decreases damage in IBD models, potentially by improving intestinal epithelial cell integrity. At this time, however, the beneficial effects of glutamine on human intestinal inflammation have not been demonstrated clearly. (14) The authors of one pediatric and two adult studies have looked both at glutamine as a supplement (15) and as part of a glutamine-enriched polymeric diet (16) and have not supported the use of glutamine for CD. Another study revealed no difference in plasma glutamine and intestinal permeability in a mixed IBD sample of patients who were randomly assigned to glutamine-enriched total parenteral nutrition versus glutamine-free total parenteral nutrition. (17) At this time, the available data do not support a recommendation of glutamine for maintenance of remission or treatment of disease flares.

Omega-3 Fatty Acids (Fish Oil)
Fish oil and other sources of omega-3 fatty acids have been theorized to be effective in IBD therapy due to their inhibitory effect on the cyclooxygenase pathway, decreasing the formation of arachadonic acid as a substrate for the production of proinflammatory cytokines. (18) A 2009 Cochrane

Abbreviations
5-ASA: 5-aminosalicylate
CAM: complementary and alternative medicine
CD: Crohn disease
IBD: inflammatory bowel disease

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meta-analysis reviewed the effectiveness and adverse events of fish oil when used for maintaining remission in CD. (19) Six randomized, placebo-controlled studies, including one pediatric trial, (20) were reviewed. The dose of fish oil ranged from 2 to 4 g per day, with varying blends of eicosapentaenoic acid and docosahexaenoic acid in differing delivery systems.

Two other trials (EPIC-1 and EPIC-2), with ~380 patients in each, revealed no significant difference in the relapse rate between omega-3 fatty acid supplementation and placebo. (21) The Cochrane review revealed that to date the existing studies do not support routine use of omega-3 essential fatty acids. The Cochrane analysis also revealed that adverse effects, including diarrhea and upper gastrointestinal symptoms, were more common in the fish oil groups compared with placebo, although the pediatric trial specifically did not reveal any adverse effects. (19) The type of fish oil preparation and delivery system would likely influence the rate of adverse reactions.

The authors of the single pediatric study compared 18 patients who received 5-ASA in combination with 3 g/day of omega-3 fatty acid with 20 patients who received 5-ASA and an olive oil placebo. (20) The omega-3 fatty acid group had a significantly lower relapse rate at 1 year compared with the placebo group (61% vs 95%, P = .0016). This small but well-designed trial is the only one to use fish oil supplementation in combination with other CD therapy. It is possible that the combination of 5-ASA and fish oil may have a synergistic anti-inflammatory effect. Additional large pediatric studies using a combination of omega-3 fatty acid supplementation and conventional immunosuppressive therapy are needed to demonstrate a role for routine fish oil use in CD.

**Probiotics**

Probiotic use is popular, with an average of 40% of pediatric patients with IBD having tried a probiotic preparation, (9)(10)(11)(12)(22) but evidence for clinical efficacy in CD is limited. In vitro and animal studies have revealed that probiotics can stimulate anti-inflammatory cytokine production and strengthen the intestinal epithelial cell barrier. (23) The authors of adult trials have examined the use of probiotics, including *Lactobacillus GG*, (24) *Lactobacillus johnsonii*, (25)(26) and a blend of pre- and probiotics (27) for prevention of postoperative recurrence; however, no effect was found. Some preliminary adult data reveal that *Saccharomyces boulardii* might be beneficial for CD by strengthening the intestinal barrier. (28) In a single randomized, double-blind trial of 75 children, *GG* versus placebo was used in addition to standard therapy. (29) There was no significant difference in time to relapse. The authors of two studies looked at a *Lactobacillus* probiotic mixture VSL number 3 and found it to be efficacious for pediatric ulcerative colitis. (30)(31) Although theoretically beneficial, to date there is insufficient pediatric research done on the effects of probiotics to treat pediatric CD. Additional research using other strains or targeting specific CD phenotypes may show more promising results.

**Diet**

Diet and bacteria may play a significant role in the etiology of IBD because they are the most common antigens to which the gastrointestinal lumen is exposed. (32) Epidemiologic data demonstrating an increased incidence of CD in emigrants to countries with a more western diet has been used as evidence that diet may be an environmental factor in the rising incidence of CD. (33) The authors of a case-control study investigated dietary patterns in pediatric CD cases and reported a positive association of CD with diets high in meats, saturated fatty foods, and desserts, whereas a diet high in vegetables, fruits, olive oil, fish, grains, and nuts was inversely associated with CD. (34)

Enteral nutrition therapy is a purely dietary approach more commonly prescribed in Canada and Europe than in the United States. Treatment consists of 50% to 100% of the diet being formula, the aim being to induce and maintain remission in some patients. (35) Because oral consumption of the volume necessary is difficult, nasogastric administration of the formula is the route most commonly used and this modality may limit acceptance.

Diet such as the specific carbohydrate diet, elimination diets, and Ayurvedic diets are anecdotally purported to be beneficial but lack evidence, and therefore further study is needed. As more research is done in the fields of epigenetics and nutrigenomics, perhaps dietary modification may become a more useful and precise tool in the prevention and treatment of CD. Until then, it is important to enforce the basic principles of a healthy diet low in saturated fats and sugar for children with CD.

**Acupuncture**

Acupuncture is thought to act on many different mediators in the inflammatory cascade, including changing the cytokine profile to reset the imbalance between T helper 1 and T helper 2 cell activity and stimulating a sustained low-concentration release of calcitonin gene-related peptide, a neuropeptide with vasodilator effect. (36)

There is one randomized controlled study in adults in which acupuncture and moxibustion for the treatment of
CD were used. (37) Remission rates and inflammatory markers did not differ between groups, but QoL measures also improved in both groups, although not significantly. More research is needed to study the effectiveness of acupuncture for CD in adults and children.

Homeopathy
Homeopathy is used by 3% to 4% of pediatric patients with IBD who are using CAM modalities. (9)(10) Although there are no randomized controlled trials to recommend routine use of homeopathic remedies, there is also no evidence that it is harmful. In general, homeopathic remedies are considered to be safe and nontoxic due to their extreme diluteness (usually 10⁻⁶ or greater), and thus can be tolerated in conjunction with conventional care.

