Fever and Rash: A Changing Landscape in the 21st Century

Dimitri Laddis, MD,* Hnin Khine, MD,* David L. Goldman, MD†

Although fever and rash is a common complaint in the pediatric emergency department, most causes are benign. Of the more severe causes, several have been greatly reduced by vaccination programs. In addition, new vaccines such as those for invasive meningococcal disease hold promise for an even brighter future. Although meningococcemia remains an important concern when evaluating a child with fever and a rash, the resurgence of measles, the emergence of invasive group A streptococcal disease and antibiotic-resistant Staphylococcus aureus, as well as the fear of agents of bioterrorism (anthrax, smallpox) have changed the landscape of fever and rash in the 21st century. The purpose of this article is not to offer a comprehensive differential of febrile exanthema, but rather to highlight some new concerns related to the evaluation of fever and rash in today's emergency department.
Clin Ped Emerg Med 9:244-249 © 2008 Published by Elsevier Inc.

KEYWORDS fever, rash, emergency, measles, anthrax, smallpox, meningococcemia, streptococcus, staphylococcus

Although an isolated rash in a previously healthy child may present an interesting differential diagnosis, in the presence of a fever, the rash often gives a cause for more urgent concern. When accompanied by fever, the cause of the rash is likely to be infectious; however, rheumatologic diseases and medications may also be responsible. The purpose of this article is not to offer a comprehensive differential of febrile exanthema, but rather to highlight some new and resurgent causes of "fever and rash" that deserve consideration in today's emergency department (ED).

Measles

Once a mainstay of pediatric infectious disease, measles has become a rare entity in the United States because of a very successful immunization program; children receive 2 doses of measles vaccines before entering the school system. Recently, the Centers for Disease Control and Prevention (CDC) reported a rise in the cases of measles in United States in the first 4 months of 2008 [1]. This outbreak is believed to have originated in parts of Europe and Israel where immunization rates have declined because of parental concerns regarding vaccine safety. Furthermore, 63 of the 64 patients with confirmed cases in the United States were not immunized against measles. Despite the seemingly small number of patients involved, this outbreak and the recent severe acute respiratory syndrome outbreak serve as reminders of the global nature of modern epidemics in an age where international air travel is commonplace. It also highlights the potential dangers of vaccine noncompliance on herd immunity, a central factor in a community's defenses against a real measles epidemic [2,3]. Therefore, patients presenting with fever and rash should be asked about recent travel, exposure to visitors from other countries, and immunization status.

The measles virus is highly contagious and is spread either via direct contact or by contact with an infected person's aerosolized respiratory secretions. Because of the

*Division of Pediatric Emergency Medicine, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY.
†Division of Pediatric Infectious Disease, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY.
Reprint requests and correspondence: Dimitri Laddis, MD, Children's Emergency Service, Children's Hospital at Montefiore, 111 East 210th Street, Bronx, NY 10467. (E-mail: dladdis@montefiore.org)

nature of this illness, patients with measles will usually be brought to medical attention. Inasmuch as physicians training today are not likely to have encountered measles, raising awareness of this resurgent disease may prove to be of great importance in combating the next outbreak. After an incubation period of 4 to 12 days, clinical symptoms usually begin with high fever and the classic triad of cough, coryza, and conjunctivitis ("the three C's"). Koplik spots, tiny white spots surrounded by a red ring present on the buccal mucosa, are pathognomonic for measles, but should not be relied on because they may be present for less than a day. The classic measles rash is an erythematous, maculopapular exanthem that appears after a child has been ill for several days. It starts from the forehead or posterior occipital area and spreads to the trunk and extremities within 3 days. The rash fades from red to copper brown and disappears in the same cephalocaudal direction [4]. Although such a quick review of signs and symptoms of measles can be helpful, clinicians encountering a possible case of measles should draw on the experience of older physicians and those from countries where measles may have been a common part of their clinical experience.

Early identification, respiratory isolation, and supportive care are the mainstay of therapy. In certain situations, vitamin A supplementation should be considered in addition to routine supportive care [4]. Children who are exposed to measles and have not received vaccine, but have no contraindications to receiving measles vaccine, should be vaccinated within 72 hours of exposure. For children who are younger than 1 year or have other contraindications (eg, immunocompromised) to vaccination, immunoglobulin can be used.

