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Surgical Infection Society Guidelines for Vaccination after Traumatic Injury

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For the Therapeutic Agents Committee of the Surgical Infection Society

ABSTRACT

Background: **Recommendations for vaccination of injured patients against infection are evolving. Newly-recognized infections, safety considerations, changing epidemiology, and redefinition of patient groups at risk are factors that may influence vaccine development priorities and recommendations for immunization. However, recommendations must often be formulated based on incomplete data, forcing reliance on expert opinion to address some crucial questions. These guidelines provide evidence-based recommendations for the prevention or treatment of infectious morbidity and mortality after traumatic injury, such as soft tissue wounds, human or animal bites, or after splenectomy.**

Methods: **A panel of experts conducted a thorough review of published literature, as well as information posted on the internet at the websites of the U.S. Centers for Disease Control and Prevention, among others. MEDLINE was searched for the period 1966–2004 using relevant terms including "anthrax," "rabies," "tetanus," "tetanus toxoid," and " splenectomy," in combination with "vaccine" and "immunization." The Cochrane database was searched also. Reference lists were cross-referenced for additional relevant citations. All published reports were analyzed for quality and graded, with the strength of the recommendation proportionate to the quality of the supporting evidence.**

Results: **Recommendations are provided for pre- and post-exposure prophylaxis of rabies and anthrax. For tetanus prophylaxis, recommendations are provided for prophylaxis of acute wounds stratified y age and prior immunization status, and for immunization of persons at high risk. After splenectomy, it is recommended that all persons ages 2–64 years receive 23-valent pneumococcal vaccine and meningococcal vaccine, with Haemophilus influenzae type B vaccine administered to high-risk patients as well (all are Grade D recommendations). Vaccination should be given two weeks before elective splenectomy (Grade C), or two weeks after emergency splenectomy (Grade D). A booster dose of pneumococcal vaccine is recommended after five years (Grade D); no re- vaccination recommendation is made for meningococcal or Haemophilus influenzae type B vaccine. Recommendations for prophylaxis of splenectomized children under the age of five years are also provided.**

Conclusion: **There are limited data on the use of vaccines after injury. This document brings together a disparate literature of variable quality into a discussion of the infectious risks after injury relevant to vaccine administration, a summary of safety and adverse effects of vaccines, and evidence-based recommendations for vaccination.**

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In the 21st Century, nearly any antigen can be prepared for use as a vaccine. The difficulties are in identifying protective antigens and persuading the immune system to respond correctly to them. Over the last 200 years, success has been achieved in controlling major infectious diseases predominantly by vaccinating with attenuated living or inactivated organisms, inactivated toxoids, or bacterial capsular polysaccharides. Vaccine preparation with attenuated or killed organisms has not required extensive knowledge of immune responses, except to be sure that antibodies are produced. Control of bacteremia or viremia has sufficed to provide efficacy against many of the diseases controlled by vaccination [1]. Now, more complex problems must be dealt with, such as microbes that are not inhibited by antibodies and immune responses that are useless or even pathologic.

In recent years, a better understanding of protective immune responses has included recognition of the need to induce both specific cellular immune responses and antibodies to control infections. Antibodies on mucosal surfaces and in serum can prevent infection or limit spread to target organs, whereas T-cell Th1 and Th2 responses that shift the immune system toward cellular or antibody-mediated immunity, respectively, destroy infected cells and eliminate infection [1].

Recommendations for immunizations are evolving. Newly recognized infections, safety considerations, changing epidemiology, and the identification of new risk groups are important factors that may influence vaccine development priorities and immunization recommendations. In addition, dramatic advances in molecular biology have made possible the development of many new and future vaccines and combination products.

Development of vaccine policy is difficult and complex work, tempered by judgment and elements of uncertainty [1]. The recommendations made by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC), the Committee on Infectious Disease of the American Academy of Pediatrics, and other authorities are not without controversy. Recommendations often must be formulated on the basis of incomplete data, necessitating vigorous debate to achieve consensus.

The purpose of this document is to provide evidence-based recommendations on the use of vaccines for the prevention or treatment of infectious morbidity and mortality after traumatic injury. Injuries necessitating immunization include trauma necessitating splenectomy, human or animal bites, and other soft tissue wounds. In addition, the threat of biologic agent attacks has added the potential for infection with microorganisms such as anthrax.

There are limited data on the current use of vaccines after injury. Although recommendations for the use of rabies and tetanus vaccines exist, their utility after injury is poorly documented [2,3]. A 2002 survey of 557 trauma surgeons documented a lack of consensus regarding the immunization of post-splenectomy patients [4].

This document presents a focused review of the infectious risk after injury, evidence supporting the use of vaccines in these circumstances, a summary of safety and adverse effects of vaccines, and evidence-based recommendations for vaccination after injuries that carry a risk of rabies or tetanus and after splenectomy. In addition, a recommendation is provided for use of anthrax vaccine.

METHODS

The recommendations were developed by an expert panel, who conducted a thorough review of the published literature as well as the information available on federal government internet sites such as that of the CDC (www.cdc.gov). The MEDLINE database was searched using multiple strategies to identify clinical trials of efficacy and reports of adverse events published from 1966 to 2004, and this was supplemented by manual search of references from all relevant journal articles. The terms used for these searches included "anthrax," "rabies," "tetanus," "tetanus toxoid," and "splenectomy," in combination with the terms "vaccine" and "immunization." In addition, the Cochrane database was searched for any relevant documents.

All published reports were categorized by quality, and each trial was graded according to the method described in Table 1 [5]. Large randomized trials with clear-cut results were given

the greatest weight, followed by small randomized trials and then by non-randomized studies. The lowest quality of evidence included case studies, uncontrolled studies, and expert opinion. A recommendation grade of A, B, or C had to be supported by randomized trials. An executive summary of the graded recommendations is presented in Table 2.

The document has been reviewed and endorsed by the Therapeutic Agents Committee and the Executive Council of the Surgical Infection Society.

RESULTS

Rabies

Risk of rabies after injury. Rabies is a viral infection transmitted in the saliva of infected animals. The infection is widespread in some animal species, and occasionally is transmitted to human beings. Over the last 50 years, the incidence of rabies has declined significantly in the industrialized world, although developing nations still have a high case rate. The geographic distribution of human cases generally follows the distribution of animal cases, but persons returning from endemic areas may import the disease to non-endemic areas [6].

Although human rabies infection is rare in the U.S., animal bites are encountered frequently in clinical practice, as several million U.S. residents are victims each year. Dog bites alone account for more than 300,000 emergency department visits annually, with total costs of more than $100 million [7].

Rabies is invariably fatal in the absence of specialized treatment, but is preventable with proper measures, including prophylaxis after certain types of animal exposure. Control of rabies in domestic animal populations and post-exposure prophylaxis has led to a decline in annual human rabies cases in the U.S. from more than 100 at the beginning of the 20th Century to 1 to 3 per year. Only 32 cases of human rabies were diagnosed in the U.S. between 1980 and 1998 [6].

Since the 1970s, the expanding epizootic of rabies in raccoons in the eastern U.S. has increased concern about potential transmission to man. In 1997, 8,509 animal rabies cases were reported in the U.S., an increase of 19.4% from 1996 [8]. Rabies appears to be expanding in raccoons, and reports of rabies in cats have increased in the same areas. Although no documented human infections have occurred with the raccoon rabies virus variant, the use of rabies post-exposure prophylaxis has increased recently [9]. In 1987, approximately 18,000 rabies post-exposure prophylaxis treatments were given in the U.S., whereas in 1997, an estimated 39,000 treatments were given. Although the costs of rabies post-exposure prophylaxis can vary greatly, the cost in the U.S. is approximately $1,500 per course for biologics alone. Physician and follow-up clinic charges add to the cost [10].

Table 1. Recommendations and Evidence Grading System

Grading of recommendations

A. Supported by at least two level I investigations
B. Supported by one level I investigation
C. Supported by level II investigations only
D. Supported by at least one level III investigation
E. Supported by level IV or V evidence

Grading of evidence

I. Large randomized trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error
II. Small randomized trials with uncertain results; moderate to high risk of false-positive (alpha) and/or false-negative (beta) error
III. Nonrandomized, contemporaneous controls
IV. Nonrandomized, historical controls and expert opinion
V. Case series, uncontrolled studies, and expert opinion

Adapted from Sackett [5].

Pathogenesis. Rabies is an acute progressive encephalitis caused by RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus* [11]. Rabies virus is the only known lyssavirus in the New World. Some locations are considered rabies-free; among them are Hawaii and many Pacific and Caribbean islands (except Cuba, Dominican Republic, Haiti, Grenada, and Puerto Rico). However, their continued freedom from rabies depends on prevention of the introduction of the virus and laboratory-based surveillance [12].

The rabies virus is highly neurotrophic and is restricted to nervous tissue during most of the course of infection. There is no viremia. After inoculation, the virus may enter the peripheral nerves immediately, but usually there

Table 2. Executive Summary of Graded Recommendations for Vaccination of Injured Patients

Rabies

Pre-exposure prophylaxis

Vaccination should be provided to persons at risk (laboratory workers, diagnosticians, veterinarians and their staffs, animal control officers, rabies researchers, and some travelers to areas where rabies is prevalent) (Grade A)

Post-exposure prophylaxis

A five-dose regimen is recommended. Five one-milliliter doses of vaccine are given intramuscularly (deltoid muscle) on days 0, 3, 7, 14, and 28 in conjunction with a single dose of human rabies immune globulin (HRIG) 20 IU/kg infiltrated into the wound on day 0. Any remaining HRIG should be administered IM at a site distant from the vaccine site (Grade D)

Anthrax

Pre-exposure prophylaxis

Vaccination may be indicated for veterinarians and other high-risk persons handling potentially infected animals in areas with a high incidence of anthrax. Routine vaccination of emergency first-responders, federal responders, medical practitioners, and private citizens is not recommended (Grade B)

Post-exposure prophylaxis

Administration of the vaccine and antibiotics against *B. anthracis* is recommended following an aerosol exposure to spores. Post-exposure vaccination should be administered as three injections of vaccine, beginning as soon as possible, at 0, 2, and 4 weeks (Grade E)

Tetanus

Prophylaxis of acute wound

Administration of tetanus immune globulin (HTIG) 250 IU is recommended only for patients with tetanus-prone wounds who have never completed a primary immunization series. The HTIG should be given at a site different from the tetanus toxoid to avoid interaction (Grade B)

For small children, the routine dose of HTIG may be calculated by body weight (4 IU/kg). However, it may be advisable to administer the entire 250 IU, because theoretically, the same amount of toxin will be produced in a child's as in an adult's body (Grade B)

If a patient with an acute soft tissue injury has not been immunized previously, a tetanus toxoid booster is required. The patient must have followup to complete the series. If the patient has been immunized previously, a booster dose is given if the last dose was more than five years previously (for a tetanus-prone wound) or more than 10 years previously (for a non-tetanus-prone wound). Patients with a contraindication to tetanus toxoid must be managed with HTIG alone (Grade B)

Immunization of high-risk persons

The elderly, HIV-infected, or otherwise immunocompromised patient may not respond adequately to vaccination alone. More liberal use of HTIG may be warranted for these patients, regardless of primary immunization status. More frequent dosing of tetanus toxoid may help to sustain adequate antibody titers (Grade E)

Intravenous drug users may present with complaints unrelated to acute wounds. However, their drug use should be considered a risk factor that requires consideration of tetanus prophylaxis (Grade E)

Vaccination after Splenectomy

The 23-valent polysaccharide pneumococcal vaccine is recommended for persons 2 to 64 years of age who have functional or anatomic asplenia (Grade D)

High-risk individuals should be considered for vaccination with *Haemophilus influenzae* type B conjugate vaccine (Grade D)

Asplenic patients should receive meningococcal vaccine (Grade D)

Timing and redosing

For patients undergoing elective splenectomy, vaccination should be performed at least two weeks before surgery to maximize the antibody against T-cell-dependent immunogens (Grade C)

Patients who undergo emergency splenectomy should receive immunizations 14 days postoperatively (Grade D)

A single revaccination with the 23-valent polysaccharide pneumococcal vaccine should be given at least five years after the first dose. No further dosing is recommended routinely (Grade D).