Biobehavioral Methods
The role that stress may play in triggering flares of IBD has been investigated in the adult IBD population. Stress has been shown to alter gut permeability and cause the release of neuropeptides that have immune modulatory effects. (38) Although some studies reveal conflicting results, several prospective studies have revealed a positive association between stress and IBD flares, particularly the perception of stressful events, as opposed to discrete events. (38)

Unpredictable and potentially embarrassing symptoms of IBD add to the stress and challenges of adolescence. The incidence of psychiatric disorders in children with CD is increased compared with healthy children and is comparable to the incidence in children with other chronic diseases, such as cystic fibrosis. (39) QoL may be impaired by pain and school absences, and patients having increased disease severity often have worse QoL. (39)

Biobehavioral CAM techniques, such as relaxation, meditation, and prayer, are popular and are used by adolescents with IBD, especially those with more severe disease. (13) Various strategies have been tried in order to improve QoL and psychosocial functioning in pediatric patients with IBD, such as a prospective analysis of children attending a 1-week camp sponsored by the Crohn’s and Colitis Foundation of America, (40) cognitive behavioral therapy, (41) and a psychological program that included relaxation, imagery, and deep-breathing as part of an overall cognitive behavioral therapy (CBT) program. (42)

Additionally, there is a potential role for “gut-focused hypnotherapy.” The authors of a small study done in the United Kingdom in 2008 demonstrated a reduction of corticosteroid requirements after 12 sessions of gut-focused hypnotherapy. (43)

There has been significant adult and pediatric research in the therapeutic applications of yoga to prevent and treat medical conditions. (44)(45) Yoga has been shown to decrease functional disability and anxiety in children with irritable bowel syndrome. (46) Yoga may be helpful for similar reasons as stated above for IBD, but further studies are needed.

The use of biobehavioral techniques in conjunction with conventional care may improve QoL in children with CD and incorporate a holistic approach.

Summary
- Although the use of CAM in pediatric CD is common, quality evidence-based research is limited. There is clearly a need for further randomized controlled trials.
- The role of psychosocial distress in children with CD should not be overlooked and thus biobehavioral techniques should be considered and incorporated when possible.
- Considering the potential for growth failure and need for surgical intervention in CD, any CAM therapies that are not harmful should be used only in combination with conventional medical treatment.
- The importance of all health care providers partnering with their patients and asking about CAM use, as well as maintaining an awareness of efficacy, safety, harm, drug-supplement interactions, and appropriate referral sources, should be kept in mind when caring for those afflicted with this chronic disease.

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Note: To view the references for this article, visit http://pedsinreview.aappublications.org and click on the article title.
The following references are included online only for the article “Complementary, Holistic, and Integrative Medicine: Crohn Disease.”

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Presentation
A 6-month-old African American girl presents for a well-child visit and is found to have multiple yellow-brown, dome-shaped papules over her face, neck, and trunk. The lesions were first noticed at her 4-month visit as three similar 5- to 7-mm papules on her forehead and were diagnosed as congenital nevi. Over the past 2 months, the lesions have increased in size and number and now extend all over her forehead, cheeks, eyelids, ears, neck, and trunk. The infant seems to be unaffected by these lesions. There have been no complaints of increased fussiness, disturbed sleep, itching, or poor feeding.

The patient’s perinatal history is unremarkable. The past medical and surgical history is noncontributory. Her only medication is sodium fluoride 0.25 mg daily. She is following her growth curves and has achieved age-appropriate milestones. There have been no similar skin lesions in her parents or grandparents.

On physical examination, the infant has multiple raised, well-demarcated, 5- to 15-mm, yellow-brown, firm, rubbery papules (Figs 1–3) located over her forehead, upper eyelids, cheeks, ear pinna, neck, axillary folds, chest, and back. No oral lesions are noted. The lesions are nontender and there is no excoriation, ulceration, or bleeding. Because of the multiplicity and rapidly progressing nature of the lesions, the patient is referred to a dermatologist.

A shave biopsy is performed and the diagnosis is made on the basis of the histologic findings.
Diagnosis: Juvenile Xanthogranuloma

On microscopy of the specimen, aggregates of foam cells admixed with variable inflammatory infiltrate were noted in the papillary and reticular dermis. Immunohistochemical studies showed strong labeling of the dermal infiltrate with CD 68 and factor XIIIa that highlighted the vacuolization of the cytoplasm. Tests for S-100 protein were negative. These histopathologic findings are consistent with a juvenile xanthogranuloma (JXG).

Discussion

JXG is a benign disorder of early childhood and occurs primarily in infants and children <2 years of age. The eruption is characterized by solitary or multiple yellow-red nodules on the skin and, rarely, in other organs. The term “xanthogranuloma” refers to the histologic findings of lipid-laden histiocytes with a vacuolated, foamy xanthomatous cytoplasm and giant cells.

JXG is the most common form of non-Langerhans cell histiocytosis. The etiology and true incidence of JXG are unknown. JXG has been shown to affect all races, with a slight male predominance of ~1.5:1.0. Most affected children present during infancy or early childhood, with about 5% to 17% of cases presenting at birth and 40% to 70% manifesting during the first year of life. Despite the term “juvenile,” onset of JXG during adulthood has been documented, but is rare.

Most cases of JXG present with cutaneous manifestations and often are mistaken as innocent moles. The lesions of JXG present as a well-demarcated, firm, rubbery, round-to-oval papule or nodule, usually varying from 0.5 to 2.0 cm in diameter, with giant lesions (up to 10 cm) occasionally seen. They are found most commonly on the head and neck, followed by the upper torso, the upper extremities, and the lower extremities, but can appear anywhere on the body surface. Early lesions are red, orange, or tan in color, but over time they become more yellow. JXG usually is asymptomatic, but complications, such as ulceration and bleeding, sometimes develop.

Extracutaneous involvement occasionally occurs with JXG. The eye is the most frequently affected site, and ocular involvement is seen in 0.3% to 0.5% of patients with JXG. Children at greatest risk for ocular involvement include those ≤2 years of age and those with multiple skin lesions. Most ocular JXGs occur on the iris, followed by the eyelid as the second most common site. Orbital involvement is unusual and appears mainly during the perinatal period; affected infants present with unilateral exophthalmos. As illustrated in an “Index of Suspicion” case by Wells Collins et al (1), one should be alert for JXG in children who present with spontaneous hyphema because JXG is the most frequent cause of spontaneous hyphema in children. Because of potential complications of ocular involvement, such as hyphemas, glaucoma, or blindness, referral to an ophthalmologist should be considered, especially for children at high risk for ocular involvement.
Other extracutaneous manifestations include intramuscular JXG, which affects infants and toddlers exclusively, and lesions in other sites, such as lung, liver, testis, pericardium, spleen, central nervous system, bone, kidney, adrenal glands, and larynx. Most patients with visceral involvement usually have cutaneous lesions.

JXG has no associated metabolic abnormalities, hyperlipidemia, or diabetes mellitus. There are, however, rare reported associations of JXG with other disorders, including childhood leukemia and epilepsy. An association between JXG and juvenile chronic myelogenous leukemia has been observed, especially in patients with neurofibromatosis-1 (NF1). Children with NF1 and JXG have been estimated to have a 20- to 32-fold higher risk for juvenile chronic myelogenous leukemia. Epilepsy has been reported in patients with JXGs and café-au-lait spots.

