ASTHMA in CHILDREN
Asthma in Children: An Update for the Clinician

The Hematologic Workup for General Pediatricians: Which Tests to Perform Prior to Hematological Referral

Retained Splinters and Thorns in Pediatric Patients

Correction to Pedapudia et al. (Winter 2020)

In the article "Healthcare Equity in an Urban Setting: The Impact of Determined Advocates" by Anangamanjari Pedapudi, Jane Carver, PhD, Patricia Emmanuel, MD (The Florida Pediatrician, Winter 2020, Vol 39, Issue 1, pp 11–14), there was an error in the spelling of the primary author’s last name. The correct spelling of the author’s name is Anangamanjari Pedapudi. All versions of this article have been corrected.
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Asthma is the most common chronic disease in children. According to the National Health Interview Survey, in 2016 its prevalence among children age 0-17 years was 8.6%, with predominance in males, non-Hispanic black children, children of Puerto Rican descent, and children from low-income households. Almost half of Native American children have asthma, and most are not on controller medications.

In the United States, pediatric asthma continues to be a burden on the health care system (e.g., ER visits and hospitalizations). Asthma is the main reason for school absence and is a well-known contributor to poor quality of life. Asthma has classically been characterized by airflow obstruction, airway hyperreactivity with underlying inflammation, and variable and recurrent symptoms including a cough, wheeze, and breathlessness. However, the definition of asthma has evolved during the past decades as we have gained more understanding about its pathophysiology. The National Institutes of Health (NIH) and the most recent update to the Global Initiative for Asthma (GINA) have developed guidelines to help direct asthma therapy. Both emphasize the importance of addressing comorbidities that could contribute to asthma therapy failure. There is accumulating evidence about the type of immune response responsible in the allergic phenotype, the clinician should determine if the patient has concomitant allergic rhinitis or eczema and in those patients with persistent or uncontrolled asthma symptoms should also include along with a detailed history, identify possible triggers through allergy skin or in vitro testing.

The clinical history, the physical exam, identifying the triggers as well as pulmonary function testing, can help assist in the diagnosis of asthma. Pulmonary function testing (PFT) is recommended as part of every asthma evaluation. Nevertheless, although it can be done preschool children from infant to 4 years of age (infant PFT, Impulse Oscillometer (IOS)), is not commonly available limiting its use. Moreover, the PFT can support the diagnosis of asthma but due to lack sensitivity and specificity it cannot serve as a sole determinant of asthma diagnosis and its interpretation should be done with caution taking into consideration the patient’s clinical history.

In older children, when the likelihood of having asthma is high if pulmonary function testing shows expiratory airflow limitation with reversibility, this supports the diagnosis of asthma. Therefore, it is recommended as part of every asthma evaluation. Exhaled Nitric Oxide (eNO) measures eosinophilic airway inflammation which helps in the diagnosis can provide with predictive value for a corticosteroid response and medication compliance in children 6 years of age and older. Other objective measurements used to diagnose asthma and or exercise-induced bronchospasm are exercise or methacholine challenge test and cardiopulmonary exercise test. Referral to pediatric pulmonologist is recommended if there is no definite diagnosis of asthma, if the patient presents with serious comorbidities, has persistent or severe symptoms, and to help with asthma education in the patient where compliance is the main reason for poorly controlled symptoms.

The National Institutes of Health (NIH) and the most recent update to the Global Initiative for Asthma (GINA) have developed guidelines to help direct asthma therapy. Both emphasize the importance of addressing comorbidities that could contribute to asthma therapy failure. There is accumulating evidence about the type of immune response responsible in the pathophysiology of asthma. There are two distinctive phenotypes, an allergy, and a non-allergic phenotype. In assessing for the allergic phenotype, the clinician should determine if the patient has concomitant allergic rhinitis or eczema and in those patients with persistent or uncontrolled asthma symptoms should also include along with a detailed history, identify possible triggers through allergy skin or in vitro testing.

Other comorbidities that could contribute to asthma therapy failure are obesity, chronic rhinosinusitis, exercise-induced laryngeal obstruction (EILO), gastroesophageal reflux (GERD), obstructive sleep apnea, depression, anxiety or cardiac conditions. Identifying and addressing these comorbidities using a multidisciplinary approach is vital for adequate symptom control. The recommendation is also to establish a goal and to accomplish this goal; it is crucial monitoring for asthma control at every clinic visit. Such monitoring may occur either by a questionnaire addressing a self-reported number of exacerbations, (e.g., Composite Asthma Severity Index (CASEI) symptoms (e.g., Childhood Asthma Control Test (ACT) or frequency of use of oral steroids (e.g.Test for Respiratory and Asthma Control in Kids (TRACK)) emergency department visits, and school...
absences. However, it is well known that self-reported adherence is not reliable. Although obtaining pharmacy refill history is helpful, asthma, monitoring compliance is not an easy task, for this, it is essential to provide with asthma education at every clinic visit. This education should be directed toward the understanding of asthma pathophysiology in basics understandable language, should consist of information about medication use, the distinction between preventive therapy and quick relief, the safety of the medications including possible side effect and should include an asthma action plan. The asthma action plan should be simple and personalized with instruction on what to do every day, during asthma exacerbation and when to seek help. (91)

Each visit should include an assessment of proper medication delivery method. The use of nebulizer while still commercially available, its use in asthma has been replaced with the use of valve holding chamber (VHC). This is due to the fact that nebulized drugs have more oropharyngeal deposition whereas the antistatic property of the VHC decreases oropharyngeal deposition; hence more drug is delivered to the lungs.19-21 It is also more convenient to use a VHC which takes 1 to 2 minutes vs. 10 to 20 minutes with a nebulized drug.