There is currently no recommendation to revaccinate for *H. influenzae* type B or meningococcus

TABLE 2. EXECUTIVE SUMMARY OF GRADED RECOMMENDATIONS FOR VACCINATION OF INJURED PATIENTS (CONTINUED)

Vaccination of children younger than five years

The 7-valent pneumococcal conjugate vaccine is recommended for all children 24 to 59 months of age who are at high risk for invasive pneumococcal infection. High-risk children include those with sickle cell disease and other types of functional or anatomic asplenia. For high-risk children 24 to 59 months of age who have received no previous dose of either the 23-valent or the 7-valent pneumococcal polysaccharide vaccine, two doses of the 7-valent conjugate vaccine are recommended, to be given at an interval of six to eight weeks, followed by a single injection of the 23-valent vaccine no less than six to eight weeks after the last dose of the 7-valent vaccine. An additional dose of 23-valent vaccine is recommended three to five years after the last dose (Grade D)

High-risk children 24 to 59 months of age should also receive vaccination against meninococcus and *H. influenzae* type B (Grade D)

Antibiotic prophylaxis is recommended for all children with sickle cell disease and functional or anatomic asplenia, regardless of whether they have received pneumococcal immunization (Grade B)

Oral penicillin V potassium is recommended in a dose of 125 mg twice a day, until three years of age and in a dose of 250 mg twice a day after three years of age. Children who have not experienced invasive pneumococcal infection and have received recommended pneumococcal immunizations may discontinue penicillin prophylaxis after five years of age (Grade B)

is an incubation period during which the virus is amplified. The virus then crosses the myoneural junction and enters the nervous system through unmyelinated sensory and motor axons. Rabies can be prevented only by post-exposure immunization during this incubation period, before the virus enters the central nervous system. The virus moves rapidly through axons until it reaches the spinal ganglia. At this time, the first symptoms of the disease (pain and paresthesia at the wound site) may appear. The virus then disseminates quickly in the central nervous system, causing rapidly progressive encephalitis that is fatal in the absence of sometimes-heroic treatment measures [13].

Transmission. In nature, the rabies virus is labile, being inactivated by sunlight, heat, desiccation, and other environmental factors. Thus, it is not viable outside the host. Exposure occurs when there is penetration of the skin by teeth or direct transdermal or mucosal contact with infectious material, such as brain tissue or saliva. Almost all cases are caused by bites from infected mammals.

All mammals are susceptible and can transmit rabies virus, but true reservoirs, which are responsible for long-term disease maintenance, persist only among *Carnivora* and *Chiroptera* (bats) [12]. Specific viruses are adapted to these hosts and typically perpetuate infection within a species by transmission before the host dies. In North America, raccoons, skunks, bats, foxes, coyotes, and bobcats are the primary reservoirs. Unvaccinated domestic animals and human beings become rabid after exposure to such reservoirs. By definition, all reservoirs are capable of transmitting infection, but not all potential vectors are reservoirs. For example, livestock die of the disease before transmitting it. Cats, usually infected by dogs or wild animals, are effective vectors but do not sustain the disease [14].

In developed countries, the incidence of human exposure to rabid domestic animals has decreased as a result of improved canine vaccination. Whereas more than 9,000 rabid dogs were reported in the U.S. in 1944, fewer than 100 were identified in 2002 [12]. Because cats are popular but less well supervised and less often vaccinated than dogs, rabid cats now outnumber rabid dogs. Rabies in small mammals such as mice and squirrels is rare, and transmission from them to humans remains undocumented. Larger rodents, such as woodchucks, are more frequently reported to be rabid [14].

"Cryptic" human rabies cases, in which there is no history of exposure to a rabid animal, are now the norm in the U.S. Molecular characterization has determined that the majority of these cases are associated with bat rabies viruses [15]. Bat bites are not dramatic and may not be appreciated when they occur or when the patient is examined. In other cases, people may recognize that a bite has occurred, but may not comprehend its implications or may believe that the risk of rabies is exceedingly low. Certain persons, such as young children or persons with disabilities, may be unable to provide an accurate history of a bite [16].

Since 1960, exposures other than bites have resulted in fewer than 35 documented human rabies cases. Most of the reported cases were attributable to poorly inactivated vaccine or to organ transplantation. Although extremely uncommon, transplantation of tissue from a donor with rabies will have disastrous consequences for the transplant recipient, as has been described recently [17]. No cases in human beings after indirect, non-bite exposure, such as touching a pet that may have been exposed to a rabid animal, have been reported. Theoretically, human-to-human transmission is possible, but no cases have been documented among healthcare workers [18].

Clinical presentation and diagnosis. The clinical course of rabies in humans is acute, usually progressing from initial symptoms to death within two to three weeks, even with intensive supportive care. The incubation period can range from a few days to several years, depending on the infecting strain. The period also is believed to be inversely related to the size of the inoculum and the proximity of the bite to the central nervous system. The subsequent clinical course can be described in three stages. In the prodromal stage, the symptoms and signs include fever, anorexia, nausea, vomiting, and malaise. Approximately one-half of the patients develop pain or paresthesia at the wound site. Within a few days, neurologic symptoms such as anxiety, agitation, irritability, or insomnia may become manifest. The acute neurologic stage follows, with objective signs of central nervous system involvement. Most patients have "furious" rabies, characterized by marked hyperactivity, disorientation, hallucination, or bizarre behavior. This hyperactivity later becomes intermittent and may be spontaneous or precipitated by tactile, auditory, or visual stimuli. Hydrophobia—spasm of the pharynx and larynx provoked by drinking or the sight of water—and aerophobia—a similar effect produced by air currents on the patient's face—are considered hallmarks of the disease. Seizures may also appear during this stage, as can dysfunction of the autonomic nervous system. A few patients die during this stage, but most go on to develop progressive paralysis and eventually coma. In some patients, the paralytic state dominates the entire clinical picture. Paralysis or paresis involves the proximal muscles and can be accompanied by constipation, urinary retention, or respiratory failure. In patients receiving intensive supportive care, the average duration of illness between the onset of paralysis and death is approximately seven days. Once neurologic symptoms have developed, survival is rare. With one exception [19], the only survivors recorded so far had received post-exposure prophylaxis or had been vaccinated previously [18].

Human rabies in the U.S. is rare, but also underdiagnosed. The diagnosis can be elusive if a history of animal exposure is not obtained. Hydrophobia and aerophobia, pathognomic when present, may be absent. Rabies, along with tetanus, Guillain-Barré syndrome, transverse myelitis, and toxic ingestion, should be considered in the differential diagnosis of any rapidly progressive encephalitis even if the history of bite is not available. It also is important to exclude other treatable encephalitides such as herpes encephalitis [20].

Routine laboratory tests and diagnostic studies are of little value in the diagnosis of rabies. Examination of the cerebrospinal fluid may show leukocytosis, but protein and glucose concentrations are often normal. Computed tomography and magnetic resonance imaging scans may be normal even in the presence of advanced rabies encephalitis. Therefore, specific diagnostic tests are necessary that include virus antigen detection, serologic studies, virus culture, and histopathologic examination. Virus antigen can be detected when a 6-mm punch biopsy of the skin from the nape of neck is stained with immunofluorescent rabies antibody, which reveals the antigen in sensory nerve endings at the base of hair follicles. This test is positive in 50% of patients in the first week of illness. Immunofluorescent antibody staining of the epithelial cells of the cornea (corneal impression test) can also help with the diagnosis. Seroconversion, in unvaccinated individuals, usually happens in the second week of illness, although it can be delayed by several days. In individuals who have been vaccinated, it is difficult to distinguish between infection and vaccination serologically, but measurable spinal fluid

titers and very high serum antibody titers suggest infection. Rabies virus also can be cultured from saliva, throat, tracheal secretions, cerebrospinal fluid, or brain biopsy specimens, but the yield is low. Postmortem examination of the brain reveals perivascular inflammation of the gray matter, neuronal degeneration, and the characteristic cytoplasmic inclusions called Negri bodies [13].

Description of rabies vaccine and human rabies immunoglobin. The Imovax Rabies Vaccine® (Aventis Pasteur, Lyon, France) is a sterile, stable, freeze-dried suspension of rabies virus prepared from strain PM-1503-3M (Wistar Institute, Philadelphia, PA). The virus is harvested from infected human diploid cells, concentrated by ultrafiltration, and inactivated by beta-propiolactone. One dose of reconstituted vaccine contains less than 100 mg of albumin, less than 150 mcg of neomycin sulfate, and 20 mcg of phenol red indicator. There is no preservative or stabilizer. The vaccine therefore should be used immediately after reconstitution or discarded. The potency of one dose (1 mL) is ≥2.5 IU of rabies antigen.

A single dose (20 IU/kg) of human rabies immune globulin (HRIG) should be given at the beginning of anti-rabies prophylaxis to provide protection for the first two weeks until the vaccine elicits an antibody response. All patients should receive HRIG except those who have previously received a cell culture vaccine as pre-exposure or post-exposure prophylaxis or who have documented rabies antibody titers after receiving another vaccine [20]. Even if there is a substantial delay between exposure and initiation of post-exposure prophylaxis, HRIG should be given. It can be given as late as the seventh day after vaccine administration, after which the vaccine should have elicited an antibody response. If possible, the full dose of HRIG should be infiltrated into the wound, and any remaining volume should be administered IM at a site distant from the vaccine site. The immune globulin should never be delivered in the same syringe as the vaccine [20].

