Index of Suspicion
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The reader is encouraged to write possible diagnoses for each case before turning to the discussion.

The editors and staff of Pediatrics in Review find themselves in the fortunate position of having too many submissions for the Index of Suspicion column. Our publication slots for Index of Suspicion are filled through 2013. Because we do not think it is fair to delay publication longer than that, we have decided not to accept new cases for the present. We will make an announcement in Pediatrics in Review when we resume accepting new cases. We apologize for having to take this step, but we wish to be fair to all authors. We are grateful for your interest in the journal.

Case 1: Lower Extremity Weakness 2 Years After Scoliosis Surgery in a Teenager

Case 2: Fever, Cough, Shortness of Breath, Jaundice, and Hepatomegaly in a Teenager

Case 3: Recurrent Infections in a Teenager

Case 1 Presentation
A 14-year-old girl presents with 10 days of progressive lower extremity weakness together with numbness from her umbilicus to her feet. She denies incontinence but notes difficulty starting her urinary stream as well as constipation. She has no fevers or headaches. There is no recent history of trauma, illness, travel, camping, or insect bites. Two years before presentation, she underwent a posterior spinal fusion for idiopathic scoliosis without complications. She has done well, and her progress is monitored regularly by her orthopedic surgeon, who notes that she has complained intermittently of mild back discomfort but has had no back pain in the past few weeks. There is no family history of tumors, neurologic disorders, or autoimmune diseases.

On physical examination, the girl is afebrile and has stable vital signs. She is alert and in no distress. Her skin is free of rashes and acne. Her cranial nerves are intact, and her neck is supple. There is no spine tenderness or erythema on her back. Her upper extremity strength is normal. Lower extremity strength is decreased to 2–3/5 on the left and 4/5 on the right, with normal tone, bilateral 4+ hyperreflexia, and 3 beats of clonus. She has normal rectal tone and decreased sensation to touch, pinprick, and vibration in her legs. Proprioception is difficult to elicit. She walks with support and without ataxia.

Laboratory evaluation shows white blood cell (WBC) count of 10.7 × 10^9/μL, her glucose level is 63 mg/dL, and the protein concentration is 225 mg/dL. Her erythrocyte sedimentation rate is 27 mm/h, and her C-reactive protein level is 4.6 mg/L. An imaging study reveals the diagnosis.

Case 2 Presentation
A 13-year-old boy presents with fever, cough, breathing difficulty, and reduced oral intake for 6 days. He was seen by his pediatrician 4 days ago for the same complaints and was started on treatment with amoxicillin/clavulanic acid and azithromycin for pneumonia. Because the symptoms have not improved, he is referred for further evaluation. He has been diagnosed as having severe developmental delay, a seizure disorder, autism spectrum disorder, and scoliosis. He takes carbamazepine. He has no history of allergies, exposure to pets, sick contacts, or recent travel.

Physical examination findings reveal a malnourished, ill-appearing boy with a temperature of 40°C. His respiratory rate is 30 breaths per minute, his pulse oximetry saturation is 95% in room air, his heart rate is 120 beats per minute, and his blood pressure is 100/70 mm Hg. He weighs 26 kg, which is well below the 5th percentile for his age. He is icteric, and his liver is enlarged (4 cm below the right costal margin with a span of 14 cm) and tender. Examination of his chest reveals decreased breath sounds at the right base. The rest of his physical findings are within his baseline limits.

Author Disclosure
Drs Yoo, Sankararaman, Wells, Vanchiere, Baker, Dickson, and Tankersley have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.
Laboratory results are as follows: WBC count is $4.3 \times 10^9/\mu L$ ($43 \times 10^9/L$), with 98% neutrophils and 2% bands; platelet count is $642 \times 10^3/\mu L$ ($642 \times 10^9/L$); erythrocyte sedimentation rate is 82 mm/h; prothrombin time is 12 seconds; C-reactive protein is 19.5 mg/dL, with a serum albumin level of 1.2 g/dL; direct bilirubin level is 5.2 mg/dL; aspartate aminotransferase level is 140 U/L; and alanine aminotransferase level is 132 U/L. Imaging studies reveal the diagnosis.