Group A β-Hemolytic Streptococcus

Group A β-hemolytic streptococcus (GAS) is held responsible for a wide array of diseases, the most common being acute pharyngotonsillitis and impetigo, and their nonsuppurative sequelae. There are numerous accounts of devastating streptococcal outbreaks in the preantibiotic era. Scarlet fever outbreaks killed thousands in Europe in the 1600s and in the New World in 1736, with mortality rates of 25% to 35%. Outbreaks of rheumatic fever and acute glomerulonephritis have also been documented through history. Each of these outbreaks reached its resolution without the availability of antibiotics, but not without taking a heavy toll. With the advent of penicillin and readily available testing, the mortality associated with scarlet fever and other GAS diseases dropped dramatically [5].

In the early 1980s, GAS received significant attention in the lay media under the moniker *flesh-eating bacteria*. In recent years, invasive, deadly diseases such as necrotizing fasciitis, myositis, and toxic shock syndrome (TSS) continue to occur sporadically with occasional clusters [6-9]. In addition, these severe forms of disease appear to affect previously healthy children and young adults, and not just vulnerable populations [10-12]. A combination of change in virulence factors in the organism (many of the implicated strains are M protein type 1 or 3) as well as host factors may play a role in the resurgence of severe invasive GAS diseases [5].

Invasive GAS disease can be classified into 4 syndromes that sometimes overlap: necrotizing fasciitis, myositis, streptococcal TSS, and invasive GAS without TSS (eg, pneumonia, osteomyelitis). For these forms of disease, the mortality remains high, despite antibiotic and supportive therapy. This likely reflects the primary role of toxin in these diseases and in particular the streptococcal pyrogenic exotoxins, which act as superantigens that overactivate the immune system. Criteria for the diagnosis of streptococcal TSS were established in the 1990s and include isolation of GAS from the host, shock, and evidence of multiorgan dysfunction (eg, renal or hepatic dysfunction, coagulopathy, adult respiratory distress).

The rash of invasive GAS infections varies and depends on the type and stage of disease. A generalized erythematous macular rash that desquamates may accompany streptococcal TSS. For patients with necrotizing fasciitis and myositis, fever, chills, and severe pain are *often out of proportion* to the early cutaneous findings, which include minimal amounts of localized swelling and erythema. In necrotizing fasciitis, infection spreads in the subcutaneous tissues, rapidly destroying fascia and fat. Late skin manifestations include swelling, purplish discoloration, hemorrhagic bullae, and necrosis.

Given the subtle dermatologic manifestations that belie the severe nature of invasive GAS disease, the diagnosis is often missed in its early stages. This is especially true when the portal of entry of the organism is not clear. Hematomas due to minor nonpenetrating trauma, deep bruises to calf muscle, vaccinations, burns, or even muscle strains have been implicated as a nidus for infection. A strong association between varicella and GAS necrotizing fasciitis has become apparent in children. Typically, necrotizing fasciitis occurs on the third to fourth day of the varicella exanthem and should be considered in the differential diagnosis of a child with varicella who develops a new fever. Several case reports have described an association between nonsteroidal anti-inflammatory drug use and necrotizing fasciitis, especially in children with varicella; and many experts advise against nonsteroidal anti-inflammatory drug use in patients with varicella.

A high level of suspicion is essential for the early diagnosis of invasive GAS disease. Elevated serum creatinine phosphokinase or rising level of creatinine phosphokinase may help with the diagnosis of myositis. Magnetic resonance imaging is helpful in diagnosing and defining the extent of fasciitis and myositis. Evidence of multisystem involvement typical of TSS should be ascertained,

including hypotension, renal or liver failure, and coagulopathy. Early aggressive surgical debridement and parenteral antibiotics are necessary for an improved outcome.

Mortality is generally much higher in cases of invasive GAS if the patient develops streptococcal TSS [9,11-13]. Streptococcal TSS may be clinically indistinguishable from staphylococcal TSS in patients who present with fever, erythroderma, and rapid-onset hypotension with multi-organ involvement. Although evidence of focal skin or deeper soft tissue infection may be present, a significant number of cases do not have an obvious source of infection. Interestingly, GAS pharyngitis has rarely been associated with TSS and invasive diseases in general. Intensive supportive therapy, along with aggressive local debridement, when indicated, is most important in managing patients with TSS.