The differential diagnosis of JXG includes Spitz nevus, pyogenic granuloma, Langerhans cell histiocytosis, mastocytoma, dermal nevus, benign cephalic histiocytosis, and xanthoma disseminatum. The visceral lesions may be mistaken for benign or malignant tumors, but the presence of cutaneous lesions aids in the diagnosis of JXG. Although cutaneous metastases from internal malignancies could be included in the differential diagnosis, they are rare.

The diagnosis of JXG usually is made on clinical presentation. Biopsy is not always necessary for the diagnosis of a solitary cutaneous JXG. A complete review of systems and physical examination is required to determine the presence of extracutaneous involvement. Because of the association between JXG and NF1, a thorough examination of the skin and review of the family history for NF1 should be obtained.

In cases having multiple skin lesions, biopsy is required to help exclude other disorders. The biopsy of the lesions typically shows dense cellular infiltrate of lipid-laden histiocytes (foam cells and Touton giant cells), lymphocytes, and eosinophils. The Touton giant cells, which are characteristic of xanthomatous lesions, are large multinucleated cells with a ring of nuclei surrounded by foamy (lipids) cytoplasm and they are formed by the fusion of macrophages. Immunohistochemical findings are important because they help separate JXG from other Langerhans cell and non–Langerhans-cell histiocytoses. Lesions of JXG usually are negative for S-100 protein, which is found in nerves, melanocytes, Langerhans cells, and myoepithelial cells.

Most cutaneous lesions of JXG regress spontaneously without any therapeutic intervention by 3 to 6 years of age. Despite the benign nature, some lesions may be excised for cosmetic or diagnostic reasons. The lesions also may be surgically removed, often by shave removal, for ulceration and persistent bleeding or pain. Cutaneous JXGs generally will decrease in size with intralesional glucocorticoid injection. If the patient is <2 years old and has multiple lesions, he or she should be referred to an ophthalmologist to rule out any ocular involvement. Topical, intralesional, and systemic corticosteroids may be used for intraocular or orbital lesions with surgery usually reserved for cases with hyphema or glaucoma. Systemic lesions require no treatment unless they interfere with vital functions. In these cases, high-dose corticosteroids, radiotherapy, and chemotherapy have been used.

**Patient Course**

By the age of 1 year, the lesions on this patient’s neck and trunk had regressed. Because of the multiple lesions and young age of onset, the patient was referred for ophthalmic examination, which did not reveal any ocular involvement. No genetic evaluation was sought in the light of a negative family history for NF1 or café-au-lait spots. The patient has been doing well without any evidence of systemic complications so far.

**Summary**

JXG is a benign disorder of early childhood and primarily occurs in infants and children <2 years of age. It is characterized by solitary or multiple yellow-red nodules on the skin and, rarely, in other organs. The clinical diagnosis of solitary cutaneous JXG usually requires confirmation by biopsy. Referral to a dermatologist should be obtained to exclude other disorders if multiple lesions are present. Clinicians should rule out ocular lesions with referral to an ophthalmologist if the patient is <2 years of age and has multiple lesions of JXG. If ophthalmologic consultation reveals no ocular lesions, screening every 6 months for the first 2 years of life is advised.

**Reference**


**Suggested Reading**


Case 1: Lymphadenopathy, Prolonged Hematuria, Proteinuria, and Weight Loss in a Teenage Boy
Case 2: Red, Swollen, Painful Eye in a 12-year-old Boy With Methylmalonic Acidemia
Case 3: Ptosis and Diplopia After a Respiratory Infection in a 7-year-old Girl

Case 1 Presentation
A 14-year-old African American boy presents with fever, right-sided neck swelling, and weight loss of 20 lb over 2-month period. He denies night sweats, illness contacts, or recent travel. He was seen 1 month ago for fatigue, body aches, decreased appetite, and 10 lb weight loss over the previous month. Due to a family history of diabetes, urinalysis was performed, which revealed moderate hemoglobin, protein of 200 mg/dL, white blood cell (WBC) count of 13/high power field, and red blood cell (RBC) count of 5/high power field. He was scheduled to be re-evaluated in 1 week but has been lost to follow-up.

The boy appears tired. His weight is 54.2 kg (>50th percentile), height is 165 cm (75th percentile), temperature is 38.9°C, heart rate is 106 beats/minute, respiratory rate is 20 breaths/minute, and blood pressure is 113/64 mm Hg. Physical examination reveals a 3 × 4 cm, tender, non-erythematous, non-fluctuant, slightly mobile right cervical mass located behind the sternocleidomastoid muscle. Findings on the rest of the examination are normal.

Complete blood count reveals a WBC count of 5.5 × 10^3/μL, with 65% granulocytes, 30% lymphocytes, and 5% monocytes, platelet count of 267 × 10^3/μL, hemoglobin level 9.5 g/dL, hematocrit 29%, mean corpuscular volume 71 fl, RBC distribution width 15.2%, and normal peripheral smear. His erythrocyte sedimentation rate (ESR) is 65 mm/h, and C-reactive protein (CRP) level is 1.081 mg/dL. Metabolic panel reveals a sodium concentration of 141 mEq/L, potassium 4.5 mEq/L, chloride 111 mEq/L, bicarbonate 24 mEq/L, serum urea nitrogen 33 mg/dL, creatinine 1.7 mg/dL, total protein 6 g/dL, and albumin 1.9 g/dL. Urinalysis reveals a protein of 200 mg/dL and rare granular casts. Chest radiograph is normal. Blood and urine cultures are obtained, and a tuberculin test is performed on admission. Additional evaluation reveals the diagnosis.

Case 2 Presentation
A 12-year-old boy with methylmalonic acidemia and secondary renal impairment presents to the emergency department with 4-day history of a red, swollen, painful left eye. The swelling has been gradual in onset and worsens with eye movements. He was diagnosed as having periorbital cellulitis in a private clinic and treated with oral amoxicillin/clavulanate for 2 days before this visit.

Physical examination reveals an alert boy whose height is 128 cm and weight is 27 kg, both below the 3rd percentile. His temperature is 37.2°C, respiratory rate 20 breaths/minute, heart rate 79 beats/minute, and blood pressure 125/91 mm Hg. The left upper eyelid is erythematous, swollen, hot, and tender. He has mild exophthalmos and bulbar conjunctivitis of the left eye (Fig 1). There is ophthalmoplegia of the left eye, more pronounced on lateral gaze.

