

Clinical Tetanus Despite a 'Protective' Level of Toxin-Neutralizing Antibody

Ab 16x†
"Primary" + 8-4 yr boost before let
more vaccine on discharge.

Unbelievable!

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TETANUS is a preventable disease. Although immunization guidelines¹ are generally very effective, tetanus has occurred in patients with prior immunization.² In most cases it was presumed that levels of toxin-neutral-

izing antibody were low. Although data on the protective level of neutralizing antibody in humans are extremely limited, animal data have been used to support the belief that 0.01 antitoxin unit/mL is protective.^{3,4}

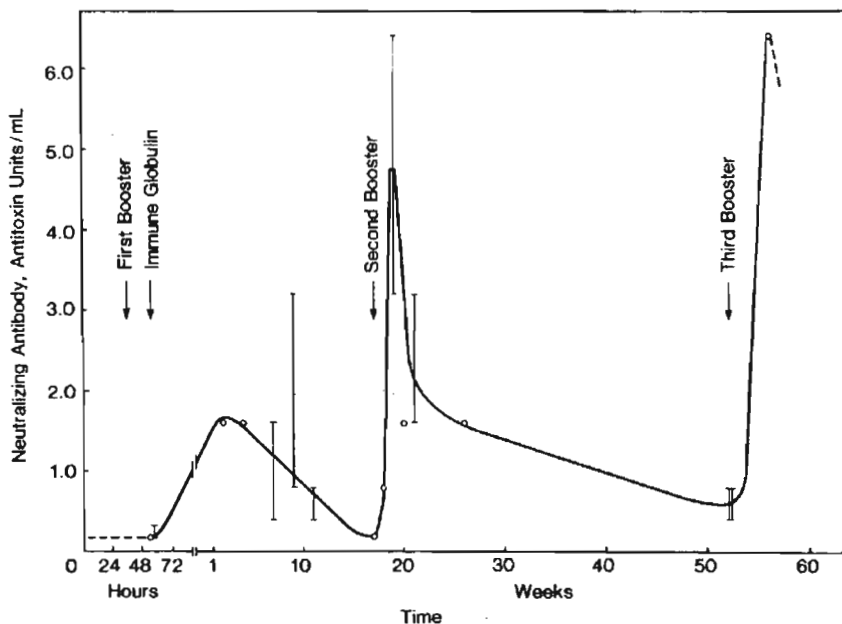
This report describes a patient with a wound, followed by severe generalized tetanus, who was found at the onset of symptoms to have a neutralizing antibody level 16 times that considered protective.

Report of a Case

A 35-year-old man sustained a puncture wound in the plantar surface of his left foot. He was seen at a community hospital 35 hours later for increasing foot pain. There was no evidence of infection, and he was treated with tetanus toxoid, dicloxacillin, and acetaminophen. Approximately 38 hours after the injury, he developed diaphoresis and intermittent, uncontrollable, painful spasms of the toes of his left foot that ascended to include the whole body. Stiffness, which developed in the foot 45 hours after the injury, progressed to include the left leg, back, abdomen, jaw, and neck. Approximately 50 hours after injury, mild dysphagia developed. He presented to the University of Illinois Hospital emergency room 52 hours after injury. There was no history of mental status change, headache, or fever, and he denied the use of any medications. His parents reported that he was fully immunized in childhood, and he had received tetanus booster injections eight and four years before this hospital admission. The medical record for the booster four years before admission was located, and it showed that the injection was given in the deltoid region.

Examination revealed labile vital signs with hypertension, tachycardia, and tachypnea. A low-grade fever was present (temperature, 38.1 °C). He was alert and coherent and had trismus with sardonic facies. Muscle spasm intermittently produced opisthotonus. Rigidity, particularly in the left lower extremity, was present between exacerbations. Results of the neurological examination revealed symmetrical deep tendon reflexes that were not hyperreflexic and impaired motor function in the left lower extremity. The plantar surface of the left foot was tender, despite no signs of infection at the site of injury. The dorsum of his foot was warm, red, swollen, and tender. There were no signs of illegal drug use.

Laboratory data revealed normal levels of serum electrolytes, calcium, magnesium, serum urea nitrogen, creatine, and hemoglobin/hematocrit and normal results of urinalysis and a chest roentgenogram. Analysis of arterial blood gas levels on room air yielded the following results: pH, 7.45; PCO_2 , 36 mm Hg; and PO_2 , 90 mm Hg. White blood cell count was 15,500/cu mm, with 81% polymorphonuclear leukocytes, 4% band forms, 9% lymphocytes, and 6% monocytes. Creatine phosphokinase level was 242 IU/mL (reference



Toxin-neutralizing antibody titers (antitoxin units per milliliter) vs time. When experimental mice had paralytic changes that were the same as those in control mice, a single end-point value was assigned. If level of paralysis fell between two serum dilutions, a unit range was indicated. Curve shows approximate changes in antibody levels. Time is in reference to wound. Arrows indicate three tetanus-toxoid booster injections (0.5 mL given in deltoid region).

range, <80 IU/mL). Results of assays for strychnine and phenothiazines were negative. Serum samples obtained on admission to the hospital and before the administration of tetanus immune globulin had a toxin-neutralizing antibody level of 0.16 antitoxin unit/mL (Figure). This value was verified on a repeated assay.

Immediate treatment with human tetanus immune globulin, 6,000 units intramuscularly, was given. Therapy with aqueous penicillin G, 1 million units intravenously every four hours, was begun. Despite his receiving a total of 44 mg of diazepam intravenously, vocal-cord spasm was noted during endotracheal intubation. Under general anesthesia and paralysis induced with pancuronium bromide, he underwent tracheostomy as well as incision and drainage of the left-foot wound along the tendon sheaths on the plantar and dorsal surfaces. There was no necrotic tissue or pus. Administration of nafcillin sodium was begun for possible cellulitis. Gram's stain and cultures were negative.

