The goal of this review is to summarize the currently available literature pertaining to meningococcal disease as it relates to the complaint of fever and petechiae. From this review, a management strategy is suggested for children who present with fever and a petechial rash. In general, invasive bacterial disease, including meningococcemia, in the child with fever and petechiae is rare. The vast majority of children with invasive bacterial disease appear ill or have an abnormal laboratory evaluation. Children who are well-appearing, who have a normal laboratory evaluation, or who have a documented streptococcal pharyngitis or petechiae only above the nipple line appear to be at low risk for invasive bacterial disease. Children identified to be at low risk may be managed as an outpatient. All others should be admitted to the hospital and treated with antibiotics pending culture results.
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Fever and Petechiae: No Time for a Rash Decision

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THE COMPLAINT of fever and petechiae causes consternation for even the most experienced clinician. The greatest fear is that this combination is a harbinger of invasive, life-threatening bacterial disease, most commonly caused by *N. meningiditis.* This fear is based on the knowledge that a petechial rash is often present in those children subsequently identified as having invasive disease caused by *N. meningiditis.*[1-3] However, most clinicians recognize that a bacterial cause is a relatively uncommon cause of fever and petechiae.[4,5] Therein lies the dilemma. Can children with a benign cause of their fever and petechiae be identified and managed differently than those who may have a more serious etiology? Can clinical and laboratory studies be used to categorize the individual child as having a more or less likely chance of invasive disease? Is empiric therapy required for all or for a subset of such children? Is a lumbar puncture (LP) required? Is admission necessary? The goal of this article is to review the findings commonly associated with meningococcal infections, and to review the available literature regarding fever and petechiae. From this review, a management strategy is suggested.

Differential Diagnosis

The causes of fever and petechiae are varied. *N. meningiditis, H. influenza* type b, and *S. pneumoniae* are bacterial infections associated with petechiae.[6] Other infectious causes include Rocky Mountain spotted fever, scarlet fever, and streptococcal pharyngitis.[6] Many viruses cause petechial eruptions. Viruses implicated are respiratory syncytial virus, influenza, parainfluenza, enterovirus, rotavirus, Epstein-Barr virus, atypical measles, rubella, dengue, and adenovirus infections.[7] Other possible

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causes include drug eruptions, acute leukemia, and subacute bacterial endocarditis.[6,8] Significant cough or emesis increases intrathoracic and intra-abdominal pressure and may lead to petechiae in the distribution of the superior vena cava.[4,9]

The history and physical examination may help the clinician develop a working differential diagnosis. Fever, headache, toxicity, mental confusion, myalgias, and a rash suggest Rocky Mountain spotted fever. The rash of Rocky Mountain spotted fever presents initially as erythematous macules that later become petechial and most often appears peripherally and progresses centrally. The rash regularly occurs on the hands and feet.[10] Bony pain, adenopathy, and hepatosplenomegaly suggest acute leukemia.[8] A history of congenital heart disease, cardiac surgery, or rheumatic fever raises the suspicion of endocarditis.[11] The history should investigate recent medication use and for the complaint of sore throat. Despite a good history and physical, the exact cause of the fever and petechiae unfortunately is often elusive.

Meningococcal Disease

Invasive bacterial disease, specifically meningococcal infection, is the most feared cause of fever and petechiae because invasive meningococcemia is associated with significant morbidity and mortality. The associated fatality rate is estimated to between 7% and 20%.[2,9,12-15] Morbidity includes neurological deficits, limb loss, and the sloughing of skin requiring skin grafts.[2,13] Fortunately, invasive meningococcal infection is uncommon. The annual incidence between 1989 and 1991 was 1.1 per 100,000.[16] The disease usually affects the young with almost one-half of the cases occurring in children younger than 24 months of age.[3,16,17] During outbreaks, illness occurs in an older population who are frequently in a close environment such as military recruits or college students.[16,17]

The spectrum of meningococcal disease is variable. Disease can range from an asymptomatic, transient bacteremia to fulminant symptoms and death.[3,18] The most common presentation of infection from *N. meningiditis* is either meningitis or severe meningococcemia.[2,17] It is well documented that meningococcal disease occurs in the outpatient setting as an occult bacteremia.[1,18-21] This outpatient presentation may progress or may resolve whether the patient is treated with oral antibiotics or not.[1,18-20]

