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Diagnosing patients with vasculitides historically has been challenging for emergency department (ED) physicians because of several unique factors associated with these diseases. Often, there is no single etiologic agent identified in vasculitic disease; there may be multi-system involvement or clinical findings limited to only a few organs; and vasculitis may be a primary problem or secondary to a number of other disease processes. In addition, these disease processes tend to evolve over time, contributing to delays in diagnosis and institution of therapy. Although vasculitic diseases generally are uncommon in the pediatric population, early recognition of processes that do occur is important to prevent sequelae. The authors provide a comprehensive review of the most common vasculitic diseases in children, with an emphasis on diagnostic clinical features, key laboratory studies, and appropriate therapy.

—The Editor

Approaching the Child with a Vasculitis: Piecing Together an Accurate Diagnosis

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Introduction

Vasculitis is defined as inflammation and necrosis of blood vessels, resulting in impaired blood flow and generating a wide spectrum of disease. Kussmaul and Meyer described the first patients with vasculitis at the end of the 19th century.[1,2]

Most classification systems for vasculitis are based on the size of the vessel that is predominantly affected in the disease. *(See Table 1.)* Other systems identify vasculitides as primary or secondary processes, or attempt to categorize the disease based on histopathologic findings. *(See Table 2.)* Historically, any system used to classify vasculitis has been fraught with difficulty because of the tremendous overlap in vessel size, clinical findings, and histology among the different processes. The most commonly used classification was developed by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis in 1993.[3]

It is important for physicians to have a consistent approach to patients with suspected vasculitic problems. A thorough evalua-

tion should include any history of recent illness or medication use. Ethnic background is important, and a familial predisposition to rheumatologic disease or autoimmune processes should be documented. Physical exam findings usually are consistent with a multi-system process, although many clinical signs and symptoms of vasculitic diseases are non-specific. Results of laboratory studies usually are not helpful in diagnosis, as the common laboratory abnormalities in vasculitides also are found in many other disease processes. Ultimately, diagnosis of many vasculitic diseases is made by identifying a preponderance of clinical findings or histology consistent with disease on biopsy. Contemplating a broad differential diagnosis in patients with vasculitic symptoms will help to ensure accuracy as well as timely institution of therapy.

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Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is the most common form of systemic vasculitis in children. It is characterized by immune complex deposition, resulting in a necrotizing vasculitis of small vessels. The clinical features of HSP have been described for nearly 200 years, as Hegerden reported a multisystem vascular disease in 1806. In 1837, Schönlein described the association of purpura and joint pain; his student Henoch identified abdominal pain, gastrointestinal bleeding, and renal involvement between 1874 and 1899.[4,5] Today, HSP is known to be a generally benign, self-limiting illness with a tetrad of clinical findings including rash, hematuria, abdominal pain, and arthralgia.

HSP most commonly is diagnosed in children, and traditionally affects patients younger than 10 years of age, with a peak incidence at 5 years. Cases have been identified, however, from age 6 months to 87 years, and the disease increasingly is being diagnosed in adults. HSP affects 10 in 100,000 children, and males are affected twice as often as females. HSP is found in a wide geographic distribution; however, it is uncommon in people of African descent. Sixty percent of cases occur in the autumn months.[4-6]

HSP is an immune complex mediated disease. A hypersensitivity reaction or antigenic mimicry by an infectious organism or drug activates the immune response. A diffuse leukocytoclastic process occurs, resulting in neutrophilic infiltration in and around vessel walls with granular deposits of IgA, C3, and fibrin in arterioles, capillaries, and venules.[4,6-10] The resultant damage to the endothelium provides the basis for the clinical symptoms. IgA is central to the pathology of the disease. IgA1 accounts for 80-90% of serum IgA; secretory IgA is largely composed of IgA2. IgA1 is the type of immunoglobulin found in high circulating levels in patients with HSP. In HSP, there is thought to be a defect in the glycosylation of IgA1 that keeps the immune complexes from being cleared effectively from the body.[5] The role of complement activation in HSP is not well understood; however the levels of C3 and CH50 generally are within normal limits. Finally, although the exact mechanisms remain unclear, there have been many recent studies that attempt to link HSP to other immune-related markers including cytokines, growth factors, adhesion molecules, tumor necrosis factor, interleukin 1, interleukin 6, leukotrienes, and free oxygen radicals.[4] Future research is necessary to define the role, if any, of these makers in the etiology of HSP.

Skin Manifestations. Rash is the most common presenting symptom of HSP. The rash is variable but usually begins with pink or red maculopapules, which coalesce and become purpuric. The lesions often are palpable and rarely are pruritic. After several days, the rash begins to fade, leaving a brownish discoloration that may persist for several weeks.[11] Less commonly, patients have petechiae, diffuse erythema, urticaria, target lesions, vesicles, and desquamation.[4,6,11] Facial edema is common in children younger than 1 year, while 60% of adults with HSP will have bullous or necrotic skin lesions associated with

Table 1. Primary Vasculitic Processes

LARGE VESSEL VASCULITIS
- Takayasu arteritis
- Giant cell (temporal) arteritis
- Isolated angiitis of the central nervous system

MEDIUM VESSEL VASCULITIS
- Kawasaki syndrome
- Polyarteritis nodosa

SMALL VESSEL VASCULITIS
- Henoch-Schönlein purpura
- Wegener granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome
- Essential cryoglobulinemic vasculitis
- Cutaneous leukocytoclastic angiitis

MISCELLANEOUS CONDITIONS
- Bechet disease
- Buerger disease
- Cogan syndrome

Table 2. Secondary Vasculitic Processes

- Infection-related vasculitis
- Drug-hypersensitivity vasculitis
- Malignancy-related vasculitis
- Post-organ transplant vasculitis
- Vasculitis secondary to connective tissue disease
- Hypocomplementemic urticarial vasculitis
- Pseudovasculitis (myxoma, endocarditis)

their disease.[5] Classically, lesions are found on the extensor surfaces of the lower extremities and buttocks; however, the trunk, head, neck, and upper extremities may be involved, as well.[4] In 10% of patients, there is no lower extremity involvement.[10] The rash is accentuated in areas of pressure, including sock and waist lines.[6] Purpuric lesions tend to resolve more quickly with bedrest; new crops of purpura have been described after heavy activity. Finally, edema of the hands, feet, and face may be an early symptom before the more classic rash appears.

Increasingly, patients with a paucity of skin findings are being diagnosed with HSP. The absence of rash often delays the diagnosis and predisposes patients to extensive laboratory and radiographic evaluations. Biopsy may be helpful in these atypical cases; however, it rarely is needed in pediatric patients. In adults, cutaneous vasculitis has a much broader differential diagnosis and biopsy may be useful when the diagnosis of HSP is uncertain. When performed, biopsy reveals the characteristic IgA complex deposition in dermal vessels.[5,12]

Renal Disease. Renal disease is common in HSP and probably is the most worrisome complication because of the potential for long-term sequelae. The overall prognosis for HSP is largely dependent on the extent of renal disease.[13,14] Fifty percent of older children and 25% of children younger than 2 years will develop renal disease with HSP.[6] Most children have hematuria (40-50%) or low-grade proteinuria (25%).[5,9,15] It is uncommon for patients to have proteinuria without hematuria. Most patients will have evidence of renal disease in the acute phase of HSP; however, 10% of children have a delayed onset of nephritis, with symptoms beginning more than four weeks after the first appearance of their illness.[5] It is rare for symptoms of nephritis to precede the onset of rash.[5] A small minority of patients will have massive proteinuria during the acute phase of HSP. These patients often have rapidly progressive renal deterioration, with 12-19% progressing to end-stage renal disease.[8,15]

The spectrum of renal disease on biopsy includes minimal change, focal or diffuse mesangial proliferation, and crescentic glomerulonephritis.[5] The histopathology is indistinguishable from that in IgA nephropathy (Berger disease).[6] Severity of renal disease is closely associated with biopsy results, particularly the identification of crescent formation in more than 50% of glomeruli, which is a poor prognostic indicator.[5,16] Biopsy is recommended for patients with hypertension, nephrotic syndrome, or significant renal dysfunction.

