UJMR, Volume 3 Number 1 June, 2018 *ISSN: 2616 - 0668*
https://doi.org/10.47430/ujmr.1831.003
Received: 22nd April, 2018 **Accepted: 31st May, 2018**

PATHOGENESIS AND MANAGEMENT OF TETANUS

***Abdullahi Samaila [1], Bashir Abdulkadir [2], Kamaladdeen Kabir[2], Sani Aliyu[2] and Zubairu Umar[2]**
[1]Department of Pharmacology, Faculty of Medicine, Umaru Musa Yar'adua University, Katsina, Nigeria.
[2] Department of Microbiology, Umaru Musa Yar'adua University, Katsina, Nigeria.
***Corresponding author**: abuuismaeel@gmail.com, mobile: 08031817444.

ABSTRACT
Tetanus is an infectious disease affecting the central nervous system caused by *Clostridium tetani*. The bacteria is an anaerobic Gram- positive bacilli that forms spores, which germinate in anaerobic condition to produce an exotoxin known as Tetanospasmin, and this is the whole mark of the pathogenesis of this disease. Tetanus remains a great public health problem in developing countries such as Nigeria. It affects all age group and both males and females. In Nigeria, the death rate differs from the range of 38% to 60%, depending on the infrastructural facilities and personnel at the reporting centre. The disease is not very common in developed nations. Mortality rate of 20-60% was reported in Africa. Four clinical types of tetanus were recognized such as generalized, cephalic, localized and neonatal type. Diagnosis is mainly clinical. The management of tetanus include Neutralization of unbound toxins, eliminating the source of the toxin and prevention of its further production, Control of spasm as well as general measures to support the life of the affected patient. It is a fatal disease with poor prognosis especially the cephalic type in adults, and neonatal tetanus. The objective of this work is to present a reviewed update on pathogenesis and management of tetanus. Additionally, to evaluate the contribution of tetanus towards the increased morbidity and mortality in Nigeria.
Key words: tetanus, tetanospasmin, spasm, immunization, trismus

INTRODUCTION

Tetanus is an infectious disease characterized by acute onset of painful muscle rigidity and spasms often manifesting as trismus (lockjaw), dysphagia, neck stiffness and abdominal rigidity (Anwer *et al.*, 2015; Hassel, 2013). The disease is caused by *Clostridium tetani,* which is a Gram- positive bacillus anaerobic bacterium. It belongs to the class of *Clostridia* in the phylum *Firmicutes* that includes a very heterogeneous assemblage of bacteria (Kunisawa, 2015). Tetanus came from a Greek word *tetanos* that was derived from *teinein* meaning to stretch (Ogunrin, 2009). It was first described in Egypt over 3000 years ago (Aliyu *et al.*, 2017). The disease is largely confined to developing countries. In developing countries, the mortality rate is as high as 28 per 100,000 cases but in developed countries is < 0.1 per 100,000 cases (Ogunrin, 2009). Efforts by the World Health Organization (WHO) to eradicate the disease by 1995 has not yield any remarkable success and still tetanus remain the major causes of mortality. It is a preventable disease with an estimated incidence of 700,000 to 1 million cases per year causing an estimated 213,000 death (World Health Organisation, 2006; Thwaites and Farrar, 2003). Tetanus remains a great public health problem especially in developing countries.

In Nigeria, the death rate differs from 38% to 60%, depending on the infrastructure of facilities and personnel at the reporting centre (Ogunrin, 2009). Babatunde *et al.*, (2014) reported a 50% CFR among cases of neonatal tetanus managed at Federal Medical Center Ido-Ekiti South-Western Nigeria. It was realized that none of the pregnant mothers received complete dose of tetanus toxoid immunization during antenatal care (ANC) and most delivered at home. Chukwubike *et al.*, (2009) conducted a 10-year retrospective survey on 86 adult tetanus patients at University Teaching Hospital Port Harcourt to assess the outcome of their management. They discovered that the case fatality rate (CFR) was 42.9%. Mortality was higher among patients of > 40 years (P< 0.001) and patients with shorter incubation period of less than 7 days (P< 0.04). The commonest portal of entry was lower limbs. Mortality rate of 26% was reported from a hospital-based study in Benin City (Ogunrin, 2009). In the report of Aliyu *et al.*, (2017) at ABUTH Zaria, 60 cases of neonatal tetanus were recorded over 14-year period. The commonest portal of entry was umbilicus. The overall CFR was 56.7% (i.e. 34 of the 60 cases). Majority of the pregnant mothers had very poor ANC attendance, had no T.T vaccine during pregnancy and delivered at home (Aliyu *et al.*, 2017).