Kirsch et al[2] and Kupperman et al[21] reviewed the clinical presentation of children with documented meningococcal infections. Kirsch et al identified 95 patients with meningococcal infection and documented that only 10% of patients present with mild or localized infection.[2] Kupperman et al identified unsuspected meningococcal infections in 45 (12%) of 381 children with documented meningococcal infections.[21] Interestingly, only 1 of these 45 children with unsuspected meningococcal disease had a petechial rash. Two (12%) of the 45 had positive cerebrospinal fluid (CSF) cultures with no CSF pleocytosis on laboratory analysis. Of the 336 remaining children with obvious meningococcal infection, 232 (69%) had a petechial or purpuric rash. Thirty-two had neither purpura nor petechiae. All but 5 of these 32 appeared ill.

The signs and symptoms of meningococcal disease are as variable as the spectrum of illness. The fulminant course of meningococcemia is easily recognized by the onset of purpura and shock.[2] However, early symptoms may be nonspecific and include fever, headache, lethargy, emesis, myalgias, or joint pains. Upper respiratory symptoms such as cough, pharyngitis, or laryngitis may occur initially.[2,3] It is recognized that a febrile child may present with mild symptoms and within hours have a rapidly progressive, fulminant course.[2,22] The clinician fears most this nonspecific presentation. A petechial or purpuric rash, however, is present in the majority of children with invasive meningococcal infection.[1,3] There are reports of meningococcemia presenting as a maculopapular rash that does not become petechial.[1] The difficulty for the clinician does not lie in identifying the fulminant course of meningococcemia. The difficulty lies in identifying the well-appearing child who may have only fever, petechiae, or a more nonspecific presentation who will then progress to invasive disease.

Fever and Petechiae

Background

There is probably little disagreement that the toxic-appearing child with fever and petechiae or developing purpura requires aggressive evaluation and therapy. The well-appearing child with fever and petechiae poses a greater challenge; there is no consensus for the evaluation of such children. A survey by Nelson et al found no consensus among general, infectious disease, academic, and emergency pediatricians for the evaluation of four hypothetical, nontoxic appearing, febrile children with petechial rashes.[23] These hypothetical children ranged in age from 12 months to 7 years. The

survey respondents were able to choose additional laboratory tests and whether to admit, observe, or discharge the patient. The respondents frequently chose blood cultures in the younger children. Only 41% requested an LP in what would be judged as the most "ill" of these well children. The decision to admit was variable and again was highest (44%) in the most "ill" child.

Literature Review

Several investigators have studied the etiology and potential laboratory evaluation of children presenting with fever and petechiae. One purpose was to determine whether there are any clinical or laboratory features that would identify those children with an invasive bacterial cause of their fever and petechial rash.

A retrospective study by Nguyen et al of 129 children admitted to the hospital with the complaint of fever and petechiae, found no single laboratory test sensitive enough to detect all children with invasive disease.[9] The investigators excluded children with shock and purpura. Twenty-six (20%) of the 129 children had invasive bacterial disease. Thirteen of these 26 had infection due to *N. meningiditis* and 8 due to *Haemophilus* influenza type b. Other bacterial causes included *S. pneumoniae, S. aureus,* and *E. coli.* The group with invasive disease as compared with the group without invasive bacterial disease had significantly higher white blood cell (WBC) counts, absolute neutrophil counts (ANC), absolute band counts (ABC), and erythrocyte sedimentation rates. An abnormal LP was associated with bacterial disease. Height of fever, age, and platelet counts were not different. No single test had 100% sensitivity to detect those children with invasive disease. However, no patients with a WBC count of between 4,500 and 15,000 cells/μL, an ANC between 1,500 and 9,000 cells/μL, an ABC less than 500 cells/μL, normal CSF analysis, and a temperature less than 40°C had invasive disease. Twelve children had petechiae only above the nipple line; three of these children had invasive disease. Seventeen had petechiae after tourniquet application; none of these children had invasive illness. This study is limited by its retrospective nature and possible selection bias because it only examined hospitalized children.