Long-term follow-up is necessary for any patient with renal disease from HSP. Progressive renal dysfunction may be identified several years after the acute phase of the illness.[5,6,16] Fortunately, the overall long-term prognosis is excellent. While 30-50% of patients will have urinary abnormalities in long-term follow-up, only 10-20% have evidence of renal insufficiency, and only 1% of patients progress to end-stage renal disease.[5,6,17] In a recent study, prognostic factors for long-term renal disease were identified. Renal dysfunction or nephrotic syndrome at disease onset and the finding of crescentic glomerulonephritis on biopsy are poor prognostic indicators. Furthermore, development of bloody stools and persistence of rash also are associated with renal dysfunction in children; however, this association is not found in adults.[7]

Abdominal Pathology. Abdominal pathology is common with HSP. Approximately two-thirds of patients will experience some type of gastrointestinal (GI) symptoms associated with their disease.[9,13] As with other systems involved, immune complex deposition in the abdominal vasculature leads to hemorrhage and edema and is the basis for the physical findings. Biopsy specimens reveal histologic findings similar to those from cutaneous samples, including mural hematomas, edema, erosions, ulcers, and thrombosis of small vessels.[13]

The most common manifestation of abdominal pathology is abdominal pain, which can be quite severe and even mimic symptoms of an acute abdomen.[6] Younger patients with HSP are less likely to have significant abdominal pain. The spectrum of abdominal pathology is broad and is described in Table 3. Most patients with abdominal pain and other GI-related processes have symptoms that persist for several days but are ultimately self-limiting and do not predispose to long-term sequelae. As

Table 3. Abdominal Pathology in HSP

HISTORY AND PHYSICAL EXAM

- Abdominal pain
- Nausea
- Vomiting or hematemesis
- Diarrhea, melena or bright red blood per rectum
- Abdominal distention
- Diffuse tenderness to palpation without guarding
- Hepatomegaly or splenomegaly

ABDOMINAL DISEASE IN ACUTE HSP

- Intussusception
- GI hemorrhage
- Pancreatitis
- Necrotizing vasculitis of the gallbladder
- Hydrops of the gallbladder
- Malabsorption
- Steatorrhea
- Paralytic ileus or functional bowel obstruction
- Bowel ischemia
- Bowel perforation
- Hemorrhage of abdominal wall musculature

LATE ABDOMINAL DISEASE (A RESULT OF ISCHEMIA AND NECROSIS)

- Stricture formation
- Fistula formation
- Bowel obstruction

many as one-third of patients with HSP present with abdominal complaints before the onset of rash, creating a diagnostic challenge.[4,18] Not surprisingly, patients who initially present with abdominal symptoms are more likely to undergo extensive laboratory and radiographic testing or even laparotomy before the diagnosis of HSP is made.[18]

Laboratory testing for abdominal symptoms with HSP generally is not helpful. Laboratory studies may be ordered to help exclude other diagnoses; however, because most tests are nonspecific, the results often do not add to the decision-making process. The role of abdominal ultrasound (US) in HSP is increasing. US may demonstrate increased mural thickness or evidence of hematoma in the patient with abdominal pain, and particularly is useful in the diagnosis of intussusception.

Intussusception is the most common surgical complication of HSP and has an overall incidence of 3.5%. The average age of patients with HSP-associated intussusception is 6 years, which is much older than the traditional age group affected. Furthermore, 58% of intussusceptions associated with HSP are ileo-ileal in nature; 80% of intussusceptions in patients without HSP occur in the ileo-cecal location.[13] Mural edema and hemorrhage in the small bowel act as a lead point for intussusception. Air contrast enema has become the standard for diagnosis and treatment of ileo-colic intussusception; however, it is less useful and even potentially contraindicated in patients with ileo-ileal disease who have a competent ileo-cecal valve. US particularly is helpful for identification of small bowel intussusception, and some authors even have suggested a conservative approach for treatment, recognizing that in many cases the process may resolve by itself. Serial abdominal exams and, if needed, repeated US examinations are helpful for following the progression of intussusception.

Other. Although the skin, renal, and GI symptoms are the most common in HSP, other body systems may be involved. Joint symptoms occur in 70-80% of cases of HSP, and as with abdominal pain, may precede the onset of rash.[6,9] Ankle and knee joints most commonly are affected, with edema, warmth, and tenderness prevalent. Although true non-migratory arthritis with synovial inflammation occurs, most joint symptoms are likely from extensive periarticular soft tissue edema. Regardless of the etiology, joint symptoms are transient and self-limiting. Central nervous system (CNS) symptoms are common and probably underreported because of the non-specific nature of many of the clinical findings. CNS vasculitis may cause headache, irritability, behavior changes, altered mental status, seizures, peripheral neuropathy, cerebral hemorrhage with focal deficits or hemiparesis, and ataxia.[6,12,19] Less commonly, CNS symptoms may be secondary to corticosteroid use or metabolic derangements from GI disease. Fortunately, patients with neurologic manifestations of HSP have a favorable outcome, most symptoms are self-limiting and resolve within a few days.[12] MRI may be useful in the diagnosis of more severe HSP-related neurologic disease to demonstrate the diffuse vasculitis and differentiate from other intracerebral processes. Genitourinary sequelae are common in boys with HSP. Vasculitis and hemorrhage of the epididymis or spermatic cord causes pain and swelling of the scrotum, which clinically may resemble an acute scrotum or testicular torsion. Orchitis and priapism also have been described.[5,6,9,19] Finally, other less common but potentially serious complications of HSP include myocarditis, myocardial infarction, pleural effusion, and pulmonary hemorrhage.[6,20]

Diagnosis. There is no single laboratory assay available for the diagnosis of HSP. There are a few characteristic laboratory abnormalities, although in general, the findings of lab tests are non-specific.[18,21] Of special note, patients with HSP are known to have coagulation abnormalities as a result of activation secondary to endothelial damage.[10] There is an increased concentration of fibrin split products and D-dimer assays, a decrease in fibrinogen and a decrease in the concentration of factor XIII.[10] Prothrombin time (PT) and partial thromboplastin time (PTT) usually are normal.[5] Despite the changes in laboratory findings, clinical symptoms suggestive of disseminated intravascular coagulation (DIC) are rare. Coagulation studies may have some role in understanding the prognosis of HSP; D-dimer levels correlate well with disease activity and might be used to predict recurrence.[10] Furthermore, decreased levels of factor XIII have been associated with increased abdominal pain and GI bleeding.[5]

Thirty-eight percent of patients have elevated levels of serum IgA; however, IgM, IgG, and complement levels usually are nor-

mal.[5] Electrolyte abnormalities and stool guaiac may be affected by GI disturbances; the urinalysis, blood urea nitrogen (BUN), and creatinine (CR) levels may be abnormal secondary to nephritis.[6] Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) generally are elevated, as may be the total white blood cell (WBC) count, often with a peripheral eosinophilia.[6] Platelet counts may be normal or elevated. Anemia is common in HSP and may be secondary to GI blood loss.[22] A recent Chinese study describes a possible link between elevated WBC, platelets, and CRP levels with an increased risk for GI bleeding.[21] Further studies are needed to define any relationship between laboratory findings and clinical symptoms in HSP.