### Case 3 Presentation
A 17-year-old boy presents to the pediatric clinic for follow-up of a pneumonia diagnosed in the local emergency department. It is his second occurrence of pneumonia in the past 6 months, documented as lobar consolidation on chest radiograph. He has experienced recurrent episodes of acute otitis media as a young child, requiring bilateral myringotomy with tube placement. He also reports recurrent sinusitis over the past several years, requiring frequent courses of antibiotic treatment. In addition, he has a recent history of intermittent diarrhea and subsequently was diagnosed as having giardiasis and was treated. He denies any daily medication use and travel outside the United States, and his immunizations are up to date.

Physical examination reveals a well-developed, well-appearing boy with a temperature of 99.1°F (37.3°C), a heart rate of 89 beats per minute, a respiratory rate of 18 breaths per minute, blood pressure of 96/64 mm Hg, and an oxygen saturation of 98% in room air. Both tympanic membranes show tympanosclerosis, his throat is clear, and tonsillar tissue is present without exudate. Findings from the rest of the examination are unremarkable.

### Case 1 Discussion
Owing to the girl’s neurologic findings, spinal cord compression was an immediate concern. MRI of the thoracic spine was nondiagnostic because of metallic artifact from the spinal rods. Computed tomographic (CT) scan of the spine with myelogram showed fusion of the thoracic spine from T4 to T12, with the left T4 pedicle screw traversing the left paracentral spinal canal, causing compression of the spinal cord (Fig 1). There was a bony lucency lateral to the left T4 pedicle screw and in the vertebral body (Fig 1). The prevertebral soft tissues were unremarkable.

The patient was taken urgently to the operating room for removal of all spinal hardware and irrigation and debridement of the posterior spine, which appeared infected with purulent fluid around the pedicle screws. Cerebrospinal fluid leaks were not noted. Treatment with vancomycin and piperacillin-tazobactam was started postoperatively. Anaerobic wound culture samples grew *Propionibacterium acnes* at day 7 (the culture specimen was requested to be held for 2 weeks).

### Background and Differential Diagnosis
There is limited literature on late-presenting infections after scoliosis surgery, with several case reports and a few retrospective studies that report an incidence of 0.3% to 8.3%. The importance of awareness of this possible complication can be drawn from the prevalence of adolescent idiopathic scoliosis at 3% of the population, with 10% of those affected requiring treatment, and the potentially devastating neurologic outcome of complications that can occur if infection is not recognized and treated promptly.

Spinal cord neoplasm and epidural abscess were high on the differential, given her indolent presentation and absence of systemic symptoms. Other possibilities were transverse myelitis and multiple sclerosis, which can present with weakness but are unlikely to have upper motor neuron signs. Guillain-Barré syndrome and tick paralysis can present with ascending paralysis, but these patients also are usually hyporeflexic.

### Clinical and Diagnostic Features
The organism that grew in this patient’s wound culture sample has been reported commonly to cause late-presenting infection after scoliosis surgery. *P. acnes* is a Gram-positive bacillus found in hair follicles. It is anaerobic but tolerates limited amounts of oxygen. The bacterium can establish chronic infections without provoking a host immune response because of its cell wall structure, which may prevent degradation from neutrophils and macrophages, and it may be able also to suppress T-cell activation. In addition to requiring anaerobic conditions for optimal growth, this microbe grows slowly, making it difficult to grow in a culture sample, unless it is suspected. Culture samples usually are positive by 8 to 10 days.
Other implant-related infections have been associated with *P. acnes*, including endophthalmitis after intraocular lens placement, ventriculoperitoneal shunt infection, and prosthetic joint infections. Other organisms implicated in late-presenting infections after scoliosis surgery are *Staphylococcus epidermidis*, *S. aureus*, and *Micrococcus varians*. Culture samples may be negative despite a purulent appearance of the site, possibly because of aseptic inflammation resulting from corrosion of the implanted metal or inadequate culture conditions. *P. acnes* typically is sensitive to penicillin and clindamycin, but sensitivities should be obtained on all culture samples because resistance to antibiotics has developed.

The first scoliosis surgery was performed in 1930, and since the 1970s, there have been advances in the implants used, with modular systems that provide more versatility in surgical correction. The bulk of these modular systems has been implicated as a possible contributing factor to the incidence of late-presenting infections. It has been thought that the delayed infection is caused by intraoperative inoculation, despite sterile technique and antibiotic prophylaxis, followed by an indolent period. Hematogenous seeding is another possibility. It also has been suggested that an aseptic process caused by metal corrosion leads to irritation and inflammation resembling infection.

