ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 03, pp.2436-2442, March, 2019
DOI: https://doi.org/10.24941/ijcr.34534.03.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

TETANUS; EXPERIENCE AND CURRENT APPROACH OF TREATMENT IN A GENERAL HOSPITAL

***Erick Magdiel Ramírez Rayón, Jorge Luis Rivera Rodriguez, Diana Fabiola López Velazquez, , Francisco Javier García Jiménez, Dulce María Astudillo de la Vega, José Francisco Guadarrama Quintana, Juan Alberto Suategui Guinto Karina Almazan Valenzo and José Manuel Blancas Cervantes**

Department of Internal Medicine Acapulco General Hospital, Acapulco de Juarez, Guerrero, Mexico

ARTICLE INFO

Article History:
Received 06th December, 2018
Received in revised form
24th January, 2019
Accepted 07th February, 2019
Published online 31st March, 2019

Key Words:
Tetanus, Toxoid,
Tetanospasmin,
Trismus.

ABSTRACT

Objective: Report of a series of cases of tetanus and learned experience in the diagnosis and treatment of this disease, which continues to prevail in developing countries such as ours. **Methods:** This is a descriptive and retrospective study of a series of cases of tetanus diagnosed in Acapulco General Hospital from January 2015 to January 2019. **Results:** A total of 6 cases of tetanus were reported in adults who had not been vaccinated or had not received an adequate tetanus vaccination. All patients were isolated in a silent, dark room in Intensive Care Unit (ICU). Five patients needed a tracheotomy and respiratory support. 4 of them underwent early tracheotomy as a management protocol of the hospital. All patients received tetanus toxoid and immunoglobulin on admission. Two deaths occurred throughout the period of the study. **Conclusions:** These cases highlight the difficulties of early diagnosing and adequately managing rare diseases such as tetanus in health care systems of developing countries such as Mexico, being this a highly preventable infectious disease by vaccination. Our hospital is characterized by a low mortality rate in patients with tetanus due to our systematized and multidisciplinary clinical experience.

***Citation*: *Erick Magdiel Ramírez Rayón, Jorge Luis Rivera Rodriguez, Diana Fabiola López Velazquez et al.*, 2019.** "Tetanus; Experience and current approach of treatment in a general hospital", *International Journal of Current Research*, 11, (xx), 2436-2442.

INTRODUCTION

Tetanus is a continuing burden on public health in the State of Guerrero, Mexico, just like in other poverty and low education zones. Despite of being a preventable disease by active immunization, isolated cases are still reported in different health institutions (Ergonul *et al*., 2016; Woldeamanuel *et al*., 2018). The agrarian lifestyle, the warm and humid tropical soil environment, which is rich in organic matter; and therefore, suitable for greater germination of tetanus spores, are among the most important factors for a higher incidence of tetanus in this region. Inadequate care of wounds in medical institutions and low education levels in our communities also contribute in the high incidence (Woldeamanuel *et al*., 2018). It is estimated that every year 1 million cases of tetanus occur worldwide, suggesting a global incidence of approximately 18 cases per 100 000 people and an estimated 300 000 to 500 000 deaths per year (Ergonul *et al*., 2016; Hassel, 2013; Finkelstein *et al*., 2017; Afshar *et al*., 2011). Clinical diagnosisis often suspected by the classical triad; Trismus, muscular stiffness and muscular spasms, which can be associated with autonomic dysfunction (Finkelstein *et al*., 2017; Murthy *et al*., 2014) (Table 1).

****Corresponding author: Erick Magdiel Ramírez Rayón***
Department of Internal Medicine Acapulco General Hospital, Acapulco de Juarez, Guerrero, Mexico.

MATERIALS AND METHODS

A descriptive and retrospective review was carried out, including all patients who were 8 years of age or older, with a diagnosis of tetanus who were admitted into the Intensive Care Unit (ICU), during a period of time from January 1st 2015 to January 1st 2019, obtained from an existing epidemiological database. The diagnosis of tetanus was made in all patients who presented the classic triad (Trismus, muscular stiffness and muscular spasms), with different severity of symptoms according to Abett's score. All this after other possible diagnoses were excluded.