HSP Recurrence. Up to one-half of patients with HSP will experience recurrence of their disease.[6,13] Recurrence is defined as reappearance of symptoms following resolution for at least two weeks.[5] Recurrence of HSP is associated with symptoms similar to those seen in the acute phase; however, recurrences usually are shorter in duration and milder in nature than the initial disease. Rash and abdominal pain are common in recurrent disease. Patients with nephritis are more likely than others to experience recurrences of HSP, although the initial severity of rash and abdominal pain, patient age, and the serum concentration of IgA have not been identified as predisposing factors.[5] The average onset of recurrence is two months after the initial resolution of symptoms and the mean number of recurrences among all patients is 1.8.[5] Successive episodes of purpura and abdominal pain are uncommon beyond the third month after diagnosis; however a small percentage of patients experience recurrence of their disease several months—or even years—after its initial onset.[4]

Treatment. There is no specific treatment for HSP, and therapy generally is not recommended in uncomplicated cases. Supportive care is the mainstay of treatment, with specific therapy directed at certain clinical manifestations.[6] There are very few double-blinded, placebo-controlled studies for any medication used in the treatment of HSP. Most current recommendations for therapy are based on retrospective studies and case reports.[23] Non-steroidal anti-inflammatory medications (NSAIDS) may be helpful for joint symptoms but should be used with care because of their effects on renal function and abdominal pain. Similarly, the antiplatelet effect of salicylates may worsen GI bleeding.[5]

The role of corticosteroids in HSP is controversial. Glucocorticoids have both anti-inflammatory and immunosuppressive activity, which makes them a logical choice for a vasculitic process. The results of many retrospective and anecdotal studies using steroids, however, are inconclusive.[23,24] Corticosteroids have no effect on the presence of rash, duration of illness, or on the prevention of recurrence of disease.[5,9] There is some evidence to suggest a shorter duration of abdominal pain, improvement in arthritic symptoms, and early resolution of CNS symptoms with steroids used in low doses.[9,12,14,18] Typical dosing is 1-2 mg/kg/day for one week.[23]

Corticosteroids commonly are used for nephritis, although there are few data to support any benefit. Renal dysfunction associated with HSP has been shown to be resistant to low-dose corticosteroids and immunosuppressive agents. Newer strategies use high-dose IV steroids with multidrug combinations, and IV steroid pulse therapy. For patients with severe crescentic glomerulonephritis, IV methylprednisolone plus oral steroids or urokinase may be helpful in preventing progression of disease.[5,8,15] Finally, there are no data to suggest that renal dysfunction associated with HSP can be prevented by beginning steroid therapy at the onset of disease.[5,14]

New treatment strategies for HSP are being studied in an attempt to decrease the use of corticosteroids and target the specific immune mechanisms associated with HSP. Investigational drugs include intravenous immunoglobulin (IVIG), cyclophosphamide, azathioprine, cyclosporine, dipyridamole, and dapsone, which may have a beneficial effect on rash by inhibiting the IgA-neutrophil interaction.[4-6,17,23,25] Heparin has been used to treat hypercoagulability associated with HSP; however, it has not been shown to alter the disease course and is not routinely recommended.[4,10] Factor XIII replacement has been studied for abdominal pain and GI bleeding.[5] Finally, plasma exchange to remove IgA complexes may be helpful in those with early onset renal insufficiency, but is contraindicated in late disease.[8]

The etiology of HSP is unknown, although studies have proposed links to the disease with a multitude of agents, most commonly infectious organisms and drugs. An infectious etiology seems likely, as HSP is preceded by URI symptoms in up to one-third of patients, although a specific infectious agent rarely is identified.[26,27] Infectious diseases that have been postulated to have a role in HSP include Group A beta-hemolytic Streptococcus (GABHS), hepatitis B, HIV, adenovirus, Epstein Barr virus (EBV), parvovirus, herpes simplex virus, Mycoplasma, Campylobacter, *Helicobactor pylori*, and *Toxocara canis*.[5,9,27,28] The strongest evidence for an infectious cause is given to GABHS, which may be an immunologic trigger for HSP.[20,29] Several reports have identified the co-occurrence of HSP with acute GABHS infection, as well as an increased incidence of rheumatic fever.[20] Positive throat cultures have been identified in 10-30% of patients with HSP, and positive antistreptolysin-O (ASO) titers in 20-50%.[5] Although no physiologic link is understood, some authors recommend testing for GABHS in any patient with acute HSP.[5,20] Furthermore, there have been anecdotal reports of HSP presenting after antibiotic therapy with flouroquinolones[30] and following vaccination for typhoid, measles, cholera, and yellow fever.[28] Although no clear association is known, a recent study by Pertuiset et al described a relationship between the diagnosis of HSP in adults and the presence of solid tumors, including tumors of the breast, lung, prostate, kidney, and GI tract.[31] Finally, a familial tendency to HSP has been reported; however, it currently is believed that most cases of HSP are sporadic in nature.

The diagnosis of any vasculitic disease has been difficult historically because of the overlap of clinical signs and symptoms between diseases, as well as changes in nomenclature over the

Table 4. Diagnostic Criteria for Henoch-Schönlein Purpura

1990 AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA

(Must have 2 of 4 criteria for diagnosis)

- Palpable purpura
- Age < 20 at onset
- GI bleeding
- Extravascular or perivascular granulocytes on biopsy

1992 DIAGNOSTIC CRITERIA (MICHAEL, ET AL)

(Must have 3 of 6 criteria for diagnosis)

- Palpable purpura
- Age < 20 at onset
- Bowel angina
- GI bleeding
- Hematuria
- No current medication use at disease onset

Table 5. Diagnostic Criteria for Kawasaki Syndrome*

PRIMARY CRITERIA

- Fever 38-41° C for five days or longer

SECONDARY CRITERIA

- **Mucous membrane changes**
  - Cracked, erythematous lips
  - Strawberry tongue
  - Erythema of the oropharynx
- **Conjunctivitis**
  - Bulbar injection with no exudate
- **Rash**
  - Polymorphous (morbiliform, maculopapular, scarlitiniform), erythematous
- **Extremity changes**
  - Induration of the hands and/or feet
  - Peripheral edema
  - Erythema of the palms and soles
  - Late desquamation of digits, palms, and/or soles
- **Lymphadenopathy**
  - Unilateral cervical lymphadenopathy greater than or equal to 1.5 cm in diameter

*For classic diagnosis, patients must meet primary criteria plus have 4 out of 5 secondary criteria.

years. In 1990, the American College of Rheumatology (ACR) created a set of diagnostic criteria for HSP.[22,32,33] *(See Table 4.)* The ACR criteria lack the identification of IgA deposition in biopsy results, which is known to be a hallmark of the disease and helps to distinguish HSP from other processes. Previously, HSP has been referred to as allergic vasculitis, leukocytoclastic vasculitis, rheumatoid purpura, or anaphylactoid purpura. Osler studied the role of anaphylaxis in HSP, although it currently is not believed to be involved in the pathophysiology of the disease.[4,5] Furthermore, HSP was synonymous with hypersensitivity vasculitis (HSV), although the two now are recognized as separate entities. In 1992, Michael et al developed clinical criteria to help delineate HSP from HSV.[32] IgA nephropathy and HSP often are discussed as being part of the same entity because they share the common histologic finding of IgA deposition in glomerular vessels. Patients with IgA nephropathy, however, lack the extra-renal symptoms characteristic in HSP. A genetic predisposition to HSP and IgA nephropathy has been described in some families; however, the majority of cases for both processes likely are sporadic.[5]

Several authors have noted that younger children seem to have a milder disease process with HSP. In particular, children younger than 2 years are likely to have a benign course, and also have findings that are somewhat atypical when compared to those in older children. It has been suggested that a separate entity known as acute hemorrhagic edema of infancy (AHEI), or Finklestein disease, is more common in younger patients. AHEI is clinically similar to HSP, with a few important distinctions. Patients with AHEI are younger than 2 years of age; have a rash that appears primarily on the face, scalp, and neck; and lack severe renal or GI disease. Histologically, IgA complex deposition is found in only 30% of patients with AHEI, whereas it is a universal finding in HSP. Overall, patients with AHEI have a better prognosis than HSP because of the paucity of renal disease.[5,11]

In addition to distinguishing HSP from other vasculitic diseases, there are several further conditions that should be included in the differential diagnosis, especially when the presentation of clinical findings is atypical. Bacterial infections, including bacteremia and sepsis, are among the most important, particularly infection with *Neisseria meningitides*, as the skin manifestations may be similar to those in HSP. Although clinicians should have a high level of suspicion for Neisseria infections, patients with *N. meningitides* and purpura fulminans usually are critically ill at the time of diagnosis. Other considerations in the differential for HSP include endocarditis with septic emboli, Rocky Mountain spotted fever and other tick-borne illnesses, viral infections, rheumatoid arthritis, systemic lupus erythematosis, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), drug reactions, Stevens-Johnson syndrome, and child abuse.[5,6]