Based on the clinical presentation, it may be necessary to provide empiric staphylococcal (see below) and streptococcal antimicrobial coverage for patients with invasive GAS disease. Once a diagnosis has been confirmed, therapy can be tailored appropriately. Group A β-hemolytic streptococcus remains susceptible to penicillin and β-lactam antibiotics in general; but resistance to macrolides, trimethoprim-sulfamethoxazole, and clindamycin has been described. For patients with TSS, clindamycin should be included in the initial antibiotic regimen (ie, not alone, but in addition to standard antimicrobial therapy). The rationale for clindamycin therapy relates in part to its ability to inhibit protein synthesis (including toxin production). Intravenous immunoglobulin therapy may provide neutralizing antibodies against streptococcal toxins and should be considered as adjunctive therapy for patients with TSS.

Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

Staphylococcus aureus has long been known as a major cause of infections of skin and wounds as well as the respiratory tract, lymphatic system, and bone. It is also known to cause a variety of toxin-mediated syndromes (ie, TSS and staphylococcal scalded skin syndrome) [14]. The epidemiology and treatment of *S aureus* disease have undergone major changes since the introduction of antibiotics in the 1940s and the subsequent emergence of antibiotic resistance. Beginning in the 1990s, community-acquired methicillin-resistant *S aureus* (CA-MRSA) emerged as a significant cause of health problems. In the lay press, the term *superbug* has been used to imply that CA-MRSA has outsmarted all available antibiotics and to bring attention to this "epidemic."

Community-acquired methicillin-resistant *S aureus* infections were first recognized in Australian Aborigines who had never had any contact with Western medical care [15]. Over the last 15 years, CA-MRSA has emerged to affect a much broader group of populations globally. Many outbreaks have been reported in groups where close contact facilitates transmission, such as among young healthy athletes, most notably in the United States among the members of the St Louis Rams football team [16]. High person-to-person transmission rates also account for the very high intrafamilial spread of this disease. Once colonized intranasally, carriers may have upward of 4 times higher rates of infection. The spread of CA-MRSA has culminated in what many are calling an epidemic [17]. The CDC estimates that between 1998 and 2005, the cases of MRSA doubled. A recent multicenter study found that CA-MRSA is the most common pathogen identified in patients with skin and soft tissue infections presenting to EDs in the United States [18].

Community-acquired methicillin-resistant *S aureus* infection is mostly limited to skin and soft tissue ranging from furuncles to cellulitis and abscesses, abscesses being by far the most common. Paradoxically, the most prevalent strain (USA 300 ST-8) of CA-MRSA is now being found in the inpatient setting causing soft tissue infections. Pyomyositis, myositis, and necrotizing fasciitis are some of the more serious invasive diseases caused by CA-MRSA with significant morbidity and mortality. Skin manifestation may be a late finding in these patients. Fever and pain that are out of proportion to physical findings may be a clue to more deep-seated infection [19].

Although it is uncommon to see systemic signs of inflammation such as fever and leukocytosis with furuncles and abscesses, cellulitis may be associated with systemic signs. Incision and drainage should be used for all infectious collections likely to be due to CA-MRSA. In fact, some data suggest that smaller isolated abscesses (<5 cm) that are not associated with any signs and symptoms of systemic diseases may be managed with simple incision and drainage alone [20]. Systemic antibiotics are warranted for larger abscesses and cellulitis. For CA-MRSA, methicillin resistance is encoded by the mec-IV plasmid. This plasmid is smaller than the plasmid found in hospital-acquired MRSA and does not encode antibiotic resistance to non–β-lactam antibiotics. As a result, agents such as trimethoprim-sulfamethoxazole, clindamycin, and doxycycline, which have been around for many years, may be effective in treating CA-MRSA in the outpatient setting. Nonetheless, resistance patterns are community specific; and antimicrobiograms should be reviewed regularly to determine current susceptibilities. Vancomycin has been the mainstay of intravenous therapy for MRSA, and reports of vancomycin-resistant MRSA are rare. Alternative agents that may be useful in the treatment of serious CA-MRSA infections include linezolid, daptomycin quinupristin/dalfopristin, and tigecycline [21]. An unusual property of CA-MRSA is its tendency to cause recurrent skin infections. Affected individuals may benefit from strategies designed to eradicate carriage of this organism. The optimal strategy for decontamination remains to be

Figure 1 Four- month–old female infant with gangrene of the hands due to meningococcemia (image 1334 of public health image library courtesy of the CDC/Mr Gust).

determined; but recommendations have included the following approaches, both separately and in combination: nasal application of mupirocin, chlorhexidine baths, and even systemic antimicrobial therapy [14].

