REVIEW OF LITERATURE
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Tetanus is an acute toxemic illness resulting from the effect of soluble exotoxins of the bacterium Clostridium tetani on the C.N.S.

This disease has a world-wide prevalence and is known by different names in different countries. It is known as "Bhanurvata" (India), "Hausa" (Nigeria), "Sal de arco" (Mexico), "Disease of Seventh day" (Algeria), "Po-Shian-Fong" (China), (Bytchenko).

The approximate global incidence of tetanus is 350,000 cases with total deaths exceeding 160,000 per year (Adams et al, 1969).

The average annual mortality rates per 10,000 inhabitants of the world range from 0.05 up to 32.00 (Bytchenko).

Mortality from tetanus rises towards the equator as compared to the polar regions, reaching its zenith in the tropical and subtropical regions, mainly in Mexico, Central America, Peru, Ecuador, Colombo, Venezuela, Guyana, Paraguay, Brazil, Equatorial Africa, India and New Guinea (Athavale et al).
History

In ancient India Charak described Tetanus as "wind disease."

Hippocrates in 460 B.C. was among the first to described this disease and its poor prognosis.

Sir, Charles Bell in 1836 first described "Cephalic tetanus" a rare clinical variety of tetanus.

The bacillus "Clostridium tetani" was isolated by Nicolaier in 1884.

Kitasato (1889) established the relationship of Clostridium tetani with tetanus. Tetanus exotoxin was isolated in 1890.

Neural transport of tetanus toxin into the C.N.S. was first described by Marie and Morax (1902) and Meyer and Ransom (1903).

Wright et al (1951), Fedinec (1965) Habermann et al (1970) & Kryzhanovsky (1967) have in the recent times confirmed the theory of neural transport of tetanus toxin into the C.N.S. Tetanus antiserum was introduced into clinical medicine in 1890 by von Behring and Kitasato.

The antitoxin was introduced for human use by Ramon and Zoeller (1933).
Bouyer (1926) suggested that pregnant women can be immunized against tetanus to protect the neonates.

**Incidence**

Although tetanus is present all over the world, it is more common in the tropical & subtropical countries. The average annual incidence of tetanus in India during the period 1973-1982 was approximately 46,000 cases in an average population of 648 million. The incidence rate was therefore 6.7 per lakh population. According to the bulletin of Central Bureau of Health Intelligence 1983, the total number of deaths due to tetanus in India during 1973 was 4569 out of 37,867 cases and during 1983 it was 5177 out of 31,369 cases reported.

**Tetanus Neonatorum**

While tetanus can occur at any age, the newborns are at a greater risk, because of the unsatisfactory and unhygienic delivery practices and lack of maternal immunization. The alarming nature of the problem due to tetanus neonatorum can be assessed from the data available. In the underdeveloped nations neonatal tetanus may affect as much as 8% of all live births and account for 30% of all neonatal deaths (Forfar J. O. 1973). According to Stanfield et al, results of community based surveys show that neonatal tetanus mortality ranges from less than 5 to more than
60 per thousand live births; these deaths represent between 23% and 72% of all neonatal deaths. Bytchenko (1972) and Cook (1983) have reported, that about 5 to 10 lakh deaths due to tetanus occur all over the world yearly, of which about 50% are neonates. According to Stanfield et al (1984) it was estimated that approximately 5 lakh deaths from neonatal tetanus occur annually in the WHO South East Asia and Eastern Mediterranean region alone.

In rural India tetanus neonatorum is rated as the second commonest cause of neonatal mortality (Shah P.M. & Udani P.M.). According to sample surveys neonatal tetanus mortality rates in 1981 were estimated to the on an average, 13.3 per 1000 live births in the rural areas and 3.2 in the urban areas in India (Sokhey et al).

It was also estimated that 2.3 to 2.5 lakh infants died within the first month of life due to tetanus neonatorum during 1981 (Sokhey et al). Nearly two thirds of these deaths were in Uttar Pradesh.

That tetanus neonatorum prevails in all the 14 States and Union territories of India has been
reported to be higher in the rural areas as compared to their urban counterparts. Tetanus as a cause of neonatal death ranged from 0 to 68.7% in the urban areas and from 16.4 to 72.5% in the rural areas (Sokhey et al). According to Sharma et al, case fatality rate of tetanus neonatorum in rural areas was around 97% and 80% in the urban areas. That neonatal tetanus mortality is not uniform in the different states of India is indicated by the available data.

The neonatal tetanus mortality rate per thousand live births was found to be 66.7 in rural Uttar Pradesh, 15.3 in Urban Uttar Pradesh, 4.7 in rural Maharashtra 4.9 in urban Maharashtra, 8.4 in rural Haryana & 1 in Delhi according to a recent nationwide survey (Basu R.N., Sokhey J, 1982).

Neonatal tetanus mortality was found to be 20 per thousand live births in Madhya Pradesh. In the rural areas of Rajasthan and West Bengal the neonatal tetanus mortality rates were between 20 & 10 per 1000 live births (Sokhey et al). It was recorded as a cause in 1/3rd or more neonatal deaths in Bihar (rural/urban), Kerala (rural/urban) and Tamil Nadu (rural).

**Tetanus in Children**

This implies tetanus in children between the age of 1 month and 12 years. Athavale et al, observed
that the maximum number of cases in children (excluding neonates) were between 2 to 5 years of age and they constituted 39% of total cases in children.

74% of the cases in children resulted from injury and otorrhoea (Athavale et al).