Nass *et al.*, (2017), computed the risk of neonatal death in Katsina Northwestern Nigeria using data from 332-recorded cases of neonatal tetanus. They discovered that neonates whose mothers had 1 dose of T.T vaccine were less prone to neonatal death compared to neonates whose mothers did not have any dose of T.T vaccine during pregnancy (P<0.04, OR = 4.12, 95% CI = 1.04-16.29).

According to the studies conducted in African patients, the prevalence of tetanus ranges from 6% to 11% whereas the reported mortality rate was between 20% and 60% generally (Fortes, 2015). Most at risk are unvaccinated individuals, elderly, newborns, migrant workers, injection drug users, animal bites and those with chronic infected wounds that may become colonized and infected by *C tetani*. (Papadakis and Mc Phee, 2016).

Risk factors of neonatal tetanus

The following risk factors increase the susceptibility to neonatal tetanus e.g.

1. Unimmunized mother, home delivery, and unsanitary cutting of the umbilical cord
2. Application of potentially infectious substances to the umbilical stump such as animal dung etc.
3. Previous history of neonatal tetanus in a child is another risk factor for subsequent neonatal tetanus (Hinfey, 2017).

Having a good knowledge on mode of transmission and development of tetanus, as well as the updated management protocol including prevention and control will certainly help to reduce the morbidity and mortality of this devastating disease.

In this review, reference literatures were accessed using various search engines on the internet such as Google scholar, Medline, Medscape etc. Selected literatures were reviewed, based on their relevance to the title and contents of the review.

The **aim** of this review is to describe the pathogenesis and management of tetanus

The objectives of the review were to:

1. Evaluate the contribution of tetanus towards the increased morbidity and mortality in Nigeria.
2. Understand the aetiology and mode of development of the disease (aetiopathogenesis).
3. Understand the updated management of tetanus.

PATHOGENESIS OF TETANUS

Clostridium tetani is a slender, obligate, anaerobic, motile, gram-positive bacillus that belongs to the class of *Clostridia* in the phylum *Firmicutes*. The bacterium gets in to the body through Umbilical stump, Female genital mutilation, Male circumcision, Abortion sites, Penetrative wounds (e.g. nail puncture, bullets etc.), Head injury; scalp wounds, Traditional scarification (e.g. for tribal identity), Post-operative surgical sites and Chronic suppurative otitis media (Federal Ministry of Health Nigeria, 2008). It develops a terminal spore, which gives it a drumstick appearance (Hunt, 2015; Hinfey, 2017) (See figure 1).