Meningococcemia

Neisseria meningitidis is a gram-negative diplococcus that causes rapidly progressive sepsis that may or may not involve meningitis. Meningococcal septicemia, which can begin as a nonspecific febrile illness, can rapidly (within hours) progress to multisystem organ failure and death. Initial nonspecific symptoms of fever, headache, myalgia, and abdominal pain may be quickly followed by signs and symptoms of shock [22]. The rash may also progress rapidly from macular, maculopapular, or urticarial to petechiae and purpura, or ecchymosis. Ultimately, these lesions may evolve into large areas of necrosis involving the skin, digits, and limbs (Figure 1). These dermatologic manifestations reflect underlying vasculitis and disseminated intravascular coagulation induced by the organism. Most deaths occur within the first 48 hours of illness. Case fatality has been reported to be as high as 50%. Predictors of poor outcomes include young age, absence of meningitis, presence of coma, temperature less than 38°C, hypotension (mean arterial pressure <2 SD below mean for age), leukopenia (white blood cell count <10 000/mm^3), and thrombocytopenia (platelet count <100 000/mm^3).

By contrast, in meningococcal meningitis, which is the most common form of invasive meningococcal disease, only about 80% of cases have a visible rash at the time of presentation [23]. In the absence of a rash, the clinical features of meningococcal meningitis (fever, headache, photophobia, lethargy, irritability, and neck stiffness) are indistinguishable from meningitis caused by any other bacteria.

Because of the rapidly fulminant nature of meningococcemia, this diagnosis should be considered in the differential diagnosis of all patients who present with fever and petechiae. All ill-appearing patients or patients with unstable vital signs, petechiae/purpura, and fever should be presumed to have invasive meningococcal disease. Blood cultures (and polymerase chain reaction if available) should be collected, but empiric therapy (antibiotics and hemodynamic support) must be initiated quickly. Pulmonary edema may necessitate mechanical ventilation, and renal insult may lead to hemodialysis. Close contacts of patients with meningococcal disease should receive chemoprophylaxis [22].

All children 11 years and older should receive the quadrivalent polysaccharide conjugate meningococcal vaccine (MCV 4) [22]. Younger children (2 years and older) with specific risk factors (eg, asplenia, complement deficiency, and travel to an endemic area) should also receive the conjugate vaccine. This vaccine contains polysaccharide from serogroups A, C, Y, and W-135. Current vaccine research is targeting the B serogroup, which is the most common cause of meningococcal disease in the United States [24]. *Neisseria meningitidis* invasive disease may be significantly reduced in decades to come [25], much as pneumococcal and *Haemophilus influenza* type B disease has with the widespread use of vaccines for those pathogens.

The development of the new meningococcal conjugate vaccine (MCV4) has provided a number of advantages over the old meningococcal polysaccharide vaccine (MPSV4), including induction of immunologic memory and booster effect with no hyporesponsiveness upon subsequent dosing. MCV4 also provides a longer immune response, and it can reduce nasopharyngeal carriage with possible herd immunity. However, MCV4 vaccine has its own limitations. The immune response in infants and very young children is less than ideal and is relatively short-lived. An association of Guillain-Barre syndrome and MCV4 vaccine (17 cases) is still being monitored, and patients with history of Guillain-Barre syndrome are advised to take the old nonconjugated polysaccharide vaccine.

Anthrax

In the fall of 2001, bioterrorism became a real threat to the American public when 22 people in the United States became infected with *Bacillus anthracis* (the causative agent of anthrax) through mail sent to media outlets and political offices. Overnight, a fear of anthrax entered the consciousness of a very threat-sensitive public after the terrorist attack on the World Trade Center and Pentagon a month earlier. As a result of the anthrax attacks, 5 people were killed and 30 000 more people received prophylactic antibiotics for possible exposure to the spores [26].

Figure 2 A cutaneous anthrax lesion on the arm (image 2332 of public health image library courtesy of the CDC/Dr Philip S Brachman).