Jolly et al, noted a mortality of 37.69% due to tetanus, in children.

Tetanus in Adults

This includes patients beyond 12 years of age. Jolly et al, observed that the maximum incidence of adult tetanus was in the age group of 21 to 30 years. It was 23%. The highest mortality due to tetanus in adults was observed in the age group of 41 to 50 years (76.47%). A very high incidence of tetanus has been noted in Punjab. It was 90.4 per 100,000 cases per year (Gordon et al). Injury has been noted as an etiological factor in most of the cases of adult tetanus (38%), while the cause of tetanus was unknown in a significantly large number of cases (35.5%), (Jolly et al).

Incidence and Mortality in relation to sex

A higher incidence of tetanus has been noted in males by many authors. Kacharevic was the first to suggest that males appear to be more sensitive to tetanus
toxin, than females. His postulation was substantiated, by his observations on experiments with pigs and other animals.

Denchev noted a similar observation. Hodi (1965) also suggested a higher incidence and mortality due to tetanus in males, as compared to females in all age groups. Raju et al also noted a slight male predominance of tetanus.

However Suri, Newell and Martin Bouyer noted that mortality did not differ significantly in the 2 sexes.

Indira Bai et al (1975) noted a lower mortality rate in males (74%) as compared to females (38%).

**Urban and Rural tetanus**

Tetanus mortality has been reported to be higher in patients in rural areas as compared to their urban counterparts. According to Sokhoy et al, mortality due to tetanus ranged from 0 to 68.7% in the urban areas and 16.4% to 72.5% in the rural areas. Stanfield et al also noted a significant rural/urban difference in tetanus mortality. It was 67 per thousand live births in rural Uttar Pradesh, whereas it was 15 per thousand live births in urban Uttar Pradesh (Stanfield et al). In an urban
centre like Delhi the mortality was 1 (Basu et al, 1982).

A survey by the Registrar Generals Office in India revealed that tetanus accounted for 15.6% of deaths below 1 year of age in rural areas and 6.6% in urban areas (Sharma et al).

Incidence rates of neonatal tetanus are highest in rural areas, where births usually occur at home and are attended by untrained personnel. Mortality in untreated cases is probably greater than 90% (Sokal et al).

Seasonal Variation of tetanus

Some authors have reported a higher incidence of tetanus during the rainy season (Gupta et al, 1977). Bhat et al, noted that maximum number of cases of tetanus neonatorum were admitted during the monsoon season i.e. between June and October. He attributed this increased incidence to the greater risk of contamination and infection during this season.

However Vakil et al (1964) found no significant seasonal variation.

As regards mortality due to tetanus, Sanders et al, found a significantly reduced mortality during the
hot, humid months of August to October as compared with
the cooler, dry months of November to February. One of
the factors of decreased mortality during the humid season
was the reduced incidence of bronchopneumonia and dehydra-
tion due to the humid season (Sanders et al).

**Puerperal tetanus**

Unhygienically and improperly performed
deliveries, poor domiciliary practices, poor post partum
care, unhygienically and improperly conducted illegal
abotions result in increased incidence of infection and
subsequently to a high incidence of post partum and post
abortal tetanus.

According to the observations of Shrivastava
puerperal tetanus contributes 10 to 12.7% of all cases.
Mortality rates due to puerperal tetanus varies from 49%
to 100%.

**Social factors**

According to Sanders et al in a study conduc-
ted by him he found that tetanus had a high prevalence
among the poverty stricken, undernourished, rural based
individuals who were working as cultivators or agricultural
labourers. Illiteracy was rampant in such a population and
they lived in a crowded atmosphere in close contact with cattle and pigs alike. He also noticed that the commonest tetanus tragedies were among potentially healthy, child bearing women who were deprived nutritionally when they needed it most. This was all due to the poor social customs.

In New Guinea, women during childbirth and puerperium are considered unclean and are forced to live in Menstrual houses where no man can visit them. In India also the pregnant women goes to her parents house for delivery (usually in a village). She is considered untouchable during the first 10 days. Naturally tetanus is more prevalent under such conditions. Jolly et al, noted an excessive prevalence of tetanus in Punjab. He attributed this to Punjab being predominantly an agricultural state and that there existed a very close contact between the animals and human population in the rural areas. Illiteracy, lack of immunisation and the vague belief that cowdung was the best antiseptic to be applied on the wounds, all contributed to a high incidence of this disease.

Tetanus neonatorum may be considered as one of the penalties of underdevelopment manifested by poverty, illiteracy, ignorance, dangerous rituals, unhygienic customs, superstitions, religious prejudices and inappropriate
medical care. The incidence of tetanus neonatorum varies inversely with the development of MCH and obstetrical services. In the developing countries midwifery is still practiced by untrained midwives or local elderly women. They are known as "dais" in India, "dukun" in Indonesia and "montemyae" in Thailand (Bytchenko 1966).

Newell et al (1966), reported that the highest rate of 35 tetanus cases per 100 births was observed in neonates delivered by a blind midwife in Guachena, Columbia, South America.

**Incubation period**

Incubation period is defined as the time interval between the entry of the organism in the host and the appearance of the first symptoms. In tetanus neonatorum the incubation period corresponds to the age of the baby in most cases (Athavale et al).

A shorter incubation period has been found to be associated with a greater mortality by most workers (Athavale et al, Jolly et al, Phatak et al, Bhandari et al, Beaty and Jaffari et al) especially if it is less than 7 days. Bhat et al noted a mortality of 100% in neonates in whom the incubation period was less than 5 days.