Visits should also include assessing for environmental control including secondhand smoke, and other environmental irritants. For those whose allergy sensitivity test is positive and supported by the patient’s clinical history, the education should include avoidance of known environmental triggers. Such measurement includes impermeable mattress covers, examine the house for mold, water leaks, cockroach infestation among others. For the patient with a significant allergy profile should consider consulting an Allergist-Immunologist for possible adjunctive therapy and or immunotherapy.

The NIH and GINA guidelines, provide an approach for the management of asthma based on adequacy of control of the symptoms. Establishing if the patient has intermittent or persistent symptoms is the first step. Those patients who are symptom-free for an extended period (with asthma symptoms less than twice a week) with no activity limitation are considered having intermittent asthma and could be treated with albuterol only when they present with symptoms. For patients with persistent asthma symptoms, those patients with continuous or frequently recurring symptoms, the most effective therapy based on randomized control trials continues to be an inhaled corticosteroids (ICS). These have shown ICS to be more effective than long-acting beta 2-agonists (LABA), leukotriene modifiers, or theophylline in improving pulmonary function, preventing symptoms and exacerbations, reducing the need for emergency department treatment, and decreasing deaths due to asthma. It is also the most effective anti-inflammatory agent for exercise-induced bronchoconstriction (EIB).22

Both guidelines concur that an asthma specialist should be involved in the management with those patients who are difficult to treat, for those whom the diagnosis of asthma is in doubt, those who have comorbidities or concern for medication side effects, and those who have frequent exacerbations including hospital admissions. If symptom control is not achieved, the guidelines recommend adding other controller medications. Given the flat ICS dose–response curve for efficacy, doubling the dose of an ICS is less effective than adding a LABA. High doses of ICS can cause systemic effects without additional benefits.23 When adding a LABA this should always be done in combination with ICS for asthma controlled and due to safety concerns when using alone in asthma patients.24

In very severe asthmatics whose asthma is not under control with the traditional medications, the newer biologic therapies provide an additional option. Most of these biologics have been shown to decrease asthma symptoms and number of exacerbations and to improve quality of life. Some of these are approved for in-patients ages 6 or older.

For those patients with an allergic phenotype, the options are numerous with biologic targeting several pathways in the immune cascade. From anti IL-4, anti IL-13 to biologics targeting G2D treatments (e.g., anti-TNF, IL17, IL23, IL8) for non-allergic phenotype continue to be investigated with little definitive outcome. The use of azithromycin has been proposed based on immunomodulatory effect. In a recent meta-analysis in adults with asthma, the use of macrolides antibiotics improved quality of life and symptom scores, but there was no effect on lung function. Other studies have shown similar results.25 At this moment the use of azithromycin as adjunct therapy routinely for asthma is not recommended due to concerns about side effects and resistance to treatment. More longitudinal studies are needed.

Another adjunctive therapy proposed is the use of Vitamin D. Vitamin D has several protective roles in the pathophysiology of epithelial injury in allergic and nonallergic inflammation. Currently, the recommendation is to treat Vitamin D if it is deficient, but there is no definite recommendation on screening for Vitamin D deficiency in asthmatic patients or adding Vitamin D as an adjunct asthma therapy. Long-term cohort studies are ongoing.26

CONCLUSION

Asthma is a heterogeneous disease and understanding the patient's phenotypes helps direct therapy. Inhaled corticosteroids remains the most effective therapy in asthma. A VHC is a more effective method of delivery when used with proper technique. There are biomarkers and newer biologics for the treatment of allergy phenotype. However, for nonallergic phenotypes biomarkers and therapy options are underway. Studies on safety and prolonged outcomes are needed. Addressing comorbidities should be part of asthma control and should integrate asthma education and promoting adherence. Asthma management should be reassessed to maintain asthma symptoms control with minimal therapy needed.

REFERENCES


INTRODUCTION

General pediatricians care for patients with a wide variety of diseases, including hematologic disorders. These disorders are frequently encountered in inpatient and outpatient settings, and it can be challenging to determine which patients require further workup or referral. We review some of the most common pediatric hematologic disorders, provide guidance regarding initial workups and when referral to a subspecialist is indicated, and describe some hematologic emergencies.