Adverse reactions. Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic reactions to the vaccine. Reactions after vaccination with human diploid cell vaccine (HDCV) are less common than with previous vaccines. In a study using five doses of HDCV, local reactions such as pain, erythema, and swelling or itching at the injection site were reported by approximately 25% of recipients, and mild systemic reactions such as headache, nausea, abdominal pain, muscle aches, or dizziness were reported by 20%. A small percentage of recipients experienced immune complex reactions characterized by generalized urticaria, arthralgias, arthritis, angioedema, or malaise developing typically 2 to 21 days after administration of the booster dose of HDCV. These reactions have been attributed to the presence of beta-propiolactone-altered human albumin in the HDCV [21,22]. Local reactions usually can be managed with anti-inflammatory agents. Steroids should not be given because they can interfere with the development of immunity to the vaccine. When a person has a serious hypersensitivity reaction to the vaccine, revaccination should be undertaken only after careful consideration of the risk of acquiring rabies and then should be supervised carefully, with epinephrine readily available to counteract any anaphylactic reactions [23].

The HRIG can cause pain and low-grade fever. There have been no specific reported adverse reactions to HRIG, although immune globulins have been associated with angioneurotic edema, nephrotic syndrome, and anaphylaxis [20].

Evidence-based recommendations. The efficacy of pre-exposure immunization was documented by high-titer antibody responses to the Imovax Rabies Vaccine in trials conducted in England, Germany, France, and Belgium [24–27]. Seroconversion often was obtained with only one dose. With two doses one month apart, 100% of the recipients developed specific antibody, with a geometric mean titer of approximately 10 IU/mL. In the U.S., Imovax Rabies Vaccine resulted in geometric mean titers of 12.9 IU/mL at day 49 and 5.1 IU/mL at day 90 when three doses were given intramuscularly over one month [28].

Post-exposure efficacy of the Imovax Rabies Vaccine was proved during clinical experience

in Iran, where 45 persons received the vaccine after being bitten by rabid dogs or wolves. All except one also received one injection of HRIG. In contrast to the experience with other vaccines, this treatment protected all of the individuals against rabies [29].

The ACIP publishes protocols for prevention of human rabies in the U.S. [20]. The information presented in this article is consistent with the ACIP guidelines. The recommendations of the American Academy of Pediatrics are in accord with those of the ACIP. Vaccine doses during post-exposure prophylaxis are equivalent in adults and children [30].

Pre-exposure prophylaxis. The ACIP recommends three injections of 1 mL each of Imovax Rabies Vaccine, one on day zero, one on day seven, and one on either day 21 or day 28. It is recommended that vaccination be provided to persons at risk (laboratory workers, diagnosticians, veterinarians and their staffs, animal control officers, rabies researchers, and some travelers to areas where rabies is prevalent) before exposure [20,28] (Grade A). This strategy simplifies the management of a subsequent exposure because fewer vaccine doses are needed and HRIG is not required. Routine serologic analysis for verification of the presence of virus-neutralizing antibody is unnecessary after primary vaccination unless major interruptions in the schedule occur or questions arise about immune competence. Thereafter, the need for routine booster vaccination may be monitored by serologic testing performed every six months to two years as long as the person remains at risk. If titers fall below a minimal acceptable value (complete neutralization at a serum dilution of 1:5), a single vaccine booster dose is administered. Persons who work with rabies virus in research laboratories or vaccine production facilities are at highest risk of exposure and should have their rabies antibody titers checked every six months. Other laboratory workers (those performing rabies diagnostic testing), spelunkers, veterinarians and their staffs, and animal control and wildlife officers in areas where animal rabies is enzootic, also should have antibody measurements done every two years [31].

Post-exposure prophylaxis. Bites from bats and high-risk wild carnivores such as raccoons, skunks, foxes, bobcats, and coyotes warrant consideration of immediate post-exposure prophylaxis. In the case of direct contact between a person and a bat, the possibility of a bite should be considered unless the exposed person can be reasonably certain that a bite did not occur. Post-exposure prophylaxis should be considered for persons who were in the same room as a bat, and who might be unaware or unable to communicate that a bite occurred [30]. Rabies has been reported in large rodents (woodchucks and beavers) in areas where rabies is enzootic. Rabies has been diagnosed rarely in small mammals such as rabbits and small rodents (squirrels, chipmunks, rats, hamsters, gerbils, guinea pigs, and mice), and there has never been a documented case of transmission from these small mammals to a human being. Post-exposure prophylaxis may be considered for the latter in unusual circumstances (a bite from a small mammal with a history and clinical signs compatible with rabies), unless the animal tested negative. An apparently healthy dog, cat, or ferret that bites a person should be confined and observed daily for ten days. The animal should not receive rabies vaccine during the observation period. A veterinarian should evaluate the animal at the first sign of illness. Management of animals other than dogs, cats, and ferrets depends on the species, the circumstances of the bite, the local rabies epidemiology, and the biting animal's history, health status, and potential for exposure to rabies. Because prior vaccination of any animal may not be 100% effective, current vaccination does not preclude the necessity for an observation period, or as warranted, euthanasia and testing. If the animal exhibits signs of rabies during the ten-day observation period, the exposed person should immediately begin to receive prophylaxis, and the animal should be euthanized and its brain tissue tested for rabies. If the animal is confirmed to have rabies, post-exposure prophylaxis should be completed, whereas if the test results are negative, post-exposure prophylaxis can cease. Diagnostic testing of brain tissue should be completed within 24–48 h so that a decision about start-

ing post-exposure prophylaxis can be made. If testing will take longer, prophylaxis should be started, pending the results of testing [30].

Post-exposure prophylaxis consists of three primary elements: Wound care, infiltration of HRIG, and vaccine administration. Immediate, thorough washing of all bite wounds and scratches with soap and water is perhaps the most effective measure for preventing rabies. In experimental animals, local wound cleansing markedly reduces the likelihood of rabies [32]. Post-exposure anti-rabies immunization should always include administration of HRIG and vaccine, with one exception. Persons who have been immunized previously with the recommended pre-exposure or post-exposure regimens of HDCV, or who have been immunized with other types of vaccines and have a documented adequate rabies antibody titer, should receive vaccine only [30].

The ACIP recommends a five-dose regimen for post-exposure prophylaxis. Five 1-mL doses of Imovax Rabies Vaccine are given in the deltoid muscle on days 0, 3, 7, 14, and 28 in conjunction with a single dose of HRIG 20 IU/kg on day 0. As much as possible of the dose of HRIG should be infiltrated into the wound. Any remaining volume should be administered IM at a site distant from the vaccine site [20, 29] (Grade D).

Anthrax

Biological warfare. The clinical disease known as anthrax is caused by *Bacillus anthracis*, a gram-positive, spore-forming bacillus capable of infecting human and animal hosts. Several factors affect the destructive capabilities of anthrax as a biological weapon. The delivery of spores has been a major obstacle to the creation of widespread anthrax contamination. Spores can be spread easily in the air by missiles, rockets, aerial bombs, or sprayers, but the accompanying explosions damage the anthrax particles considerably [33]. Particle size also affects virulence and infective potential. When a particle is larger than 5–10 micrometers, infectivity may decrease substantially, as the 8,000 to 10,000 spores necessary for infection may not be inhaled. One- to two-micrometer spores are highly lethal, but the creation of stable spores smaller than five micrometers has not been reported outside state-sponsored laboratories [33]. Also, the concentration of the powder affects the quality of the anthrax. The U.S. has produced the most concentrated anthrax known, with as many as one trillion spores per gram. Lastly, clumping of multiple spores limits wide-spread dissemination. To limit this clumping, sophisticated processing is carried out with substances such as silica and treatment to offset the electrostatic charge of the particles to allow maximum dispersal. Anthrax spores that are smaller than five micrometers and have been treated to prevent clumping and then concentrated are referred to as "high-grade" or "weapons-grade" anthrax [34].

Pathogenesis. Anthrax is worldwide in prevalence and affects primarily herbivores that while grazing ingest spores imbedded in the soil, which may harbor the bacteria for years. In humans, the anthrax toxin consists of three proteins that combine for the lethal effect (see below). The toxin affects neutrophils and macrophages, inhibiting bacterial phagocytosis and preventing the oxidative burst of neutrophils [35].

Clinical presentation. The human disease has three forms: Cutaneous, pulmonary, and gastrointestinal. The incubation period is generally 2–60 days. In developed countries, 95% of affected patients have the cutaneous form, acquired by contact with infected goats, sheep, or cattle. The cutaneous form starts as a painless pruritic papule resembling an insect bite, sometimes surrounded by vesicles. This papule develops into an ulcer with a necrotic center. The lesions usually start on the extremities and spread to the head and neck. Lymphadenopathy with systemic signs and symptoms of fever, malaise, and headache may accompany the cutaneous lesions. The case-fatality rate of cutaneous anthrax is 20% without antibiotic treatment but less than 1% with treatment [36].

Many public health and U.S. State Department officials believe that the most likely scenario for a biological attack using anthrax would be a release of aerosolized spores over

densely populated areas, causing large numbers of cases of pulmonary anthrax [33]. The pulmonary or inhalational form can result from the inhalation of concentrated spores in a biological attack, but it has also been described in handlers of Pakistani goat hair in textile workers in Switzerland and the U.S. [37]. The presentation of the pulmonary form is classically biphasic but can be variable. Early symptoms can mimic an upper respiratory infection with a dry cough, low-grade fever, and malaise for several days. As the symptoms become apparent, the process can involve the hilar and mediastinal lymph nodes, causing substernal pain, bloody pleural effusions, and a wide mediastinum on chest radiography. A fulminant acute phase develops later with severe respiratory distress, high fever, meningitis, and shock. Hemorrhagic mediastinitis is considered a pathognomic sign. The pulmonary form is invariably fatal if untreated and 80% fatal if treated after the onset of symptoms [38].

Ingestion of contaminated meat causes gastrointestinal anthrax. Some of the abdominal manifestations are nonspecific, including abdominal pain, fever, nausea, and vomiting. More severe symptoms can also occur, including upper or lower gastrointestinal bleeding or peritonitis. The gastrointestinal type can progress to death within five days. It has never been described in the U.S. [39].

On recognizing the symptoms of anthrax, health care workers should send any affected body fluids for culture. These specimens would include material from vesicles, pleural fluid, cerebrospinal fluid, and stool. Standard blood cultures should yield large gram-positive bacilli within 6–24 h, and the clinical laboratory should be alerted to the possibility of anthrax so the organism is not dismissed as a skin contaminate. Sputum culture and gram stain are unlikely to be diagnostic. An enzyme-linked immunosorbent assay (ELISA) is available only in a national reference laboratory [33,37].