Author Disclosure
Drs Ananthanarayanan, Gereige, Al-Owain, Nguyen, Kansagra, Shaw, and McLean have disclosed no financial relationships relevant to these cases. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.
The remaining findings are normal except for mild hypotonia associated with the methylmalonic acidemia.

Laboratory evaluation reveals a WBC count of \(7.81 \times 10^3/\mu L\) with 64.9% neutrophils and 27.2% lymphocytes, hemoglobin of 10.2 g/dL, and platelet count of 151 \(\times 10^3/\mu L\). His serum creatinine level is elevated at 116 \(\mumol/L\). However, serum levels of serum urea nitrogen, electrolytes, ammonia, creatine kinase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, angiotensin converting enzyme (ACE), thyroid stimulating hormone, free thyroxine, and antithyroid peroxidase antibody are within normal range. His ESR is 30 mm/h, and CRP is 5.9 mg/dL. An imaging study leads to the correct diagnosis.

### Case 3 Presentation
A previously healthy 7-year-old girl is hospitalized for evaluation of right eyelid droop and double vision for 2 days. She denies eye pain, redness, or drainage. Two weeks before presentation, she had several days of runny nose, fever to 38.3°C, and cough. Those symptoms resolved; however, she has since experienced intermittent headaches. She denies recent travel or known tick exposure. She reports no trauma, vertigo, syncope, weakness, numbness, paresthesias, dysphagia, or dysarthria. Her family history is significant for a grandmother who had a brain aneurysm.

Physical examination reveals an alert, oriented, obese girl who has normal cardiovascular, pulmonary, and abdominal findings. The neurologic examination reveals a right eye that is deviated downward and laterally with notable ptosis. She is able to abduct the right eye, with only to abduct the right eye, with mild proptosis. Note that the vascular engorgement is located more toward the lateral aspect of the left eye (lateral rectus position).

Figure 1. Chemosis and bulbar conjunctivitis associated with redness around the eye with mild proptosis. Note that the vascular engorgement is located more toward the lateral aspect of the left eye (lateral rectus position).

The patient was started empirically on clindamycin for lymphadenitis. The differential diagnosis at this point included cervical lymphadenopathy or lymphadenitis, malignancy, and an autoimmune disorder. Ultrasonography of his neck revealed right posterior cervical and supraclavicular lymphadenopathy. Rheumatoid factor was <20, antinuclear antibody was positive, and antidouble stranded DNA antibody titer was positive at 3663. He was diagnosed as having systemic lupus erythematosus (SLE). It was important to rule out malignancy and active tuberculosis (TB) before starting corticosteroids. The tuberculin test was negative and this result was attributed to low T lymphocyte numbers (absolute CD3 count of 511/mm³ [71%], absolute CD4 count of 252/mm³ [35%], absolute CD8 count of 238/mm³ [33%]).

Therefore, a serum interferon-γ release assay was done and came back positive. This test measures a cell-mediated immune response as a sign of TB infection. Right cervical lymph node biopsy revealed lupus lymphadenopathy, and kidney biopsy revealed stage III lupus nephritis (LN). The patient was presumed to have latent TB and started on isoniazid and pyridoxine and treated for 9 months. He also was started on lisinopril and corticosteroids. He was placed on a high calorie/high protein diet and has started gaining weight.

### The Condition
LN is one of the most serious manifestations of SLE and usually arises within 5 years of the diagnosis of SLE. LN is an inflammatory process caused by glomerular deposition of autoantibodies. The incidence is 3:10,000 in the general population and occurs in 30% to 90% of individuals who have SLE. LN is more common
in African American individuals, Asian individuals, children older than 15 years, and females.

The causes of SLE are unknown. SLE is more common in first-degree relatives of patients who have the disorder, with higher concordance in monozygotic than in dizygotic twins. The concordance rate in monozygotic twins is not 100%, suggesting an environmental trigger. Other risk factors include human lymphocyte antigen class II, cytokine and mannose–binding lectin genes, and complement C2, C4 deficiencies. The pathogenesis of LN is based on at least three potentially overlapping mechanisms: (1) circulating DNA anti-DNA immune complexes deposited in the kidney; (2) complement activation and leukocyte-mediated injury triggered by in situ antigen-antibody complexes; and (3) renal injury caused by antibodies against specific cellular targets.

Clinical Manifestations
Fewer than one-half of patients have symptoms such as fever, fatigue, weight loss, rash, arthritis, serositis, and anemia of SLE at the time of diagnosis of LN. Patients with active LN often present with proteinuria, hypoalbuminemia, peripheral and sometimes periorbital edema, normal or mildly elevated creatinine levels, and hypertension. Clinically, the disease is evaluated by urinalysis, concentrations of serum creatinine and albumin, anti-DNA titers, and serum complement levels. Abnormal urinary findings include albuminuria, leukocyturia, hematuria, casts (granular, hyaline, RBC, and fatty), and oval fat bodies. A rising anti-DNA titer, together with hypo-complementemia and a low C3 level, is a strong indicator of active lupus renal disease. Hypoalbuminemia with significant proteinuria and hypercholesterolemia are markers of the nephrotic syndrome, which may accompany active lupus renal disease.

LN is defined also histologically by renal biopsy, light microscopy, immunofluorescence, and electron microscopy. A kidney biopsy is used to confirm the diagnosis, determine the stage, and guide the choice of appropriate treatment. Patients with “silent” LN have normal urinalyses and serum creatinine levels but may show evidence of mesangial to proliferative nephritis on renal biopsy.

Management
Treatment depends on clinical manifestations and the results of renal biopsy. Treatment is indicated for patients with membranous changes and severe nephrotic syndrome. Patients generally are started on corticosteroids, ACE-inhibitors, lipid lowering agents, and anticoagulants as needed. Immunosuppressive therapy is used in patients with membranous LN who have persistent severe and symptomatic nephrotic syndrome; in patients with nephrotic syndrome experiencing protein excretion >3.5 g/day; and in patients with mixed membranous and proliferative lesions on biopsy. Agents used are cyclophosphamide, cyclosporine, mycophenolate mofetil, and chlorambucil. Maintenance of adequate nutrition with high protein and calories is very important. Despite treatment, some patients with LN develop progressive loss of kidney function leading to renal failure requiring dialysis and eventually transplantation.

Complications and Prognosis
Complications include nephrotic syndrome, acute renal failure, chronic renal failure, and end-stage renal disease. Prognosis depends on the specific form of LN. Better outcomes are reported in patients with pure membranous LN. Patients with proliferative lesions are more likely to develop end-stage kidney disease.

Lessons for the Clinician
- In patients with LN, active or latent TB must be ruled out before starting corticosteroids.
- An interference–γ release assay should be considered as the test of choice in patients with an SLE flare-up and negative tuberculin skin test to rule out active or latent TB.
- Dietary modification is very important and includes restrictions in sodium intake in patients with hypertension, restrictions in protein intake in patients with renal insufficiency, and restrictions in fat intake in patients with hypercholesterolemia. In the absence of the conditions mentioned above, a diet high in protein, fat, and calories is recommended.

