Chapter 2-12-4. Anaerobic infections (individual fields): tetanus

Introduction

In recent years, tetanus has become a disease rarely seen in daily clinical practice owing mainly to widespread vaccination and deliveries in clean medical facility environments. However, the mortality rate is still unacceptably high, 20–30% even with the advanced intensive care now available. In addition, physical and psychological sequelae may often be inevitable in tetanus survivors. In Japan, with its aging population, tetanus tends to occur more frequently in older people who were born before the introduction of vaccination against tetanus. Elderly people are susceptible to trauma due to falls or traffic accidents, which can result in the development of tetanus. On the other hand, tetanus is a preventable disease. Educating the elderly as well as young people about the importance of vaccination is essential in our aging society.

Definition

Tetanus is a toxic disease caused by Clostridium tetani neurotoxin produced in the wound. The cardinal signs of this disease are hypertonicity and spasms of skeletal muscles associated with impaired neural transmission.

Epidemiology

Currently, tetanus occurs in about 1,000,000 people annually worldwide, and most patients are newborns in developing countries located in tropical areas. The World Health Organization (WHO) estimated that there were 715,000 deaths from tetanus among newborns in 1990.

In 1950 in Japan, the reported number of tetanus patients was 1,915, and the number of deaths was 1,558 (81% of all patients; the majority were children under 15 years of age). However, since introduction of the combined diphtheria–pertussis–tetanus (DPT) vaccine in 1968, the numbers of patients and deaths have decreased steadily [1]. Over the 1991–2000 decade, the annual reported numbers of patients and deaths were 50 and 14 (28%), respectively, on average. In relation to age, those born before introduction of the DPT vaccine in 1968 accounted for 95% of all patients. The occurrence of tetanus is particularly frequent from early summer to autumn, coinciding with increased outdoor activities in older men. The disease occurs nationwide in a virtually uniform fashion, involving slightly more men. Trauma is regarded as a major trigger in about 80% of cases. Since the 1980s, the reported number of patients has been leveling off or showing a slight tendency to increase, whereas the number of deaths has been decreasing steadily. Tetanus was officially added to the list of target diseases of the routine vaccination program in April 1995 in Japan.

Etiology

C. tetani is an obligately anaerobic gram-positive rod that forms a terminal spore, resulting in a “drumstick-like” or “tennis racket-like” appearance. The organisms occur worldwide in soil. Spores are found in dust and soil, particularly densely in surface soil of the garden, agricultural fields, and shorefronts of ponds or rivers [2]. C. tetani can also be isolated from feces of animals and humans.

Vegetative C. tetani produces two exotoxins, i.e., the neurotoxin tetanospasmin and the hemolytic toxin tetanolysin. Tetanospasmin is referred to as tetanus toxin,
because it can cause tetanus. Spores of \textit{C. tetani} germinate under anaerobic conditions (decreased redox potential), such as in the presence of necrotic tissues or foreign bodies, and develop into vegetative cells to produce tetanus toxin. This toxin is synthesized as a polypeptide within bacterial cells under plasmid control, and released by autolysis of the cells. Although humans and horses are highly susceptible to the toxin, they can be immunized with tetanus toxoid. The low incidence of tetanus, relative to the frequent opportunities for contamination through trauma, may be explained by the fact that \textit{C. tetani} requires strictly anaerobic conditions for its proliferation.

Tetanus toxin is highly potent; a lethal dose is estimated to be 2.5 ng/kg body weight (1 g of toxin corresponds to the lethal dose for 6,000,000 adults weighing 60 kg). Thus, the amount of toxin required for development of tetanus is not enough to stimulate the immune system, making toxoid injections necessary for active immunization.

\textit{C. tetani} is susceptible in vitro to \(eta\)-lactams [penicillins, particularly benzylpenicillin (penicillin G) (PCG), cephalosporins, carbapenems], macrolides, tetracycline (TC) and metronidazole, but is resistant to aminoglycosides. Vegetative cells are susceptible to heat and the commonly used disinfectants. Although glutaraldehyde is most active against spores, it is not applicable to humans. To kill spores, boiling at 100°C for at least 4 h or autoclaving at 121°C for 12 min is required.

