



# THE WEEK IN REVIEW

## EDUCATIONAL HIGHLIGHTS FROM THE CHIEF RESIDENTS' OFFICE

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### CASE 1—A 10 WEEK OLD MALE WITH COUGH AND VOMITING

A 10 week old previously healthy male presents to the triage clinic with a 4 day history of congestion, sneezing, and coughing. Mother reports that the child has “fits of coughing” during which the baby’s face turns red, and he occasionally seems to stop breathing. These fits occasionally follow feeds but also occur independently of feeding, and the child will sometimes vomit after coughing. Mother noted a fever 4 days ago to 100.4 by ear thermometer but says the baby has been otherwise afebrile. Of note, the baby received his two month vaccines two weeks ago, and there is a 2 year old sibling in the home who has had cough and runny nose. In the triage clinic the baby was felt to be well appearing until a witnessed coughing episode during which the baby became weak and pale with O<sub>2</sub> saturation of 90-91%. CXR revealed only slight prominence of central bronchovascular markings with no consolidations. He was admitted to the floor from the clinic subsequent to this visit. CBC with differential yielded a WBC count of 18.71 K/uL with 71% lymphocytes; smear showed many lymphocytes with cleaved nuclei. Given his clinical presentation, a pertussis PCR was sent and azithromycin therapy was initiated for a 5 day total course. A cough log was kept by mother and nursing. Infection control was notified and the patient’s entire family was treated with azithromycin. When 48 hours passed with no recorded desaturations or apneas, he was discharged home.

#### Diagnosis: Pertussis

Pertussis, or “whooping cough,” is caused by the nonmotile, gram-negative coccobacillus *Bordetella pertussis* or less commonly by a close species, *Bordetella parapertussis* (Fig. 2). Most cases in the US occur between June and October, with transmission occurring from an infected person to a susceptible host by direct contact with droplets produced by coughing or contact with respiratory secretions. Significantly higher morbidity and mortality rates occur in infants less than six months of age, prior to completing the primary DTaP immunization series (recommended at two, four and six months). Classically, the symptoms of pertussis are described as occurring in three phases:

**Catarrhal phase**—lasts 2-10 days, characterized by rhinorrhea, lacrimation, malaise, and occasional low grade fever

**Paroxysmal phase**—begins 10-14 days after symptom onset; characterized by paroxysms of coughing (sudden onset of continuous cough with no inspiration between coughs). Older children or adults may have the characteristic “whoop” upon deep inspiration after a paroxysmal coughing episode (deep inspiration against a still partially closed glottis); infants, however, lack the inspiratory muscle strength to generate this force and more commonly will display apnea at the end of a spell. These paroxysms of cough will usually generate a color change and oxygen desaturation, and in infants may require either blow-by oxygen therapy or positive pressure ventilation for recovery. The paroxysmal phase may last anywhere from 1-8 weeks.

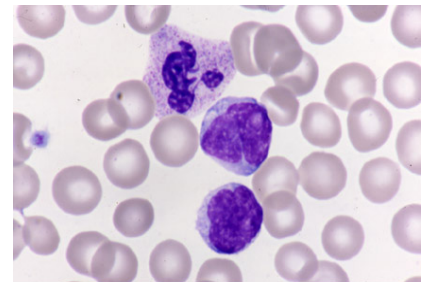
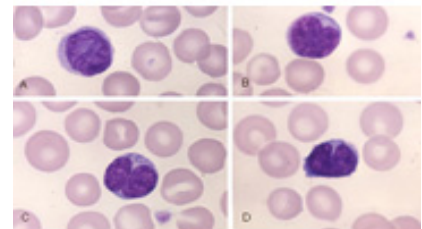
**Convalescent phase**—begins as the intensity and frequency of the coughing paroxysms diminish. This phase can last up to several months.

Upon laboratory evaluation with a CBC and differential, a leukocytosis with a predominant lymphocytosis is commonly seen beginning at the end of the catarrhal phase and persists throughout the paroxysmal phase. On examination of the peripheral blood smear in a patient with pertussis, the lymphocytes are commonly noted to have cleaved nuclei (see figure 1). Lymphocytosis has been found to parallel the severity of the illness. In one study, median WBC count was 94,000 in fatal infant cases versus 18,000 in nonfatal cases.