ANEMIA

Anemia is defined as a reduction in the red blood cell (RBC) mass or hemoglobin (Hg) concentration. In general, evaluation of pediatric anemia should consider age and sex, include a complete and thorough history and physical exam, and consider the results of initial laboratory tests. The history should include birth weight, prematurity, ethnicity, family history, drug/toxin exposure, and dietary history. The physical exam should evaluate for tachycardia, irritability, pallor, scleral icterus, jaundice, and organomegaly. Considering the patient’s age at presentation is important as the normal ranges for Hg and mean corpuscular volume (MCV) vary by age. Anemia between birth and three months of age is most commonly due to physiologic anemia of infancy, while iron deficiency anemia (IDA) typically occurs in children and adolescents. Both the AAP and WHO recommend universal screening for anemia in children 9 to 12 months of age. Initial laboratory workup can include a complete blood cell count.
Iron without additional laboratory testing. Indications for referral should be considered when there is poor response to iron therapy or when diagnosis is unclear. IDA, one of the most common types of anemia in children, results in hypochromic microcytic anemia with low serum iron level, low reticulocyte count, elevated TIBC, and a MCV index >13.5. In most cases, IDA is treated with supplemental iron without additional laboratory testing. Indications for referral should be considered when there is poor response to iron therapy or when diagnosis is unclear.

### BLEEDING DISORDERS

Children who present with mild bleeding symptoms, such as epistaxis and easy bruising, are quite common in inpatient and outpatient pediatric practices. However, identifying which cases are pathologic can be challenging. A thorough history and physical exam should provide most useful information, including age of onset, severity and length of bleeding, site(s) of bleeding, trauma, history of menstrual bleeding, previous surgical/dental procedures, and delayed or slow healing. The physical exam should focus on cutaneous system, mucous membranes, and extremities.

Initial laboratory evaluation in patients with a history of bleeding or who are actively bleeding should include CBC, platelet count, prothrombin time (PT), partial prothrombin time (PTT) with or without platelet function analyzer and/or Von Willebrand Factor Activity (Ristocetin CoFactor). Thrombocytopenia refers to a reduction in platelet count to <150 x 10^9/L and is a common cause of acquired bleeding diathesis in children. Most patients with a platelet count >50,000/mm^3 have no significant clinical signs. The most common cause of acute isolated thrombocytopenia in an otherwise well child is immune thrombocytopenic purpura (ITP); a recent history of viral illness is described in 50-65% of childhood cases. Children commonly present with sudden onset generalized petechiae and purpura and/or bleeding gums. The presence of leukopenia or leukocytosis, anemia not explained by bleeding, hepatosplenomegaly, bone or joint pain, or remarkable lymphadenopathy suggests other diagnoses. Persistent or severe thrombocytopenia or thrombocytopenia requires further evaluation by a subspecialist. PT and PTT are used to evaluate the mechanisms of the activating clotting system, in both intrinsic (PT) and extrinsic (PTT) pathways. PT is a measure of the activation of clotting by tissue factor in the presence of calcium, and PTT is a measure of the initiation of clotting at the level of the factor XII. Both PT and PTT allow for the evaluation of clotting factor deficiencies, and the prolongation of one or both of these tests may reveal an underlying bleeding disorder. Other tests, such as mixing studies and those for lupus anticoagulant or other coagulation factor inhibitors may also help in distinguishing clotting disorders. If neither PT nor PTT are prolonged, factor XIII deficiency may be considered.

Bleeding time evaluates the function of platelets with the vascular wall. Due to difficulties in standardizing lab tests and significant variations between laboratories’ bleeding times, its use has been declining. The ongoing development of the platelet function analyzer is aimed at facilitating assessment of the early stages of hemostasis, specifically platelet and von Willebrand factor function. These in vitro tests, which measure platelet adhesion-aggregation in whole blood when mixed with either collagen-epinephrine or collagen-ADP, appear to be sensitive enough to detect the most severe types of von Willebrand disease. Many pediatric cases of bleeding disorders are complex and should be referred to a pediatric hematologist. Other indications for referral after initial laboratory evaluation include abnormal bleeding time, abnormal bleeding time plus low platelet count, or unclear diagnosis.

### PANCYTOPENIA

Pancytopenia refers to a reduction below normal values of all 3 peripheral blood lineages: leukocytes, platelets, and erythrocytes. There are two types of pancytopenia, inherited and acquired. Inherited pancytopenia accounts for approximately 30% of cases of pediatric marrow failure, with Fanconi anemia being the most common. Common physical characteristics of Fanconi anemia include abnormalities of the face, hypopigmentation of the skin, café-au-lait spots, vitiligo, short stature, absence of radius and thumbs, and anomalies of the feet, hips, and/or legs.

Acquired pancytopenia results from the direct destruction of hematopoietic progenitors, disruption of the marrow microenvironment, or immune-mediated suppression of marrow elements. A careful history of exposure to known risk factors should be obtained for every child presenting with pancytopenia including radiation drugs and chemicals, viruses (CMV, EBV, HIV, Hepatitis B, etc.), autoimmune disorders, leukemia, and myelodysplasia. The severity of the clinical course of pancytopenia is related to the degree of myelosuppression. Since pancytopenia requires microscopic examination of a bone marrow biopsy specimen and a marrow aspirate to assess overall cellularity and morphology, suspected cases should be immediately referred to a specialist.