RESULTS

During the 4 years of analysis a total of 6 cases occurred, all presented with the generalized form of the disease. According to Abett's severity score (Figure 1). Three patients were in grade 3, two patients in grade 4 and only one patient in grade 2. Annual frequency varied from 1 to 2 cases per year (Figure 2). All cases were male in our study. Ages varied from 8 to 76 years old with an average of 49 years. The mean number of days of hospitalization was 20 ± 15.5 days. During the period of study 2 patients died (33%), being the main cause of death multiple organ dysfunction and pneumonia. One hundred

percent of the patients came from agrarian areas, of which 5 (83%) were engaged in related to agriculture activities. Two cases (33%) were documented during autumn and winter seasons. Information regarding their state of tetanus immunity was not known or vaccination had not been applied. The average incubation time was 7.5 ± 6 days. All cases received tetanus vaccine and immunoglobulin at the time of admission in the hospital, with application of a second and a third dose of tetanus vaccine after 14 and 42 days after admission. Lower extremities were more commonly affected (5 patients, 83%), followed by upper extremities (1 patient, 16%). The maximum Coles period was 3 days and minimum of 1 day, with an average of 2 ± 1. APACHE II scale score was 12 ± 8 points at the time of admission. Five patients needed a tracheotomy and respiratory support. The number of days of mechanical ventilation was 16 ± 12, 4 of them (66%) underwent early tracheotomy. Medication for sedation was diazepam and vecuronium for muscle relaxation. All cases received metronidazole and in some cases adjunctive penicillin was added, depending on Abett's score. The length of stay in ICU was 15 ± 14.5 days. Complications are reported in Figure 2.

DISCUSSION

Tetanus is caused by toxins produced by Clostridium tetani, an obligated anaerobic gram-positive bacillus. During early growing stages, bacilli have flagella, move slowly and produce two toxins: tetanospasmin (commonly called tetanus toxin) and tetanolisin (uncertain importance in pathogenesis). Mature organisms lose their flagella, and develop a terminal spore, which gives them an appearance like a squash racket; in this form they are extremely stable in the environment (Ergonul *et al*., 2016; Finkelstein *et al*., 2017). The natural course of the disease usually begins when C. tetani spores enter in a contaminated by soil, manure or oxidized metal wound. Injuries caused by sharp objects are the most common way of entry, but tetanus has also been reported after fractures, burns, skin scratches made by animals, medial otitis, contaminated surgical wounds involving the gastrointestinal tract and, after abortions, and even after umbilical cord contamination. However, it is reported that in approximately 20% of cases, an entry site cannot be identified (Ergonul *et al*., 2016; Gibson *et al*., 2009). After a period of anaerobic incubation, they change from spores to bacilli which release tetanus toxin, this is activated by bacterial or tissue proteases, contains a heavy chain responsible for binding and entringin to neurons, and a light chain responsible for its toxic properties. Pepsins cleave heavy chains into specific fragments, which individually mediate binding to specific types of neural cells.

The presynaptic inhibition of neurotransmitter release is mediated through light chains. Toxin enters into the nervous system mainly through the presynaptic terminals of lower motor neurons, where it can produce local failure of the neuromuscular transmission. Then, toxin migrates retrogradly through the axonal transport system and is transported towards the cell bodies of these neurons in the brainstem and spinal cord, where it performs its main pathogenic action. Toxin destroys synaptobrevin, a required protein for the coupling of neurotransmitter vesicles with their release site in the presynaptic membrane, hence preventing the release of neurotransmitters (GABA and glycine). Tetanospasmin leaves motor neurons uninhibited, causing muscular rigidity by increasing stimulation time of motor neurons and also generating spasms by not limiting reflex responses to the existing stimuli. Autonomic nervous system is also affected, presented mainly as a hypersympathetic state induced by the inability of inhibiting adrenal release of catecholamines. Apparently the binding of the toxin is an irreversible event, which explains the long lasting clinical symptoms in the patient (Ergonul *et al*., 2016; Gibson *et al*., 2009; Ataro *et al*., 2011; Rossetto *et al*., 2013). The incubation period of tetanus (time from inoculation to the first symptom) can be as short as 1 day, or until 60 days, an average estimate of 8 days. The duration of this period is directly proportional to the distance between the site of lesion and the central nervous system. This assertion is not always reliable since the production of toxins in the wound occurs only under anaerobic conditions. This is followed by the Coles period, which is the time between the first symptom and the first spasm, reflecting the rate of toxin arrival into the central nervous system and may vary from 1 to 7 days (Ergonul *et al*., 2016; Murthy *et al*., 2014; Thwaites, 2002). Tetanus is classified into four clinical types: generalized, localized, cephalic and neonatal types (Ergonul *et al*., 2016; Gibson *et al*., 2009). Local tetanus involves only the site of the injury, but is often not recognized until it becomes generalized. Cephalic tetanus is a form of local tetanus that originates from head injuries or infections, such as medial otitis. Generalized tetanus is the most common form and accounts for 80% of cases (Finkelstein *et al*., 2017). Neonatal tetanus is a form of generalized tetanus that occurs within 28 days after birth (Gibson *et al*., 2009).