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Case 2 Discussion
The symptoms and findings on physical examination (see Fig 1) suggested the diagnosis of orbital cellulitis in this patient. The normal thyroid studies and ACE level excluded orbital thyroptathy and sarcoidosis, respectively. Both computed tomography (CT) and MRI are valuable for diagnosing orbital pathology. The orbital CT in this patient revealed moderate enlargement of the lateral rectus muscle on the left with associated enlargement of the muscle tendon at the insertion into the sclera (Fig 2). The medial, superior, and inferior rectus muscles appeared normal. There was no sinus involvement or abnormality in the course of the optic nerve. This pattern was diagnostic of orbital pseudotumor.

The Condition
The best definition of orbital pseudotumor is an inflammatory mass of
Orbital pseudotumor is more prevalent in adults than children. In two large series, only 6% to 16% of patients who had orbital pseudotumor were younger than 20 years of age. The condition usually is unilateral, and the majority of studies indicate no sexual predilection.

The cardinal feature of orbital pseudotumor is acute orbital pain exacerbated by eye movement. Other characteristics include decreased ocular motility, lid or conjunctival edema, and proptosis of varying degrees. Unusual symptoms include cluster headache. Bilaterality, trauma, and iritis are more common in children than in adults with orbital pseudotumor.

The cause of orbital pseudotumor still remains obscure. The condition is likely to be autoimmune in origin, with viral, genetic, and environmental factors implicated as possible triggers. Involvement can range from a single extraocular muscle to the entire orbit. Pathologically, the pseudotumor is characterized by a mixed infiltrate of plasma cells, lymphocytes, macrophages, and polymorphonuclear cells, with fibrosis seen in the chronic form.

**Diagnosis**

Orbital pseudotumor should be considered in a patient with an acutely painful, proptotic eye. Leukocytosis and elevated ESR and CRP levels are nonspecific findings that suggest an active inflammatory process. Thyroid stimulating hormone and free thyroxine tests are performed to exclude thyroid-related ophthalmopathy. Testing for antinuclear antibody and more specific autoantibodies may be warranted if autoimmune diseases such as SLE are suspected. Imaging with orbital CT or MRI is essential for the diagnosis. Fine needle aspiration and biopsy should be reserved for patients having an atypical clinical course, a poor response to systemic steroid therapy, or recurrence of the disorder. These imaging techniques are helpful also in ruling out orbital malignancies or other diseases.

Orbital pseudotumor is associated with SLE, myasthenia gravis, Crohn disease, Lyme disease, Kawasaki disease, and paraneoplastic syndromes.

Differentiating orbital tumor from orbital cellulitis is extremely important. Imaging techniques are helpful in ruling out orbital malignancies or other diseases.

Systemic corticosteroid therapy is the accepted primary treatment for the pseudotumor of the orbit. Recurrent or chronic orbital myositis may be difficult to treat, requiring long-term corticosteroids, immunotherapy, chemotherapy, radiation therapy, or surgery. Failure to institute early therapy may result in permanent restriction of ocular mobility. Although orbital pseudotumor is considered a self-limiting disease, the duration without treatment is unpredictable. The condition responds rapidly to corticosteroids, and complete resolution occurs within 1 to 2 weeks. However, the process may recur in up to 30% of patients, usually within the first 6 months.

This patient was started on intravenous ceftazidime and clindamycin and did not reveal any response for 48 hours. Once the diagnosis of orbital pseudotumor was established, he was started on oral prednisone (2 mg/kg per day) for 3 weeks, followed by tapering over another 3 weeks. He showed dramatic improvement within 48 hours and full resolution within 2 weeks. Follow-up at 3, 6, and 12 months revealed normal eye findings without recurrence.

**Lessons for the Clinician**

- Orbital pseudotumor, also known as orbital myositis, is an idiopathic orbital inflammation.
- The diagnosis relies on clinical, radiologic, and sometimes pathologic findings.
- The condition should be differentiated from orbital cellulitis and neoplasms.
- Orbital pseudotumor has a good response to systemic corticosteroid therapy.

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**Case 3  Discussion**

MRI of the head revealed thickening and abnormal enhancement of the cisternal segment of the right oculomotor nerve (Fig 3). Magnetic resonance angiography did not reveal a vascular aneurysm. MRI/magnetic resonance angiography was chosen over...
CT/CT angiography for greater diagnostic specificity of structural brain lesions as well as less radiation exposure; additionally, there was low suspicion for a hemorrhage or vasculopathic process. These images could not distinguish tumor from an infectious or inflammatory condition.

Blood and CSF samples were obtained in search of an infectious agent and for markers of inflammation. CSF studies were negative for evidence of neurosyphilis, Lyme disease, acid fast bacilli, Cryptococcus, fungal infections, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. The CSF also revealed no evidence of leukemic cell infiltrate, oligoclonal bands suggestive of multiple sclerosis, or ACE levels suggestive of neurosarcoidosis. Serology for Lyme disease was negative and serum ACE levels were normal. However, serum immunoglobulin M (IgM) and IgG antibody titers against Mycoplasma were elevated by enzyme immunoassay. The positive IgM Mycoplasma titer was later confirmed by immunofluorescence antibody assay.

### Differential Diagnosis

The differential diagnosis of isolated cranial nerve III (CNIII) palsy is extensive, ranging from acutely life-threatening to relatively benign conditions. One important point of discrimination is the presence or absence of isolated extraocular movement involvement, isolated pupillary involvement, or both. The parasympathetic fibers that mediate pupillary constriction run along the outside of the oculomotor nerve, whereas innervation to extraocular muscles and the levator palpebrae muscle are more interior. Therefore, structural lesions that are compressive are more likely to present initially with pupillary involvement with sparing of extraocular movements, whereas vascular injuries to the nerve are more likely to affect extraocular movements with pupillary sparing. The following discussion

