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Tetanus in developing countries: A review and case series

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Abstract
Tetanus is vaccine preventable disease still measure cause of fatality in developing country like India. We review the history, epidemiology, pathophysiology, clinical presentation, diagnosis and management of tetanus along with series of 3 cases reported in our district hospital in last 2 years. Among 3 cases, two were of otogenic tetanus in children with incomplete or unknown immunization status and 1 case was reported in adult who had not received tetanus vaccine for his wound after road traffic accident. The differential diagnosis of tetanus may be confusing and survival depends on the early diagnosis and treatment with antitoxin, as well as adequate supportive care. All patients had received supportive care immediately. After conformation of diagnosis clinically and/or microbiologically, tetanus toxoid and immunoglobulin were given to patients due to limited resources. Adult patient died due to respiratory failure while both child were recovered with treatment. To conclude, as tetanus is vaccine preventable disease it is important to strengthen existing immunization program against tetanus and educating people and health care worker regarding importance of immunization against tetanus.

Keywords: Clostridium tetani, Otogenic tetanus, Tetanus toxoid.

Introduction
Tetanus is an ancient disease – as old as humans. It is a global health problem. Despite the availability of a highly effective vaccine making it preventable, tetanus continues to be a significant burden on the health resources worldwide. The WHO included tetanus in its Expanded Programme of Immunization (EPI) with the aim to eradicate the disease. In spite of the efforts of the WHO and various other health authorities, it is estimated that the annual incidence of tetanus is about 1 million cases. The majority of these cases occur in the developing countries and the disease is uncommon in the developed world. It is associated with a high mortality rate varying from 30-50% [1].

Tetanus is caused by *Clostridium tetani* (*Cl. tetani*), gram-positive bacilli, the spores of which are highly resistant to temperature and humidity and survive for extended periods in the soil. Contaminations of wounds leads to the inoculation of the spores. Anaerobic conditions found within necrotic tissue provide the ideal environment for the spores to germinate into the toxin producing bacilli. They secrete two type of exotoxins: Tetanolysin and Tetanospasmin. Tetanolysin is thought to optimize conditions within the wound, whereas tetanospasmin is one of the most potent neurotoxins known. It is the effect of tetanospasmin on the central nervous system that causes clinical tetanus. It is one of the most potent toxins in nature—240 g is estimated to be sufficient to kill the world's population [2].

Historical Aspect [3].
The word tetanus comes from the Greek tetanos, which is derived from the term teinein, meaning to stretch. Although records from antiquity (5th century BCE) contain clinical descriptions of tetanus, it was Carle and Rattone in 1884 who first produced tetanus in animals by injecting them with pus from a fatal human tetanus case. During the same year, Nicolaier produced tetanus in animals by injecting them with samples of soil. In 1889, Koch's pupil Kitasato isolated the organism from a human victim, showed that it produced disease when injected into animals, and reported that the toxin could be neutralized by specific antibodies. The nineteenth and twentieth centuries however witnessed rapid and significant advances in the understanding of the pathophysiology of tetanus and this brought about the introduction of tetanus toxoid vaccination by Behring and Knorr in 1886.In 1897,

Nocard demonstrated the protective effect of passively transferred antitoxin, and passive immunization in humans was used for treatment and prophylaxis during World War I. A method for inactivating tetanus toxin with formaldehyde was developed by Ramon in the early 1920's which led to the development of tetanus toxoid by Descombey in 1924. It was first widely used during World War II.

Epidemiology [4]

i) **Occurrence**- Tetanus occurs worldwide but is most frequently encountered in densely populated regions in hot, damp climates with soil rich in organic matter.
ii) **Reservoir** - Organisms are found primarily in the soil and intestinal tracts of animals and humans.
iii) **Mode of Transmission** - Transmission is primarily by contaminated wounds (apparent and inapparent). The wound may be major or minor. In recent years, however, a higher proportion of patients had minor wounds, probably because severe wounds are more likely to be properly managed. Tetanus may follow elective surgery, burns, deep puncture wounds, crush wounds, otitis media (ear infections), dental infection, animal bites, abortion, and pregnancy.
iv) **Communicability** - Tetanus is not contagious from person to person. It is the only vaccine-preventable disease that is infectious but not contagious.