### LEUKOPENIA

Leukopenia is a decrease in the total WBC count. In the pediatric population, reference values are age-specific. Leukopenia in adolescents and adults is defined as a total WBC count <4,000/µL. Initial evaluation should always aim to differentiate between acute and chronic leukopenia. It is important to ask about past medical history and medications, since some congenital syndromes and drug exposures can cause leukopenia. The physical exam should also include evaluation for stomatitis, gingivitis, dental defects, congenital anomalies and splenomegaly. Laboratory exams can help guide diagnosis by comparing different cell lines and evaluating shape and morphologic characteristics. Obtaining a CBC with differential and reticulocyte count is essential.

### NEUTROPENIA

Neutropenia is defined as a decrease in the absolute number of circulating neutrophils and band forms in the blood. The absolute neutrophil count (ANC) normally ranges from 1.5 and 8.0 x 10^9/L (African American population may have ANC levels as low as 0.8 and be considered normal). Mild, moderate and severe neutropenia are defined as an ANC of 1,000-1,500/µL, 500-1,000/µL, and <500/µL, respectively. Only patients with severe neutropenia have significantly increased susceptibility to life-threatening infections. In addition to identifying the level of neutropenia, one should determine if it is acute or chronic. Acute neutropenia evolves over a few days and often occurs when neutrophil recruitment is rapid and production is compromised. Chronic neutropenia lasts months or years and arises from reduced production, increased destruction, or excessive splenic sequestration of neutrophils. A common cause of transient neutropenia is viral infections. Neutropenia associated with common childhood viral disease occurs during the first 1-2 days of illness and may persist for 3-8 days. It usually corresponds to a period of acute viremia, commonly due to RSV, dengue fever, mumps, EBV, CMV, rubella, influenza, measles, varicella or HIV. The most common clinical presentation of profound neutropenia includes fever >38°C, aphthous stomatitis and gingivitis, cellulitis, perirectal inflammation, colitis, sinusitis, and otitis media. The most common pathogens causing infections in neutropenic patients are Staphylococcus aureus and gram-negative bacteria.

Selection of further laboratory tests is determined by the duration and severity of the neutropenia, relevant physical examination findings, and past medical history. If the ANC is <1000/µL in acute onset neutropenia (first time finding), the blood count should be repeated in 3 to 4 weeks, as it is most likely transient myelosuppression due to viral infection. If the ANC is <500/µL in 3 separate tests, if there is pancytopenia, or diagnosis is not clear, the patient should be referred to a pediatric hematologist, as bone marrow aspiration and biopsy with cytogenetics would be indicated. Other indications for referral include at least one of the listed clinical features within a 1 year period:

1. More than 2 systemic bacterial infections (sepsis, meningitis, osteomyelitis)
2. More than 2 serious respiratory infections (pneumonia)
3. Multiple bacterial infections (cellulitis, draining otitis media, lymphadenitis)
4. Unusual infections involving the liver or a brain abscess

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**Table 1: Differential Diagnosis of Anemia**

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<th>Microcytic anemia</th>
<th>Normocytic anemia</th>
<th>Macrocytic anemia</th>
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<tr>
<td>Low reticulocyte count</td>
<td>- Iron Deficiency Anemia</td>
<td>- Chronic Renal Disease</td>
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<td>- Thalassemia</td>
<td>- Malignancy</td>
<td>- Megaloblastic Anemia</td>
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<td>Intermediate or Major</td>
<td>- Red Cell Aplasia</td>
<td>- Acute Bleeding</td>
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<td>- Endocrine disorders</td>
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<td>- Connoitive anemia</td>
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<td>Hypersplenism</td>
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<td>- Hemolytic anemia</td>
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**Table 2:**

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<th>Macrocytic anemia</th>
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<tr>
<td>Low reticulocyte count</td>
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<td>- Vitamin B12 deficiency</td>
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<td>- Aplastic anemia</td>
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<td>- Hypothyroidism</td>
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<td>- Drug Induced</td>
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**Table 3:**

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<th>Low reticulocyte count</th>
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<td>- Active hemolysis</td>
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<td>- Typically with brisk reticulocytosis</td>
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**Table 4:**

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<th>Neutropenia</th>
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3. Multiple bacterial infections (cellulitis, draining otitis media, lymphadenitis)
4. Unusual infections involving the liver or a brain abscess
The need for further workup is determined by the history and physical examination. If malignancy is considered unlikely, etiology is benign or malignant. Among severe conditions, cancer occurs at a rate lower than 1%.8

It is unclear despite a thorough history and physical examination and other diagnostic workup, imaging may be helpful. In cases where malignancy or granulomatous disease is suspected, imaging is recommended. In cases of high suspicion for mycobacterial disease, imaging is recommended. In cases of high suspicion for mycobacterial disease, imaging is recommended.