The progression of the disease will be predictable until it becomes generalized. The early involvement of the head and neck are manifested as trismus and "sardonic laughter" (tetanus facies), which is caused by spasm of the facial muscles. Stiffness of the chest wall, abdominal muscles and paralysis or spasm of the diaphragm may cause respiratory failure due to hypoventilation. In addition, paroxysms affecting pharynx and larynx can cause acute obstruction of the respiratory tract. Generalized paroxysms may mimic epileptic seizures, without losing consciousness. Fractures of long bones and tendon ruptures have been reported. Trunk spasm keeping the patient in the classic position of opisthotonus may also occur. Finally, renal failure due to rhabdomyolysis has been reported due to muscle rigidity in progress (Hassel, 2013). Tetanus is characterized by being a state of clinically significant autonomic instability, with episodes of tachycardia, hypertension and diaphoresis, alternating rapidly with episodes of bradycardia and hypotension. These tend to occur a week after the onset of motor symptoms, (Gibson *et al*., 2009; Hassel, 2013) and was the most frequent cause of death in our series (Gibson *et al*., 2009).

The diagnosis of tetanus is clinical, typical physical findings are muscle stiffness, spasms and trismus plus a history of injury in the previous 3 weeks. So far there is no specific laboratory test to confirm the diagnosis of tetanus. Tetanus antibodies are undetectable in most patients, but many reports document the disease in patients with higher antibody levels than in patients with immunity. Laboratory tests to be performed in a patient with suspected tetanus are: levels of strychnine, analysis of dopamine antagonists, electrolytes, urea nitrogen, creatinine, creatine kinase, C-reactive protein, procalcitonin and urinary myoglobin. Electromyographic studies are sometimes useful for differential diagnosis. Growth attempts in culture of C. tetani obtained from wounds have not proven to be useful in the diagnosis, because of the necessary

Table 1. Abett Classification of Tetanus Severity

Mild trismus, spasticity, no respiratory problems, no dysphagia
Moderate trismus, short spasms, mild dysphagia, respiratory rate> 30
Severe trismus, generalized spasticity, prolonged spasms, respiratory rate> 40, severe dysphagia, pulse> 120.
Same findings of grade III plus severe autonomic dysfunction of the cardiovascular system.

Table 2.

Collected data	2015	2015	2016	2017	2018	2018
Age	30	72	62	48	76 años	8
Sex	Male	Male	Male	Male	Male	Male
Co morbidities	Without chronic diseases	Without chronic diseases	DMT2 and AH	Without chronic diseases	Without chronic diseases	Without chronic diseases
Clinical presentation	Generalized	Generalized	Generalized	Generalized	Generalized	Generalized
Classification of Ablett	III	III	IV	IV	II	III
Incubation period	7 days	3 days	5 days	10 days	15 days	5 days
Period of Cole	3 days	2 days	1 day	3 day	3 days	1 day
Location of the tetanogenic lesion	Plantar region of the right foot	Plantar region of the left foot	First toe of the left foot	Gluteal region	Palm lefth and	Plantar region of the left foot
Days from Beginning of the ventilatory support (VS)	Third day	First day	Second day	Second day	Not apply	Secondday
Day on which tracheotomy was performed from VS	Second day	Immediate	Second day	Second day	Not apply	Not apply
Days of VS	31 days	17 days	7 days	7 days	Not apply	21 days
Days of stay in ICU	20 days	15 days	7 days	9 days	5 days	34 days
Hospitalization days	38 días	23 días	7 días	9 días	9 días	34 días
Previous Vaccination	No	No	No	Yes	No	No
Immunoglobulin administration	6 000 UI	6 000 UI	6 000 UI	6 000 UI	6 000 UI	6 000 UI
Intrahospitalary Vaccination	Applied	Applied	Applied	Applied	Applied	Applied
Antibiotic treatment	Penicillin / Metronidazole	Penicillin / Metronidazole	Metronidazole	Penicillin / Metronidazole	Metronidazole	Penicillin / Metronidazole
Death cause	Not apply	Not apply	Multiple organ dysfunction and pneumonia	Multiple organ dysfunction and pneumonia	Not apply	Notapply
Complications	Pneumonia / Bleeding from digestive tract / Seizures	Myopathy of the critical patient	Dysautonomia	Dysautonomia	Myopathy of thecritical patient	Myopathy of the critical patient