\section*{Contributing factors}

The presence of necrotic tissues, abscess or foreign bodies provides an anaerobic environment suitable for germination of \textit{C. tetani} spores. In such a wound \textit{C. tetani} begins to proliferate about 6 h after contamination with its spores. Tetanus often results from wound contamination with soil, dust, feces or saliva. Wood or bamboo chips, soil or sand remaining in the wound are also dangerous. In addition, attention needs to be paid to tooth extraction, gastrointestinal or hemorrhoid surgery, artificial abortion, drug abuse (use of unclean syringes), chronic eczema, chronic otitis media, tinea pedis, cleaning of the navel, decubitus ulcers, gangrenous lesions (e.g., diabetes mellitus and arteriosclerosis obliterans), and dental abscess. Spore contamination of the umbilical stump may trigger neonatal tetanus.

Although it is difficult to exclude the possibility of tetanus development from the appearance of a wound, risk is relatively small for a shallow, clean cut made by a new knife or razor. However, it has been reported that a minor wound which the patient did not remember resulted in tetanus. In general, wounds associated with a high risk of developing tetanus are those with a long course from injury to initiation of treatment, severe contamination, the presence of necrotic tissues or foreign bodies, and deep injury (Table 1) [3].

\section*{Pathogenesis}

Toxin released in the wound is taken up from the motor nerve ending, and ascends along the axon in a retrograde fashion to the \(\alpha\)-motor neuron of the ventral horns of the spinal cord, and reaches the synaptic clefts. Then, the toxin is transmitted to presynaptic and postsynaptic inhibitory neurons (presynaptic inhibitory neurons in the brainstem and postsynaptic inhibitory interneurons in the spinal cord), and blocks the release of inhibitory neurotransmitters from these neurons [\(\gamma\)-aminobutyric acid (GABA) and glycine, respectively]. Thus, presynaptic excitatory neurons become predominant, and the frequency of the resting impulse discharges from \(\alpha\)-motor neurons is increased (continuous discharges of the motor units), causing muscular hypertonicity, which progresses to tonic spasms (Fig. 1) [4]. Although transmitter release at the excitatory amino acid synapse is also inhibited, affinity of the toxin for the inhibitory synapse surpasses such inhibition, resulting in enhanced muscular hypertonicity. On the other hand, acetylcholine release from the motor nerve ending at the neuromuscular junction is also inhibited. This may cause

\begin{table}[h]
\centering
\caption{Clinical characteristics of tetanus-prone wounds (modified from Ref. [3])}
\begin{tabular}{|l|l|l|}
\hline
Clinical characteristics & Tetanus-prone wounds & Non-tetanus-prone wounds \\
\hline
Time after injury & \(\geq 6\) h & \(\leq 6\) h \\
External features of wound & Irregular wound, laceration, abrasion & Linear wound \\
Depth of wound & \(\geq 1\) cm & \(\leq 1\) cm \\
Mechanism of injury & Bullet wound, crush injury, burn, frostbite & Sharp surface (knife, glass) \\
Signs of infection & Present & Absent \\
Necrotic tissue & Present & Absent \\
Contaminants (dust, feces, soil, saliva) & Present & Absent \\
Denervated/ischemic tissue & Present & Absent \\
\hline
\end{tabular}
\end{table}
flaccid paralysis, but the effect of the toxin on the central nervous system (CNS) is the major clinical picture of the disease. In severe tetanus, there is accompanying disinhibition of preganglionic sympathetic neurons present in the lateral grey matter of the spinal cord, leading to sympathetic hyperactivity and increased blood levels of catecholamines. The neural affinity of tetanus toxin is so strong that binding of the toxin is irreversible. Therefore, recovery from tetanus requires generation of new axon terminals.

Tetanus toxin spreads to local and distant nerve endings through direct diffusion into neighboring muscles, lymphogenic or hematogenic carriage, and retrograde intra-axonal transport. However, the toxin does not pass the blood–brain barrier. Assuming that the velocity of intra-axonal transport (75–250 mm/day) is equal among different nerves, short nerves should be affected earlier than long nerves. This explains why nerves in the head are affected first, followed by those of the trunk and extremities.