Pathophysiology

Clostridium tetani spores usually enter the tissue through a penetrating contaminated wound, and after a period of anaerobic incubation, they become bacilli that release tetanus toxin. The toxin enters peripheral neurons and travels retrograde up axons to the central nervous system. It can enter motor, sensory, and autonomic neurons, although radiolabelled assays have shown a predilection for inhibitory neurons. Most of the clinical disease results from motor and autonomic inhibition. Tetanospasmin is a metalloprotease substance which acts at the presynaptic membrane to cleave synaptobrevin, a protein that allows fusion of neurotransmitter vesicles to nerve membranes. When this fusion process is prevented, neurotransmitters are not released into the synapse and neurotransmission is blocked. Centrally, transmission along the inhibitory gamma-amino butyric acid (GABA) and glycinergic neurons is interrupted, and at the level of the spinal cord, inhibitory interneurons are blocked [5].

It is important to recognize that tetanus is not an infection, and therefore patients do not usually experience symptoms of the disease until the toxin is disseminated and reaches the interneurons. Early treatment with immune globulin is critical, because it binds free toxin. However, it does not treat the effects of toxin protected within the neuron or cell body. Treatment of the effects of toxin already within the nervous system is purely supportive. Clinically, the effect of the toxin on the neuron lasts approximately 4–6 weeks and may be irreversible until the re-growth of a new nerve terminal; however, the mechanism of functional recovery is not clear [6].

Clinical Features [7] – The incubation period ranges from 3 to 21 days, usually about 8 days. In general the further the injury site is from the central nervous system, the longer is the incubation period. Shorter incubation periods are associated with a higher chance of death. In neonatal tetanus, symptoms usually appear from 4 to 14 days after birth, averaging about 7 days. On the basis of clinical findings, three different forms of tetanus have been described.

1. Local tetanus is an uncommon form of the disease, in which patients have persistent contraction of muscles in the same anatomic area as the injury. These contractions may persist for many weeks before gradually subsiding. Local tetanus may precede the onset of generalized tetanus but is generally milder. Only about 1% of cases are fatal.
2. Cephalic tetanus is a rare form of the disease, occasionally occurring with otitis media (ear infections) in which *Cl. tetani* is present in the flora of the middle ear, or following injuries to the head. There is involvement of the cranial nerves, especially in the facial area.
3. The most common type (about 80%) of reported tetanus is generalized tetanus. The disease usually presents with a descending pattern. The first sign is trismus or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles. Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms continue for 3–4 weeks. Complete recovery may take months.

Neonatal tetanus (NT) is a form of generalized tetanus that occurs in new born infants. Neonatal tetanus occurs in infants born without protective passive immunity, because the mother is not immune. It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with an unsterile instrument. Neonatal tetanus is still common in some developing countries. On 27 August 2015 WHO and UNICEF declared that maternal and neonatal tetanus was eliminated from India [8].

Laboratory Diagnosis- No laboratory findings are characteristic of tetanus. The diagnosis is entirely based on clinical presentation and microbiological confirmation.

i) Clinical diagnosis- depending on clinical presentation of patient as describe above.
ii) Microbiological diagnosis-Wound Swabs were inoculated into anaerobically prepared Robertson's cooked meat broth, which was then incubated at 37^0 C. Films made from the broth 48 hours later and stained by Gram's method. Presence of Gram positive bacilli and few of them showing terminal spores, gives probable diagnosis of *Cl. tetani* infection. Robertson's cooked meat broth also shows proteolytic changes. Confirmation was obtained from animal inoculation and protection tests. Four mice were used. Two were injected intraperitoneally with 0.5 ml. of antitetanus serum. Half an hour later 1 ml. of the broth culture from each ear was injected intraperitoneally into a protected and an unprotected mouse. The mice were observed at intervals. After six hours one of the unprotected mice showed rhythmic contractions of the tail and the other showed paralysis of the hind legs. Both unprotected mice succumbed, but the mice protected by antitetanus serum remained apparently well. But its use is restricted to research purpose only. Further studies were carried out on the broth cultures. Each was heated to 60^0 C for one hour and then inoculated on to two blood agar plates. One of these was incubated anaerobically and the other aerobically. Presence of a fine fimbriated swarming growth on the anaerobic plate which on Gram-stained films shows gram

positive bacilli, some with "drumstick" appearance, confirmed the diagnosis of *cl. tetani* infection. Ultimately, confirmation was performed by polymerase chain reaction (PCR) for the tetanus neurotoxin gene TeTX but its use is limited to reference laboratory only [9, 10]

Management - All wounds should be cleaned. Necrotic tissue and foreign material should be removed. If tetanic spasms are occurring, supportive therapy and maintenance of an adequate airway are critical.