Kawasaki Syndrome

Kawasaki syndrome (KS) is an acute, febrile, systemic vasculitis of childhood. In 1967, Dr. Tomisaku Kawasaki reported 50 pediatric patients with a newly identified febrile illness.[34] The disease was independently identified in the early 1970s at the University of Hawaii.[35] KS is the second most common vasculitic illness in children. The etiology of the disease is not known but is suspected to be infectious in nature. KS has been identified in multiple geographic regions and among patients of different ethnic origins; however, it is most common in Japan and in Japanese children living abroad. Korean children also have a high rate of disease.[36] There are approximately 3000-3500

cases diagnosed annually in the United States.[37] The highest incidence of KS is in the winter and spring months; however, seasonal patterns vary in different geographical regions.[35] Epidemics may occur, but also vary by region. Ninety percent of KS cases reported involve children younger than 8 years; the majority of cases (80%) occur in children younger than 5 years.[37,38] The peak age of incidence is 18-24 months of age. There is a predilection for male patients; males develop KS 1.5 times more often than females.[37] The incubation period for KS is unknown, and there is no evidence to support any direct transmission from person to person.[37]

Diagnosis. The diagnosis of KS relies on the identification of certain clinical signs and symptoms. *(See Table 5.)* The criteria used for diagnosis are the same in all age groups. There are numerous other clinical findings associated with KS that are reflective of the underlying process, a vasculitis of medium-size arteries. *(See Table 6.)* There is a predilection for involvement of the coronary arteries in KS, and thus the most worrisome clinical findings are associated with cardiac disease. There is no single laboratory assay available to distinguish KS from other febrile illnesses. There are a multitude of laboratory findings that, while not diagnostic, are characteristic of KS. *(See Table 7.)* If untreated, KS is self-limited and usually resolves in 2-3 months.[39] Without treatment, the mean duration of fever is 12 days.[37] The subacute phase may last for 2-3 weeks with symptoms of irritability, desquamation, and anorexia prominent. The recurrence rate of disease months to years later is low.[37] The mortality rate in the United States is less than 0.05%, with the majority of deaths occurring in the first six weeks of illness, and resulting from myocardial infarction or coronary artery rupture.[40] Mortality is highest in children older than 10 years of age.[41]

KS is the most common cause of acquired heart disease in children in the United States.[42] While other types of cardiac disease may be present in the acute phase, the presence of coronary artery disease is the greatest concern for future prognosis. Coronary artery aneurysms develop in 15-25% of untreated patients.[43] The spectrum of disease in the coronary arteries ranges from ectasia to aneurysm formation to giant aneurysm formation.[44] The peak time for development of coronary aneurysms is 2-4 weeks after the onset of fever. Aneurysms rarely form before the 10th day of illness; however, early echocardiography may reveal a perivascular brightness that is an indication of arteritis.[39] Development of new aneurysms more than six weeks after diagnosis is rare. Risk factors for development of coronary aneurysms include age younger than 6 months, male gender, fever for more than 10 days, low serum albumin, low hemoglobin concentration, thrombocytosis, and any signs or symptoms of cardiac dysfunction during the acute phase of illness.[37,42] Of all coronary artery lesions, 50% will regress within five years after the onset of disease. Most small aneurysms (3-4 mm) will regress to normal size in 1-2 years.[45] Giant aneurysms are unlikely to resolve.[36] The site of any previous aneurysm may be associated with persistent abnormal vascular wall morphology and predispose patients to the development of stenosis and early atherosclerotic disease, increasing the risk for coronary thrombosis and myocardial infarction.[37,46,47] The current recommendation from the American Heart Association for initial and follow-up evaluation of KS is echocardiography at presentation and again at 6-8 weeks, and at 6-12 months after diagnosis for patients with no evidence of coronary disease.[48] Although some authors recommend lifelong follow up for any patient with a history of KS,[49] this may not be necessary for patients with normal cardiac evaluations 6-12 months after disease onset.[50-52]

Differential Diagnosis. There are a number of other diseases that must be considered in the differential diagnosis for KS. There are several infectious illnesses that mimic KS, including sepsis and occult bacterial infections, scarlet fever, mycoplasma, adenovirus, parvovirus, cytomegalovirus, EBV, and enterovirus infections. Other processes to be considered include Stevens-Johnson syndrome, toxic shock syndrome, Staphylococcal scalded skin syndrome, and drug reactions.[36,39,42] Although recurrent KS is seen in a small percent of patients, for those in whom symptoms persist beyond the acute phase or recur weeks to months in the future the differential diagnosis should include diseases such as systemic onset juvenile rheumatoid arthritis, polyarteritis nodosa (PAN), malignancy (especially lymphoma), and other autoimmune disorders.[36]

Incomplete KS. There is a growing population of patients who present with certain characteristics of KS but who do not

Table 6. Clinical Findings Associated with Kawasaki Syndrome*

CENTRAL NERVOUS SYSTEM	Irritability, lethargy, aseptic meningitis, headache
CARDIAC	Rhythm disturbances, congestive heart failure, pericarditis, pericardial effusion, coronary artery disease
GASTROINTESTINAL	Abdominal pain, diarrhea, vomiting, abdominal distention, hepatomegaly, hematemesis, liver dysfunction, gall bladder hydrops, jaundice
PULMONARY	Pneumonitis, lobar consolidation
EYE	Anterior uveitis
GENITOURINARY	Urethritis
JOINT	Arthralgias, arthritis

*Clinical findings not part of the classic diagnostic criteria for Kawasaki Syndrome

Table 7. Laboratory Evaluation in Kawasaki Syndrome

- Leukocytosis
- Elevated percentage of bands/immature forms in WBC differential
- Anemia
- Thrombocytosis (generally after the 1st week of illness)
- Elevated CRP, ESR
- Sterile pyuria
- Aseptic meningitis
- Elevated liver enzyme tests, ALT, LDH
- Hypoalbuminemia

Key:
WBC = white blood cell count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ALT = alanine aminotransferase; LDH = lactic dehydrogenase

meet the criteria for diagnosis of classic disease. The term "incomplete KS" is used to represent this group. Incomplete KS may be synonymous with the phrase "atypical KS" in the literature; however, incomplete is a preferable term because, although patients in this group may lack certain clinical findings consistent with KS, they do not present with any features not typically observed in classic disease.[39] Incomplete disease represents approximately 7-10% of all cases of KS.[42] Incomplete KS is more common in children younger than 1 year or older than 8 years of age at presentation.[39] While the disease is uncommon in children younger than 3 months of age, the neonatal age group has a very high incidence of incomplete disease.[43] Clinical features may be subtle with incomplete KS; however, fever and rash still are the most common presenting symptoms.[42] Laboratory findings are similar in classic and incomplete disease. Although not diagnostic, the characteristic laboratory changes may be helpful in raising suspicion for diagnosis in incomplete cases. Patients with incomplete disease and those outside the normal age range for the disease are more likely to undergo extensive laboratory (and even surgical) workup before the diagnosis is made.[39] Incomplete KS is particularly worrisome because patients may have a delay in their ultimate diagnosis. The benefit of early intervention for KS clearly has been established; any delay in the diagnosis and treatment predisposes patients to the development of coronary artery disease. The use of IVIG has been shown to be as effective in preventing coronary disease in incomplete disease as in classic KS if therapy is started within the first 10 days of illness.[39] It is important to understand the full spectrum of disease in KS to ensure timely diagnosis and therapeutic intervention.

Treatment. Treatment for KS relies on supportive care along with the use of IVIG and aspirin therapy. When the disease first was identified, aspirin alone was used for treatment. Currently, aspirin is used in the acute phase for its anti-inflammatory and antipyretic effects and in the convalescent phase for inhibition of platelet aggregation.[43] Multiple dosing strategies for aspirin have been studied. Current recommendations are to use aspirin in its anti-inflammatory dose of 80 mg/kg/day divided QID in the acute phase. Once the fever is controlled for several days, the dose is decreased to 3-5 mg/kg/day in one daily dose for platelet inhibition. This dose is maintained for 6-8 weeks until the platelet count and erythrocyte sedimentation rate (ESR) are normalized. Although aspirin routinely is used as adjunctive therapy, there is no evidence to support that aspirin alone is beneficial in KS. Serious side effects from the use of aspirin are rare.