Baker et al were the first to prospectively evaluate children who presented to the emergency department (ED) with a temperature of 38°C or higher and a petechial rash.[5] Exclusion criteria included purpura fulminans, a known bleeding diathesis, and neonates. A total of 190 patients were evaluated. All but one of the children were admitted and treated with antibiotics. Fifteen (8%) of the children had invasive bacterial disease. Thirteen of these 15 had meningococcal disease. One child had *H. influenzae* type b. The investigators considered the remaining child who had normal laboratory values and an unremarkable clinical course as having occult pneumococcal bacteremia. Children with invasive bacterial disease were more ill-appearing and were more likely to have signs of meningeal irritation. The children with invasive disease had a significantly increased WBC count, an increased ABC, and CSF abnormalities. In the nonbacteremic group, 19 children had group A streptococcal pharyngitis. No patient with petechiae located only above the nipple line had invasive disease. If the WBC count was less than 15,000 cells/μL, the ABC was less than 500 cells/μL, and the CSF analysis was normal, then invasive disease was unlikely. The only child missed by this evaluation was the child with occult pneumococcal bacteremia. The investigators conclude that fever and petechiae can be a marker for invasive bacterial disease and suggest an aggressive evaluation of such patients. In children with petechiae above the nipple line and normal laboratory evaluation, the risk of invasive bacterial disease is low. In older children with the complaint of sore throat, clinical pharyngitis, and a positive streptococcal antigen test, less aggressive evaluation is appropriate.

Mandl et al also prospectively examined the incidence of serious bacterial disease and the clinical characteristics of children with fever higher than 38°C and petechiae who presented to an ED.[4] Included were ill-appearing children and children with purpura. They identified 411 children, representing 1.8% of children who presented to the ED with the complaint of fever. Most (58%) were between 3 and 36 months of age. Sixty-three percent were admitted to the hospital. Of those treated as outpatients, 66% were given antibiotics. Of the 411 identified, 8 (1.9%) had invasive disease. Only 2 (0.5%) children had cultures positive for *N. meningiditis.* Three had purpura fulminans and clinical sepsis with negative cultures; one child had sepsis caused by group A streptococcus. The two children who had occult bacteremia with *S. pneumoniae* were not considered to have serious disease. Overall, 87% of the children were described as well-appearing. All of the children with meningococcal infection or sepsis appeared ill and had purpura. Ill-appearing was defined as being "toxic" or lethargic in appearance or as having inconsolable crying or screaming. None of the well-appearing children had serious invasive disease. Forty percent of the

children had petechiae only above the nipple line. No child with petechiae only above the nipple line had invasive disease. Purpura occurred in 16 patients all of whom had meningococcemia or presumed sepsis. Two hundred nineteen (48%) children received an LP. CSF pleocytosis was present in 11% and all but two children were thought to have viral meningitis. A WBC count of greater than 15,000 cells/μL or less than 5,000 cells/μL had a sensitivity of 100% for detecting serious disease. A normal prothrombin time was rarely associated with invasive disease. The investigators concluded that invasive disease is exceedingly unlikely in children with fever and petechiae who are well-appearing, do not have purpura, have a normal WBC count, and a normal prothrombin time.

Literature Summary

What can be gleaned from the review of meningococcal infections and prospective studies of children with fever and petechiae? It is apparent that meningococcal infections are rare but cause serious illness when they occur. Infants and toddlers are at greatest risk except during outbreaks, which tend to occur in teenagers and younger adults. Sepsis or meningitis is the usual presentation of meningococcemia and a petechial or purpuric rash is often but not always present. Children with occult bacteremia caused by *N. meningiditis* typically do not have a petechial or purpuric rash. The children with bacteremia may have spontaneous resolution or may have progressive, serious disease.[18] Children with unsuspected meningococcal disease often have an increased band count but not always an increased absolute WBC.[21,22,24] The presentation and outcome of children with occult bacteremia caused by *N. meningiditis* appears to be different from those who present with fever and petechiae. Consequently, the specific management of occult bacteremia caused by *N. meningiditis* will not be considered in this review.