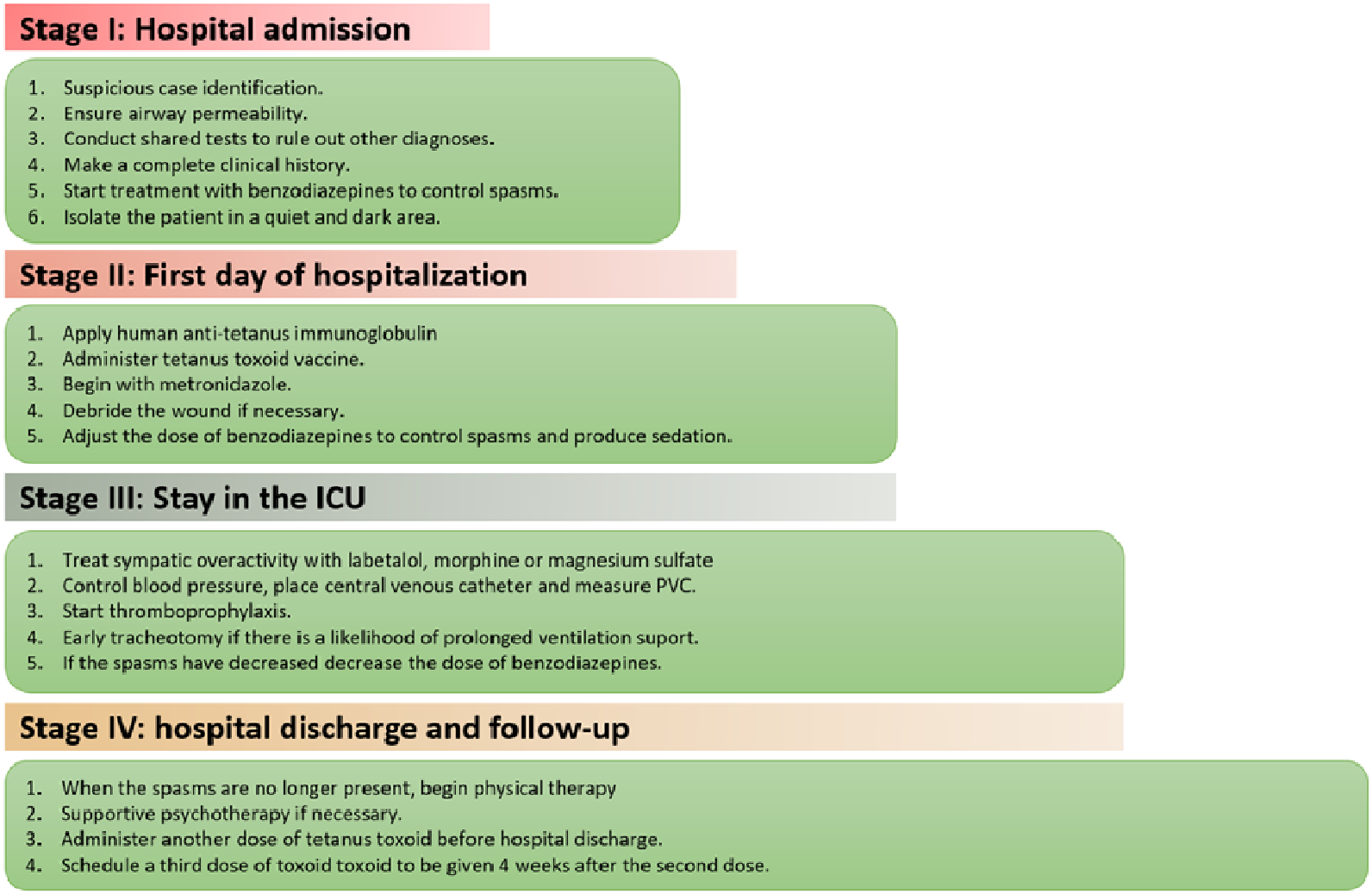

Figure 1: Standardized tetanus treatment in stages. Ramírez et al

Figure 2. Comparison of hospital management of tetanus patients Ramfrez *et al*

conditions for their growth (temperature of 37 ° C and strict anaerobic environment), others lack diagnostic value. A complete medical history should be obtained, emphasizing inthe search for the entrance point, the incubation period, the Cole period and the immunization status (Ergonul *et al*., 2016; Gibson *et al*., 2009). The goals of tetanus management include; stopping the production of toxins, neutralization of the unbound toxin, ensuring of a patent airway, muscle spasms control, management and control of dysautonomies, hemodynamic monitoring, and other general support measures (Ergonul *et al*., 2016; Gibson *et al*., 2009; Quasim, 2006) All patients with tetanus should undergo debridement of the wound to eradicate spores and necrotic tissue (Ergonul *et al*., 2016; Finkelstein *et al*., 2017). Endotracheal intubation is justified initially, but early tracheotomy is often indicated by the likelihood of prolonged mechanical ventilation need and to protect the respiratory tract. This is part of the standard protocol in our hospital (Gibson *et al*., 2009). Antibiotics probably play a minor role in the management of tetanus, but its use is recommended. Methonidazole (500 mg IV every 6 to 8 h) is the first-choice treatment for tetanus, but penicillin G (100,000-200,000 IU / kg / day or 2 to 4 million IV units every 4 to 6 h) is a safe and effective alternative, but it should be avoided due to a possible inhibition of the GABA receptor, which could increase muscle rigidity (not yet supported by clinical studies) (Hassel, 2013). Other acceptable options of antibiotic schemes include; erythromycin, tetracycline, chloramphenicol and clindamycin with a treatment duration of 7 to 10 days for all antibiotics (Ergonul *et al*., 2016; Quasim, 2006; Afshar *et al*., 2011).

The authors propose standardized treatment schemes which are represented in figure 1. Since tetanus toxin is irreversibly bound to the tissues, only the unbound toxin is available for neutralization. The use of passive immunization to neutralize unbound toxin is associated with better survival and is considered a standard treatment (Ergonul *et al*., 2016). Human