The most common presenting symptoms are back pain after a pain-free interval and swelling with or without fluctuance and drainage. Fever is uncommon. This infection presents an average of 2 to 3 years after the procedure and was described in one case report to present after 14 years. Lower extremity weakness similar to this patient’s was described in one case report but is not reported as a frequent presenting symptom in retrospective studies. Laboratory evaluation results usually are normal. Most patients have elevated levels of inflammatory markers, but normal levels do not rule out this infection.

### Management and Prognosis

The recommended treatment includes removal of instrumentation, irrigation, debridement, and a course of antibiotic treatment. Naturally there is concern for loss of correction or pseudoarthrosis if instrumentation is removed, but these complications appear to be significant only if the implants are removed earlier than 18 months after surgery. No significant difference in pain, function, self-image, or satisfaction was observed between those who had late-presenting infection and those who did not. This patient received 1 week of treatment with intravenous vancomycin and piperacillin-tazobactam until culture sample and sensitivity results were available; she was then discharged from the hospital on a regimen of oral clindamycin for 6 weeks. She recovered well and has full function of her lower extremities. Although we treated the patient for osteomyelitis, shorter antibiotic durations have been effective in some reported cases, a finding that leads some to consider that this infection involves only soft tissues.

### Lessons for the Clinician

- Patients can develop postsurgical complications, including infection, years after successful scoliosis surgery; such patients may present with neurologic symptoms and minimal pain.

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**Figure 1.** CT scan of the spine with myelogram showing a left pedicle screw traversing the left paracentral spinal canal causing compression of the spinal cord (red arrow) and a bony lucency lateral to the pedicle screw and in the vertebral body (blue arrows).
In such cases, the surgical service should be consulted urgently.

In a patient having a persistent localized infection, a foreign body should be suspected and, conversely, infection should be suspected in a patient who has new symptoms at a site where there is a known implant.

If a fastidious organism is suspected, the microbiology laboratory staff should be notified of the need for optimal culture conditions and extended observation of the culture sample.

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Case 2 Discussion

Two important diagnostic clues were the presence of high fever and tender hepatomegaly. These findings, along with leukocytosis, abnormal liver study results, and elevation of right hemidiaphragm seen on chest radiograph, were suggestive of liver abscess. Ultrasonography showed two heterogeneous masses in the liver measuring 9 × 13 cm and 7 × 8 cm in diameter, located predominantly in the right lobe. Both masses had multiple small cystic spaces separated by septae with a larger central hypoechogenic cystic component, which favored the diagnosis of liver abscess. The remaining findings from abdominal ultrasonographic examination were within normal limits. CT scan results confirmed the above findings (Fig 2). The presence of an aggregation of small abscesses with the formation of a larger abscess cavity is an important clue to the diagnosis of pyogenic liver abscess (PLA). The absence of significant travel history to an endemic area for amebiasis further strengthened the clinical suspicion of PLA.

A blood culture sample was drawn, and treatment with antibiotics (ampicillin, gentamicin, and metronidazole) chosen to cover Gram-positive, Gram-negative, and anaerobic organisms. An interventional radiologist placed a percutaneous pigtail catheter for drainage, which drained frank pus (Fig 3). Gram stain and stain for acid-fast bacilli did not show any organisms in the pus. Bacterial, fungal, and mycobacterial culture specimens from the pus and the blood culture sample did not grow any organisms.

The negative culture sample for this patient probably is due to earlier partial treatment with antibiotics. Moreover, 20% of PLAs reported in adults are culture-negative. Multiple stool studies (microscopy and culture) did not show any abnormality. Serology test results for Entamoeba histolytica, cat-scratch disease, and fungi were negative. The patient improved clinically and follow-up ultrasonography showed a decrease in the size of the abscess cavities.

A biopsy specimen taken from the wall of the abscess cavity showed normal liver cells with a prominent inflammatory response. Prolonged antibiotic therapy for 6 weeks resulted in complete resolution of the liver abscess.

The Condition

The liver is the most common visceral organ for the development of abscesses. Liver abscess may be bacterial, parasitic, or fungal in origin. In the United States, bacterial liver abscesses are the most common cause, whereas in the developing world, infection with *E histolytica* is the most common etiology. PLAs are relatively rare in children, and the reported incidence in developed countries is variable, ranging from 3 to 25 per 100,000 pediatric hospital admissions. Almost one-half of cases in children are associated with immunocompromised conditions, such as leukemia, chronic granulomatous disease, or sickle cell disease.