Tetanus immune globulin (TIG) is recommended for persons with tetanus. TIG can only help remove unbound tetanus toxin. It cannot affect toxin bound to nerve endings. A single intramuscular dose of 500 units is generally recommended for children and adults, with part of the dose infiltrated around the wound if it can be identified. Intravenous immune globulin (IVIG) contains tetanus antitoxin and may be used if TIG is not available. Because of the extreme potency of the toxin, tetanus disease does not result in tetanus immunity. Active immunization with tetanus toxoid should begin or continue as soon as the person's condition has stabilized [11].

Here we are presenting series of case reports of tetanus diagnose and treated in our tertiary care hospital in last 2 years.

1. A 40-year-old man after road traffic accident presented to a local health centre with a soft tissue injury on his both leg. The wound was cleaned and bandaged, but no tetanus toxoid was given. After a week patient returned to the clinic complaining of fever, arthralgia and myalgia. Due to malaria endemicity, presumptive diagnosis of malaria was given, and antimalarial drugs were prescribed. But within 2 days he again returned with complained of neck pain, difficulty in swallowing and opening his mouth. The patient was referred to a district hospital. Based on history of trauma, unknown vaccination coverage, cervical rigidity, and trismus differential diagnosis of Tetanus and meningitis was given. Wound swab and CSF was send for microbiological processing. As patient was not able to maintain spontaneous respiration, he was transferred to intensive care unit on ventilation and tracheostomy was carried out. Diazepam and Cefotaxime was given to patient.

Wound swabs were inoculated into Robertson's cooked meat broth at 37 ^{0}C. After 48 hours smear was prepared and Gram staining done which shows Gram positive bacilli, some of them were "drumstick" forms with terminal round spores and Proteolytic changes were also noted in the broth giving probable diagnosis of *Cl. tetani* infection. Based on which tetanus immunoglobulin was given to patient. Robertson's cooked meat broth was heated up to 60 °C for 1 hour and then inoculated on two blood agar plates, one for anaerobic and other for aerobic incubation. No growth was obtained on aerobically kept plate. While gray, matte surface, irregular margin, translucent, flat growth showing a fine fimbriated swarming was obtained on the anaerobic plate. Gram-stained films from this showed gram positive bacilli, some with "drumstick" appearance. Confirmed diagnosis of clostridium tetani infection was given. Based on which metronidazole and anti-tetanus serum was given. No pathogenic microorganism was found on gram stain and culture of cerebrospinal fluid.

On 7th day in ICU, patient diagnose left sided pneumonia clinically and radiologically with further deterioration in oxygenation. We were not able to maintain adequate oxygen saturation. Pseudomonas aeruginosa grown on tracheal aspirate culture. Pipracillin-tazobactam was given to him. On 9th day patient was hypotensive may be due to septic shock secondary to ventilator-acquired pneumonia. Next morning, the patient died of respiratory failure.

2) A 5- year-old unimmunized male child presented with history of fever since 4 days, trismus, and constant cry, watery non-foul smelling discharge from ear since 6 days, and gradually progressing breathlessness, progressively increasing after coughing and sneezing. Inability to open mouth, especially after coughing and sneezing, and dysphagia for solid food were complained by mother. Physical examination revealed tautness of neck muscles with no neck swellings, trismus and rhesus sardonicus. Patient had an opisthotonus posture, history of trauma to left ear due to match stick insertion 6 days back. Clinical diagnosis of tetanus was given. Based on which tetanus immunoglobulin 500 IU IM was given to patient and ear discharge swabs were send for microbiological confirmation.

On physical examination, Pulse rate -180/min, respiratory rate -28/min and oxygen saturation - 94%. Swabs from ear discharge collected in Robertson's cooked meat (RCM) broth on gram staining showed gram positive bacilli with round terminal bulging spores. Further incubation of RCM broth showed proteolytic activity and anaerobic cultures on freshly prepared blood agar showed thin transparent film of growth with swarming typical of *Cl. tetani.* The patient was given tetanus toxoid 0.5 mL IM stat and oxygen by mask, Metronidazole and Diazepam was given for 7 days. The child recovered well with this treatment and was discharged after a week.

3) A 6 year female with history of incomplete immunization presented with history of fever, trismus, difficulty in swallowing and breathing, non-foul smelling discharge from left ear, neck stiffness and single episode of convulsion with past history of trauma in left ear while playing. On physical examination, patient was anxious and unable to open her jaw more than 1inch. Reflexes were brisk but symmetrical with a slight degree of neck stiffness. Temperature was 100 ^{0}F (37.8 °C.), pulse rate -130/min. There was no tenderness, swelling, or oedema over the left mastoid. On the clinical basis differential diagnosis of tetanus and meningitis was given.