Vaccine description. The anthrax vaccine is an inactivated cell-free filtrate of *B. anthracis* adsorbed to aluminum hydroxide (BioThrax®, Bioport Corporation, Lansing, MI). Anthrax manifestations are the result of three major toxins: Protective antigen (PA), lethal factor (LF), and edema factor (EF). Lethal factor is a zinc metalloprotease that inhibits mitogen-activated protein kinase. Edema factor is a calmodulin-dependent adenylate cyclase that generates cyclic adenosine monophosphate in the cytoplasm of eukaryotic cells. Protective antigen, the only major antigen in the vaccine [40,41], is an 82-kD protein that binds to receptors on most mammalian cells. It is then cleaved by a cell surface protease, exposing a site that binds competitively to either EF or LF, creating a complex that enters the cell.

The vaccine is recommended for administration to adults 18 to 65 years of age in six subcutaneous injections at 0, 2, and 4 weeks and at 6, 12, and 18 months. An annual booster injection is recommended to maintain immunity. Shorter vaccination schedules are being investigated. With this administration schedule, antibody titers to PA peak within 14 days after the third dose [42], and 95% of vaccinated individuals seroconvert with a four-fold increase in anti-PA titer. However, the protective titer has not been defined, and the duration of protection is not known [43].

Vaccine efficacy. Because of the infrequent occurrence of natural infection and the unpredictability of human-induced exposure, the efficacy of the vaccine is unclear. Only one controlled trial in human beings has been published, and it is more than 40 years old [44]. This was a single-blind, placebo-controlled trial of approximately 800 mill workers at risk of infection from animal products (379 received vaccine and 414 received the placebo injection). The vaccine efficacy was 92.5% (the lower 95% confidence limit was 65%).

Adverse reactions. Many individuals have received the vaccine in military and civilian programs in recent years, providing a reasonable assessment of the risk of adverse effects. In a summary of prelicensure vaccine administration to 7,000 individuals, severe local reactions occurred in 1%, moderate local reactions (edema and induration) in 2%, and mild local reactions in 20% of recipients. Systemic reactions (e.g., fever, chills, body aches) were reported by fewer than 0.1% of vaccinees [44].

From 1990 to 2000, 1,544 adverse events were

reported to the Vaccine Adverse Event Reporting System (VAERS), of which 5% were serious [45]. The most frequent were injection site hypersensitivity, injection site edema, pain, headache, arthralgia, and pruritus. There were two reports of anaphylaxis, and two deaths were associated with the vaccine, but a causal relationship was not established. The incidence of adverse effects per dose of vaccine cannot be ascertained from the available data.

More than 425,000 military service personnel received more than 1.6 million vaccine doses from 1998 to 2000, and "no patterns of unexpected local or systemic adverse events have been identified" [46]. A review of the experience of 1,583 employees of the Army Medical Research Institute of Infectious Diseases who received the vaccine over the past 25 years demonstrated that 1% of inoculations were associated with systemic effects [47]. The most frequent adverse effects were headache (0.4%) and local or injection site reactions (2.6%). In one series of almost 5,000 vaccinated military personnel, most adverse events were localized, minor, and self-limited, including arthralgia, headache, and fatigue [46].

The potential for congenital anomalies in children when the vaccine is administered to their mothers in the first trimester of pregnancy has not been studied. Therefore, the vaccine is not licensed or recommended for use in pregnancy and is rated Pregnancy Category D by the Food and Drug Administration. The ACIP recommends that pregnant women be vaccinated against anthrax only if the potential benefits outweigh the potential risk to the fetus [38].

The Institute of Medicine concluded that although no significant adverse effects of the anthrax vaccine have been reported, the evidence is inadequate to determine whether an association exists between anthrax vaccination and long-term health outcomes [48]. The CDC concluded that the chronic multi-system illness experienced by some Persian Gulf War veterans was not associated with the vaccine or other specific anthrax exposures [49].

Evidence-based recommendations. There is insufficient evidence to document the efficacy of the anthrax vaccine in individuals who are exposed or have high risk of exposure to anthrax. Pre-exposure efficacy has been documented only in mill workers who were exposed in the workplace [44]. Despite the lack of clinical trial data, anthrax vaccine is recommended in certain individuals by the ACIP [38,50].

Pre-exposure prophylaxis. For pre-exposure prophylaxis, anthrax vaccine use should be based on quantifiable risk of exposure. The vaccine should be administered by subcutaneous injection at 0, 2, and 4 weeks and then at 6, 12, and 18 months [38]. Groups at risk for repeated exposure should be given priority for vaccination, including: All U.S. active and reserve-duty military personnel; laboratory personnel handling environmental specimens; workers who will be making repeated entries into known *B. anthracis* spore-contaminated areas after a terrorist attack; and workers in other settings in which repeated exposure to aerosolized *B. anthracis* spores might occur. Laboratory workers using standard Biosafety Level 2 practices in the routine processing of clinical samples or environmental swabs are not considered at increased risk. Routine vaccination of veterinarians in the U.S. is not recommended because of the low incidence of animal cases. However, vaccination might be indicated for veterinarians and other high-risk persons handling potentially infected animals in areas with a high incidence of anthrax. Routine vaccination of emergency first-responders, federal responders, medical practitioners, and private citizens is not recommended [38,44,50,51] (Grade B).

Post-exposure prophylaxis. Post-exposure vaccination should be administered as follows: Three injections of vaccine, one as soon as possible and the others at two and four weeks. Post-exposure prophylaxis with the vaccine and antibiotics against *B. anthracis* is recommended following an aerosol exposure to spores [38] (Grade E). The vaccine is effective at preventing disease in non-human primates after exposure [52,53].

A major issue with post-exposure prophylaxis is how long antimicrobial therapy should be given when the vaccine is used. The ACIP recommends at least a 30-day course of ciprofloxacin or doxycycline post-exposure for

persons who have been vaccinated partially or fully. Antibiotics should be administered at least until the third vaccine dose is given [38]. Although the shortened vaccine regimen has been effective post-exposure when co-administered with antibiotics, the duration of protection from vaccination is not known. Because human-to-human transmission has not been documented, contacts and friends do not need prophylaxis unless they also were exposed to the aerosol [38].

Tetanus

Epidemiology, etiology, and pathophysiology. Since 1975, fewer than 100 cases of tetanus have been reported annually in the U.S., and for the past ten years, the number has averaged less than 50 per year [54]. Thus, tetanus has become rare, ranking in frequency behind botulism, brucellosis, leprosy, Rocky Mountain spotted fever, and typhoid fever. This situation can be attributed to several factors, including a decrease in environmental exposure to *Clostridium tetani*, better management of tetanus-prone wounds, and universal immunization of children and military personnel. Because the primary tetanus toxoid (TT) series induces excellent immune memory, booster doses reliably result in a brisk anamnestic antibody response, even when intervals of 20 years or more have elapsed since the last dose. Therefore, an antitoxin concentration below 0.1 IU/mL (the generally accepted minimum protective concentration) is strong evidence that either the individual never received a primary series of TT or has not received a booster dose in the previous decade [55].

A national population-based serologic survey conducted from 1988 to 1991 showed serologic evidence of immunity declining from 80% among persons aged 6 to 39 years to 28% among persons 70 years or older [3]. In national health interview surveys, only 27–36% of individuals age 65 years or older reported receiving a tetanus vaccination during the previous ten years. More than 90% of the small number of remaining tetanus cases in the U.S. occur in individuals who do not know their immunization status or report having received less than a full primary immunization series [56].

Thus, despite serologic evidence that large numbers of adults are susceptible, tetanus is rare among individuals who have had their full primary series at any previous time. This fact suggests strongly that the protective antitoxin standard of 0.1 IU/mL is not nearly as reliable as a history of full immunization in predicting protection from disease. Additional evidence of the long-term protective effect of the primary immunization series is the lifelong amelioration of disease severity. In more than 20 years of CDC data, no deaths have been reported from tetanus among individuals who have been fully immunized at any time [56–58].

Universal diphtheria-tetanus (acellular)-pertussis (DTP/DTaP) immunization of children has all but eliminated pediatric tetanus except among immigrant children and other pockets of subpar vaccine delivery, and tetanus has become primarily a disease of adults who have never been immunized fully. Special risk factors include injection drug use and chronic wounds, in addition to acute traumatic injuries. The recommendations for the use of TT and tetanus immune globulin in the treatment of tetanus-prone wounds remain intact and would not be affected by a decrease in the availability or utilization of tetanus boosters [56].

Tetanus-diphtheria toxoid (Td) and TT are used almost exclusively in adults, and approximately 16 million doses are distributed annually in the U.S. [54]. Approximately one-half of the total is delivered as part of routine care (decennial booster) and the other half in the management of tetanus-prone wounds.

Clostridium tetani is a spore-forming, gram-positive bacillus. Although the organism is an obligate anaerobe, its spores remain viable at ambient oxygen concentrations. The spores are resistant to extremes in temperature and humidity and can survive indefinitely. Spores are ubiquitous in soil and in the feces of many animals and human beings [59]. Carried into wounds along with soil, spores may not germinate immediately because of unfavorable local tissue conditions only to be activated after the wound has healed, which may account for the cases of tetanus that have no identifiable source.

When conditions favor anaerobic proliferation, the spores germinate into mature bacilli, which then elaborate the toxins tetanolysin and

tetanospasmin. Tetanolysin has an unclear role in clinical tetanus; it may contribute to an anaerobic environment by damaging viable tissue [60]. Tetanospasmin is primarily responsible for the clinical manifestations of tetanus, entering peripheral nerves and traveling via axonal retrograde transport to the central nervous system. Tetanospasmin then enters presynaptic neurons and disables neurotransmitter release, most importantly of the inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine. This results in disinhibition of end-organ neurons such as motor neurons and those of the autonomic nervous system, accounting for the muscle spasms characteristic of tetanus and the autonomic instability of severe tetanus. The rapidity of disease onset correlates with its severity. Recovery involves synthesis of new presynaptic components and their transport to the distal axon, accounting for the typical 2–3 week period before clinical improvement begins [60].

Clinical presentation and diagnosis. There are four clinical forms of tetanus, depending on the extent and location of the involved neurons: Generalized, local, cephalic, and neonatal. In the U.S. and other developed countries, generalized tetanus is the most common form, occurring in 80% of cases [56]. In 50–75% of cases, the initial symptom is trismus or "lockjaw" secondary to masseter muscle spasm. Risus sardonicus, the "ironical smile" of tetanus, occurs because of facial muscle contraction. Nuchal rigidity and dysphagia also may be initial complaints. As the disease spreads, generalized muscle spasms occur, either spontaneously or in response to minor stimuli such as touch or noise. Opisthotonus, a tonic contraction similar to decorticate posturing, is described classically. Severe spasms can result in vertebral and long bone fractures and detachment of tendons from their insertions. Unfortunately for the patient, mental status is not affected, and the spasms are accompanied by severe pain [61].