All current methods for confirmation of infection due to *B. pertussis* have limitations. Culture of nasopharyngeal secretions on charcoal agar is the gold standard; however, cultures must be allowed to grow for 7-10 days. Polymerase chain reaction of nasopharyngeal sections (obtained via NP wash), used most frequently at CHLA, yields a result more quickly but is dependent on skilled sample collection and PCR operation. Consequently, a patient with classic clinical symptoms of pertussis with a negative PCR should still be treated as having pertussis.

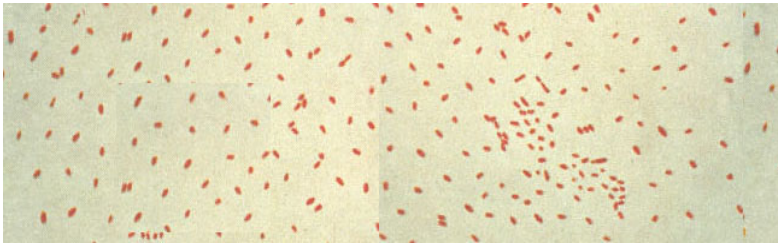
The most common source of pertussis in infants is an adult whose immunity has waned and harbors the disease with only mild clinical symptoms. As a result, treatment is aimed at eradicating the bacteria from the patient and presumed sources, as well as those who have come in contact with the patient, in the hopes of preventing reinfection. *B. pertussis* has shown excellent susceptibility to erythromycin. Azithromycin has proven to be a superior choice given its once daily dosing schedule, and is also used more often given the association shown between oral erythromycin and infantile hypertrophic pyloric stenosis in infants less than six weeks. The Red Book recommends 10 mg/kg/d as a single dose for 5 days in infants less than six months and 10 mg/kg/d on day 1 followed by 5/kg/d on days 2-5 in children greater than 6 months. It should be again noted that treatment is aimed not at shortening the course of disease but eradicating the carrier state and preventing reinfection. A confirmed case of pertussis does not confer life long immunity and the DTaP immunization schedule should continue as recommended.

Fig. 1: Lymphocytes with cleaved nuclei



Source: Lichtman MA, Shafer MS, Felgar RE, Wang N: Lichtman's Atlas of Hematology: <http://www.accessmedicine.com>

Hospitalization is aimed at close monitoring and supportive care; droplet precautions are recommended. A cough log, noting each paroxysm, associated oxygen saturation and color change, and any intervention required, should be initiated on admission. It should also be noted that health care workers are at high risk of becoming infected and spreading infection to other children. It is highly recommended that health care workers receive a Tdap booster in place of a tetanus booster (Td) only.



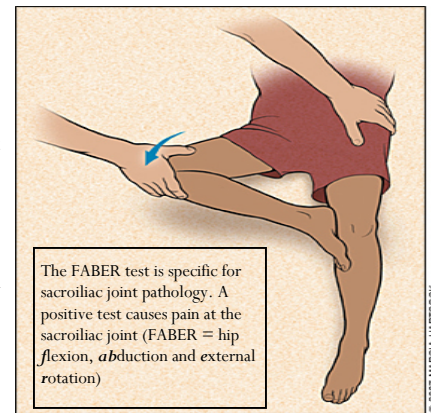
**Fig. 2**

*Bordetella pertussis*, the agent of pertussis or whooping cough. Gram stain. (CDC)

2005 Kenneth Todar University of Wisconsin-Madison Department of Bacteriology

## CASE 2—A 7 YEAR OLD MALE WITH A HISTORY OF PROGRESSIVE BILATERAL LEG PAIN, FEVER AND INABILITY TO WALK

A 7 year old previously healthy male presented to the emergency department with a two month history of bilateral progressive leg pain localized to his knees. He began to limp two months prior to presentation and was diagnosed with growing pains by his PMD. Additionally, two weeks prior to admission, he also started having intermittent low back pain and his ambulatory difficulty worsened. Finally, five days prior to presentation, he began to have warmth and swelling of his knees and on the day of admission, he had hand and wrist involvement as well. On review of systems, he had low grade fevers, denied weight loss, vision changes, eye pain, paresthesias and reported no bowel or bladder incontinence. On exam, he had limited range of motion at the left elbow, had bilateral swelling at the second and third MCPs, DIPs and PIPs. Moreover, his right hip illustrated limitation of flexion associated with pain but normal extension and rotation. His left knee illustrated some swelling. Of note, he had a negative FABER and full range of motion of his spine. His work up included an erythrocyte sedimentation rate and C-reactive protein which were both elevated, a CBC and serologic markers that were negative. He also had extensive radiologic imaging including plain films that illustrated a right knee effusion and a bone scan that suggested diffuse uptake likely indicating a rheumatologic process. He was discharged home on naprosyn and methotrexate and was scheduled to follow up with rheumatology.



