# Tetanus

**Tetanus**, also known as **lockjaw**, is a bacterial infection characterized by muscle spasms.[1] In the most common type, the spasms begin in the jaw and then progress to the rest of the body.[1] Each spasm usually lasts a few minutes and spasms occur frequently for three to four weeks.[1] Spasms may be severe enough to cause bone fractures.[6] Other symptoms of tetanus may include fever, sweating, headache, trouble swallowing, high blood pressure, and a fast heart rate.[1][6] Onset of symptoms is typically three to twenty-one days following infection.[1] Recovery may take months.[1] About ten percent of cases prove fatal.[1]

Tetanus is caused by an infection with the bacterium *Clostridium tetani*,[1] which is commonly found in soil, saliva, dust, and manure.[2] The bacteria generally enter through a break in the skin such as a cut or puncture wound by a contaminated object.[2] They produce toxins that interfere with normal muscle contractions.[3] Diagnosis is based on the presenting signs and symptoms.[1] The disease does not spread between people.[1]

Tetanus can be prevented by immunization with the tetanus vaccine.[1] In those who have a significant wound and have had fewer than three doses of the vaccine, both vaccination and tetanus immune globulin are recommended.[1] The wound should be cleaned and any dead tissue should be removed.[1] In those who are infected, tetanus immune globulin or, if unavailable, intravenous immunoglobulin (IVIG) is used.[1] Muscle relaxants may be used to control spasms.[3] Mechanical ventilation may be required if a person's breathing is affected.[3]

Tetanus occurs in all parts of the world but is most frequent in hot and wet climates where the soil contains a lot of organic matter.[1] In 2015 there were about 209,000 infections and about 59,000 deaths globally.[4][5] This is down from 356,000 deaths in 1990.[7] In the US there are about 30 cases per year, almost all of which have not been vaccinated.[8] An early description of the disease was made by Hippocrates in the 5th century BCE.[1] The cause of the disease was determined in 1884 by Antonio Carle and Giorgio Rattone at the University of Turin, and a vaccine was developed in 1924.[1]

| Tetanus | |
|---|---|
| **Other names** | Lockjaw |
| |  |
| | Muscle spasms (specifically opisthotonos) in a person with tetanus. Painting by Sir Charles Bell, 1809. |
| **Specialty** | Infectious disease |
| **Symptoms** | Muscle spasms, fever, headache[1] |
| **Usual onset** | 3–21 days following exposure[1] |
| **Duration** | Months[1] |
| **Causes** | *Clostridium tetani*[1] |
| **Risk factors** | Break in the skin[2] |
| **Diagnostic method** | Based on symptoms[1] |
| **Prevention** | Tetanus vaccine[1] |
| **Treatment** | Tetanus immune globulin, muscle relaxants, mechanical ventilation[1][3] |
| **Prognosis** | 10% chance of death[1] |
| **Frequency** | 209,000 (2015)[4] |
| **Deaths** | 56,700 (2015)[5] |

# Contents



# Signs and symptoms

Tetanus often begins with mild spasms in the jaw muscles—also known as lockjaw or trismus. The spasms can also affect the facial muscles resulting in an appearance called *risus sardonicus*. Chest, neck, back, abdominal muscles, and buttocks may be affected. Back muscle spasms often cause arching, called opisthotonos. Sometimes the spasms affect muscles that help with breathing, which can lead to breathing problems.[1]

Prolonged muscular action causes sudden, powerful, and painful contractions of muscle groups, which is called "tetany". These episodes can cause fractures and muscle tears. Other symptoms include fever, headache, restlessness, irritability, feeding difficulties, breathing problems, burning sensation during urination, urinary retention and loss of stool control.[9]

Even with treatment, about 10% of people who contract tetanus die.[1] The mortality rate is higher in unvaccinated people and people over 60 years of age.[1]

## Incubation period

The incubation period of tetanus may be up to several months, but is usually about ten days.[10][11] In general, the farther the injury site is from the central nervous system, the longer the incubation period. The shorter the incubation period, the more severe the symptoms.[12] In neonatal tetanus, symptoms usually appear from 4 to 14 days after birth, averaging about 7 days. On the basis of clinical findings, four different forms of tetanus have been described.[1]