In the early 1980s, the use of IVIG was added to the treatment regimen for KS. Several studies have demonstrated that IVIG reduces the incidence of coronary artery disease and decreases the duration of fever.[43,53] While several studies have tried to define a beneficial dosing regimen for IVIG,[54-57] the prevalence of cardiac disease appears to be inversely related to the total dose given.[58] The current recommendation for IVIG is 2 gm/kg given over 6-12 hours.[37] There are no data to suggest that any particular preparation of IVIG is superior to another.[36] Twenty percent to 30% of children will have persistent fever (more than three days) after IVIG.[40,44] The optimal management of patients who remain febrile after one dose of IVIG is not yet clearly established; however, there are growing data to suggest that patients who remain febrile 24 hours after the first dose should be retreated. Retreatment has been shown to lessen the incidence of coronary disease.[44] A few studies have linked very early treatment with IVIG (before days 3-5 of illness) to an increased incidence of persistent fever or disease recrudescence.[59,60] The latest research suggests that treatment before day five with IVIG may indeed be linked to persistent fever but is not associated with any increased risk of coronary disease or other adverse outcome if patients are retreated with IVIG promptly.[46,61] Finally, as a note to primary caregivers, treatment with IVIG should preclude the dosing of any live viral vaccines for three months.[36]

The use of corticosteroids is controversial in KS. This is surprising, because corticosteroids figure prominently into the treatment of other vasculitic conditions. An early study by Kato et al suggested that cardiac disease is more common in those treated with prednisolone compared to aspirin alone.[62] New studies compare the use of corticosteroids with IVIG. Okada et al suggests that steroids help curtail symptoms by reducing cytokine levels in patients with KS.[63] Sundel et al reports a faster resolution of fever and improvement in markers of inflammation, as well as shorter hospitalization, with the use of IV methylprednisolone in conjunction with traditional therapy.[64] Steroids may prove to be useful, particularly in those who are resistant to IVIG or who refuse IVIG for religious reasons.

In patients diagnosed with coronary artery disease, the use of low-dose aspirin is continued indefinitely for prevention of coronary thrombosis. Warfarin therapy usually is recommended for patients with giant aneurysms.[36] Dipyridamole (4 mg/kg/day divided TID) is given to some patients with coronary disease and may be synergistic with aspirin for its antiplatelet effect,

although there is no evidence to support its use.[37] Finally, the use of glycoprotein IIb/IIIa receptor blockade agents is being studied and may be helpful in the future.[65]

Although the exact cause of KS remains unclear, current research is focused on certain immunologic reactions that may be the basis for the disease. Acute KS is associated with an overactivation of several immunologic parameters resulting in a deficiency of circulating $CD8^+$ suppressor/cytotoxic T cells and an abundance of circulating B cells spontaneously producing immunoglobulins.[35] There is data to suggest that this overactivity of the immune system may selectively target the vascular endothelium. A recent study by Wang et al identifies CD40 Ligand as a transmembrane protein structurally related to tumor necrosis factor alpha. This protein, identified on $CD4^+$ T cells, has been associated with other types of vasculitic processes and may affect the modulation of the immune response. The use of IVIG down-regulates the expression of CD40L.[47] Finally, although no specific genetic predisposition to KS is recognized, a recent study by Uehara et al reports that when compared to the general population, a higher incidence of KS is noted in parents whose children are diagnosed with the disease.[66]

As KS has been identified relatively recently, long-term complications of the disease beyond cardiac pathology are not yet fully understood. A recent study by Baker et al attempted to identify any impact that KS may have on the general health status of children. Children with normal coronary artery exams, regressed aneurysms, and those with small to moderate-sized aneurysms were found to have similar physical and psychosocial status compared to children previously unaffected by KS. Children with giant coronary aneurysms were found to have overall worse physical health status than other populations of children. Overall, the parents of children previously diagnosed with KS reported lower general health perceptions about their children. This raises the possibility that the diagnosis of a serious illness of childhood not yet fully understood may cause parents to be conservative regarding health-related issues in their children in the future. The study also identified a greater frequency of comorbid conditions, including chronic allergies, sinus problems, and eczema in children previously diagnosed with KS.[67]

Miscellaneous Vasculitic Conditions

Takayasu Arteritis. Takayasu arteritis (TA) is a chronic, inflammatory vasculitis that primarily affects large vessels including the aorta and its major branches. TA is characterized by a granulomatous inflammation of histiocytes, lymphocytes, and plasma cells that begins in the adventitia and progresses to the intimal lining of vessels.[1] Ultimately, necrosis of vessel walls leads to stenosis and aneurysm formation. As with many other vasculitic diseases, the etiology of TA is unknown, although it has been linked to several infectious and rheumatologic processes, including mycobacterium, Streptococcus, rheumatic fever, and rheumatoid arthritis.[2,68] The onset of TA usually occurs later in childhood; the peak age of incidence is 14 years. Eighty percent of patients are female.[2,69]

Disease progression with TA generally is slow, and the insidious nature of symptoms may make the diagnosis challenging.[70] Children with TA have clinical symptoms similar to those found in adults with the disease. Systemic symptoms including fever, night sweats, weight loss, and malaise, however, are more common in younger patients.[2] Clinically, the spectrum of findings in TA is wide, ranging from headache, unequal blood pressure measurements, and bruits to congestive heart failure and stroke.[2,68] Treatment of TA primarily involves the use of high-dose steroids; however, the adverse effect of hypertension with steroid use is worrisome. Newer regimens use immunosuppressive agents such as methotrexate and cyclophosphamide.[2,69] Antihypertensive agents also are effective, as the finding of hypertension ultimately is the factor that is most closely associated with disease prognosis.[71]

If TA is suspected, complete arteriographic evaluation of the aorta and its branches traditionally has been the standard of care used to identify the extent of disease. The use of MRI recently has become invaluable as a non-invasive way to diagnose TA and follow disease progression. MRI can identify thickened vessel walls, mural edema, and increased wall vascularity.[68] Overall, if identified and treated early, TA has a good prognosis. Young children with TA are more likely to have an aggressive course, however, and the five-year mortality may be as high as 35-40%.[68]

Polyarteritis Nodosa. PAN was one of the first vasculitic conditions recognized in humans. It is a multi-system, necrotizing vasculitis of small and medium-size arteries in which neutrophilic deposition leads to extensive destruction of vessel walls.[72] Historically, other vasculitic processes, including microscopic polyangiitis (MP), Wegener granulomatosis (WG), and Churg-Strauss syndrome (CSS), were thought to be variants of PAN, although they now are recognized as separate entities. PAN shares many clinical and histiologic features with KS. There is a more disseminated vascular involvement in PAN, however, as the vessel walls may be obliterated by necrosis, leading to more aggressive and diffuse symptoms.[70]

Clinical findings associated with PAN involve several body systems. Skin findings are among the most common symptoms in children, including livedo reticularis, tender nodules, and purpura.[2,70,73] Other findings include renal dysfunction, GI symptoms, and systemic complaints such as fever, malaise, and irritability. Ozen et al proposed a set of clinical criteria to help with the diagnosis of PAN; identifying involvement in several body systems is necessary with this scheme.[73] Ultimately, the diagnosis of PAN is made by recognizing vascular abnormalities with angiography, or finding characteristic results on biopsy specimens.[70,73]

Treatment of PAN is associated with a marked increase in survival, so early recognition of the disease is important. Corticosteroids are the primary therapy, with cyclophosphamide, mycophenelate mofetil, IVIG, and TNF inhibitors playing a growing role. Plasmapheresis has been used for patients with

life-threatening emergencies.[2] Most long-term sequelae from PAN are associated with renal disease and the presence of seizures.[70,73]

WG, CSS, and MP are vasculitic syndromes characterized by antineutrophil cytoplasm antibodies (ANCA)-positive, pauci-immune involvement of small vessels. ANCA are increasingly being implicated as important in several vasculitic disorders. Although the mechanism of ANCA in vasculitis is not completely understood, neutrophil activation with ANCA is a predominant factor.

WG is a necrotizing vasculitis that primarily affects the respiratory tract and kidneys. Symptoms involving the upper respiratory tract—including sinusitis, nasal mucosal ulceration, and saddle nose deformity—are important early clues to the diagnosis and may be overlooked.[70] Systemic symptoms—including fever, malaise, and weight loss—are common in children, as is presentation with pulmonary hemorrhage. Disease relapse is common.[69] WG is rare in children and is far more likely to be diagnosed in males than in females. Treatment is similar to that of other vasculitic conditions, including corticosteroids and immunosuppressive agents. Despite appropriate therapy, WG is an extremely aggressive disease with significant morbidity and mortality.