antitetanus immunoglobulin should be administered at a dose of 500 IU which is as effective as higher doses (3,000 to 6,000 IU) (Gibson *et al*., 2009; Blake *et al*., 1976) by the intramuscular or intrathecal route as soon as a diagnosis of tetanus is considered (Ergonul *et al*., 2016; Gibson *et al*., 2009; Hassel, 2013). Since tetanus is one of the few diseases that does not confer immunity after recovery, all patients with tetanus should receive immunization with a total of three doses, administered at least 2 weeks apart, starting immediately upon diagnosis (Ergonul *et al*., 2016; Afshar *et al*., 2011). Generalized muscular spasms are potentially fatal because they can cause respiratory insufficiency, even in an intubated patient, because of the restriction of expansion of the chest wall which could lead to atelectasis and eventually increasing the production of bronchial secretions obstructing the respiratory tract. Numerous approaches to relieving stiffness and spasms are reported in the literature, including benzodiazepines, which have been traditionally used like diazepam (200-400 mg / 24h) as first-line treatment. Other benzodiazepines, such as midazolam and lorazepam, are also effective, and barbiturates, anticonvulsants, narcotics, baclofen, dantrolene and propofol can be used appropriately. Even botulinum toxin applied in muscle groups, has been used in clinical trials to treat muscle stiffness and spasms, givingbeneficial effects to treatment. For the management of autonomic dysfunction, several drugs have been used to produce an adrenergic blockage and suppression of autonomic hyperactivity. Magnesium sulfate at an intravenous loading dose of 5 g (75 to 80 mg / kg in 30 minutes), followed by 2 to 3 g / h, to maintain serum concentrations between 2 and 4 mg / dl (Afshar *et al*., 2011; Rodrigo *et al*., 2014; Rodrigo *et al*., 2012) has shown a reduction in the requirement of medications used for muscle spasms and cardiovascular instability in several studies. Labetalol (0.25 - 1.0 mg / min) and morphine sulfate (0.5-1.0 mg / kg / hour in continuous intravenous infusion) are commonly used to control autonomic dysfunction and to induce sedation. The use of β-blocker drugs as a single therapy should be avoided due to reports of sudden death associated with the use of propranolol (Ergonul *et al*., 2016).