### Table 1. Differential Diagnosis of Orbital Pseudotumor

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Important Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital cellulitis</td>
<td>Characterized by proptosis, chemosis, ophthalmoplegia, and potentially decreased visual acuity and commonly caused by direct bacterial extension from the ethmoid sinus. Aggressive and prompt treatment is mandatory. Very uncommon in the setting of normal sinuses in children.</td>
</tr>
<tr>
<td>Preseptal (periorbital) cellulitis</td>
<td>No limitation of eye movement and no proptosis. CT scan reveals swelling of the lids and subcutaneous tissue anterior to the orbital septum. Antibiotic therapy is the treatment of choice.</td>
</tr>
<tr>
<td>Contiguous sinusitis</td>
<td>Nasal congestion and discharge, cough, fever, halitosis, and less commonly periorbital edema and facial pain. There is sinus tenderness sometimes. Sinus CT scan helps in establishing the diagnosis.</td>
</tr>
<tr>
<td>Dacryoadenitis (inflammation of the lacrimal gland)</td>
<td>Acute form can be viral or bacterial. Chronic form is seen with systemic diseases such as syphilis, tuberculosis, and sarcoidosis.</td>
</tr>
<tr>
<td>Orbital neoplasm</td>
<td>Benign tumors include hemangiomas and dermoid and epidermoid cysts. The most common malignant tumors are rhabdomyosarcoma, retinoblastoma (orbital extension), lymphosarcoma, metastatic neuroblastoma, and optic glioma. Biopsy is required for definitive diagnosis. Although lymphoid tumors probably are the most common orbital neoplasms in adults, they are exceedingly rare in children.</td>
</tr>
<tr>
<td>Trauma</td>
<td>Should be suspected in the pediatric age group, especially in the presence of stigmata of child abuse.</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Conjunctival foreign body may give a picture indistinguishable from pseudotumor. Thorough ophthalmologic examination is necessary for diagnosis.</td>
</tr>
<tr>
<td>Orbital thyroid disease</td>
<td>Secondary to immune mechanism leading to inflammation of the extracocular muscles and fat. Characterized by exophthalmos, proptosis, and lid retraction and associated with late motility problems. Usually bilateral and not accompanied by constitutional symptoms.</td>
</tr>
</tbody>
</table>

Figure 3. Contrasted T-1 axial image of patient’s brain MRI, revealing thickening and abnormal enhancement of the cisternal segment of the right oculomotor nerve.
applies to processes that may lead to complete CNIII palsies.

The location of injury to the oculomotor nerve can be within its midbrain nucleus or anywhere along the nerve as it courses through the brainstem, subarachnoid space, and cavernous sinus, then into the orbit. A brainstem process is likely to affect additional cranial nerves, but this involvement may not always occur. It is worth noting that many cases of isolated oculomotor nerve palsies are idiopathic.

The causes of CNIII palsy include vascular, malignant, infectious or parainfectious, inflammatory, traumatic, congenital, toxic, and migraineous conditions. Vascular causes merit particular attention, because an expanding aneurysm, most commonly of the posterior communicating artery, needs prompt intervention. Although more common in adults, aneurysms must be excluded in children. Other vascular causes include infarct or ischemia of the nucleus or nerve, vasospasm of the arterial blood supply, carotid artery-cavernous sinus fistula, and vascular malformation within the midbrain.

Malignant causes include schwannoma, carcinomatous meningitis, teratoma, meningioma, lymphangiomata, and leukemia. Infectious causes are numerous but most notable are Mycoplasma pneumoniae infection, cysticercosis, measles, Cryptococcus infection, Lyme disease, TB, and HIV. The CNIII palsy may be due to either direct infection or result from a parainfectious process that may be immune-mediated. Abscess formation within the brainstem may selectively affect only a single cranial nerve.

Inflammatory causes include Wegener granulomatosis, Tolosa-Hunt syndrome, vasculitis, sarcoidosis, SLE, and demyelinating processes such as multiple sclerosis. Trauma to the orbit and ophthalmoplegic migraines can lead to isolated CNIII palsy but should be diagnosed with caution in the appropriate clinic setting and only after other conditions have been carefully excluded. The same caution applies to the diagnosis of congenital CNIII palsy.

**The Condition**

Central nervous system (CNS) manifestations are the most common extrapulmonary manifestations of *M. pneumoniae* infections, occurring in 1 in 1000 cases. CNS involvement more commonly presents as acute encephalitis, although meningitis, myelitis, facial nerve palsy, and radiculitis have been reported. A literature search reveals only one case report of another patient having specifically a CNIII palsy associated with *Mycoplasma* infection. (1) The pathophysiologic mechanism still is debated. *Mycoplasma* has been found in CSF, but the organism has never been recovered from brain tissue, making direct invasion less likely. The most accepted pathophysiologic explanation remains a postinfectious autoimmune inflammatory response targeting the CNS, often appearing ∼1 week after a respiratory illness, usually accompanied by evidence of edema, perivascular infiltration, microthrombi, or areas of demyelination of CNS tissue.

**Management and Prognosis**

There are no published guidelines or case reports that discuss treatment of *Mycoplasma*-associated CNIII palsy. This patient was given initial treatment of prednisone 30 mg twice a day (0.75 mg/kg per day) on day 2 of admission, due to concern for a progressive inflammatory or parainfectious process. Within 24 hours, she had subtle improvement in her ptosis and pupillary constriction to light. She was started on azithromycin once the *Mycoplasma* result was obtained. On follow-up 1 week after discharge, improvement had continued and she was able to adduct her involved eye past midline. At this point, she was placed on a corticosteroid wean, to be completed over a 2-week period.

She was lost to follow-up after this visit, so recovery could not be documented. A previous case report reveals recovery of function by 4 months (1); similarly, a report of a *Mycoplasma*-associated abducens nerve palsy revealed spontaneous resolution within 21 days and no recurrence at 10 months. (2)

**Lessons for the Clinician**

- There are many causes for isolated oculomotor nerve palsy.
- It is important to determine whether there is extraocular involvement, pupillary involvement, or both in order to help guide evaluation.
- Evaluation of isolated oculomotor nerve palsy may involve neuroimaging and lumbar puncture.
- *M. pneumoniae* infection has been associated with many CNS disorders, including isolated oculomotor nerve palsy.

(Lisa Nguyen, MD, MPH, Sujay Kansagra, MD, Andrew Shaw, MD, Heather McLean, MD, Duke University Medical Center, Durham, NC.)

**References**


To view Suggested Reading lists, for these cases, visit http://pedsinreview.aappublications.org and click on “Index of Suspicion.”
The following Suggested Reading lists are included online only for the “Index of Suspicion.”

**Suggested Reading for Case 1**

**Suggested Reading for Case 2**
Mottow LS, Jakobiec FA. Idiopathic inflammatory orbital pseudotumor in childhood.

**Suggested Reading for Case 3**
Koskiniemi M. CNS manifestations associated with Mycoplasma pneumoniae infections: summary of cases at the University of Helsinki and review. *Clin Infect Dis*. 1993;17(suppl 1):S82–S57


Ryan M. Antiel, MA,* Robert M. Jacobson, MD,† Philip R. Fischer, MD‡

Editor’s Note
In his article published in May 2010, Dr. Yates discussed the ethical principles involved in various forms of enhancement (Yates FD. Ethics for the pediatrician: the persuasion of enhancements in pediatrics. Pediatr Rev. 2010;31:216–218). In this commentary, Drs. Antiel, Jacobson, and Fischer address the same concept of enhancement, providing their personal views as well as those of others, reminding the reader that pediatricians face ethical decisions in situations much more commonly encountered than the classic clinical dilemmas that involve serious illness and matters of life and death.

