The next stage in toxin trafficking is less clearly understood but involves tetanus toxin's escaping normal lysosomal degradation processes and undergoing translocation across the synapse to the GABA-ergic presynaptic inhibitory interneuron terminals. Here the light chain, which is a zinc-dependent endopeptidase, cleaves vesicle-associated membrane protein 2 (VAMP2, also known as *synaptobrevin*). This molecule is necessary for presynaptic binding and release of neurotransmitter; thus tetanus toxin prevents transmitter release and effectively blocks inhibitory interneuron discharge. The result is unregulated activity in the motor nervous system. Similar activity in the autonomic system accounts for the characteristic features of skeletal muscle spasm and autonomic system disturbance. The increased circulating catecholamine levels in severe tetanus are associated with cardiovascular complications.

Relatively little is known about the processes of recovery from tetanus. Recovery can take several weeks. Peripheral nerve sprouting is involved in recovery from botulism, and similar central nervous system sprouting may occur in tetanus. Other evidence suggests toxin degradation as a mechanism of recovery.

APPROACH TO THE PATIENT: Tetanus

The clinical manifestations of tetanus occur only after tetanus toxin has reached presynaptic inhibitory nerves. Once these effects become apparent, there may be little that can be done to affect disease progression. Treatment should not be delayed while the results of laboratory tests are awaited. Management strategies aim to neutralize remaining unbound toxin and support vital functions until the effects of the toxin have worn off. Recent interest has focused on intrathecal methods of antitoxin administration to neutralize toxin within the central nervous system and limit disease progression (see "Treatment," below).

CLINICAL MANIFESTATIONS

Tetanus produces a wide spectrum of clinical features that are broadly divided into generalized (including neonatal) and local. In the usually mild form of local tetanus, only isolated areas of the body are affected and only small areas of local muscle spasm may be apparent. If the cranial nerves are involved in localized cephalic tetanus, the pharyngeal or laryngeal muscles may spasm, with consequent aspiration or airway obstruction, and the prognosis may be poor. In the typical progression of generalized tetanus (Fig. 177-1), muscles of the face and jaw often are affected first, presumably because of the shorter distances toxin must travel up motor nerves to reach presynaptic terminals. Neonates typically present with inability to suck.

In assessing prognosis, the speed at which tetanus develops is important. The incubation period (time from wound to first symptom) and the period of onset (time from first symptom to first generalized spasm) are of particular significance; shorter times are associated with worse outcome. In neonatal tetanus, the younger the infant is when symptoms occur, the worse the prognosis.

The commonest initial symptoms are trismus (lockjaw), muscle pain and stiffness, back pain, and difficulty swallowing. In neonates, difficulty in feeding is the usual presentation. As the disease progresses, muscle spasm develops. Generalized muscle spasm can be very painful. Commonly, the laryngeal muscles are involved early or even in isolation. This is a life-threatening event as complete airway obstruction may ensue. Spasm of the respiratory muscles results in respiratory failure. Without ventilatory support, respiratory failure is the commonest cause of death in tetanus. Spasms strong enough to produce tendon avulsions and crush fractures have been reported, but this outcome is rare.

Autonomic disturbance is maximal during the second week of severe tetanus, and death due to cardiovascular events becomes the major risk. Blood pressure is usually labile, with rapid fluctuations from high to low accompanied by tachycardia. Episodes of bradycardia and heart block can also occur. Autonomic involvement is evidenced by gastrointestinal stasis, sweating, increased tracheal secretions, and acute (often high-output) renal failure.

DIAGNOSIS

The diagnosis of tetanus is based on clinical findings. As stated above, treatment should not be delayed while laboratory tests are conducted. Culture of *C. tetani* from a wound provides supportive evidence. Serum anti-tetanus immunoglobulin G may also be measured in a sample taken before the administration of antitoxin or immunoglobulin. Serum levels >0.1 IU/mL are deemed protective and do not support the diagnosis of tetanus. If levels are below this threshold, a

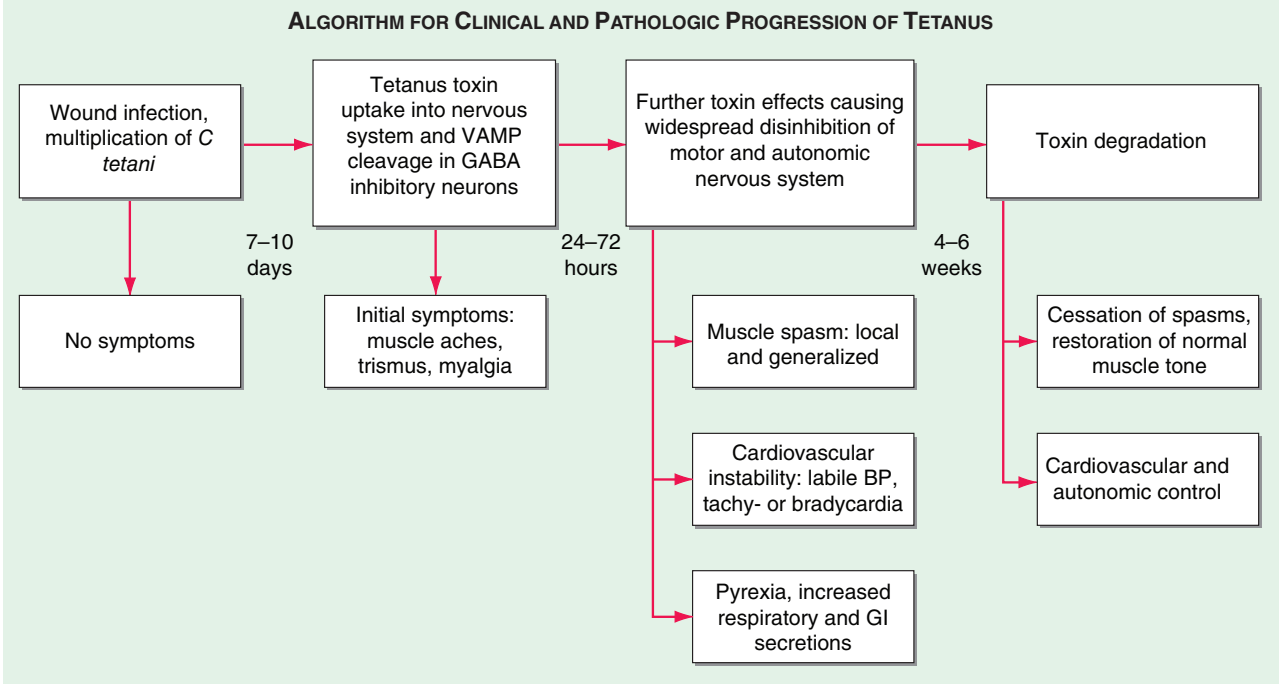

FIGURE 177-1 Clinical and pathologic progression of tetanus. BP, blood pressure; GABA, γ-aminobutyric acid; GI, gastrointestinal; VAMP, vesicle-associated membrane protein (synaptobrevin).