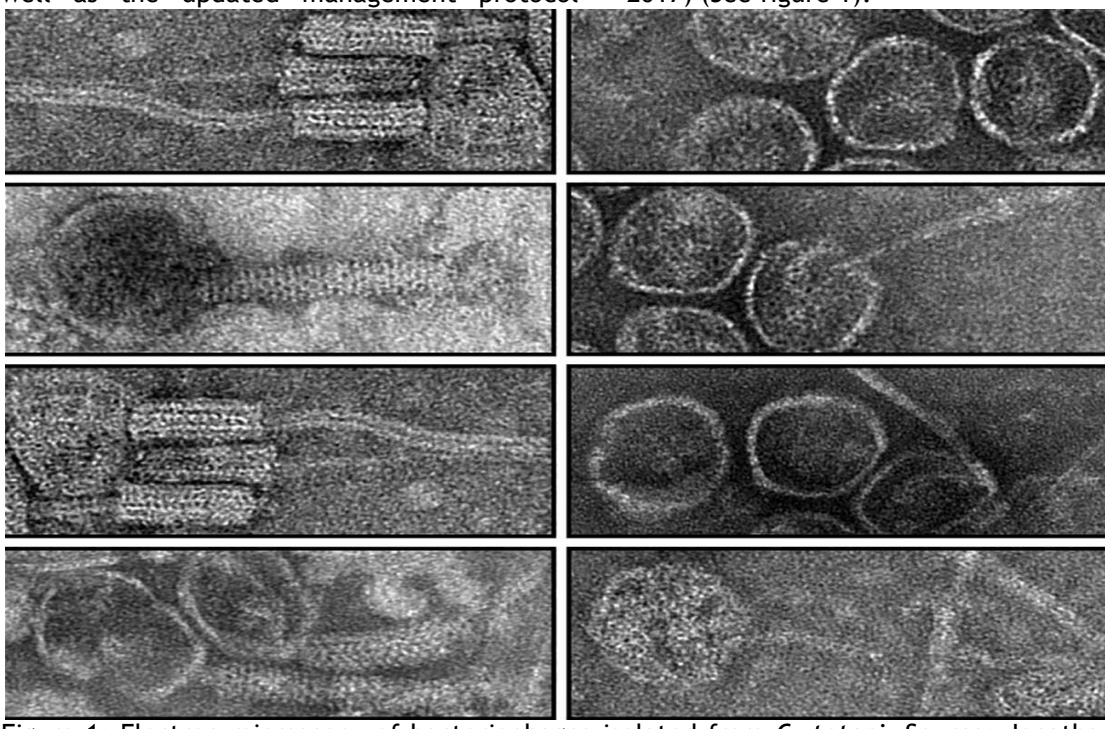

Figure 1: Electron microscopy of bacteriophages isolated from *C. tetani*. Source: Jonathan *et al.*, (2017).

The spores are resistant to heat, desiccation and disinfectants. However, vegetative cells are easily inactivated and are susceptible to several antibiotics. The spores are found in soil, house dust, animal intestine, and occasionally human faeces. They can also persist in normal tissues for months to years (Hinfey, 2017). The spores require anaerobic condition to germinate such as wounds with low oxygen tension like dead or necrotic tissue, active infection and foreign body. Infection by *C tetani* results in benign appearance at the portal of entry because the organism is unable to induce inflammatory reaction unless coinfection with other organism occurs (Bleck, 1995; Hinfey, 2017). In the presence of proper anaerobic condition, the spores germinate and produce two toxins as follows: **Tetanolysin**-- This toxin is a hemolysin with no recognized pathologic activity. **Tetanospasmin** – This toxin is responsible for the clinical manifestations of tetanus (World Health Organization, 2010). Tetanospasmin consists of a heavy chain and a light chain joined by a disulfide bond (Sanford, 1995). The heavy chain mediates binding of tetanospasmin to the presynaptic motor neuron and creates a pore for the entry of the light chain into the cell (See figure 2).

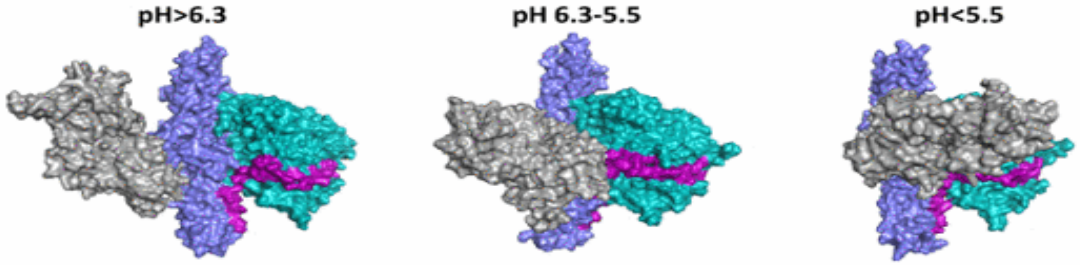

Figure 2: The crystal structure of tetanus holotoxin revealing pH-mediated domain rearrangements that enables the tetanus toxin to adopt environmental changes during intoxication. Source: Masuyer, (2017).

Once the light chain enters the motor neuron, it travels by retrograde axonal transmission from the contaminated site to the spinal cord in 2-14 days. When the toxin reaches the spinal cord, it enters central inhibitory neurons (See figure 3).

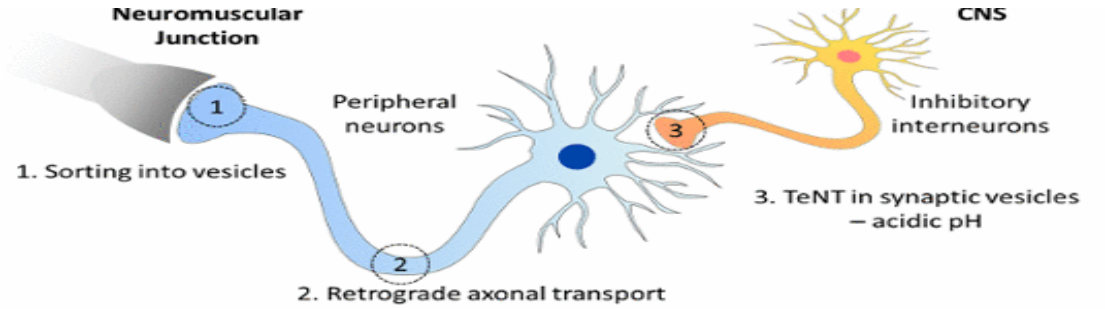

Figure 3: The mechanism of action of tetanus toxin and its effects on central nervous system (CNS) resulting in loss of inhibitory action on motor and autonomic neurons. Source: Masuyer, (2017).

