

Abstract

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CURRENT CONCEPTS IN THE MANAGEMENT OF TETANUS

The study focuses on the problem of severe tetanus cases, which continue to be reported worldwide. The population of countries with low vaccination rates, including Ukraine, is particularly at risk. Despite the increase in the level of DPT vaccination in our country among adults and children, it remains insufficient, which leads to the registration of new cases of tetanus.

The aim of the study was to analyze the main directions in the treatment of tetanus. The authors searched for information in electronic databases such as MEDLINE/Pub Med and Google Scholar for the last 20 years. The search was performed on such terms as tetanus, treatment, benzodiazepines, tetanus immunoglobulin (medical topics). The main components of modern treatment are analyzed in the paper, which include removal of the pathogen by careful surgical treatment of wounds, rational antibiotic therapy. Drugs of choice for the eradication of vegetative forms of the pathogen are benzylpenicillin and metronidazole, but can also be used antibacterial drugs of other groups (macrolides, tetracyclines, cephalosporins). Specific immunotherapy with tetanus immunoglobulin can neutralize the toxin that freely circulates in the blood. Those who do not have vaccination data are also indicated for the introduction of tetanus toxoid. Intrathecal administration of anti-tetanus immunoglobulin remains a debatable issue. In the treatment of convulsions, drugs of the benzodiazepine group are preferred. Infusions of high doses of magnesium, dexmetomedin, baclofen, propofol or their combination can also be used. In the case of severe muscular rigidity, muscle relaxants of nondepolarizing action are used. If the spasms are prolonged, botulinum toxin A may be recommended as an injection into peripheral muscles. B-blockers (esmolol), dexmetomedin, clonidine are used to overcome autonomic dysfunction of the nervous system. Supportive therapy is important. It is aimed at providing the patient with complete nutrition. Adequate ventilation with early tracheostomy helps to avoid complications of prolonged intubation.

The above methods can significantly reduce mortality from tetanus from 100% (in the absence of treatment) to 10%–20%.

**Keywords:** tetanus, management, benzodiazepines, magnesium sulfate, tetanus immunoglobulin, tracheostomy.

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**Резюме**

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**СУЧАСНІ КОНЦЕПЦІЇ В ЛІКУВАННІ ПРАВЦЯ**

Дослідження присвячене проблемі поширення випадків важких форм правця, які продовжують реєструватися по всьому світу. Особливо схильне до ризику захворюти населення країн з низьким рівнем вакцинації, включаючи і Україну. Незважаючи на зростання рівня вакцинації АКДП в нашій країні серед дорослих і дітей, він залишається недостатнім, що призводить реєстрації нових випадків правця.

Метою дослідження був аналіз основних напрямків в лікуванні правця. Автори провели пошук інформації в електронних базах даних, таких як MEDLINE/Pub Med і Google Scholar за останні 20 років. Пошук проводився за такими термінами, як правець, лікування, бензодіазепіни, протиправцевий імуноглобулін, магnezії сульфат, трахеостомія (медичні тематичні рубрики). В роботі проаналізовано основні компоненти сучасного лікування, які включають видалення збудника шляхом ретельної хірургічної обробки ран, раціональну антибіотикотерапію. Препаратами вибору для знищення вегетативних форм збудника є бензилпеніцилін і метронідазол, але також можуть бути використані антибактеріальні препарати інших груп (макроліди, тетрацикліни, цефалоспорини). Специфічна імунотерапія протиправцевим імуноглобуліном дозволяє нейтралізувати токсин, що вільно циркулює в крові. Особам, які не мають даних про вакцинацію, також показано введення правцевого анатоксину. Дискусійним питанням залишається інтратекальне введення протиправцевого імуноглобуліну. У лікуванні судом перевагу мають препарати групи бензодіазепінів. Також можуть бути використані інфузії високих доз магnezії, дексметомедіна, баклофена, пропофолу або їх комбінація. При вираженій м'язовій ригідності використовуються міорелаксанти недеполяризуючої дії. У разі розвитку тривалого спазму може бути рекомендований ботулотоксин А у вигляді ін'єкції в периферичні м'язи. Для боротьби з автономною дисфункцією нервової системи застосовуються b-блокатори (есмолол), дексметомедін, клонідин. Важливе значення має підтримуюча терапія, спрямована на забезпечення хворого повноцінним харчуванням. Адекватна вентиляція з проведенням ранньої трахеостомії дозволяє уникнути ускладнень тривалої інтубації.

Перераховані вище методи дозволяють істотно знизити летальність від правця зі 100% (у разі відсутності лікування) до 10%–20%.

**Ключові слова:** правець, лікування, бензодіазепіни, сульфат магnezію, протиправцевий імуноглобулін, трахеостомія.

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**Introduction**

According to the European Center for the Prevention and Control of Disease in the European Union, 82 cases of tetanus were recorded in 2017, 54% of cases were reported in Italy and Poland [1]. There were no reported cases of this disease in 10 countries: Germany, Belgium, Finland, etc., where the level of vaccinated people ranged from 91 to 98%. In the world in 2017, 86% of infants were

vaccinated with 3 doses of DTP vaccine. At the same time, according to the Ministry of Health of Ukraine in 2017, about half of children under 18 months of age were not vaccinated against diphtheria, pertussis and tetanus and less than half of adults underwent routine booster vaccination against the mentioned infections. And although by 2018 the total level of DTP vaccination among adults and children in Ukraine has grown to 69%

(in 2017 – 50%), cases of tetanus are regularly recorded in the country. So in Ukraine in 2018, 17 cases of this disease were registered [2].