Since C. tetani itself does not cause inflammation, the responsible wound may look clean as long as there is no infection with other bacteria.

**Vaccination against tetanus (active immunization)**

For prevention of tetanus as well as diphtheria and pertussis, the DPT vaccine was introduced as part of a vaccination program in infants in 1968. Since 1995, DPT vaccination comprising 3 initial doses and 1 booster dose (phase I) and DT vaccination (1 dose) (phase II) have been performed as part of the routine vaccination program. Therefore, adults currently age 41 years or older, i.e., those born before 1968, probably do not have antibody (antitoxin) against tetanus toxin. Vaccination against tetanus is carried out in Japan, as shown in Table2 [5]. Although tetanus can affect anyone, at any time or place, vaccination is particularly recommended for people who are more likely to suffer trauma with a risk of exposure to C. tetani. Such people include those engaged in civil engineering and construction, stock farming, agriculture or landscaping, police officers, firefighters, self-defense officials, housewives, and those aged 60 years or older.

Individuals can achieve basic immunity to tetanus after at least 3 doses of tetanus toxoid (a primary series). Thereafter, 1 booster dose is given every 10 years and may...
be required every 5–10 years, taking into account the occupation of the vaccinated person.

In order to prevent neonatal tetanus, unvaccinated pregnant women should be given 2 doses of adsorbed tetanus toxoid (0.5 mL) at an interval of at least 4 weeks after 5 months of gestation, and a third dose 3 months later (e.g., vaccine inoculations at 20, 24 and 36 weeks of gestation) [5]. The WHO’s Expanded Programme on Immunization recommends that 2 doses be given at an interval of 4 weeks or more, and that the second dose be scheduled at least 2 weeks before delivery. There are virtually no vaccine side effects when vaccination is performed according to this schedule.

Clinical symptoms

There are four clinical types of tetanus: generalized, cephalic, neonatal and localized. These clinical types reflect differences in host immunity against tetanus, the portal of entry, and the primary site of toxin action. Generalized tetanus accounts for 85–90% of reported cases. The incubation period and the “onset period” are used for evaluating the severity of tetanus in the initial stage and its prognosis (Table 3) [6]. The incubation period refers to the time between injury (spore inoculation) and the development of the initial symptom (in most cases difficulty in opening the mouth, or trismus), and the “onset period” refers to the time between trismus development and the first generalized spasms.

Generalized tetanus

The incubation period is usually 7–10 days (range 2–30 days), and depends largely on the distance between the wound site and the CNS. In severe cases, the incubation period is usually within 7–9 days, and the onset period

Table 2 Current vaccination against tetanus (modified from Ref. [5])

<table>
<thead>
<tr>
<th>Phase I</th>
<th>4 doses with DPT vaccinea in infants 3 months or older, within 90 months after birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial vaccination: basically, 3 doses at 3- to 8-week intervals in infants 3 months or older and not more than 12 months after birth</td>
<td></td>
</tr>
<tr>
<td>Booster vaccination: basically, 1 dose 12-18 months after completion of initial vaccination regimen</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>1 dose of DT toxoidb in children 11 years of age or older but younger than 13 years; basically, sixth graders (12-year-old children)</td>
</tr>
</tbody>
</table>

2. Basic immunity in people not vaccinated against tetanus (spontaneous vaccination)

| Initial vaccination: 2 doses of adsorbed tetanus toxoid at a 4- to 8-week interval |
| Booster vaccination: basically, 1 dose of adsorbed tetanus toxoid 6–18 months after completion of the initial vaccination regimen |

3. Booster vaccination in people who are more than 13 years old and have not received phase II vaccination and those in whom 10–15 years have elapsed since the last dose (spontaneous vaccination)

| One dose of adsorbed tetanus toxoid |

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Table 3 Rating scale for the severity and prognosis of tetanus (modified from Ref. [6])

<table>
<thead>
<tr>
<th>Total score</th>
<th>Severity</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>Mild</td>
<td>&lt;10</td>
</tr>
<tr>
<td>2–3</td>
<td>Moderate</td>
<td>10–20</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>20–40</td>
</tr>
<tr>
<td>5–6</td>
<td>Serious</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