In the acute phase, death results from acute respiratory failure caused by diaphragmatic paralysis or laryngeal spasm [60]. With intensive medical intervention, including the use of neuromuscular blockade and mechanical ventilation, early death can be averted. In patients surviving beyond the acute phase, autonomic instability becomes the major cause of death, with a fatality rate of 11–28% [62]. Autonomic instability appears several days after the onset of generalized spasms and manifests most importantly as labile hypertension, tachycardia, and pyrexia. Dysrhythmias and myocardial infarction are the most common fatal events. The exact mechanism of the late-phase syndrome is unclear but likely involves disinhibition of the sympathetic nervous system. Case reports have documented elevated concentrations of catecholamines in patients with autonomic instability; concentrations decrease with successful treatment [63,64].

Local tetanus presents as persistent muscle rigidity close to the site of injury. The rigidity may linger from weeks to months but often resolves without sequelae. A caveat is that what appears to be localized tetanus may instead be the first sign of generalized tetanus. Local tetanus is responsible for 13% of all tetanus cases, and its case-fatality rate is about 1% [65].

Cephalic tetanus is an uncommon variant of localized tetanus that involves the cranial nerves and accounts for 6% of all cases of tetanus [56]. Cephalic tetanus uniquely results in nerve palsies as well as muscle spasms. The seventh cranial nerve (CNVII) is most often involved, followed by CNVI, CNIII, CNIV, and CNXII in decreasing order of frequency. Cephalic tetanus also presents as trismus, but in 42% of cases, cranial nerve deficits precede trismus. In such cases, cephalic tetanus is easily misdiagnosed. With its predilection for CNVII, it commonly mimics Bell's palsy. Head trauma and otitis media are commonly cited etiologies. About two-thirds of patients progress to generalized tetanus, and the overall mortality rate is 15–30% [66].

Neonatal tetanus is generalized tetanus that occurs around the end of the first week of life. Symptoms begin with nonspecific irritability and poor feeding and progress rapidly to generalized spasms. The portal of entry is the freshly cut umbilical cord. The risk of contracting neonatal tetanus is directly related to the cleanliness of delivery conditions and to maternal immunization because passive transfer of maternal immunoglobins is protective [67]. Mortality is high, 50–100%, because of the

high load of toxin in relation to body weight. Neonatal tetanus occurs largely in developing countries, with an estimated 80% of cases concentrated in twelve countries in Africa and Asia [68].

The diagnosis of tetanus must be made on clinical grounds alone, as there are no laboratory tests that can diagnose or rule it out. A protective serum antitoxin antibody concentration, commonly accepted as 0.1 IU/mL, makes the diagnosis of tetanus unlikely, although not impossible, as there are reports of tetanus in immunocompetent individuals having protective antibody concentrations. Unfortunately, antitoxin antibody values are not likely to be available at the time management decisions must be made. Fortunately, the presentation of tetanus is so characteristic that a presumptive diagnosis is possible in most cases [69].

The differential diagnoses are few. Trismus can be caused by peritonsillar or odontogenic abscesses, which can be excluded by history and physical examination. Dystonic reactions can present as trismus. A positive response to diphenhydramine will quickly differentiate non-specific trismus from tetanus. Strychnine poisoning can resemble generalized tetanus grossly. Strychnine disables glycine release, as does tetanospasmin, but does not affect GABA release. There were 40 cases of strychnine poisoning in the U.S. in 1997, an incidence similar to that of tetanus [70]. In most cases, timely measurement of the blood strychnine concentration will not be available to the emergency physician. Nevertheless, the test should be ordered for inpatient followup. Hypocalcemia causing tetany is another mimic, which can easily be excluded with laboratory testing. Other entities that cause diffuse muscle spasm, such as seizures and encephalopathies, are accompanied by changes in mental status. Processes that affect muscles locally, such as myopathies or neuropathies, tend to cause weakness rather than spasm and rigidity.

Description of tetanus toxoid, tetanus-diphtheria toxoid, and human tetanus immune globulin. Tetanus is preventable with proper use of TT and human tetanus immune globulin (HTIG). Tetanus toxoid is an inactivated form of tetanospasmin available in three forms, variably combined with diphtheria and pertussis vaccine: DTaP, Td, and TT. DECAVAC® (Tetanus and Diphtheria Toxoids Absorbed for Intramuscular Injection; Aventis Pasteur) is a sterile suspension of aluminum-precipitated toxoids in isotonic sodium chloride solution. Tetanus and diphtheria toxins produced during the growth of cultures are detoxified with formaldehyde and then purified separately by serial ammonium sulfate fractionation and diafiltration [67].

The DECAVAC vaccine is supplied in a unit dose of 0.5 mL in a preservative-free syringe. Seroprevalance studies indicate that one-half or more of adults in the U.S. lack what is considered a protective antitoxin concentration (0.1 IU/mL) against diphtheria [71,72]. Despite the serologic evidence of susceptibility and the corollary that most adults have not complied with the decennial booster recommendation, diphtheria remains a disease of negligible incidence in the U.S. [67]. Because diphtheria has been a pediatric disease historically, the focus of diphtheria immunization programs has been children. Before the Td combination was developed in the mid-1960s, there was no recommendation for diphtheria boosters for adults. The adult diphtheria toxoid recommendation came about because of the availability of the combined Td product rather than an independent concern about diphtheria [73]. Tetanus-diphtheria toxoid is the recommended preparation for active tetanus immunization and wound management of patients older than seven years. In such persons, Td is preferred to single-antigen TT to enhance diphtheria protection [67].

Tetanus immune globulin (BayTet®; Bayer Biological Products, Research Triangle Park, NC) is a sterile solution of tetanus hyperimmune globulin for intramuscular administration. Tetanus immune globulin is prepared by cold ethanol fractionation from the plasma of donors immunized with TT. The inactivation and removal of enveloped and non-enveloped viruses during the manufacturing process has been validated in laboratory studies [67]. Tetanus immune globulin supplies passive immunity to those individuals who have low or no immunity. The antibodies neutralize the free form of the powerful exotoxin produced

by this bacterium. Historically, such passive protection was provided by antitoxin derived from equine or bovine serum. However, the foreign protein in these products often produced severe allergic manifestations, even in individuals who demonstrated negative skin or conjunctival tests prior to administration. Estimates of the frequency of these foreign protein reactions after injection of equine antitoxin range from 5–30%. If passive immunization is needed, intramuscular injection of HTIG is therefore the treatment of choice, as it provides longer protection than antitoxin of animal origin and causes fewer adverse reactions [74]. Consisting of immunoglobulin (Ig)G, its half-life of 25 days ensures long-lasting protection [75]. Intradermal injection (not recommended) causes local irritation that does not represent an allergy to HTIG. Intravenous injection can cause hypotension.

Adverse reactions. Common adverse reactions to TT, including erythema, swelling, and tenderness at the injection site, are minor and of no long-term consequence. In a clinical study involving individuals six years of age and older, 19% of vaccinees noted local reactions, whereas 2% had systemic reactions consisting of headache, malaise, or temperature elevation. Arthus-type hypersensitivity reactions, characterized by severe local reactions generally starting 2–8 h after the injection, may follow receipt of TT. Such reactions may be associated with high concentrations of circulating antitoxin in persons who have had overly frequent injections of TT [76].

Patients who give a history of allergy to tetanus vaccine are most likely referring to a local or nonspecific systemic reaction. These events are not contraindications to receiving TT. Other false contraindications include mild, acute illness; fever; and a family history of an adverse reaction to vaccination. Anaphylactic reactions, neuropathies, and encephalopathies are rare and constitute the only true contraindications to TT. Patients with a history of anaphylaxis should be referred for skin testing because they may no longer be reactive and if not, can receive future vaccinations [67].

Adverse reactions to properly administered HTIG are rare and consist largely of discomfort at the injection site and a slight temperature elevation. A history of a severe adverse reaction likely represents previous use of equine antitoxin, which has a 10% incidence of serum sickness and a 1/100,000 incidence of fatal anaphylaxis [75]. Human tetanus immune globulin is widely available in the U.S., so that equine antitoxin is rarely used. In contrast, equine antitoxin is used extensively in developing countries because of greater availability and affordability.

Evidence-based recommendations. Spores of *C. tetani* are ubiquitous, but serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the U.S. Thus, universal primary vaccination with subsequent maintenance of adequate antitoxin concentrations by means of appropriately timed boosters is necessary to protect all age groups [67]. After adequate immunization with TdT, it is believed that protection persists for at least 10 years. Protection against disease is attributable to the development of neutralizing antibodies to tetanus and diphtheria toxin.

The efficacy of TdT used in DECAVAC vaccine was determined by comparison with a serological correlate of protection (0.1 IU/mL) established by the Panel on Review of Bacterial Vaccines and Toxoids [54,77]. A clinical study to evaluate the serological responses and adverse reactions was performed in individuals six years of age and older. Protective concentrations of antibody were achieved in more than 90% of the study subjects after primary immunization with both components. Booster effects were achieved in 100% of the individuals with existing antibodies [78].

Talan et al. measured the prevalence of protective anti-tetanus antibody concentrations in approximately 2,000 adults presenting for wound care in five academic emergency departments. More than 90% of the patients had anti-tetanus antibody concentrations above the protective cutoff value of 0.1 IU/mL. Lower prevalences of protection were found in elderly patients, those with less education, immigrants from countries outside North America or Western Europe, and those with an unknown vaccination history or known inadequate vaccination [79].

Table 3. Risk of Tetanus According to Wound Characteristics

Non-tetanus prone	*Tetanus prone*
<6 h old	>6 h old
<1 cm deep	>1 cm deep
Clean	Contaminated
Linear	Stellate
Neurovascular intact	Denervated, ischemic
Not infected	Infected

Adapted from Edlich et al. [65].

Given the present low incidence of tetanus in the U.S. and the relatively high prevalence of protective tetanus antitoxin in individuals who are not members of defined risk groups, questions have arisen regarding the appropriateness of the ACIP guidelines for tetanus prophylaxis in wound care [79]. Nevertheless, the current recommendations should be maintained for several reasons. As reviewed by Wassilak and Galazka, individual antibody responses and the duration of immunity after tetanus immunization differ widely [54]. Tetanus occurs when the amount of toxin produced by wounds contaminated with *C. tetani* overwhelms available antitoxin. Periodic reports of tetanus cases occurring in the face of protective tetanus antitoxin concentrations support the concept that no single antibody titer value can define minimum protection for all patients. Anti-tetanus antibody concentrations used to define population immunity do not guarantee individual protection [54].

