Other Clinical Manifestations *C. diphtheriae* causes rare cases of endocarditis and septic arthritis, most often in patients with preexisting risk factors, such as abnormal cardiac valves, injection drug use, or cirrhosis.

COMPLICATIONS

Airway obstruction poses a significant early risk in patients presenting with advanced diphtheria. Pseudomembranes may slough and obstruct the airway or may advance to the larynx or into the tracheobronchial tree. Children are particularly prone to obstruction because of their small airways.

Polyneuropathy and myocarditis are late toxic manifestations of diphtheria. During a diphtheria outbreak in the Kyrgyz Republic in 1999, myocarditis was found in 22% and neuropathy in 5% of 656 hospitalized patients. The mortality rate was 7% among patients with myocarditis as opposed to 2% among those without myocardial manifestations. The median time to death in hospitalized patients was 4.5 days. Myocarditis is typically associated with dysrhythmia of the conduction tract and dilated cardiomyopathy.

Polyneuropathy is seen 3–5 weeks after the onset of diphtheria and has a slow indolent course. However, patients may develop severe and prolonged neurologic abnormalities. The disorders typically occur in the mouth and neck, with lingual or facial numbness as well as dysphonia, dysphagia, and cranial nerve paresthesias. More ominous signs include weakness of respiratory and abdominal muscles and paresis of the extremities. Sensory manifestations and sensory ataxia also are observed. Cranial nerve dysfunction typically precedes disturbances of the trunk and extremities because of proximity to the site of infection. Autonomic dysfunction also is associated with polyneuropathy and can lead to hypotension. Polyneuropathy is typically reversible in patients who survive the acute phase.

Other complications of diphtheria include pneumonia, renal failure, encephalitis, cerebral infarction, pulmonary embolism, and serum sickness from antitoxin therapy.

DIAGNOSIS

The diagnosis of diphtheria is based on clinical signs and symptoms plus laboratory confirmation. Respiratory diphtheria should be considered in patients with sore throat, pharyngeal exudates, and fever. Other symptoms may include hoarseness, stridor, or palatal paralysis. The presence of a pseudomembrane should prompt strong consideration of diphtheria. Once a clinical diagnosis of diphtheria is made, diphtheria antitoxin should be obtained and administered as rapidly as possible.

Laboratory diagnosis of diphtheria is based either on cultivation of *C. diphtheriae* or toxigenic *Corynebacterium ulcerans* from the site of infection or on the demonstration of local lesions with characteristic histopathology. *Corynebacterium pseudodiphtheriticum*, a nontoxigenic organism, is a common component of the normal throat flora and does not pose a significant risk. Throat samples should be submitted to the laboratory for culture with the notation that diphtheria is being considered. This information should prompt cultivation on special selective medium and subsequent biochemical testing to differentiate *C. diphtheriae* from other nasopharyngeal commensal corynebacteria. All laboratory isolates of *C. diphtheriae,* including nontoxigenic strains, should be submitted to the CDC.

A diagnosis of cutaneous diphtheria requires laboratory confirmation since the lesions are not characteristic and are indistinguishable from other dermatoses. Diphtheritic ulcers occasionally—but not consistently—have a punched-out appearance (Fig. 175-2). Patients in whom cutaneous diphtheria is identified should have the nasopharynx cultured for *C. diphtheriae*. The laboratory medium for cutaneous diphtheria specimens is the same as that used for respiratory diphtheria: Löffler's or Tinsdale's selective medium in addition to nonselective medium such as blood agar. As has been mentioned, respiratory diphtheria remains a notifiable disease in the United States, whereas cutaneous diphtheria is not.

TREATMENT DIPHTHERIA

DIPHTHERIA ANTITOXIN

Prompt administration of diphtheria antitoxin is critical in the management of respiratory diphtheria. Diphtheria antitoxin, a horse antiserum, is effective in reducing the extent of local disease as well as the risk of complications of myocarditis and neuropathy. Rapid institution of antitoxin therapy is also associated with a significant reduction in mortality risk. Because diphtheria antitoxin cannot neutralize cell-bound toxin, prompt initiation is important. This product, which is no longer commercially available in the United States, can be obtained from the CDC by calling the Bacterial Vaccine Preventable Disease Branch of the National Immunization Program at 404-639-8257 (8:00 A.M. to 4:30 P.M., U.S. Eastern time) or, at other hours, the Emergency Operations Center at 770-488-7100; the relevant website is *www.cdc.gov/diphtheria/dat.html*. The current protocol for the use of diphtheria antitoxin involves a test dose to rule out immediate hypersensitivity. Patients who demonstrate hypersensitivity require desensitization before a full therapeutic dose of antitoxin is administered.

ANTIMICROBIAL THERAPY

Antibiotics are used in the management of diphtheria primarily to prevent transmission to susceptible contacts. Antibiotics also prevent further toxin production and reduce the severity of local infection. Recommended treatment options for patients with respiratory diphtheria are as follows:

- Procaine penicillin G, 600,000 U IM q12h (for children: 12,500–25,000 U/kg IM q12h) until the patient can swallow comfortably; then oral penicillin V, 125–250 mg qid to complete a 14-day course
- Erythromycin, 500 mg IV q6h (for children: 40–50 mg/kg per day IV in two or four divided doses) until the patient can swallow comfortably; then 500 mg PO qid to complete a 14-day course

A clinical study in Vietnam found that penicillin was associated with a more rapid resolution of fever and a lower rate of bacterial resistance than erythromycin; however, relapses were more common in the penicillin group. Erythromycin therapy targets protein synthesis and thus offers the presumed benefit of stopping toxin synthesis more quickly than a cell wall–active β-lactam agent. Alternative therapeutic agents for patients who are allergic to penicillin or cannot take erythromycin include rifampin and clindamycin. Eradication of *C. diphtheriae* should be documented after antimicrobial therapy is complete. A repeat throat culture 2 weeks later is recommended. For patients in whom the organism is not eradicated after a 14-day course of erythromycin or penicillin, an additional 10-day course followed by repeat culture is recommended. Drug-resistant strains of *C. diphtheriae* exist, and several reports have described multidrug-resistant strains, predominantly in Southeast Asia. Drug resistance should be considered when efforts at pathogen eradication fail.

Cutaneous diphtheria should be treated as described above for respiratory disease. Individuals infected with toxigenic strains should receive antitoxin. It is important to treat the underlying cause of the dermatoses in addition to the superinfection with *C. diphtheriae*.

Patients who recover from respiratory or cutaneous diphtheria should have antitoxin levels measured. If diphtheria antitoxin has been administered, this test should be performed 6 months later. Patients who recover from respiratory or cutaneous diphtheria should receive the appropriate vaccine to ensure the development of protective antibody titers.

MANAGEMENT STRATEGIES

Patients in whom diphtheria is suspected should be hospitalized in respiratory isolation rooms, with close monitoring of cardiac and respiratory function. A cardiac workup is recommended to assess the possibility of myocarditis. In patients with extensive pseudomembranes, an anesthesiology or an ear, nose, and throat consultation is recommended because of the possible need for