Cephalic tetanus should be rated as severe or serious, and neonatal tetanus as serious.
disease. The condition is considered to reflect partial severe painful muscle spasms progressing to generalized weakness (due to disturbed neuromuscular transmission) to severity varies widely among patients, from simple muscle the limb associated with a contaminated wound. Symptom This type of tetanus is characterized by muscle spasms in local hematomas.

rhabdomyolysis, rupture of muscles, and intramuscular (e.g., aspiration pneumonia), decubitus ulcers, dehydration, formation, are not performed, because the organism is rarely isolated from the wound and because occasionally any wound cannot be found. In addition, tetanus will not necessarily occur even if the characteristic spore-forming organisms are observed by microscopic examination of smear preparations, or if C. tetani is isolated by culture.

Tetanus should be suspected and the patient’s course followed carefully when subtle prodromal symptoms have occurred after an injury (stiffness of muscles around the wound, jaw or neck, and equivocal complaints such as a general feeling of illness). If muscular hypertonicity with associated generalized spasms are more prominent in the

### Cephalic tetanus

This type is a special form of localized tetanus. Usually, the disease is secondary to trauma involving the head or face, or results from contamination with C. tetani spores in chronic otitis media. The incubation period is only 1–2 days. Characteristic clinical symptoms include trismus and isolated or combined cranial motor nerve palsies, with conspicuous muscle weakness in areas innervated by the seventh (facial) nerves. Extraocular muscles may also be involved. The condition may remain localized, or progress into generalized tetanus.

### Neonatal tetanus

This type of tetanus arises from unclean procedures for treating the umbilical stump in neonates mostly in developing countries. In general, the disease onset is 3–10 days after birth (incubation period). Based on the average incubation period, this disease is called “the disease of the seventh day.” The affected neonate initially presents general debility, poor sucking and irritability, followed by generalized tonic spasms. The primary causes of death among neonates 1 and 2 weeks after birth are apnea and sepsis (primary focus: bacterial infection of the umbilical stump), respectively. The mortality rate exceeds 90%, and growth retardation is noted in survivors. The antepartum immune status of the mother, particularly lack of vaccination, is key to the development of neonatal tetanus.

### Diagnosis

A clinical diagnosis of tetanus is made based on the characteristic symptoms, i.e., hypertonicity and spasms of skeletal muscles. In general, microbiologic examinations, consisting of isolation of C. tetani from the wound and toxin production, are not performed, because the organism is rarely isolated from the wound and because occasionally any wound cannot be found. In addition, tetanus will not necessarily occur even if the characteristic spore-forming organisms are observed by microscopic examination of smear preparations, or if C. tetani is isolated by culture.

Tetanus should be suspected and the patient’s course followed carefully when subtle prodromal symptoms have occurred after an injury (stiffness of muscles around the wound, jaw or neck, and equivocal complaints such as a general feeling of illness). If muscular hypertonicity with associated generalized spasms are more prominent in the

### Localized tetanus

This type of tetanus is characterized by muscle spasms in the limb associated with a contaminated wound. Symptom severity varies widely among patients, from simple muscle weakness (due to disturbed neuromuscular transmission) to severe painful muscle spasms progressing to generalized disease. The condition is considered to reflect partial immunity to tetanus. Muscle spasms may persist for several weeks to several months, but the prognosis is favorable as long as the muscle involvement is localized.
central part of the body (face, neck, chest, back and abdomen) than in the extremities, tetanus should be strongly suspected.

It is important to investigate the history of vaccination against tetanus. Tetanus is quite unlikely if the serum antitoxin level is equal to or higher than the commonly cited protective concentration of 0.10 IU/mL (or 0.15 IU/mL), although there have been some reports of exceptional cases [5, 7].

Leukocytosis, particularly neutrophilia, occurs, but there are generally no abnormal cerebrospinal fluid findings. The levels of muscle-derived enzymes, such as serum creatine kinase, are increased. Electroencephalographic studies generally show a sleep pattern, and the electromyogram exhibits continuous motor unit discharges and shortening of the non-discharge period following the action potential. However, these findings are not sufficiently specific to establish a diagnosis.

Tetanus is designated by what is called the Infectious Diseases Control Law as an infectious disease of Type V, a group subject to complete-count survey. Therefore, if tetanus is suspected, the physician in charge is legally required to report the case to a local healthcare center near by within 7 days of diagnosis.