Tetanus prophylaxis for the acute wound. In the setting of an acute injury, the CDC recommendations for tetanus prophylaxis depend on the wound characteristics and the patient's immunization history (Tables 3 and 4) [67]. Many characteristics of wounds encountered in the emergency department render them non-tetanus-prone: Recent; linear with sharp edges; well vascularized; and not obviously contaminated or infected. All other wounds are considered tetanus-prone, particularly those resulting from blunt trauma and bites and those that are grossly contaminated or infected. The CDC recommends HTIG 250 IU, given at a site separate from the TT to avoid interaction between the two, only for patients with tetanus-prone wounds who have never completed a primary immunization series. In small children, the routine dose of HTIG may be calculated by the body weight (4 IU/kg). However, it may be advisable to administer the entire 250 IU regardless of the child's size, because theoretically, the same amount of toxin will be produced in a child's as in an adult's body by the infecting organism (53,66,76) (Grade B).

If a patient has not completed a primary immunization series, a tetanus booster is required, and the patient will need followup to complete the series. If the patient has had primary immunization, a booster is given if the last dose was more than five years previously with a tetanus-prone wound or more than ten years previously with a non-tetanus-prone wound. Patients with a contraindication to TT must be managed with HTIG alone [54,67,77,78] (Grade B).

Immunization in high-risk groups. Patients from certain high-risk groups often present to the emergency department for care and require special attention, as standard prophylaxis may not provide sufficient protection from tetanus. These groups include elderly patients, human immunodeficiency virus (HIV)-infected individuals, and intravenous drug users (IVDUs).

Because of a declining immune system, elderly patients do not respond as well to vaccination as do children and younger adults. The formation of tetanus antibodies after vaccination is not as rapid as in younger adults, the peak titer is not as high, and the antibodies do not last as long [80]. In a similar fashion, the immunogenic response to vaccination in HIV-infected individuals is blunted, and antitoxin antibody concentrations decline more quickly than in HIV-negative individuals. As expected,

Table 4. Tetanus Prophylaxis of Acute Wounds

	Clean wounds	*Tetanus-prone wounds*	
Primary immunization	Td	Td	HTIG
Not complete	Yes	Yes	Yes
Completed <5 years	No	No	No
Last booster >5 years	No	Yes	No
>10 years	Yes	Yes	No

Adapted from ACIP [67]. See text for abbreviations.

the response to vaccination deteriorates as HIV infection progresses [56].

The elderly, HIV-infected, or otherwise immunocompromised patient may not have a protective concentration of tetanus antibodies at the time of injury, and vaccination alone may not lead to prompt or sufficient formation of antibodies to protect the patient. If prophylaxis is indicated, more liberal use of HTIG may be warranted in these patients, regardless of primary immunization, to ensure protection against tetanus. More frequent dosing of TT may help sustain antibody concentrations in the protective range. There are no official guidelines endorsing this approach. However, in considering the risks and benefits to a given patient, it should be kept in mind that HTIG and TT are safe, whereas the morbidity and mortality associated with acute tetanus are considerable [81] (Grade E).

Intravenous drug users are a burgeoning group at high risk for tetanus. They accounted for 18% of all cases of tetanus between 1995 and 1997 but only 2.1–4.5% of the cases seen between 1982 and 1994 [56]. Factors that place IVDUs at risk include low rates of immunization, contaminated drugs, repeated injection wounds under dirty conditions, and formation of skin abscesses and chronic ulcers, which provide ideal conditions for tetanus development [56]. Social and behavioral factors often lead to delayed or sporadic medical care, which compound these risk factors. Intravenous drug users may present for complaints unrelated to acute wounds. However, their drug use should be considered a risk factor that requires attention to tetanus prophylaxis [56,81] (Grade E).

Post-splenectomy vaccination

The spleen was once viewed as a superfluous organ, similar to the appendix, and it was removed with impunity if injured. It was not until the 19th Century that the spleen was associated with immune function. The earliest association linking splenectomy to life-threatening infection was reported by Morris and Bullock in 1919, when they demonstrated a four-fold increase in lethal infection with *Bacterium enteritidis* in splenectomized rats [82]. Subsequently, King and Schumacker reported five cases of severe infection in infants following splenectomy for spherocytosis [83]. Subsequent reports confirmed these observations, and the term "overwhelming post-splenectomy infection" (OPSI) was popularized by Diamond in 1969 [84].

The surgical management of splenic injuries has evolved over the past several decades, resulting from sound scientific evaluation. Although the infectious consequences of splenectomy are well known, preventive practices differ substantially among surgeons. Few written guidelines delineate evidence-based recommendations for vaccination, and what information is available is not well disseminated [4].

Splenic function. Because of its unique architecture and abundant blood flow, the spleen plays a prominent role in the defense against blood-borne organisms. Ninety percent of arterial blood flow to the spleen is directed through the red pulp and circulates in the meshwork of splenic cords before squeezing through the endothelial pores of the splenic sinuses [85]. Because of the organization of the microcirculation, blood-borne bacteria remain in contact with splenic phagocytes, allowing clearance of even poorly opsonized bacteria.

Invasive, encapsulated bacterial pathogens possess a surface polysaccharide capsule that impedes opsonization by Ig or complement in the circulation. The spleen plays an important role in the production of immune mediators that aid in the clearance of bacteria and viruses. The mediators, known as opsonins, coat circulating bacteria and viruses and convert them into immune complexes. Although the liver clears some of these circulating immune complexes, the spleen is predominant [85].

Several lines of evidence suggest that splenectomized patients have compromised humoral immunity, deficient in both complement and Ig. A particular subset of circulating memory B cells (IgM memory B cells, which respond to bacterial polysaccharides; 86), are absent in congenitally asplenic patients and are severely depleted immediately after splenectomy. Memory B cells are highly specific, long-lived cells generated in germinal centers after somatic mutation, selection, and class switch, in response to a specific etiologic agent or

vaccine. They persist and produce antibodies rapidly on a second challenge with the same antigen. In humans, 30–60% of B cells are considered memory B cells, one-half of which are IgM memory B cells. The IgM memory cells are dependent on a functional spleen for their generation and survival and are responsible for the T-cell-independent response to bacterial polysaccharides [87].

The spleen produces tuftsin, a tetrapeptide (Thr-Lys-Pro-Arg) that stimulates phagocytosis. Tuftsin is part of the specific carrier molecule leukokinin, which is cleaved following passage through the spleen, leaving a molecule known as leukokinin-S. Tuftsin binds to specific receptors on granulocytes, monocytes, macrophages, and natural killer cells. Once activated, tuftsin modulates the biological activities of phagocytic cells [88]. The amount of tuftsin is significantly lower after splenectomy [89]. Szendroi et al. demonstrated a return to normal tuftsin concentrations in children after splenectomy for trauma following autotransplantation of minced splenic tissue into the omentum [90].

The spleen produces properdin, an opsonin that plays a crucial role in the alternative pathway of complement activation. The alternative pathway is activated in the absence of antibody, and generates both soluble and membrane-bound forms of C3 convertase, an enzyme that catalyzes the proteolysis of C3. The alternative pathway form of C3 convertase decays rapidly unless it is stabilized by binding with properdin. Binding of properdin with C3 convertase allows conversion of C3 to C3b. Post-splenectomy patients lack properdin, which may contribute to the risk of developing OPSI [91].

An exclusive function of the spleen, pitting, is clearance of intraerythrocyte inclusions, while maintaining the integrity of the red blood cell. The inclusions removed by the spleen include particulate matter, Heinz bodies (denatured hemoglobin), Howell-Jolly bodies (nuclear remnants), and Pappenheimer bodies (iron granules) [91]. Red blood cells must deform to pass through slit-like fenestrations of the sinus endothelium. Rigid inclusions, unable to traverse the narrow passage, are entrapped, excluded from the cell, and phagocytized by resident macrophages. Asplenic and hypersplenic patients lose their ability to clear damaged red blood cells and inclusions from the circulation. These patients display a variety of abnormal erythrocytes in peripheral blood smears [91].

The spleen acts as a reservoir for platelets and granulocytes. In non-pathologic states, the spleen sequesters approximately 30% of the body's platelets, and can release them into the circulation in response to certain stimuli. In hypersplenism secondary to portal hypertension, the spleen can sequester as many as 90% of platelets, resulting in severe thrombocytopenia. In contrast, there is a significant increase in circulating platelet and granulocyte counts after splenectomy. These counts usually normalize within a few days [91].

Overwhelming post-splenectomy infection. Overwhelming post-splenectomy infection is a fulminant, potentially life-threatening condition that may occur weeks to years after removal of the spleen. The precise incidence of OPSI remains controversial; published estimates differ considerably for many reasons, including different disease definitions, duration of followup, stratification for age, indication for splenectomy, and underlying disease [92].

The risk of post-splenectomy sepsis is highest in children, especially those under two years of age. There are, however, reported cases 20 to 40 years after splenectomy [93]. A collective critical review of the literature on OPSI from 1952 to 1987 showed that the incidence in children under 16 years of age was 4.4% with a mortality rate of 2.2%. The corresponding figures for adults were 0.9% and 0.8%. The incidence of sepsis after splenectomy caused by trauma was 15.7% in infants and 10.4% in children younger than 5 years [94].

Splenectomy performed for a hematologic disorder such as thalassemia, hereditary spherocytosis, or lymphoma carries a higher risk than splenectomy performed as a result of trauma. One recent study calculated the risk of sepsis as 0.73 per 1,000 person-years after splenectomy for hereditary spherocytosis [95]. Several studies reported the risk for patients with thalassemia to range from 11–25% [94,96]. Patients with Hodgkin disease, particularly

those who received chemotherapy, are at the greatest risk (25–33%) [94,96].

A potential contributor to the lower rate of infection after splenectomy for trauma is the frequent existence of splenic implants or accessory spleens [97]. Small implants of splenic tissue (splenosis) are found in the peritoneum of 50% of patients who undergo splenectomy for trauma. About 10% of such patients may also have accessory spleens [98]. Unfortunately, the degree of protection offered by splenosis or accessory spleens is both variable and unpredictable. A number of cases of OPSI have been reported in the presence of residual splenic tissue or splenic implants [99].

Unfortunately, most of the published data on OPSI occurrence antedate the widespread availability of the pneumococcal and *Haemophilus influenzae* vaccines, so the current incidence may be lower. For example, a Danish study found that the incidence of pneumococcal infection in splenectomized children decreased dramatically following the introduction of the pneumococcal vaccine and the promotion of early penicillin therapy for febrile episodes [100].

One of the most reliable reports relating to the incidence of OPSI is that of Schwartz et al., who applied actuarial methods to a population free of selection bias that had consistent long-term followup. The risk of OPSI was estimated to be in the range of one case per 500 person-years of observation. However, the cumulative risk of infection severe enough to necessitate hospitalization was 33% by the end of 10 years [101].

The time since splenectomy is also an important risk factor. Several studies have shown that 50–70% of admissions to the hospital for serious infections occur within the first two years. In splenectomized young children, 80% of OPSI cases occur within this time [98,102,103]. However, some degree of risk persists indefinitely. Thirty-three percent of post-splenectomy pneumococcal infections and 42% of OPSI occurred more than five years post-splenectomy [104]. There also are individual cases of OPSI reported more than 40 years after splenectomy [92].