The light chain cleaves the protein synaptobrevin, which is a vesicle associated membrane protein (VAMP) essential for the release of neurotransmitter. As a result, gamma-aminobutyric acid (GABA)-containing and glycine-containing vesicles are not released, and there is a loss of inhibitory action on motor and autonomic neurons. With this loss of central inhibition, there is autonomic hyperactivity and uncontrolled muscle contractions and spasms in response to normal stimuli such as noises or lights (Yeh *et al.*, 2010; Hinfey, 2017). Muscle rigidity and spasms ensue, often manifesting as trismus/lockjaw, dysphagia, opistotonus, or rigidity and spasms of respiratory, laryngeal, and abdominal muscles, which may cause respiratory failure (Hassel, 2013). Once the toxin is fixed to neurons, it cannot be neutralized with antitoxin. It was also described that the tetanospasmin interferes with acetylcholine/cholinesterase balance at the peripheral motor nerve ending. This results in excess production of acetylcholine uninterruptedly leading to sustained muscle contraction. The toxin also causes extreme hyper-excitability of motor neurons in the anterior horn cells resulting in explosive and

widespread reflex spasm of muscles in response to even a minor stimulus (Badoe, 2000).

CLINICAL PRESENTATION

The incubation period is 5 days to 15 weeks, with the average being 8–12 days. Pain and tingling sensation at the site of inoculation are the first symptoms followed by spasticity of the muscles nearby. Stiffness of the jaw, neck stiffness, dysphagia and irritability. Spasms of the jaw muscles (trismus) or facial muscles. Spasm of the muscles of the abdomen, neck, and back. Painful tonic convulsions precipitated by minor stimuli. Hyperreflexia develops later. The patient is awake and alert throughout the illness no loss of consciousness. The temperature may be normal or only slightly elevated. Sweating, episodic arrhythmias, swinging and blood pressure (Papadakis and Mc Phee, 2016; Hinfey, 2017). Other important clinical findings are opistotonus and risus sardonicus characterized by Hassel, (2013).

CLINICAL TYPES OF TETANUS

Based on clinical presentation, tetanus can be categorized into four clinical types as follows:

1. Generalized tetanus
2. Localized tetanus
3. Cephalic tetanus
4. Neonatal tetanus

Generalized tetanus

It is the most commonly recognized form of tetanus that occurs in in about 50-75% of patients. It begins with trismus ("lockjaw"), which is the inability to open the mouth due to masseter muscle spasm. Risus sardonicus occurs due to increased tone in the orbicularis oris. It is also known as scornful smile of tetanus. Dysphagia; simply means difficulty in swallowing. There may be Stiffness in the neck, shoulder and back muscles. Rigidity abdomen and stiffness of proximal limb muscles may also occur. Opisthotonos; is the flexion of the arms and extension of the legs (Figure 4).The patient does not usually lose consciousness (Ogunrin, 2009, Hinfey, 2017).

Figure 4: Opisthotonos posture in tetanus patient. Source: Longmore *et al.*, (2014)

Localized tetanus

It characterized by increased muscle tone and rigidity restricted to the site of the wound. It may be mild or persistent and often resolves spontaneously. Localized tetanus is more commonly a prodrome of generalized tetanus. Mortality is low (Federal Ministry of Health Nigeria, 2008; Ogunrin, 2009).

Cephalic tetanus

It usually occurs following head injury/trauma or ear infection. Patients present with cranial nerve palsies (particularly facial nerve palsy) and trismus. The infection may be localized or may become generalized. Mortality is high (Federal Ministry of Health Nigeria, 2008; Bhargavan & Ravi, 2016).

Neonatal tetanus

It is also known as tetanus neonatorum. Infection results from contaminated umbilical cord during unhygienic delivery, coupled with a lack of maternal immunization during pregnancy. Infected infants present with irritability, poor feeding, rigidity and spasms at the end of the first week of life (Figure 5). Neonatal tetanus has a very poor prognosis. It is one of the major cause of infant mortality in developing countries (Thwaites *et al.,* 2015; Prevots, 1999).