**Period of onset**

This denotes the time interval between the
the first symptom is usually persistent crying or inability to suck. In children & adults it is usually trismus. The prognostic value of the period of onset was first noticed by Cole when he found that a shorter period of onset was associated with a worse prognosis. Similar observations have been noted by Athavale et al, Jolly et al, Bhat et al, Bhattachar et al, Armitage et al(1978) & Patel et al.

**Increased neuromuscular irritability**

In tetanus patients increased neuromuscular irritability manifests in the form of generalised rigidity and spasms. The generalised rigidity is because of the increased muscle tone. This persists throughout the illness and is not affected by sedatives. Spasms (convulsions) are spasmodic contractions of muscles which may be tonic or clonic (usually tonic), which it self limiting and can be controlled by sedatives. Increased neuromuscular irritability of the facial muscles results in Risus sardonicus and that of masseters in lock jaw.

**Grading of severity in tetanus**

This is done on the basis of the criteria laid down by Patel and Joag (1959). According to this system a tetanus patient may present with any or all of the following five criteria.
Criterion no. I: Presence of lockjaw/ inability to suck.

II: Presence of spasms.

III: Incubation period of 7 days or less.

IV: Period of onset = 48 hours or less.

V: Fever on admission i.e. Axillary temperature of 99°F or Rectal temperature of 100°F on admission or within 24 hours of admission.

The cases having one of the five criteria are termed as grade I, the cases having only two of the five criteria, as grade II, cases having all the five criteria as grade V and so on.

Differential Diagnosis

Diagnosis of tetanus is usually straightforward and is based on the characteristic clinical features of this disease namely, risus sardonicus, lockjaw, generalised/localised rigidity, opisthotonus, neck rigidity, dysphagia, reflex spasms, spasms (convulsions).

However there are certain conditions from which it has to be distinguished:

a) Meningitis

Trismus is usually absent in meningitis. There is high fever along with signs of meningeal irritation (positive leg raising test etc.). WBC counts and C.S.F. examination are diagnostic.
b) Epilepsy

In epilepsy the patient may lose consciousness which may be even momentary, whereas a tetanus patient remains conscious throughout the illness. The patient may also give a previous history of similar seizures with completely symptom-free intervals.

c) Strychnine poisoning

This results by the accidental ingestion of broken seeds of nux vomica usually in villages. It mimics tetanus, but the onset in this case is sudden and in between spasms the muscles are completely relaxed. A history of intake of the above is usually present. Chemical analysis reveals the poison.

d) Hypocalcemia & Hypomagnesemia

These may present with seizures, tremors and laryngospasm. Hypocalcemia may present as neonatal tetany but generalised rigidity and trismus are absent. Blood levels of calcium & magnesium clinch the diagnosis.

e) Neonatal hypoglycemic convulsions

Here the patient presents with symptoms of irritability of the C.N.S., manifested by jitteriness, coarse tremors, twitchings and convulsions. The neonates may also present with refusal of feeds, apathy, limpness and coma. Blood glucose estimation will be diagnostic. Also, there will be a prompt disappearance of symptoms on administering intravenous glucose solutions.
f) Phenothiazine & metoclopramide toxicity

These may manifest as pseudotetanus producing dystonic reaction and features of extrapyramidal rigidity manifested by spasm of the muscles of the back and neck, trismus and dysphagia. The rapid tonic seizures of tetanus are not found in individuals suffering from such a toxicity. A careful history of drug intake and metabolic studies of blood and urine are diagnostic.

In intracranial haemorrhage and kernicterus trismus is absent. The patient is jaundiced in kernicterus. An altered sensorium is present in these conditions (in tetanus the patient is alert). C.S.F. findings and serum bilirubin levels are diagnostic.

Organism and Pathogenesis

The Clostridium tetani is a 2-5 micron long and 0.3 to 0.8 micron wide, anaerobic, gram positive, motile, spore bearing bacillus. Spores are usually at the terminal end of the bacillus which impart a drumstick appearance to the organism.

The organism releases two types of exotoxins (1) Tetanospsasmin and (2) Tetanolysin. However it is mainly the former that produces the neurotoxic effects.
Tetanospsmin is a selective neurotoxin which is a water soluble, easily diffusable protein, having a molecular weight of nearly 67000. Tetanospsmin acts on the motor end plates of skeletal muscles, spinal cord, brain and sympathetic nervous system (Kerr 1968).

Pathways of tetanus toxin to C.N.S.

There is a neural transport of the tetanus toxin into the Central Nervous System (C.N.S.), (Karie and Morex, Fedinec, Kryzhanovsky). The toxin spreads by the neural pathway with a definite rate depending on the quantity in the muscles, the particular features of the neural pathway and the muscle activity.

The neural pathway of the spread of toxin to the C.N.S. has the following links: Neural motor endings in muscles - Muscle nerve - Anterior roots - Anterior horns of the gray matter of spinal cord or motor-nuclei in the brain stem (Kryzhanovsky).

The toxin enters the C.N.S. by two pathways -
1) Regional neural pathway
2) General neural pathway

The clinical features of the disease greatly depend on the pathway which has been involved in the toxin
transport to C.N.S. If the toxin enters by the regional neural pathway there arises a local and ascendens tetanus in animals and partial tetanus in humans. Such a condition may arise if the toxin spread is blocked by anti-toxins.