Most serious infections after splenectomy are caused by encapsulated bacteria. Pneumococcal infections account for approximately 50–90% of reported cases, with a mortality rate as high as 60%. *Haemophilus influenzae* type b, *Neisseria meningitidis*, and Group A *Streptococcus* account for an additional 25% of infections. *Haemophilus* infections are particularly important in children [92]. Other rarely implicated organisms are *Capnocytophaga canimorsus* (formally called DS-2), which can cause fulminant sepsis after dog bites. Others are group B streptococci, *Enterococcus* spp., *Bacteroides* spp., and *Pseudomonas aeruginosa*. Bacterial proliferation in OPSI may be so extreme that bacteria are noted in buffy coat preparations, extracellularly, or within neutrophils in a smear made from unspun peripheral blood [105].

The splenectomized host is also more susceptible to infections with intraerythrocytic organisms. Protozoal infections following tick bites (babesiosis) have been responsible for a fulminant hemolytic febrile state in asplenic individuals. Fatal falciparum malaria has been noted more frequently in asplenic hosts [103,106].

Overwhelming post-splenectomy infection is also known as post-splenectomy sepsis syndrome or post-splenectomy overwhelming sepsis [93,104]. Although meningitis or pneumonia will accompany OPSI in approximately 50% of cases, in many adults, there is no obvious source of infection, and a cryptic source originating in the nasopharynx is postulated. In children younger than five years, focal infections are more common, particularly meningitis [92].

The prodrome of OPSI may be mild and nonspecific with flu-like symptoms of fever, malaise, myalgia, headache, vomiting, diarrhea, or abdominal pain. Gastrointestinal symptoms should never distract the physician from entertaining the diagnosis of OPSI. Many patients have had true rigors for a day or two before receiving definitive medical management [107]. Prodromal symptoms may be followed by rapid evolution to bacteremia and septic shock accompanied by hypotension, anuria, and clinical evidence of disseminated intravascular coagulation, making this syndrome a true medical emergency. Severe hypoglycemia may also be present. The subsequent clinical course often mirrors that of the Waterhouse-Friderichsen syndrome with bilateral adrenal hemorrhages noted at autopsy [92]. Extremity gangrene necessitating ampu-

tation has been reported in survivors secondary to the combination of hypotension and disseminated intravascular coagulation [107]. Despite appropriate antibiotics and intensive therapeutic intervention, the overall mortality rate in older published studies of established cases of OPSI ranged from 50–70% [107,108]. More recent information suggests that when informed patients seek medical attention promptly, their mortality rate may be reduced to approximately 10%. Of patients who die, more than 80% do so within the first 48 hours of hospital admission, illustrating the importance of early diagnosis and therapy. Among survivors, other sequelae, in addition to gangrene and amputation, include deafness associated with either meningitis or mastoid osteomyelitis and aortic insufficiency secondary to endocarditis [92,109].

Vaccines. The first pneumococcal polysaccharide vaccine was released in the 1940s, but was withdrawn from the market when penicillin and sulfonamide drugs became widely available, primarily on the assumption that pneumococcal disease would be eradicated by antibiotics. When this proved to be untrue, and the morbidity and mortality of pneumococcal disease once again were recognized, pneumococcal vaccines were re-licensed in the U.S. in 1977, when a 14-valent polysaccharide vaccine was released, to be replaced by a 23-valent vaccine in 1980. In February 2000, a 7-valent protein conjugate pneumococcal vaccine was licensed for pediatric use in the U.S. [110].

At least 90 serotypes of *Streptococcus pneumoniae* are known. The most important virulence factor of the bacterium appears to be the polysaccharide capsule that facilitates evasion of host defenses, as opsonization and phagocytosis of the organism leading to a humoral immune response yields clearance and eradication. Current vaccines are based on stimulating immunity to capsular polysaccharide antigen [110].

Three pneumococcal polysaccharide vaccines are licensed and marketed in the U.S., namely Pneumovax 23 (Merck, West Point, PA), Pnu-Immune 23 (Wyeth Laboratories, Madison, NJ) and Prevnar, a 7-valent protein conjugate vaccine (Wyeth). The first two vaccines contain 25 mcg of capsular polysaccharide from each of 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F), which collectively account for 85–90% of invasive pneumococcal disease in adults in the U.S. Serotypes 4, 6B, 9V, 14, 18C, and 23F account for 80% of invasive infections among U.S. children. The six pneumococcal serotypes that most frequently cause invasive drug-resistant disease in the U.S. (6B, 9V, 14, 19A, 19F, 23F) are included in the vaccines [110,111].

The limitations of the current pneumococcal polysaccharide vaccines have driven efforts to develop the next generation of pneumococcal vaccines, in particular, protein conjugates. Serotype-specific antibody concentrations decline substantially after 5 to 10 years [112]. In addition, current pneumococcal vaccines are T-cell-independent immunogens, and therefore do not induce T-cell-dependent responses (i.e., no immunologic memory is induced). Furthermore, the vaccine is not immunogenic, and hence is not effective, in children under the age of two years, who suffer the highest rates of morbidity and mortality from invasive pneumococcal infections [110].

In 2000, the 7-valent conjugated pneumococcal vaccine (Prevnar) was approved by the Food and Drug Administration. This vaccine contains a solution of the capsular antigens of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, each individually conjugated to a non-toxic variant of diphtheria toxin, namely CRM 197 protein. Conjugation of a polysaccharide to a protein changes the nature of the anti-polysaccharide antibody response from a T-cell-independent to a T-cell-dependent type. This induces T helper cells to stimulate polysaccharide-specific B cells to mature into antibody-producing plasma cells or memory cells independent of splenic function [113].

Concerns about efficacy surround the use of pneumococcal vaccine. These concerns first surfaced after the results of a national Veterans Administration cooperative trial demonstrated lack of efficacy in preventing pneumococcal pneumonia [114]. Although this study influenced physicians' perceptions of the vaccine, the results were not statistically significant owing to a type II error in the study design [110].

Other clinical studies have likewise failed to demonstrate efficacy in preventing pneumococcal pneumonia in high-risk, elderly persons [115,116], but each of these trials had serious methodologic flaws (inadequate sample sizes, type II errors), problems with disease definition or diagnosis, or problems with unusual subject cohorts [116]. In contrast, studies of South African gold miners, New Guinea highlanders, and younger persons at high risk of pneumococcal infection but otherwise immunologically intact have demonstrated efficacy [117,118]. Similarly, studies published in the last 20 years have demonstrated vaccine effectiveness rates of 40–100% in preventing invasive pneumococcal disease in adult, including elderly, patients [119,120].

A review of published pediatric trials demonstrated that conjugate pneumococcal vaccines, when administered in a three-dose series at 2, 4, and 6 months of age, are safe and more immunogenic than the polysaccharide vaccines [121]. A trial in U.S. infants using a seven-serotype conjugate vaccine induced high titers of type-specific antibody to all serotypes included in the vaccine, which included 78% of the serotypes responsible for invasive disease in children less than two years of age in the U.S., and induced immunologic memory to a booster dose of polysaccharide vaccine [122].

Although safe and effective, pneumococcal polysaccharide vaccine does have side effects. For example, as many as 50% of recipients experience mild, self-limited local effects after the first dose. Fortunately, moderate to severe local or systemic reactions are rare. A review of nine randomized controlled clinical trials of pneumococcal vaccine revealed local reactions in fewer than one-third of recipients, and no reports of severe febrile or anaphylactic reactions [123]. Early studies reported a higher than expected frequency and severity of systemic and local reactions in persons receiving a second dose of vaccine in a 2–4-year period [124]. Subsequently, it was determined that re-immunization of otherwise immunocompetent persons at least five years after the first dose was not associated with a higher risk of adverse events or hospitalization [125]. Published data demonstrate the safety of the pneumococcal conjugate vaccine in infants, children, and adults [126].

Invasive *H. influenzae* disease is caused by one of six serotypes, designated "A" to "f". Before the introduction of vaccines for *H. influenzae,* approximately one in 200 children developed invasive disease before the age of five years, with a mortality rate of 4%. By 2000, *H. influenzae* type B invasive disease reported to the CDC among children under the age of five years had declined by 96%, from 41 cases per 100,000 in 1987, to 1.6 cases per 100,000 in 2000 [127]. Ninety-five percent of the cases of invasive *H. influenzae* disease among children younger than 5 years were caused by organisms of serotype B [128].

The first *H. influenzae* vaccine, introduced in 1985, contained purified polyribosyl-ribitol phosphate (PRP), a high molecular weight polymer prepared from type b strains. By 1989, the vaccine was conjugated, thereby conferring T-cell-dependent characteristics that substantially increased the immune response. Currently, the approved *H. influenzae* vaccines are conjugated to TT (PRP-T), diphtheria toxoid (PRP-D), modified diphtheria toxoid (HbOC), or external antigens of *Neisseria meningitidis* outer membrane protein (PRP-OMT). ActHIB® (*Haemophilus influenzae* B Conjugate Vaccine; Aventis Pasteur), is a polysaccharide–protein conjugate vaccine, with each dose of 0.5 mL formulated to contain 10 mcg of purified capsular polysaccharide conjugated to 24 mcg of inactivated TT [129,130].

The immunogenicity of ActHIB has been demonstrated in worldwide studies. On average, ActHIB induced anti-PRP concentrations $\geq$1.0 mcg/mL in 90% of infants after the primary series and in more than 98% of infants after a booster dose [131].

The conjugate vaccine is immunogenic in children with sickle cell anemia, a condition that may increase susceptibility to *Haemophilus* serotype B disease. Two doses of ActHIB given at two-month intervals induced anti-PRP antibody titers of at least 1.0 mcg/mL in 89% of these children with a mean age of 11 months. This is comparable to the anti-PRP antibody titers demonstrated in normal children of similar age following two doses of ActHIB [132].

More than 7,000 infants and children two years of age or younger received at least one dose of ActHIB during U.S. clinical trials. Of

these, 1,064 subjects 12–24 months of age who received ActHIB alone had no serious or life-threatening adverse reactions. Adverse reactions commonly associated with a first ActHIB immunization of children 12–15 months of age, who previously had not been immunized with any *Haemophilus* conjugate vaccine, included local pain, redness, and swelling at the injection site (2–10%). Systemic reactions included fever, irritability, and lethargy (1–12%) [128].

Neisseria meningitidis is classified into 13 serogroups on the basis of the antigenic properties of the capsular polysaccharide. Serogroups A, B, and C account for more than 90% of disease worldwide. Serogroups A and C predominate throughout Asia and Africa, whereas serogroups B and C are responsible for the majority of disease in Europe and the Americas. In the U.S., 45% of meningococcal infections are caused by serogroup C, and as many as 40% of infections are caused by serogroup B. In addition, in several countries, including the U.S., the proportion of disease attributable to serogroup Y has increased over the past decade [133].