The presentation of fever and petechiae is rare when compared with the number of visits for fever without petechiae. The studies by Nguyen,[9] Baker,[5] and Mandl[4] suggest that the incidence of invasive bacterial infection in children with fever and a petechial rash is between 1.9% and 20%. The only prospective study to include children managed as outpatients and done after widespread use of the *H. influenzae* vaccine described an incidence of 1.9%.[4] This is probably a more accurate representation of the incidence of invasive bacterial disease for children presenting with fever and a petechial rash. The incidence of invasive disease identified by Baker[5] and Nguyen[9] included only children managed as inpatients and consequently, may overestimate the incidence of outpatient disease.

Management

These studies also appear to identify children with fever and petechiae who are at low risk for invasive bacterial or meningococcal disease. These children are well-appearing, have petechiae above the nipple line, and have normal laboratory evaluation. The laboratory evaluation includes a normal total WBC, ABC, prothrombin time, and possibly CSF analysis. Children with pharyngitis and a positive rapid streptococcal antigen test are also at low risk. Children identified to be at low risk for invasive bacterial disease can be considered for outpatient management. Any child who is ill-appearing or has an abnormal laboratory evaluation should be admitted and treated empirically with antibiotics pending culture results.

It is clear that all physicians do not perform an LP on all children with fever and petechiae, and all physicians do not admit every child with fever and petechiae.[4,23] The presentation of meningitis may be subtle in infants and an analysis of the CSF and admission should be strongly considered in this younger age group. In addition, children 2 years of age or younger are at greatest risk for sporadic meningococcal disease.[3,16,17] Whether an LP should be performed on the well-appearing toddler or child who does not have meningeal signs and who is admitted because of an abnormal laboratory evaluation, is subject to individual preference.

If the practitioner decides that outpatient management is appropriate, explicit instructions must be given to include follow-up within 24 hours or sooner if there is any concern that the child is becoming more ill. Children who are immunocompromised, were pretreated with antibiotics, have a documented exposure to meningococcus, or present during a known epidemic of meningococcal disease need to be managed differently and should not be considered at low risk for meningococcal disease.

Specific questions that were not addressed in any of the studies include whether a period of observation or the use of outpatient antibiotics is appropriate in managing children with fever and petechiae. Personal experience suggests that many physicians use an observation period of a few hours to determine if the petechiae and the clinical course are progressive. These same physicians are reassured when the petechiae do not