LFN

Introduction
Brave New World, Aldous Huxley’s masterpiece of dystopian literature, begins with a tour of the fertilizing room at the Central London Hatchery and Conditioning Center. The hatchery director, Mr. Foster, describes the work in progress to the new employees: “We also predestine and condition. We decant our babies as socialized human beings, as Alphas or Epsilons, as future sewage workers or future Directors of Hatcheries.” (1)

In Huxley’s world with the scientific wherewithal, the state determined the destiny of each child. The state predetermined everyone to a particular class, that is, limited the potential ability of everyone to fulfill specific functions in society. Thankfully, there are no hatchery directors in the modern pediatric clinic. However, children’s parents, sometimes with the spoken or unspoken support of their pediatricians, attempt to use biotechnology in a similar manner: to condition and so predestine their children. Perhaps what we now view as well-meaning attempts to increase the odds of success for our children will prove a prelude to a fearsome brave new world.

Height Augmentation
Although the majority of parents may not be willing to pay exorbitant amounts of money on a gamete for the chance of having a tall child, many parents come to the pediatric clinic with a desire to augment the height of their children. And pediatricians quite frequently and indiscreetly praise parents when their children measure above average in height. Although well meaning, these gestures carry an implicit critique that equates “tall” with “good.” Is it better to be taller? At present, our society greatly values height. For example, a meta-analysis found that height makes a clear difference in workplace success and is a stable variable throughout one’s career. (2) Furthermore, the study demonstrated that height makes a clear difference in workplace success and is a stable variable throughout one’s career. (2) Furthermore, the study demonstrated that height is significantly and positively correlated with one’s income potential. Others found that at age 16 years, for every additional inch of adult height, one’s wages would increase by 2.6%. (3)
In the past, growth hormone was limited to the treatment of growth hormone deficiency and other endocrinologic and genetic conditions. The US Food and Drug Administration has approved the use of growth hormone for treating Turner syndrome, chronic renal insufficiency, Prader-Willi syndrome, and even non–growth-hormone-deficient idiopathic short stature. (4) There is, at present, no consensus on the ethics of using growth hormone for children with idiopathic short stature. Growth hormone treatment does increase adult height on average by 4 to 6 cm, which corresponds to treatment costs of $35,000 per inch. (5) Some families and insurance companies might consider the price to be prohibitive, but others would claim that the psychological and fiscal benefits make growth hormone a worthwhile investment.

Performance Enhancement
With >30 million children and adolescents participating in organized sports in America, the pediatrician frequently addresses issues related to athletics. One area of concern has been the rise in the use of substances such as anabolic steroids, creatine, and dietary supplements in hopes that these agents will improve athletic performance. (6) Among high school athletes, 12% of juniors and 44% of seniors use creatine. (7) In a survey of high school students, 11% admitted to using anabolic hormones. (6) Certainly, it is now commonplace for role models in professional sports to use nutritional supplements as well as pharmaceuticals to enhance their athletic performance. Whatever their role and effectiveness, these performance enhancers have not been rigorously studied with regard to safety in children and adolescents. And <20% of school-age children report that their pediatrician educated them on the potential dangers of performance-enhancing substances. (6)

We have similar concerns with attempts to enhance academic performance. Many people lament the growing epidemic of stimulant usage on college campuses.interestingly, nonmedical use of prescription stimulants is highest at colleges with more competitive admission standards. (8) The debate over the use of cognition-enhancing drugs is also taking place among educators and scientists. (9) Should methylphenidate or other enhancers be prescribed to improve late-night studying?

And how should the pediatrician correctly evaluate the patient who presents in the teens with a personal and parental report of lifelong distraction and inattention, but up until now has been an A student? Given that the diagnosis of attention deficit hyperactivity disorder depends on those reports, is it possible that pediatricians are being set up to diagnose attention deficit hyperactivity disorder to facilitate the availability of a study-enhancing drug?

Cosmetic Improvement
Although questions of cosmetic care are not new to the practice of medicine, more recently, there has been a growing demand for cosmetic procedures among adolescents. According to American Society of Plastic Surgeons statistics, nearly 219,000 cosmetic plastic surgery procedures were performed on people aged 13 to 19 years in 2010. (10) What adjustments of normal variations in physical appearance should we promote? More and more adolescents are undergoing otoplasty, rhinoplasty, breast augmentation, and liposuction in hopes that these pricey quick fixes will bring them happiness and a heightened sense of self-esteem. Although some view plastic surgery among adolescents as extreme, orthodontic appliances (braces) have become mainstream among the affluent, even when they do not improve chewing mechanics or dental health.

Best Possible Life
Height augmentation, performance enhancement, and cosmetic improvements are just a few examples. And although, unlike Brave New World, most parents would not use biotechnology simply for purposes of social utility, parents are concerned with their child’s happiness and precariousness. They want their children to have the best life possible, and pediatricians certainly want to help. Thus, “enhancement” recommendations are common in everyday pediatric practice. Pediatricians strongly advocate immunization, which is an example of using biotechnology to enhance immune defenses. As a result of vaccinations, humans now live longer and healthier lives. Pediatricians also talk frequently about enhancing the environment to maximize well-being. We encourage healthy eating, proper sleep, helmet use when riding bikes, enrollment in educational opportunities, and other healthy means to enhance life experiences and health. Our Reach Out and Read program (now reaching 4.5 million children in the United States) not only provides opportunities for teaching parents developmental appropriateness, but also has at its core an objective to improve the child’s academic functioning.

Yet, many physicians do not feel comfortable with some enhancements.

Procreative Beneficence
Julian Savulescu argues that reproductive ethics should be guided by two principles: procreative beneficence and reproductive autonomy. (11) We will examine his first argument. For Savulescu, procreative beneficence requires that parents select
the child with the “best opportunity of having the best life.” Although he is arguing that couples should utilize preimplantation genetic tests, we believe he would extend his argument to postnatal enhancements, as well. Michael Parker challenges the principle of procreative beneficence, the duty to bring about the best possible life for a child. (12) His critique is fourfold: the pursuit of the best possible life is underdetermining, paradoxical, self-defeating, and overly individualistic.