Bacillus anthracis makes a good biologic agent for terrorism because its spores are highly stable and the inhalational form of anthrax has a high mortality. Anthrax can present in 3 forms: cutaneous, inhalational, and gastrointestinal tract disease. Mortality rate for cutaneous cases are usually less than 1%, whereas inhalational and gastrointestinal forms can exceed 50%. The disease, in its most common cutaneous form, causes vesicles or papules at the site of exposed, broken skin. Over several days, the vesicles may rupture, leaving a necrotic ulcer, with subsequent development of a painless black eschar (Figure 2). There is usually surrounding edema and erythema with regional lymphadenopathy. All forms of anthrax have an incubation period of less than 2 weeks. With the inhalational form, an initial prodrome of nonspecific, flu-like symptoms (fatigue, fever, sweats, cough, and vomiting) is followed in 2 to 5 days with dyspnea, hypoxia, and fulminant shock. Early chest x-ray findings of hilar fullness, mediastinal widening and effusions, or hemorrhagic infiltrates can be helpful in distinguishing early anthrax from viral infections. The gastrointestinal form can initially present with either oropharyngeal ulcers or symptoms of nausea, anorexia, or vomiting followed by signs and symptoms of gastrointestinal bleed and shock. In all suspected cases of anthrax, patients should be initially treated with either ciprofloxacin or doxycycline regardless of the patient's age until susceptibility testing indicates otherwise [5,27,28].

Smallpox

Schoolchildren are taught of the 19th century success of Edward Jenner in using cowpox exposure to immunize against smallpox. Since then, smallpox eradication by vaccination (the last reported case was in 1977) is one of the triumphs of modern preventive medicine. The disease, if reintroduced, would likely cause havoc because routine vaccination has been discontinued throughout the world. To prevent a devastating outbreak, there have been recommendations for reintroduction of the vaccine in select groups, such as at-risk laboratory workers, some health care providers, military personnel, and first responders [29]. With a mortality rate of about 30%, potential for rapid spread, and no known cure, smallpox was propelled, along with anthrax, into our collective awareness of potential bioterrorism threats [30].

The disease is characterized by severe prodromal symptoms (including high fever, severe headache, backache, and malaise) that are debilitating. These symptoms are followed initially by lesions on the mucosa of the mouth and pharynx with progression to the skin. The skin lesions progress from macules to papules to vesicles to deep-seated hard pustules over 1 week, spreading cephalocaudally. In contrast to varicella, these lesions are more deep seated, often involve the palms and soles, and tend to be of the same stage on each affected part of the body. Death often occurs in the second week of illness because of severe viremia [27,29].

Smallpox vaccine is a live virus vaccine that contains a related, but relatively attenuated, vaccinia virus. In contrast to the most common vaccines, this vaccine is administered by 2-pronged needle that is dipped in vaccine solution. The vaccine, when given before exposure, is highly effective in preventing smallpox. In addition, vaccination of exposed individuals (within 7 days of exposure) may significantly shorten and lessen the severity of the disease. The vaccine has adverse effects and associated mortality in people with atopic dermatitis, those who are immunocompromised, or those who have heart conditions [31]. A hyperimmune globulin is being studied for the treatment of adverse effects associated with smallpox vaccination. The vaccine produces a local vesiculopustular lesion that itself is contagious and must be covered to prevent autoinoculation and exposure to others.

At the present time, although the US government has enough vaccine to immunize everyone in the United States, the risks far outweigh the benefits for routine immunization [32]. Isolation of sick patients, surveillance, and reporting are the mainstays of a public health response to a smallpox scare.

Summary

Although "fever and rash" is a common complaint in the pediatric ED, most causes are benign. Of the more severe causes, several have been greatly reduced by vaccination programs. Indeed, new vaccines such as those for invasive meningococcal disease hold promise for an even brighter future. However, the resurgence of forgotten oldies such as measles, the emergence of invasive group A streptococcal disease, the superbug status of antibiotic-resistant *S. aureus*, and the fear of a bioterrorism attack have changed the landscape of fever and rash in the 21st century.

References

1. Measles—United States, January 1-April 25, 2008. MMWR Morb Mortal Wkly Rep 2008;57:494-8.

2. Ehresmann KR, Crouch N, Henry PM, et al. An outbreak of measles among unvaccinated young adults and measles seroprevalence study: implications for measles outbreak control in adult populations. J Infect Dis 2004;189(Suppl 1):S104-7.

3. Parker AA, Staggs W, Dayan GH, et al. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. N Engl J Med 2006;355:447-55.