### **Diagnosis: Polyarticular Juvenile Idiopathic Arthritis**

We began our discussion with the appropriate definition of arthritis which is the presence of swelling of the joint or two or more of the following: limitation of motion, tenderness, pain with motion or joint warmth. Furthermore, we also reviewed the musculoskeletal exam including the importance of evaluating swelling, tenderness and range of motion at each joint and eliciting sacroiliac joint tenderness with exam skills such as the FABER (flexion, abduction, external rotation of the hip), Schober test and straight leg raise.

Juvenile idiopathic arthritis (JIA) is defined as the presence of objective signs of arthritis in at least one joint for more than six weeks in a child younger than 16 years after other types of childhood arthritis have been excluded. These causes include infectious and postinfectious etiologies (septic arthritis, Lyme disease, acute rheumatic fever), hematologic and neoplastic disease such as leukemia; connective tissue diseases such as systemic lupus erythematosus, juvenile dermatomyositis; vasculitis such as Henoch Schonlein purpura and familial Mediterranean fever and serum sickness caused by medications such as isoniazid and penicillin.

The incidence and prevalence of JIA is 0.07-4.01 per 1000 and in particular oligoarticular JIA accounts for 40% of all new cases. Although the pathogenesis of JIA is not well understood, there is substantial evidence that it results from an autoimmune process. Specifically, HLA B27 has long been associated with enthesitis-related JIA patients. From a clinical standpoint, JIA is divided into 8 categories based on clinical symptoms during the first 6 months of disease including: 1) systemic 2) oligoarthritis-persistent 3) oligoarthritis-extended 4) polyarthritis rheumatoid factor (RF)-negative 5) polyarthritis RF-positive 6) enthesitis-related arthritis 7) psoriatic arthritis and 8) other. This ILAR classification scheme is highlighted on page 3. Of note, it is important to distinguish between leukemia and systemic onset JIA. Systemic onset JIA can be characterized by twice daily high spiking fevers, lymphadenopathy, hepatosplenomegaly and pericarditis with systemic features preceding overt arthritis by weeks to months. Complications of systemic JIA include pericardial tamponade, systemic vasculitis and macrophage activation syndrome, characterized by high fever, pancytopenia, abnormal liver function and DIC.

JIA is a chronic illness and treatment should involve a multidisciplinary team to address growth, social development and physical functioning with physical and occupational therapy. The pharmacologic treatment of the articular and extra-articular manifestations involves NSAIDs as the first line treatment for relief of joint symptoms. Notably, at least two thirds of children who have active joint disease require an additional disease modifying agent such as methotrexate which is used most frequently in children who have polyarticular onset and 70% have a favorable response. Other modalities have included etanercept, a TNF receptor antagonist, and systemic oral or IV pulse corticosteroids. At the conclusion of our conference, the rheumatology service emphasized the importance of ophthalmologic screening including evaluation every 3 months for the first 4 years especially in patients with oligoarthritis or pauciarticular JIA because of the increased incidence of uveitis.