The seriousness of the problem lies in the high mortality rate, which among infectious diseases is second only to botulism and pulmonary plague. Mortality cannot be reduced due to the development of complications associated with the action of the bacterial toxin. The overall incidence of tetanus deaths varies between 10% and 70%, depending on the treatment, age and general health of the patient. Without hospitalization and intensive treatment, mortality is almost 100% among elderly and pediatric patients. When conducting the most optimal treatment, mortality can be reduced to 10%–20% [3].

Evidence of a successful tetanus control program worldwide is a reduction in infant mortality. If in 1988, 787 000 newborns died from tetanus, then in 2015, 34 000 died, that is, mortality due to large-scale vaccination decreased on 96% [3].

**Purpose:** analysis of the main recommendation devoted to the treatment of tetanus.

**Methods:** The authors searched for information in electronic databases such as MEDLINE/Pub Med and Google Scholar for the last 20 years. The search was performed on such terms as tetanus, management, benzodiazepines, tetanus immunoglobulin, magnesium sulfate, tracheostomy (medical topics).

#### **Research results and discussion:**

Tetanus treatment is supportive and in most cases should be carried out in intensive care units. The treatment strategy is based on the following therapies principles:

- eradication of the pathogen to prevent further secretion of the toxin;
- neutralization of the toxin outside the CNS by specific immunotherapy;
- detoxification therapy to neutralize the toxin that has already entered the CNS cells;
- therapy of muscle rigidity and convulsive syndrome;
- reducing of autonomic dysfunction;
- other supportive measures of intensive care [4].

Etiopathogenetic treatment consists in thorough primary surgical treatment of the wound, as well as antibiotic eradication of *Clostridium tetani*. Properly performed surgical treatment of wounds leads to a significant elimination of the pathogen. The debatable issue is the use of antibiotic therapy to protect from vegetative forms. This type of

treatment is not primary, because the vegetative form of bacteria multiplies locally and is not disseminated through blood and lymph (as opposed to a toxin). According to the recommendations of the European protocols, penicillin and metronidazole should be used as antibiotic prophylaxis and treatment, but tetracyclines, macrolides, clindamycin, cephalosporins and chloramphenicol can also be effective [5]. However, benzylpenicillin is a GABA antagonist and enhances the action of tetanospasmin, causing convulsions. Therefore, metronidazole has been proposed as an alternative to the treatment [6]. According to studies by other authors, the use of metronidazole, benzylpenicillin, and penicillin benzathine was characterized by approximately the same efficacy and prognosis [7].

Specific immunotherapy by the human anti-tetanus immunoglobulin TIG is administered in the treatment of tetanus (3,000 to 6,000 IU). TIG is also indicated in the treatment of tetanus neonatorum [8]. The antitoxin is given for inactivation any free tetanus toxin. The toxin that has been taken up into CNS is probably not available to the TIG. Anti-tetanus serum can be used in the absence of specific human anti-tetanus immunoglobulin; however, its administration is often accompanied by severe allergic manifestations. It is necessary to take into account the presence of pyrogenic substances in horse serum. In addition, anti-tetanus serum is characterized by instability, which can lead to a decrease in antitoxin levels during storage of the drug [9, 10]. Anti-tetanus serum is recommended in the dose 50,000 to 100,000 U. Also tetanus toxoid (TT) is administrated for patients without a history of primary vaccination in dose 0.5 ml by intramuscular injection, a second dose 1–2 months later, and a third dose 6–12 months after first injection [8]. Human polyvalent intravenous immunoglobulin is recommended only for prophylaxis tetanus, not for treatment due to the variable levels of tetanus antitoxin [11].

According to some authors, an intrathecally administered epidural or subarachnoid drug anti-tetanus immunoglobulin increased the survival of patients with a generalized form of tetanus, probably blocking the transmission of toxin within the synapses. The benefits from receiving intrathecal antitoxin are - decrease in mortality and complications (nosocomial infection, myocardial infarction, hyper- and hypotension), improvement of long-term outcomes [12, 13, 14]. One of the variants for specific treatment is the simultaneous

administration of intramuscular (3000 IU) and intrathecal (1000 IU) TIG, which led to a decrease in the severity of convulsive syndrome and a decrease in the hospital stay [15]. Although, according to other authors, the effectiveness of intrathecal administration of anti-tetanus immunoglobulin has not been proven [16].

Another problem in treatment of tetanus is associated with great difficulties related to muscle spasms relief. Benzodiazepines are the standard choice for the treatment of tetanus muscle spasms due to their anticonvulsant, sedative and muscle relaxant effects. For adults, diazepam is administered intravenously with a gradual increase in dose by 5 mg every 2-6 hours. In some cases, large doses of up to 600 mg/day are required. The initial dose of diazepam for children is 0.1–0.2 mg/kg. Lorazepam may also be used in increments of 2 mg [5].