## Generalized tetanus

Generalized tetanus is the most common type of tetanus, representing about 80% of cases. The generalized form usually presents with a descending pattern. The first sign is trismus, or lockjaw, and the facial spasms called *risus sardonicus*, followed by stiffness of the neck, difficulty in swallowing, and rigidity of pectoral and calf muscles. Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes with the body shaped into a characteristic form called opisthotonos. Spasms continue for up to four weeks, and complete recovery may take months.[1]

## Neonatal tetanus

Neonatal tetanus is a form of generalized tetanus that occurs in newborns, usually those born to mothers who themselves have not been vaccinated. If the mother has been vaccinated against tetanus, the infants acquire passive immunity and are thus protected.[13] It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with a non-sterile instrument. As of 1998 neonatal tetanus was common in many developing countries and was responsible for about 14% (215,000) of all neonatal deaths.[14] In 2010 the worldwide death toll was 58,000 newborns. As the result of a public health campaign, the death toll from neonatal tetanus was reduced by 90% between 1990 and 2010, and by 2013 the disease had been largely eliminated from all but 25 countries.[15] Neonatal tetanus is rare in developed countries.

## Local tetanus

Local tetanus is an uncommon form of the disease, in which people have persistent contraction of muscles in the same anatomic area as the injury. The contractions may persist for many weeks before gradually subsiding. Local tetanus is generally milder; only about 1% of cases are fatal, but it may precede the onset of generalized tetanus.[1]

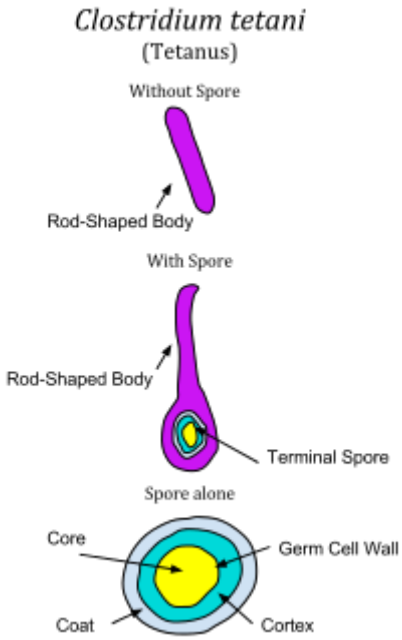
## Cephalic tetanus

Cephalic tetanus is the rarest form of the disease (0.9–3% of cases)[16] and is limited to muscles and nerves in the head.[17] It usually occurs after trauma to the head area, including skull fracture,[18] laceration,[18] eye injury,[17] dental extraction,[19] and otitis media,[20] but it has been observed from injuries to other parts of the body.[21] Paralysis of the facial nerve is most frequently implicated, which may cause lockjaw, facial palsy, or ptosis, but other cranial nerves can also be affected.[19][22] Cephalic tetanus may progress to a more generalized form of the disease.[16][22] Due to its rarity, clinicians may be unfamiliar with the clinical presentation and may not suspect tetanus as the illness.[17] Treatment can be

complicated as symptoms may be concurrent with the initial injury that caused the infection.[18] Cephalic tetanus is more likely than other forms of tetanus to be fatal, with the progression to generalized tetanus carrying a 15–30% case fatality rate.[16][18][22]

# Cause

Tetanus is caused by the tetanus bacterium *Clostridium tetani*.[1] Tetanus is an international health problem, as *C. tetani* endospores are ubiquitous. Endospores can be introduced into the body through a puncture wound (penetrating trauma). Due to *C. tetani* being an anaerobic bacterium, it and its endospores thrive in environments that lack oxygen, such as a puncture wound.




*Clostridium tetani* is durable due to its endospores. Pictured is the bacterium alone, with a spore being produced, and the spore alone.

The disease occurs almost exclusively in persons inadequately immunized.[23] It is more common in hot, damp climates with soil rich in organic matter. Manure-treated soils may contain spores, as they are widely distributed in the intestines and feces of many animals such as horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens.[1] In agricultural areas, a significant number of human adults may harbor the organism.