Figure 2. CT scan of the abdomen showing the presence of two abscess cavities (arrows) in the liver.
In children, the liver is seeded by Gram-negative organisms or anaerobes through portal circulation from intra-abdominal infections such as appendicitis, pylephlebitis (infective suppurative thrombosis of the portal vein), and inflammatory bowel disease, or through a hematogenous route by *S. aureus* from distant primary sources of infections such as endocarditis, pneumonia, or infected indwelling catheters.

In neonates, sepsis, necrotizing enterocolitis, and umbilical vein cannulation commonly predispose to liver abscess, whereas in adults, ascending cholangitis associated with biliary tract obstruction caused by gallstones is the most common cause of PLA. Early symptoms usually are minimal and nonspecific and include fever, chills, malaise, fatigue, nausea, vomiting, and abdominal pain. Physical examination findings may be completely normal or may reveal right upper quadrant tenderness or mild hepatomegaly. Other physical signs include decreased breath sounds in the right base due to pleural effusion or a fixed elevated hemidiaphragm.

Diagnosis of PLA in the pediatric population is challenging and often delayed. A high degree of suspicion is necessary. Serum levels of liver enzymes and bilirubin, WBC count, sedimentation rate, and C-reactive protein may be elevated but also can be normal. Liver abscess should be considered strongly in the evaluation of fever of unknown origin, especially in the presence of underlying risk factors such as immunosuppression.

**Differential Diagnosis**
Amoebic liver abscess should be considered in patients having a recent travel history to an endemic area; usually these patients have positive serologic test results for amebiasis. Abscesses due to *Candida albicans* and mycobacteria occur in individuals with reduced immunity caused by conditions such as hematologic malignancies, solid-organ transplants, and acquired immunodeficiency disorders. One also must consider a diagnosis of chronic granulomatous disease in the presence of liver abscess infected with *S. aureus*. Vascular lesions and tumors of the liver can be differentiated from hepatic abscess by contrast-enhanced CT scan.

**Treatment**
Untreated or undiagnosed liver abscess is fatal. Complications of hepatic abscess include peritonitis, subphrenic abscess, septicemia, and shock. Treatment requires ultrasonographic or CT-guided percutaneous needle aspiration and empiric broad-spectrum antibiotic therapy. In the case of small abscesses, medical management alone may be tried; however, in most cases, the abscesses are multiple and relatively large in size, so percutaneous catheter placement or open surgical drainage is required. These catheters usually are removed in ~2 weeks, when the drainage becomes nonpurulent and scant. Most cases require prolonged treatment for 4 to 8 weeks for complete resolution of the abscesses.

**Lessons for the Clinician**
- Symptoms and signs of PLAs usually are nonspecific, so a high degree of suspicion is required for the diagnosis.
- Liver abscess should be considered in a patient experiencing fever of unknown origin.
Case 3 Discussion

Serum quantitative immunoglobulin (Ig) evaluation revealed low IgG (324 mg/dL), IgA (21 mg/dL), and IgM (7 mg/dL) levels. Total hemolytic complement concentration was within the normal age-appropriate range. Antibodies against diphtheria and tetanus antigens were undetectable, and the patient also failed to develop protective antibody titers 6 weeks after vaccination. This patient was diagnosed as having common variable immunodeficiency (CVID).

The history of recurrent sinusopulmonary infections, low quantitative Ig levels, and a poor response to immunizations should raise the suspicion of a primary immunodeficiency, but the diagnosis cannot be made without first ruling out other conditions that may cause secondary antibody deficiency. Medications such as cyclophosphamide, phenytoin, gold, penicillamine, and sulfasalazine are known causes of hypogammaglobulinemia. HIV, cytomegalovirus, and Epstein-Barr virus infections as well as protein-losing states and malignancy can lower Ig levels.

The Condition

Selective IgA deficiency is the most common primary immunodeficiency, with reported incidences of 1 per 533 to 1 per 700 individuals in the general population; however, most patients with selective IgA deficiency are asymptomatic. CVID is the most common symptomatic antibody deficiency a pediatrician encounters. It is a heterogeneous disorder involving both B- and T-lymphocyte dysfunction causing impairment of both antibody synthesis and response. The true incidence of CVID is unknown, but it is estimated to affect between 1 per 50,000 to 1 per 75,000 individuals.

Symptoms may occur at any age, with a peak onset of symptoms in the first and third decade of life. Most cases are sporadic, but at least 10% are familial, occurring predominantly in an autosomal-dominant inheritance pattern. Both genders are affected equally.