In conclusion, most of the lymphadenopathies that occur in childhood are benign in etiology. As demonstrated in a study by Orguz, et al.11; they are usually a result of a self-limited disease that will resolve without any sequelae. In this study in particular, the specific etiology was found in 53.8% of the patients; 46.2% seemed to be of unknown origin and were classified as benign. A total of 24.3% were malignant causes, this number is thought to be higher than in previous studies due to the population of the study which was patients referred to a hematology-oncology service.

HEMATOLOGIC EMERGENCIES

The decision to refer a patient with no prior history of a hematologic disorder for emergent evaluation and intervention can be life-saving. We briefly review several common hematologic scenarios that require emergent interventions.

Scenario One: A symptomatic patient with a rapidly decreasing Hg level. Common causes of acute anemia are gastrointestinal bleeding, menstrual bleeding, malignancy or hemolytic anemia. Symptoms that require acute intervention include orthostatic hypotension, exercise intolerance, respiratory difficulty/shortness of breath, chest pain, syncope, and/or ongoing blood loss. These symptoms or the presence of sustained tachycardia, hypotension or decreased oxygen saturation should prompt emergent evaluation and treatment to correct the anemia and underlying disorders. Current guidelines from the American Association of Blood Banks (AABB) for packed red blood cell (PRBC) transfusion generally only include adult patients.12 There are several other adult guidelines, from which PRBC transfusion indications for children can be extrapolated. These guidelines generally recommend a transfusion trigger for a Hg level of less than 7-8 g/dL in hospitalized patients as this is the level where patients tend to become symptomatic. Patients with chronic anemia, such as those with JDA secondary to inadequate iron intake, may tolerate lower Hg levels and therefore may not require transfusion at 7-8 g/dL. Alternatively, patients with rapid blood loss may be symptomatic at higher levels and may require an increased PRBC transfusion trigger.

Patients with signs of vigorous hemolysis such as increased jaundice, pallor, and fatigue will benefit from immediate management and treatment. Patients with a chronic hemolytic anemia such as sickle cell anemia or spherocytosis who have the above symptoms and a decreased Hg from baseline, along with either a decreased reticulocyte count (or in the case of sickle cell, an enlarged spleen) will likely benefit from a PRBC transfusion. Patients with new signs of hemolysis should be promptly evaluated including a CBC, reticulocyte count, bilirubin level (both total and indirect), direct antiglobulin test (DAT, aka direct Coombs test), LDH and haptoglobin. An increase in reticulocyte count, indirect bilirubin and LDH, and a decrease in haptoglobin support the diagnosis of hemolytic anemia. If the patient has a warm autoimmune hemolytic anemia as demonstrated by a positive DAT for IgG +/- C3, prompt treatment with steroids should be started.13 If the patient is symptomatic from autoimmune anemia, the treating physician should confer with the blood bank to ensure that the least incompatible PRBC transfusion is made available as finding a well-matched PRBC unit is often difficult in these circumstances. Fortunately, the least incompatible unit is generally considered to be tolerance, allowing for treatment of the anemia.14,15

Scenario Two: Microangiopathic hemolytic anemias. These anemias include the combination of anemia with schistocytes, and thrombocytopenia, and should be promptly referred for immediate workup for severe infection/disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia purpura (TTP) or hemolytic uremic syndrome (HUS) with investigation of end organ damage including neurologic and renal involvement depending on symptoms.

Scenario Three: Severe neutropenia. A child with a newly diagnosed fever and severe neutropenia, or chemotherapy-resistant infection should be referred for further workup for severe infection/disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia purpura (TTP) or hemolytic uremic syndrome (HUS) with investigation of end organ damage including neurologic and renal involvement depending on symptoms.
induced fever and neutropenia should be referred for blood cultures and broad spectrum IV antibiotics. Patients with benign neutropenia of childhood/autoimmune neutropenia of infancy and who have a history of neutrophils that increase to >1000/μL during febrile episodes likely do not require referral to the ED for CBC and antibiotics. Their infections can generally be managed with PO antibiotics.

Scenario Four: New onset leukocytosis. Children with newly diagnosed leukocytosis (>100,000/μL) and peripheral blasts consistent with acute leukemia, especially if neurologic or respiratory symptoms are present, should be emergently evaluated due to concerns for leukostasis. These patients require IV hydration and possible leukopheresis depending on the symptoms. They are also at risk for tumor lysis syndrome and require monitoring of electrolytes, kidney function, phosphorus and uric acid in order to avoid complications.3

CONCLUSION
A review of some of the most common hematologic disorders reveals that general pediatricians can initiate a hematologic workup for disorders such as anemia, bleeding diathesis, leukopenia, neutropenia, and lymphopenopathy before referral to a hematologic specialist. A thorough history and physical examination is crucial in identifying further risk factors for disorders that require more urgent referrals. As discussed, it is critical to recognize cases that are hematologic emergencies so that appropriate evaluation and treatment can be promptly initiated.