In cases of severe spasms, it is possible to use magnesium sulfate in the form of a continuous infusion while maintaining the level of this electrolyte in the blood from 2 to 4 mmol/l. The smallest number of patients receiving magnesium therapy needed mechanical ventilation. The mechanism of action of magnesium sulfate is the presynaptic blockade of nerve impulses and the stabilization of the autonomic nervous system by inhibiting the secretion of catecholamines and reducing the sensitivity of receptors to their effects. The recommended loading dose of magnesia for adult patients is 40 mg/kg in 30 minutes, then a maintenance dose of 2 g/hour [13, 17, 18].

To stop the convulsive syndrome, baclofen, which is a centrally acting muscle relaxant, a derivative of gamma-aminobutyric acid (GABA-b stimulator), can also be used. It blocks polysynaptic spinal reflexes, reducing muscle tension. Oral administration of this drug is not effective (it does not cross the blood-brain barrier). However, its intrathecal administration can reduce muscle tone, especially in combination with benzodiazepines. The disadvantage of intrathecal administration of baclofen is the risk of secondary infection of the central nervous system and respiratory depression, requiring respiratory support [13]. Endolumbally administered baclofen can be successfully combined with epidurally administered fentanyl and bupivacaine. Using this method, the authors were able to reduce both pain and spasmodic syndrome [19].

The use of a dexdor (dexmedetomidine) – selective alpha-2 adrenergic agonist has not been

fully studied. Some authors provide observations of a decrease in the frequency and severity of convulsive syndrome and a decrease in the dosage of sedation drugs when using it. In addition, it successfully helps overcome autonomic dysfunction, stopping the manifestations of arterial hypertension and tachycardia. The development of bradyarrhythmia, which requires a dose reduction, may be a side effect [20, 21].

The combined use of propofol and dexdor, described by a team of authors, also demonstrated efficacy in the treatment of convulsive syndrome and autonomic disorders without the use of muscle relaxants and other anticonvulsants [22].

With the ineffectiveness of the above methods of dealing with the convulsive syndrome, muscle relaxants are recommended. Pancuronium, traditionally used in such cases, can enhance the dysfunction of the autonomic nervous system, because it inhibits the reuptake of catecholamines, leading to the development of tachyarrhythmias and arterial hypertension. At the same time, pipecuronium and rocuronium are more preferable, because they have a more prolonged effect and less often cause autonomic disorders. Rocuronium at a dose of 10 mg/kg/min in combination with midazolam can be successfully used for obstinate convulsion to benzodiazepines [20, 23].

Botulinum toxin A can also be used to treat muscle stiffness and spasms, which inhibits acetylcholine release and skeletal muscle hyperactivation. Injections into the temporalis and masseter muscles were used to overcome trismus, and in the cricopharyngeal muscles to stop dysphagia. Botulinum toxin A was also administered to treat painful neck stiffness by injecting it into the trapezius, levator scapula and sternocleidomastoid muscle. These measures prevented the development of aspiration pneumonia, facilitated oral hygiene and food intake [24, 25]. In addition the successful use of botulinum toxin A to manage long-term joint deformities by injection of this agent in peripheral muscle has been reported too [26].

Autonomic dysfunction is characterized by overactivity of the both sympathetic and parasympathetic nervous system. It is manifested through lability of pulse and blood pressure, profuse sweating and hyperpyrexia. The use of magnesium sulfate or morphine is recommended to overcome vegetative instability. The prescription of  $\beta$ -blocker esmolol is in priority. Propranolol is no longer used due to the risk of hypotension and

sudden death [5]. The antisymphathetic effect of dexmedetomidine is associated with blocking the release of norepinephrine by stimulation of the presynaptic  $\alpha$ -2 receptor. It explains its efficacy in maintaining hemodynamic stability [27, 28]. Clonidine (the central  $\alpha$ -receptor agonist) decreases peripheral arteriolar tone and has also been used to manage cardiovascular instability [29].

Supportive care should be provided, including keeping patients in a calm environment. A

### Conclusions

For the management of generalized forms of tetanus, the evidence favours the administration of the human anti-tetanus immunoglobulin binding the unbound toxin, use the benzodiazepines for controlling muscle spasm, esmolol for autonomic

minimum of sensory stimulation will help avoid muscle cramps. For enteral feeding, a gastrostomy tube is preferred over a nasogastric tube, as it can provoke gastroesophageal reflux. For adequate ventilation, early tracheostomy is recommended, because prolonged endotracheal intubation is associated with immobility of vocal cord, subglottic stenosis and laryngeal granuloma. Anticoagulant therapy should be prescribed in advance to prevent thromboembolism [30, 31, 32].

instability and early tracheostomy for airway management. For eradication of the pathogen and prevention further secretion of the toxin all tetanus-prone wounds should undergo surgical debridement and adequate antibiotic therapy should be provided.

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### Conflict of interest

The authors declare no conflict of interest.

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