JIA (ILAR) Classification	Clinical Features of JIA as Defined by ILAR Classification	JRA (ACR) Classification	General Comments
Systemic arthritis	Arthritis with/preceded by daily fever for at least 2 weeks and one/more of: evanescent nonfixed erythematous rash, generalized lymphadenopathy, hepatosplenomegaly and serositis.	Systemic-onset JRA	<ul style="list-style-type: none"> <li>● 50% remit in year 1</li> <li>● 25% have severe destructive joint disease</li> <li>● General growth abnormalities</li> <li>● Macrophage activation syndrome</li> </ul>
Oligoarthritis	Arthritis of one to four joints during the first 6 months of disease.	Pauciarticular (JRA) Type I	<ul style="list-style-type: none"> <li>● Young age onset</li> <li>● Uveitis, especially ANA+</li> <li>● Leg length discrepancy</li> </ul>
• Persistent	Affects no more than four joints throughout the disease course.		
• Extended	Affects more than four joints after the first 6 months.		<ul style="list-style-type: none"> <li>● Destructive joint disease</li> <li>● Therapy as for poly JIA</li> </ul>
Polyarthritis (RF-negative)	Affects five or more joints in the first 6 months of disease. Tests for RF are negative.	Polyarticular JRA (RF does not alter classification)	<ul style="list-style-type: none"> <li>● 10% destructive joint disease</li> </ul>
Polyarthritis (RF-positive)	Affects five or more joints in the first 6 months of disease. Tests for RF are positive on two occasions at least 2 months apart.	Polyarticular JRA (RF does not alter classification)	<ul style="list-style-type: none"> <li>● Like adult RA</li> <li>● Seen in late childhood</li> <li>● Severe destructive joint disease</li> </ul>
Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis with at least two of: sacroiliac tenderness and/or inflammatory spinal pain, human leukocyte antigen (HLA) B27-positive, family history in a first- or second-degree relative of medically confirmed HLA B27-associated disease.	Excluded in JRA classification, but some youth in this group at onset may be similar to late-onset pauciarticular JRA type II in JRA classification	<ul style="list-style-type: none"> <li>● Develops into juvenile spondyloarthropathies (including juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter syndrome, and arthropathies of inflammatory bowel disease)</li> <li>● Acute uveitis seen</li> </ul>
Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least two of: dactylitis, nail abnormalities, family history of psoriasis in at least one first-degree relative.	Excluded in JRA classification	<ul style="list-style-type: none"> <li>● Develops into juvenile spondyloarthropathies (including juvenile ankylosing spondylitis, juvenile psoriatic arthritis, Reiter syndrome, and arthropathies of inflammatory bowel disease)</li> <li>● Acute uveitis seen</li> </ul>
Other	Arthritis of unknown cause persisting for at least 6 weeks that either does not fulfill criteria for any categories or fulfills criteria for more than one category		

Goldmuntz, Ellen and Patience White. Juvenile Idiopathic Arthritis: A Review for the Pediatrician. Pediatrics in Review: Volume 27, No. 4 April 2006

## CASE 3—A 4 YEAR OLD WITH HEMOPTYSIS AND RESPIRATORY DISTRESS

A 4 year old Cambodian female presents to the emergency department for a 1 week history of cough, tactile fevers, dyspnea and pleuritic chest pain. She has a past medical history that is significant for iron deficiency anemia that was associated with hemoptysis at 3 years of age, but was treated and presumably normalized after iron supplementation. Early in the course of the present illness a hemoglobin level was checked by the PMD which was 10 g/dl. Three days prior to admission, the patient developed blood streaked sputum, and subsequent coffee ground emesis prompting an ED visit. There she was found to be hypoxic to 89%, tachypneic with a respiratory rate in the 50s, with tachycardia and a normal blood pressure. She was in the 75<sup>th</sup> percentile for height and 50<sup>th</sup> percentile for weight. The patient had a moderate degree of respiratory distress with intercostal retractions and bilateral rales. There was mild conjunctival pallor, but no digital clubbing or cardiac murmur, and the pulses were equal and strong. There was no obvious evidence of epistaxis or oropharyngeal trauma. A chest x-ray revealed bibasilar infiltrates, and a CBC revealed a hemoglobin of 6 g/dl with a normal platelet count. She was started on supplemental oxygen and IV antibiotics, and was transfused with packed red blood cells for the anemia. Subsequent laboratory tests included normal prothrombin and partial thromboplastin times, negative cANCA, pANCA, anti-GBM antibodies, and RAST to cow milk protein, as well as a negative PPD. Blood and sputum cultures were negative and the patient was started on a course of IV steroids which caused a resolution of symptoms.