MP is another ANCA-positive small vessel vasculitis. It is associated primarily with pulmonary and renal disease, although purpura and neurologic manifestations are not uncommon.[12] Clinically, the disease is most similar to PAN; however, there is a lack of immune-complex deposition. CSS is another ANCA-positive disease characterized by fever, pulmonary disease, and skin lesions. It is identified primarily in patients with asthma, and a recent association with the use of leukotriene inhibitors has been reported.[71] Peripheral eosinophilia is an important feature of the disease, often greater than 1500/mm³. Arthralgias and arthritis are noted in 50% of patients.[70]

Finally, a few other conditions with vasculitic symptoms deserve mention. Buerger disease, also known as thromboangiitis obliterans, is a segmental occlusive inflammatory disease that occurs primarily in young male patients and in those who smoke.[71] Bechet disease is associated with thrombosis and thrombophlebitis, folliculitis, and retinal vasculitis. A link with familial Mediterranean fever and HLA-B5 has been identified.[71] Finally, Sneddon syndrome is a rare disease characterized by skin findings and stroke, which occurs early in childhood. Endothelial proliferation leads to obstruction and necrosis of vessels.[1]

Conclusion

Vasculitis is an uncommon process in children. HSP and KS represent the majority of pediatric vasculitides, with sporadic occurrence of other diseases. Understanding the classification of vasculitic processes and their clinical presentations is helpful in making timely, accurate diagnoses. The recent surge in publications based on vasculitic processes demonstrates a new level of understanding of the epidemiology and clinical pathology associated with vasculitis. Furthermore, new treatment strategies being developed target specific mechanisms of disease, thereby reducing the previously high levels of associated morbidity and mortality.

References

1. Cuttica RJ. Vasculitis, Kawasaki disease, and pseudovasculitis. *Curr Opin Rheumatol* 1997;9:448-457.
2. Cuttica RJ. Vasculitis in children: A diagnostic challenge. *Curr Probl Pediatr* 1997;27:309-318.
3. Jennette JC, Falk R, Andrassy K, et al. Nomenclature of systemic vasculitides: Proposal of an International Consensus Conference. *Arthritis Rheum* 1994;37: 187-192.
4. Rai A, Nast C, Adler S. Henoch-Schönlein purpura nephritis. *J Am Soc Nephrol* 1999;10:2637-2644.
5. Saulsbury FT. Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine* (Baltimore) 1999;78:395-409.
6. Kraft DM, McKee D, Scott C. Henoch-Schönlein purpura: A review. *Am Fam Physician* 198;58:405-408.
7. Lahita RG. Influence of age on Henoch Schönlein purpura. *Lancet* 1997; 350:1116-117.
8. Scharer K, Krmar R, Querfeld U, et al. Clinical outcome of Schönlein-Henoch purpura nephritis in children. *Pediatr Nephrol* 1999;13:816-823.
9. Lind J, Mackay A, Withers SJ. Henoch-Schönlein purpura and priapism. *J Paediatr Child Health* 2002;38:526-527.
10. Brendel-Muller K, Hahn A, Schneppenheim R, et al. Laboratory signs of activated coagulation are common in Henoch-Schönlein purpura. *Pediatr Nephrol* 2001;16:1084-1088.
11. Nussinovitch M, Prais D, Finkelstein Y, et al. Cutaneous manifestations of Henoch-Schönlein purpura in young children. *Pediatr Dermatol* 1998;15: 426-428.
12. Bulun A, Topaloglu R, Duzova A, et al. Ataxia and peripheral neuropathy: Rare manifestations in Henoch-Schönlein purpura. *Pediatr Nephrol* 2001;16: 1139-1141.
13. Choong CK, Beasley SW. Intra-abdominal manifestations of Henoch-Schönlein purpura. *J Paediatr Child Health* 1998;34:405-409.
14. Reinehy T, Burk G, Andler W. Does steroid treatment of abdominal pain prevent renal involvement in Henoch-Schönlein purpura? *J Pediatr Gastroenterol Nutr* 2000;31:323-324.
15. Kawasaki Y, Suzuki J, Nozawa R, et al. Efficacy of methylprednisolone and urokinase pulse therapy for severe Henoch-Schönlein nephritis. *Pediatrics* 2003;111:785-789.
16. Beevers DG. Outcome after childhood Henoch-Schönlein purpura. *Lancet* 2003;361:81-82.
17. Lamireau T, Rebouissoux L, Hehunstre JP. Intravenous immunoglobulin therapy for severe digestive manifestations of Henoch-Schönlein purpura. *Acta Paediatr* 2001;90:1081-1082.
18. Leung SP. Use of intravenous hydrocortisone in Henoch-Schönlein purpura. *J Paediatr Child Health* 2001;37:309-310.
19. Chiaretti A, Caresta E, Piastra M, et al. Cerebral hemorrhage in Henoch-Schönlein syndrome. *Childs Nerv Syst* 2002;18:365-367. Epub 5/17/2002.
20. Eisenstein EM, Navon-Elkan P. Acute rheumatic fever associated with Henoch-Schönlein purpura: Report of three cases and review of the literature. *Acta Paediatr* 2002;91:1265-1267.
21. Lin SJ, Huang JL, Hsieh KH. Clinical and laboratory correlation of acute Henoch-Schönlein purpura in children. *Zhonghua Min Guo Xiao Er Ke Yi Xue Za Zhi* 1998;39:94-98. (In Chinese with English abstract).
22. Blanco, R, Martinez-Taboada VM, Rodriguez-Valverde V, et al. Henoch-Schönlein purpura in adulthood and childhood: Two different expressions of the same syndrome. *Arthritis Rheum* 1997;40:859-864.