REFERENCES
Retained Splinters and Thorns in Pediatric Patients

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ABSTRACT
Injuries involving embedded wood and thorny foreign bodies may present with nonspecific symptoms, diagnostic challenges, and recurrence of symptoms due to inadequate removal. More than one mode of imaging is often required for an accurate diagnosis. Left untreated, splinters and thorns may lead to synovitis, bony "pseudotumors," soft tissue injury, and infection. The only curative therapy is complete removal of the offending foreign body. In children who present with signs of inflammation or infection of soft tissue, bone, or joint, with no response to conventional therapy, the diagnosis of retained vegetative foreign body should be considered.

INTRODUCTION/BACKGROUND
The medical literature concerning wood and thorny foreign body related injuries is limited. The available data shows an increased risk in the pediatric population.1-2 Children often play outside and are likely to fall and have an embedded foreign body. They may not be aware of the injury or may not tell an adult about the incident, which can lead to complications as illustrated by our literature review. It is also challenging to obtain accurate history from children. Adults who work in agriculture and gardening are also at an increased risk of acquiring a vegetative foreign body. Adults have a greater awareness of this type of injury, but failure to remove the foreign body completely may lead to painful symptoms, most commonly in the extremities due to less protection from clothing. This review article attempts to provide a clinical picture of retained wood and thorny foreign bodies and the associated complications, as well as an examination of the current literature for imaging methods to aid an accurate diagnosis.

CLINICAL PRESENTATION
History, Signs, and Symptoms
When a penetrating injury by thorn or wood foreign body occurs, the child or parents are typically aware of the injury and may attempt to remove the foreign body. However, if a retained fragment is left behind or if removal is unsuccessful, symptoms may develop over time.1 Because of the latent period, the patient and parents may not relate the initial penetrating injury to the presenting symptoms.

Patients will often present with monoarticular arthritis, tenosynovitis, or bursitis that is unresponsive to conventional treatment of rest, antibiotics, and anti-inflammatory medications. Many patients will experience mild, transient symptoms that resolve, followed by a latent asymptomatic period for several days, weeks, or even months before symptoms of chronic inflammation occur.1 The patients are usually afebrile, with nonspecific symptoms of synovitis or pain in the affected area if there is bone involvement.1 The most commonly affected joints are knees, ankles, and hands.3,4

Diagnostic Differences
In patients who present with monoarticular arthritis, the differential diagnosis includes juvenile idiopathic arthritis (particularly the fluctuating intensity of symptoms), septic arthritis, traumatic arthritis, reactive arthritis due to another substance or foreign body, and transient synovitis.4 When there is bony involvement, osteomyelitis or bone tumors—benign or malignant, such as Ewing's sarcoma—may be suspected.2,4

Common Plants
The two most commonly reported plants involved in thorn-induced bone and joint injuries are the date palm and the blackthorn bush.5,6 The date palm thorn tip dries quickly and can break into fragments. Splinters from fragments of wood are also common in children playing outside.6 Other agents reported causing synovitis and bone complications include hawthorn, blackthorn, cactus, and rose thorn.4

DIAGNOSIS
Imaging
Identification of retained wood or plant thorn foreign bodies may require more than one mode of imaging.10 X-rays are not ideal for locating radiolucent material such as wood.6,10 One study reported that only 15% of wood foreign bodies were seen on plain radiography.10 However, if the foreign body has migrated to the bone and results in a "pseudotumor" reaction, X-rays will show osteolytic lesions or periosteal reaction.5,10

Some reports suggest efficacy of magnetic resonance imaging (MRI) for localizing foreign bodies in the joint, as well as synovitis in the surrounding tissue. Other reports caution that the results may be ambiguous; injection with gadolinium may help with visualization of the foreign body.1,10 While MRI is a highly sensitive test, it is cumbersome and expensive.2 Additionally, young pediatric patients require sedation in order to remain still during the test.1,10

Computed tomography (CT) scans have also been used to identify foreign bodies in the joint.11 Several cases have been reported in which CT scans detected wooden foreign bodies in extremities and provided accuracy for preoperative planning for deep foreign bodies removal; however, the test is less sensitive for identifying thorns or splinters less than 0.5 cm long.10,12 One case report described use of a multidetector CT scan, which has the advantage of higher resolution and three-dimensional images. This may be useful for preoperative planning, particularly if the thorn is deeply embedded in hypertrophied synovium and difficult to visualize by arthroscopic exploration.13

Ultrasound (US) imaging is an easily accessible mode of imaging that is less expensive than MRI or CT and does not carry the risk of radiation. It can identify foreign bodies in soft tissue, reveal synovium hypertrophy and effusion in the joint, and detect splinters and thorns smaller than 0.5 cm long.13 It is a useful diagnostic tool in the emergency department, and portable handheld US allows for on-site management and more prompt removal, reducing risk of infection and subsequent hospitalizations.11