Unlike the serogroup A and C polysaccharide antigens, serogroup B antigen is poorly immunogenic in humans. Even after a natural infection with a serogroup B meningococcus, antibodies against capsular polysaccharide antigen consist primarily (more than 95%) of IgM, with low avidity and poor bactericidal activity with human complement. The poor antigenicity of the serogroup B polysaccharide likely is explained by its structural identity to a glycoprotein found on human tissues, the fundamental role of which is to modulate the migration of neural tissues. Naturally occurring anti-B polysaccharide antibodies are present in 80% to 90% of healthy adults and in cord sera of apparently healthy full-term babies [134]. These naturally occurring antibodies usually have low avidity. However, anti-B monoclonal antibodies bind to human embryonic neural tissue in vitro [135], although no adverse effects have been associated with the presence of either natural or vaccine anti-B capsular polysaccharide antibody. However, overcoming the apparent immune tolerance to this self-antigen carries the theoretical risk of inducing autoimmunity and interfering with normal cell migration [136].

The only meningococcal vaccine currently available in the U.S. (Menomune; Aventis Pasteur) contains polysaccharide serogroups A, C, Y, and W-135. The vaccine therefore does not protect against serogroup B. Each 0.5-mL dose is formulated to contain 50 mcg of purified capsular antigen from each of the serogroups.

The immunogenicity and clinical efficacy of the meningococcal vaccines has been established in children and adults. A study performed using four lots of Menomune in 150 adults showed at least a four-fold increase in antibodies to all serogroups in more than 90% of the subjects [137]. A study conducted in 73 children ages 2–12 years revealed seroconversion rates, measured by a two-fold rise in antibody titers in a solid-phase radioimmunoassay, to be 99% for group A, 99% for group C, 97% for group Y, and 89% for group W-135 [138].

Adverse reactions to meningococcal vaccine are mild and consist primarily of pain and redness at the injection site for one or two days. Pain at the site of injection is the most commonly reported adverse reaction; transient fever developed in fewer than 2% of young children. Adverse events reported in adults include pain and tenderness at the injection site, occurring in 2–10% of recipients, and headache, malaise, fever, and chills, occurring in 1–12%. On rare occasion, IgA nephropathy has followed vaccination with Menomune; however, a causal relation has not been established [137,138].

Evidence-based recommendations. The organisms responsible for OPSI for which vaccines are available are *S. pneumoniae*, *N. meningiditis*, and *H. influenzae* type B. There are few controlled trials evaluating the use of vaccines in the prevention of OPSI, but two modern reports add substantial evidence in favor of post-splenectomy vaccination. Utilizing the Danish National Patient Registry, all children up to 15 years of age who underwent splenectomy during the period 1979 to 1987, and all children of the same age group who were admitted to a hospital during the same period because of *S. pneumoniae* meningitis or bacteremia, were studied [100]. A similar Danish study covering the period 1969 to 1978, when pneumococcal vaccine was not available, was used as a con-

trol. During the pre-vaccine period, 4% of splenectomized children developed invasive pneumococcal infection, in contrast to none of the children vaccinated during the period 1979 to 1987. Since 1982, antibiotic treatment of splenectomized children having a fever has been recommended in Denmark. The program of pneumococcal vaccination and defined antibiotic prophylaxis has been highly efficacious in preventing post-splenectomy infection in children [100]. The second report was a series of more than 200 asplenic adult hematology patients who had been immunized with pneumococcal vaccine, in whom only four episodes of pneumococcal sepsis were reported in 13 years. Notably, all four of these episodes involved an infecting serotype that was not covered by the vaccine, lending indirect support to the efficacy of the pneumococcal vaccine even in immunocompromised patients [139].

The ACIP recommends the use of the 23-valent polysaccharide pneumococcal vaccine for persons 2 to 64 years of age who have functional or anatomic asplenia [140] (Grade D). Because the true incidence of OPSI is unknown, the efficacy of vaccination cannot be ascertained precisely. Although some cases of OPSI have resulted from uncommon serotypes not included in the vaccine, a large percentage of post-splenectomy patients with serious pneumococcal infections were never vaccinated [141], which suggests that pneumococcal disease is likely prevented in most vaccinated patients. True vaccine failures are uncommon [142].

The ActHIB conjugate vaccine has been in widespread use for infant immunizations in the U.S. and Europe, and has reduced *H. influenzae* type B disease transmission, as well as the risk to non-immunized individuals [143]. The protective concentration of HIB antibody is not known, although previous studies have shown that as many as 96% of adults have titers above the presumed protective concentration (>1 mcg/mL) [144]. Therefore, some countries do not recommend *H. influenzae* type B vaccination of people older than 15 years [145]. Overall, because of naturally occurring antibody, vaccination of the general population is not recommended. However, because ActHIB vaccine is free of any serious side effects, and because splenectomized individuals are more susceptible to lethal sepsis than the general population, 8–10% of which is attributable to *H. influenzae* type B, these high-risk individuals should be considered for ActHIB conjugate vaccine [146] (Grade D).

The available meningococcal vaccine protects against serotypes A, C, Y, and W-135 of *N. meningiditis,* an important cause of bacterial meningitis and sepsis in children and young adults in the U.S. [147]. However, vaccination will not eliminate the risk because the vaccine does not protect against serotype B and because protection against serogroups C and Y is only partial [147]. Nevertheless, those at risk for the disease (including asplenic patients) should be vaccinated (Grade D).

Timing. Patients undergoing elective splenectomy should be vaccinated at least two weeks preoperatively to maximize the antibody response against T-cell-independent immunogens. Giebink et al. demonstrated that antibody titers were 50% lower when patients were vaccinated after splenectomy than when they were vaccinated at least two weeks preoperatively [148] (Grade C).

The timing of immunization after emergency splenectomy for trauma is debated, with conflicting data supporting a variety of recommendations [4]. Part of the problem has stemmed from studies using antibody assays, which may be misleading. Barringer et al. studied the effect of anesthesia and splenectomy on the antibody response to pneumococcal vaccination [149]. Measuring the antibody response by radioimmunoassay showed no significant difference between groups immunized preoperatively, immediately postoperatively, or three weeks later. Similarly, Caplan et al. studied 16 patients undergoing splenectomy for trauma and, by enzyme-linked immunosorbent assay (ELISA), measured the antibody response to 12 antigens in the patients and control subjects [150]. The rates of response and the geometric mean increase in the titer in the groups were not different. The authors therefore suggested that the vaccine could be administered in the immediate postoperative period.

Conversely, extensive studies in Denmark led to the establishment in 1991 of national

guidelines for vaccination and revaccination of splenectomized children and adults [151]. The Danish guidelines recommend that patients undergoing urgent or otherwise unplanned splenectomy be immunized no less than 14 days postoperatively.

Waiting two weeks before vaccinating carries the risk of forgetting to vaccinate, but solid data suggest that the antibody response is suboptimal when patients are vaccinated less than 14 days post-splenectomy. Shatz et al. showed that although geometric mean antibody concentrations measured by ELISA were similar among trauma patients immunized at post-splenectomy day 1, 7, or 14, functional antibody titers, measured by opsonophagocytosis assay, were significantly higher in the 14-day group [152]. This assay measures only functional antibody and eliminates non-protective antibodies that may cross-react against the capsule or antigen, which can be falsely elevated when measured by radioimmunoassay and ELISA [153]. Therefore, there is likely a higher correlation between opsonophagocytic antibody titers and pneumococcal vaccine efficacy than between IgG antibody concentrations measured by ELISA and efficacy [154]. Delaying vaccination beyond 14 days did not appear to improve the immune response. In another study by Shatz et al., antibody titers were not significantly different in splenectomized trauma patients vaccinated at 14 vs. 28 days postoperatively [155]. Therefore, patients undergoing emergency splenectomy should receive immunizations 14 days later (Grade D).

Revaccination. Antibody persistence after vaccination, and the presence of an anamnestic response with reintroduction of a specific antigen, dictate the need for and timing of revaccination. The antigens in commercial vaccines induce the production of serotype-specific antibodies. Higher titers develop within two to three weeks in most healthy adults, with a comparable response occurring in anatomic or functionally asplenic patients of the same age. Because polysaccharide antigens alone do not illicit a T cell response, and therefore provide no immunologic memory, future responses to the specific antigen depend on the circulating antibody concentrations present at the time of re-exposure. Therefore, the need for revaccination of splenectomized patients is dependent on the persistence of the antibody [4].

Mufson et al. demonstrated that five years after immunization, in healthy adult subjects, the titers of type-specific pneumococcal antibodies to serotypes 1, 3, 4, 8, 12F, 14, and 23F were 90% of those obtained one month after vaccination [156]. At 10 years, antibody concentrations measured by radioimmunoassay remained elevated only for serotypes 4 and 8, and were not significantly different from prevaccination levels for the other capsular antigens tested. Other studies have demonstrated similar patterns in antibody retention lasting at least 3 to 4 years, with a subsequent decline that was more pronounced in splenectomized children [157].

The literature demonstrates a variety of revaccination practices. However, the CDC suggests a single booster dose for those older than two years of age who are at high risk for serious pneumococcal infection and those most likely to have a rapid decline in antibody titers, which includes those with either functional or anatomic asplenia. A single revaccination should be given at least five years after the first dose, with further dosing not recommended routinely (Grade D). There currently is no recommendation to revaccinate for *H. influenzae* type b or meningococcus [140].

Children younger than five years. The 7-valent pneumococcal conjugate vaccine is recommended for all children 24–59 months of age who are at high risk for invasive pneumococcal infection. High-risk children include those with sickle cell disease or other types of functional or anatomic asplenia [158]. For high-risk children 24–59 months of age who have not received either the 23-valent pneumococcal polysaccharide vaccine or the PCV7, two doses of PCV7 should be given at an interval of six to eight weeks, followed by a single dose of the 23-valent vaccine no less than six to eight weeks after the last dose of PCV7. An additional dose of the 23-valent vaccine is recommended three to five years after the last dose [158] (Grade D). Current immunogenicity data suggest that PCV7 induces a primary immune response that will provide immune memory for boosting an-

tibody responses to some serotypes when the 23-valent vaccine is given. Because this vaccine provides substantially expanded serotype coverage, its use is recommended for high-risk children [158]. This age group should also receive vaccination against meningococcus and *H. influenzae* type b [128,138] (Grade D).

Antibiotic prophylaxis is recommended for all children with sickle cell disease and functional or anatomic asplenia, regardless of whether they have received pneumococcal immunizations (Grade B). Oral administration of penicillin V potassium is recommended at a dose of 125 mg twice a day until three years of age and 250 mg twice a day thereafter. Children who have not been vaccinated appropriately and who have had an invasive pneumococcal infection may discontinue penicillin prophylaxis after five years of age [158].

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