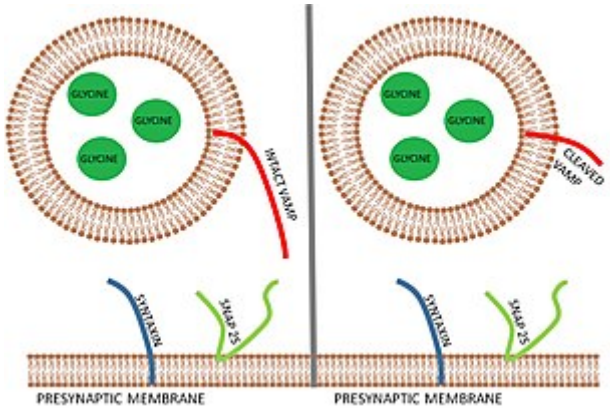
The spores can also be found on skin surfaces and in contaminated heroin.[1] Heroin users, particularly those that inject the drug subcutaneously, appear to be at high risk of contracting tetanus.[1] Rarely, tetanus can be contracted through surgical procedures, intramuscular injections, compound fractures, and dental infections.[1] Animal bites can transmit tetanus.[1]

Tetanus is often associated with rust, especially rusty nails. Although rust itself does not cause tetanus, objects that accumulate rust are often found outdoors or in places that harbor anaerobic bacteria. Additionally, the rough surface of rusty metal provides a habitat for *C. tetani*, while a nail affords a means to puncture skin and deliver endospores deep within the body at the site of the wound.[24] An endospore is a non-metabolizing survival structure that begins to metabolize and cause infection once in an adequate environment. Hence, stepping on a nail (rusty or not) may result in a tetanus infection, as the low-oxygen (anaerobic) environment may exist under the skin, and the puncturing object can deliver endospores to a suitable environment for growth.[25] It is a common misconception that rust itself is the cause and that a puncture from a rust-free nail is not a risk.[26][27]

# Pathophysiology

Tetanus neurotoxin (TeNT) binds to the presynaptic membrane of the neuromuscular junction, is internalized and is transported back through the axon until it reaches the central nervous system.[28] Here, it selectively binds to and is transported into inhibitory neurons via endocytosis.[29] It then leaves the vesicle for the neuron cytosol where it cleaves vesicle associated membrane protein (VAMP) synaptobrevin, which is necessary for membrane fusion of small synaptic vesicles (SSV's).[28] SSV's carry neurotransmitter to the membrane for release, so inhibition of this process blocks neurotransmitter release.

Tetanus toxin specifically blocks the release of the neurotransmitters GABA and glycine from inhibitory neurons. These neurons keep overactive motor neurons from firing and also play a role in the relaxation of muscles after contraction. When inhibitory neurons are unable to release their neurotransmitters, motor neurons fire out of control and muscles have difficulty relaxing. This causes the muscle spasms and spastic paralysis seen in tetanus infection.[28]




A neurotransmitter-filled vesicle before and after exposure to the tetanus toxin. The cleavage of the VAMP protein by the toxin inhibits vesicle fusion and neurotransmitter release into the synapse.

The tetanus toxin, tetanospasmin, is made up of a heavy chain and a light chain. There are three domains, each of which contribute to the pathophysiology of the toxin.[30] The heavy chain has two of the domains. The N-terminal side of the heavy chain helps with membrane translocation, and the C-terminal side helps the toxin locate the specific receptor site on the correct neuron. The light chain domain cleaves the VAMP protein once it arrives in the inhibitory neuron cytosol.[30]

There are four main steps tetanus's mechanism of action: binding to the neuron, internalization of the toxin, membrane translocation, and cleavage of the target VAMP.

## Neurospecific binding

The toxin travels from the wound site to the neuromuscular junction through the bloodstream where it binds to the presynaptic membrane of a motor neuron. The heavy chain C-terminal domain aids in the binding to the correct site, recognizing and binding to the correct glycoproteins and glycolipids in the presynaptic membrane. The toxin binds to a site that will be taken into the neuron as an endocytic vesicle that will travel all the way down the axon, past the cell body, and down the dendrites to the dendritic terminal at the spine and central nervous system. Here it will be released into the synaptic cleft and allowed to bind with the presynaptic membrane of inhibitory neurons in a similar manner seen with the binding to the motor neuron.[29]

## Internalization

Tetanus toxin is then internalized again via endocytosis, this time in an acidic vesicle.[30] In a mechanism not well understood, depolarization caused by the firing of the inhibitory neuron causes the toxin to be pulled into the neuron inside vesicles.