The general neural pathway represents the sum of regional neural pathways from all the muscles. When the toxin enters the blood, it enters all the muscles and then through the general neural pathway enters the C.N.S. In such a condition the toxin first enters the motor nuclei and travels through the shortest neural pathways to the muscles of head and face, imparting the typical features i.e. trismus and risus sardonicus. The toxin enters the C.N.S. by longer neural pathways to produce opisthotonos and generalised rigidity. This is known as tetanus descendens (Kryzhanovsky, 1966). However more important than this descendant phenomenon is the sequence of involvement of motor nuclei into intoxication in relation to the length of the neural pathway (Kryzhanovsky).

**Toxin binding by brain tissue**

The physico-chemical receptor of tetanus toxin in brain substance is represented by gangliosides for-
ming a complex with the cerebroside (Heyningen, 1959), aided by the sialic acid in gangliosides (Kallenby et al., 1957). The toxin possesses three functional groups (Sondartchuk N.G. et al., 1973). (1) Antigenic—ensures binding of toxin with antitoxin. (2) Neurotropic—ensures binding with brain receptors or gangliotropic. (3) Toxophoric—ensures its pathogenic effects.

**Binding of toxins by neuronal membranes**

Synaptosomes have the greatest affinity for toxin binding. This is probably due to the reason that the membrane of synaptosomes contain gangliosides. Toxin neutralized by antitoxin is also bound by synaptosomes.

**Effect of tetanus toxin on the Presynaptic Apparatus**

Tetanus toxin acts on the presynaptic apparatus of central synapses in the spinal cord (Curtis et al., 1968) and on the neuromuscular junction (Kryzhanovsky). This causes the disturbance of transmitter release, at the neuromuscular junction and central synapses, both for the neuromuscular excitatory transmitter (acetylcholine) and the central inhibitory transmitters—glycin and GABA.

Tetanus toxin has a universal effect on the presynaptic apparatus of various synapses and does not depend on the nature of synapse. In tetanus intoxication the affe-
cted neural tissues show a disturbance of transport of \textit{N.T.P.'ase}. Under such a situation, the toxophoric group of toxin is activated, which might then split off and penetrate the neuronal membrane (Kryzhanovsky).

\textbf{Functional effects of tetanus toxin on Synaptic Apparatus}

A disturbance of the transmitter release by the presynaptic apparatus causes a block of synaptic transmission in tetanus intoxication.

The characteristic effect of tetanus toxin on C.N.S. during the course of its action, is the disturbance of the functioning of inhibitory synapses and the resulting block of various forms of postsynaptic and presynaptic inhibition (Kryzhanovsky). This causes a disturbance of segmental as well as of some forms of descendent inhibition in the spinal cord.

\textbf{Pathogenesis of muscle rigidity and generalised convulsions}

Muscle rigidity and generalised convulsions are produced by the basic mechanism of disturbance of inhibitory processes.

\textbf{Muscle rigidity}

This occurs due to the disturbance of inhibitory processes in the efferent output system of the spinal cord (i.e. in the motoneurons and the associated interneurons).
This results in an increased efferent output, enhanced polysynaptic reflexes and the periphery receives a strengthened and nearly permanent flow of efferent impulses. This results in a growing muscular tension, contraction and hypertonicity. This is attributed to the hyperactivity of the alpha motoneurons (Kryzhánovsky). Recently gamma system has been implicated in the pathogenesis of tetanic muscle contractions (Takano et al., 1973).

**Convulsions**

The disturbance of the inhibitory mechanisms in the spinal interneurons causes convulsions (Kryzhánovsky).

Groups of spinal interneurons with disturbed inhibitory processes following the action of toxin become generators of "Universal dispatch station" (pathologically potentiated excitation), following triggering stimuli (afferent flow from tetanus limb). This spreads over the whole C.N.S. to produce generalised convulsions (Kryzhánovsky).

**Functional changes in the Vegetative (Autonomic Nervous System)**

A state of sympathetic hyperactivity due to the affection of sympathetic nervous system by the tetanus toxin occurs (Kerr et al., 1972). This results in tachy-
cardia, changes in arterial pressure, increased basal metabolism, intense perspiration, hyperthermia etc. However it is thought that an imbalance in the autonomic nervous system rather than hyperactivity of the sympathetic system is responsible for this (Kryzhanovsky).

In neonates sympathetic overactivity has been not described (Wesley A.G. et al).

Changes in the endocrine system

Tetanus intoxication affects the hypothalamic-hypophyseal system. In tetanus there occurs a water and electrolyte imbalance (Nikhalov, 1968). Catecholamine levels in hypothalamus are increased. There is a peculiar lack of glucocorticoids and noradrenaline in the tissues (Zorkin et al 1972).

Important visceral changes:

Pulmonary complications

Pulmonary complications in tetanus are one of the most common causes of death. Special investigations carried out by Kryzhanovsky et al, show that ultrastructural and microcirculatory changes in lungs are serious concomitants of tetanus intoxication. These lead to extensive pulmonary congestions (erroneously considered sometimes as pneumonia). Pulmonary complications also result from coagulation changes in pulmonary vessels, trophic disturbances in pulmonary
tissue and fall of pulmonary resistance.

Myocardial changes

A complex myocardial change takes place in tetanus. This consists of protein and vacuole dystrophy, inhibition of the activity of oxidative restorative ferments (in particular of succinyl dehydrogenase), disturbance of microcirculation, intrevascular thrombosis, perivascular haemorrhage and disturbance of lymphocirculation (Kryzhanovsky et al.). Under experimental conditions tetanolysin is found to produce changes in heart activity. However the immediate effect of the toxin on the myocardium remains open.