Differential diagnoses include strychnine poisoning, dystonic reactions or oculogyric crisis due to phenothiazine or metoclopramide toxicity, meningitis/encephalitis, epileptic seizures, subarachnoid hemorrhage, dental abscess, tetany due to hypocalcemia or alkalosis, alcohol withdrawal syndrome, rabies, and acute abdomen (due to abdominal guarding). Although strychnine poisoning particularly resembles tetanus, patients with the former disease show muscle spasms not accompanied by hypertonicity and have high blood and urine strychnine levels, allowing differentiation from tetanus. Strychnine antagonizes glycine at the inhibitory synapse. Dystonic reactions also resembles tetanus, but responds to anticholinergic drugs unlike tetanus and can thereby be distinguished from tetanus.

**Therapeutic management**

**Primary treatment goals**

Treatment of tetanus is roughly divided into wound and general management. Wound management consists of (1) removal of the source of toxin by deterging or debridement of the wound, (2) neutralization of unbound toxin by antitoxin (passive immunization), and (3) control of infection with antibacterial therapy. General management requires (1) control of muscle spasms using sedative and antispasmodic agents or muscle relaxants, (2) respiratory care with artificial ventilation, (3) treatment of autonomic dysfunction, particularly sympathetic hyperactivity (administration of β-blockers or ganglion blockers), and (4) supportive care (nutritional support with nasal feeding or parenteral nutrition, prevention and treatment of decubitus ulcers and deep venous thrombosis, vaccination to prevent further attacks, mental and psychological support). Therefore, it is recommended that patients with suspected or diagnosed tetanus be transferred to medical facilities having a critical care center or ICU.

**Antibacterial agents**

PCG (10,000,000–12,000,000 units/day, in 4 divided doses, i.v., for 10 days) is generally administered to kill vegetative cells, the source of toxin. In Europe and the US, however, metronidazole (500 mg per dose, 4 times a day, per os or i.v., for 7–10 days: this treatment is not covered by health insurance in Japan) tends to be preferred. In this regard, it is known that PCG serves as a GABA antagonist [8]. When there is contamination with soil or feces, appropriate antibacterial agents should be used with suspicion of mixed infection with other bacteria [for example, PIPC 4 g/day, in 4 divided doses; or cefazolin (CEZ) or cefmetazole (CMZ) 3–4 g/day, in 3–4 divided doses]. Deterging or debridement of the wound and removal of foreign bodies are necessary for successful antibacterial therapy.

**Administration of antitoxin (passive immunization)**

**Critical prevention immediately after injury**

Antitoxin [human tetanus immunoglobulin (TIG)] neutralizes circulating toxin in the blood (and some in the wound as well) before it can bind to the neural tissues. The risk of developing tetanus should be estimated from the condition of the wound (Table 1), and 250 IU of TIG for prophylaxis should be given intramuscularly or intravenously as soon after the injury as possible. For severe trauma cases, 1,500 IU should be given intravenously. Repeated administration is necessary for extensive second-degree burns. It is recommended that TIG be administered prior to providing debridegment or opening of the wound. The serum antitoxin titer is maintained above 0.01 IU/mL, the lower limit of the protective level range [minimum protective level (MPL)] within 4 weeks after intramuscular or intravenous injection of 250 IU (covering almost the entire incubation period of tetanus). The peak blood level of antitoxin is attained about 2 days after intramuscular injection.
**Therapeutic administration after onset**

In order to shorten the course after the onset or to alleviate symptoms of tetanus, TIG should be administered prior to providing debridement or opening of the wound. At least 5,000 IU, administered intramuscularly (usually in divided doses because of the large quantity), or 1,500–3,000 IU for mild to moderate cases and 3,000–4,500 IU for severe cases, administered intravenously, should be used, with increasing doses according to the disease state. The optimal doses have not been established, and intramuscular injection of 500 IU reportedly achieves an efficacy comparable to that of higher doses. The biological half-life of TIG in the blood is 3–4 weeks after intravenous or intramuscular administration. There are no established criteria for choosing intravenous or intramuscular TIG. The route presumably most appropriate for the individual patient should be chosen.