## Membrane translocation

The toxin then needs a way to get out of the vesicle and into the neuron cytosol in order for it to act on its target. The low pH of the vesicle lumen causes a conformational change in the toxin, shifting it from a water-soluble form to a hydrophobic form.[29] With the hydrophobic patches exposed, the toxin is able to slide into the vesicle membrane. The toxin forms an ion channel in the membrane that is nonspecific for Na+, K+, Ba2+, and Cl- ions.[28] There is a consensus among experts that this new channel is involved in the translocation of the toxin's light chain from the inside of the vesicle to the neuron cytosol, but the

mechanism is not well understood or agreed upon. It has been proposed that the channel could allow the light chain (unfolded from the low pH environment) to leave through the toxin pore,[31] or that the pore could alter the electrochemical gradient enough, by letting in or out ions, to cause osmotic lysis of the vesicle, spilling the vesicle's contents.[32]

### Enzymatic target cleavage

The light chain of the tetanus toxin is a zinc-dependent protease. It shares a common zinc protease motif (His-Glu-Xaa-Xaa-His) that researchers hypothesized was essential for target cleavage until this was more recently confirmed by experiment: when all zinc was removed from the neuron with heavy metal chelators, the toxin was inhibited, only to be reactivated when the zinc was added back in.[28] The light chain binds to VAMP and cleaves it between Gln76 and Phe77. Without VAMP, vesicles holding the neurotransmitters needed for motor neuron regulation (GABA and Glycine) cannot be released, causing the above-mentioned deregulation of motor neurons and muscle tension.[33]

## Diagnosis

There are currently no blood tests for diagnosing tetanus. The diagnosis is based on the presentation of tetanus symptoms and does not depend upon isolation of the bacterium, which is recovered from the wound in only 30% of cases and can be isolated from people without tetanus. Laboratory identification of *C. tetani* can be demonstrated only by production of tetanospasmin in mice.[1] Having recently experienced head trauma may indicate cephalic tetanus if no other diagnosis has been made.

The "spatula test" is a clinical test for tetanus that involves touching the posterior pharyngeal wall with a soft-tipped instrument and observing the effect. A positive test result is the involuntary contraction of the jaw (biting down on the "spatula") and a negative test result would normally be a gag reflex attempting to expel the foreign object. A short report in *The American Journal of Tropical Medicine and Hygiene* states that, in an affected subject research study, the spatula test had a high specificity (zero false-positive test results) and a high sensitivity (94% of infected people produced a positive test).[34]

## Prevention

Unlike many infectious diseases, recovery from naturally acquired tetanus does not usually result in immunity to tetanus. This is due to the extreme potency of the tetanospasmin toxin. Tetanospasmin will likely be lethal before it will provoke an immune response.

Tetanus can be prevented by vaccination with tetanus toxoid.[35] The CDC recommends that adults receive a booster vaccine every ten years,[1] and standard care practice in many places is to give the booster to any person with a puncture wound who is uncertain of when he or she was last vaccinated, or if he or she has had fewer than three lifetime doses of the vaccine. The booster may not prevent a potentially fatal case of tetanus from the current wound, however, as it can take up to two weeks for tetanus antibodies to form.[36]

In children under the age of seven, the tetanus vaccine is often administered as a combined vaccine, DPT/DTaP vaccine, which also includes vaccines against diphtheria and pertussis. For adults and children over seven, the Td vaccine (tetanus and diphtheria) or Tdap (tetanus, diphtheria, and acellular pertussis) is commonly used.[35]

The World Health Organization certifies countries as having eliminated maternal or neonatal tetanus. Certification requires at least two years of rates of less than 1 case per 1000 live births. In 1998 in Uganda, 3,433 tetanus cases were recorded in newborn babies; of these, 2,403 died. After a major public health effort, Uganda in 2011 was certified as having eliminated tetanus.[37]

### Post-exposure prophylaxis

Tetanus toxoid can be given in case of a suspected exposure to tetanus. In such cases, it can be given with or without tetanus immunoglobulin (also called *tetanus antibodies* or *tetanus antitoxin*[38]). It can be given as intravenous therapy or by intramuscular injection.