Intraoperative localization of the foreign body using US assists the physician in visualization of surrounding structures and small fragments and allows for smaller, more precise incisions. One limitation of US is that it is operator dependent and may require an experienced technician to localize the foreign body accurately. Additionally, it may be more difficult to visualize foreign bodies in deeper tissues using US.1

Surgical Exploration
If imaging results are inconclusive and there is a high level of clinical suspicion of penetrating wood or thorn injury, surgical exploration with local anesthesia may be a reasonable option.4 The physician should generally attempt to identify and remove the foreign body, followed by irrigation and debridement of the affected area and drains to prevent infection. Some report good results with the use of a laser to remove small wood fragments.14
exploration may provide accurate diagnosis and is ultimately required for treatment. For injuries involving joints, the literature suggests that arthroscopy provides the best visualization and is associated with lower morbidity than arthroscopy. While arthroscopy is a more technically demanding procedure than arthrotomy, it still allows for effective removal of the foreign body. Several case reports have described visualization and retrieval of vegetative foreign bodies and fragments that were not previously seen on imaging. However, smaller fragments may be more difficult to visualize via arthroscopy, and hyper trophy of the plica may hinder the surgeon’s view.

In the case of patients with potentially life-threatening complications, urgent surgical exploration is especially important. Yanay et al described an 8-year-old boy with an unrecognized wooden foreign body in the lower extremity, who suffered debilitating complications due to necrotizing fasciitis and gangrene as a result of deep tissue infection. Cases such as these emphasize the importance of prompt identification, as there is rapid onset of severe symptoms, and the necessity of early surgical therapy to localize and remove the foreign body.

Analysis of Synovial Fluid and Pathological Findings

In cases of synovitis, analysis of the synovial fluid may aid in diagnosis. There is often a high leukocyte count with a predominance of polymorphonuclear cells. Bacteria is often not seen on direct examination. Centrifugation of the synovial fluid and inspection under polarized light may reveal birefringent, noncrystalline plant debris. Other histological findings may include signs of acute on chronic inflammation with plasma cells and lymphocytes, as well as the presence of foreign-body granulomas in soft tissue with multinucleated giant cells. Barry et al described a 6-year-old boy with a mass in the dorsum of the hand who was misdiagnosed and treated for tuberculosis after histologic findings revealed a giant cell granuloma; eventually, a plant thorn was found in his hand and removal of the foreign body resulted in resolution of his symptoms.

Microbiology

Previously, it was hypothesized that the monoarticular arthritis associated with retained wood and thorns was asptic arthritis, and that the symptoms were due to alkaloid compounds from the plant causing an inflammatory reaction. This may be because cultures can fail to detect presence of microorganisms. Of 15 reported cases with positive cultures, 73% of them revealed Gram-negative rods. The most commonly reported causative organism is Pantoea agglomerans (formerly called Enterobacter agglomerans), found in plants and feces of humans and animals. It is a facultative, anaerobic bacterium with low virulence factor. A slow-growing organism, its indolent nature may lead to late or missed diagnosis, particularly if clinical suspicion is low. P. agglomerans is often resistant to multiple antibiotics, including ampicillin and 1st and 2nd generation cephalosporins, but it is usually sensitive to semisynthetic penicillin, tetracycline, chloramphenicol, amikacin, trimethoprim, and quinolones. Two cases reported Enterobacter cloacae as the causative organism in pediatric patients with penetrating wood and thorn injuries. E. cloacae is a Gram-negative plant pathogen that has rarely been reported in cases of soft tissue infections. Immunocompromised patients are at higher risk for sepsis and bacteremia due to the bacterium’s opportunistic nature.

COMPLICATIONS

Numerous complications due to foreign body can occur due to the failure of removing the foreign body in a timely manner. They are more commonly seen in young patients. Many children will not be aware that they have had penetrating injury or may be resistant to tell their parents in the chance that they were being mischievous. In addition, parents might attempt to remove the foreign body, but a small piece may be left behind. The time for clinical symptoms to appear is variable, and the association with the initial penetrating event may not be made. Table 1 summarizes the complications in the literature.

Infectious complication has been reported in the literature with varying organisms. Infective process is a secondary and not primary cause of the arthritis. A prompt diagnosis may be delayed due to blood or aspirated fluid culture and gram stain testing negative. Rosenfeld et al reported a 3.5-year-old boy with swelling and pain on his left hand. A month prior to presentation he had a Hawthorn embedded in his hand. Prior to the admission, he underwent three debridement procedures and received penicillin. Three blood cultures were negative. Laboratory results indicated an infection. Culture from pus indicated P. agglomerans. After administration of an antibiotic to which the organism is susceptible, the fever subsided. Removal of the thorn resulted in an uneventful recovery. Kratz et al also reported a case in a 14-year-old boy who was diagnosed with septic arthritis following a thorn penetration to his right knee. Although initial cultures from arthrocentesis failed to grow bacteria, the organism was later found to be P. agglomerans, the most commonly reported causative organism. As stated previously, low clinical suspicion may lead to delayed or missed diagnosis due to the slow-growing nature of the organism.