Conclusion

This series of cases despite of being a retrospective study and that the number of cases is not statistically significant, reflects the characteristics of patients with generalized tetanus according to the classification of Abett treated in the intensive care unit of Acapulco General Hospital. Tetanus is nowadays a rare disease and hence an unsuspected diagnosis (Thwaites, 2002). The absence of a potentially tetanogenic trauma during a medical consultation does not exclude the possibility of diagnosis. A physician should consider the risk factors for tetanus in the adult population. Patients with painful muscle spasms without known explanation should be considered as potential cases of tetanus. The protocols for treatment of tetanus should be known and updated continuously, especially by the medical personnel who work in areas where cases are reported (Ergonul *et al*., 2016; Thwaites and Loan, 2015)In this article, recommendations for management are issued based on the experience with tetanus cases in our hospital Figure 1. Early diagnosis and treatment of tetanus improves the prognosis of the disease, however diagnosis is often confused by the lack of confirmatory laboratory tests. Better survival is associated with an early administration of antitoxin as well as offering suitable vital support (Gibson *et al*., 2009). We recommend starting medical tratment and general support as early as posible, at the same time performing necessary testing for reaching a definite diagnosis during hospital stay. Differential diagnosis of tetanus includes: temporo-mandibular joint disease, alveolar abscess, meningitis, cerebral malaria, encephalitis, subarachnoid hemorrhage, epilepsy, hypocalce mia, drug-induced movement disorders, Rigid man disease, drug abstinence, rabies, and strychnine poisoning (Ataro *et al*., 2011) High doses of sedatives and muscle relaxants, as well as prolonged mechanical ventilation are usually required, that is why early tracheotomy is suggested in this article. However, despite our suggested measures, mortality rate remains high, usually as a result of late respiratory failure, cardiovascular collapse and autonomic instability. Anesthesiologists and critical care physicians play an important role in the management of these patients. Including them in protocols has led to a reduction in mortality rate in our hospital. In this study, it was observed that a long incubation period and a prolonged period of Coles was associated with lower mortality. It was also observed that the furthest a wound is located from the central nervous system will have a longer incubation period, which is compatible with medical literature (Ergonul *et al*., 2016).

REFRENCES

Afshar, M., Raju, M., Ansell, D. and Bleck, T. 2011. Narrative Review: Tetanus A Health Threat After Natural Disasters in

Developing Countries. *Annals of Internal Medicine,* 154(5), 329. doi: 10.7326/0003-4819-154-5-201103010-00007.

Aktug Demir, N., Sumer, S., Ural, O., Ozturk, S. and Celik, J. (2014). An alternative treatment approach in tetanus: Botulinum toxin. Tropical Doctor, 45(1), 46-48. doi: 10.1177/0049475514 550063.

Andrade, L.A. and Brucki, S.M. 1994. Botulinum toxin A for trismus in cephalic tetanus. *Arq. Neuropsiquiatr*, 52, 410–413.

Ataro, P., Mushatt, D. and Ahsan, S. 2011. Tetanus. *Southern Medical Journal,* 104(8), 613-617. doi: 10.1097/smj.0b 013e318224006d.

Blake, P., Feldman, R., Buchanan, T., *et al*., 1976. Serologic therapy of tetanus in the United States, 1965Y1971. *JAMA.,* 235:42Y44.

Brook, I. 2004. Tetanus in Children. Pediatric Emergency Care, 20(1), 48-51. doi: 10.1097/01.pec.0000106245.722 65.71.

Díez Rodríguez, M., González Maldonado, C., González Fernández, G., Alonso Pelluz, C. and Escribano Romo, G. 2005. El tétanos. SEMERGEN - Medicina De Familia, 31(6), 259-264. doi: 10.1016/s1138-3593(05)729 25-7.

Duarte-Mote, J., González-Vargas, A., Díaz-Meza, S. and Rubio-Gutiérrez, J. 2004. Tétanos, experience of 10 years in an Intensive Care Unit of a General Hospital. Report of 3 cases. *Rev Asoc Mex Med Crit and Ter Int.,* 18 (5): 160-165.

Durán-Nah, J., Ceh-Gómez, E., Díaz-Cervera, I. and Mis-Fernández, R. 2001. Epidemiological characteristics of tetanus in adults in Yucatan, Mexico. *Rev Invest Clin.,* 53 (6): 536-542.