Mode of infection in tetanus

Tetanus occurs due to inoculation of the wound by tetanus spores which are present in the soil, dust etc. Soil enriched with manure, used in agricultural fields contain animal faeces and form a rich source of Clostridia. Certain accessory factors include trauma, haemorrhage, necrosis, chemical damage to tissues and infection by other microbes. These help in the germination of spores by producing anaerobic conditions in the defenceless tissues which might also be necrotic.

Improperly sterilized surgical instruments or dressings may harbour tetanus bacilli as well as the
contaminated dust of operation theatres. Catgut (infected) has been indicated as a source of post operative tetanus (Javoleinen, 1950). Tetanus may also follow burns, ear infections, dental infections, abortion and pregnancy. Neonatal tetanus usually follows umbilical sepsis caused by improper handling of the cord, with unsterile techniques during labour. Spores may survive in the body for months to years and may result in the disease after some minor trauma which alters the local condition (Tullock, 1919).

Clinical forms of tetanus

Tetanus may be of three clinical types.

1) **Localised tetanus**

   This results from the localised involvement of a group of muscles of a limb resulting in pain and spasm of muscles in proximity to the site of injury. Localised tetanus may convert into generalised tetanus.

2) **Generalised tetanus**

   This results due to the generalised tonic rigidity and reflex convulsions. Trismus is the first indication of tonic rigidity and usually the first symptom. Spasm of the masseters leads to lock jaw, that of the facial muscles causes risus sardonicus. Tonic contraction of the abdominal and spinal muscles causes opisthotonos. Generalised convulsions appear as the severity increases.
3) Cephalic tetanus

This usually follows injuries of the head or face, especially around the orbits, though it can occur in cases with injuries to other parts and also without any apparent wound. Mortality is low and it carries a good prognosis (owing to its localised nature), Vakil et al. Cephalic tetanus usually remains confined to the head or neck though at times it may involve the entire body.

Prevention of tetanus

Tetanus is a preventable disease. It has in fact been suggested by some authors that it can be virtually eliminated by universal immunization. This unfortunately is lacking in our country in the real sense. Consequently there is a high incidence of tetanus in India and particularly in Uttar Pradesh and the adjoining areas of Madhya Pradesh.

Two forms of immunization are available against tetanus.


1. Active immunization

This results in a much longer period of immunity as compared to passive immunization. But on the other hand active immunity takes a longer time to
develop. Immunity is conferred late to the patient, unfortunately lacking when the patient needs it most, whereas passive immunity provides immediate protective antibodies against tetanus, to the patient.

Two vaccines are available for active immunization (1) Plain tetanus toxoid

(2) Adsorbed vaccine

Though plain tetanus toxoid is a quite effective vaccine, the incorporation of an immunological adjuvant in the vaccine such as aluminium hydroxide confers a number of advantages on this adsorbed vaccine -

(i) The immunity develops more quickly after using adsorbed toxoid. Immunity develops within 4 to 5 weeks of administration of adsorbed vaccine (Smith J.W.G.), while the plain variety may take a longer time.

(ii) The immunity stimulated by the adsorbed toxoid reaches a higher level and is longer lasting than the plain toxoid.

(iii) When administered concurrently with passive immunization, the adsorbed toxoid is more reliable. With plain toxoid, the injected antitoxin may interfere with the development of active
immunity, but interference with aluminium hydroxide adsorbed toxoid is minimal (Smith J.W.G.).

Plain tetanus toxoid consequently finds little place nowadays in tetanus prophylaxis as the adsorbed vaccine stimulates a quicker, higher and more durable immunity than plain toxoid.

Reactions to Tetanus Toxoid

These may be generalised or localised but are relatively uncommon. Local reactions were found to have a higher incidence in women as compared to men (White).

Generalised reactions may manifest as fever, malaise etc. but are uncommon. Reactions resembling anaphylaxis or serum sickness are very rare.

Local reactions to tetanus toxoid are not serious and usually consist of local pain and tenderness accompanied with an area or visible erythema and swelling between 2 and 5 cms in diameter usually. Sometimes such reactions may become more marked with tenderness or swelling of the whole of the upper arm (where it is usually injected). However these reactions usually subside within 2-3 days.

Immunization schedule against tetanus

This process should be started right from the stage of pregnancy when the fetus and motor are
both provided with immunity by vaccination of the mother. Transplacental passage of maternal antitoxin prevents tetanus neonatorum. The active immunity produced in the mother prevents post partum/abortal tetanus. The accepted protective level of antitoxin titre is 0.01 I.U. of tetanus antitoxin per millilitre of cord blood (Hacclennan et al).

In pregnancy, the recent schedule for immunization is the administration of two doses of adsorbed tetanus toxoid, the first at 7 months of pregnancy and the second at 8 months.

In the newborn child the first dose of vaccine in the form of D.P.T. (triple vaccine) should be administered within 2 to 3 months of birth. It should be followed by two more doses at 4 to 6 weeks interval. A 4th dose should be given after one year of third dose. A booster is required at intervals of 10 years. School going children should be immunized with 3 doses of tetanus and diphtheria toxoid starting from the age of 5 years, if already immunized earlier during infancy (even earlier if unimmunized before). The second dose should be given at 4-6 weeks after the first dose and the third dose 6 months to 1 year after the second dose. A booster is required every
6 to 10 years (Smith et al). In adults also a similar regime is followed starting at any age, as required.