Figure 5: General muscle spasm in a neonate with tetanus. Source: Centre for Disease Control. Available @*https://www.cdc.gov/tetanus/about/photos.html*

DIAGNOSIS

Generally, diagnosis comprises of clinical and laboratory aspects. Clinical diagnosis is based on the clinical presentations of the patient, which may depict the clinical type of the disease. The essential for clinical diagnosis include; History of wound and possible contamination, Jaw stiffness followed by spasms of jaw muscles (trismus), stiffness of the neck and other muscles, dysphagia, irritability and finally painful convulsions precipitated by minimal stimuli (Papadakis and Mc Phee, 2016). Another important clinical diagnostic tool is **Spatula test**. A simple bedside diagnostic test that is performed by touching the oropharynx with a spatula or tongue blade. The test is negative when the patient develop a gag reflex and try to expel the spatula as it occurs in normal situation. However, the test is positive when the patient develop a reflex spasm of the masseter muscle and bite the spatula indicating the presence of tetanus. The test has a sensitivity of 94 % and specificity of 100 %. There was no reported complication or adverse effect associated with the test (Apte & Karnad, 1995).

For laboratory diagnosis, no specific laboratory tests exist for diagnosis of tetanus because the organism is rarely isolated from the wound site of the affected patients. It is also possible to culture the organism in patients who do not have the disease. Hence, the diagnosis is mainly clinical (Levinson, 2016; Hinfey, 2017). However, wound swab microscopy culture and sensitivity is still carried out for the isolation of the organism or co-infective organism. Cerebrospinal fluid sample for biochemistry culture and sensitivity. Electrolyte, urea and creatinine to check for kidney function. Urinalysis and urine microscopy culture and sensitivity. Full blood count and differential for evidence of any infective process. Blood sugar monitoring since the patient may not able to take orally (Federal Ministry of Health Nigeria, 2008).

DIFFERENTIAL DIAGNOSIS

Some of the differential diagnosis include meningitis, dental abscess, phenothiazine toxicity (e.g. chlorpromazine), and strychnine poisoning (Papadakis and Mc Phee, 2016; Longmore *et al.*, 2014).

COMPLICATIONS

Some of the common complications of tetanus are:

- Severe effects of autonomic instability such as hypertension and cardiac arrhythmias, which can lead to sudden death (Lin *et al.*, 2011)
- Spasm of the vocal cord and respiratory muscles can lead to airway obstruction and respiratory failure (Bunch *et al.*, 2002)
- Others include aspiration pneumonia, urinary retention, bone fracture, coma and death (Hinfey, 2017).

MANAGEMENT OF TETANUS PATIENT

Tetanus is a medical emergency, prompt medical intervention is necessary to avoid increased morbidity and improve survival. Thus the, principles treatment of tetanus are:

Neutralization of unbound toxins

Neutralization of absorbed and unbound toxins is achieved by administration of antitoxin, human tetanus immunoglobulin (TIG) 250-500 units by intramuscular or intravenous injection as soon as possible after a test dose. In addition, 0.5 ml of tetanus toxoid vaccine is administered by intramuscular injection at separate site. If patient is immunosuppressed or if active Immunization with tetanus vaccine is contraindicated, a second dose of 250 units should be given after 4 weeks (Federal Ministry of Health Nigeria, 2008; World Health Organization, 2010).

Eliminating the source of the toxin and prevention of its further production

The most frequently used antibiotics for the treatment of tetanus are penicillin G and metronidazole. Antibiotics are used to decrease the vegetative forms of *C. tetani* in the wound. Metronidazole (500 mg 6 hourly) was observed to have better efficacy compared to penicillin, which has some antagonistic effect on GABA (Ahmadsyah & Salim, 1985; Longmore *et al.*, 2014; Hinfey, 2017). Wound debridement is encouraged after administration of human tetanus immune globulin to remove all the infected or necrotic tissues and discourage the condition making the organism favourable to continue with the spore production (Nicholas et al., 2006).

Control of spasm

Diazepam is one of the commonly prescribed drugs for symptomatic treatment of tetanus. Diazepam belongs to class of benzodiazepines. It decreases anxiety, produces sedation, acts as muscle relaxant and controls spasm and convulsion. Phenobarbital is another anticonvulsant useful for the control of severe muscle spasm and provides sedation. Chlorpromazine is alternative anticonvulsant for controlling spasm. Diazepam is given either with phenobarbital to prolong its effect or with chlorpromazine to achieve profound sedation (Longmore *et al.*, 2014).