Ergonul, O., Egeli, D., Kahyaoglu, B., Bahar, M., Etienne, M., and Bleck, T. 2016. An unexpected tetanus case. *The Lancet Infectious Diseases,* 16(6), 746-752. doi: 10.1016/s1473-3099 (16)00075-x

Finkelstein, P., Teisch, L., Allen, C. and Ruiz, G. 2017. Tetanus: A Potential Public Health Threat in Times of Disaster. *Prehospital And Disaster Medicine*, 32(03), 339-342. doi: 10.1017/s104 9023x17000012

Gaber, T.A. and Mannemela, S. 2005. Botulinum toxin for muscle spasm after tetanus. *J. R. Soc. Med.,* 98, 554.

García-García, A., Gandara-Rey, J.M., Crespo-Abelleira, A. and Jorge-Barreiro, J. 2007. Botulinum toxin A for treating muscular contractures in cephalic tetanus. *Br. J. Oral Maxillofac. Surg.,* 45, 573–575.

Gibson, K., Bonaventure Uwineza, J., Kiviri, W. and Parlow, J. (2009). Tetanus in developing countries: a case series and review. *Canadian Journal of Anesthesia/Journal Canadien D'anesthésie*, 56(4), 307-315. doi: 10.1007/s1 2630-009-9058-1

Hassel, B. 2013. Tetanus: Pathophysiology, Treatment, and the Possibility of Using Botulinum Toxin against Tetanus-Induced Rigidity and Spasms. Toxins, 5(1), 73-83. doi: 10.3390/toxins5010073

Hemilä, H. and Koivula, T. 2013. Vitamin C for preventing and treating tetanus. Cochrane Database of Systematic Reviews. doi: 10.1002/14651858.cd006665.pub3.

Herrman, H., Brækhus, A., Aaserud, O., Aukrust, P., Stubhaug, A. and Hassel, B. 2008. Early treatment of tetanus-induced trismus with botulinum toxin A. *Anesth. Analg.,* 106, 1591.

Murthy, J., Dastur, F., Khadilkar, S. and Kochar, D. 2014. Rabies, tetanus, leprosy, and malaria. Handbook Of Clinical Neurology, 1501-1520. doi: 10.1016/b978-0-7020-4088-7.00101-2

Pascual, FB., McGinley, EL., Zanardi, LR., Cortese, MM. and Murphy, TV. 2003. Tetanus surveillance—United States, 1998-2000. MMWR Surveill Summ. 52:1-8. [PMID: 12825541].

Quasim, S. 2016.. Management of Tetanus. Anaesthesia UK (2006). http://www.anaesthesiauk.com/documents/tetanus. pdf. Accessed February 19.

Restivo, D.A. and Marchese-Ragona, R. 2006. Botulinum toxin treatment for oropharyngeal dysphagia due to tetanus. *J. Neurol.,* 253, 388–389.

Rhee, P., Nunley, M., Demetriades, D., Velmahos, G. and Doucet, J. 2005. Tetanus and Trauma: A Review and Recommendations. *The Journal of Trauma: Injury, Infection, And Critical Care*, 58(5), 1082-1088. doi: 10.1097/01.ta.0000162148.03280.02.

Rodrigo, C., Fernando, D. and Rajapakse, S. 2014. Pharmacological management of tetanus: an evidence-based review. *Critical Care,* 18(2), 217. doi: 10.1186/cc13797

Rodrigo, C., Samarakoon, L., Fernando, S. and Rajapakse, S. 2012. A meta-analysis of magnesium for tetanus. *Anaesthesia*, 67(12), 1370-1374. doi: 10.1111/anae.12020

Rossetto, O., Scorzeto, M., Megighian, A. and Montecucco, C. 2013. Tetanus neurotoxin. Toxicon, 66, 59-63. doi: 10.1016/j.toxicon.2012.12.027

Thwaites, C. 2002. Tetanus. Practical Neurology, 2(3), 130-137. doi: 10.1046/j.1474-7766.2002.05061.x

Thwaites, C. and Loan, H. 2015. Eradication of tetanus. *British Medical Bulletin,* ldv044. doi: 10.1093/bmb/ldv044

Woldeamanuel, Y., Andemeskel, A., Kyei, K., Woldeamanuel, M. and Woldeamanuel, W. 2018. Case fatality of adult tetanus in Africa: Systematic review and meta-analysis.

****