4. Pickering LK. Measles. Red book: 2006 report of the Committee on Infectious Diseases. Elk Grove Village (Ill): American Academy of Pediatrics; 2006.

5. Stevens DL. The flesh-eating bacterium: what's next? J Infect Dis 1999;179(Suppl 2):S366-74.

6. Aguero J, Ortega-Mendi M, Eliecer Cano M, et al. Outbreak of invasive group A streptococcal disease among children attending a day-care center. Pediatr Infect Dis J 2008;27:602-4.

7. Cockerill FR, MacDonald KL, Thompson RL, et al. An outbreak of invasive group A streptococcal disease associated with high carriage rates of the invasive clone among school-aged children. JAMA 1997; 277:38-43.

8. Efstratiou A. Group A streptococci in the 1990s. J Antimicrob Chemother 2000;45(Suppl):3-12.

9. Steer AC, Danchin MH, Carapetis JR. Group A streptococcal infections in children. J Paediatr Child Health 2007;43:203-13.

10. Carapetis JR, Steer AC, Mulholland EK, et al. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005;5:685-94.

11. Luca-Harari B, Ekelund K, van der Linden M, et al. Clinical and epidemiological aspects of invasive *Streptococcus pyogenes* infections in Denmark during 2003 and 2004. J Clin Microbiol 2008;46: 79-86.

12. O'Loughlin RE, Roberson A, Cieslak PR, et al. The epidemiology of invasive group A streptococcal infection and potential vaccine implications: United States, 2000-2004. Clin Infect Dis 2007;45:853-62.

13. Darenberg J, Luca-Harari B, Jasir A, et al. Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. Clin Infect Dis 2007;45:450-8.

14. Pickering LK. MRSA. Red book: 2006 report of the Committee on Infectious Diseases. Elk Grove Village (Ill): American Academy of Pediatrics; 2006.

15. Riley TV, Pearman JW, Rouse IL. Changing epidemiology of methicillin-resistant *Staphylococcus aureus* in Western Australia. Med J Aust 1995;163:412-4.

16. Benjamin HJ, Nikore V, Takagishi J. Practical management: community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA): the latest sports epidemic. Clin J Sport Med 2007;17: 393-7.

17. Safdar N, Bradley EA. The risk of infection after nasal colonization with *Staphylococcus aureus*. Am J Med 2008;121:310-5.

18. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med 2006;355:666-74.

19. Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 2008;46(Suppl 5):S368-77.

20. Lee MC, Rios AM, Aten MF, et al. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcus aureus*. Pediatr Infect Dis J 2004;23:123-7.

21. Levine DP. Vancomycin: understanding its past and preserving its future. South Med J 2008;101:284-91.

22. Pickering LK. Meningococcus. Red book: 2006 report of the Committee on Infectious Diseases. Elk Grove Village (Ill): American Academy of Pediatrics; 2006.

23. Andersen J, Backer V, Voldsgaard P, et al. Acute meningococcal meningitis: analysis of features of the disease according to the age of 255 patients. Copenhagen Meningitis Study Group. J Infect 1997;34:227-35.

24. Jodar L, Feavers IM, Salisbury D, et al. Development of vaccines against meningococcal disease. Lancet 2002;359:1499-508.

25. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria* meningitidis. Lancet 2007;369: 2196-210.

26. Inglesby TV, O'Toole T, Henderson DA, et al. Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA 2002;287:2236-52.

27. Kman NE, Nelson RN. Infectious agents of bioterrorism: a review for emergency physicians. Emerg Med Clin North Am 2008; 26:517-47, x-xi.

28. Pickering LK. Anthrax. Red book: 2006 report of the Committee on Infectious Diseases. Elk Grove Village (Ill): American Academy of Pediatrics; 2006.

29. Pickering LK. Smallpox. Red book: 2006 report of the Committee on Infectious Diseases. Elk Grove Village (Ill): American Academy of Pediatrics; 2006.

30. O'Brien KK, Higdon ML, Halverson JJ. Recognition and management of bioterrorism infections. Am Fam Physician 2003;67:1927-34.

31. Richard JL, Grimes DE. Bioterrorism: class A agents and their potential presentations in immunocompromised patients. Clin J Oncol Nurs 2008;12:295-302.

32. Smallpox fact sheet: vaccine overview. CDC 2004, Available at: http://emergency.cdc.gov/agent/smallpox/vaccination/facts.asp [Accessed 9/2/08].