The guidelines for such events in the United States for non-pregnant people 11 years and older are as follows:[1]

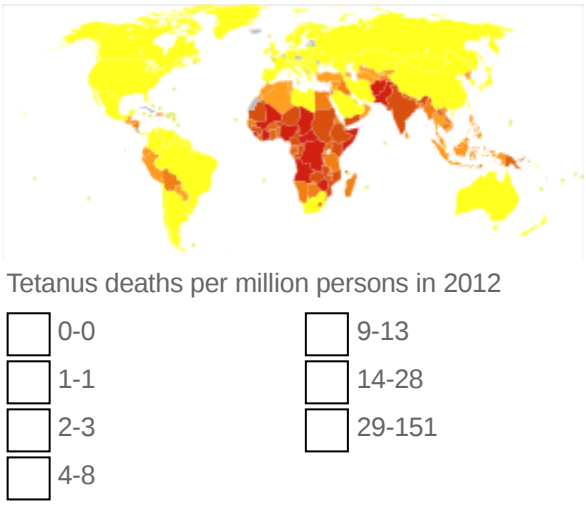
| Vaccination status | Clean, minor wounds | All other wounds |
|---|---|---|
| Unknown or less than 3 doses of tetanus toxoid containing vaccine | Tdap and recommend catch-up vaccination | Tdap and recommend catch-up vaccination<br>Tetanus immunoglobulin |
| 3 or more doses of tetanus toxoid containing vaccine AND less than 5 years since last dose | No indication | No indication |
| 3 or more doses of tetanus toxoid containing vaccine AND 5–10 years since last dose | No indication | Tdap preferred (if not yet received) or Td |
| 3 or more doses of tetanus toxoid containing vaccine AND more than 10 years since last dose | Tdap preferred (if not yet received) or Td | Tdap preferred (if not yet received) or Td |

## Treatment

### Mild tetanus

Mild cases of tetanus can be treated with:[39]

- tetanus immunoglobulin (TIG),[1] also called *tetanus antibodies* or *tetanus antitoxin.*[38] It can be given as intravenous therapy or by intramuscular injection.
- metronidazole IV for 10 days
- diazepam oral or IV




### Severe tetanus

Severe cases will require admission to intensive care.
In addition to the measures listed above for mild tetanus:[39]

- Human tetanus immunoglobulin injected intrathecally (increases clinical improvement from 4% to 35%)
- Tracheotomy and mechanical ventilation for 3 to 4 weeks. Tracheotomy is recommended for securing the airway because the presence of an endotracheal tube is a stimulus for spasm
- Magnesium sulfate, as an intravenous (IV) infusion, to control spasm and autonomic dysfunction

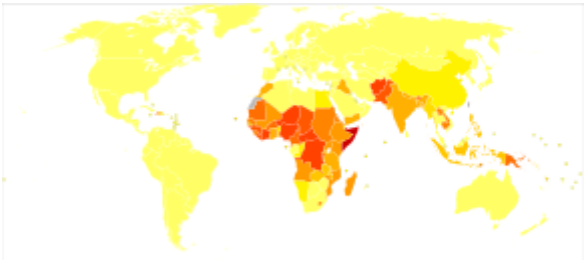
- Diazepam as a continuous IV infusion
- The autonomic effects of tetanus can be difficult to manage (alternating hyper- and hypotension hyperpyrexia/hypothermia) and may require IV labetalol, magnesium, clonidine, or nifedipine

Drugs such as diazepam or other muscle relaxants can be given to control the muscle spasms. In extreme cases it may be necessary to paralyze the person with curare-like drugs and use a mechanical ventilator.

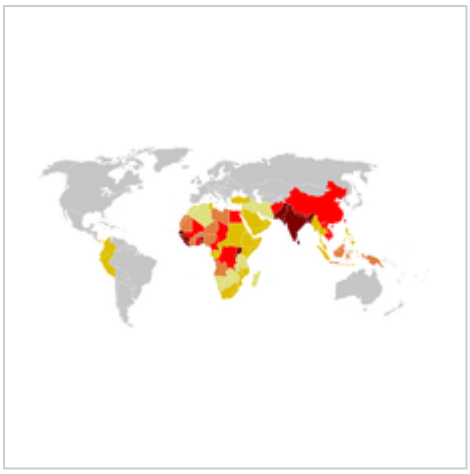
In order to survive a tetanus infection, the maintenance of an airway and proper nutrition are required. An intake of 3,500 to 4,000 calories and at least 150 g of protein per day is often given in liquid form through a tube directly into the stomach (percutaneous endoscopic gastrostomy), or through a drip into a vein (parenteral nutrition). This high-caloric diet maintenance is required because of the increased metabolic strain brought on by the increased muscle activity. Full recovery takes 4 to 6 weeks because the body must regenerate destroyed nerve axon terminals.