Ear swabs and cerebrospinal fluid were send for microbiological processing. A course of intravenous cefotaxime and adequate intravenous fluid and electrolyte replacement were started. Regular ear toilet was done. Patient had difficulty in swallowing and had some spill over into her respiratory tract. She was transferred to intensive care unit. Under anaesthesia, a feeding-tube was introduced and bronchial toilet was carried out. To maintain adequate spontaneous respiration she was shifted on ventilator. Tracheostomy was carried out and the patient was maintained fully for 2 weeks on the ventilator. Gram staining and Culture of ear discharge sample diagnosed it to be *Cl. tetani* infection. Patient was successfully treated with Antitetanus serum and Tetanus toxoid along with supportive management. After 5 weeks of care patient was discharged.

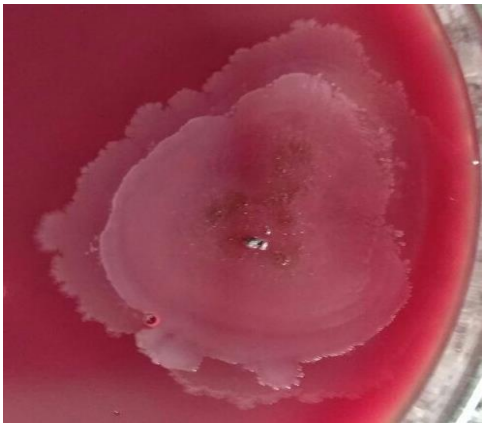
Discussion –Tetanus is a vaccine preventable disease and WHO has projected eradication by 1995. However, the disease is still present in most developing countries causing morbidity and mortality [12]. Poor socioeconomic condition and low educational status in developing country might make the parents not to see the need to complete the vaccination. Prognosis of tetanus varies according to duration of

incubation, the speed with which signs become generalized, the severity of clinical presentation and access to the suitable treatment regimen. In developing countries, without facilities for prolonged intensive care and ventilator support, death from severe tetanus exceed 50% with airway obstruction, respiratory failure, cardiovascular or metabolic complication and renal failure as prominent cause [3, 7].

Prompt diagnosis and treatment of tetanus improves the patients prognosis [13]. A common reason for delayed treatment is the often confusing differential diagnosis but confirmed laboratory diagnosis improves outcome [6]. Among our case series, clinical diagnosis of 2 cases was confusing where microbiological diagnosis played an important role for confirmation. Early treatment with antitetanus serum is critical, because it binds free toxin. However, it does not treat the effects of toxin protected within the neuron or cell body. Treatment of the effects of toxin already within the nervous system is purely supportive [5]. According to Onuki T, rapid gram staining report is expected to improve recovery from *Cl. tetani* infection. Because based on staining report patient can be given antitetanus serum and tetanus immunoglobulin with supportive management to improve outcome [14].

Infection by *Cl. tetani* does not confer immunity. Vaccination is the only way to prevent it. Despite the widespread availability of a safe and effective vaccine against tetanus, it remains a major health problem in developing countries like India due to low immunization coverage rate [3]. According to previous reports, low socioeconomic status, incomplete or unknown immunization status, urban dwelling, impoverished neighbourhoods, single-parent families, mobile populations and minority cultural status may be the reason behind low immunization coverage [15, 16].

Immunisation against tetanus is the most effective tool for controlling the disease in children and adults. According to the World Health Organisation (WHO), six doses of TT containing vaccine within the age of 16 years provide lifelong immunity against the disease [17]. The National immunisation Schedule in India advocates the administration of 7 doses of TT by the age of 16 years. It provides protection that lasts 3 weeks, throughout the duration of the disease incubation period [18]. In our case series either patients immunization status was unknown or incomplete. Knowledge regarding TT vaccination among all levels of health care personnel is important not only for the prevention of neonatal tetanus but also tetanus in the children and adults. A thorough knowledge of the tetanus immunisation in wounds is also necessary to prevent the occurrence of wound related tetanus [19].



Photograph 1: Clostridium tetani colony on blood agar.

Photograph 2: Proteolytic Changes by Clostridium Tetani in Robertson's Cooked Meat Broth

Photograph 3: Opisthotonus in Tetanus.

Conclusion- Tetanus is a preventable disease characterized by the presence of classic symptoms and signs and associated with a high fatality rate. Early diagnosis and management in the intensive care settings is important to reduce fatality. Identification of the poor prognostic markers early in the course of the disease will helpful in improving outcome. Widespread use of vaccination is the cornerstone of effective prevention of tetanus. So it is important to strengthen existing immunization program against tetanus and educating people and health care worker regarding importance of immunization against tetanus.

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