23. Hyams JS. Corticosteroids in the treatment of gastrointestinal disease. *Curr Opin Pediatr* 2000;12:451-455.
24. Szer IS. Henoch-Schönlein purpura: When and how to treat. *J Rheumatol* 1996;23:1661-1665.
25. Rostoker G, Desvaux-Belghiti D, Pilatte Y, et al. High-dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schönlein purpura. *Ann Intern Med* 1994;120:476-484.
26. Bhullar N, Folzenlogen DD. Henoch-Schönlein purpura: Upper respiratory tract infection or drug induced? *Arch Intern Med* 2002;162:222-223.
27. Heegaard ED, Taaning EB. Parvovirus B19 and parvovirus V9 are not associated with Henoch-Schönlein purpura in children. *Pediatr Infect Dis J* 2002; 21:31-34.
28. Szer IS. Henoch-Schönlein purpura. *Curr Opin Rheumatol* 1994;6:25-31.
29. Robson WL, Leung AK. Acute rheumatic fever and Henoch-Schönlein purpura. *Acta Paediatr* 2003;92:513.
30. Gamboa F, Rivera JM, Gomez-Mateos JM, et al. Ciprofloxacin-induced Henoch-Schönlein purpura. *Ann Pharmacother* 1995;29:84.
31. Pertuiset E, Liote F, Launay-Russ E, et al. Adult Henoch-Schönlein purpura associated with malignancy. *Semin Arthritis Rheum* 2000;29:360-367.
32. Michel BA, Hunder GG, Bloch DA, et al. Hypersensitivity vasculitis and Henoch-Schönlein purpura: A comparison between the two disorders. *J Rheumatol* 1992;19:721-728.
33. Mills JA, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for classification of Henoch-Schönlein purpura. *Arthr Rheum* 1990;33:1114-1121.
34. Kawasaki T. *Jpn J Allergy* (Japanese) 1967;16:178-222.
35. Burns JC, Kushner HI, Bastian JF, et al. Kawasaki disease: A brief history. *Pediatrics* 2000;106:335-336.
36. Brogan PA, Bose A, Burgner D, et al. Kawasaki disease: An evidence based approach to diagnosis, treatment and proposals for future research. *Arch Dis Child* 2002;86:286-290.
37. American Academy of Pediatrics. Kawasaki Disease. In: Pickering LK, ed. *2000 Red Book: Report on the Committee on Infectious Diseases.* 25th ed. Elk Grove Village, IL:American Academy of Pediatrics; 2000:360-363.
38. Bell DM, Morens DM, Holman RC, et al. Kawasaki syndrome in the United States 1976-1980. *Am Dis Child* 1983;137:211-214.
39. Rowley A. Incomplete (atypical) Kawasaki disease. *Pediatr Infect Dis J* 2002;21:563-565.
40. Koren G, Lavi S, Rose V, et al. Kawasaki disease: Review of risk factors for coronary aneurysm. *J Pediatr* 1986;108:388-392.
41. Chang R-K. Hospitalizations for Kawasaki disease among children in the united states, 1988-1997. *Pediatrics* 2002;109:1162.
42. Genizi J, Miron D, Spiegel R, et al. Kawasaki disease in very young infants: High prevalence of atypical presentation and coronary arteritis. *Clin Pediatr* 2003;42:263-267.
43. Saulsbury FT. Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of kawakasi syndrome. *Clin Pediatr* (Phila) 2002;41:597-601.
44. Chiyonobu T, Yoshihara T, Mori K, et al. Early intravenous gamma globulin retreatment for refractory Kawasaki disease. *Clin Pediatr* 2003;42:269-272.
45. Shulman ST, DeInocencio J, Hirsch R. Kawasaki disease. *Pediatr Clin North Am* 1995;42:1205-1222.
46. Tse, SM, Silverman ED, McCrindle BW, et al. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease. *J Pediatr* 2002; 140:450-455.
47. Wang C-L, Wu Y-T, Liu C-A, et al. Expression of CD40Ligand on CD4+ T Cells and platelets correlated to the coronary artery lesion and disease progress in Kawasaki disease. *Pediatrics* 2003;111:e140-147.
48. Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;89:916-922.
49. Brogan PA, Bose A, Burgner D, et al. Kawasaki disease: An evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002;86:286-290.
50. Murugan SJ, Thomson J, Parsons JM. Is lifelong follow up for patients with Kawasaki disease indicated? *Arch Dis Child* 2003;88:91.
51. Tuohy AMM, Tani Ly, Cetta F, et al. How many echocardiograms are necessary for follow up evaluation of patients with Kawasaki disease? *Am J Cardiol* 2001;88:328-330.
52. Scott JS, Ettegui JA, Neches WH. Cost-effective use of echocardiography in children with Kawasaki disease. *Pediatrics* 1999;104:e57.
53. Durongpisitkul K, Gururaj VJ, Park JM, et al. The prevention of coronary artery aneurysm in Kawasaki disease: A meta-analysis on the efficacy of aspirin and immunoglobin treatment. *Pediatrics* 1995;96:1057-1061.
54. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984;2:1055-1058.
55. Nagashima M, Matsushima M, Matsuoka H, et al. High-dose gammaglobulin therapy for Kawasaki disease. *J Pediatr* 1987;110:710-712.
56. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315:341-347.
57. Newburger JW, Takahashi M, Beiser AS, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633-1639.
58. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997;131:888-893.
59. Yanagawa H, Nakamura Y, Sakata K, et al. Use of intravenous gamma-globulin for Kawasaki disease: Effect on cardiac sequelae. *Pediatr Cardiol* 1997; 18:19-23.
60. Morgan GJ, MacLeod C, Jenkins J, et al. IVIG, aspirin and Kawasaki disease. *J Pediatr* 2003;143:280-281.
61. Fong NC, Hui YW, LI CK, et al. Evaluation of the efficacy of treatment of Kawasaki disease before day 5 of illness. *Pediatr Cardiol* 2003;Oct 13 [epub ahead of print].
62. Kato H, Koike S, Yokoyama T. Kawasaki disease: Effect of treatment on coronary artery involvement. *Pediatrics* 1979;63:175-179.
63. Okada Y, Shinohara M, Kobayahi T, et al. Effect of corticosteroids in addition to intravenous gammaglobulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. *J Pediatr* 2003;143:363-367.
64. Sundel RP, Baker AL, Fulton DR, et al. Corticosteroids in the initial treatment of Kawasaki disease: Report of a randomized trial. *J Pediatr* 2003;142:611-616.
65. Etheridge SP, Tani LY, Minich LL, et al. Platelet glycoprotein IIb/IIIa receptor blockade therapy for large coronary aneurysms and thrombi in Kawasaki disease. *Cathet Cardiovasc Diag* 1998;45:264-268.
66. Uehara R, Yashiro M, Nakamura Y, et al. Kawasaki disease in parents and children. *Acta Paediatr* 2003;92:694-697.
67. Baker AL, Gauvreau K, Newburger JW, et al. Physical and psychosocial health in children who have had Kawasaki disease. *Pediatrics* 2003;111:579-583.
68. Aluquin VP, Albano SA, Chan F, et al. Magnetic resonance imaging in the

CME Objectives

The CME objectives for *Pediatric Emergency Medicine Reports* are to help physicians:

a.) Quickly recognize or increase index of suspicion for specific conditions;

b.) Understand the epidemiology, etiology, pathophysiology, historical and physical examination findings associated with the entity discussed;

c.) Be educated about how to correctly formulate a differential diagnosis and perform necessary diagnostic tests;

d.) Apply state-of-the-art therapeutic techniques (including the implications of pharmacologic therapy discussed) to patients with the particular medical problems discussed;

e.) Provide patients with any necessary discharge instructions.

diagnosis and followup of Takayasu's arteritis in children. *Ann Rheum Dis* 2002;61:526-529.
69. Yalcindag A, Sundel R. Vasculitis in childhood. *Curr Opin Rheumatol* 2001; 13:422-427.
70. Sundel R, Szer I. Vasculitis in childhood. *Rheum Dis Clin North Am* 2002; 28:625-54.
71. Watts RA, Scott DGI. Epidemiology of the vasculitides. *Curr Opin Rheumatol* 2003;15:11-16.
72. Jennette JC. Implications for pathogenesis of patterns of injury in small- and medium-sized-vessel vasculitis. *Cleve Clin J Med* 2002;69:S1133-1138.
73. Ozen S, Besbas N, Saatci U, et al. Diagnostic criteria for polyarteritis nodosa in childhood. *J Pediatr* 1992;120:206-209.

Physician CME Questions

111. Which of the following laboratory findings is characteristic in patients with Henoch-Schönlein purpura?
    A. Decreased levels of C3 and CH50
    B. Decreased levels of serum IgA
    C. Elevated levels of serum IgA
    D. Elevated levels of serum IgG

112. Which of the following infectious diseases has been most closely identified as an etiologic agent in Henoch-Schönlein purpura?
    A. *Streptococcus pneumoniae*
    B. Group A beta-hemolytic Streptococcus
    C. Influenza A virus
    D. Respiratory syncytial virus

113. For which of the following clinical manifestations of Henoch-Schönlein purpura is the use of low-dose corticosteroids most likely to be helpful?
    A. Nephritis
    B. Dermal involvement
    C. Abdominal pain
    D. Prevention of disease recurrence
    E. Length of disease in the active phase

114. Which of the following is part of the 1990 ACR criteria for the diagnosis of Henoch-Schönlein purpura?
    A. Palpable purpura
    B. Age younger than 10 at onset
    C. Proteinuria
    D. Evidence of central nervous system disease

115. Which of the following statements is true regarding the epidemiology of Kawasaki syndrome?
    A. Kawasaki syndrome occurs most commonly in the summer months.
    B. Females are more likely than males to have Kawasaki syndrome.
    C. The incidence of Kawasaki syndrome is most common in children of American descent.
    D. Eighty percent of cases of Kawasaki syndrome involve children younger than 5 years of age.

116. Which of the following is true regarding coronary artery disease in Kawasaki syndrome?
    A. Coronary artery aneurysms develop in 50% of untreated patients.
    B. Coronary artery aneurysms are less common in younger patients.
    C. Prolonged duration of fever is a risk factor for coronary artery aneurysm formation.
    D. The peak time for coronary artery aneurysm formation is within the first two weeks of illness.

117. Which of the following statements is true regarding the treatment of Kawasaki syndrome?
    A. The use of high-dose aspirin has been well-studied and proven to reduce the incidence of coronary artery disease.
    B. The use of IVIG decreases the risk for coronary artery disease and shortens the duration of fever.
    C. Retreatment with IVIG for patients with persistent fever does not decrease the incidence of coronary artery disease.
    D. Corticosteroids are routinely used in the treatment of Kawasaki syndrome.