# Epidemiology

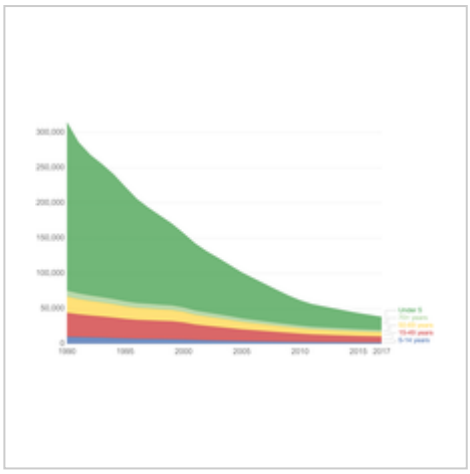
In 2013 it caused about 59,000 deaths – down from 356,000 in 1990.[7] Tetanus – in particular, the neonatal form – remains a significant public health problem in non-industrialized countries with 59,000 newborns worldwide dying in 2008 as a result of neonatal tetanus.[40][41] In the United States, from 2000 through 2007 an average of 31 cases were reported per year.[1] Nearly all of the cases in the United States occur in unimmunized individuals or individuals who have allowed their inoculations to lapse.[1]



Disability-adjusted life year for tetanus per 100,000 inhabitants in 2004.



Tetanus cases reported worldwide (1990-2004). Ranging from some (in dark red) to very few (in light yellow) (grey, no data).



Tetanus deaths between 1990 and 2017 by age group[42]

# History

Tetanus was well known to ancient people who recognized the relationship between wounds and fatal muscle spasms.[43] In 1884, Arthur Nicolaier isolated the strychnine-like toxin of tetanus from free-living, anaerobic soil bacteria. The etiology of the disease was further elucidated in 1884 by Antonio Carle and Giorgio Rattone, two pathologists of the University of Turin, who demonstrated the transmissibility of tetanus for the first time. They produced tetanus in rabbits by injecting pus from a person with fatal tetanus into their sciatic nerves.[1]

In 1891, *C. tetani* was isolated from a human victim by Kitasato Shibasaburō, who later showed that the organism could produce disease when injected into animals, and that the toxin could be neutralized by specific antibodies. In 1897, Edmond Nocard showed that tetanus antitoxin induced passive immunity in humans, and could be used for prophylaxis and treatment. Tetanus toxoid vaccine was developed by P. Descombey in 1924, and was widely used to prevent tetanus induced by battle wounds during World War II.[1]

## Etymology

The word tetanus comes from the Ancient Greek: τέτανος, romanized: *tetanos*, lit. 'taut', which is further from the Ancient Greek: τείνειν, romanized: *teinein*, lit. 'to stretch'.[44]

# See also

- Renshaw cell
- Tetanized state
- Tetanospasmin

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# External links

- Tetanus Information from Medline Plus (https://www.nlm.nih.gov/medlineplus/ency/article/000615.htm)
- Tetanus Surveillance -- United States, 1998-2000 (Data and Analysis) (https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5203a1.htm)

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| **Classification** | **ICD-10**: A33 (http://apps.who.int/classifications/icd10/browse/2016/en#/A33)-A35 (http://apps.who.int/classifications/icd10/browse/2016/en#/A35) · **ICD-9-CM**: 037 (http://www.icd9data.com/getICD9Code.ashx?icd9=037), 771.3 (http://www.icd9data.com/getICD9Code.ashx?icd9=771.3) · **MeSH**: D013742 (https://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?field=uid&term=D013742) · **DiseasesDB**: 2829 (http://www.diseasesdatabase.com/ddb2829.htm) |
| **External resources** | **MedlinePlus**: 000615 (https://www.nlm.nih.gov/medlineplus/ency/article/000615.htm) · **eMedicine**: emerg/574 (https://emedicine.medscape.com/emerg/574-overview) |