Soft Tissue

Soft tissue wounds due to foreign body can lead to complications ranging from cellulitis to necrotizing fasciitis. Cengiz et al reported a case of a 5-year-old boy who was admitted with localized swelling and erythema in his left forearm with purulent drainage; cultures grew E. cloacae. Patient was unresponsive to initial incision and drainage and antibiotics. After ultrasound and MRI revealed a foreign body, the patient underwent surgical procedure for drainage and removal of foreign body, which resulted in complete recovery without any recurrence. In another case report, Yanay et al described an 8-year-old boy who presented with puncture wound on the posterior aspect of the right thigh when he fell from a tree. Two days after initial irrigation and debridement, the patient experienced swelling, erythema, fever, and pain in his thigh. Surgical exploration revealed hemorrhagic, tense, and necrotic deep fascia, and a piece of wood was retrieved. However, necrosis spread to right anteromedial thigh and right lateral abdominal wall, and the patient experienced altered mental status, seizures, and systemic inflammatory response syndrome. The patient’s overall condition eventually continued to improve, coordination and fine motor skills were significantly impaired bilaterally, and vision was compromised.

Bone and Joint

Wood splinters and thorns can also invade the joint and cause foreign body synovitis, which may mimic an acute septic arthritis. If the initial diagnosis is missed, it may lead to a transient synovitis followed by an asymptomatic period and later, chronic arthritis. The onset of symptoms can vary from hours to years. Cases of foreign body-induced synovitis can be misdiagnosed as posttraumatic synovitis due to a relatively small number of cases in the literature. This is especially true when the foreign body is thought to be completely removed, and the cultures and gram stain are negative. Case reports have been published of patients developing synovitis after incomplete removal of foreign bodies.

Another complication that has been reported in the literature is the formation of bony pseudotumors. A case of a 14-year-old boy who developed a granuloma on his right thigh was reported after a wooden splinter was found during surgical exploration. On histological examination, many foreign body giant cells were present with a surrounding inflammatory reaction. When a foreign body comes into contact with bone tissue, it can induce a local reaction which can show structural changes on radiograph. The foreign body becomes encapsulated with fibrous tissue and forms a granuloma. There may be osteoplastic change or punched out lytic lesions. Radiographic changes may resemble a tumor or a pseudotumor lesion. The periosteal reactions may mimic osteomyelitis, trauma or even malignant tumors such as Ewing’s sarcoma. Curiel et al reported three cases of patients with osteolytic changes on imaging, suggestive of an osteomyelitic sequestrum or an osteoid ostema. Patients underwent surgical intervention, and a palm tree thorn was found to be the underlying cause in all three cases.

Kolzsikovski et al reported a case of a foreign body that caused a reaction that presented as sclerosing or onion-like lamellated peritissis, which can be mistaken for a malignant tumor. Other case reports in the literature support these findings.

LONG-TERM

Long-lasting complications due to chronic inflammation can also occur. Delayed diagnosis may lead to multiple hospitalization, procedures and unnecessarily high cost for patients. Clarke et al reported a case of a 34-year-old male who experienced swelling in the medial aspect of his right leg about eight inches below the patella, with a tender almond-sized mass. A thorn of three quarter of an inch was discovered; the patient recalled that 21 years prior he had fallen on a Hawthorn bush with a
thorn piercing into the knee above the patella. He had had episodes of abscess which regressed and relapsed multiple times; over the years, the thorn migrated over 30 cm in the leg. Once a thorn has penetrated the skin and is not completely removed, it can migrate to other parts in the body.20 Thorns may travel subcutaneously or within a tendon sheath.1 Another theory is that the migration possibly occurs due to repeated muscle contraction from the affected area.20

MANAGEMENT

The ultimate management of a foreign body is removal of the offending agent. It has been established by the literature that it is the only curative treatment.6,11,23 Failure to completely remove the foreign body or fragments may lead to recurrence of symptoms.17 Incision and drainage may be necessary to facilitate removal if abscess is present. The use of direct ultrasound visualization aids in approximating length of foreign body, distance from the skin and the identification of the surrounding structures. The transverse and longitudinal axis view help to determine the position and identify fragments. Antibiotic therapy is also important in the management but should not be used as monotherapy. Culture should be acquired prior to administering antibiotics.7,18 Tetanus status of patient should also be noted and if immunization is not up to date then administration of tetanus toxoid should also be considered.8

CONCLUSION

As demonstrated by our literature review, retained wood splinters and thorns can be challenging to diagnose and manage promptly. In pediatric patients who present with signs of joint, bone or soft tissue infection or inflammation, penetrating vegetative foreign bodies should be considered and ruled out by appropriate imaging methods. This is especially true when symptoms do not respond to conventional methods of treatment. Increased clinical suspicion of wood and thorny foreign bodies can lead to earlier accurate diagnoses, fewer unnecessary treatments and procedures, and ultimately improved care for pediatric patients.

REFERENCES

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