A newer type of vaccine containing 3 times more potency (17.5 Lf as compared to normal 5 Lf by the ordinary toxoid) has been found to be very effective by only a single dose of toxoid. It takes 12 months for appropriate protective response to develop (Efeman et al 1981).

Recently Talwar (1985) has developed a double acting vaccine against pregnancy and tetanus. Such a vaccine produces antibodies acting against Human chorionic gonadotropic hormone and also against tetanus toxin.

**Passive Immunization**

This is available in two forms

1) The equine antitoxin (A.T.S.) antitetanus serum.
2) Human antitetanus immunoglobulin.

This type of immunization confers immediate protection against tetanus and is particularly useful in tetanus prone situation, especially after exposure. The human form (T.I.G.) is devoid of any reaction or complications whereas the equine form (A.T.S.), dose produce at times severe sensitivity reactions and anaphylaxis. It is therefore administered after
appropriate sensitivity tests. Unfortunately the protection provided by passive vaccination is very short lasting.

*Human anti tetanus immunoglobulin (H.I.G.)* is administered in a dose of 250 I.U. i.m. deep. It ensures serum antibody levels of 0.01 unit/ml in all patients for 28 days or more. This may be combined with adsorbed tetanus toxoid (in a dose of 10 Lf) for active-passive immunization.

*A.T.S. (antitetanus serum)* is administered in doses of 1500 I.U. to 6000 I.U. i.m. after sensitivity tests.

**Management of tetanus cases**

**Investigations**

A differential count examination of W.B.C. reveals granulocytosis in one-third of the patients. Microscopic examination of pus or necrotic material may reveal bacilli (tetanus) with spores in 30% of cases. Culture methods are more reliable. Sometimes raised levels of Serum Aldolase and Serum Creatinine phosphokinase are found. These may be diagnostic (Mullan et al 1964). An electrocardiographic record usually shows sinus tachycardia.
Therapy

The treatment policy in tetanus is as follows:

(b) Elimination of the toxin source — local measures.
(c) Control of convulsions and muscle rigidity.
(d) Maintenance of adequate airway and ventilation.
(e) Symptomatic treatment and nursing care.
(f) Treatment of complications.

II. Prevention of recurrence.

III. Prophylaxis.

Neutralisation of the toxin

Antitetanus serum (a.T.S.)

Over the years tetanus antitoxin in the form of equine antitetanic serum (a.T.S.) has been used by various routes for the treatment of tetanus. Sherrington (1917) demonstrated the efficacy of intrathecal a.T.S. in monkeys. Ildirim (1974) & Sanders et al (1977) noted the efficacy of intrathecal a.T.S. along with parenteral steroids in humans. However some have doubted its usefulness. Negquaye et al found that A.T.S. failed to improve survival in neonates despite its intrathecal use.

Bryant and Fairman (1940) were of the opinion that A.T.S. has a controversial role in tetanus therapy.
besides producing allergic reactions. Damage to the C.N.S. by the preservatives used in it have discouraged its use. Pratt even suggested that intrathecal administration of A.T.S. should be stopped.

It has been suggested that antitetanus serum (A.T.S.) does not neutralize tetanus toxin already fixed in the C.N.S. and does little to ameliorate symptoms already present.

**Human Antitetanus Immunoglobulin**

This specific antitetanus hyperimmune globulin (human) is obtained by fractionation of Hepatitis-B surface antigen and AIDS antibody negative plasma, of human donors hyperimmunized with tetanus toxoid. This immunoglobulin is further purified by affinity chromatography, column chromatography and gel filtration techniques. Optimal purity of above 99% can be obtained. This is tested by immunoelectrophoresis.

**Presentation**

Advantages of antitetanus human immunoglobulin

1) There is no risk of sensitization to heterologous protein — since T.I.G. is of human origin it is virtually free from the risk of inducing hypersensitivity reactions, unlike A.T.S. which is of equine origin, containing heterologous protein and hence having greater risk of hypersensitivity reaction.

2) Antibody levels of the homologous (human) T.I.G. persist considerably longer than the heterologous (equine) A.T.S. The half life of T.I.G. is 20 to 40 days, while it is only 7 to 14 days in case of A.T.S. Hence T.I.G. protects longer.

3) Antitetanus human immunoglobulin does not interfere with patients antibody production.

4) It does not require sensitivity tests.

5) T.I.G. is devoid of any preservative and lyophilized.

It can be thus used intrathecally..

For therapeutic purposes 3000 I.U. to 6000 I.U. of T.I.G. have been recommended (Behrman et al, 1963) deep intramuscularly. For more rapid action part of this can be given intrathecally. In children some authors have recommended a dose of 4 units/kg body weight. However it is logical to administer at-least 250 I.U. regardless of age of the child, since theoretically the same amount of toxin will be produced in

Varying results have been reported on the use of intrathecal T.I.G. Gupta P.B. et al (1980) found that intrathecal T.I.G. was useful in reducing mortality in patients with mild tetanus. He found that in patients who were given T.I.G. by i.m. route had a higher mortality. Chopra et al (1986) pointed the usefulness of intrathecal T.I.G. in high doses in more severe cases of tetanus.

Sgnihotri et al (1984) also showed a reduction in mortality with intrathecal T.I.G. It also reduced hospital stay.