First, the pursuit is underdetermining in that it is extremely difficult, if not impossible, to be able to actually say what specifically makes a life good. In a pluralistic society, there are competing notions of what “the best life” actually is. For example, is it really possible to correlate “testable features of embryos in any useful or deterministic sense to concepts as rich and complex as that of the ‘good life’”? (12) Does height, athletic performance, or straight teeth produce a more fulfilled life? For Aristotle, to live a full human life, one must include the pursuit of virtue. He wrote, “Human good turns out to be activity of soul in conformity with excellence.” (13) He was careful to differentiate a full human life from money, honor, or pleasure. He did so because one can always attain more money, honor, or pleasure. In a similar fashion, one could always be taller, perform better, or be more attractive.

Second, this pursuit is, according to Parker, paradoxical. Parker argues that the best possible life is not a life devoid of all suffering or struggle. He writes, “both strengths and weaknesses of character, and of our lives more broadly, are essential and interdependent elements of the good life.” This argument may seem incomprehensible to a culture obsessed with avoiding suffering or discomfort at any cost. Yet, there may be valuable lessons from certain types of suffering or failure. Failure, although it can bring humiliation, can also bequeath humility, which would prevent people from being foolhardy. Suffering, eg, the pain that comes with burning your finger on a hot stove, causes you to pull your hand back, thus saving your hand.

Parker further argues that, from a consequentialist perspective, the pursuit of the best possible life is actually self-defeating. Given that actually obtaining the best possible life is impossible, even with enhancements pre- or postnatal, the pursuit of this unreachable destiny “would inevitably be both exhausting and unlikely to lead to stable, satisfying or deep interpersonal relationships.” We stay away from individuals who are engrossed in their own happiness and well-being. In contrast, a life demonstrating self-effacement will beget a different kind of happiness and well-being—a lasting one, which will influence not only the said individual, but also those around her. In Lines Written a Few Miles Above Tintern Abbey, William Wordsworth claimed that the best portions of a good person’s life are those “little, nameless, unremarked acts of kindness and of love.” (14)

Finally, Parker argues that this pursuit is overly individualistic. He acknowledges the fact of reasonable pluralism in a liberal society and the difficulties that subsequently arise from competing notions of the good life. “What counts as the good in a particular case,” writes Parker, “will be meaningful and reasonable only within the context of discursive rules, including rules of justification, of the communities within which it is being used as a justification.” Thus, not only are conceptions of the good life “inseparable from relatively complex intersubjective and social practices and values,” but even the justifications for what constitutes a good life are intricately tied to one’s particular community. Parker attempts to avoid relativism by appealing to an outside notion of beneficence or perhaps nonmaleficence. But not all parents are able to agree on what is beneficial or harmful. Furthermore, even the actualization of a principle such as beneficence is tied to social and community meta-narratives.

Along similar lines, another potential problem with enhancement would be the “lack of imagination” if improvements were focused on a very simplistic idea of what constituted a good life. Frances Kamm offers music as an example. Suppose a parent, who lived 50 years ago, wanted a child who was a gifted classical musician. Kamm believes that these parents “could not have conceived that it would be good to have a child who turned out to be one of the Beatles.” (15) Thus, she argues that there are cases where “greater goods are more likely to come about if chance rather than unimaginative choice is in control.” (15) By extrapolation, what about other advancements? Albert Einstein in physics or Marie Curie in chemistry? In challenging life settings, the imagination allows for advancement in every sphere of knowledge.

Although Parker believes the duty of procreative beneficence is underdetermining, paradoxical, self-defeating, and individualistic, he still believes that the concept of beneficence is important in reproductive ethics. With the exception of rare cases, he argues that women should be free to act according to their own understanding of what would result in a reasonable chance of a good life for their child. Thus, Parker upholds Savulescu’s principle of reproductive autonomy. Whether or not one accepts this principle of reproductive autonomy, we must ask what type of goods the
postnatal enhancements described here actually are.

Competitive Enhancement
Although absolute or intrinsic goods (and harms) may still be debated, a good deal of overlap exists regarding intrinsic goods from a variety of social and community perspectives. Yet, many of the enhancements that parents are requesting from pediatricians are advantageous not because of their absolute good, but rather only in comparative terms. In fact, it may be helpful to understand enhancements such as height determinations, athletic performance, or even academic performance as competitive enhancement. These enhancements are derived from competitive motives. The desire is to produce taller, faster, smarter, and better-looking children. Each of these adjectives assumes that the particular child possesses the desired quality in a quantity greater than her or his peers. The desire to enhance is the result of the individual’s (often the parent’s) assessment that the child must always be above average in comparison with her or his peers, yet half of all children will always fall below the average by definition.

Take height enhancement as an example. If one child is enhanced and thereby grows in linear stature above average, another child’s height will become below average as a result. Despite that being taller is correlated with a higher income (as noted above), it cannot be said to be an intrinsic good. Peter Singer argues that, in actuality, it would be better if all humans were shorter for “we would require less food to sustain us, could live in smaller houses, drive smaller, less powerful cars, and reduce our impact on the environment.” (16)

Therefore, the majority of enhancements parents seek are not to provide their children with intrinsic goods, but rather to provide them with what Singer calls “provisional goods.” Of course, not all children will be or could be above average, and simply ensuring equal access will not negate this fact. Even if the rich and poor had equal access to growth hormones, we would still see a normal distribution regarding height. Singer points out that, “If everyone does better [on an admissions examination], the scores needed to get in will rise.” (16) Ultimately, even a Scholastic Aptitude Test score is a provisional good. This focus is to be contrasted with a love of learning, a thoughtful analytical disposition, or a committed work ethic.

Conclusion
Pediatric medicine involves important ethical questions that extend far beyond rare clinical situations into commonplace, everyday concerns. These issues include, but are not limited to, height augmentation, athletic and academic performance enhancement, and cosmetic improvements. Although some of these issues have existed for decades, there is a new demeanor that parents bring when they approach these issues with their pediatricians. This new attitude comes from our ability to engage biotechnology to meet parents’ requests. Many parents in our individualistic society feel a sense of entitlement to satisfy their own desires for their children, and many pediatricians will be enticed to participate in competitive enhancement. Along with motives to improve patients’ “happiness” and to regulate the safety of the technologies, there will be a large monetary incentive for physicians to use these technologies.

In competitive enhancement, there is an overarching purpose to the use of biotechnology that seeks to differentiate an individual from others, to obtain a personal advantage, and to put others at a disadvantage, regardless of health and disease. The desire is to produce taller, faster, smarter, and more beautiful children.

Competitive enhancement may always take place, yet it is our hope that pediatricians will bravely advocate for the intrinsic dignity of all children and promote thoughtful and authentic concepts of happiness and self-worth that do not depend on extrinsic characteristics or competitive performance. In the new world of pediatrics, failure to thwart parental demands for competitive enhancement could drastically alter the meaning of childhood, parenting, and the very practice of pediatrics.

References