If benzodiazepines (e.g. diazepam) cannot provide adequate spasm control, pancuronium or vecuronium are alternative muscle relaxants (Hinfey, 2017). Propofol is an anesthetic agent, which induces sedation. It was observed to be useful in treatment of severe tetanus in children (Petitjeans et al., 2009). The use of magnesium sulfate (5g or 75 mg/kg as loading dose, followed by continuous infusion at a rate of 2.5 g/hour) either alone or in combination with diazepam is recommended until spasm control is adequately attained (World Health Organization, 2010).

General measures

They are initial supportive measures or therapies are considerable when the patient is presented to emergency unit. Tetanus patients are admitted in a dark and quite room in the intensive care unit (ICU). Majority of the patients with moderate to severe tetanus require rapid sequence endotracheal intubation with succinylcholine and ventilatory support. Similarly, tracheostomy is performed in patients who need intubation for a period greater than 10 days. Adequate hydration with intravenous fluid to avoid dehydration. Nutritional support by nasogastric tube feeding to avoid hypoglycaemia. Insertion of urinary catheter to drain urine from the bladder due to possible urinary retention. Treatment of intercurrent infection and anaemia if present. If the wound is identifiable should be explored cleaned and debrided after administration of antitoxin for several hours to avoid disseminating the toxin into the blood (Hinfey, 2017; Longmore *et al*., 2014; Badoe, 2000).

PROGNOSIS

Hinfey, (2017) described the assessment of clinical severity and prognosis of tetanus using a rating scale. The scale has parameters, and each parameter has a score of 1 point. The parameters are as follows:

- Incubation period of <7 days
- Period of onset of < 48 hours
- Portals of entry such as burns, surgical wounds, compound fractures, septic abortion, umbilical stump, or intramuscular injection
- Sedative drug addiction
- Generalized tetanus
- Temperature > 40°C
- Tachycardia > 120 beats/min (150 beats/min in neonates)

The total score is indicative of prognosis and possible mortality based on the clinical severity of the disease (Table 1).

Table 1: Prognosis of tetanus based on clinical severity.

Score	Clinical severity	Mortality (%)
0 or 1	Mild tetanus	< 10%
2 or 3	Moderate tetanus	10-20%
4	Severe tetanus	20-40%
5 or 6	Very severe	> 50%

Source: Hinfey, (2017).

PREVENTION AND CONTROL

The most important preventive measure of tetanus is immunization. Primary active immunization of adults is administered as first dose at first contact; second dose is given 4-6 weeks after the first dose and third dose after 6-12 month of the second dose. Booster doses are given every 10 years or at the time of major injury that occurs in > 5 year after a dose. Passive immunization is administered as tetanus immune globulin 250 units to individuals with contaminated wounds and their immunization status is unclear. Active immunization with tetanus toxoid (TT) is commenced concomitantly. Patients with potentially infected wound and who have not been previously immunized for tetanus must be given human anti-tetanus serum (ATS) 250 unit parenterally, followed by active immunization with tetanus toxoid (TT) 0.5 ml to be repeated at six weeks and six month. The wound should also be debrided, cleaned and dressed appropriately to avoid further toxin production and spread (Papadakis & Mc Phee, 2016; Badoe, 2000).

CONCLUSION

Tetanus is a preventable infectious disease with neurological manifestations. It is still a great public health problem in most developing countries such as Nigeria. The people at risk are farmers, unvaccinated individuals, elderly, neonates and injection drug users. It affects all age groups and both sexes. Morbidity and mortality are still high in Nigeria due to poor utilization of preventive measures (e.g. immunization) and application of traditional practices predisposing to acquisition of the disease. Tetanus is a medical emergency, prompt medical intervention is highly needed to reduce morbidity, mortality and improve survival.

RECOMMENDATIONS

It can be recommended that:

- All wounds should be cleaned and properly dressed to avoid contact with soil.
- Every accident victim who sustained injury in any part of the body should receive a prophylactic dose of tetanus toxoid.
- Application of animal dung or other contaminated substances on umbilical stump of a neonate should be avoided.
- Clean and sterile surgical equipment should be used for cutting umbilical cord during delivery.
- Newborns should be fully immunized against tetanus.
- All pregnant mothers should receive a prophylactic dose of tetanus toxoid during pregnancy and avoid home delivery.
- Unvaccinated adults should be immunized against tetanus.
- There should be an increased awareness on deadly effect of tetanus particularly in local communities.
- Personal hygiene and environmental sanitation should be improved.

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