Contrary to the above Vakil et al (1977) found no difference in mortality in adult tetanus patients who received intrathecal T.I.G. Chugh et al (1985) also found no beneficial response of intrathecal T.I.G. in neonatal tetanus. McCraken (1971) pointed that there was no significant difference in mortality by intramuscular T.I.G. over intramuscular A.T.S.

It has been postulated that the initial spasms are due to the tetanus toxins circulating free
in the C.S.F. not yet fixed to anterior horn cells. Thus free toxin is available for neutralisation by intrathecal tetanus antitoxin which circumvents the blood-brain barrier. But probably after 48 hours when the toxin is presumed to be fixed to the nervous tissue, intrathecal antitoxin is not of much value (Sanders et al).

Other uses of T.I.G.
- It is useful in all tetanus prone wounds as in crush injuries, compound fractures and accidental cases particularly if there is no clear evidence of prior immunization.
- In pre-operative preparations especially in emergency surgery.
- In unvaccinated cases of M.T.P. and septic abortions.
- In previously unimmunized mothers, when given during the antepartum period prior to delivery it provides dual protection to the mother and fetus. T.I.G. being 7S type, crosses the placental barrier giving protection to the fetus besides the mother.

Elimination of the toxin source - local measures

This is a very important step in the management of tetanus. It has been suggested by some authors that if wound toilet is properly performed within 6
hours of injury it will destroy the spores. But
wound toilet alone if performed after 6 hours fails
to prevent tetanus. However, meticulous toileting is
still essential to prevent further absorption of
toxins. Proper wound debridement should be carried
out as soon as possible. Grossly contaminated wounds
need to be cleaned with hydrogen peroxide solution.
Use of local antibiotics may also be effective. In
case of suppuration all pus should be drained out
and wound cleaned.

In neonates the umbilical cord should be
handled with all aseptic and antiseptic precautions.
The cord should be cleaned with spirit and 1% gentian
violet paint should be applied. Ear infections need to be
taken care of promptly. Any discharge should be clea-
ned with spirit swabs and ear kept dry. Handling with
dirty hands or entry of water and the instillation of
any household medicament in the ear needs to be
stopped. Appropriate antibiotic and if necessary local
ear drops should be used.

Chemotherapy

Antibiotics notably Penicillin are quite
effective against Clostridium tetani and their use
similarly has been thought to affect the outcome
favourably (Percy et al). The usefulness of penicillin has also been suggested by Bhat et al (1979) and Shandari (1980).

In a patient sensitive to penicillin, kanamycin in two divided doses of 10 mg/kg body weight may be used.

Metronidazole is effective against anaerobic bacteria. Some have pointed its usefulness in the disease.

Control of convulsions and muscle rigidity

The control of muscle spasms is one of the most important factors in the prognosis of patients with severe tetanus.

Many muscle relaxants have been advocated but some have their own demerits. To name a few—Centrally acting muscle relaxants like methocarbamol, mephenesin, meprobromate etc.; Peripheral muscle relaxants like d-tubo-curarine, succinylcholine, mytolon etc. Peripheral muscle relaxants are usually administered along with I.F.P.V.

Mephenesin is an effective muscle relaxant when given intravenously. Its drawback is that it causes hypotension and sometimes haemoglobinuria (Furks).
Leprohromate has been described as one of the most effective drugs in relieving muscle spasticity (Hiqquist et al). It has a prolonged action. However, it has the disadvantage of causing thrombosis, hemolysis and possibly, glomerular damage on intravenous therapy.

Nethocarbamol appears to possess the ideal pharmacological action to control the muscle spasm induced by tetanus toxin. It has a greater potency and acts for a longer duration (Crandall et al).

It has the added advantage of suppressing spasms without appreciable suppression of respiration. The dose is 2 to 20 gm per day by intravenous infusion or orally in divided doses.

Diazepam - In addition to being a hypnotic, diazepam is a potent muscle relaxant. It acts by depressing the ascending reticular activating system and internuncial neurons. Diazepam was first used by Weinberg (1964). Hendrickse and Sherman found that diazepam was very effective in controlling convulsive spasms during the early phase of treatment. Kazim reported that intravenous diazepam relieved opisthotonos but the effect lasted slightly more than an hour. Benjamin and Baltimore recommended diazepam as an alternative to
phenobarbital or phenothiazines. He found that parenteral diazepam was very useful.

However, a combination of muscle relaxants has been found to be more effective than massive dose of any single drug (Jolly et al, 1973). Diazepam was first used in combination with chlorpromazine by Hendrickse et al (1965).

**Maintenance of airway and tracheostomy**

Maintenance of a clean airway and adequate ventilation is of utmost importance in tetanus care. All secretions should be aspirated by suction. The mouth and nasal cavities should be kept as clean as possible. All froth should be cleaned. Children and neonates should be nursed with their head on one side to prevent aspiration of fluids into lungs. If necessary endotracheal intubation may be carried out. If it is not possible then tracheostomy should be performed. The indication for tracheostomy is either laryngospasm or copious secretions. Endotracheal suction can then be carried out. However, care of tracheostomy is then required.

The need for tracheostomy should be recognised early and should rather be performed electively than as an emergency procedure. Shah et al (1984)
found a mortality of 19.26% with tracheostomy. However the drawback is that it needs meticulous post-tracheostomy care and trained nursing personnel for its management.

Oxygen inhalation should be given as and when necessary.

**Total paralysis and ventilation**

In severe tetanus complete muscular relaxation (paralysis with peripheral muscle relaxants eg. d-tubocurarine) combined with tracheostomy and intermittent positive pressure ventilation (I.P.P.V.) has been a landmark in tetanus therapy.