**Toxoid administration (active immunization)**

**Vaccination immediately after injury**

Vaccination immediately after injury is not necessary if the patient has completed a primary 3-dose series and it has not been more than 5 years since the last dose (Table 4) [9]. Those who have completed a primary series and in whom more than 5–10 years have elapsed since the last dose should receive a booster dose if at risk of developing tetanus. Prompt acquisition of a high serum antitoxin titer can be expected from this dose (booster effect). Non-immunized or partially immunized individuals who have received <3 doses should immediately aim to complete the 3-dose series. Patients with an unknown history of vaccination (including those who were born before introduction of the DPT vaccine in 1968) should be dealt with as non-immunized individuals in case of emergency.

**Vaccination during convalescence**

Recovery from tetanus does not confer immunity. Considering the risk of sustaining a similar injury, it is necessary to complete a primary vaccination series to avoid recurrent tetanus. Therefore, active immunization by means of adsorbed tetanus toxoid should be initiated during the recovery period. It is desirable that the unvaccinated patient be given 2 doses during hospitalization and discharged with a fixed schedule for the third dose. When TIG is given intramuscularly, the toxoid should be inoculated at a distant site from the injection site, e.g., by a contralateral subcutaneous or intramuscular route.

**Control of muscle spasms**

Benzodiazepines (diazepam or midazolam) are often used to control muscle spasms and produce sedation. In particular, diazepam, which exerts a GABA-ergic effect, is the drug of choice, and is administered with a dose escalation of 5 mg increments according to the symptoms. When tonic spasms subside, doses of benzodiazepines should be reduced over at least 2 weeks to avoid withdrawal reaction. However, it is often difficult to obtain sufficient control of muscle spasms even with high doses of diazepam, necessitating combined use of a sedative (propofol), antispasmodic (baclofen) or muscle relaxant (vecuronium or dantrolene).

Since even minor sensory stimuli induce spasms, a darkened, quiet environment is optimal.

**Respiratory care**

The airway and ventilatory function should be evaluated immediately after the first examination. In severe cases, artificial ventilation (maintenance of adequate ventilation) should be initiated after endotracheal intubation (protection of the airway), because there is a risk of respiratory failure or suffocation due to excessive sedation or spasms of the...
glottis or respiratory muscles. If endotracheal intubation induces spasms, tracheostomy is indicated. It is recommended that nasogastric intubation be carried out at the same time as endotracheal intubation.

Control of autonomic dysfunction

Autonomic dysfunction results from excessive catecholamine release associated with sympathetic hyperactivity. To control blood pressure, the β-blocker labetalol is usually used. In treating hypertension, infusion of morphine on magnesium sulfate, and epidural blockade of the renal plexus may also be performed. In hypotensive cases, infusion of dopamine or noradrenalin is used in addition to fluid therapy. The use of a pacemaker may be necessary to treat bradycardia.

Prognosis

The mortality rate from generalized tetanus is 20–30% even with current advanced respiratory and circulatory management in an ICU (the mortality rate is about 10% in mild to moderate cases, but reaches up to 60% in severe cases). The cause of death is most frequently pneumonia, but autopsy reveals no significant findings in some cases. Such cases probably represent deaths due to autonomic dysfunction, particularly cardiovascular complications, attributable to the neurotoxicity of tetanus toxin. Neonates and elderly patients have a poor prognosis. The prognosis is also poor in patients with a short incubation period or “onset period” and in those with a short interval between the clinical manifestation (trismus) and admission. In general, the prognosis is influenced by the history of vaccination.

Patients usually recover in 4–6 weeks even when they have the generalized form of moderate or severe disease. During this period, patients usually need intensive care with ventilatory support. Patients may suffer from muscular hypertonicity or minor spasms over several months, but the premorbid condition is usually restored. Neuromuscular transmission disorder of lower motor neurons may become apparent after spasms have resolved, and recovery from this disorder requires several weeks. The seriousness of tetanus (pain and dyspnea due to severe tonic spasms under clear consciousness) and its treatment (prolonged ICU management using artificial ventilation) can produce persistent psychic trauma long after recovery from the disease, and psychotherapy may be required.

References