Laboratory evaluation results demonstrate low serum IgG levels at least 2 SDs below the mean. Patients typically also have low serum IgA levels and frequently have low IgM levels. An essential part of the diagnosis also involves confirming impaired production of specific antibodies, demonstrated by poor responses to protein or polysaccharide vaccine challenges. Protein vaccine responses usually are assessed by measuring tetanus or diphtheria toxoids. Because of the immaturity of the T-cell response in young children, polysaccharide vaccine responses typically are expected in individuals 2 years and older. Polysaccharide response usually can be assessed with the administration of either pneumococcal polysaccharide vaccine or meningococcal polysaccharide vaccine.

Classically, patients who have CVID present with recurrent otitis media, sinusitis, bronchitis, and pneumonia, primarily due to infections by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus. Asthma, bronchiectasis, and hearing loss because of recurrent otitis media are well described for this condition.

Gastrointestinal complications affect 20% to 25% of individuals. Patients often report mild abdominal pain, bloating, and recurrent episodes of mild, watery diarrhea. Common gastrointestinal tract diseases include lymphomunodular hyperplasia, inflammatory bowel disease, and Helicobacter pylori-induced chronic gastritis. Pathogens such as Giardia lamblia, Campylobacter, and Salmonella species are the most common organisms that cause enteritis.

Autoimmune disorders occur in 20% to 25% of patients with CVID. The spectrum of autoimmune disorders varies widely: autoimmune thrombocytopenia and hemolytic anemia are the most common manifestations. Patients who have CVID have a significantly higher predisposition for all cancers. There is a strikingly high prevalence of gastric carcinoma and non-Hodgkin’s lymphoma with CVID. Estimated relative risks are 10-fold higher for developing gastric carcinoma and an astonishing 30- to 400-fold higher for non-Hodgkin’s lymphoma, compared with the general population.

Classic findings on physical examination and specific laboratory values provide important information in differentiating CVID from other primary immunodeficiencies. The presence of palpable lymph nodes and visible tonsils essentially rules out X-linked (Bruton) agammaglobulinemia and makes the diagnosis of severe combined immunodeficiency unlikely. Children who experience transient hypogammaglobulinemia of infancy closely resemble patients who have CVID, and that condition should be considered in patients younger than 3 years of age.

Treatment

Intravenous immunoglobulin or subcutaneous immunoglobulin replacement, antibiotic therapy for acute

• Although ultrasonography is the preferred initial investigation for liver abscesses, CT scan is the definitive investigation of choice because of its higher sensitivity.

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bacterial infections, and appropriate treatments for noninfectious complications are the mainstay of therapy for CVID. Intravenous immunoglobulin and subcutaneous immunoglobulin replacement are fractionated blood products made from pooled human plasma from thousands of individuals, incorporating a mixture of antibodies against a wide spectrum of infectious diseases. Immunoglobulin helps neutralize bacterial toxins, superantigens, and viruses. Immunoglobulin also activates complement and promotes phagocytosis and antibody-mediated cytotoxicity. This therapy can be life saving in most individuals and improves their overall prognosis.

When patients who have CVID present with respiratory tract infections, physicians should have a lower threshold for starting antibiotics that have activity against *S pneumoniae*, *H influenzae*, and *S aureus*. Longer duration of therapy may be needed. This patient decided to undergo weekly subcutaneous immunoglobulin replacement therapy. His initial doses were given in the clinic to monitor for adverse reactions and then successfully transitioned to home subcutaneous immunoglobulin therapy. At his most recent visit, at 19 years of age, all investigative studies, including complete blood cell count, trough immunoglobulin levels, pulmonary function testing, and high-resolution CT scan, yielded normal results. He has not required treatment for any severe infections since initiating subcutaneous immunoglobulin.

**Lessons for the Clinician**

- Patients who present with infections that are frequent, do not resolve with typical antibiotic therapy, involve unusual organisms, or affect unusual sites should raise concern for a primary or secondary immunodeficiency.
- A general immunodeficiency evaluation should include complete blood cell count with differential, with special attention to both the absolute neutrophil count and absolute lymphocyte count, total hemolytic complement concentration, and quantitative immunoglobulin levels.
- Patients suspected of having CVID should be referred to an immunologist and require a multidisciplinary team approach for management and for surveillance for autoimmune disease, malignancies, and infections.
- Intravenous immunoglobulin or subcutaneous immunoglobulin replacement is the treatment of choice in patients with CVID and can be life saving.

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