Lessen (1953); Smith et al (1956) and Hendricks et al have reported favourably on the use of tracheostomy, total paralysis and I.P.P.V.

However only limited effectiveness has been claimed by Alhaudy et al, by this regime. Sinha and Athavale found this type of treatment unsuitable in India on account of its cumbersoness, costs and the need of skilled medical and para-medical personnel.

**General management and nursing care**

The patients should be nursed in an isolated, quiet and calm environment to cut off all external stimuli. Adequate care of bowel, back and bladder is
required. Frequent turning in bed along with the application of powder and spirit to clean the back is necessary to prevent bedsores. The patient should be catheterized to avoid possible urinary retention and incontinence. Appropriate antibiotic coverage may be given and should be changed according to culture and sensitivity reports. Constipation should be taken care of with suppositories or low enema as necessary.

Oral nutrition is maintained as far as possible. However, if dysphagia increases intravenous fluids are given and oral supplementation stopped till protective reflexes of swallowing and coughing are present. If necessary, naso tube feeding may be supplemented.

As regards fluid requirements, a minimum fluid intake of 130 ml/kg/day in children under 6 years and 80-130 ml/kg/day in older children has been recommended (Kerr J.H.). In adults, the amount should be regulated in relation to urine output and fluid losses. This may vary from 1.5 to 4 litres per day as necessary under the circumstances.

Small daily fluid deficits may accumulate to produce subclinical dehydration (Kerr J.H. 1981). As such, it may be produced by fluid losses in saliva and sweating. Hence, it is important to maintain adequate hydration.
Other miscellaneous forms of therapy

Corticosteroids

Sandsers et al have pointed the usefulness of steroids in tetanus therapy, in particular betamethasone.

The explanations given by them were that:

(1) Part of the action of betamethasone is antihistaminic. This results in reduction of pericellular oedema around motor nerves and ganglions.

(2) It is possible that betamethasone either reduces the amount of acetylcholine produced, or inhibits its action (Fal, W. et al (1963). Betamethasone may also support a failing suprarenal function (Sandsers et al).

(3) Betamethasone may have an antitoxaemic action in tetanus.

Beta blockers

Sainani et al, found that the tetanus toxin has a beta stimulant effect on the frog’s heart and this effect could be blocked by propranolol (beta-blocker). Kerr et al, observed that there was sympathetic overactivity in tetanus patients. This sympathetic overactivity manifested as disproportionate tachycardia, fluctuating high blood pressure and profuse sweating. Such patients having features of sympathetic overacti-
vity when treated with beta-adrenergic blocking drugs showed improvement (Kerr et al). Prye Roberts et al also observed beneficial effects of propranolol.

However the role of beta blockers is disputed and still under clinical trial. The literature now contains that removing sympathetic stimuli to the heart may remove the ability to sustain adequate blood flow through the constricted peripheral vasculature (Admonton R.S. et al).

**Pyridoxine**

Godet et al (1982), observed that pyridoxine hydrochloride in a dose of 100 mg per day by intramuscular route decreased tetanus mortality upto 15%.

**Cholinesterase restoring therapy**

Leonardi et al observed that the tetanus toxin had an anticholinesterase effect somewhat similar to organophosphorus agents and that antidotes to such agents, the oxime group of compounds could, by their cholinesterase restoring action, be of benefit in tetanus therapy. They used pralidoxime methanosulphonate 40 mg/kg/day together with vitamin $B_{12}$ in a dose of 100 mg/kg/day for 10 days intramuscularly and found it to be of some benefit. But this still requires further trials.
Hyperbaric oxygenation

In a trial conducted by Pascale et al, it was observed that there was active regression of symptoms following hyperbaric oxygen therapy. The progression of the disease was arrested and reversed. However its use is limited, owing to its limited availability in hospitals. Furthermore, it requires more trials.

Prognostic factors

Age - Vaishnava et al found that the survival rate was influenced by the patients age. In children and adult patients he found that higher the age the worse was the prognosis. In neonates the lesser the age at the time of admission the worse is the prognosis (Phatak et al, Bhat et al).

Sex - Vaishnava et al, found no difference in the mortality in two sexes. Vakil et al (1974) also found a similar observation. However Modi (1965) found a higher mortality in males.

Incubation period - Mortality varies inversely with the incubation period. The longer the incubation period, the lesser is the mortality (Patel et al (1965), Vakil (1964).


Fever - Fever has been reported as a bad prognostic sign (Bhandari et al, Spaeth et al).

Complications and causes of death

Oversedation is one of the major complications of the treatment given (Sehgal et al).

Respiratory complications including aspiration pneumonia are very important and commonly encountered complications (Sehgal et al, Bhat et al, Athavale et al). Injection abscess may occur occasionally (Sehgal et al). Parotitis has also been reported by some workers (Athavale et al, Bhat et al). Other complications include hyperpyrexia, constipation, thrombophlebitis, electrolyte imbalance, bed sores, septicemia and retention of urine (Bhat et al).

Athavale et al have reported dehydration, acidosis, facial palsy and compression fracture of vertebrae as important complications.

Respiratory spasms with apnoeic spells are the commonest cause of death (Athavale et al, Bhat et al). Death may also occur due to hyperpyrexia, laryngeal spasms,
laryngeal or pulmonary oedema, electrolyte imbalance, hypoxia etc. However all of the above complications may contribute to death, although some of the complications may be reversed when diagnosed and treated early and the patient may be saved.