Following surgery, mechanical ventilation was weaned over 12 hours as pancuronium's effect diminished. Sedation and muscle relaxation were maintained with intravenous diazepam. Analgesia was maintained with intravenous meperidine. Spasms did not recur after paralysis, and rigidity gradually resolved. Medications were diminished over ten days, and he was discharged.

Serum samples for evaluation of toxin-neutralizing antibodies were obtained at various times during the course of his

treatment, recovery, and follow-up with toxoid immunization. Coded specimens were assayed at the Massachusetts Department of Public Health by the mouse neutralization assay using a paralysis end point.⁷ The antibody levels are shown in the Figure.

Comment

Our patient developed generalized tetanus following a puncture wound. The ascending muscle rigidity and spasms with trismus, opisthotonus, and sympathetic overactivity are classic findings of this disease.⁸ There was no evidence of diseases that mimic tetanus.⁹ The immunization history was reliable and partially confirmed by available documentation of the most recent booster. The optimal antitoxin assay was used to determine protective levels of antibody because the mouse neutralization test⁷ measures a biologic activity directly caused by the toxin. The occurrence of tetanus in this patient despite prior immunization and a serum antibody level of 0.16 antitoxin unit/mL raises questions about the true protective level.

Perhaps there is no absolute or universal protective level of antibody. Protection may simply result when there is sufficient toxin-neutralizing antibody in relation to the toxin load.

The level of neutralizing antibody in humans currently considered protective,⁶ 0.01 antitoxin unit/mL, is based on animal studies that correlated levels with symptoms or death.¹⁴ In fact, many animals were completely protected with levels less than 0.01 antitoxin unit/mL, while some had tetanus with levels greater than 0.01 antitoxin unit/mL. In 1937, Sneath et al⁷ observed that guinea pigs were protected from death if the antibody level was at least 0.01 antitoxin unit/mL and extrapolated this value to humans. It was subsequently accepted by most investigators, although Ipsen⁸ found that there is a distinct but specific relationship to toxin challenge in each species. Experimental human data are extremely limited and insufficient for analysis.¹⁴ Because a serum sample is rarely obtained before treatment, only two reports of tetanus in persons with levels greater than 0.01 antitoxin unit/mL before treatment have appeared. Berger et al⁹ reported one patient with 0.04 antitoxin unit/mL at the onset of tetanus, while Goulon et al¹⁰ found ten of 64 patients with titers greater than 0.01 antitoxin unit/mL.

Our patient further demonstrates that prevention of tetanus in certain situations may require neutralizing antibody levels higher than 0.01 antitoxin unit/mL. A serum sample obtained at the onset of tetanus revealed a level of 0.16 antitoxin unit/mL by the mouse neutralization assay (Figure), demonstrating that tetanus is possible with 16 times the level considered protective. This result was confirmed by repeating the assay, and it reflects the patient's prophylactic immunization status. Tetanus is not known to induce detectable levels of neutralizing antibody.¹ Human studies also have shown that titers do not begin to increase until four days after a booster.¹¹ Therefore, the booster our patient received 24 hours before he developed tetanus (the first booster in the Figure) should not have elevated his neutralizing titer. An extraordinarily rapid response in our patient was ruled out by the lack of titer rise 24 hours after the final booster was given, indicated by two identical titer ranges that surround the third booster in the Figure.

It has been suggested that if tetanus occurred in an immunized or seemingly partially protected individual, the course could be modified.¹² There is little information about this entity. Rabbits challenged with toxin had lower "death scores" with increasing preexisting antitoxin titers, however.⁸ Similarly, the patients of Goulon et al¹⁰ had less severe tetanus with increasing preexisting antibody levels. Our patient's prognosis was poor because of the short incubation period, rapid progression from initial symptoms to generalized spasms, and severe disease manifestations at admission.¹³ His survival and rapid recovery may have been the consequence of partial protection from preexisting toxin-neutralizing antibody in addition to his relatively young age and good general health.

Active immunization also may have influenced the course. While it is not possible to measure an immediate rise in neutralizing titer in rabbits after booster, toxin challenges have demonstrated almost immediate increase in protection.⁸ If this phenomenon occurs in humans, an early booster following injury may be more important than previously realized.

Therapeutic passive immunization with equine or human tetanus immune globulin is known to decrease but not eliminate fatalities in humans.¹⁴ Human tetanus immune globulin is preferred, and the recommended dose of 3,000 to 10,000 units intramuscularly produces peak levels much greater than 0.01 antitoxin unit/mL in one to two days. While the therapeutic dose does not prevent effects of toxin bound to the tissue, it should be given promptly because it may modify the course by neutralizing free toxin that would later cause symptoms.

Clostridium tetani is ubiquitous and will always present a risk of tetanus. It is better to prevent illness, since tetanus still has significant mortality with aggressive treatment. Primary tetanus immunization and periodic boosters are safe, effective, and recommended for all. In the United States tetanus now occurs preponderantly in adults never immunized or failing to maintain their immune status with boosters.¹ It is largely presumed that their neutralizing antibody levels are less than

0.01 antitoxin unit/mL because population serosurveys indicate diminished levels, with a significant proportion less than 0.01 antitoxin unit/mL as age increases. Although our observations suggest that higher antibody titers produced by more frequent boosters might be advisable, particularly for tetanus prevention in high-risk individuals, we do not recommend this until additional data are available. We do, however, concur with the need to keep the immune status of all patients up-to-date according to the present guidelines.¹ For those who do develop tetanus, some preexisting antibody and prompt active-passive immunization treatment may be advantageous.

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