118. Which of the following is a part of the diagnostic criteria for Kawasaki syndrome?
    A. Exudative conjunctivitis
    B. Fever between 38-41° C for two days
    C. Migratory polyarthritis
    D. Polymorphous, erythematous rash

119. Which of the following diseases is thought to be one of the first vasculitic processes identified in humans?
    A. Polyarteritis nodosa
    B. Microscopic polyangiitis
    C. Wegener granulomatosis
    D. Henoch-Schönlein purpura
    E. Takayasu arteritis

120. Which of the following diseases is considered a secondary vasculitic process?
    A. Wegener granulomatosis
    B. Giant cell arteritis
    C. Kawasaki syndrome
    D. Drug-hypersensitivity vasculitis
    E. Churg-Strauss syndrome

Answer Key

111. C **116. C**
112. B **117. B**
113. C **118. D**
114. A **119. A**
115. D **120. D**

In Future Issues: **Common Newborn Complaints**

PEDIATRIC Emergency Medicine Reports
The Practical Journal of Pediatric Emergency Medicine

Vasculitis

Primary Vasculitic Processes

LARGE VESSEL VASCULITIS
- Takayasu arteritis
- Giant cell (temporal) arteritis
- Isolated angiitis of the central nervous system

MEDIUM VESSEL VASCULITIS
- Kawasaki syndrome
- Polyarteritis nodosa

SMALL VESSEL VASCULITIS
- Henoch-Schönlein purpura
- Wegener granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome
- Essential cryoglobulinemic vasculitis
- Cutaneous leukocytoclastic angiitis

MISCELLANEOUS CONDITIONS
- Bechet disease
- Buerger disease
- Cogan syndrome

Diagnostic Criteria for HSP

1990 AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA

(Must have 2 of 4 criteria for diagnosis)
- Palpable purpura
- Age < 20 at onset
- GI bleeding
- Extravascular or perivascular granulocytes on biopsy

1992 DIAGNOSTIC CRITERIA (MICHAEL, ET AL)

(Must have 3 of 6 criteria for diagnosis)
- Palpable purpura
- Age < 20 at onset
- Bowel angina
- GI bleeding
- Hematuria
- No current medication use at disease onset

Secondary Vasculitic Processes

- Infection-related vasculitis
- Drug-hypersensitivity vasculitis
- Malignancy-related vasculitis
- Post-organ transplant vasculitis
- Vasculitis secondary to connective tissue disease
- Hypocomplementemic urticarial vasculitis
- Pseudovasculitis (myxoma, endocarditis)

Abdominal Pathology in HSP

HISTORY AND PHYSICAL EXAM
- Abdominal pain
- Nausea
- Vomiting or hematemesis
- Diarrhea, melena or bright red blood per rectum
- Abdominal distention
- Diffuse tenderness to palpation without guarding
- Hepatomegaly or splenomegaly

ABDOMINAL DISEASE IN ACUTE HSP
- Intussusception
- GI hemorrhage
- Pancreatitis
- Necrotizing vasculitis of the gallbladder
- Hydrops of the gallbladder
- Malabsorption
- Steatorrhea
- Paralytic ileus or functional bowel obstruction
- Bowel ischemia
- Bowel perforation
- Hemorrhage of abdominal wall musculature

LATE ABDOMINAL DISEASE (A RESULT OF ISCHEMIA AND NECROSIS)
- Stricture formation
- Fistula formation
- Bowel obstruction

Diagnostic Criteria for Kawasaki Syndrome*

PRIMARY CRITERIA

- Fever 38-41° C for five days or longer

SECONDARY CRITERIA

- **Mucous membrane changes**
  - Cracked, erythematous lips
  - Strawberry tongue
  - Erythema of the oropharynx
- **Conjunctivitis**
  - Bulbar injection with no exudate
- **Rash**
  - Polymorphous (morbiliform, maculopapular, scarlitiniform), erythematous
- **Extremity changes**
  - Induration of the hands and/or feet
  - Peripheral edema
  - Erythema of the palms and soles
  - Late desquamation of digits, palms, and/or soles
- **Lymphadenopathy**
  - Unilateral cervical lymphadenopathy greater than or equal to 1.5 cm in diameter

*For classic diagnosis, patients must meet primary criteria plus have 4 out of 5 secondary criteria.

Laboratory Evaluation in Kawasaki Syndrome

- Leukocytosis
- Elevated percentage of bands/immature forms in WBC differential
- Anemia
- Thrombocytosis (generally after the 1st week of illness)
- Elevated CRP, ESR
- Sterile pyuria
- Aseptic meningitis
- Elevated liver enzyme tests, ALT, LDH
- Hypoalbuminemia

Key:
WBC = white blood cell count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ALT = alanine aminotransferase; LDH = lactic dehydrogenase

Clinical Findings Associated with Kawasaki Syndrome

CENTRAL NERVOUS SYSTEM
Irritability, lethargy, aseptic meningitis, headache

CARDIAC
Rhythm disturbances, congestive heart failure, pericarditis, pericardial effusion, coronary artery disease

GASTROINTESTINAL
Abdominal pain, diarrhea, vomiting, abdominal distention, hepatomegaly, hematemesis, liver dysfunction, gall bladder hydrops, jaundice

PULMONARY
Pneumonitis, lobar consolidation

EYE
Anterior uveitis

GENITOURINARY
Urethritis

JOINT
Arthralgias, arthritis

*Clinical findings not part of the classic diagnostic criteria for Kawasaki Syndrome

Supplement to *Pediatric Emergency Medicine Reports*, December 2003: "Approaching the Child with a Vasculitis: Piecing Together an Accurate Diagnosis." *Authors:* **Laura L. Sells, MD,** Assistant Professor of Clinical Pediatrics, Department of Pediatrics, The Ohio State University College of Medicine and Public Health, Columbus; and **Leslie K. Mihalov, MD,** Assistant Professor of Clinical Pediatrics, Department of Pediatrics, The Ohio State University, Columbus; Chief, Section of Emergency Medicine, Children's Hospital Department of Pediatrics, Columbus, OH. *Peer reviewer:* **Larry B. Mellick, MD, MS, FAAP, FACEP,** Vice Chairman for Academic Development and Research, Department of Emergency Medicine, Professor of Emergency Medicine and Pediatrics, Medical College of Georgia, Augusta.

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Pediatric Cardiopulmonary Arrest: Current Concepts and Future Directions

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Managing a Winter Season Risk: Bronchiolitis in Children

Authors: Jeffrey F. Linzer Sr., MD, MICP, FAAP, and Cecilia Guthrie, MD

Peer Reviewer: James E. Colletti, MD

MARCH 2003

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Author: Ghazala Q. Sharieff, MD, FACEP, FAAP

Peer Reviewer: Marc S. Leder, MD

APRIL 2003

Common Pediatric ENT Infections: Diagnosis and Management in the ED

Author: Kirsten Bechtel, MD

Peer Reviewer: Brian Skrainka, MD, FAAP, FACEP

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Beat the Heat: Recognizing and Managing Heat-Related Illness

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JUNE 2003

Pediatric Thoracolumbar Spinal Injury: Frequently Hidden, but Not Harmless

Author: Jeffrey Proudfoot, DO, FACOEP, FACEP

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JULY 2003

Sports-Related Head Injuries: Learn the Rules of this Serious Game

Authors: Don W. Penney, MD, MSc, FACEP, and Ronald M. Perkin, MD, MA, FAAP, FCCM

Peer Reviewer: Norman Christopher, MD

AUGUST 2003

Wheezing in Children Younger than 3: Differential Diagnosis and Initial Approach to Management

Authors: Karin M. Hillenbrand, MD, and Ronald M. Perkin, MD, MA, FAAP, FCCM

Peer Reviewer: Mark S. Mannenbach, MD

SEPTEMBER 2003

A Clear-Sighted Approach to Conjunctivitis: State of the Art Clinical Practice

Authors: Linda D. Arnold, MD, FAAP, and Walter J. Eppich, MD

Peer Reviewer: Robert A. Felter, MD, FAAP

OCTOBER 2003

Tremors vs. Seizures: Recognizing and Managing Seizures in Children

Authors: William E. Novotny, MD, and Ronald M. Perkin, MD, MA, FAAP, FCCM

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NOVEMBER 2003

Pediatric Migraine: Recognizing and Managing Big Headaches in Small Patients

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Approaching the Child with a Vasculitis: Piecing Together an Accurate Diagnosis

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