## Diagnosis: Idiopathic Pulmonary Hemosiderosis

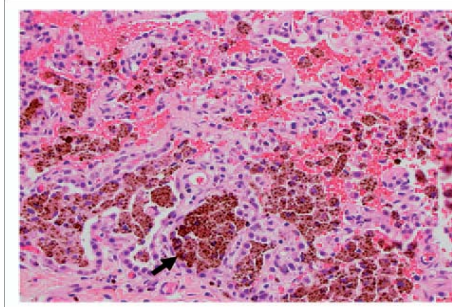
Idiopathic Pulmonary Hemosiderosis (IPH) is a condition that has no known etiology and 80% of the time presents in children under 10 years of age. It is characterized by thickening of alveolar walls, increased numbers of type II pneumocytes, hemosiderin laden macrophages and parenchymal fibrosis from hemosiderosis. It is differentiated from other causes of diffuse alveolar hemorrhage by lack of antigen-antibody complex deposition, negative pANCA and cANCA serologies, lack of anti-glomerular basement membrane antibodies (which bind to epitopes on Type IV collagen in the basement membranes of lung alveoli and renal glomeruli), and negative ANA. The diagnosis is suggested by the clinical findings of respiratory distress, hemoptysis (although frequently children don't generate enough force to expectorate blood and this symptom may be absent), ground glass pulmonary infiltrates, and significant anemia. Bronchoscopy with bronchoalveolar lavage of affected lobes may reveal hemosiderin laden macrophages which strongly suggests, but is not pathognomonic for, the diagnosis.

Theories have been proposed in the past regarding the etiology of IPH being related to an autoimmune phenomenon, and therefore early therapies included splenectomy, corticosteroids and immunosuppressants. Splenectomy had little effect on the outcomes of these patients, but corticosteroids and immunosuppressants have become a mainstay of treatment. Some of these patients require extracorporeal membrane oxygenation during life threatening bleeding episodes. Lung transplantation has been attempted in some patients only to find that the disease recurs in the transplanted lung. Data indicate that people who survive with IPH for greater than 10 years have independent risk of developing an autoimmune disease of approximately 25%. Overall, prognosis is worse in children with IPH than in adults.

An interesting variant of IPH is an entity known as Heiner Syndrome. This includes all of the characteristics of IPH with cow milk protein allergy. It is rarely reported in the medical literature, but a recent report studied 8 children with IPH and associated cow milk protein allergy. Dairy was withheld in these children and the symptoms improved. Interestingly, upon re-introduction of dairy, symptoms returned in three patients.

A salient component of the discussion included differentiating the source of bleeding in patients with hematemesis and hemoptysis. The clinical situation surrounding the symptoms was deemed to be the key differentiating factor, with characteristics of the blood to be equally important. A patient who is coughing vigorously, then later vomits coffee ground material is more likely to have pulmonary bleeding rather than GI bleeding. Likewise, bright red blood in emesis or expectorant is more likely to have a proximal source for the bleeding such as oropharyngeal trauma, a vascular lesion in the airway or esophagus, etc. Blood that has been sitting in alveoli tends to be processed by alveolar macrophages and the hemoglobin in the red blood cells is converted to hemosiderin, which accumulates in the macrophages. A patient with alveolar bleeding may have a cough productive of rust colored sputum or pink, frothy sputum. Frequently, these secretions are also swallowed and may result in coffee ground, dark colored emesis and hemocult positive stools.

Our patient was discharged home on room air with a hemoglobin of 17 after transfusions of packed red blood cells by the time of this writing. Although her RAST panels were negative, she was placed on a dairy free diet in addition to the corticosteroid therapy. She did not have a lung biopsy or bronchoscopy with BAL as her clinical symptoms, lack of serology and improvement with corticosteroids were felt to be sufficient for the diagnosis.



At low magnification, lung biopsy reveals marked hemosiderin-laden macrophages in airspaces. H and E stain. 20X. Image courtesy of Dr Megan Dishop, Department of Pathology from Texas Children's Hospital, Houston, Texas, USA.

### Differential Diagnosis for Hemoptysis in Children (As discussed in conference)

#### Airway

- Foreign Body
- Epistaxis
- Non-accidental Trauma

#### Pulmonary

##### *Parenchymal/Alveolar*

- Goodpastures Syndrome
- Idiopathic Pulmonary Hemosiderosis
- Heiner Syndrome
- Pulmonary Abscess
- Lobar Pneumonia
- Bronchiectasis
- Cystic Fibrosis
- Tuberculosis
- Mycoplasma pneumonia infection
- Mycotic aneurysm

##### *Vascular*

- Wegeners Granulomatosis
- Arteriovenous malformation
- Osler-Weber-Rendu
- Pulmonary Sequestration
- Collagen Vascular Disease

#### Cardiac

- Left sided heart failure
- Mitral valve stenosis

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