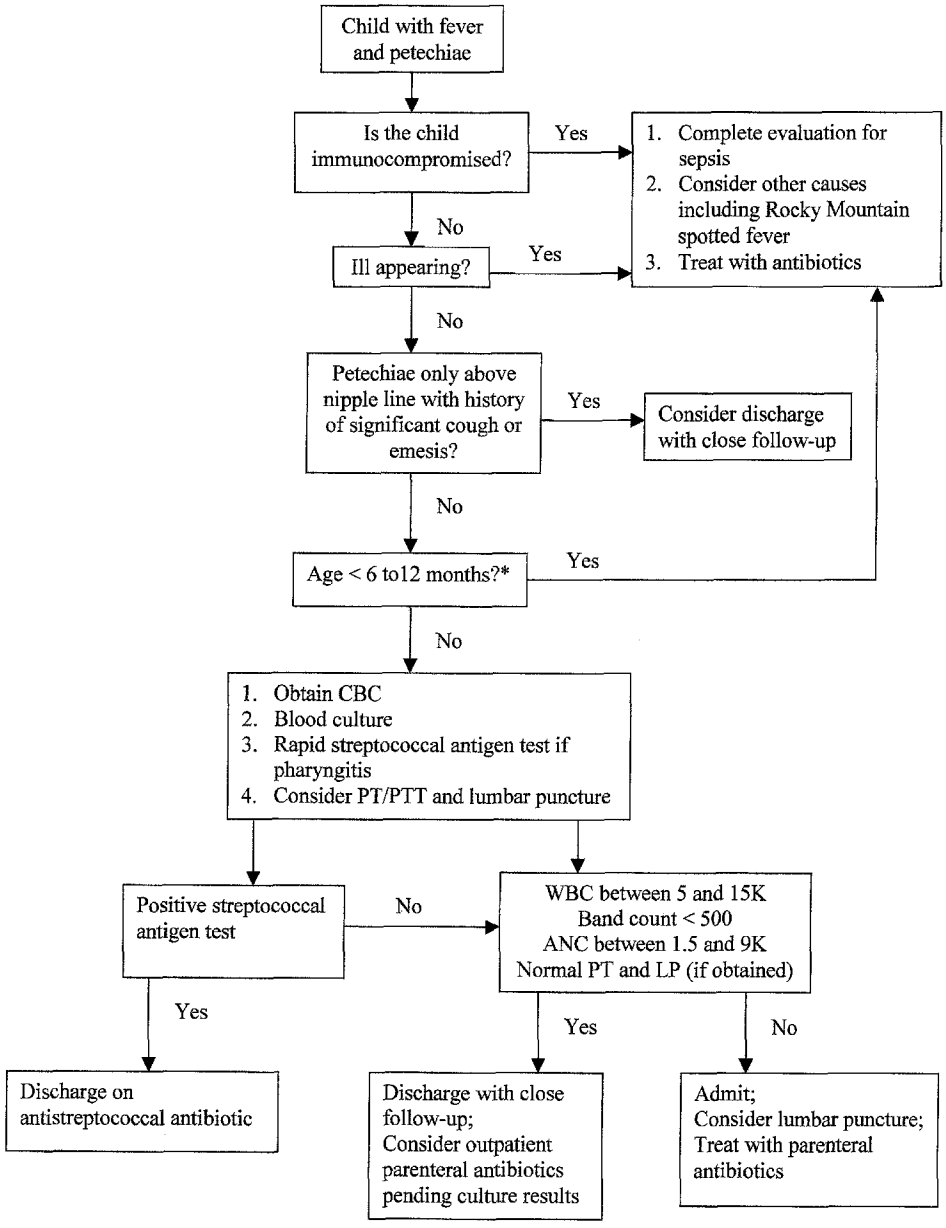

Figure 1. Approach to the child with fever and petechiae. *Age cut-off will vary depending on physician comfort.

progress. The question as to whether empiric parenteral or oral antibiotics are indicated for children treated as an outpatient is also not clear. From the literature describing occult meningococcal infection, it is apparent that children who received oral antibiotics probably have an attenuated course as compared with children who did not receive oral antibiotics.[18-20] However, meningococcal disease can and does progress despite oral antibiotic therapy.[4,18,20] The experience with outpatient, parenteral antibiotics in meningococcal disease is limited. The number of children with meningococcal infections managed as outpatients who received or did not receive antibiotics is small, and consequently, it is difficult to draw a meaningful conclusion as to the exact role of antibiotics in presumed meningococcal infection. Empiric antibiotic use should be considered on a case-by-case basis. It is apparent that the use of antibiotics cannot replace vigilance in the management of these children.

Other potential diagnostic tests often considered during the evaluation for a potential bacterial infection include bacterial antigen for *N. meningiditis* by either counterimmune electrophoresis or latex agglutination. These tests are of limited value in the acute setting because of poor sensitivity and specificity in the face of a low incidence of true bacterial disease.[17] Antigen detection may assist when evaluating the child who

has been pretreated with antibiotics.[3,17] Diagnosis by polymerase chain reaction is currently being used only in research labs.[17]

The algorithm presented in Figure 1 is a proposed management strategy for the child who presents with fever and a petechial rash. It summarizes the available literature and the personal experience of the author and his colleagues. It recognizes that in general, invasive bacterial disease, including meningococcemia, in the child with fever and petechiae is rare. The vast majority of children with invasive disease will appear ill or have abnormal laboratory evaluations. Selected children identified to be at low risk for invasive bacterial disease may be managed as outpatients. Because meningococcal infection occurs most often in children 24 months of age or younger, some clinicians may elect to manage children in this age group as high risk. All other children should be admitted and treated with antibiotics pending culture results.

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